

Patterns and Predictors of Early Mortality in Incident Hemodialysis Patients: New Insights

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Key Words

Incident hemodialysis patients · Mortality predictor · Population attributable fraction

Abstract

Background: Incident hemodialysis patients have the highest mortality in the first several months after starting dialysis treatments. We hypothesized that the patterns and risk factors associated with this early mortality differ from those in later dialysis therapy periods. **Methods:** We examined mortality patterns and predictors during the first several months of hemodialysis treatment in 18,707 incident patients since the first week of hemodialysis therapy and estimated the population attributable fractions for selected time periods in the first 24 months. **Results:** The 18,707 incident hemodialysis patients were 45% women and 54% diabetics. The standardized mortality ratios (95% confidence interval) in the 1st to 3rd month of hemodialysis therapy were 1.81 (1.74–1.88), 1.79 (1.72–1.86), and 1.34 (1.27–1.40), respectively. The standardized mortality ratio reached prevalent mortality only by the 7th month. No survival advantage for African Americans existed in the first 6 months. Patients with low albumin <3.5 g/dl had the highest proportion of infection-

related deaths while patients with higher albumin levels had higher cardiovascular deaths including 76% of deaths during the first 3 months. Use of catheter as vascular access and hypoalbuminemia <3.5 g/dl explained 34% (17–54%) and 33% (19–45%) of all deaths in the first 90 days, respectively. **Conclusions:** Incident hemodialysis patients have the highest mortality during the first 6 months including 80% higher death risk in the first 2 months. The presence of a central venous catheter and hypoalbuminemia <3.5 g/dl each explain one third of all deaths in the first 90 days.

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Introduction

The number of patients with end-stage renal disease (ESRD) in the United States has increased from about 60,000 in 1980 to over half a million in 2008 [1]. It is projected that this number would surpass 800,000 by 2020

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[2]. These patients would not have survived without kidney transplantation or dialysis therapy, which currently comprises mostly of hemodialysis treatment in this country. However, dialysis patient mortality is unacceptably high, currently approximately 20% per year in the United States. Mortality appears to be even higher during the first year of dialysis therapy, especially in the first few months [2], while factors contributing to early death are widely unknown.

The most common cause of death in dialysis patients is cardiovascular followed by infectious disease. In a recent study that examined the early mortality among incident hemodialysis patients during the first 120 days versus the subsequent 121 to 365 days [3], cardiovascular causes were still the most common for the entire first year. Even though previous studies identified several important factors associated with elevated mortality among incident hemodialysis patients, few have addressed the risk factor patterns and their changes over time during the first few months of dialysis therapy. It is crucial to assess whether those risks remain constant or whether the risk patterns are altered over time, so that focused interventions can be used at different periods of time. Comorbidities including severity of kidney disease at the time of dialysis initiation could play an important role in survival of dialysis patients [3]. Several recent observational studies [4–6] and at least one randomized trial [7] have indicated that a higher glomerular filtration rate at the time of dialysis initiation was associated with elevated mortality risk in dialysis patients, although this may be due to the fact that sicker and older patients start dialysis therapy earlier [8]. Use of central venous catheters (CVC), which exists in up to 82% patients at the start of hemodialysis therapy [9–12], has been implicated as an important mortality predictor in several studies [9, 12].

We hypothesized that mortality rate is substantially higher during the first few months of dialysis initiation and that the risk factors associated with this high mortality are different from those in later periods of dialysis therapy. We examined the associations between the mortality and the putative risk factors during different time periods within the first 24 months after the start of hemodialysis therapy among a large group of incident hemodialysis patients who had started treatment at one of the DaVita dialysis facilities in the United States between July 2001 and June 2006 and whose clinical outcomes were followed during the 5-year period.

Methods

Sources of Data, Study Population and Follow-Up

DaVita is one of the largest dialysis providers in United States. For this study we examined the cohort of all incident hemodialysis patients who started the first week of hemodialysis treatment from July 1, 2001, to June 30, 2006, at one of the DaVita dialysis centers. Patients who used peritoneal dialysis modality at any given time were excluded. Information about the date when the patient entered the DaVita cohort, dialysis treatment modality, date when the first hemodialysis treatment started, demographic characteristics, comorbidities, and laboratory and other clinical measures were collected at the time of the start of enrollment in DaVita. Using unique identifiers, data from DaVita and the United States Renal Data System (USRDS) databases were cross-linked to corroborate the information about dates of the events including death and transplantation, and comorbidities at the start of dialysis therapy, dialysis modality and laboratory data prior to the dialysis treatment were verified as well [13]. To examine the patterns of survival in the first 2 years of hemodialysis treatment, the cohort time was divided into a priori selected smaller groups, i.e., <3 months, 3 to <6 months, 6 to <12 months, and 12 to 24 months. Patients were followed for up to 5 years (1,830 days) or until death, kidney transplantation, or the end of the follow-up. Person-time was obtained by calculating the difference between the dates when the first hemodialysis treatment started at one of the DaVita clinics and the end of follow-up or other censoring events.

Laboratory Parameters

All blood samples were drawn using standardized procedure and transported to the Central DaVita Laboratory located in Deland, Fla. usually within 24 h. Blood or serum levels of albumin, creatinine, phosphorus, calcium, bicarbonate, total iron-binding capacity (TIBC), iron (transferrin) saturation ratio (ISAT or TSAT, i.e., iron divided by TIBC), white blood cell count (WBC), and lymphocyte counts were usually measured monthly. Serum ferritin was measured at least quarterly. Hemoglobin was measured weekly to biweekly. Estimate of prescribed dialysis treatment dose, known as Kt/V (single pool) [14], and protein intake, known as normalized protein catabolic rate (nPCR) [15], were obtained using urea dynamic equations. All measurements were averaged over the first calendar quarter (up to 13 weeks) to calculate one single value for each laboratory parameter per each patient. Since most of these laboratory measurements (albumin, creatinine, phosphorus, calcium, bicarbonate, TIBC, WBC, lymphocyte, ferritin, and nPCR) and body mass index (BMI) may reflect the nutritional and/or inflammatory status of dialysis patients, they are referred to as the 'malnutrition-inflammation cachexia syndrome' (MICS) throughout this study [16].

