Predictors of Loss of Residual Renal Function among New Dialysis Patients

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Abstract. Residual renal function (RRF) in end-stage renal disease is clinically important as it contributes to adequacy of dialysis, quality of life, and mortality. This study was conducted to determine the predictors of RRF loss in a national random sample of patients initiating hemodialysis and peritoneal dialysis. The study controlled for baseline variables and included major predictors. The end point was loss of RRF, defined as a urine volume <200 ml/24 h at approximately 1 yr of follow-up. The adjusted odds ratios (AOR) and *P* values associated with each of the demographic, clinical, laboratory, and treatment parameters were estimated using an "adjusted" univariate analysis. Significant variables ($P < 0.05$) were included in a multivariate logistic regression model. Predictors of RRF loss were female gender (AOR = 1.45; $P < 0.001$), non-white race (AOR = 1.57; $P = <0.001$), prior history of diabetes (AOR = 1.82; $P = 0.006$), prior history of congestive heart failure (AOR = 1.32; $P = 0.03$), and time to follow-up (AOR = 1.06 per month; $P = 0.03$). Patients treated with peritoneal dialysis had a 65% lower risk of RRF loss than those on hemodialysis (AOR = 0.35; $P < 0.001$). Higher serum calcium (AOR = 0.81 per mg/dl; $P = 0.05$), use of an angiotensin-converting enzyme inhibitor (AOR = 0.68; $P < 0.001$), and use of a calcium channel blocker (AOR = 0.77; $P = 0.01$) were independently associated with decreased risk of RRF loss. The observations of demographic groups at risk and potentially modifiable factors and therapies have generated testable hypotheses regarding therapies that may preserve RRF among end-stage renal disease patients.

In recent years, there has been a greater focus on residual renal function (RRF) of patients on chronic dialysis therapy. Although RRF is often used to indicate remaining GFR, it also reflects remaining endocrine functions such as erythropoietin production (1), calcium, phosphorus and vitamin D homeostasis (2,3), volume control, and removal of "middle molecules" or low molecular weight proteins (4,5). RRF is clinically important in that it can account for major differences in dialysis requirements, since it contributes to measures of adequacy, both Kt/V urea and creatinine clearance (C_{Cr}) (6,7). RRF has also been shown to be associated with mortality. Analysis of the CANUSA study (8) has shown that every 0.5 ml/min higher GFR was associated with a 9% lower risk of death (relative risk = 0.91) (9). It has been shown that clinically important and statistically significant decreases in nutritional parameters occur with RRF loss (8). Furthermore, it has been demonstrated that small increments in RRF may account for major differences in quality of life (10,11). It is therefore vitally important to determine and understand the predictors of loss of RRF in the dialysis patient.

The importance of identifying factors that protect and preserve RRF has been recognized among patients with chronic renal failure, pre-end-stage renal disease (ESRD). Control of BP, angiotensin-converting enzyme (ACE) inhibition, decreasing proteinuria, dietary modification, avoidance of nephrotoxins, and glucose control have all been considered integral parts of the pre-ESRD care (12). However, few studies have comprehensively evaluated whether these or other factors are important in preserving RRF after initiation of dialysis. Also on a clinical level, evaluating and monitoring factors that preserve RRF in patients who have just started dialysis has not received the same level of care as among the chronic renal failure population.

Several authors have observed that preservation of RRF is prolonged with peritoneal dialysis (PD) compared to hemodialysis (HD) (13–15). Others have noted a more rapid decline in RRF among patients on automated PD *versus* continuous ambulatory PD (CAPD) (16). For HD patients, there has been debate in the literature about whether the type of dialyzer membrane has an effect on RRF. Some have suggested that biocompatible membranes preserve RRF for a longer time period (17–19). Cause of ESRD, level of BP, and various medications have all been implicated as having an effect on RRF (12,20,21). However, these studies have methodologic

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limitations, including small sample size with inadequate statistical power, retrospective design, and lack of inclusion of all known predictor variables and other modifying factors.

Because our knowledge of the factors that preserve RRF in ESRD is limited, we undertook a study to determine the predictors of RRF loss in a national sample of incident patients initiating ESRD treatment with dialysis. We used a large patient population, controlled for baseline variables, and included major potential predictors. An epidemiologic study of this type can help generate hypotheses regarding modifiable factors associated with loss of RRF, and these factors can subsequently be tested in interventional studies or confirmed in other epidemiologic studies.

