Potential Novel Predictors of Mortality in End-Stage Renal Disease Patients With Sleep Disorders

Robert L. Benz, MD, Mark R. Pressman, PhD, Edward T. Hovick, MD, and Donald D. Peterson, MD

• **Patients with end-stage renal disease (ESRD) have an annual mortality rate exceeding 20%, although some survive many years. The ESRD population has a high incidence of sleep disorders, including sleep apnea and periodic limb movements in sleep (PLMS). Sleep disorders result in sleep deprivation, which can negatively affect immune function and cardiovascular-related outcomes, common causes of death in patients with ESRD. This study examined predictors of mortality in patients with ESRD with sleep problems. Twenty-nine consecutive patients with ESRD reporting disrupted sleep or daytime sleepiness were studied by all-night polysomnography. All patients were followed up until death, transplantation, or study termination. Among the variables studied, including such previously reported predictors as serum albumin level, urea reduction ratio, and hematocrit, only the PLMS index (PLMSI), arousing PLMSI (APLMSI), and total number of arousals per hour of sleep significantly predicted mortality. The 20-month survival rate with a PLMSI less than 20 was greater than 90% versus 50% for a PLMSI of 20 or greater (exact log-rank, *P* = 0.007). For the deceased versus survivor groups, mean PLMSI was 119.1 versus 19.8 (*P* = 0.01) and APLMSI was 48.1 versus 7.8 (*P* = 0.00006), with a mean survival of 10.3 versus greater than 25.5 months, respectively (*P* = 0.001). Median survival of patients with a PLMSI greater than 80 was only 6 months. PLMSI, APLMSI, and total arousals per hour of sleep were strongly associated with mortality in patients with ESRD with sleep disorders independent of other factors and may be novel predictors of near-term mortality.**

INDEX WORDS: Mortality; predictors of mortality; end-stage renal disease (ESRD); dialysis; sleep apnea; periodic limb movements in sleep (PLMS); sleep disorders; sleep; anemia; urea reduction ratio (URR).

Editorial, p. 1221

PATIENTS WITH end-stage renal disease (ESRD) undergoing maintenance dialysis are reported to have an annual mortality rate in excess of 20%.[1] However, some patients survive on dialysis treatment for more than 20 years. A variety of risk factors, including low serum albumin levels and inadequate dialysis, are associated with increased mortality in the dialysis population.[2-7]

Sleep disturbance is a common feature of ESRD.[8] Recent questionnaire-based surveys of dialysis patients reported that 41% to 83% report problems about their sleep or daytime alertness.[9-13] When dialysis patients with a sleep problem were studied objectively in the sleep laboratory, 53% to 75% were found to have either sleep apnea, periodic leg movements in sleep (PLMS), or both.[14-17] In a series of 45 patients with ESRD with sleep problems, 71% were found to have PLMS, and 95%, sleep apnea.[18] The only randomized study of sleep disorders in dialysis patients to date found a 72% incidence of sleep apnea, although it did not test fully for PLMS.[19] This finding is of potential significance because untreated obstructive sleep apnea is associated with both increased cardiovascular morbidity and increased mortality in the general population.[20-22] Because the incidence of both sleep complaints and objective findings of sleep apnea and PLMS are considerably greater in the ESRD population than in the general population, the potential effects could also be greater.[23]

A better estimate of the incidence of sleep disorders in the ESRD population is lacking because of the absence of a full laboratory-based study of sleep disorders in a randomly selected ESRD population. Additionally, many patients with such sleep disorders as PLMS may be unaware of their sleep disorder.[16]

The strong link between renal failure and

From the Division of Nephrology; Department of Medicine, Division of Pulmonary and Critical Care Medicine, Sleep Medicine Services, Jefferson Health System–Main Line, The Lankenau Hospital and Medical Research Center, Wynnewood; and the Department of Medicine, Jefferson Medical College, Philadelphia, PA.

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Address reprint requests to Robert L. Benz, MD, Chief, Division of Nephrology, Jefferson Health System–Main Line, Suite 130, The Lankenau Hospital, 100 Lancaster Ave, Wynnewood, PA 19096. E-mail: benz@op.net

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sleep disorders is highlighted by a limited number of studies showing that sleep disorders of patients with ESRD improve significantly or are completely eliminated after successful renal transplantation.[24,25] However, hemodialysis is not reported to have significant beneficial effects on sleep apnea of ESRD.[26]

In preparation for a study investigating the causes of sleep disorders in patients with ESRD, records of patients who had previously undergone polysomnography (sleep studies) were reviewed. A greater than expected number had died since their sleep study. Retrospective review of parameters to distinguish deceased patients from longer term survivors was undertaken. Additional patients with ESRD with reports of sleep problems were studied prospectively and followed up to determine whether sleep disorders, along with clinical, dialytic, and biochemical profiles, could predict mortality.