In order to calculate summary estimates of the exposure variability as putative risk of death in a clinically relevant and commensurate format, we rescaled some laboratory measures by defining biologically and clinically meaningful increments including 0.2 g/dl of albumin, 0.2 g/kg/day of nPCR, 2 mEq/l of bicarbonate, 2 index points of BMI, 10% of lymphocyte percentage, 100 pg/ml of parathyroid hormone, 10% of ISAT, 50 mg/dl of TIBC, 500 ng/ml of ferritin, and 5×10^3 /HPF of WBC. For other laboratory values, one conventional unit was used such as 1 mg/dl increase in serum calcium or phosphorus concentrations. Age

was also examined as decades of increments. Additionally we also examined the associations between the mortality and clinically relevant dichotomies for selected laboratory variables including serum albumin (comparing mortality for patients with <3.5 vs. ≥ 3.5 g/dl), hemoglobin (≥ 10 vs. <10 g/dl), and nPCR (≥ 1 vs. <1 g/kg/day).

Statistical Analyses

Descriptive analyses were conducted to examine the population characteristics across the a priori selected survival periods of <3 months, 3 to <6 months, 6 to <12 months and 12 to <24 months. Estimated hazard functions were examined by the life table methods. Five-year unadjusted and adjusted survival curves using Kaplan-Meier (KM) estimation were produced for the entire population as well as for the important demographic characteristics and comorbidities. Survival curves were adjusted for four main demographic features including age, gender, presence or absence of diabetes mellitus upon dialysis therapy and race, i.e., African Americans vs. others. We also calculated monthly standardized mortality ratios (SMRs) for each of the first 24 months of dialysis treatment for the incident hemodialysis patients under study. The rates were standardized to age, gender, diabetes status, and race using the cohort of all other patients who started hemodialysis treatment in a DaVita clinic within 90 days from dialysis initiation. Multivariate logistic regression models were fit in order to estimate the SMR for each month [17]. Cox proportional hazard models were used to calculate hazard ratios of death at different time periods during the 24 months and for the 5-year survival for the patient characteristics including demographics, comorbidities and laboratory values. For each selected period, deaths before and after the period were censored and the person-time was limited to the given period.

Two levels of multivariate adjustments were used in most survival analyses: (1) *Case-mix- and dialysis treatment-adjusted models*, which included adjustment for age, gender, four mutually exclusive race/ethnicity categories (African Americans, Hispanics, non-Hispanic whites, and others), primary insurance (Medicare, Medicaid, and other), marital status (married, single, divorced, widowed), dialysis vascular access, i.e., CVC, arteriovenous fistula, or arteriovenous graft; dialysis dose (single pool Kt/V), diabetes mellitus as well as 11 additional comorbid conditions including atherosclerosis, congestive heart failure (CHF), other cardiac conditions, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, hypertension, inability to ambulate, and smoking status; and entry calendar quarter for secular trend. (2) *Fully adjusted models*, which included adjustment for all of the above, as well as 10 above-mentioned laboratory surrogates of the MICS and BMI. Some of the adjustors were also examined as independent predictors of death risk.

The population attributable fractions (PAF) [18] were calculated for the relevant comorbidities and the CVC vascular access to assess the percent of deaths that could be attributable to those factors, and therefore, hypothetically preventable proportion by eliminating or reducing them. The 95% confidence interval for each PAF was calculated by the substitution method [19]. All the analyses were conducted by using SAS 9.2 software (SAS Inc., N.C., USA).

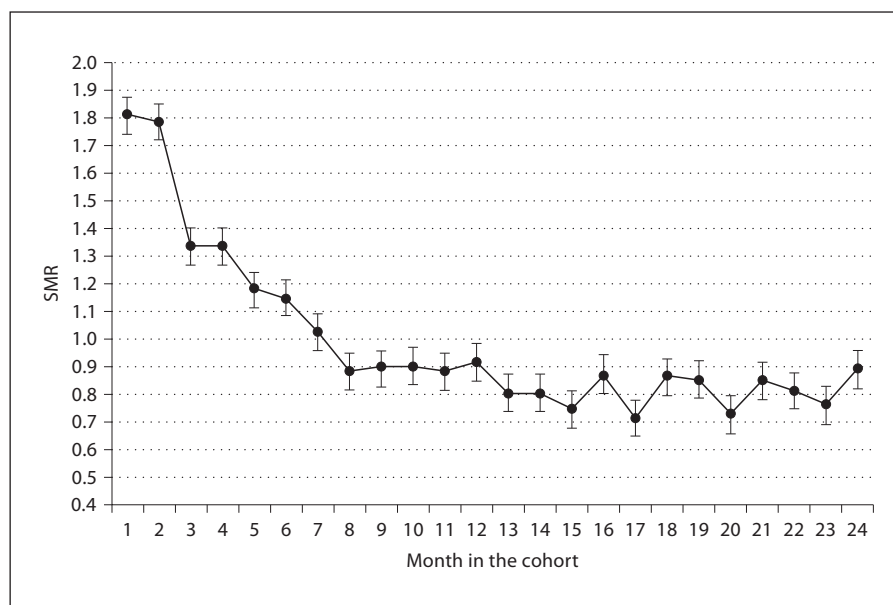
Results

From July 1, 2001 to June 30, 2006 a total of 82,566 incident (new) dialysis patients started chronic dialysis treatment in a DaVita dialysis clinic within the first 90 days of therapy initiation. After excluding patients younger than 18 years ($n = 637$), incident peritoneal dialysis patients or those who switched modality at any given time ($n = 4,763$), hemodialysis patients with missing person-time ($n = 6$) and hemodialysis patients who initiated the first week of dialysis therapy outside of a DaVita clinic ($n = 58,453$, which served as the 'reference' population to calculate SMRs, see above and below), a total of 18,707 incident hemodialysis patients who had never switched modality remained in the cohort. These patients had received at least one treatment of the first therapy week in a DaVita clinic and had remained in DaVita throughout the entire first 90 days or until death or transplantation.