Materials and Methods

Data Source

The Dialysis Morbidity and Mortality Study (DMMS) is a U.S. Renal Data System (USRDS) special study, including more than 20,000 randomly selected dialysis patients. The study includes four "waves" of data collection over 3 yr. A standard core of data was collected for all patients included in the DMMS study to address research questions that require a larger sample size. The data used in these analyses were from the USRDS DMMS Wave 2. Wave 2 was a prospective study of incident HD and PD patients (Medicare and non-Medicare) who initiated ESRD in 1996 and early 1997. PD patients were over-sampled by a factor of 5 to result in comparable numbers of PD and HD patients. Wave 2 focused on PD prescription and delivery, PD and HD selection and outcomes, RRF, quality of life, pre-ESRD care, and medication use. The dialysis units included in Wave 2 were a random selection of 25% of the dialysis units in the United States listed on the Master List of Dialysis Facilities as of December 31, 1993, with addition of all new dialysis units opened during 1994. Modality type was identified on day 60 of ESRD. Patients treated with PD or HD on this date (day 60) were eligible. The modality assignment for patients who were on HD but who were training for PD on day 60 was deferred for 10 d. The study start date was considered the date that the modality type was identified (about day 60 of ESRD).

Patient-specific data were collected at the time of enrollment (study start) and were compiled for more than 4000 patients in Wave 2. Data were collected by means of a medical questionnaire, completed by dialysis facility personnel as well as a questionnaire completed by the patient. Questionnaires included patient-specific data such as demographics, prior medical history, laboratory results, dialysis prescription and dialysis delivery, data on vascular access, RRF, medications, pre-ESRD care, and quality of life.

Follow-up data collection was completed 8 to 18 mo after the initial data collection. The follow-up patient questionnaire included information on change in health status or treatment modality and questions related to vascular access. Data on estimated urine volume was collected and was reported as a dichotomous variable, less than or greater than 200 ml/24 h. For patients with estimated urine volume greater than 200 ml/24 h, timed urine collection data (urine volume, creatinine, and urea concentration) were collected on a voluntary basis (at the dialysis facilities' discretion). Patients with estimated urine output of less than 200 ml/24 h were considered to have lost their RRF and no further timed urine samples were collected. Personnel at each dialysis unit completed the follow-up questionnaire by medical abstraction. Personnel were also instructed to obtain information directly from the patient. Copies of the questionnaires used for the DMMS Wave 2 are published in the USRDS 1997 Annual Report, Appendix B.

Analytical Methods

Patients from USRDS DMMS Wave 2 study were included in these current analyses if they had a follow-up form completed and if, at the time of follow-up, they were known to be alive, on PD or HD, and dialyzing in the same facility as at baseline. Patients were excluded at the time of follow-up data collection if they had died ($n = 495$), had return of renal function ($n = 41$), had transferred to an alternate dialysis facility ($n = 234$), had received a transplant ($n = 169$), were <18 yr old or of unknown age ($n = 60$), or if vital status was unknown ($n = 80$). Patients with implausible or inaccurate critical data were also excluded ($n = 426$).

We operationally defined our outcome (dependent) variable, loss of RRF, as estimated urine output <200 ml/24 h at the time of follow-up (8 to 18 mo from initiation of dialysis). The published association between urine volume and renal clearance supports this definition (4,22).

We selected 33 baseline variables for evaluation as possible independent predictors of RRF loss as shown in Table 1. These included age, gender, race, etiology of ESRD (diabetes, hypertension, glomerulonephritis, other), data on pre-ESRD care including late referral to a nephrologist (defined as less than 4 mo before ESRD) and dietary consult pre-ESRD, a number of baseline comorbid conditions, laboratory values at study start including serum albumin, calcium, phosphate, total cholesterol, hematocrit, body mass index (BMI), baseline mean arterial pressure (2/3 DBP + 1/3 SBP) calculated from the average of three BP readings taken postdialysis at study start, dialysis modality (PD or HD), and a number of medications in use at the time of study start including ACE inhibitors, calcium channel blockers, diuretics, erythropoietin, β-hydroxy-β-methylglutaryl (HMG) CoA reductase inhibitors, nonsteroidal anti-inflammatory agents, and vitamin D. Because the level of RRF at the start of ESRD varies for each patient and was expected to be associated with subsequent loss of RRF, it was important to adjust for such baseline differences. Baseline data on urine volume were not collected. It was assumed that most patients would have some baseline RRF, because this was a study of incident dialysis patients with chronic renal failure. However, data necessary to calculate an estimated GFR at ESRD onset were available and the analyses were therefore adjusted for this. Baseline GFR, corrected for body surface area, was estimated using the MDRD formula, which includes serum creatinine (taken before initiation of dialysis), age, gender, race, serum blood urea nitrogen, and albumin (23). This formula was developed and validated from data on 1628 patients with decreased GFR (average ^{125}I-iothalamate clearance = 39.9 ml/min per 1.73 m^2) in the MDRD study. This formula, however, has not been validated in patients with ESRD on dialysis. Analyses were adjusted for time from study start to follow-up because it also varied for each patient and was expected to be associated with loss of RRF.

