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## Disparities in Early Mortality among Chronic Kidney Disease patients who Transition to Peritoneal Dialysis and Hemodialysis with and without Catheters

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### Abstract

**Purpose**—The early period after chronic kidney disease (CKD) patients transition to end stage renal disease (ESRD) represents the highest mortality risk but is variable among different patient populations and clinical circumstances. We compared early mortality outcomes among a diverse CKD population that transitioned to ESRD.

**Methods**—A retrospective cohort study (1/1/2002 through 12/31/2013) of CKD patients (age $\geq$ 18years) who transitioned to peritoneal dialysis (PD), hemodialysis (HD) with arteriovenous fistula/grafts, and HD with catheters was performed. Multivariable cox regression modeling used to estimate 6-month all-cause mortality hazard ratios (HR) among the 3 treatment groups after adjustment for patient and clinical characteristics.

**Results**—Among 5,373 ESRD patients (62.7 years, 41.3% females, 37.5% Hispanics, 13.3% PD, 34.9% HD with fistula/graft, 51.8% HD with catheter), 551 (10.3%) died at 6 months. Mortality rates were highest immediately after transition (299 deaths-per-1000 person-years in first month). Compared to PD patients, the 6-month mortality HR (95% CI) was 1.87 (1.06-3.30) in HD with fistula/graft patients and 3.77 (2.17-6.57) in HD with catheter patients. Inpatient transition (HR

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Each author contributed important intellectual content during the manuscript drafting or revision and accepts accountability of the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JJS takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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1.32), acute kidney injury (HR 2.06), and an eGFR $\geq$  15 vs 5-9 (HR 1.68) at transition were also associated with higher early mortality risk.

**Conclusion**—Among a diverse CKD population who transitioned to ESRD, we observed considerable differences in early mortality risk among PD, HD with fistula/graft, and HD with catheter patients. The identification of patient specific and clinical environmental factors related to high early mortality may provide insights for managing advanced stages of CKD and shared decision making.

### Keywords

mortality; end stage renal disease transition; chronic kidney disease; epidemiology; comparative outcomes

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### Introduction

While the end stage renal disease (ESRD) population itself experiences high mortality, the early period after transition to ESRD appears to be most vulnerable. High mortality rates of up to 30% have been described within the first year of transition from chronic kidney disease (CKD) to ESRD [1–6]. While the evidence is not entirely consistent, studies have described a mortality spike within the first few weeks to months of ESRD transition while others have not [7,3,8,9]. This alarmingly high rate of mortality has been the impetus to one of the Healthy People 2020 goals to reduce ESRD mortality to 329 deaths per 1000 patient years at risk within the first 3 months of ESRD transition [10].

A better understanding of the late CKD and early ESRD populations could provide insight into the reasons for this high transition mortality. It could have important implications for prognostication and help guide management strategies and shared decision making. An important consideration is to identify the patients that pose risk for early mortality as they may represent a different populations and circumstances altogether. The identification of these populations earlier in the course of CKD could help inform treatment plans and manage expectations through shared decision making.

Currently, there are limitations to available information on late stage CKD and early ESRD outcomes. Large data registries such as the United States Renal Data System (USRDS) historically have not comprehensively captured the early period after transition, due to a 3-month gap or an ascertainment bias [11,2]. Medicare coverage does not go into effect until 90 days after start of ESRD for those without existing Medicare including those under age 65 years without disabilities [3]. This lag period can contribute to an under-ascertainment of ESRD patients in the United States [2]. In addition, late stage CKD cohort studies often pool information from different data sources and clinical care environments, potentially limiting the interpretation of findings [12,13]. Thus the ideal management strategies prior to and at the initiation of renal replacement continues to evolve.

We hypothesize that early dialysis mortality is affected by the circumstances at transition from CKD to ESRD. These factors may include the timing, clinical setting and events preceding dialysis, and ultimately the dialysis modality itself which may be manifestation a

pre-ESRD care. In this USRDS special center study[14,1], we identified a large diverse CKD population that transitioned to ESRD from a single integrated health system with comprehensive electronic health records (EHR). Among patients who started peritoneal dialysis (PD), hemodialysis (HD) with a fistula/graft (AVF/AVG), and HD with a catheter, we sought to compare 6-month mortality risk and determine risk factors for early ESRD mortality.