METHODS

Subjects

Twenty-nine consecutive patients with ESRD who reported difficulty sleeping or daytime sleepiness and were referred for evaluation to the Sleep Disorders Center between 1990 and 1993 were studied. Mean age was 58.7 $\pm$ 12.7 (SD) years (median, 59 years; range, 45 to 75 years), and there were 18 men and 11 women and 15 white and 14 black patients. As part of clinical evaluation for sleep complaints, all patients underwent all-night polysomnography in the American Sleep Disorders Association–accredited Lankenau Hospital Sleep Disorders Center (Wynnewood, PA). Patients were followed up until death, transplantation, or study termination. Survival time was measured from the date of polysomnography.

Polysomnography was performed on evenings after dialysis for all patients. The standard electrodes and sensors used and parameters monitored were electroencephalogram (C3 or C4), electro-oculogram (bilateral outer canthi), electromyogram (bilateral anterior tibialis and mentalis muscles), electrocardiogram, airflow (bilateral nares and mouth), respiratory effort (chest and abdomen), and oxygen saturation (finger pulse oximetry). Patients went to bed at their usual times and awakened spontaneously. Data were recorded continuously and stored both on paper and computer using the Semi-Automatic Sleep Scoring System (Telefactor, Conshohocken, PA).

All analyses of the polysomnographic data were performed visually. No automatic computer analysis was performed. All sleep data were analyzed using the standard method of Rechtshaffen and Kales.[27] Additionally, brief arousals (not included in the manual by Rechtshaffen and Kales) were analyzed as recommended by the Atlas Task Force of the American Sleep Disorders Association.[28]

PLMS were scored according to the technique of Coleman et al.[29] All PLMS were required to consist of at least four consecutive, repetitive, dorsiflexion movements of the legs or feet lasting 0.5 to 5 seconds, with an interval of 5 to 90 seconds during sleep.

PLMS were required to meet these criteria and to occur independently of other events in the sleep recording. Because legs and feet may move as part of a general arousal complex that might occur after apneas and hypopneas, apparent movements of the legs or feet that occurred at the termination of apneas or hypopneas or were associated with snores or other sources of sleep disturbance were not included in the analysis of PLMS. PLMS were further subdivided as arousing PLMS (APLMS) when arousals as previously defined occurred secondary to the limb movements.

Obstructive hypopneas were scored if their duration was 10 seconds or longer and there was a visible reduction in airflow or respiratory effort associated with at least a 3% decline in Sa_{O_2} and/or arousal from sleep. Obstructive apneas were scored in the absence of airflow but with continued presence of respiratory effort for at least 10 seconds associated with at least a 3% decline in Sa_{O_2} and/or an arousal from sleep. Central apneas required the complete absence of airflow and respiratory effort for at least 10 seconds associated with at least a 3% decline in Sa_{O_2} and/or an arousal from sleep.

Statistical Methods

Analysis. Two general approaches to data analysis were taken. First, descriptive analyses comparing mean values between deceased and surviving patients were performed using independent-group *t*-tests. Deceased was defined by death within 14 months after polysomnography. Survivors lived longer than 14 months after polysomnography. All patients included in this first analysis were treated by dialysis only. Patients undergoing transplantation were excluded from this analysis only because they did not continue to be treated with dialysis. They were included in the Kaplan-Meier survival analyses noted next. Parameters compared included sleep and clinical, dialytic, and biochemical parameters (Table 1). Parathyroid hormone values were not compared because of a change in laboratory methods during the study period. The urea reduction ratio (URR) is a surrogate measurement of urea clearance obtained by dialysis calculated by the formula:

$$\text{URR} = (\text{predialysis BUN} - \text{postdialysis BUN}) \times 100 \text{ /predialysis BUN}$$

where BUN is blood urea nitrogen level.

