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The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis

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The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis.

Background. While the survival ramifications of dialysis modality selection are still debated, it seems reasonable to postulate that outcome comparisons are not the same for all patients at all times. Trends in available data indicate the relative risk of death with hemodialysis (HD) compared to peritoneal dialysis (PD) varies by time on dialysis and the presence of various risk factors. This study was undertaken to identify key patient characteristics for which the risk of death differs by dialysis modality.

Methods. Analyses utilized incidence data from 398,940 United States Medicare patients initiating dialysis between 1995 and 2000. Proportional hazards regression identified the presence of diabetes, age, and the presence of comorbidity as factors that significantly interact with treatment modality. Stratifying by these factors, proportional and nonproportional hazards models were used to estimate relative risks of death [RR (HD:PD)].

Results. Of the 398,940 patients studied, 11.6% used PD as initial therapy, 45% had diabetes mellitus (DM), 51% were 65 years or older, and 55% had at least one comorbidity. Among the 178,693 (45%) patients with no baseline comorbidity, adjusted mortality rates in nondiabetic (non-DM) patients were significantly higher on HD than on PD [age 18–44: RR (95% CI) = 1.24 (1.07, 1.44); age 45–64: RR = 1.13 (1.02, 1.25); age 65+: RR = 1.13 (1.05, 1.21)]. Among diabetic (DM) patients with no comorbidity, HD was associated with a higher risk of death among younger patients [age 18–44: RR = 1.22(1.05, 1.42)] and a lower risk of death among older patients [age 45–64: RR = 0.92 (0.85, 1.00); age 65+: RR = 0.86 (0.79, 0.93)]. Within the group of 220,247 (55%) patients with baseline comorbidity, adjusted mortality rates were not different between HD and PD among non-DM patients [age 18–44: RR = 1.19 (0.94, 1.50); age 45–64: RR = 1.01 (0.92, 1.11); age 65+: RR = 0.96 (0.91, 1.01)] and younger DM patients [age 18–44: RR = 1.10 (0.92, 1.32)], but were lower with HD among older DM patients with baseline comorbidity [age 45–64: RR = 0.82 (0.77, 0.87); age 65+: RR = 0.80 (0.76, 0.85)].

Conclusion. Valid mortality comparisons between HD and PD require patient stratification according to major risk factors known to interact with treatment modality. Survival differences between HD and PD are not constant, but vary substantially according to the underlying cause of ESRD, age, and level of baseline comorbidity. These results may help identify technical advances that will improve outcomes of patients on dialysis.

Key words: hemodialysis, peritoneal dialysis, survival, case-mix adjusted.

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Over the past decade, a number of large-scale cohort studies have examined the impact of dialysis modality on the survival of individuals with end-stage renal disease (ESRD) [1–15]. Results appear to vary by country and, in some cases, even within a country. For example, registry data from Canada [6] and Denmark [11] show that patients treated with peritoneal dialysis (PD) have a lower risk of death than those treated with hemodialysis (HD). In contrast, results in the United States appear to be mixed, with some studies showing more favorable outcomes for patients on HD compared to PD [4, 12, 13], others showing little or no difference between modalities [7, 16], and still others showing better outcomes for patients on PD [9, 15]. Discrepant results among some of these studies can be attributed to methodologic differences, such as the use of prevalent versus incident patients [4, 7–9], proportional versus nonproportional hazards models [5–7, 9], and the degree of case-mix adjustment [11–13, 15].

Despite these differences, some very important trends have emerged from these studies. First, mortality rates for PD and HD are not proportional over time [5, 6, 8–14]. The risk of death for PD is generally lower during the first year or two of dialysis. Thereafter, the risk of death is either comparable between the two modalities or higher in patients on PD. A second trend common to these studies is the identification of significant interactions between various risk factors and treatment modality. For example, it has been consistently demonstrated that the relative risk of death between PD and HD varies by age and by primary cause of ESRD (diabetes vs. nondiabetic causes) [1, 2, 4, 6–9, 11–14, 16–18]. Recently, Ganesh et al [12] and Stack et al [13] identified important interactions

between comorbidity and dialysis modality that had not been accounted for in previous studies. The inclusion of such key interactions is necessary if an accurate assessment of mortality differences between PD and HD is to be made.

We hypothesize that in the United States, differential trends in mortality between HD and PD exist for important segments of the ESRD population. We further postulate that, consistent with previous studies, the key segments are defined by age, cause of ESRD, and baseline level of comorbidity. The purpose of this study was to examine these hypotheses using data from a large cohort of United States Medicare patients. Our specific goals were to identify key risk factors for which the risk of death differs by dialysis modality, and to adjust mortality comparisons between HD and PD by stratifying on these factors. The results were then compared with findings from other studies (United States and international) to identify any consistent themes.

METHODS

Study population

Data on 398,940 United States Medicare patients who began dialysis between 1995 and 2000 were obtained from the Centers for Medicare & Medicaid Services (CMS) on Medical Evidence Form 2728. New incident patients who survived the first 90 days of ESRD were included in the analysis. Initial modality (HD vs. PD) was defined by the 60-day rule of the United States Renal Data System (USRDS), whereby treatment modality is designated as HD or PD if the patient was on that modality for at least 60 days prior to and including day 90 of ESRD. In order to reflect temporal changes in practice patterns, patients were grouped into two incident cohort periods: 1995 to 1997 ($N = 185{,}704$, HD = 160,008, PD = 25,696) and 1998 to 2000 ($N = 213{,}236$, HD = 192,698, PD = 20,538).

The primary outcome variable was all-cause mortality. Patients were followed a maximum of three years (through September 30, 2001), or until death or transplantation. Baseline covariates were: cohort period (1995–1997, 1998–2000), age (18–44, 45–64, ≥65), gender, race (Asian, black, white, other), cause of ESRD [diabetes (DM) vs. nondiabetic causes (non-DM)], the presence of comorbid conditions, body mass index (BMI, kg/m^2), glomerular filtration rate (GFR, mL/min), serum albumin (SA, g/dL), and hemoglobin (Hgb, g/dL). Comorbid conditions included congestive heart failure (CHF), ischemic heart disease/myocardioal infarction (MI) (i.e., coronary artery disease, CAD), cardiac arrest/dysrhythmia, cerebrovascular disease (CVD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), current smoking status, cancer, and the inability to ambulate/transfer. Baseline GFR was determined using the formula from the Modification of Diet in Renal Disease study, which is based on serum creatinine, age, gender, and race [19].