## Methods

KPSC is an integrated health system geographically located in southern California and comprised of 15 medical centers and over 200 satellite medical office buildings. Members have similar coverage benefits including co pays for visits and medications. This study was approved by the KPSC institutional review board and exempted from informed consent (IRB #10591).

### Study population

The study population was comprised of KPSC adults age 18 years and older who had CKD that transitioned to ESRD between January, 2002 through March, 2015 and had at least one estimated glomerular filtration (eGFR) measurement within 90 days before transition. CKD was defined as 2 separate eGFR<45 ml/min/1.73m<sup>2</sup> that were 90 days or more apart. eGFR<45 ml/min/1.73m<sup>2</sup> was chosen as the inclusion criteria for the CKD cohort because of the higher risk for ESRD in this population regardless of proteinuria[15]. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[16]. ESRD was defined as treatment with HD (in center, home, or nocturnal) and PD. Patients who underwent preemptive renal transplantation were excluded.

All health information is collected as part of routine clinical care in a shared EHR. Study information on demographics, vitals, co morbidities, medications, and outcomes were extracted from the EHR and KPSC regional quality information data sources. The KPSC Renal Business Group captures and tracks all patients who initiated renal replacement therapy at an outpatient dialysis center or received a renal transplant. It also maintains a patient registry of all adult KPSC members who meet criteria for CKD [17]. Patient characteristics including vital signs, demographics, and laboratory results within 90 days prior to ESRD transition were extracted from the EHR. Comorbidity information was retrieved from the EHR using the *International Classification of Diseases* (ICD) codes. The cause of ESRD was extracted from the internal KPSC Renal Business Group records which was derived from clinician assessment and documentation by the physicians. Information on type of HD access used at the start of HD (AVF/AVG, or vascular catheter), setting of first ESRD (inpatient vs outpatient start), and acute kidney injury (based on ICD codes) within 90 days before ESRD transition were also extracted. Patients were categorized based on ESRD treatment types (PD, HD with AVF/AVG, or HD with catheter), age in years (>80, 70-79, 60-69, <60), and pre-ESRD transition eGFR. Patients were passively followed through the EHR for up to 6 months after ESRD transition.

## Outcomes

The primary outcome evaluated was early all-cause mortality as defined as within 6 months after transition to ESRD. Mortality information was obtained from the KPSC Mortality database which combines information from seven data sources, including California State Death Master Files, California State Multiple Cause of Death Master Files, Social Security Administration Death Master Files, KPSC Hospital and Emergency Room records, KPSC Membership System, Perinatal Data Mart, and Outside Claims Processing System. Mortality rates were calculated for each month following ESRD transition up to 6 months and reported as events per 1000 patient years. Patients were followed until a mortality outcome occurred, until 6 months of follow up after ESRD, or until the end of the study observation period (March, 2015). Because mortality information was captured from KPSC and California state files, we did not censor any patients who lost membership or left the health plan. Despite the fact that ESRD patients may switch modalities or receive renal transplantation within the 6 months after ESRD transition, we analyzed our variables at the time of ESRD similar to an “intention to treat” approach.

## Statistical Analysis

Patient characteristics were compared across the 3 ESRD treatment types. Categorical variables were presented as counts (frequencies), and continuous variables were presented as means (standard deviation).  $\chi^2$  test was performed to compare independent categorical variables, and ANOVA was used to test the difference of continuous variables. Mortality rates were compared by treatment type (PD, HD with AVF/AVG, HD with catheter), prelude (pre-ESRD transition) eGFR, and age categories. The primary analysis was 6-month mortality risk after transition to ESRD using Cox proportional hazards modeling. 6-month HR's were estimated for ESRD treatment type. Multivariable hazard ratios (HR) were estimated adjusting for age, sex, race/ethnicity, comorbidities DM and heart failure, transition setting (inpatient or outpatient, acute kidney injury, and prelude laboratory values, including eGFR. We tested proportional assumption by introducing the interactions between exposure variables and time. No indication of proportionality violation was found. This was also confirmed by Supremum Test for Proportional Hazards. All hypothesis tests were 2-sided with a significance level of  $p < 0.05$ . Statistical analysis was conducted using SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC).