Missing values for numerical variables were set to the mean for the overall group with the exception of estimated GFR at ESRD onset, which was set to the mean by race and gender. We adjusted for these two factors because GFR is known to differ for these factors. For comorbid conditions, missing values were considered to indicate absence of the condition.

Statistical Analyses

A logistic regression analysis, adjusted only for estimated baseline GFR and time to follow-up, was performed for each covariate to

Table 1. List of covariates and baseline descriptive statistics for total study population, HD only, and PD only reported as mean (SD) or percent[a]

Variable	Total (n = 1843)	HD (n = 811)	PD (n = 1032)
Demographics			
mean age, (yr)	57.8 (15.0)	60.9 (14.7)	55.5 (14.6)
race (% white)	62.6	56.7	68.6
gender (% female)	47.2	48.8	47.5
Cause of ESRD (% of total population)			
diabetes mellitus	44.5	46.7	43.6
hypertension	25.0	27.6	22.9
glomerulonephritis	9.1	6.8	10.9
other causes	21.0	18.1	22.6
Comorbid conditions (% yes)			
diabetes mellitus (history of and/or nephropathy)	51.4	54.6	49.0
coronary artery disease (history of)[b]	39.0	41.6	33.3
peripheral vascular disease (history of)[c]	20.4	23.1	18.2
congestive heart failure (history of)	32.7	39.2	27.6
left ventricular hypertrophy (history of)	18.7	21.9	16.2
Laboratory values, means (SD) (at day 60)			
albumin (g/dl)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
calcium (mg/dl)	8.7 (1.0)	8.7 (1.0)	8.7 (1.1)
phosphate (mg/dl)	5.5 (1.8)	5.5 (1.9)	5.5 (1.7)
hematocrit (%)	30.8 (6.1)	29.8 (5.7)	31.6 (6.4)
total cholesterol (mg/dl)	197.1 (51.6)	181.0 (47.9)	208.4 (63.24)
estimated GFR at ESRD onset (ml/min)	7.4 (2.7)	7.33 (2.8)	7.5 (2.7)
body mass index	26.2 (6.0)	26.2 (6.4)	26.2 (5.7)
MAP (mmHg)	100.6 (12.8)	98.4 (13.2)	102.2 (12.4)
late referral (<4 mo pre-ESRD) (% of total)	56.1	59.8	52.7
dietary consult pre-ESRD (% of total)	37.8	36.3	39.0
months from onset ESRD to follow-up RRF	12 (1.8)	12.2 (1.8)	11.9 (1.7)
Dialysis modality			
peritoneal dialysis (% of all dialysis)	56.0		
CAPD (% of all PD patients)			70.0
dialyzer membrane (% biocompatible)[d]		81.7	
Medications at baseline (day 60) (% of total population)			
any antihypertensive	79.3	77.1	81.7
ACE inhibitors	27.3	26.98	29.7
calcium channel blockers	56.5	56.2	58.3
diuretics	22.1	18.5	24.2
EPO	78.8	85.2	73.8
vitamin D analogues	37.2	41.4	33.9
HMG CoA reductase inhibitors	12.8	9.1	15.7
NSAIDS	1.8	1.7	1.9

[a] HD, hemodialysis; PD, peritoneal dialysis; ESRD, end-stage renal disease; MAP, mean arterial pressure; RRF, residual renal function; CAPD, continuous ambulatory peritoneal dialysis; ACE, angiotensin-converting enzyme; EPO, erythropoietin; HMG CoA, β-hydroxy-β-methylglutaryl coenzyme A; NSAIDS, nonsteroidal anti-inflammatory drugs.

[b] Includes a history of coronary heart disease or coronary artery disease, coronary artery bypass surgery, angioplasty, or abnormal angiogram.

[c] Includes histories of peripheral vascular disease, amputation, absent pulses, or claudication.

