Causes of Death in Dialysis Patients: Racial and Gender Differences

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ABSTRACT

The risk of death in the dialysis population is high and has previously been shown to be accentuated in male (versus female) and white (versus black) subgroups. To better understand the difference in mortality among these subgroups, the causes of death between males and females as well as between whites and blacks adjusting for age, cause of ESRD (diabetic versus nondiabetic), dialysis modality, and time on dialysis (<1 yr versus >1 yr) were compared, with national data obtained from the U.S. Renal Data System. A total of 42,372 deaths occurring over 170,700 patient years at risk were analyzed. Males had a 22% higher risk of death than females (P < 0.001), attributable to a higher risk of death due to acute myocardial infarction (relative death rate ratio [RR] = 1.48; P = 0.001), all other cardiac causes (RR = 1.3; P = 0.001), and malignancy (RR = 1.59; P < 0.001). Whites had a 29% higher risk of death than blacks (P < 0.001), accounted for by an increased risk of death due to acute myocardial infarction (RR = 1.34), all other cardiac causes (RR = 1.30), withdrawal from dialysis (RR = 2.72) (all P < 0.001), and infection (RR = 1.09; P = 0.005). This analysis expands the knowledge and understanding of the excess mortality seen in male and white subgroups, which is a necessary step in designing strategies to reduce the high mortality in dialysis patients.

Key Words: ESRD, hemodialysis, peritoneal dialysis, mortality, death rates

Patients treated for ESRD have a high mortality rate. Reports have shown that the risk of mortality among patients treated for ESRD is higher for males than for females and for whites than for blacks. The U.S. Renal Data System (USRDS) has shown that 1-yr survival rates for ESRD patients incident during the 1980s are typically two to three percentage points higher for females than for males when adjusted for age. These gender and racial differences in mortality have also been reported in studies restricted to the dialysis population in which transplant recipients are excluded. A higher risk of mortality in males and whites was found in an analysis of all Medicare-treated U.S. hemodialysis (HD) patients incident in 1977 (4). More recent studies have also shown these gender and/or racial differences but less consistently (5-7). Studies performed on data from HD and peritoneal dialysis (PD) patients in Michigan (5) and HD patients in Georgia (6) confirmed the racial but not the gender difference in DR. In the USRDS Special Study of Case Mix Severity, the gender difference was confirmed among HD patients; however, the higher risk of mortality for white compared with black patients was not statistically significant (7).

Cause of death statistics are of vital importance in medical epidemiologic research and serve as a source of new hypotheses that can be explored by in-depth epidemiologic and clinical research. Few studies have compared the causes of death in ESRD patients by gender or race. Those that have are somewhat limited in that they are from single programs (8) or deal with only one or few specific causes of death (9-13). Furthermore, previous studies have generally compared the percentage distribution of causes of death among patients who died and thus have been primarily descriptive in nature. In this type of analysis, an observed excess of one cause of death may represent a true risk but may also merely represent a deficit of deaths due to another cause. The USRDS has published cause-specific mortality rates; however, these have not been adjusted for important demographic covariates nor analyzed to determine comparative risks between subgroups by race and gender. The
The purpose of this study therefore was to confirm the previously reported increased risks of mortality among whites and males and to compare actual DR between race and gender subgroups for major causes of death in order to achieve a better understanding of the excess mortality in gender- and race-specific subgroups.

METHODS

Source of Data and Study Population

Data were obtained from the USRDS. The USRDS collects demographic and clinical information on patients who survive at least 90 days on renal replacement therapy and qualify for Medicare (approximately 93% of the total treated ESRD population). Patients receiving continuous ambulatory peritoneal dialysis/continuous cycles-assisted peritoneal dialysis (PD) or HD were included. Data as received from the USRDS were obtained from three cohorts of dialysis patients prevalent on January 1 of 1987, 1988, and 1989, each with 1 yr of follow-up.

Patients starting dialysis less than 3 months before January 1 were excluded for that year because data were potentially incomplete for these patients. Patients who had a previous renal transplant were excluded to enhance the homogeneity of the study population. Patients transplanted during the year were censored on the day of transplantation. Switches in dialytic modality during the 365 days of follow-up were not considered.

Each cohort was monitored for one calendar year for deaths, cause of death, and days at risk of death. Time at risk of death was summed from the beginning of the year to the date of death, to the date of transplant, or to the end of the year for each patient. Patients surviving until the end of the year contributed 1 yr of risk, whereas patients dying midyear contributed 1/2 yr at risk on average. A patient prevalent at the beginning of more than one calendar year contributed data to more than one cohort. Patient follow-up was characterized by age, race, gender, dialysis modality, cause of ESRD, and time on dialysis at the beginning of each cohort year, better reflecting the effect of covariates that change in a given patient from one cohort year to another (age, modality, and time on dialysis). The total number of patient deaths and years at risk for the three cohorts were aggregated to enhance the stability of the estimated DR.