## Results

Among 71,127 individuals identified with CKD between 2002-2013, a total of 5,819 (8.2%) transitioned to ESRD before March, 2015. The study cohort was comprised of 5,373 CKD patients who transitioned to ESRD, had a documented eGFR within 90 days pre-transition, and had an ESRD modality identified (Figure 1). The mean age was 62.7 years with 41.3% females, 37.5% Hispanics, 27.7% non-Hispanic whites, 22.7% blacks, and 9.8% Asians. The cause of ESRD were DM (69.1%), hypertension (12.9%), glomerulonephritis (5.8%) and other (12.2%). Overall, DM was identified in 79.1% and listed as the primary cause of ESRD for 69.1% of the study cohort. A total of 2,266 (42.2%) patients had acute kidney injury within 90 days before ESRD transition (Table 1). The median hemoglobin level was 10.2 g/L and 26.4% had a serum CO<sub>2</sub> measurement under 20 mEq/L (Table 1).

Within the study cohort, 714 (13.3%) patients transitioned to PD, 1,874 (34.9%) patients transitioned to HD with AVF/AVG, and 2,785 (51.8%) patients transitioned to HD with a catheter. There were 1,915 (35.6%) patients who transitioned to ESRD in an inpatient setting (40.7% of HD patients and 2.5% of PD patients). Arteriovenous grafts were present in 4% of the total study cohort. The majority of the cohort transitioned to ESRD with an eGFR in the range of 5-14 mL/min/1.73m<sup>2</sup>.

## Mortality

At 6 months following transition to ESRD, 551 patients had died (14 PD, 97 HD with AVF/AVG, and 440 HD with a catheter). Mortality rates were highest immediately (within month 1) after transition and then declined (Figure 2A). Mortality rates were 299 (deaths per 1000 person-years) at month 1 and then declined to 224 by month 3 (Figure 2A). This trend was mostly observed among the HD population but not among PD patients (Figure 2B). Patients with a HD catheter had higher early mortality compared to HD patients who transitioned with an AVF/AVG. Higher early mortality was also observed in those who transitioned with eGFR  $\leq$  15 mL/min/1.73 m<sup>2</sup> and in older patients (Figures 2C/D).

## Regression Analyses for Early ESRD Mortality

Compared to patients who transitioned to PD, the fully adjusted 6-month mortality HR's (95% CI) were 1.87 (1.06-3.30) and 3.77 (2.17-6.57) for HD with AVF/AVG and HD with a catheter, respectively (Table 2). There was no difference in mortality risk between males and females. Older age demonstrated an incremental pattern of higher mortality risk with age  $\geq$  80 years having a 6-month HR of 4.19 (3.14-5.59) compared to age  $<$ 60 years. Non-Hispanic whites had worse survival compared to Hispanics, Asians, and blacks. Pre-ESRD transition eGFR  $<$ 5, 10-14, and  $\leq$  15 ml/min/1.73 m<sup>2</sup> had 6-month mortality HR's of 1.04 (0.69-1.58), 1.38 (1.11-1.73), and 1.68 (1.34-2.11) respectively compared to eGFR 5-9 ml/min/1.73 m<sup>2</sup>. Heart failure or CO<sub>2</sub> $>$ 20 mEq/L were not associated with higher early mortality risk. Overall, having DM had a lower 6-month mortality HR [0.67 (0.55-0.81)] within our study population (Supplemental Table 1). The circumstances around the transition appeared to affect early mortality. Patients who transitioned to ESRD in the hospital (inpatient) had a HR of 1.32 (1.11-1.58) compared to those who started dialysis on an outpatient basis. Patients diagnosed with acute kidney injury within 90 days prior to ESRD had a 6-month HR of 2.06 (1.66-2.54) (Supplemental Table 1).

Sensitivity analyses using cause of ESRD in the multivariable modeling demonstrated 6-month mortality HR's of 1.96 (1.11-3.46) and 4.62 (2.67-8.00) for HD with AVG/AVF and HD with a catheter, respectively compared to PD (Supplemental Table 1).

## Discussion

We evaluated early ESRD mortality in 5,373 CKD patients who transitioned to dialysis among 3 different treatment types (PD, HD with an AVF/AVFG, and HD with a catheter) and found that PD patients had the lowest risk for early mortality. Compared to PD patients, HD patients had a two to four-fold higher 6-month mortality risk depending on the type of access used at ESRD transition. Early mortality was also associated with patients who

started dialysis at a higher eGFR, who were older, and who endured more acute circumstances prior to ESRD transition. The highest mortality was manifested within the first month. Our findings from a real world clinical care environment demonstrate that the period immediately after ESRD represents the most vulnerable stage for CKD patients transitioning to ESRD.