[d] Includes substituted cellulose and synthetic membranes.

determine whether any of these covariates were associated with loss of RRF ("adjusted" univariate analyses). Variables with "adjusted" univariate associations at $P \leq 0.05$ significance level were included in the multivariate analysis to determine whether these baseline variables were independently predictive of loss of RRF. Additional analyses were performed looking at predictors of RRF loss in HD and PD populations separately. In the HD-only analysis, the effect of membrane type (modified cellulose and synthetic membranes compared to unmodified cellulose membranes) was also evaluated. In the analysis limited to PD, the effect of type of PD (APD or CAPD) was evaluated. Additional analyses, including other explanatory variables, were performed as appropriate in an attempt to better understand the association of certain predictor variables with loss of RRF.

Results

There were 2211 patients eligible for the study. Data on the outcome variable, urine volume, were reported for 83% of patients at the time of follow-up, leaving 1843 patients for analysis in this study. Comparison of the groups with and without urine volumes recorded at follow-up revealed significant associations for two factors. Female patients (adjusted odds ratio [AOR] = 1.37; $P = 0.01$) and patients treated with PD (AOR = 2.13; $P < 0.001$) were more likely to have data on urine volume reported on the follow-up forms.

The mean age of the patients was 57.8 yr. Sixty-three percent of patients were white, 47% were female, 51.4% reported a history of diabetes, and 44.5% reported diabetic nephropathy as the cause of ESRD. The average time from onset of ESRD to follow-up was 12 mo. The mean GFR at ESRD onset was 7.46 ml/min as estimated by the MDRD formula (23). The average postdialysis systolic BP was 143 mmHg, and the average diastolic BP was 78.9 mmHg for a mean arterial pressure (MAP) of 100 mmHg. By study design, 56% of the patients in the study sample were on PD, and of those 70% were using CAPD and the remainder were using a cycler (APD). Among HD patients, 81.7% were using synthetic and semisynthetic ("biocompatible") membranes, and the remainder were using unmodified cellulose membranes. The frequency of comorbid conditions and mean values for laboratory data at study start are shown in Table 1.

The "adjusted" univariate odds ratio (AOR) for each covariate tested, adjusted only for estimated GFR at ESRD onset and time to follow-up, is shown in the first column of Table 2. Using only the variables that were significant at $P \leq 0.05$ in the "adjusted" univariate analysis, several covariates continued to be significantly associated with a loss of RRF in the multivariate model, including female gender (AOR = 1.45; $P < 0.001$), non-white race (AOR = 1.57; $P < 0.001$), prior history of diabetes (AOR = 1.82; $P = 0.006$), and prior history of congestive heart failure (CHF) (AOR = 1.32; $P = 0.03$). As expected, the risk of loss of RRF was increased for longer time to follow-up (AOR = 1.06 per month; $P = 0.03$). Higher levels of C_{Cr} at ESRD onset was of borderline significance in predicting a lower risk of RRF loss (AOR = 0.97 per ml/min, $P = 0.07$). Patients treated with PD had a 65% lower risk of RRF loss than those treated with HD (AOR = 0.35; $P < 0.001$). Patients with a higher serum calcium had a lower risk of RRF loss (AOR = 0.81 per mg/dl; $P = 0.05$). Interestingly, treatment with an ACE inhibitor (AOR = 0.68; $P < 0.001$) and treatment with a calcium channel blocker (AOR = 0.77; $P = 0.01$) were independently associated with decreased risk of RRF loss in this analysis, which was controlled for baseline BP. This relationship was present in patients with diabetic-related ESRD and as well as in patients with ESRD from all other causes. When all 33 variables were added to the model without consideration of the results from the univariate analysis, the significant predictors of RRF were the same.

Age, cause of ESRD, comorbid factors other than history of diabetes and CHF, late referral, postdialysis MAP, and baseline BMI serum albumin, hematocrit, phosphate, total cholesterol, and baseline use of diuretics, erythropoietin, HMG CoA reductase inhibitors, vitamin D preparations, or nonsteroidal anti-inflammatory agents were not associated with RRF loss in the multivariate analysis.

At follow-up, 38% of PD patients and 69% of HD patients had loss of RRF defined as urine volume <200 ml/24 h. We divided the follow-up time into three equal intervals, and at each time interval HD patients were 3 times more likely to have lost RRF as PD patients.

In a separate analysis of PD patients only ($n = 1032$), factors that were significantly associated with loss of RRF included female gender (AOR = 1.42; $P = 0.02$), non-white race (AOR = 1.94; $P < 0.001$), time to follow-up (AOR = 1.11 per month; $P = 0.01$), history of diabetes (AOR = 2.16; $P = 0.01$), and a history of CHF (AOR = 1.50; $P = 0.02$). Treatment with an ACE inhibitor (AOR = 0.69; $P = 0.02$) or a calcium channel blocker (AOR = 0.88; $P = 0.006$) remained independently associated with lower risk of RRF loss. A higher baseline GFR was associated with a lower risk of RRF loss (AOR = 0.94; $P = 0.04$). Among PD patients, there was no significant difference in RRF loss between use of APD *versus* CAPD (AOR = 0.96; $P = 0.96$).