During the first 24 months, 6,666 patients died (36% or 30 deaths per 100 person-years) and 1,399 received a kidney transplant. Online supplementary table 1S (see www.karger.com/doi/10.1159/000338673 for all online suppl. material) compares the baseline demographic, clinical and laboratory features of the entire 18,707 patients with the reference cohort of 58,453 patients. The overall probability of survival of these incident hemodialysis patients for 3 and 6 months, and 1, 2 and 5 years were 0.90 (0.89–0.91), 0.80 (0.79–0.82), 0.72 (0.71–0.73), 0.58 (0.57–0.59), and 0.26 (0.25–0.27), respectively. Figure 1 shows the monthly SMRs over the first 24 months after dialysis therapy initiation in 18,707 incident hemodialysis patients under study using the cohort of the other 58,453 incident hemodialysis patients (see above) as the reference population. The highest mortality occurred during months 1 and 2, and mortality rates decreased over a period of 7 months. The calculated SMR (and 95% confidence interval) for the 1st to 4th month of dialysis therapy were 1.81 (1.74–1.88), 1.79 (1.72–1.86), 1.34 (1.27–1.40) and 1.35 (1.28–1.41), respectively (see fig. 1).

Examining the distribution of 6,666 deaths in the first 24 months, crude mortality rates during the 4 a priori selected periods of <3 , 3 to <6 , 6 to <12 , and 12 to <24 months were 1,994 (30% of all deaths or 47 deaths per 100 person-years), 1,271 (19% or 35 per 100 person-years), 1,550 (23% or 25 per 100 person-years), and 1,851 (28% or 22 per 100 person-years), respectively. Table 1 shows the characteristics for the deceased patients across the 4 a priori selected mortality periods of <3 , 3 to <6 , 6 to <12 , and 12 to <24 months compared to ≥ 24 -month

Fig. 1. Monthly standardized mortality ratios (SMRs) during the first 2 years for the incident dialysis patients ($n = 18,707$). SMRs are standardized by age, gender, diabetes and race using the reference cohort of 57,456 hemodialysis patients who started DaVita cohort within 30 days after starting dialysis treatment (see text).



survivors. Early death was associated with more advanced age, higher proportion of CVC, and higher prevalence of cardiovascular diseases. Those who died during the first 3 months had 1.9 comorbidities per person compared to 1.1 among those who survived ≥ 2 years. Figure 2 shows the common kidney disease etiologies, i.e., ESRD diagnoses, among patients who died during each of the a priori selected periods of the first 24 months. Diabetes and hypertension were the 2 most common ESRD diagnoses; however, hypertension was more frequent among those with earlier deaths, whereas diabetes was more frequent among those who survived the earlier months. Figure 3 shows the causes of death during the first 24 months. Nearly similar death cause distribution was noticed in the first 90 days indicating that half of all deaths were marked as cardiovascular. Mortality due to withdrawal from dialysis was the lowest during the first 90 days and rose over time from 2 to 8% in the second year. Table 2 shows case-mix-adjusted death hazard ratios during the 4 survival periods. The known survival advantage of African American race was noticeable only after 6 months of therapy but not prior to that. Diabetes mellitus and lower nPCR were paradoxically associated with greater survival at early time periods but they were predictors of higher mortality during later periods.

In addition to all-cause mortality, we also examined the associations of cause-specific mortality, i.e., cardiovascular and infection-related deaths, with race (non-

Hispanic whites, African Americans and Hispanics), history of CHF, CVC vascular access and hypoalbuminemia as presented in table 3. Compared to whites, both African Americans and Hispanics showed slightly better survival in terms of cardiovascular and infection-related mortality, although the associations were uncertain initially. Of note, patients with CHF showed elevated risk of death independently of the cause of death. Moreover the associations were higher for both cardiovascular (1.68 [1.41–1.99] during the first quarter) and infection-related deaths (1.56 [1.14–2.14] during the first quarter) comparing to all-cause mortality (1.31 [1.11–1.54]). Use of CVC access was associated with the deaths from infections much stronger (3.32 [2.14–5.16] during the first quarter) comparing to cardiovascular deaths. Similarly, low serum albumin levels were associated with infection-related mortality much stronger (4.92 [3.45–7.00] in the first 3 months) than with cardiovascular mortality during the same time period.

Online supplementary table 2S shows selected PAF including for vascular access and comorbidities. CVC as the dialysis access could explain 34% of all deaths in the first 3 months of dialysis therapy. A low serum albumin < 3.5 g/dl had a similar death contribution, i.e., 33% of deaths in the first 90 days could have been prevented if albumin levels were above 3.5 g/dl. CHF and serum level of hemoglobin under 10 g/ml each contributed to 10 and 9% of all deaths during the first 90 days.

Table 1. Comparing patient characteristics across selected mortality periods of the first 24 months in 18,707 incident hemodialysis patients who started dialysis therapy during July 1, 2001–June 30, 2006 in a DaVita clinic