These insights into the high mortality in early ESRD could have important implications for both prognostication and management purposes. Catheter use, volume overload, infrequent CKD care, and perhaps rapid eGFR decline emphasizes the importance of pre-ESRD transition *care*[18–21]. Early initiation of dialysis, however, does not seem to be associated with ESRD survival[22,23]. By contrast, earlier ESRD transition may even be associated with worse outcomes[24,23]. Although confounding by clinical indication may affect the assessment, we similarly observed that patients who transitioned with eGFR 15mL/min/m<sup>2</sup> or greater experienced the highest early mortality.

The high rates of mortality immediately after ESRD were mostly accounted for by the HD with catheter population. Our findings were similar to prior observations that demonstrated that HD patients with catheters had higher mortality compared to HD with AVF/AVG[25,20,26]. The HD with AVF/AVG population also demonstrated a higher mortality rate immediately after ESRD transition, though not as pronounced as the catheter population. Conversely, the PD population appeared to have stable monthly mortality rates for the first 6 months after ESRD transition. The improved short-term outcomes in PD vs HD appear consistent with prior observations that compared dialysis modalities[27–29].

Our findings underscore the need to recognize the differences in patient characteristics and clinical circumstances among patients that transition to ESRD. These patient specific, clinical environment-related, and treatment-related influences may help identify more optimal management strategies prior to and at the initiation of renal replacement. Unfortunately, there remains questions about the ideal management strategies in terms of blood pressure, DM, CKD-Mineral Bone Disorders (CKD-MBD), and anemia management strategies. The real world clinical care and outcomes among a large diverse ESRD transition population could help provide additional and important insights.

In addition, the recognition of patients who are at highest risk for early mortality has potential benefit[30,9]. The subgroup that experiences early mortality appears to represent a different population (or populations) altogether. More aggressive and timely management strategies such as earlier and more frequent nephrology care may be beneficial[21]. Conversely, the elderly and patients with high comorbidity burdens may have shortened life expectancies regardless of whether they receive dialysis [31,32]. These represent populations/situations in which renal replacement may not improve or extend lifespan. The information may improve shared decision-making discussions which might more easily include conservative care of ESRD without dialysis as a viable option. With hundreds of thousands of people transitioning to ESRD throughout the world on an annual basis[33], the instances in which ESRD treatment and expenditures are futile and dialysis may not affect or prolong survival are of great concern. One potentially modifiable risk factor we observed was that patients with acidemia (CO<sub>2</sub><20) at ESRD transition had higher early mortality risk.

Perhaps earlier and improved management of acidemia may lead to better survival during the early period after starting dialysis.

The information from our integrated health system captures early mortality events more comprehensively and accurately than traditional USRDS data sources[11,2]. As Medicare coverage does not go into effect until 90 days after start of ESRD for those without existing Medicare coverage including those under age 65 years without disabilities who experience early mortality. This accounts for up to 60% of patients who transition to ESRD[3]. By definition, our study from a single integrated health system with comprehensive clinical documentation and follow up, allowed a detailed assessment of pre-and post ESRD transition outcomes that are likely to be captured without ascertainment bias or information gaps.

### Potential Limitations

Our study population may not reflect the experience of all individuals who start ESRD treatment given the fact that our cohort was selected based on CKD patients who were relatively stable, with 2 eGFR measurements 90 or more days apart. Thus, patients with normal baseline renal function who abruptly transitioned to ESRD were not included in our study. Catheter use and inpatient ESRD transitions were lower in our cohort than what has been described for the United States ESRD population overall[1]. This may suggest that they may have been managed differently and perhaps were more “prepared” for ESRD transition. While we evaluated race/ethnicity, sex, and age on our outcome, we did not explore more granular patient information including socioeconomic and sociodemographic backgrounds. We also did not have reliable information on lifestyle including smoking and substance abuse. In addition, information on dialysis adherence or missed dialysis during the observation window was not available. Another consideration is that within the Kaiser Permanente integrated health system, there is more standardizations in care among the CKD population. CKD specific interventions such as blood pressure control, anemia management, CKD-MBD management, and CKD related patient education are accessible to all CKD patients. Moreover, KPSC has an internal CKD registry that identifies patients and gives feedback to providers on management. Similar mechanisms are in place for other chronic conditions such as hypertension and patient safety nets[34,35]. Thus, our findings may not reflect the heterogeneity in practice patterns and treatment environments found in pooled cohorts.