Statistical analysis

Baseline characteristics of HD and PD patients were compared using Pearson chi-square tests. Factors associated with the likelihood of using PD or HD were determined using multiple logistic regression with adjustments made for baseline demographics, comorbidity, and laboratory values. To adjust for case-mix differences, a modality-specific analysis was conducted to identify key factors that may have a significant interaction with the two treatment modalities. This was done by fitting a proportional hazards model separately to HD and PD patients using an intent-to-treat (ITT) approach, and adjusting for gender, age, race, cause of ESRD, comorbidity, and baseline values of GFR, BMI, SA, and Hgb. This initial analysis identified cause of ESRD (DM, non-DM), age (18–44, 45–64, ≥65), and the presence of comorbidity at baseline (none vs. 1 or more) as key factors that significantly interact with treatment modality. Stratifying by these factors, proportional and nonproportional hazards models using interval Poisson regression were used to compare case-mix adjusted mortality rates between HD and PD at successive 6-month intervals [8, 20, 21]. Average or time-independent relative risks (RR) of death for HD compared to PD patients were estimated using a proportional hazards model, while time-dependent relative risks and adjusted patient survival curves were estimated with a nonproportional hazards model. Relative risks and corresponding 95% confidence intervals (CI) were adjusted for case-mix differences in cohorts, age, gender, race, cause of ESRD, individual comorbidities, and laboratory values. To maintain an overall 5% error rate associated with performing multiple comparisons across 12 possible strata, Sidak's procedure was used to compute 95% simultaneous confidence intervals and corresponding P values [22]. To avoid imputing missing values and making unnecessary parametric assumptions (e.g., assuming age has a linear effect on the risk of death), age, BMI, GFR, SA, and Hgb were analyzed as discrete categorical variables using previously defined categories [23]. Missing laboratory values were categorized as not available (NA) within the various analyses, a strategy that has been used successfully in previous studies to avoid excluding patients with missing values [2, 23]. All analyses were done using the SAS statistical software package version 8.2 (SAS, Inc., Cary, NC, USA); in particular, the GENMOD procedure was used for interval Poisson regression.

The primary analysis was carried out using an ITT approach in which death was assigned to a patient's initial treatment modality regardless of a change in therapy during the course of follow-up. An as-treated (AT)

analysis was also performed in which survival times were censored 60 days following a change in therapy. In this case, any death that occurred within 60 days following a therapy change was attributed to the initial treatment modality. Model goodness-of-fit was assessed by an analysis of deviance in which quasi-likelihood ratio tests were conducted comparing the measured deviance of a set of reduced stratified models to the deviance of a set of full stratified models [24]. Specifically, separate models were fit to each of four subgroups formed by stratifying patients according to their cause of ESRD (DM, non-DM) and their level of baseline comorbidity (none vs. one or more). Each model was adjusted for the effects associated with all other covariates studied (including individual comorbidities for those having one or more comorbid conditions) as well as all two-way interactions between those covariates and treatment modality. To evaluate overall goodness-of-fit across the four strata, these full two-way interaction models were compared to reduced models obtained by excluding all two-way interactions except for the age $\times$ modality interaction. Additionally, goodness-of-fit tests were done to determine if the age by modality interaction could also be dropped from the final set of models. To account for unexplained variation caused by the exclusion of higher-order interactions (i.e., three-way interactions and higher), the usual likelihood ratio test statistic was divided by an estimate of overdispersion computed from the full model. The resulting quasi-likelihood ratio test, as described and implemented in the SAS procedure GENMOD, allows a goodness-of-fit comparison that takes into account any lack of fit associated with three-way, four-way, and higher order interaction terms not included in the full two-way interaction model. As a result of these goodness-of-fit tests, patients were subsequently stratified by age, as well as by cause of ESRD (DM vs. non-DM) and comorbidity. A main-effects proportional hazards model was then used to estimate and compare average relative risks (HD:PD) within each of the 12 strata, while a main-effects nonproportional hazards model was used to estimate and compare time-dependent relative risks (HD:PD).

RESULTS

Baseline characteristics

The baseline characteristics of the patient population are summarized in Table 1. Patients selected to PD were generally younger, more likely to be white, and less likely to have comorbid illnesses compared to those on HD. Patients on PD also were more likely to have diabetes, a slightly higher baseline GFR, significantly higher SA and Hgb values, and less likely to be underweight or obese. These patient characteristics are consistent with those in previous studies [12, 13, 23], and demonstrate the need to adjust for case-mix differences when comparing mortality rates between the two therapies.

Risk adjusted comparisons—Intent-to-treat analysis

Modality-specific estimates of RR associated with patient cohort, gender, age, race, cause of ESRD, the presence of comorbidity, and baseline values of GFR, BMI, SA, and Hgb are summarized in Table 2. Also included are chi-square tests that compare the differences (interactions) in log relative risks between HD and PD. Based on the magnitude of the chi-square tests, diabetes and age stand out as two factors for which the RR of death differs substantially by treatment modality. A third factor that indirectly stands out as constituting a significant interaction with treatment modality is the presence of comorbid conditions. Specifically, except for cancer, the RR of death associated with the presence of a comorbidity was higher among PD patients regardless of the specific comorbidity. In agreement with recent publications [12, 13], we found a significant interaction between treatment modality and the presence of CAD and CHF. Significant interactions were also present between modality and peripheral vascular disease, cardiac arrest/dysrhythmia, and the inability to ambulate/transfer.

To compare modalities in the presence of the various interactions, patients were stratified into 12 groups defined by age (18–44, 45–64, $\geq$65), cause of ESRD (DM, non-DM), and the presence or absence of comorbid conditions at baseline (none vs. one or more). Stratifying patients according to the presence of comorbid conditions was done for two reasons. First, it provided a means to account for the various interactions observed between modality and comorbidity (Table 2). Second, it allowed for comparison of mortality rates between HD and PD in a large (45%) subgroup of patients with no reported comorbidity at baseline (Table 1). This is an important subgroup in that it avoids issues related to severity of comorbidity, at least to the extent that comorbidity was assessed in this study.

Table 3 presents the number of deaths and corresponding crude death rates (DR) and unadjusted and adjusted RR of death for each of the 12 strata defined above. Among non-DM patients, use of HD was associated with significantly higher mortality among patients having no reported baseline comorbidity (27% of the population). Specifically, the risk of death was 24% higher among HD patients aged 18–44 [RR (HD:PD) = 1.24, $P < 0.001$)] and 13% higher among HD patients aged 45 and older [RR (HD:PD) = 1.13, $P < 0.01$]. Among non-DM patients with comorbid conditions at baseline (28% of the population), there were no overall differences in the relative risk of death; time-averaged relative risks (HD:PD) ranged from 0.96 to 1.19 (P = NS).