For each death occurring in the U.S. ESRD population, the Health Care Financing Administration (HCFA) requires the primary cause of death to be reported by the patient's renal physician. This occurs by means of a Death Notification Form (HCFA-2746), which lists 22 cause of death categories (e.g., acute myocardial infarction [MI], sepsis, etc.). The USRDS data base includes these data as well as a "missing" cause of death category for those patients who, by means of the Social Security System and/or hospital discharge records, are known to have died but for whom no Death Notification Form was received. For the purpose of this analysis, these 22 cause of death categories were collapsed into 8 categories: acute myocardial infarction, "other cardiac causes" (all cardiac causes other than acute MI), cerebrovascular disease, infection, malignancy, withdrawal from dialysis, other, and unknown/missing. Because revisions to the cause of death categories on the Death Notification Form were made in 1990, this study uses data only through 1989.

Data Analysis

DR were compared between females and males as well as between blacks and whites for each of the six collapsed known causes of death (acute MI, "other cardiac causes," cerebrovascular disease, infection, malignancy, and withdrawal from dialysis). Crude DR, computed as the aggregate number of deaths divided by the aggregate number of patient years at risk for the three cohorts, are reported per 100 patient years at risk.

Poisson regression was used for each cause of death to compare the DR of various subgroups while adjusting for all other demographic characteristics. All comparisons were adjusted for age, gender, race (white, black, or other), cause of ESRD (diabetic nephropathy versus all others), and dialysis modality (HD or PD). It was speculated that differences in specific causes of death may exist between patients who die soon after the initiation of ESRD treatment and those who die after a longer duration of dialysis therapy. Therefore, patients who started ESRD therapy less than or equal to 1 yr before each January 1 study start date were classified as "incident" and the remainder were classified as "nonincident." Patients who were new ("incident") in 1 yr were classified as "nonincident" in subsequent years. Comparisons were also adjusted for this characteristic. Age on January 1 of each year was entered by 5-yr age categories, as obtained from USRDS. All other covariates were entered into the model as dichotomous variables. DR comparisons are presented as a relative risk (RR), which is the ratio of adjusted death rates among the two subgroups being compared, e.g., males compared with females or blacks compared with whites.

Additional analyses assessed if differences between subgroups in the cause-specific DR varied by other demographic characteristics by including interaction terms in the regression model. If an interaction was statistically significant (e.g., interaction of gender by modality), an RR was computed for each subgroup (e.g., male/female [M/F] RR for PD and HD separately). P values were also obtained to determine if each of the two individual RR were significantly different from 1.0. If only one subgroup (e.g., HD) had an RR significantly different from 1, the excess risk was said to be present only in that subgroup. If, however, both RR were significantly different from 1, the risk (e.g., gender) was said to be accentuated in the subgroup with the greater RR. Statistical analyses were performed with the PROC LOGISTIC procedure of SAS v6.01 (Cary, NC).

For comparison of overall DR, all deaths were included (N = 42,372). In 18.0% of the deaths during 1987 to 1989, the cause of death was either unknown or missing. To ensure that a difference in a DR due to a specific cause was not simply due to a difference in the proportion of patients within a subgroup with cause of death missing/unknown, both the number of deaths (N = 7,653) and the number of patient years that these patients contributed (31,901 patient years) for the missing/unknown category were excluded from the comparison of individual causes of death. This assumes that the distribution of cause of death in those patients who have an unknown cause of death or missing data is similar to the distributions noted in the patients with cause of death reported.

To account for the multiple comparisons performed, we applied the Bonferroni procedure to this analysis of six causes of death, requiring a P value of less than 0.008 (0.05 divided by 6) to conclude that a significant difference existed. Similarly, to conclude that there was a significant interaction with another covariate, a P value less than 0.01 (0.05/5) was
required because five covariates were tested. We chose to label an RR value of 0.95 to 1.05 or a P value of greater or equal to 0.01 as not significantly different from 1 in the comparisons of gender (or race) risk within subgroups (e.g., PD and HD). Because the Bonferroni correction provides a conservative statistical criterion, true differences may be missed. The data are therefore presented with the level of confidence noted. Items that are significant with the Bonferroni correction are indicated.

RESULTS

A total of 42,372 deaths occurred over 170,700 patient years at risk in this study population of chronic dialysis patients. The study population was 60% white, 36% black, and 4% other races. Almost 50% were females. Other demographic features are shown in Table 1.

Gender

Of deaths occurring between 1987 and 1989, 22,261 occurred in males and 20,111 deaths occurred in females. DR per 100 patient years at risk for all causes and for each cause individually were compared between males and females with statistical adjustment for other factors. Overall, for all causes, the DR for males was 22% higher than that for females (RR = 1.22; P < 0.001), adjusted for age, race, diabetic versus nondiabetic ESRD, dialysis modality, and "incident" versus "nonincident." Figure 1 shows DR for males (24.1/100 patient years) compared with females (19.7/100 patient years) for patients with the average characteristics of the total study population.