Another potential limitation of our study is the lack of information on cause of death. Cardiovascular events are high in the early ESRD period and are a major contributor to ESRD mortality[36]. Given the potential for discrepancies and reliability concerns, we were cautious about solely relying on the Center for Medicare and Medicaid Services (CMS) ESRD death notification form 2746 [37]. We also did not censor patients who switched dialysis modalities or received a renal transplant within the first 6 months. In addition, we did not censor patients that may have left the health plan because the state files would have captured any mortality although, we may have missed deaths among patients who left the health plan and state and then died within 6 months.



## Conclusion

Among a CKD population who transitioned to ESRD, we observed high mortality immediately after the start of dialysis especially among HD patients who transitioned with a catheter. Patients who transitioned in an inpatient setting, who had higher eGFR at transition, and who were recently diagnosed with AKI also had higher early mortality risk. This information may lead to more effective management strategies and inform shared decision making.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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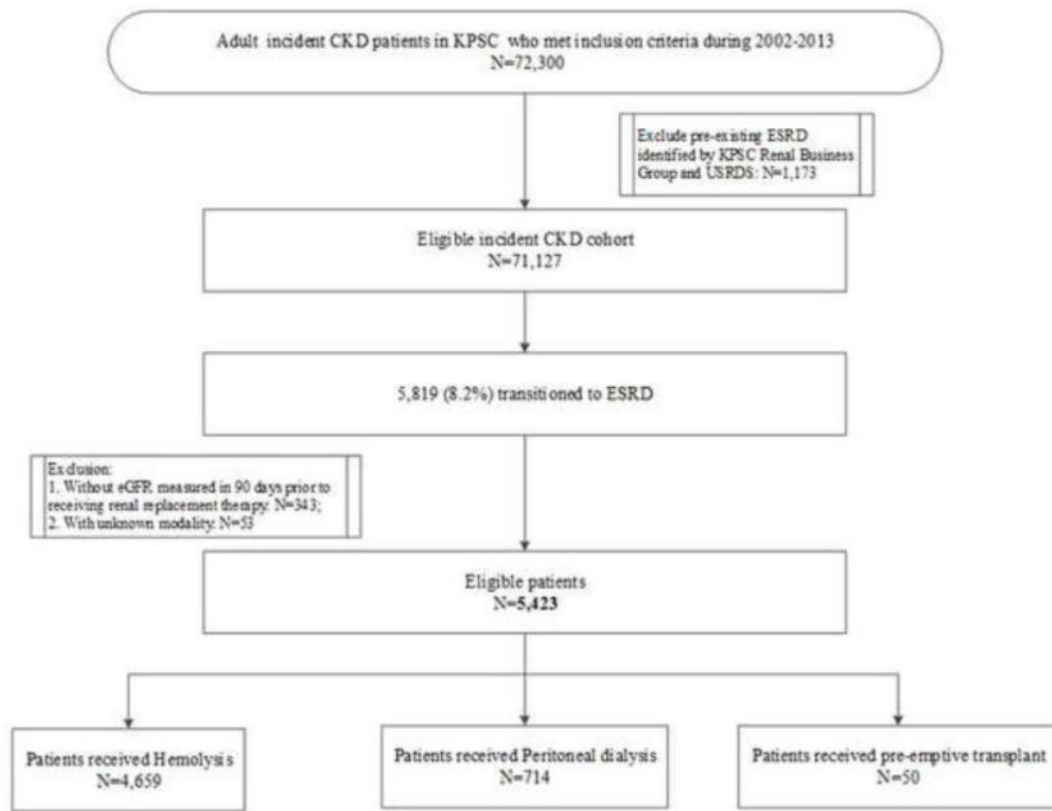
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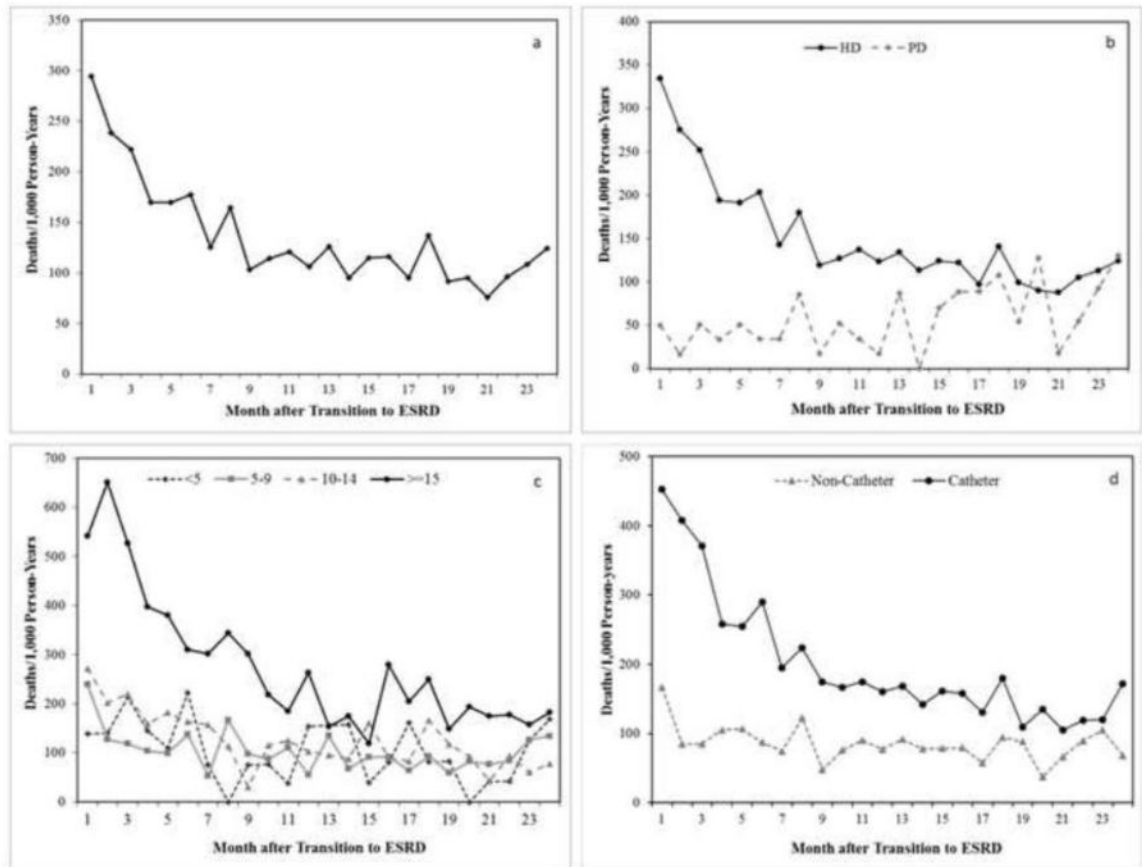
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**Figure 1.**