Table 1. Patient characteristics and association with modality selection

Factor category	Total (398,940)	HD (352,706)	PD (46,234)	*P* value	Odds ratio
Gender					
Female	46%	46%	46%	0.411	1.00[ref]
Male	54%	54%	54%		0.86[a]
Age *years*					
18–44	14%	13%	23%	<0.001	2.81[a]
45–64	35%	34%	41%		1.95[a]
≥65	51%	53%	36%		1.00[ref]
Race					
White	54%	53%	65%	<0.001	1.00[ref]
Black	30%	31%	21%		0.45[a]
Other/NA	3%/12%	3%/13%	3%/11%		0.81[a]/0.63[a]
Cause of ESRD					
Non-DM	55%	56%	55%	<0.001	1.00[ref]
DM	45%	44%	45%		1.14[a]
Comorbidity					
Congestive heart failure	30%	31%	22%	<0.001	0.75[a]
Coronary artery disease	25%	25%	21%	<0.001	0.98[NS]
Cardiac arrest/dysrhythmia	6%	6%	5%	<0.001	1.10[a]
Cerebrovascular disease	8%	9%	6%	<0.001	0.84[a]
Peripheral vascular disease	14%	14%	11%	<0.001	0.93[a]
COPD	6%	7%	4%	<0.001	0.71[a]
Current smoker	5%	5%	5%	<0.001	1.03[NS]
Cancer	5%	5%	3%	<0.001	0.69[a]
Unable to ambulate/transfer	4%	4%	2%	<0.001	0.53[a]
No comorbid conditions	45%	43%	56%	<0.001	1.64[a]
GFR *mL/min*					
<5.0	16%	16%	15%	<0.001	0.75[a]
5.1–10.0	53%	53%	54%		0.95[a]
>10.0	22%	22%	20%		1.00[ref]
NA	9%	9%	11%		0.99[NS]
BMI kg/m^2					
Underweight (<18.5)	6%	6%	4%	<0.001	0.68[a]
Normal (18.5–25.0)	38%	38%	37%		1.00[ref]
Overweight (25.1–30.0)	25%	25%	28%		1.13[a]
Obese (>30.0)	22%	22%	20%		0.88[a]
NA	9%	9%	11%		0.82[a]
Albumin *g/dL*					
<3.1	28%	29%	19%	<0.001	0.45[a]
3.1–3.4	17%	18%	15%		0.63[a]
>3.4	26%	25%	38%		1.00[ref]
NA	28%	28%	28%		0.65[a]
Hemoglobin *g/dL*					
<11	70%	71%	62%	<0.001	0.65[a]
11–12	11%	10%	14%		0.93[a]
>12	7%	6%	9%		1.00[ref]
NA	12%	12%	14%		0.73[a]

NS, not significant ($P > 0.05$).
[a] $P < 0.001$ compared to the reference group.

For DM patients, the risk of death varied significantly by age. Among younger (age <45) DM patients with no baseline comorbidity, HD was associated with a 22% higher rate of mortality compared to PD [RR (HD:PD) = 1.22, $P < 0.001$]. No difference in risk was seen among the younger DM patients with baseline comorbidity [RR (HD:PD) = 1.10, P = NS]. Among DM patients age 45 and older (40% of the population), PD was associated with higher mortality regardless of the presence of comorbidity. Specifically, among DM patients with no baseline comorbidity (15% of the population), the risk of death was 8% lower among HD patients aged 45–64 [RR (HD:PD) = 0.92, $P < 0.05$], and 14% lower among HD patients aged 65 and older [RR (HD:PD) = 0.86, $P < 0.001$]. For those older DM patients with baseline comorbidity (25% of the population), the risk of death was 18% lower among HD patients aged 45–64 [RR (HD:PD) = 0.82, $P < 0.001$], and 20% lower among HD patients aged 65 and older [RR (HD:PD) = 0.80, $P < 0.001$].

As in previous studies, the RR of death between HD and PD in this study was not proportional over time. Using nonproportional hazards Poisson regression, we estimated adjusted time-dependent RRs over consecutive 6-month intervals for each of the 12 strata shown

Table 2. Modality-specific relative risks (RR) associated with various factors

Factor category	HD RR[a]	PD RR[a]	Chi-square test $\text{Log}(RR_{HD}) - \text{Log}(RR_{PD})$	*P* value
Cohort				
1995–1997	1.00[ref]	1.00[ref]	–	–
1998–2000	1.00	0.94	14.805	<0.001
Gender				
Female	1.00	1.00	–	–
Male	0.97	0.97[NS]	0.132	0.411
Age				
18–44	1.00[ref]	1.00[ref]	–	–
45–64	1.57	1.97	51.028	<0.0001
≥65	2.80	3.82	95.321	<0.0001
Race				
White	1.00[ref]	1.00[ref]	–	–
Black	0.74	0.77	2.088	NS
Asian	0.61	0.53	6.723	<0.01
Other/NA	0.73	0.77	3.926	0.048
Cause of ESRD				
Non-DM	1.00[ref]	1.00[ref]	–	–
DM	1.13	1.45	202.874	<0.0001
Comorbidity				
Congestive heart failure	1.23	1.37	33.905	<0.0001
Coronary artery disease	1.07	1.23	48.778	<0.0001
Cardiac arrest/ dysrhythmia	1.14	1.21	4.373	0.037
Cerebrovascular disease	1.16	1.21	2.423	NS
Peripheral vascular disease	1.10	1.16	5.434	0.020
COPD	1.18	1.19	0.069	NS
Current smoker	1.05	1.11	2.480	NS
Cancer	1.42	1.18	22.095	<0.0001
Unable to ambulate/ transfer	1.53	1.95	29.856	<0.0001
GFR *mL/min*				
<5.0	0.66	0.70	2.852	NS
5.1–10.0	0.78	0.78	0.012	NS
>10.0	1.00[ref]	1.00[ref]	–	–
NA	0.96	1.24	17.137	<0.0001
BMI kg/m^2				
Underweight (<18.5)	1.32	1.32	0.004	NS
Normal (18.5–25.0)	1.00[ref]	1.00[ref]	–	–
Overweight (25.1–30.0)	0.82	0.87	9.932	<0.01
Obese (>30.0)	0.75	0.92	75.810	<0.0001
NA	0.92	0.89	0.293	NS
Albumin *g/dL*				
<3.1	1.37	1.54	25.285	<0.0001
3.1–3.4	1.20	1.25	3.500	NS
>3.4	1.00[ref]	1.00[ref]	–	–
NA	1.23	1.23	0.082	NS
Hemoglobin *g/dL*				
<11	0.99[NS]	1.00[NS]	0.144	NS
11–12	0.99[NS]	0.97[NS]	0.162	NS
>12	1.00[ref]	1.00[ref]	–	–
NA	1.03[NS]	0.93[NS]	4.043	0.044