The second approach characterized survival of patients with and without high PLMS indices (PLMSI) or APLMS indices (APLMSI). Kaplan-Meier survival curves were constructed to estimate median survival times with appropriate accounting for censoring. Exact log-rank tests (StatExact version 3 for Windows; Cytel Software Corp, Cambridge, MA) were used to test hypotheses of equivalency in mortality rates, taking into account the small sample sizes.[30] Incidence-density rates and incidence-density ratios (IDRs) were computed instead of risk ratios.

The mortality incidence density is the average number of deaths per unit of time over a specified time interval. It can

Table 1. Comparison of Deceased Versus Surviving Groups

	Deceased		Survivors		
Variable	Mean	SD	Mean	SD	*P*
General					
Survival post-PSG (mo)	10.3	6.3	25.5	12.2	0.001
Age (y)	61.0	14.9	57.3	9.4	NS
Duration of dialysis (mo)	44.6	29.4	32.8	24.3	NS
Movements					
PLMSI (per h)	119.1	159.6	19.8	27.8	0.01
APLMSI (per h)	48.1	32.3	7.8	10.6	0.00006
Sleep					
Total recording time (min)	393.9	69.0	454.1	108.3	NS
Total sleep time (min)	263.5	88.5	332.1	117.6	NS
Sleep efficiency (%)	66.6	16.6	72.2	18.7	NS
Stage 1 (%)	26.5	13.4	22.9	15.2	NS
Stage 2 (%)	47.8	11.2	51.8	11.2	NS
Stage 3 (%)	2.5	2.4	1.9	2.3	NS
Stage 4 (%)	9.9	8.9	9.4	11.4	NS
REM (%)	13.2	5.9	12.9	10.2	NS
Arousals per hour	93.2	44.4	52.7	34.2	0.01
Respiratory					
Respiratory disturbance index*	44.9	37.1	44.8	37.4	NS
Low Sa_{O_2} (%)	76.2	14.6	81.6	7.3	NS
Laboratory values					
Hematocrit (%)	29.9	3.6	33.4	4.9	0.06
BUN (mg/dL)	61.9	17.3	56.1	13.0	NS
Iron saturation (%)	24.8	17.0	26.3	9.7	NS
Ferritin (ng/mL)	61.7	39.9	80.0	61.1	NS
Calcium (mg/dL)	9.3	1.4	9.6	1.2	NS
Phosphorus (mg/dL)	5.8	1.4	5.9	1.7	NS
Albumin (g/dL)	3.63	0.29	3.81	0.27	NS
Urea reduction ratio	58.5	8.5	63.6	4.2	NS

Abbreviations: PSG, polysomnogram; NS, not significant; REM, rapid eye movement.
*Number of apneas per hour of sleep.

be estimated as the total number of deaths divided by the total accrued population-time expressed in, for example, person-months. It differs from mortality risk in that it is inherently a population-level description of mortality risk rather than a patient-level measure. The computational advantage of incidence risk in contrast to mortality risk is that patients need not be followed up for equal lengths of time. Moreover, patient-level risks (ie, probabilities) for particular time intervals of interest (eg, 2-year survival) may be derived by computation of cumulative incidence.

The IDR is simply the ratio of two incidence densities. The IDR was used to compare mortality rates between groups of patients (eg, high versus low PLMSI or APLMSI rates). For example, a value of 2.0 means that the mortality rate in one group of patients is two times as large as the other. Adjusted IDRs were computed from proportional hazards regression models using exact estimation methods. The statistical precision of IDR estimates was determined using confidence intervals. Cox proportional hazards regression models were used to determine whether controlling for other clinical variables (Table 2) significantly affected estimates of the mortality rates. Multivariable models were restricted to one grouping factor and one potential confounding variable at a time in light of the small sample size.

To eliminate bias resulting from post hoc group definitions, categories of variables were defined without regard to survival outcome, using cumulative distribution functions. For example, in the definition of categories of PLMSI, data were plotted in a PLMSI cumulative distribution graph. Based on the distribution curve, three categories of patients were determined: those with PLMSI values less than 20 (group I), PLMSI values of 20 or greater but less than 80 (group II), and PLMSI values of 80 or greater (group III). Before assessing group differences in mortality, these groups were compared using one-way analysis of variance for interval variables and chi-square or generalized Fisher's exact tests for categorical variables to identify the most important potential confounders.[31]

Two patients underwent kidney transplantation before 14 months of follow-up. These patients were treated as censored at the time of transplantation in the survival analyses but excluded in the descriptive comparison between deceased and surviving groups.