In a separate, similar analysis of HD patients only ($n = 811$), factors that were significantly associated with a lower risk of RRF included higher postdialysis MAP calculated at study start (day 60) (AOR = 0.87 per 10 mmHg; $P = 0.04$), higher predialysis serum calcium (AOR = 0.79 per mg/dl; $P = 0.01$), and treatment with an HMG CoA reductase inhibitor (AOR = 0.56; $P = 0.03$). The effects of gender, race, and a prior history of CHF or diabetes were no longer statistically significant, but the AOR values were in the same direction as for the main and PD-only model. Treatment with ACE inhibitors (AOR = 0.71; $P = 0.06$) and calcium channel blockers (AOR = 0.69; $P = 0.12$) was no longer significantly associated with a decreased risk of RRF loss, but the AOR remained of the same magnitude as in the main and PD model. There was no significant difference in RRF loss between biocompatible *versus* cellulose dialyzer membranes (AOR = 0.84 biocompatible; $P = 0.42$); however, the numbers were small for use of unmodified cellulose dialyzers (19%). Use of high-flux synthetic dialyzer membranes *versus* all other dialyzer membranes was also not significantly associated with RRF loss.

Female gender predicted increased risk of RRF loss in the main model and the PD-only model independent of differences in BMI, MAP, or albumin. To further explore this relationship

Table 2. Adjusted odds ratios for RRF loss[a]

Variable (reference)	Overall (n = 1843)				PD only (n = 1032)		HD only (n = 811)	
	"Adjusted" Univariate[b]		Multivariate[c]					
	AOR	*P* Value	AOR	*P* Value	AOR	*P* Value	AOR	*P* Value
Adjusting variables								
time to follow-up (per month)	1.10	0.0005	1.06	0.03	1.11	0.01	1.02	0.86
estimated GFR at ESRD onset (ml/min)	0.97	0.07	0.97	0.09	0.94	0.04	0.99	0.74
Demographics								
age (per 10 yr)	1.02	0.0001	1.01	0.18	1.01	0.24	1.00	0.60
female (*versus* male)	1.42	0.0006	1.45	<0.001	1.42	0.02	1.38	0.06
non-white race (*versus* white)	1.72	0.0001	1.57	<0.001	1.94	<0.001	1.08	0.66
Etiology of ESRD								
glomerulonephritis (reference)	1.00	(ref)	1.00		1.00		1.00	
diabetes mellitus	1.76	0.002	0.68	0.14	0.59	0.13	0.81	0.61
hypertension	1.61	0.01	1.17	0.43	1.47	0.14	1.02	0.94
other causes	1.26	0.24	1.05	0.82	1.35	0.25	0.78	0.47
Pre-ESRD care								
late referral (<4 mo pre-ESRD)	1.23	0.04	.99	.99	1.04	0.85	0.93	0.72
dietary consult	0.90	0.33						
Comorbid factors								
diabetes mellitus	1.59	0.0001	1.82	0.006	2.17	0.01	1.66	0.10
coronary artery disease	1.40	0.002	1.13	0.33	1.25	0.19	0.98	0.89
cerebrovascular disease	1.17	0.31						
congestive heart failure	1.60	0.0001	1.32	0.03	1.5	0.02	1.16	0.45
peripheral vascular disease	1.28	0.06						
left ventricular hypertrophy	1.57	0.0006	1.27	0.08	1.30	0.17	1.26	0.26
MAP (per 10 mmHg)	0.993	0.003	01.03	0.49	1.04	0.41	0.87	0.04
body mass index (per kg/m^2)	0.99	0.49						
Laboratory parameters								
serum albumin (per g/dl)	0.88	0.18						
blood hematocrit (per %)	0.98	0.04	.99	0.68	0.99	0.94	1.01	0.53
serum calcium (per mg/dl)	0.90	0.02	0.81	0.05	0.99	0.94	0.79	0.006
phosphate (per mg/dl)	1.05	0.07						
total cholesterol (per 10 mg/dl)	0.99	0.03	1.00	0.93	1.01	0.47	1.01	0.42
Treatment parameters								
PD (*versus* HD)	0.28	0.0001	0.35	0.001	NA	NA	NA	NA
pre/post dialysis delta MAP(HD)	1.04	0.0001	1.00	0.33	NA	NA	0.99	0.87
ACE inhibitor (*versus* no)	0.74	0.01	0.68	<0.001	0.70	0.02	0.71	0.06
calcium channel blocker (*versus* no)	0.77	0.01	0.77	0.01	0.71	0.02	0.81	0.21
diuretics (*versus* no)	0.90	0.41						
EPO (*versus* no)	1.29	0.05	1.12	0.37	1.15	0.39	0.69	0.12
HMG CoA reductase inhibitor (*versus* no)	0.60	0.001	0.81	0.17	0.95	0.78	0.56	0.03
NSAIDS (*versus* no)	0.72	0.43						
vitamin D (*versus* no)	1.02	0.89						
Included in PD only analysis								
APD (*versus* CAPD)					0.96	0.96	NA	NA
Included in HD only analysis								
biocompatible membrane (*versus* cellulose)					NA	NA	0.84	0.42