	Patients who died during the first 24 months				Survived ≥2 years	p value
	1–3 months	4–6 months	7–12 months	13–24 months		
Number	1,994	1,271	1,550	1,851	12,041	
Age, years	72 ± 13	70 ± 13	69 ± 13	69 ± 13	60 ± 15	<0.0001
Gender (% female)	45	47	47	44	44	0.16
Diabetes mellitus, %	50	57	58	61	53	<0.0001
Race, %						
White	62	57	60	58	47	<0.0001
Black	20	24	21	22	27	<0.0001
Hispanic	12	11	11	12	15	<0.0001
Other	6	8	8	8	11	<0.0001
Primary insurance, %						
Medicare	65	68	70	69	51	<0.0001
Medicaid	5	7	7	4	6	0.06
Other	30	25	13	12	43	<0.0001
Marital status, %						
Married	49	46	47	54	54	<0.0001
Divorced	5	7	7	6	7	0.21
Single	21	22	20	21	26	<0.0001
Widowed	25	25	26	19	13	<0.0001
Kt/V (dialysis dose)	1.36 ± 0.4	1.41 ± 0.4	1.42 ± 0.4	1.40 ± 0.4	1.39 ± 0.4	0.01
Vascular access, %						
Dialysis catheter	81	74	65	58	53	<0.0001
AVF	8	12	16	21	30	<0.0001
Graft	11	14	19	21	17	<0.0001
Comorbid conditions, %						
AIDS	0.6	1	0.7	0.7	0.4	0.02
Cancer	9	8	7	6	4	<0.0001
Atherosclerotic heart disease	32	27	28	27	17	0.005
Heart failure	41	37	35	33	20	<0.0001
COPD	12	8	9	8	4	<0.0001
Cerebrovascular disease	11	11	10	11	6	<0.0001
History of hypertension	73	74	75	79	81	0.04
Other heart diseases	6	10	7	7	5	<0.0001
Non-ambulatory	10	7	5	5	2	<0.0001
Peripheral vascular disease	17	18	17	16	9	<0.0001
HIV	0.8	0.6	1	2	0.3	0.15
Smoker	4	4	5	5	4	0.17
Serum levels						
Albumin, g/dl	3.1 ± 0.6	3.3 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	3.6 ± 0.5	<0.0001
Albumin <3.5 g/ml, %	72	63	56	48	35	<0.0001
Creatinine, mg/dl	5.6 ± 2.4	5.6 ± 2.3	5.7 ± 2.5	5.6 ± 2.3	6.6 ± 2.7	<0.0001
TIBC, mg/dl	193 ± 63	205 ± 58	214 ± 57	222 ± 51	232 ± 50	<0.0001
Bicarbonate, mg/dl	22.6 ± 4	22.6 ± 4	22.6 ± 4	22.4 ± 4	22.0 ± 4	<0.0001
Phosphorus, mg/dl	4.9 ± 1.7	5.0 ± 1.6	5.0 ± 1.5	5.1 ± 1.5	5.3 ± 1.4	<0.0001
Calcium, mg/dl	8.7 ± 0.8	8.8 ± 0.8	8.8 ± 0.8	8.7 ± 0.8	8.9 ± 0.8	<0.0001
Ferritin, ng/ml	549 ± 749	419 ± 522	374 ± 490	314 ± 365	278 ± 347	<0.0001
ISAT, %	24 ± 15	23 ± 11	23 ± 11	23 ± 11	23 ± 10	0.01
Alkaline phosphatase, U/l	151 ± 149	135 ± 106	123 ± 82	116 ± 832	109 ± 78	<0.0001
Parathyroid hormone, pg/dl	349 ± 340	381 ± 365	407 ± 417	411 ± 373	469 ± 419	<0.0001
nPCR, g/kg/day	0.88 ± 0.3	0.84 ± 0.3	0.85 ± 0.3	0.86 ± 0.3	0.88 ± 0.3	<0.0001
nPCR >1 g/kg/day, %	27	24	24	25	27	0.0400
Blood hemoglobin, g/dl	10.5 ± 1.5	10.7 ± 1.4	10.8 ± 1.4	10.9 ± 1.4	11.0 ± 1.4	<0.0001
Hemoglobin <10 g/dl, %	24	31	29	25	24	<0.0001
WBC, × 10 ³ /μl	9.5 ± 5.6	8.3 ± 3.1	8.2 ± 3.1	7.9 ± 2.9	7.7 ± 2.5	<0.0001
Lymphocytes, % of WBC	14 ± 7.6	16 ± 7.1	17 ± 7.1	18 ± 7.2	19 ± 7.4	<0.0001
Erythropoietin dose, units/HD	9,817 ± 5,844	9,752 ± 5,231	9,385 ± 5,040	9,038 ± 5,155	9,031 ± 5,081	<0.0001
Paricalcitol dose, μg/HD	3.8 ± 3.1	3.8 ± 3.0	3.6 ± 3.0	3.7 ± 3.3	3.9 ± 3.4	0.07
BMI	25.7 ± 9	25.5 ± 7	26.1 ± 7	26.4 ± 7	28.2 ± 7	<0.0001
eGFR, ml/min	11.4 ± 5	10.9 ± 4	10.8 ± 5	10.8 ± 5	9.6 ± 3	<0.0001
eGFR >10, %	39	52	58	51	39	<0.0001
eGFR >15, %	10	16	18	16	10	<0.0001

COPD = Chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate.