[a] All RRs are significantly different from 1.00 ($P < 0.05$) unless otherwise noted.

in Table 3. The results, shown in Figures 1 and 2, are qualitatively consistent with the average RRs presented in Table 3. However, these time-dependent RRs reflect an important and consistent trend across various patient subgroups. Specifically, the risk of death is initially higher among HD patients, and then, depending on the subgroup, either reaches a level comparable to that of PD (non-DM patients, younger DM patients) or becomes lower than that of PD (older DM patients). This trend of nonproportional mortality rates is also reflected in the corresponding population-averaged adjusted survival curves shown in Figures 3 and 4. Among non-DM patients and younger DM patients, adjusted patient survival is initially higher among PD patients, and the survival advantage is retained throughout the 3-year follow-up period. Conversely, among the older DM patients, survival is comparable between PD and HD through the first year of dialysis, but because PD mortality rates exceed those of HD after 6 to 12 months, long-term survival is better among HD patients.

Model goodness-of-fit

Goodness-of-fit was evaluated across the four strata formed by the presence or absence of comorbidity (none vs. one or more) and cause of ESRD (non-DM, DM). To evaluate the need to also stratify by age, goodness-of-fit tests across the four strata were done by comparing full two-way interaction models with reduced models obtained by excluding all two-way interactions except for the age by modality interaction. Table 4 shows that there was no significant lack of fit across the four strata when the age by modality interaction was included ($P > 0.319$). However, when the age by modality interaction was excluded from the individual models, there was a significant lack of fit ($P < 0.05$) in three of the four strata. These results indicate the need to further stratify by age when comparing treatment modalities. Once patients were stratified by cause of ESRD (DM vs. non-DM), age (18–44, 45–64, ≥65), and the presence of baseline comorbidity, no other risk factors were found to significantly interact with treatment modality.

As-treated analysis

The results for time-averaged RR in the AT analysis are shown in Table 5. In general, although this analysis was qualitatively similar to the ITT analysis, it yielded higher RRs of death for HD versus PD, a result that is consistent with other studies carried out in the United States, Canada, and Europe [5, 6, 11–13]. Likewise, time-dependent analyses also yielded RR profiles that were consistently higher for patients on HD compared to PD (data not shown). These higher RRs for HD may reflect the effects of informative censoring associated with switching modalities, especially in light of the higher rate of switching from PD to HD. However, given that deaths occurring within 60 days following a switch were attributed to the initial modality, it is unlikely that the differences in RR could be due solely to informative censoring. Conversely, in an ITT analysis there is a strong possibility that the estimated RRs will be attenuated due to the misclassification of patients by modality. The

Table 3. Crude death rates (DR) per 100 patient years with unadjusted and adjusted relative risks (HD:PD) stratified by comorbidity, cause of ESRD, and age

Patient stratum			HD		PD			Relative risk (HD:PD)	
Comorbid conditions	Cause of ESRD	Age	Deaths	DR	Deaths	DR	%Pts	Crude RR	Adjusted RR(95% CI)
None	Non-DM	18–44	3244	6.4	453	4.2	8%	1.52	1.24 (1.07, 1.44)[a]
		45–64	5887	10.3	958	8.5	9%	1.21	1.13 (1.02, 1.25)[b]
		≥65	18,216	28.2	1878	24.1	10%	1.17	1.13 (1.05, 1.21)[a]
	DM	18–44	1960	12.3	468	10.2	3%	1.21	1.22 (1.05, 1.42)[b]
		45–64	8275	14.5	1665	16.8	8%	0.86	0.92 (0.85, 1.00)[c]
		≥65	12,564	27.5	1515	33.0	7%	0.83	0.86 (0.79, 0.93)[a]
One or more	Non-DM	18–44	1623	10.4	174	7.8	2%	1.33	1.19 (0.94, 1.50)[NS]
		45–64	8791	18.1	1027	16.5	7%	1.10	1.01 (0.92, 1.11)[NS]
		≥65	42,343	38.7	3354	38.2	19%	1.01	0.96 (0.91, 1.01)[NS]
	DM	18–44	1636	17.0	329	15.5	2%	1.10	1.10 (0.92, 1.32)[NS]
		45–64	15,103	22.0	2502	27.8	11%	0.79	0.82 (0.77, 0.87)[a]
		≥65	30,926	38.5	2994	48.2	14%	0.80	0.80 (0.76, 0.85)[a]

NS, not significant ($P > 0.05$).
[a] $P < 0.001$; [b] $P < 0.01$; [c] $P < 0.05$.

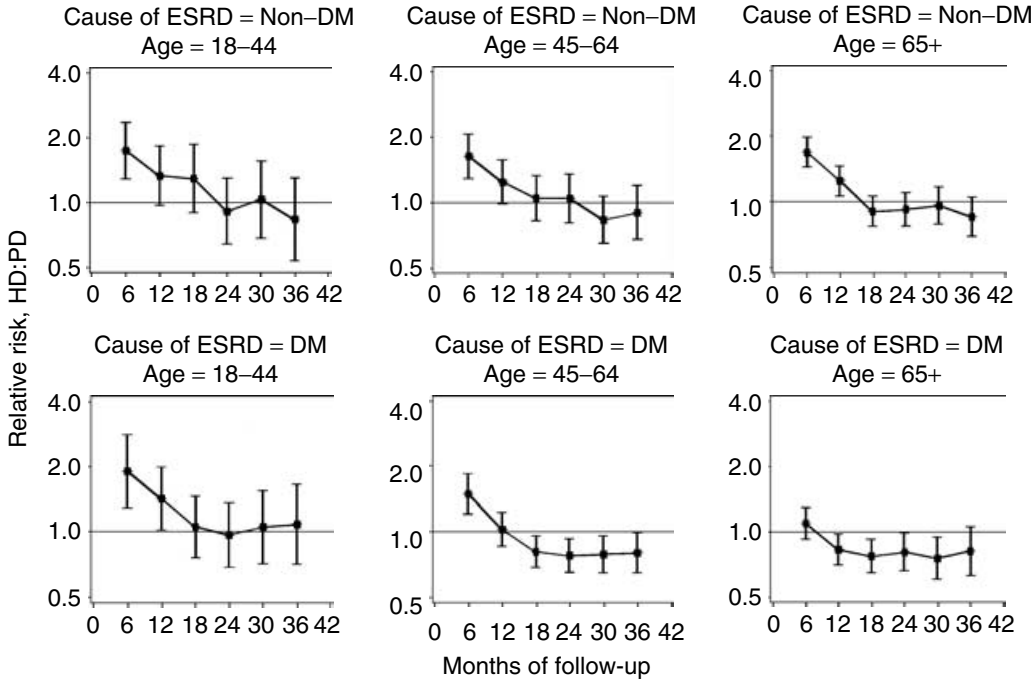

Fig. 1. Relative risk of death, RR(HD:PD), among patients with no reported comorbidity at baseline. RRs are adjusted for age, gender, race, and cause of ESRD, and baseline values of GFR, albumin, hemoglobin, and BMI.