[a] AOR, adjusted odds ratio; APD, ambulatory peritoneal dialysis; NA, not applicable; other abbreviations as in Table 1.
[b] Adjusted for time to follow-up and estimated GFR at ESRD onset only.
[c] Adjusted for all covariates significant in univariate analysis.

between female gender and RRF loss, we controlled for use of estrogen and for HDL cholesterol. Adjusting for use of estrogen did not change the relationship (AOR = 1.67; $P < 0.001$). We had data on HDL cholesterol on 280 patients. When controlling for HDL cholesterol, the gender relationship was of similar magnitude but not significant, likely reflecting the decrease in power due to the small sample size (AOR = 1.74; $P = 0.09$). To determine whether the relationship varied by menopause status, we stratified the female population by two age categories, <50 yr old or ≥50 yr old. The relationship was similar for the two age categories: age <50 yr (AOR = 1.46; $P = 0.03$) and age ≥50 (AOR = 1.45; $P = 0.003$).

Non-white race was found to be associated with loss of RRF in the overall and PD-only models. To further understand this relationship, blacks (27.3%) and others of non-white race (Asians, North American Indians, and others) (9.6%) were analyzed as two separate groups in the main multivariate model. Both blacks (AOR = 1.83 $P = 0.001$) and those of non-white race (AOR = 1.53; $P = 0.04$) were more likely to have RRF loss. We were unable to determine the specific relationship of Asian or North American Indian race and loss of RRF due to the limited number of patients in these race categories. Because one may speculate that non-whites may have greater risk of loss of RRF due to poorer pre-ESRD care, we further explored the role of late referral to a nephrologist (<4 mo pre-ESRD) and the occurrence of a dietary consult pre-ESRD. Controlling for these interventions did not alter the relationships.

Higher serum calcium was predictive of less RRF loss. Although there was a trend to greater loss of RRF with higher serum phosphate in the univariate analysis (AOR = 1.05, $P = 0.07$), it was not an independent predictor when included in an additional multivariate model. To further understand the relationship of calcium and phosphate and RRF loss, we also explored the role of the calcium phosphate product, parathyroid hormone levels, use of phosphate binders, and vitamin D use in univariate and multivariate models. These covariates were nonsignificant predictors of RRF loss, and their addition to the multivariate model did not change the previously identified relationships with RRF.

To further clarify the role of BP, we used postdialysis MAP and the pre- to postdialysis change in MAP both as univariate predictors and in the multivariate analysis. Neither was significantly predictive of RRF loss. Because there is debate in the literature as to which BP measurement to use, we also analyzed postdialysis systolic and diastolic BP, and the relationship with RRF did not change. To examine RRF loss and different levels of MAP as a categorical variable compared to a continuous variable, we divided the MAP into quintiles using the middle range as the reference group. At no level did mean arterial pressure predict RRF loss, and there was no suggestion of a J-shaped correlation.

Discussion

Accurate measurement and monitoring of RRF in ESRD patients remains a challenge as we approach the 21st century. GFR measured by isotope clearance is considered to be the standard measure of renal function. Other tests, such as serum creatinine, creatinine clearance (C_{Cr}), urea clearance (C_{urea}), an average of the C_{Cr} and the C_{urea}, and urine volume (UV) have been used to assess RRF in chronic renal failure (24). An average of the C_{Cr} and the C_{urea} is commonly recommended in ESRD (25,26).