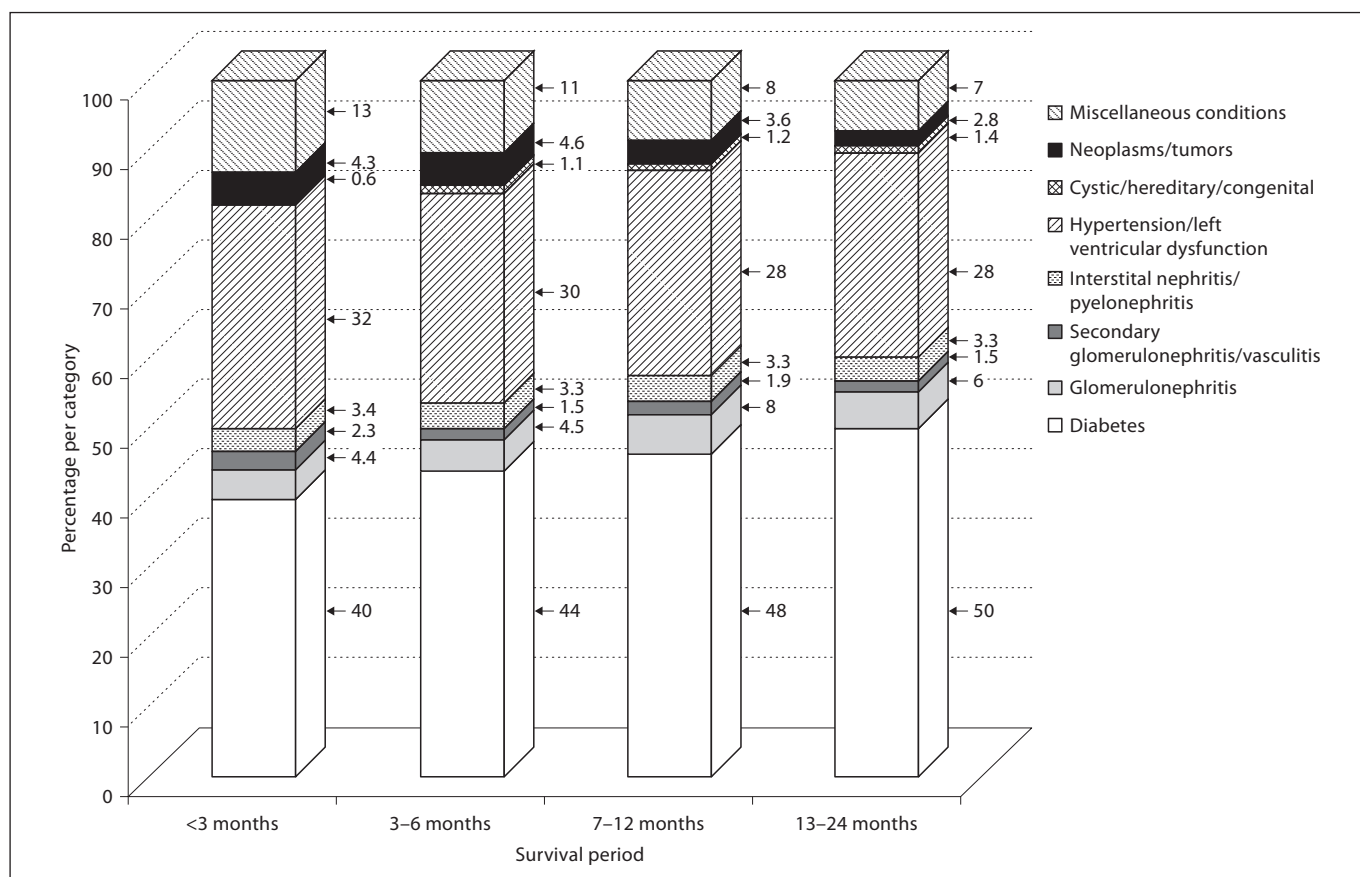


Fig. 2. Primary causes of ESRD for incident hemodialysis patients who died within 24 months after dialysis initiation from the 5-year DaVita cohort July 2001–June 2006 (n = 6,507) compared to survivors (n total = 17,871).

Discussion

Examining the mortality patterns during the first 24 months of a contemporary (2001–2006) and nationally representative cohort of 18,707 incident hemodialysis patients who received treatment from the first week of hemodialysis therapy in a DaVita dialysis clinic, we found that mortality was exceptionally high in the first 6 months, especially during months 1 and 2. SMRs were 1.81 and 1.79, respectively, compared to all incident hemodialysis patients of the same cohort period. We also assessed the risk of death during different time periods to identify modifiable risk factors and their contributions to death over time and found that use of CVC as the vascular access and hypoalbuminemia <3.5 mg/dl could explain 34 and 33% of all deaths in the first 90 days, respectively. These novel findings may have important clinical and public health implications, since they may offer im-

petus for designing interventions and trials to reduce early death among incident dialysis patients.

We found that both all-cause and cardiovascular mortality rates were the highest during the first 2 months of dialysis therapy, which is consistent with several previous reports [3, 12].

Among demographic predictors of death, older age, white race, Medicaid coverage, and being single or widowed were also associated with higher death risk in the first 24 months.

Worse survival of non-Hispanic white dialysis patients is consistent with previous reports [3, 20]. Even though it remains unclear as to why African Americans have lower dialysis mortality risk, in our study the survival advantage of African Americans or other minorities was almost nonexistent in the first 6 months. Of note, the racial distribution of patients who died within the first 3 months consisted of 62% non-Hispanic whites, 20%