misclassification occurs over time because some patients who switch and are receiving HD are classified as being on PD, while others listed as being on HD are actually being treated with PD [8].

DISCUSSION

In the present study, we showed that differences in mortality rates between HD and PD vary across segments of the ESRD population. Using a modality-specific risk assessment, three key factors that influence the RR of death between HD and PD were identified: cause of ESRD (DM vs. non-DM), age (18–44, 45–64, ≥65), and baseline level of comorbidity (none vs. one or more comorbid conditions). When we accounted for these interactions in a stratified analysis, we found that HD was associated with an increased risk of death in the 30% of the ESRD population comprised of non-DM and younger DM patients with no reported baseline comorbidity. Conversely, we found that PD was associated with an increased risk of death in the 40% of the population comprised of DM patients aged 45 and older. There were no differences in adjusted patient survival between the two modalities in the remaining 30% of the population comprised of non-DM patients and younger DM patients with baseline comorbidity.

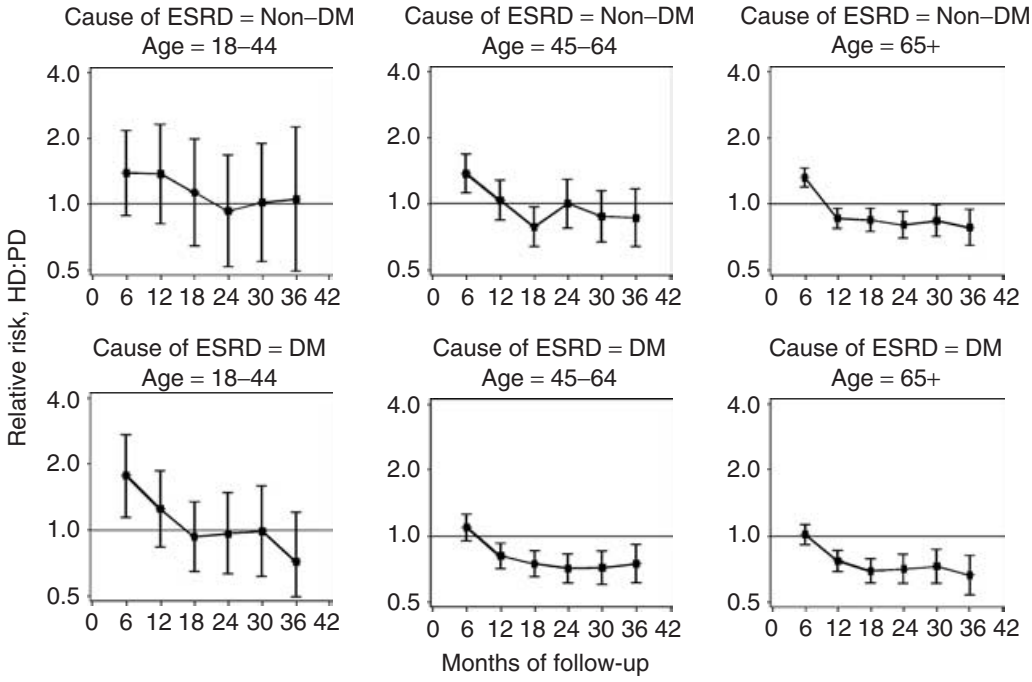

Fig. 2. Relative risk of death, RR(HD:PD), among patients with one or more reported comorbid conditions at baseline. RRs are adjusted for age, gender, race, cause of ESRD, individual comorbid conditions, and baseline values of GFR, albumin, hemoglobin, and BMI.

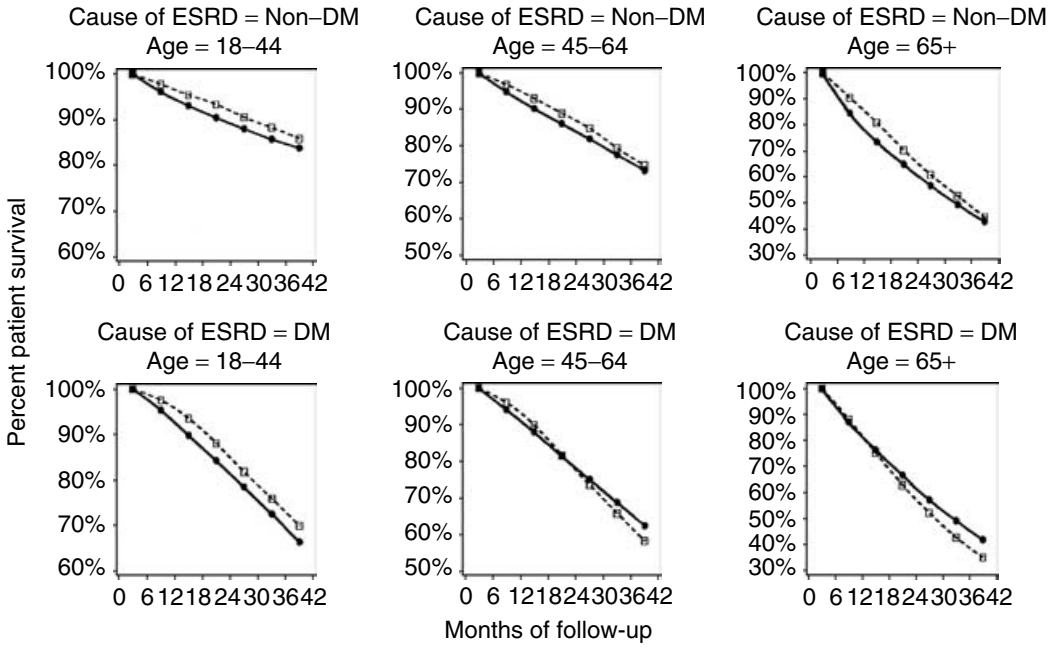

Fig. 3. Adjusted patient survival among patients with no reported comorbidity at baseline. Survival curves (HD, solid line; PD, dashed line) are adjusted for age, gender, race, and cause of ESRD, and baseline values of GFR, albumin, hemoglobin, and BMI.