In the DMMS Wave 2, timed urine collection was requested both at baseline and follow-up, if patients had an estimated urine output >200 ml (or approximately 1 cup) per day. The C_{Cr} was then calculated using the average of the creatinine and urea clearance. Unfortunately, data necessary for this calculation were available for <5% of HD patients and 30% of PD patients at baseline and fewer patients at follow-up. These data are unlikely to be representative of RRF in the ESRD population given the low rate of reporting, and therefore could not be used for our measure of RRF loss.

We therefore defined loss of RRF as estimated urine volume <200 ml/24 h. Despite its shortcomings, urine volume has been correlated to GFR in previous studies. Milutinovic *et al.* compared urine volume to inulin clearance in 38 patients on HD with GFR <5 ml/min (4). Using Milutinovic's data, we calculated a correlation coefficient for urine volume and inulin clearance and found an r value of 0.71 ($P = 0.001$). The correlation coefficient was 0.94 correlating inulin clearance to the average of creatinine and urea clearance from the same data set. Van Olden *et al.* also showed that urinary volume, in the interdialytic interval, is directly related to changes in GFR (22).

Among patients in our data set for whom a C_{Cr} could be calculated using the average of the creatinine and urea clearance, the correlation coefficient for the association between urine volume and the average of the creatinine and urea clearance was $r = 0.57$ at baseline and $r = 0.49$ at follow-up.

These analyses and prior data support the use of urine volume as a useful measure of RRF. Despite the imprecision of this measure, the advantages of potentially developing hypotheses regarding factors predictive of RRF loss from a large data set were believed to outweigh the limitations of using this measure as the outcome variable. It is interesting that patients were more likely to have the outcome variable, urine volume, reported if they were on PD or if they were female. It has been recognized that RRF is important in CAPD due to its contribution to small solute clearance, and more attention may be paid to monitoring RRF in this population. The reason for the gender difference is not clear.

Follow-up data forms were completed after a mean of 12 mo from the initiation of dialysis, with a range of 8 to 18 mo. Several articles on the progression of chronic renal disease have reported that the decline in renal function is either linear or exponential (12,27). Thus, it was assumed that longer follow-up and lower levels of renal function at the start of ESRD would be associated with a greater likelihood of loss of RRF. It was therefore necessary to control for these factors when evaluating the effect of other potential predictors. Duration of time on dialysis was indeed a significant predictor of RRF loss in the overall population and among the PD population, but, interestingly, not among the HD population. Among the PD patients, there was an increasing risk of loss of RRF over time,

suggesting that time on dialysis is an important variable. Likewise, higher estimated GFR at ESRD initiation was associated with lower risk of loss of RRF at follow-up among PD-treated patients but not among HD-treated patients.

Increasing age was not associated with RRF loss. This is consistent with data from the MDRD study (12), in which age was not an independent predictor of progression of renal disease among patients with chronic renal failure. Female gender independently predicted RRF loss in the overall analysis and in the analysis limited to PD patients. This gender effect could not be explained by differences in BMI, MAP, albumin, estrogen use, or menopausal status because the effect remained despite controlling for these variables. As mentioned, females were more likely to have data on urine volume reported on the follow-up form. It is unclear how this may have influenced our results. This gender effect is contradictory to previous studies that showed a slower rate of progression of RRF in females with chronic renal failure (28–31). Data from the MDRD study indicated a slower mean GFR decline in women compared to men with chronic renal failure. However, gender differences were reduced and no longer significant after controlling for baseline proteinuria, MAP, and HDL cholesterol (12).

Non-white race was associated with RRF loss in the overall analysis; however, this effect was found to be limited to PD patients only. This was true of both blacks and the category "other non-white race." These relationships were independent of cause of ESRD and MAP at dialysis initiation, and also could not be explained by reported differences in pre-ESRD care. Blacks are known to have a faster rate of progression of renal failure in the chronic renal failure population (12,32). This analysis suggests that, at least among PD-treated patients, this race effect may persist after ESRD initiation.

The presence of diabetes predicted RRF loss particularly in the PD population. Diabetic patients with hypertension and proteinuria have been shown to have an increased rate of loss of renal function in the chronic renal failure population. A history of congestive heart failure also was predictive of RRF loss, likely due to decreased blood flow to the compromised kidney.

Higher serum calcium was significantly associated with a lower risk of RRF loss in the total analysis and in the HD population. The magnitude of risk was less and was not significant among the PD population. The mean serum calcium was not different between the two populations. Although these relationships did not change with adjustment of several other related covariates, this observation would be consistent with the hypothesis that increased calcium and frequently concurrent lower phosphate levels may contribute to less RRF loss. This may provide further support for the necessity of good phosphate control in the ESRD population.