Survival analyses. The primary null hypothesis tested with Kaplan-Meier analysis was that survival curves for patients with PLMS rates less than 20, 20 or greater but less than 80, and 80 or greater per hour were equal. Testing of this hypothesis was performed using an exact log-rank

Table 2. Patient Characteristics by PLMI Group

	PLMSI						Group Comparison*	
	≥80/h (n = 7)		20-<80/h (n = 9)		<20/h (n = 13)			
Variable	Mean	SD	Mean	SD	Mean	SD	F	*P*
Age (y)	66.7	9.3	54.5	11.1	57.1	14.0	2.2	0.144
RDI (events/h)	42.8	33.9	38.8	57.1	52.7	35.9	0.3	0.758
Mean sat (%)	90.1	3.2	92.5	0.5	90.9	3.0	1.6	0.213
Dialysis (mo)	53.0	31.5	37.2	25.5	23.3	15.5	3.2	0.057
URR	65.0	5.6	57.6	7.5	59.6	7.1	1.9	0.184
Albumin	3.52	0.23	3.90	0.36	3.60	0.34	2.5	0.119

Abbreviation: RDI, respiratory disturbance index; Sat, oxygen saturation.
*F tests from one-way analysis of variance for interval.

statistic (StatExact).[32] The exact log-rank test is a widely cited technique valid in small samples that are based on exact conditional distributions. It represents an alternative approach to those techniques relying on maximizing the unconditional likelihood function for parameter estimation that usually require large samples for justification of their validity.[32] Exact log-rank is increasingly recognized as a method of choice for dealing with small sample inference in the analysis of clinical trial data.[33] Survival curves for patients with PLMSIs less than 20 and greater than 20 were also constructed and compared with exact log-rank tests. Survival curves for APLMSI groups of less than 20, 20 to 40, and greater than 40 were also constructed and tested in a similar manner.

To rule out substantial confounding, Cox regression models were estimated that included the PLMS or APLMS factors and one potential covariate at a time. We sought to show that the difference between unadjusted and adjusted mortality ratios did not differ by a clinically significant amount, thus ruling out substantial confounding. If control for a variable results in no substantial parameter estimate change, confounding is not regarded as a major problem (Table 3).[34,35]

RESULTS

Of the 29 patients studied, 10 died within 14 months of initial polysomnographic testing. Me-

Table 3. Cox Regression Analysis of Mortality Rates

	Adjusted Rate Ratio for PLMSI				PLMSI *P* From Cox Regression After Adjustment for Covariate (χ^2 with *df* = 2)
	≥80/h *v* <20/h		20-<80/h *v* <20/h		
Variable	IDR*	95% CI	IDR*	95% CI	
PLM (unadjusted)	25.5	3.0-215.7	4.3	0.5-41.7	0.002†
Age (decade)	59.9	4.2-846.4	4.7	0.5-45.5	0.007
RDI	24.7	2.8-216.7	3.2	0.3-35.5	0.009
Mean sat (%)	30.1	3.2-281.7	3.0	0.3-34.3	0.004
Years of dialysis	26.6	2.7-266.2	4.1	0.4-40.5	0.006
BUN	26.2	3.1-221.8	4.4	0.5-42.7	0.002
MCV	113.8	8.7-1,496	3.7	0.3-34.1	0.0008
Calcium	29.2	3.4-253.1	3.4	0.3-34.2	0.002
Glucose	27.7	3.3-235.3	5.7	0.6-64.4	0.003
Phosphorus	26.8	3.1-232.7	2.7	0.2-31.0	0.002
URR	59.5	4.1-872.1	6.4	0.6-64.4	0.007
Albumin	24.2	2.8-212.8	4.7	0.5-45.9	0.007
Male	29.0	3.3-253.0	3.8	0.4-36.8	0.002
White	26.9	3.1-232.7	4.5	0.5-44.2	0.002
Coronary artery	41.1	4.0-421.1	4.6	0.4-53.1	0.002
Diabetes	16.0	1.7-147.9	10.8	0.7-178.3	0.049

Abbreviations: RDI, respiratory disturbance index; PLMSI, periodic leg movements in sleep index; MCV, mean corpuscular volume.
*Incidence density ratio.
†Unadjusted Wald chi-squared test (*df* = 2) from Cox regression.

dian survival time of patients in the deceased group was 10.3 months (range, 3 to 14 months) compared with 25.5 months (range, 15 to 48 months) in the surviving group. Nine of 29 subjects had no PLMS. Eight of these 9 subjects were survivors. The one patient with no PLMS who died had severe sleep apnea with 99 apneas and/or hypopneas per hour of sleep. Virtually all deaths were attributed to arteriosclerotic-, cardiovascular-, or infection-related events. Unexplained sudden deaths were diagnosed as cardiovascular by assumption. Arteriosclerotic cardiovascular disease was twice as common as infection and/or sepsis diagnoses as causes of death.