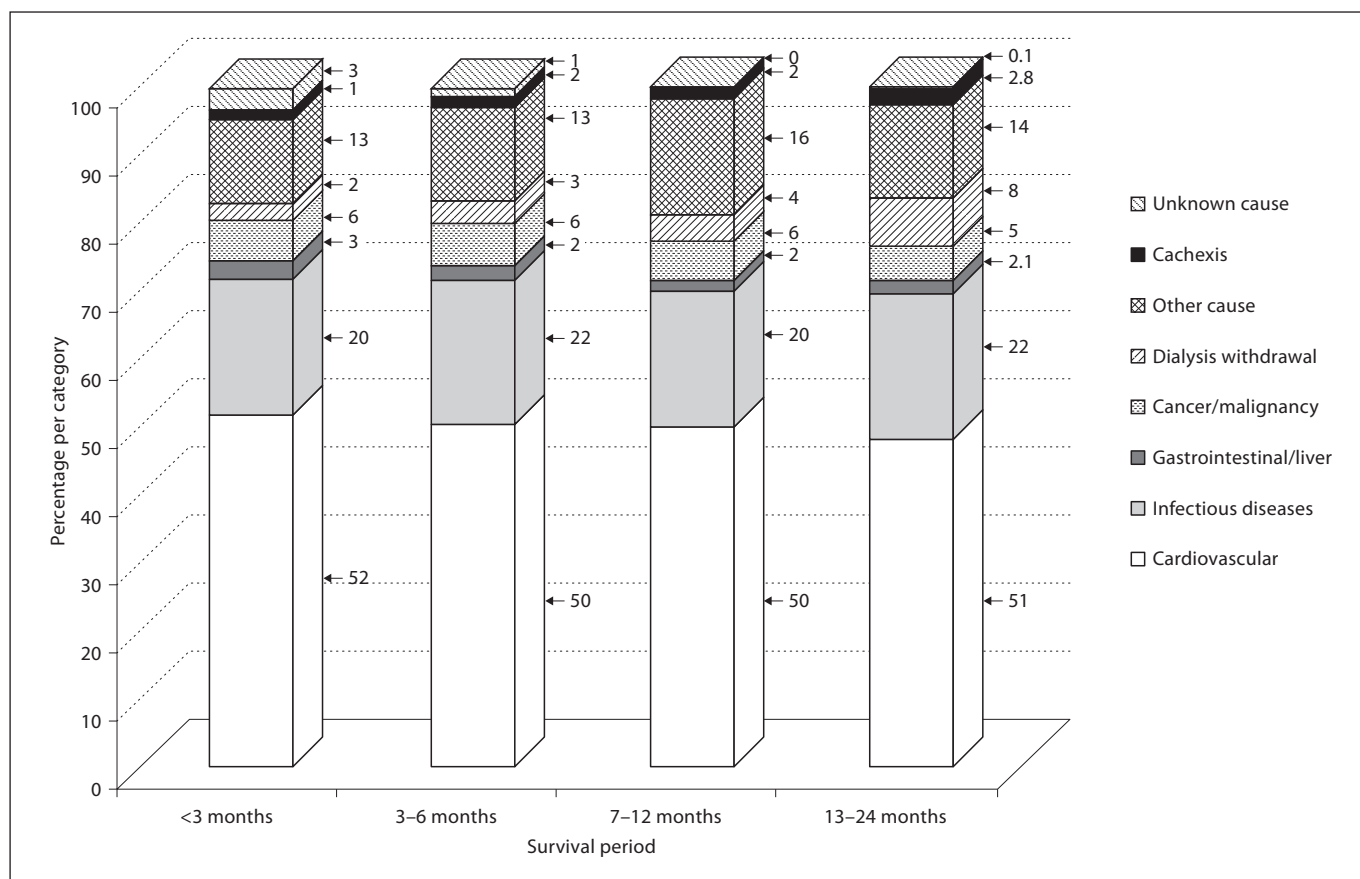


Fig. 3. Causes of death by the mortality periods for incident hemodialysis patients from the 5-year DaVita cohort, excluding patients with missing causes of death; n = 6,867 (2,236 cases with no documented cause of death were excluded).

blacks and 12% Hispanics in contrast to 47% whites, 27% blacks, and 15% Hispanics among survivors over 2 years (table 1), and was consistent with the survival advantage of minorities [21]. However, after case-mix adjustment, the advantage for African Americans during early dialysis period disappeared. Similar to the all-cause mortality result African Americans exhibited essentially the same pattern with cardiovascular mortality with practically no survival advantage over whites in early time periods, although a somewhat better survival in infection-related mortality. The observation that African Americans had somewhat lower CVC use than whites (data not shown) might explain the higher infection-related mortality in whites. Hispanics, too, showed better survival in infectious deaths analyses; however, although whites had somewhat higher percentage of CHF history, Hispanics contributed to a higher percentage of patients with low serum albumin levels and CVC use similar to whites.

Both hypoalbuminemia and CVC access are known to be associated with infectious events and death. It might be that, while Hispanics were more likely to develop infections, they might have been less likely to die from them. Another explanation as to why Hispanics and, to some extent, African Americans had higher rates of hypoalbuminemia but lower infection-related mortality could be that, for most of the minorities, low albumin levels may be more indicative of malnutrition than infection [22].

An interesting finding was the seemingly paradoxical association between diabetes and lower mortality in the first months, which was previously reported by Bradbury et al. [3]. The possible explanation may be that they were more likely to see a physician on regular basis compared to nondiabetics and therefore may have been better prepared for the transitional period of early dialysis therapy. However, this survival advantage mitigated and even reversed over time probably because nondiabetics who sur-

Table 2. Case-mix-adjusted death hazard ratios (95% confidence intervals) for the association between mortality at different time periods and individual predictors for incident hemodialysis patients in 18,707 incident hemodialysis patients