These results are in partial agreement with results from other countries. For example, registry data from Canada (N = 14,483 incident patients) [6] and Denmark (N = 7011 incident patients) [11] indicate that patients receiving PD have an overall lower risk of death than those receiving HD. However, in both registries, the lower risk of death with PD was less pronounced for DM patients compared to non-DM patients, and was significant for DM patients only in an AT analysis. In an ITT analysis, neither the Canadian nor the Danish registry showed a significant difference in survival between PD and HD among older DM patients [RR (PD:HD) = 1.04, P = NS

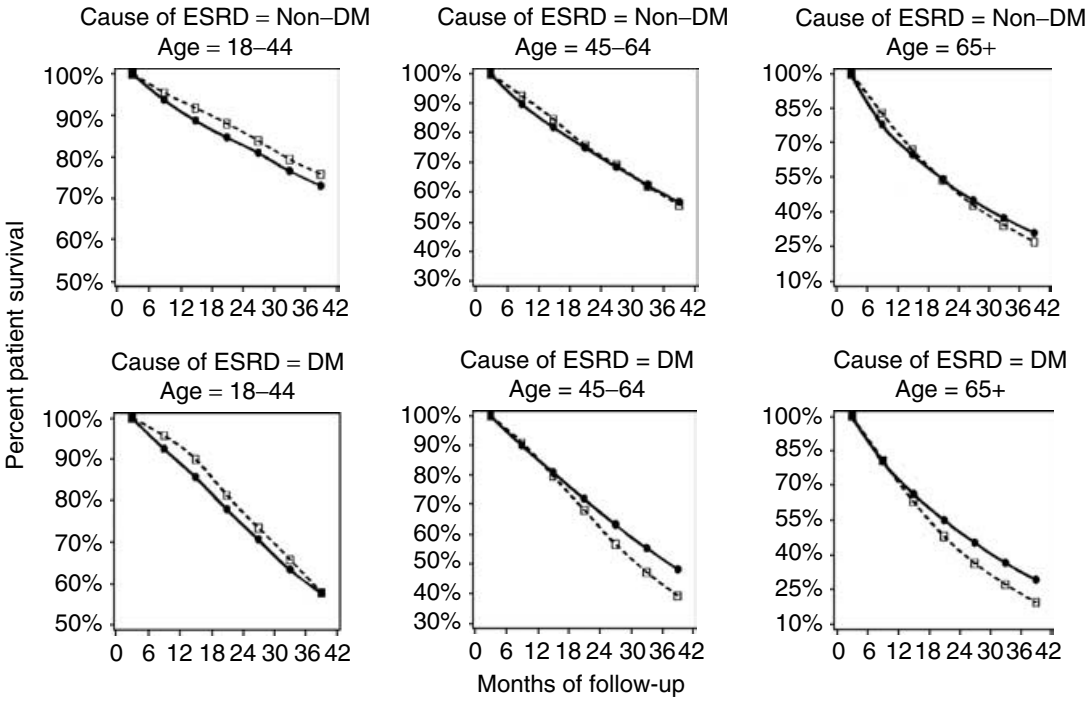

Fig. 4. Adjusted patient survival among patients with one or more reported comorbid conditions at baseline. Survival curves (HD, solid line; PD, dashed line) are adjusted for age, gender, race, cause of ESRD, individual comorbid conditions, and baseline values of GFR, albumin, hemoglobin, and BMI.

Table 4. Model goodness-of-fit based on an analysis of deviance chi-square test with degrees of freedom, χ^2(DF), and corresponding *P* value

		Chi-square goodness-of-fit test			
		Age × modality included		Age × modality excluded	
Baseline comorbidity	Cause of ESRD	Chi-square test	*P* value	Chi-square test	*P* value
None	Non-DM	$\chi^2(18) = 14.83$	0.674	$\chi^2(2) = 6.09$	0.047
	DM	$\chi^2(18) = 18.61$	0.416	$\chi^2(2) = 10.83$	0.004
One or more	Non-DM	$\chi^2(28) = 30.96$	0.319	$\chi^2(2) = 3.75$	0.153
	DM	$\chi^2(27) = 24.74$	0.589	$\chi^2(2) = 7.79$	0.020

Table 5. Average relative risks (HD:PD) by method of analysis

Patient stratum			ITT analysis Adjusted RR (HD:PD) (95% CI)	As-treated analysis Adjusted RR (HD:PD) (95% CI)
Comorbid conditions	Cause of ESRD	Age		
None	Non-DM	18–44	1.24 (1.07, 1.44)[a]	1.55 (1.30, 1.84)[a]
		45–64	1.13 (1.02, 1.25)[b]	1.23 (1.10, 1.38)[a]
		≥65	1.13 (1.05, 1.21)[a]	1.18 (1.09, 1.28)[a]
	DM	18–44	1.22 (1.05, 1.42)[b]	1.45 (1.21, 1.74)[a]
		45–64	0.92 (0.85, 1.00)[c]	0.98 (0.89, 1.07)[NS]
		65+	0.86 (0.79, 0.93)[a]	0.86 (0.79, 0.94)[a]
One or more	Non-DM	18–44	1.19 (0.94, 1.50)[NS]	1.34 (1.03, 1.76)[c]
		45–64	1.01 (0.92, 1.11)[NS]	1.10 (0.98, 1.22)[NS]
		≥65	0.96 (0.91, 1.01)[NS]	0.98 (0.93, 1.04)[NS]
	DM	18–44	1.10 (0.92, 1.32)[NS]	1.35 (1.09, 1.68)[b]
		45–64	0.82 (0.77, 0.87)[a]	0.84 (0.78, 0.91)[a]
		≥65	0.80 (0.76, 0.85)[a]	0.82 (0.77, 0.87)[a]

NS, not significant ($P > 0.05$).
[a] $P < 0.0001$; [b] $P < 0.001$; [c] $P < 0.05$.

in both cases]. Since the percentage of DM patients is much lower in these countries than in the United States, the overall lower risk of death favoring PD in these studies probably reflects the relatively lower risk of death among the comparatively higher percentage of non-DM patients.