Figure 2 shows the DR for each individual cause of death. DR due to "other cardiac causes" (all cardiac causes other than acute MI) were the highest, more than twofold greater than the next leading cause of death, which was infection for females and acute myocardial infarction for males. Withdrawal from dialysis, cerebrovascular disease, and malignancy constituted the next highest death rates in decreasing order. This figure also shows the M/F RR for dialysis patients. In particular, males have a higher DR due to acute myocardial infarction (RR = 1.48; P = 0.001).

TABLE 1. Demographic characteristics of study population

<table>
<thead>
<tr>
<th>Race</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% White</td>
<td>60.4</td>
</tr>
<tr>
<td>% Black</td>
<td>35.8</td>
</tr>
<tr>
<td>% Other</td>
<td>3.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% Female</td>
<td>49.8</td>
</tr>
<tr>
<td>Mean Age, yr (SD)</td>
<td>60.2 (9.3)</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
</tr>
<tr>
<td>%Diabetic Nephropathy</td>
<td>25.0</td>
</tr>
<tr>
<td>Modality</td>
<td></td>
</tr>
<tr>
<td>% Hemodialysis</td>
<td>87.1</td>
</tr>
<tr>
<td>Time on Dialysis</td>
<td></td>
</tr>
<tr>
<td>% Incident (&lt;1 yr)</td>
<td>26.8</td>
</tr>
</tbody>
</table>

“other cardiac causes” (RR = 1.30; P = 0.001), and malignancy (RR = 1.59; P < 0.001) than females. The DR for males and females on dialysis are not significantly different (P > 0.008) for infection (RR = 1.08; P = 0.01), cerebrovascular disease (RR = 0.93; P = 0.05), and withdrawal from dialysis (RR = 1.03; P = 0.37) when the Bonferroni correction is applied.

Further subanalyses were done to determine if the observed M/F differences for total deaths or for each individual cause of death varied by race, cause of ESRD (diabetes versus other causes), dialysis modality, or length of time on dialysis ("incident" = less than
or equal to 1 yr or "nonincident" = greater than 1 yr).
The results for race, cause, modality, and time on dialysis are summarized in Table 2. Interactions found to be significant are discussed subsequently.

Deaths due to All Causes. Although the "all-cause" DR was higher for males compared with females, further analysis showed that this difference was significantly greater among patients treated with HD than for patients treated with PD (P < 0.001). The increased DR for males compared with females in patients on PD is small and only of borderline significance (RR = 1.06; P = 0.01) (Figure 3), whereas in patients treated with HD, males have a 25% higher DR than females (RR = 1.25; P < 0.001). Although there is a statistically significant interaction by race (P = 0.006), the difference in M/F RR is unlikely to be clinically important (RR = 1.23 for blacks and RR = 1.20 for whites). Interactions of gender by age, cause of ESRD, and time on dialysis ("incident" versus "nonincident") were not significant for all cause mortality.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Overall</th>
<th>Race</th>
<th>Cause of ESRD</th>
<th>Modality</th>
<th>Time on Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Black</td>
<td>Non-Diabetics</td>
<td>Diabetes</td>
<td>HD PD Incident Prevalent</td>
</tr>
<tr>
<td>Total</td>
<td>1.22a</td>
<td>1.23ab</td>
<td>1.2a</td>
<td>1.23a</td>
<td>1.25a 1.06a 1.19a 1.24a</td>
</tr>
<tr>
<td>MI</td>
<td>1.45a</td>
<td>1.40a</td>
<td>1.50a</td>
<td>1.56a</td>
<td>1.52a 1.33a 1.40a 1.52a</td>
</tr>
<tr>
<td>Other Cardiac</td>
<td>1.30a</td>
<td>1.22a</td>
<td>1.32a</td>
<td>1.30a</td>
<td>1.30a 1.24a 1.26a 1.31a</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>0.93</td>
<td>0.93</td>
<td>0.92</td>
<td>0.92</td>
<td>0.96 0.73a 0.84 0.95</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>0.98</td>
<td>1.16 1.06 0.85 1.04 1.03</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.59a</td>
<td>1.52a</td>
<td>1.62a</td>
<td>1.60c</td>
<td>1.61c 1.42 1.49a 1.64a</td>
</tr>
<tr>
<td>Infection</td>
<td>1.08</td>
<td>1.19a</td>
<td>1.01</td>
<td>1.04</td>
<td>1.15c 0.90 1.00 1.10c</td>
</tr>
</tbody>
</table>

** Different from 1.00; P < 0.001.
ab Boldface areas represent RR that are significantly different from each other (interaction is present) with Bonferroni correction (P < 0.01).
c Different from 1.00; P ≤ 0.01.