Predictor	<3 months	4 to <6 months	7 to <12 months	13 to <24 months
Age (decades)	1.50 (1.43–1.56)	1.44 (1.35–1.54)	1.32 (1.26–1.38)	1.33 (1.28–1.39)
Gender (female vs. male)	1.00 (0.90–1.11)	0.95 (0.83–1.09)	0.89 (0.79–1.01)	0.95 (0.85–1.05)
Diabetes mellitus	0.86 (0.78–0.94)	0.95 (0.84–1.07)	1.03 (0.93–1.15)	1.11 (1.00–1.23)
Race				
Whites versus blacks	1.12 (0.97–1.28)	1.01 (0.86–1.18)	1.33 (1.16–1.52)	1.29 (1.14–1.46)
Whites versus Hispanics	1.09 (0.94–1.27)	1.24 (1.02–1.52)	1.53 (1.23–1.85)	1.33 (1.14–1.56)
Whites versus others	1.40 (1.15–1.70)	1.18 (0.93–1.49)	1.43 (1.17–1.75)	1.48 (1.23–1.77)
Health insurance				
Medicaid versus Medicare	1.48 (1.17–1.87)	1.74 (1.32–2.29)	1.68 (1.30–2.18)	1.07 (0.84–1.37)
Other versus Medicare	1.10 (0.93–1.31)	0.90 (0.77–1.05)	0.78 (0.66–0.91)	0.78 (0.69–0.89)
Marital status				
Divorced versus married	0.90 (0.60–1.33)	1.09 (0.67–1.80)	1.15 (0.69–1.92)	0.86 (0.60–1.25)
Single versus married	1.39 (1.16–1.65)	1.33 (1.10–1.60)	1.19 (0.94–1.51)	1.08 (0.88–1.34)
Widowed versus married	1.12 (0.87–1.45)	1.25 (0.83–1.88)	1.46 (1.08–1.97)	1.00 (0.82–1.21)
Kt/V (0.2 ↓)	0.92 (0.88–0.96)	0.96 (0.93–1.00)	0.99 (0.92–1.03)	0.98 (0.95–1.01)
Vascular access				
CVC versus AVF	2.99 (2.49–3.59)	2.46 (1.89–3.20)	2.06 (1.76–2.40)	1.63 (1.39–1.91)
CVC versus graft	2.48 (1.94–3.17)	1.84 (1.40–2.40)	1.43 (1.21–1.69)	1.34 (1.15–1.55)
CVC versus AVF + graft	2.66 (2.27–3.11)	2.22 (1.81–2.72)	1.80 (1.53–2.12)	1.52 (1.37–1.69)
BMI (2 index points)	0.92 (0.90–0.94)	0.93 (0.91–0.95)	0.94 (0.92–0.96)	0.92 (0.91–0.94)
Comorbidities				
Cardiac disorders				
Atherosclerotic heart disease	1.09 (0.97–1.23)	0.96 (0.83–1.11)	1.04 (0.92–1.18)	1.05 (0.93–1.18)
Heart failure	1.31 (1.11–1.54)	1.36 (1.20–1.55)	1.29 (1.15–1.45)	1.33 (1.19–1.48)
Other cardiac disease	1.23 (1.05–1.44)	1.45 (1.20–1.76)	1.02 (0.83–1.25)	1.00 (0.82–1.22)
Vascular/pulmonary				
Cerebrovascular disease	1.07 (0.92–1.24)	1.09 (0.91–1.31)	1.08 (0.91–1.28)	1.27 (1.09–1.48)
Peripheral vascular disease	1.11 (0.98–1.27)	1.27 (1.08–1.49)	1.28 (1.10–1.49)	1.16 (1.01–1.33)
COPD	1.43 (1.23–1.67)	1.02 (0.82–1.27)	1.14 (0.94–1.37)	1.13 (0.95–1.36)
Other comorbidities				
Cancer	1.31 (1.11–1.54)	1.36 (1.11–1.67)	1.30 (1.06–1.60)	1.15 (0.95–1.40)
Non-ambulatory	2.01 (1.70–2.38)	1.73 (1.38–2.18)	1.46 (1.15–1.84)	1.66 (1.33–2.09)
Smoking	0.93 (0.73–1.18)	1.13 (0.86–1.50)	1.29 (1.02–1.63)	1.14 (0.91–1.43)
Hypertension	0.74 (0.67–0.82)	0.72 (0.63–0.82)	0.71 (0.63–0.80)	0.82 (0.73–0.92)
Lab parameters				
Albumin (0.2 g/dl ↓)*	1.21 (1.18–1.24)	1.17 (1.15–1.20)	1.15 (1.13–1.18)	1.12 (1.10–1.14)
Albumin <3.5 g/ml*	2.56 (2.30–2.84)	2.04 (1.81–2.31)	1.89 (1.70–2.10)	1.59 (1.44–1.75)
Hemoglobin (1 g/dl ↓)*	1.24 (1.20–1.28)	1.13 (1.09–1.18)	1.07 (1.03–1.11)	1.05 (1.01–1.08)
Hemoglobin <10 g/ml	1.58 (1.33–1.74)	1.37 (1.21–1.55)	1.25 (1.11–1.49)	1.11 (0.99–1.24)
Creatinine (mg/dl ↓)*	1.03 (1.01–1.06)	1.04 (1.01–1.07)	1.03 (1.00–1.05)	1.05 (1.03–1.08)
Calcium, mg/dl*	1.14 (1.07–1.22)	1.09 (1.00–1.18)	1.11 (1.04–1.19)	1.03 (0.97–1.09)
Phosphorus, mg/dl*	1.06 (1.02–1.10)	1.03 (0.99–1.08)	1.04 (1.00–1.09)	1.01 (0.97–1.05)
nPCR (0.2 g/kg/day)	1.08 (1.03–1.13)	0.94 (0.89–1.00)	0.93 (0.89–0.97)	0.96 (0.92–1.00)
nPCR >1.0 g/kg/day	1.21 (1.06–1.38)	0.96 (0.8–1.14)	0.89 (0.74–1.07)	0.99 (0.87–1.13)
WBC (5,000/HPF ↑)	1.52 (1.45–1.59)	1.26 (1.15–1.39)	1.26 (1.16–1.37)	1.14 (1.04–1.25)
Lymphocytes (10%)*	1.87 (1.70–2.05)	1.42 (1.31–1.55)	1.33 (1.24–1.44)	1.17 (1.09–1.26)
TIBC (50 g/dl)*	1.51 (1.43–1.59)	1.40 (1.31–1.49)	1.30 (1.22–1.38)	1.20 (1.14–1.26)
Ferritin (500 ng/dl)*	1.24 (1.20–1.28)	1.23 (1.18–1.29)	1.27 (1.21–1.33)	1.20 (1.14–1.28)
Parathyroid hormone (100 pg/ml)	0.96 (0.94–0.97)	0.97 (0.95–0.99)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
ISAT (10%)	1.09 (1.05–1.13)	1.05 (0.99–1.11)	1.02 (0.98–1.08)	1.07 (1.02–1.13)
eGFR (each 1 increment)	1.03 (1.02–1.04)	1.01 (1.00–1.03)	1.01 (1.00–1.03)	1.03 (1.02–1.04)
eGFR >10	1.29 (1.17–1.42)	1.20 (1.07–1.35)	1.04 (0.94–1.16)	1.11 (0.97–1.28)
eGFR >15	1.43 (1.27–1.60)	1.09 (0.93–1.28)	1.29 (1.12–1.48)	1.02 (0.83–1.24)

Note that deaths and person-times before and/or after each period are censored.

AVF = Arteriovenous fistula; graft = arteriovenous graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate.

* Decrease per unit change of serum level of laboratory parameter.