While our results may appear to differ from those of other studies of the United States Medicare population, they are actually quite similar. In a study of 117,158 incident Medicare patients (1994–1996), Collins et al demonstrated an increased risk of death with HD versus PD among non-DM patients and younger DM patients, and an increased risk of death with PD among older DM patients, especially older female diabetics [9]. Unlike past studies of prevalent-based Medicare patients [4, 7], the study by Collins et al was restricted to incident patients and, therefore, not prone to a vintage effect associated with prevalent-based analyses. Other strengths of their study include the stratification of patients by age and diabetic status and the use of interval Poisson regression to account for nonproportionality in mortality rates between HD and PD. With regards to the latter, Collins et al found that patients treated with HD generally had higher adjusted mortality rates during the first 6 to 12 months of dialysis compared to those treated with PD, a finding that is consistent with both our results and those from the Canadian registry [5, 6] and Danish registry [11].

A major limitation of the Collins study was that no adjustments were made for case-mix differences in comorbidity and/or baseline laboratory values. Recent studies have attempted to address these shortcomings. In a study of 112,077 incident Medicare patients (1995–1997), Xue et al compared 1-year survival rates between HD and PD with adjustment for baseline demographics, BMI, and laboratory values [15]. Consistent with our findings, these authors found that HD was associated with a higher adjusted risk of death among non-DM patients [RR (HD:PD) = 1.135, $P < 0.0001$] and a lower adjusted risk of death among DM patients [RR (HD:PD) = 0.882, $P < 0.0001$].

In two related studies, Ganesh et al [12] and Stack et al [13] address the limitations of the Collins study by adjusting for differences in baseline comorbidity and laboratory values using a nonproportional Cox regression analysis. Their analyses of 107,922 incident Medicare patients revealed a significant interaction between treatment modality and CAD [12] or CHF [13] as a comorbidity. When the authors accounted for these important interactions in their respective analyses, they both found that HD was associated with a lower adjusted risk of death in DM patients and in non-DM patients with CAD or CHF, a group comprising approximately 60% of the ESRD population. Of the remaining 40% of patients (non-DM patients without CAD or CHF), there were no significant differences in adjusted survival between HD and PD.

As in the Collins study, the Ganesh [12] and Stack [13] studies accounted for the known interaction between diabetes and modality, and used a nonproportional hazards model to estimate adjusted time-dependent relative risks. A further strength of these two studies is that, in addition to stratifying patients by comorbidity (CAD or CHF) and diabetes, they also adjusted for further case-mix differences in patient demographics (gender, race, age), baseline comorbidity, and baseline values of GFR, SA, hematocrit, and BMI. Unfortunately, these studies, as well as the study by Xue et al, failed to account for an age by modality interaction that has been shown to be present in numerous other studies [1, 2, 4, 6, 7, 9, 14]. This interaction, if ignored, can result in estimated RRs that may be misleading. In particular, if the RR of death differs according to age (i.e., an age by modality interaction exists), then a RR that is adjusted for age, but averaged over the different age groups, can be strongly influenced by the RR of a particular age group that has a disproportionately larger sample size. For example, in our study, 69% of deaths occurred in the 51% of patients age 65 and older. Since this older population contributes the majority of deaths, ignoring the age by modality interaction can lead to an estimate of overall risk that is unduly influenced by the RR of death in this group, a result known as Simpson's paradox [25]. As shown in our study, when the analysis is stratified by age as well as comorbidity and cause of ESRD, one finds an increased risk of death associated with HD among non-DM patients and an increased risk of death associated with PD among older DM patients. These results are consistent with other studies that have estimated an age by modality interaction [7, 9].

Interestingly, unlike Ganesh et al [12] and Stack et al [13], we did not find PD to be consistently associated with an increased risk of death among non-DM patients with baseline comorbidity. Only among non-DM patients aged 65 and older was there any evidence of a higher risk of death associated with PD and only after 6 to 12 months (Fig. 2). Moreover, this later increase in risk associated with PD was offset by the 32% excess mortality associated with HD during the first 6 months [RR (HD:PD) = 1.32, $P < 0.0001$], as evident in a comparison of corresponding adjusted survival curves for HD and PD [Fig. 4, time-averaged RR (HD:PD) = 0.96, $P = 0.268$]. Since we used the presence of any comorbidity as a stratifying variable rather than a specific comorbid condition, it is possible that our degree of stratification was too broad to provide a careful assessment of risks in the non-DM population, despite adjustment for the presence of individual comorbidities. To evaluate this possibility, we performed a sensitivity analysis in which patients with one or more comorbid conditions at baseline were further stratified into those with and without CHF. Results of that analysis (Table 6) show no significant differences in the adjusted risk of death between HD and PD among

Table 6. Average relative risks (HD:PD) by presence or absence of CHF

Patient stratum				
Comorbid conditions	Cause of ESRD	Age	CHF absent RR (95% CI)	CHF present RR (95% CI)
One or more	Non-DM	18–44	1.20 (0.90, 1.61)[NS]	1.10 (0.74, 1.63)[NS]
		45–64	1.10 (0.97, 1.25)[NS]	0.88 (0.76, 1.02)[NS]
		≥65	0.99 (0.91, 1.06)[NS]	0.94 (0.87, 1.00)[NS]
	DM	18–44	1.14 (0.89, 1.46)[NS]	1.04 (0.80, 1.35)[NS]
		45–64	0.84 (0.76, 0.93)[a]	0.80 (0.73, 0.86)[a]
		≥65	0.81 (0.74, 0.89)[a]	0.80 (0.74, 0.85)[a]

NS, not significant ($P > 0.05$).
[a] $P < 0.0001$.

non-DM patients regardless of whether they had CHF. This result is consistent with the overall goodness-of-fit tests (Table 4) in that no interactions were found to exist between treatment modality and any of the individual comorbidities, including CHF after stratification by cause of ESRD, age, and the presence of comorbidity. This finding probably reflects the importance that comorbidity in general plays in modifying the risk profile of patients on dialysis. Indeed, we found remarkably good agreement between crude RRs (Table 3) and the adjusted RRs, especially among diabetic patients.

A key feature of our study was the application of a modality-specific risk assessment to identify factors of the ESRD population that impact mortality associated with HD and PD. Specifically, we found that non-DM patients had a higher adjusted risk of death on HD compared to PD, with the degree of risk dependent on the presence of comorbidity at baseline. In contrast, among DM patients, outcomes differed between HD and PD according to age, with younger patients (age <45) generally having better outcomes on PD and older patients (age ≥45) having better outcomes on HD.