Acute Myocardial Infarction. The M/F RR due to acute myocardial infarction was significantly accentuated (P = 0.005) in patients with nondiabetic causes of ESRD compared with patients with diabetes (interaction was present). The M/F RR was 1.56 in nondiabetics and 1.35 in diabetics (Figure 4). In addition, the M/F RR for acute MI increases with age (P = 0.003). At ages older than 65, there is a significant difference in DR by gender (P < 0.01). At ages younger than 47, there is no significant difference in DR by gender (P > 0.05) (Figure 5).

Infection. No significant difference was found between the DR for all males versus all females due to infection (Figure 2). However, further analysis showed that among HD-treated patients, the DR due to infection was significantly greater for males than for females (RR = 1.11; P < 0.001), whereas among PD-treated patients, there was no significant difference in infection DR by gender (Figure 6a). There was a 19% higher DR for males compared with females among
blacks (RR = 1.19; P < 0.001), although there was no gender difference among whites (Figure 6b).

**Malignancy.** The M/F RR of 1.59 due to malignancy was significantly accentuated in older patients (P = 0.007).

**Cerebrovascular Disease, Withdrawal From Dialysis and "Other Cardiac Causes."** The M/F RR for these causes (Figure 2) were not significantly modified by age, race, cause of ESRD, dialysis modality, and time on dialysis ("incident" versus "nonincident") when the Bonferroni correction was applied.

**Race**

There were 12,536 deaths occurring among blacks and 28,458 deaths occurring among whites during the study period. The white-to-black (W/B) RR was 1.29 (P < 0.001), indicating that the DR among whites is 29% higher than among blacks adjusted for age, gender, cause of ESRD (diabetic versus others), dialysis modality, and length of time on dialysis ("incident" versus "nonincident"). The estimated DR for patients with the average characteristics of the total population was 24.1 among whites and was 18.7 among blacks (Figure 7).

Figure 8 shows the DR for each individual cause of death and compares the DR for whites and blacks for each cause of death. As in the male and female subgroups, "other cardiac causes" had by far the highest death rate, followed by acute MI, infection, cerebrovascular disease, withdrawal, and malignancy in decreasing order. Whites were 34% more likely to die of an acute MI (RR = 1.34; P < 0.001), 30% more likely to die of "other cardiac causes" (RR = 1.30; P < 0.001), 9% more likely to die of infection (RR = 1.09; P = 0.005), and almost three times as likely to withdraw from dialysis (RR = 2.72; P < 0.001) than blacks. Differences in DR due to cerebrovascular disease and malignancy were negligible and not statistically significant.

Subgroup analyses were done to determine if these W/B differences for total deaths or for each cause varied by other covariates. These results are summarized in Table 3. Significant interactions are discussed subsequently.

**Deaths due to All Causes.** The all-cause W/B RR was significantly accentuated (P < 0.001) in patients with diabetic ESRD (P < 0.001) and in "incident" patients (P < 0.001). The W/B RR for patients with diabetes was 1.54 (P < 0.001), whereas it was only 1.17 (P < 0.001) in patients with ESRD due to causes other than diabetes (Figure 9a). The W/B RR for patients treated for less than 1 yr was 1.4 (P < 0.001) and was 1.25 (P < 0.001) in patients treated for more than 1 year (Figure 9b). The W/B difference in DR due to all causes increased significantly with age (P = 0.001), with the DR for whites becoming significantly greater than that for blacks above age 35 (P < 0.01).

**Acute MI.** As for the all-cause DR, the increased W/B RR due to acute MI was significantly accentuated (P < 0.001) in patients with diabetic nephropathy (RR = 1.61; P < 0.001) compared with patients with ESRD due to other causes (RR = 1.20; P < 0.001).

"Other Cardiac Causes." Similarly, the W/B RR was significantly accentuated (P < 0.001) in patients with diabetic nephropathy (RR = 1.56; P < 0.001) compared with other causes of ESRD (RR = 1.18; P < 0.001) and in "incident" patients (RR = 1.53; P < 0.001) compared with "nonincident" (RR = 1.25; P < 0.001).

**Infection.** Although the DR due to infection was higher in whites compared with blacks, this difference was noted only in patients with diabetic nephropathy (RR = 1.22; P < 0.001) and not in patients with other causes of ESRD (RR = 1.03; P = 0.48). Race differences existed among females (RR = 1.18; P < 0.001) but not men (RR = 0.99; P = 0.68). Death rates by gender are shown in Figure 6b.

**Cerebrovascular Disease.** Although the W/B RR due to cerebrovascular disease was overall not significantly different from 1.0, further analysis revealed that, in patients with diabetic nephropathy, whites had a significantly greater risk (RR = 1.28; P < 0.001), whereas in patients with other causes of ESRD, there was no significant difference in the death rate between blacks and whites (RR = 0.89; P > 0.01) (Figure 10).