Table 3. Case-mix-adjusted death hazard ratios (95% confidence intervals) for the association between cardiovascular and infection-related mortality at different time periods and several individual predictors for incident hemodialysis patients in 18,707 incident hemodialysis patients (outcome 1: cardiovascular mortality, outcome 2: Infectious mortality)

Predictor	Deaths 0–3 months	Deaths 4–6 months	Deaths 7–12 months	Deaths 13–24 months
Whites versus blacks				
Cardiovascular mortality	1.14 (0.92–1.41)	1.02 (0.81–1.30)	1.20 (0.94–1.54)	1.46 (1.18–1.80)
Infectious mortality	1.26 (0.85–1.89)	1.28 (0.84–1.96)	1.70 (1.12–2.58)	1.20 (0.85–1.70)
Whites versus Hispanics				
Cardiovascular mortality	1.28 (0.98–1.66)	1.16 (0.84–1.62)	1.75 (1.28–2.39)	1.60 (1.22–2.10)
Infectious mortality	0.91 (0.60–1.37)	1.38 (0.42–2.33)	3.43 (1.76–6.69)	1.58 (0.96–2.62)
Heart failure				
Cardiovascular mortality	1.68 (1.41–1.99)	1.74 (1.42–2.14)	1.86 (1.53–2.24)	1.43 (1.20–1.71)
Infectious mortality	1.56 (1.14–2.14)	1.76 (1.24–2.50)	1.17 (0.80–1.70)	1.69 (1.24–2.31)
CVC versus AVF + graft				
Cardiovascular mortality	2.45 (1.74–3.44)	2.09 (1.57–2.80)	1.58 (1.31–1.93)	1.59 (1.30–1.97)
Infectious mortality	3.32 (2.14–5.16)	4.03 (2.66–6.09)	2.23 (1.50–3.32)	1.74 (1.23–2.47)
Albumin <3.5 versus >3.5 g/dl				
Cardiovascular mortality	2.15 (1.81–2.55)	1.89 (1.54–2.33)	1.83 (1.53–2.19)	1.80 (1.53–2.11)
Infectious mortality	4.92 (3.45–7.00)	3.21 (2.23–4.62)	2.34 (1.65–3.30)	1.48 (1.09–2.01)

Note that deaths and person-times before and/or after each period are censored.
AVF = Arteriovenous fistula; graft = arteriovenous graft.

vived the transitional period might be healthier than patients with diabetes.

Among clinical predictors, type of the vascular access was exceptionally strongly associated with mortality across all studied periods but in particular during the first 90 days, including both among cardiovascular and infection-related deaths. Although our finding was consistent with previous reports indicating that CVC was associated with higher mortality in hemodialysis patients [9–12], our study uniquely shows that the association of vascular access type with mortality is the strongest at the time of dialysis initiation and decreased over time, which suggests the importance of replacing CVC with a more permanent access within the first few weeks – if not days – of dialysis therapy. Our results are consistent with findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) reporting higher mortality for patients with CVC access comparing to other types. That study found that US patients had 36 to 43% higher mortality risk due to widespread use of CVC use compared to European countries and about 30% higher when compared to Japan [23].

The resilient role of low serum albumin level in predicting high mortality of dialysis patients has been previously identified [3, 24, 25]; this is verified in our current study. A 10-year cohort study from Japan reported that

patients with serum albumin levels >3.8 g/dl consistently had better survival [24]. We found 21% increase in mortality in the first 90 days per 0.2 g/dl lower serum albumin compared to 12% during the 12–24-month period. We found that infection-related and cardiovascular mortality rates were, respectively, 5-fold and 2-fold higher among patients with low serum albumin levels <3.5 g/dl compared to higher levels. We also found that, among patients with no history of CHF and hypoalbuminemia, the percentage of deaths related to infections was the highest especially during the first 6 months on dialysis (19–21%), while patients with history of CHF and serum albumin >3.5 g/dl accounted for only 8% of infection-related deaths in the first 3 months of dialysis treatment (table 3). Although hypoalbuminemia was strongly associated with both cardiovascular and infection-related mortality, it seems that, among patients who died from cardiovascular disease, CHF, which is usually due to volume overload, could be responsible for the patient outcomes especially during the early months of the dialysis treatment. Patients with CHF had higher cardiovascular mortality than patients without it, and the highest cardiovascular mortality of 76% was observed during the first 3 months of dialysis treatment in patients with CHF and serum albumin >3.5 g/dl.

In a recent study from the UK Renal National Registry cohort, using several models for predicting the first 3-year survival of incident dialysis patients, older age, white race, diabetes mellitus and other primary causes of ESRD, history of cardiovascular disease and smoking were predictive of increased mortality [27]. Among laboratory parameters, serum levels of albumin, hemoglobin, and calcium were also predictors of 2-year mortality [27]. These findings are somewhat similar to our results. We also found an elevated mortality risk of 58% for patients with blood hemoglobin <10 g/ml during the first 3 months of dialysis treatment.

Our study should be qualified for including only DaVita patients rather than the entire national dialysis population. However, DaVita patients are likely good representatives of average ESRD patients. We purposely excluded the incident patients who initiated their first week of therapy elsewhere to mitigate selection bias. It can be argued that there could be differences between the patients who started dialysis at an inpatient versus outpatient facility. Nevertheless, the annualized mortality in our cohort for the first 3 months was about 30%, which was consistent with mortality reported for US patients in the same period [2]. We had no reliable information about patient visiting nephrologists prior to dialysis initiation (80% missing values), which precluded examination of this potential predictor of early mortality.

Conclusion

Incident hemodialysis patients have the highest mortality during the first 6 months of dialysis therapy, in particular in the first 2 months, and cardiovascular disease

is the most common cause of death. Use of CVC as vascular access and hypoalbuminemia <3.5 mg/dl each explains one third of all deaths in the first 90 days. Hence, replacing or avoiding CVC and improving hypoalbuminemia could theoretically reduce early dialysis death by 30%. These findings warrant imminent design of clinical trials to examine interventions to target imminent arteriovenous fistula placement and to increase serum albumin in order to reduce early death among incident dialysis patients. Low hemoglobin level could explain 9% of deaths in the first 3 months indicating the potential role of proper anemia management in improving outcomes of new hemodialysis patients.

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Disclosure Statement

The authors declare that there are no potential conflicts of interest.

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