The present study confirms earlier observations that patients receiving treatment with PD had a reduced risk of RRF loss when compared to HD-treated patients (13–15). In this study, we controlled for possible risk cofactors of age, gender, comorbid conditions, hypertension, medications, and level of estimated GFR at the start of ESRD and still found a significant difference in RRF loss between the HD and PD populations. It has been hypothesized that inflammatory mediators generated by the extracorporeal circulation, rapid intravascular contraction inherent in HD, lower preglomerular arterial pressure, and lower protein intake among PD patients may explain these findings. Patients treated with PD were significantly more likely to have urine volume reported on the follow-up forms. It is unclear how this may have influenced the results.

Several comparative studies of PD and HD mortality have shown that the relative mortality risk favors PD to the greatest degree early after ESRD start and the relative mortality risk increases for PD with time on dialysis (33–36). One reason that PD may offer this early advantage may be the greater preservation of RRF.

Higher postdialysis MAP at baseline significantly correlated with a lower risk of RRF loss in the HD-only population but was an insignificant predictor in the total and PD-only analysis. We speculated that this relationship was likely driven by an increased risk of RRF loss associated with low BP, resulting from postdialysis intravascular volume depletion due to excessive fluid removal. However, the relationship did not change adjusting for intradialytic weight loss. Accurate data on volume status, which would allow further exploration of this hypothesis, are not available in this epidemiologic study. Several studies have observed a relationship of higher mortality associated with low predialysis BP (37–39). A similar phenomenon may exist for RRF.

Several interesting results of our study were related to medication use. We observed an independent lowering of risk of RRF loss among ESRD patients being treated with ACE inhibitors and/or calcium channel blockers. The effect of ACE inhibition and calcium channel blockers, which was adjusted for MAP, was significant in the total and PD-only analyses but was not significant in the HD population, although the magnitude and direction of risk were in general similar to the main model. HMG CoA reductase inhibitors were significantly predictive of a reduction in RRF loss in the HD-only analysis.

Among patients with chronic renal failure, there is considerable evidence that ACE inhibitors (40,41) and perhaps calcium channel blockers (42,43) preserve renal function, independent of BP. The data from this study would suggest that the benefit of slowing progression of RRF loss might be a continuum even when on dialysis. This association was present in ESRD due to diabetes as well as ESRD due to other causes.

Baseline treatment with HMG CoA reductase inhibitors was associated with a 44% lower risk of loss of RRF among HD patients. Treatment with a HMG CoA reductase inhibitor may also have some renoprotective effects, independent of its lipid-lowering effect, by directly inhibiting mesangial cell proliferation and production of monocyte chemoattractants (44). The question of whether lipids or lipid-lowering agents have an effect on RRF loss is important and deserves further exploration.

It has been suggested that exposure to automated PD (use of a cycler) hastens RRF loss when compared to CAPD (16). It is hypothesized that the acute changes in volume status and osmotic load induced at each nightly PD session could potentially accelerate deterioration of RRF. However, in our study

we did not observe a significant difference in loss of RRF by PD modality type. This area deserves further research, as automated PD is becoming a more common form of therapy.

Previous studies have shown that use of cellulose dialyzer membranes among HD patients hastens RRF loss (17–19) due to blood and cellulose dialysis membrane interactions, which may induce potentially nephrotoxic inflammatory mediators (45). We did not observe a significant difference in loss of RRF when we compared cellulose membranes to those generally more biocompatible membranes. However, the proportion of patients using cellulose membranes was small (19%), and our sample size may have been too small to detect a difference. Comparing PD patients to HD patients using biocompatible membranes revealed that PD patients were still significantly less likely to lose RRF than HD patients.

Four hundred and ninety-five patients died before follow-up. We were unable to associate mortality with loss of RRF due to lack of data on RRF at the time of death.

Preservation of RRF is an important goal. In addition to identifying demographic groups at risk, this study has identified several potentially modifiable factors (calcium, MAP) and therapies (dialysis modality, ACE inhibitors, calcium channel blockers, and HMG CoA reductase inhibitors) that were associated with decreased loss of RRF in a national random sample of patients initiating dialysis in the United States. There appear to be substantial differences in both the actual loss of RRF and the contributing risk factors among PD compared to HD patients. These analyses are limited by the use of estimated urine volume $<$200 ml/24 h as a measure of loss of RRF. However, several of the significant associations with RRF loss have generated testable hypotheses regarding potential therapies that may preserve RRF among ESRD patients. Additional prospective studies, ideally clinical trials, are necessary to determine whether these possible interventions are efficacious.

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