**Withdrawal From Dialysis and Malignancy.** The large W/B DR ratio (RR = 2.72) for withdrawal and the DR ratio for malignancy (RR = 1.00), in subanalyses, did not differ significantly by age, race, cause of ESRD, or dialysis modality or among "incident" versus "nonincident" patients when the Bonferroni correction was applied.
Causes of Death in Dialysis Patients

6a. Death Rate (per 100 patient years)

Figure 6. Comparison of male and female DR due to infection by subgroups: (a) by modality (CAPD and HD) and (b) by race. DR are for patients with average characteristics of the study population. RR, DR ratio (M/F), adjusted for age, race, diabetes, dialysis modality, and duration of dialysis (< or > 1 yr). * Significant using criteria outlined in Methods. ** Significant at the 0.05 level with Bonferroni correction.

6b. Death Rate (per 100 patient years)

DISCUSSION

In all subgroups analyzed in this study (males, females, whites, blacks), DR due to "other cardiac causes" were the highest. This category includes congestive heart failure, subacute and chronic ischemic heart disease, cardiomyopathy, arrhythmias, valvular disease, and pericarditis. DR due to acute MI were either the second or third highest, depending on the subgroup. The high prevalence of cardiac disorders in ESRD patients has been noted previously (7,14,15) and has been shown to be associated with an elevated risk of mortality (16,17). Proposed etiologic factors include chronic volume overload, chronic hypertension, anemia, arteriovenous fistula, metabolic acido-

sitis, hyperparathyroidism, β-2-microglobulinemia (18), and complement activation (19).

DR due to infection were similar to those due to acute MI. Dialysis patients are known to have a high incidence of infection due common bacterial pathogens as well as opportunistic infections, which are more prevalent in the dialysis patient. Potential contributing factors include altered host defense systems due to uremia and the dialysis procedure (19–25), the transcutaneous access necessary for both HD and PD (26), and poor nutrition (14).

Withdrawal from dialysis constituted the fourth
TABLE 3. Adjusted W/B RR of death for each cause of death by race, cause, modality, and time on dialysis

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Overall</th>
<th>Gender</th>
<th>Cause of ESRD</th>
<th>Modality</th>
<th>Time on Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Nondiabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Total</td>
<td>1.29a</td>
<td>1.26a</td>
<td>1.31a</td>
<td>1.17a</td>
<td>1.54a</td>
</tr>
<tr>
<td>MI</td>
<td>1.34a</td>
<td>1.37a</td>
<td>1.32a</td>
<td>1.20a</td>
<td>1.61a</td>
</tr>
<tr>
<td>Other Cardiac</td>
<td>1.30a</td>
<td>1.35a</td>
<td>1.27a</td>
<td>1.18a</td>
<td>1.56a</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1.02</td>
<td>1.01</td>
<td>1.03</td>
<td>0.89</td>
<td>1.28a</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>2.72a</td>
<td>2.71a</td>
<td>2.74a</td>
<td>2.60a</td>
<td>2.96a</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.00</td>
<td>1.02</td>
<td>0.97</td>
<td>0.99</td>
<td>1.03</td>
</tr>
<tr>
<td>Infection</td>
<td>1.09c</td>
<td>0.99</td>
<td>1.16a</td>
<td>1.03</td>
<td>1.22a</td>
</tr>
</tbody>
</table>

* Different from 1.00; P < 0.001.
** Boldface areas represent RR that are significantly different from each other (interaction is present) with Bonferroni correction (P < 0.01).
† Different from 1.00; P < 0.01.

9a. Death Rate (per 100 patient years)

9b. Death Rate (per 100 patient years)

Figure 9. Comparison of white and black DR due to acute MI by subgroups: (a) by cause of ESRD and (b) for patients treated < or ≥ 1 yr. DR are for patients with average characteristics of the study population. RR, DR ratio (W/B), adjusted for age, gender, cause of ESRD (diabetes versus other causes), modality, and duration of dialysis (< or ≥ 1 yr). * Significant according to criteria outlined in Methods. ** Significant at the 0.05 level with Bonferroni correction.

highest DR in all subgroups except for blacks. It has previously been shown to be a common cause of death (9,10,13,27-29), accounting for up to 22% of deaths in one study of predominantly white ESRD patients (27). Studies have suggested that it is increasing as a cause of death in the dialysis population (9,30).

DR due to malignancy were low relative to other major causes of death; however, previous studies have suggested an increased risk of malignancy (31-33) or of specific malignancies (34) in the ESRD as compared with the general population. An increased risk of malignancy in ESRD patients may be due to the effect of therapy (19,25), the presence of uremia, or the selection to dialysis of patients with an underlying malignancy (7).

Effect of Gender

Similar to other studies (4,7), this study has confirmed that the "all-cause" DR is lower for females than for males, when adjusted for race, age, cause of ESRD, dialysis modality, and incidence. However, examining this by modality reveals that this is only true among HD-treated patients. All-cause mortality rates among PD-treated females are statistically only marginally different than among males and similar to HD-treated males. Nolph et al. have previously documented the absence of a gender effect on mortality in PD patients (35). In PD-treated patients, males had higher DR due to MI, other cardiac causes, and malignancy but lower DR due to cerebrovascular disease, withdrawal from dialysis, and infection, with the overall result of a small increased risk of mortality in males that is of borderline significance. The M/F RR were in general higher among HD-treated than among PD-treated patients for all causes of death; however, these were only significantly different for infection (Table 2).