These results suggest several areas where technical improvements to both HD and PD may lead to better outcomes for patients undergoing maintenance dialysis. For example, given that PD is associated with higher mortality in older DM patients, it is natural to ask whether there are any modifiable features of PD that could lower this risk, or whether such excess mortality may be due to other confounding factors. To that end, Collins et al observed that older (age ≥55) female DM patients on PD were at an increased risk of death due to infection compared to those on HD [9]. These findings parallel the 20% higher rate of peritonitis observed among DM versus non-DM patients on PD [26], and suggest that continued improvements in PD connectology may help lower the risk of infection and, in turn, lower mortality due to infection. However, a higher rate of mortality due to infection among DM patients on PD may also reflect a degree of negative selection bias associated with diabetes. Winkelmayer et al recently showed that during the first 3 months of dialysis, 12% of patients who started on HD switched to PD [27]. They also showed that patients who switched from HD to PD were 50% more likely to have diabetic nephropathy as their primary cause of ESRD (adjusted hazards ratio = 1.49, $P = 0.004$), independent of timing of referral. This higher rate of switching may be due in part to a greater incidence of HD access complications in DM patients [28–31]. Any negative selection of diabetics to PD because of problems such as poor venous access or poor hemodynamic stability may be a signal of emerging comorbidity that is not captured by the classification of patients to DM or any other conditions listed in the CMS medical evidence form, and might explain in part the higher mortality associated with PD in older DM patients.

Of equal concern is the degree to which glucose-containing PD solutions inhibit glycemic control in DM patients and elevate levels of advanced glycation end products (AGEs) [32–35]. Tighter glycemic control has been associated with better outcomes, including survival, in pre-ESRD and ESRD diabetics patients [36–38]. The fact that younger DM patients on PD have equal or better survival compared to HD may reflect their ability to better metabolize and utilize daily glucose loads that range from 100 to 300 grams per day. Likewise, accumulation of AGEs in dialysis patients has been associated with accelerated atherosclerotic cardiovascular disease [39]. It remains to be seen whether alternative non–glucose-based solutions will help reduce morbidity and mortality, especially in older DM patients undergoing PD.

We found that HD was associated with a higher risk of death compared to PD for non-DM patients and younger DM patients, especially for those with no comorbidity. The increased risk of death with HD was confined to the first 6 to 12 months of follow-up, and was significant even for those patients with baseline comorbidity (Figs. 1 and 2). At 6 months, adjusted death rates for non-DM and younger DM patients on HD were 1.32 to 1.91 times higher than for those on PD. Such excess early mortality can have a significant impact on long-term patient survival, as is evident in Figure 3. A survival advantage for PD is maintained for these patients throughout the 3-year follow-up period, despite death rates comparable to HD after 1 year. The early increased risk of death associated with HD may be due in part to a better preservation

of residual renal function (RRF) with PD, a higher incidence of late referral with HD, and/or early complications associated with vascular access in HD.

Peritoneal dialysis has been shown to better preserve RRF compared to HD [40, 41]. Further, PD patients with diabetes are twice as likely to lose their RRF after 1 year compared to those without diabetes (adjusted odds ratio = 2.17, $P = 0.01$) [41]. These results could explain in part why non-DM patients on HD have higher mortality during the first year of dialysis compared to those on PD. However, it is unlikely that such large reductions in mortality over such a short time period (as much as 48% in the first 6 months) can be attributed solely to better preservation of RRF with PD [9].

The impact of late referral on mortality is unclear. Some studies have shown an association between late referral and an increased risk of death, while other studies have shown no relationship [42–48]. In some studies, late referral seems to have had an impact on mortality early in therapy [43, 48]. Winkelmayer et al [48] showed that late referral was associated with a 36% increase in mortality compared to early referral, but the excess mortality was restricted to the first 90 days of dialysis. Moreover, there does not seem to be any overwhelming evidence to suggest that patients who are referred late are more likely to use HD than PD. For example, two recent studies showed that timing of referral was not a determinant factor in the initial choice of modality [27, 49]. Since our study was restricted to Medicare patients who survived the first 90 days of treatment, any immediate direct effect of late referral on mortality should be minimal for both PD and HD patients.

A high incidence of sepsis and other access-related infections early in treatment is a plausible explanation for the high initial mortality associated with HD. Infectious complications of HD vascular access continue to be one of the leading causes of morbidity and mortality in the United States [28–31, 50–55]. Although evidence suggests a higher mortality in association with the use of catheters versus fistulas or grafts [51–54], the use of permanent catheters in the United States is increasing at a rate faster than that for AV fistulas [55].

At least some of the excess mortality associated with HD during the first 6 to 12 months of treatment is likely caused by access-related infections. In a study of nearly 5000 incident patients, the RR of death following an episode of hospital-managed septicemia was 38% higher for patients treated with HD compared to PD [56]. When restricted to deaths from septicemia, the adjusted RR for HD patients was twice that for PD patients. Similarly, data from the 2003 USRDS Annual Data Report shows that adjusted first-year hospitalization rates for sepsis are up to three times higher for patients on HD compared to PD, and the risk of death in the 6 months following the first septicemia event is nearly 7-fold greater than in patients without sepsis [55]. The use of AV fistulas versus venous catheters has been shown to reduce the risk of septicemia [28, 56, 57] and death [51–54]. Since the risk of septicemia associated with venous catheters is elevated during the first 6 months of dialysis [56], and mortality and hospitalizations are also elevated during this time, a decrease in the use of permanent catheters and an increase in the use of AV fistulas may lead to a reduction in the first-year mortality associated with HD. Improvements in catheter design and implementation may also help reduce the incidence of septicemia, and thereby, reduce mortality.

As with any observational study, there are inherent limitations to the current study. For example, no adjustments were made for factors that directly relate to dialysis modality selection, such as length of time patients were aware of kidney failure, timing of nephrology referral, the timing and type of modality options education, and patient attitude to the management of their disease process. Given the fundamental differences between PD and HD with respect to lifestyle and patient attitude, such factors may be important determinants of survival differences between the two modalities. Likewise, data were not available in this study to adjust for various socioeconomic factors that may be associated with patient outcomes. Such factors, for example, may explain the enormous gap in utilization of PD in the United States (10% PD vs. 90% HD) compared to countries such as Canada and Denmark (25% PD vs. 75% HD) [55]. Consequently, while there is some degree of synergism in outcome comparisons among various countries, care should be taken not to generalize results from this United States Medicare population to other countries.

CONCLUSION

We found that mortality risks between HD and PD vary substantially in clinically relevant and easily identifiable segments of the United States Medicare ESRD population. If confirmed, findings like this may help in matching patients to therapies, and in selecting interventions amenable to hypothesis testing in a more formal randomized controlled trial setting.

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