Among a total of 71,127 individuals (between 2002-2013) who were identified with CKD, 5,819 (8.2%) transitioned to ESRD. The study cohort was comprised of 5,373 CKD patients who transitioned to ESRD, had a documented eGFR within 90 days pretransition, and had an ESRD modality identified.



**Figure 2.** Monthly mortality rates up to 24 months of follow-up are reported in deaths per 100 person-years. a) Mortality rates for the entire ESRD transition population (N=5,373). b) Mortality rates for hemodialysis with catheter(HD-catheter), hemodialysis with AVF/AVG (HD-AVF/AVG) and peritoneal dialysis (PD) populations separately not including transplant. c) Mortality rates of the entire study cohort categorized by eGFR at transition (<5, 5-9, 10-14, and ≥15ml/min/1.73 m<sup>2</sup>). d) Mortality rates of the entire study cohort categorized by age (<60, 60-69, 70-79, and ≥80).

**Table 1**  
 Characteristics and Comparisons by Treatment group among CKD Patients who Transitioned to ESRD (N=5,373)

Characteristics	Total N=5,373	PD N=714	HD with AVF/AVG N=1,874	HD with Catheter N=2,785	pvalue
Age group, N(%)					<0.0001
<50	2049 (38.3%)	403 (56.5%)	655 (34.9%)	991 (35.6%)	
60-69	1532 (28.5)	178 (24.9%)	554 (29.6%)	800 (28.7%)	
70-79	1332 (24.8)	104 (14.6%)	506 (27.0%)	722 (25.9%)	
80+	460 (8.6)	29 (4.1%)	159 (8.5%)	272 (9.8%)	
Female, N(%)	2221 (41.3%)	301 (42.2%)	746 (39.8%)	1174 (42.2%)	0.3
Race/Ethnicity, N(%)					0.0002
White	1488 (27.7%)	180 (25.2%)	512 (27.3%)	796 (28.6%)	
Asian	525 (9.8%)	91 (12.7%)	207 (11%)	227 (8.2%)	
Black	1221 (22.7%)	133 (18.6%)	413 (22%)	675 (24.2%)	
Hispanic	2014 (37.5%)	291 (40.8%)	704 (37.6%)	1019 (36.6%)	
Other	125 (2.3%)	19(2.7%)	38 (2.1%)	68 (2.5%)	
Diabetes, N(%)	4252 (79.1%)	522 (73.1%)	1514 (80.8%)	2216 (79.6%)	0.0001
Heart Failure, N(%)	3657 (68.1%)	343 (48%)	1213 (64.7%)	2101 (75.4%)	<0.0001
HTN, N(%)	5330 (99.2%)	711 (99.6%)	1868 (99.7%)	2751 (98.8%)	0.002
Inpatient transition, N(%)	1915 (35.6%)	18 (2.5%)	476 (25.4%)	1421 (51%)	<0.0001
AKI in 90 days prior to ESRD, N(%)	2266 (42.2%)	114 (16%)	419 (22.4%)	1733 (62.2%)	<0.0001
eGFR category, N(%)					
<5	345 (6.4)	27 (3.8%)	106 (5.7%)	212 (7.6%)	
5-9	2396 (44.6)	348 (48.7%)	966 (51.6%)	1082 (38.9%)	
10-14	1743 (32.4)	289 (40.5%)	665 (35.5%)	789 (28.3%)	
>=15	889 (16.6)	50 (7%)	137 (7.3%)	702 (25.2%)	
CO <sub>2</sub> in blood, median mEq/L (IQR)	22 (19.5-25.0)	22.0 (20.0-25.0)	22.0 (20.0-24.5)	22.0 (19.0-25.0)	<0.0001
<20	1420 (26.4%)	143 (20%)	458 (24.4%)	819 (29.4%)	
>=20	3884 (72.3%)	571 (80%)	1402 (74.8%)	1911 (68.6%)	
Unmeasured	69 (1.3%)	0 (0%)	14 (0.7%)	55 (2%)	
HGB, median g/dL (IQR)	10.2 (9.3 - 11.2)	10.9 (9.9 - 11.8)	10.4 (9.4 - 11.2)	10.0 (9.1 - 10.9)	<0.0001
PTH, median pg/ml (IQR)	111.0, 287.0	194 (121.0 - 288.0)	190 (117.0 - 302.0)	178 (105.0 - 277.0)	0.02

Characteristics	Total N=5,373	PD N=714	HD with AVF/AVG N=1,874	HD with Catheter N=2,785	pvalue
Ferritin, median ng/ml (IQR)	241.9 (123.3 - 425.5)	211 (106.7 - 384.0)	246 (124.0 - 420.0)	248.4 (130.7 - 449.1)	0.002
Albumin, median g/L (IQR)	3.1 (2.6-3.5)	3.5 (3.0-3.9)	3.2 (2.7-3.6)	2.9 (2.4-3.3)	<0.0001

/ All lab data were defined by the value in 90 days prior to baseline



**Table 2**

Hazard Ratios for 6-Month Mortality among incident ESRD patients by Treatment Group

	HR (95% CI) <sup>1</sup>	HR (95% CI) <sup>2</sup>	HR (95% CI) <sup>3</sup>
Modality			
PD		Reference	
HD with AVF/AVG	2.65 (1.51-4.64)	2.10 (1.20-3.68)	1.87 (1.06-3.30)
HD with Catheter	8.55 (5.02-14.55)	6.65 (3.90-11.34)	3.77 (2.17-6.57)

<sup>1</sup>Unadjusted

<sup>2</sup>Adjusted for age, sex, and race/ethnicity

<sup>3</sup>Adjusted for age, sex, race/ethnicity, eGFR prior to transition, diabetes, heart failure, acute kidney injury, inpatient transition, bicarbonate level, and albumin.

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