The higher risk of death in male as compared with female dialysis patients appears to be due to an excess of deaths from acute MI, other cardiac causes, and malignancy. For deaths due to acute MI, gender had a smaller effect among patients with diabetic nephropathy than among patients with causes of ESRD other
Although this explanation requires consideration, the absence of a significant decrease in the M/F 

![Graph](image)

**Figure 10.** Comparison of differences in the W/B DR due to cerebrovascular disease by subgroups by cause of ESRD. DR are for patients with average characteristics of the study population. RR, DR ratio (W/B), adjusted for age, gender, cause of ESRD (diabetes versus other causes), modality, and duration of dialysis (< or > 1 yr). * Significant according to criteria outlined in Methods. ** Significant at the 0.05 level with Bonferroni correction.

than diabetes, although as expected, the DR due to acute MI infarction are much higher overall in diabetics than in nondiabetics (Figure 4). The excess risk of death for males due to these identified causes requires the consideration of a number of potential explanations, including the following.

1. **Selection Resulting From Differential Comorbidity.** Selection could lead to higher mortality among males, if males with comorbid conditions such as coronary artery disease, other cardiac disease, or underlying malignancy were more likely to be offered dialysis therapy than females. Likewise, if females with any of these conditions were more likely to refuse dialysis therapy, similar differences in mortality would result. To our knowledge, no studies have specifically examined this issue. The smaller gender effect present among PD-treated patients could result if males selected to PD were relatively healthier than women selected to this modality. The influence of these factors and their possible interactions on modality choice deserve further study.

2. **Selection Resulting From Differential Transplantation Rates.** It has been shown that transplantation rates are higher for males than in females, controlling for age and race (1,36–38). Because the presence of cardiac disease is a surgical risk and the presence of malignancy is a contraindication to transplantation, patients with these conditions are less likely to receive a transplant. If males were more likely to receive transplants than females, then the proportion of males remaining on dialysis with cardiac disease or malignancy would be higher than the proportion of females with these comorbid conditions. Although this explanation requires consideration, the absence of a significant decrease in the M/F RR with increasing age (where transplantation is less frequent) suggests that it is not a strong possibility. It should also be noted that, despite this possible selection of presumably healthy males to transplantation, males still have a higher mortality rate than females in the general ESRD (dialysis and transplant) population (1).

3. **Treatment.** Differences in treatment could also explain the difference in DR in males versus females. Degoulet et al. (12) have shown that cardiovascular deaths are higher in patients dialyzed twice weekly as compared with those dialyzed three times weekly. This suggests that the high premature incidence of cardiac disease in ESRD patients compared with the general population could be the result of an inadequately dialyzed uremic toxin that is detrimental to the heart. If the dialysis prescription is not individualized, females, because of their smaller body size, may be more likely to be adequately dialyzed than males. A recent US RDS study has actually confirmed such gender differences in delivered KT/V among hemodi-alysis patients (P.J. Held, et al., personal communication). The smaller gender effect among PD-treated patients may suggest that these dialysis dose differences are smaller in PD- than in HD-treated patients.

4. **Biologic Factors.** Biologic differences may explain the differences in mortality by gender. In the general population, many diseases affect gender differentially, and overall, the risk of death is also higher for men than for women. For example, coronary artery disease is more common overall in males than in females. Vital Statistics data indicate that, in 1988, the overall age-adjusted DR due to MI was more than twice as high for males as for females (61.6 versus 38.8/100,000 population; RR = 2.10) (39). This RR increases with age, in part because of the loss of the protective effect of estrogen against coronary artery disease in postmenopausal women. The M/F RR noted in the dialysis population of 1.48 is lower than in the general population. This may reflect the large proportion of postmenopausal women in the ESRD population and/or the high incidence of ovarian dysfunction seen in premenopausal females with ESRD. The M/F RR (adjusted for age) for "major cardiovascular disease other than acute MI" was 1.62 in the general population compared with an RR of 1.30 in this study of dialysis patients. The M/F RR for malignant neoplasms in the general population was 1.46 compared with 1.59 in this dialysis population.

It therefore appears that similar biologic factors may be contributing to mortality in the ESRD population as in the general population; however, it must be emphasized that DR in the ESRD population are much higher than in the general population. This suggests that these disease processes are greatly accelerated before and/or after the onset of ESRD.

5. **Social/Cultural.** Social or cultural differences existing between males and females may affect mortality rates. For example, female dialysis patients have been shown to be more compliant than their male...
counterparts (S.L. Bame, et al., personal communication), which may in turn affect mortality.

Among patients treated with PD, females were more likely to withdraw from dialysis than males. Although this was not significant, nor was it significantly different than the RR among HD-treated patients, it may reflect general differences in social/cultural attitudes among males and females that may influence other treatment decisions and, as a result, affect mortality. Further studies may be helpful to determine which of these explanations related to selection, treatment, biology, or social/cultural differences are the major contributors to the excess DR seen in males.

Effect of Race

The "all-cause" adjusted DR was higher for whites than for blacks in this national study of dialysis patients, confirming a number of previous reports (5,6). Crude mortality rates as reported by the USRDS indicate that DR for black ESRD patients are higher than for whites to approximately age 40, appear similar to whites from age 40 to 55, and are lower than whites above age 55 (2). In this adjusted analysis of dialysis-only patients, DR in whites were significantly higher than in blacks above the age of 35 yr and increased with age but were not significantly different in patients less than age 35. This apparent discrepancy with the crude USRDS data could represent the effect of adjustment or the exclusion of transplant patients in our analysis. Although the USRDS Case-Mix study did not find a significant difference in mortality by race, there was a trend to higher mortality in whites (RR = 1.18), consistent with our results. The smaller sample size, difference in patients studied (all incident rather than incident and prevalent), and/or adjustment for comorbid conditions may account for the failure to find this risk difference to be significant in the Case-Mix study.

These findings of higher mortality among white dialysis patients are opposite to those in the general population, where blacks have a mortality risk that is higher relative to whites (39). Cardiovascular diseases have been shown to be the single largest contributing factor to the mortality gap between blacks and whites in the general population (40).

The higher risk of death in whites compared with blacks in this study of ESRD patients is largely due to an excess of deaths from acute MI and other cardiac causes, infection (only among females and patients with diabetic nephropathy as cause of ESRD), and withdrawal from dialysis. The race effect for deaths due to both cardiac categories combined (acute MI and other cardiac causes) was noted to be approximately three times greater in patients with ESRD due to diabetic nephropathy as compared with those with ESRD due to other causes. This can account for the greater race effect noted in diabetics in the total (all-cause) DR comparison. For both cardiac categories, the race effect was also two to three times greater among "incident" patients compared with "nonincident" patients, which is likely the chief contributor to a similar observation in the "all-cause" DR comparison.

A number of potential explanatory factors for the observed excess risk of death for whites compared with blacks require consideration. These include the following.

1) Selection Resulting From Differential Comorbidity. Many of the possible explanations discussed previously for males that relate to selection may also apply when considering the excess of mortality seen in whites, including higher dialysis acceptance rates among whites than blacks with comorbid conditions and/or a greater tendency for blacks with serious comorbid conditions to refuse therapy. In addition, there is concern that blacks have less access to medical care in general. For example, recent studies have found that whites are more likely than blacks to undergo invasive cardiac procedures (41) and coronary artery bypass grafting (42).

2) Selection Resulting From Differential Transplantation. Whites have higher transplantation rates than do blacks when controlling for age and gender (36-38), selectively leaving a greater proportion of whites with comorbid conditions including cardiac disease or perhaps infection (i.e., unacceptable surgical risk) on dialysis. However, if this were an explanation for the increased mortality in whites, one would expect the W/B RR to decrease with age because transplantation is less frequent in the elderly. In fact, it increased with age in this study, suggesting that this explanation is not a strong possibility.

3) Treatment. Although a difference in treatment would be a potential explanation, it is less plausible that the racial difference in DR is due to a treatment difference favoring blacks, unless perhaps blacks on dialysis are more compliant than whites. To our knowledge, there are no data to suggest that blacks receive a higher dose of dialysis.

4) Biology. Although race has not been found to designate important genetic factors, physiologic differences have been described between blacks and whites, including differences in renin levels (43-45), sodium-lithium cotransport (46,47), and autonomic reactivity (48-50). It is conceivable that differences in other physiologic factors may exist that are protective in the black ESRD population.

5) Social/Cultural. Many social and cultural differences exist between blacks and whites. It is conceivable that these differences may in some way play a protective role in the black ESRD population. For example, blacks in the United States have been shown to consume fewer dairy products than whites (51), perhaps allowing better dietary compliance and possible improved outcome among blacks. In addition, a higher prevalence of obesity has been found among blacks (52). Of interest is a USRDS finding of lower mortality associated with obesity in incident hemodialysis patients (7).
Social or cultural differences may in part contribute to the almost threefold higher risk of death due to withdrawal in whites than in blacks, also found previously in a study of dialysis patients in Michigan (9). Speculations as to the explanation of this finding include a higher acceptance of white patients likely to withdraw, differences in cultural attitudes or religious beliefs toward the discontinuation of therapy, or perhaps a lesser degree of trust of black patients and their families toward their predominantly white physicians.

Effect of Gender and Race

The all-cause DR for men versus women did not vary to an important degree by race. Likewise, the overall relative DR for whites versus blacks did not vary by gender. Black females had the lowest all-cause DR, whereas white males had the highest. With the exception of infectious causes, the effect of gender did not differ significantly for blacks compared with whites for individual causes of death, nor was the effect of race different between males and females. DR due to infection were similar for all groups, except black females, for whom they were significantly lower. Again, differences in selection, treatment, biologic characteristics, and social or cultural factors must be considered as possible explanatory factors for these observations.

Limitations

In order to ensure data on a large number of dialysis patient deaths, for this study, a prevalent study population was evaluated. A prevalent sample includes a spectrum of patients in terms of duration of prior therapy as distinct from an incident sample. Studies including prevalent patients may be limited by the inherent selection of patients who are survivors. It could be argued that significant relationships noted in prevalent patients only may be suspect for such "survivor selection bias." To address this issue, we used an indicator variable, time on dialysis ("incident" or "non-incident"), as discussed in Methods. Ideally, follow-up time would be classified for each patient on the basis of the exact dates of ESRD therapy start for that patient, and a consistent definition of the period of time to be labeled as "incident" could be adopted.

However, because of the tabular data available to us, we could not classify the follow-up time for each patient during a year according to the exact duration of ESRD for that patient, but had to rely on a classification of the duration at the start of the year. Our classification system has some imprecision because follow-up time intervals labeled as "incident" can correspond to an ESRD duration ranging between 3 and 24 months, whereas follow-up time intervals labeled as "nonincident" can correspond to ESRD duration ranging as low as 12 months. Despite the overlap in underlying ESRD duration caused by the tabular data available to us, our definitions do yield a rough classification of the follow-up interval into shorter versus longer ESRD duration. To determine if there was a difference in risk among "incident" and "nonincident" patients with respect to the associations of interest, interaction models by duration of dialysis ("incident" versus "nonincident") were performed. These interaction models were not significant in the analysis of effect of gender on overall or cause-specific mortality, suggesting that the M/F differences observed are not significantly different for patients with shorter versus longer ESRD duration. The effect of race (mortality higher in whites) on all-cause mortality and on "other cardiac causes" was accentuated (significantly greater) in the "incident" population, suggesting that a study of incident-only patients would be likely to yield results in the same direction. Nevertheless, a comparison of cause of death by gender and race among incident dialysis patients for whom individual data are available would allow a more detailed analysis of the role of time on dialysis.

This study has also controlled for other known or possible risk factors on gender- and race-specific mortality including age, cause of ESRD, modality, and race (in the gender comparison) or gender (in the race comparison). However, there are likely to be other differences between the subgroups compared that may be associated with mortality and that have not been measured or adjusted for in this study. For example, differences in comorbidity, nutritional status, and dose of dialysis (previously shown to be associated with mortality), as well as compliance, education, social circumstances, and patients' health attitudes and beliefs, may exist between men and women or between blacks and whites. Differential compliance and dose of dialysis between men and women have previously been described; however, to our knowledge, there are few published data regarding racial or gender differences in these other factors. In addition, differences in facility features and physician training or practices in predominately white versus predominately black dialysis units could bias racial comparisons. The role of these various factors deserves further study.

Patient follow-up is likely to be very incomplete during the first 90 days because Medicare coverage does not start until after this time period. As outlined in Methods, those patients starting dialysis less than 3 months before January 1 were excluded for that year to avoid the bias that might be introduced by basing an analysis on the distinguished patients whose data are available during the first 90 days. In addition, the cohort scheme used did not allow the capture of data on incident patients who did not survive to the first of a calendar year. If the effect of gender or race was substantially different in these excluded patients than in those included in the study, the overall effect of gender or race may be quite different. In fact, there was no significant difference in the M/F RR of all-cause mortality between the "incident" and "nonincident" patients that were included in our study; more-
However, in the comparison of mortality by race, there was accentuation of the observed W/B RR among the "incident" patients included. These findings suggest that the exclusion criteria of some incident patients are unlikely to substantially alter the overall effect of gender and race on mortality. However, the results of this study should rightfully be generalized only to patients similar to those included.

The performance of this analysis with a large national data set has obvious advantages, including the enhancement of statistical power as well as the generalizability to the United States. A limitation of a study of this type is that the cause of death is reported by renal physicians in a manner that has not been standardized. Despite the listing of 23 causes of death on the ESRD Death Notification Form, different physicians may use different definitions/criteria for each cause. This raises the issue of misclassification. Study results would be compromised if there was a selective difference in misclassification between the groups compared. One may argue that this is unlikely, however, for example, there is a growing literature suggesting less aggressive treatment of coronary artery disease in blacks and females. It follows that coronary artery disease may also be less frequently diagnosed in these subgroups, and thus, their deaths would be less likely attributed to this cause.

As with most studies evaluating cause of death statistics, these limitations restrict this study to being one that may be used to generate hypotheses that can be evaluated by future detailed epidemiologic and clinical studies. The need for prospective studies that use standardized definitions and criteria for each cause of death and that are rigorously designed to eliminate threats of biases is emphasized.

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REFERENCES