Table 1 lists the results of comparisons between means of variables in deceased and surviving groups with independent *t*-test results. All patients had clinically significant sleep apnea, PLMS, or both. Differences in means were statistically significant for PLMSI (119.1 versus 19.8; $P = 0.01$), APLMSI (48.1 versus 7.8; $P = 0.00006$), and total arousals per hour of sleep (93.2 versus 52.7; $P = 0.01$). Arousals consisted of brief periods of electroencephalography-defined wakefulness lasting less than 15 seconds but more than 2 seconds.

In both groups, these occurred almost exclusively after sleep-disordered breathing and/or APLMS. Because sleep apnea was equally high in each group, the increased number of arousals in the deceased group was secondary to increased APLMS. Sleep apnea occurred frequently in both the deceased and survivor groups. However, there were no significant differences in the respiratory disturbance index or low Sa_{O_2} values between the two groups. Compared with the survivor group, there was a trend for increased stage 1 sleep and decreased sleep efficiency (both indicative of more fragmented sleep) in the deceased group. The deceased group also showed a trend for less time in bed and less total sleep time.

Among non–sleep-based variables, hematocrit showed a trend toward lower values in the deceased group (29.9% versus 33.4%; $P = 0.06$). URR, serum albumin level, and comorbidity were not different between groups. Note that URR values listed in Table 1 are less than those targeted currently because patients in this study underwent polysomnography from 1990 to 1993. Values in the longer term survivors tended to drift up over time because of changes in acceptable target URRs.

The Kaplan-Meier survival curves related to the primary hypothesis test are shown in Fig 1. The exact log-rank statistic rejected the null hypothesis of equivalency in survival distributions between patients with a PLMSI less than 20 versus a PLMSI between 20 and 79 versus a PLMSI of 80 or greater at $P < 0.00001$. For patients with a PLMSI greater than 80 (group III), the estimated median survival time was 6 months (95% confidence interval, 4 to 20).

Controlling for the effects of albumin level, hematocrit, and duration of dialysis (months) still resulted in large IDRs for PLMSI, but these reduced the size of the unadjusted values by one half or less. Despite the reduction in size of the statistical effect, controlling for the effects of hematocrit, albumin level, and duration of dialysis by Cox regression did not result in loss of statistical significance of PLMSI or APLMSI as independent predictors of survival time. Clinically significant differences in mortality continued to exist after controlling for potential confounding from these variables. However, these findings suggest that the greatest PLMSIs are more likely to be found in patients with the lowest hematocrit and albumin values. Cox re-

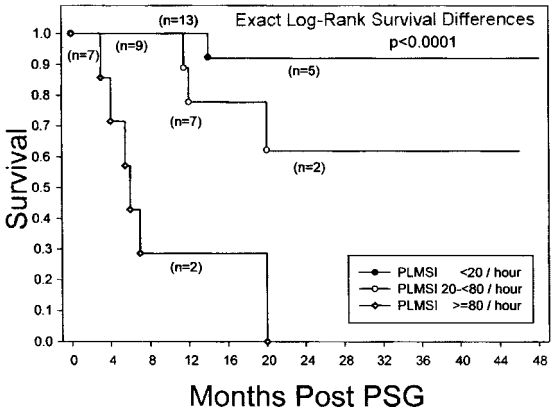

Fig 1. Kaplan-Meier survival curves comparing patients with PLMSI of 80 or greater (n = 7) versus 20 to less than 80 (n = 9) versus less than 20 (n = 13) per hour. The unadjusted differences among the survival curves were significantly different (exact log-rank test, $P < 0.0001$). Differences remained significant controlling for group differences in mean length of time undergoing dialysis, age RDI, URR, albumin, sex, coronary artery disease, and diabetes. Abbreviation: PSG, polysomnography.

gression–adjusted mortality ratios were estimated for other potentially confounding clinical, biochemical, dialytic, and sleep-related factors as well. No appreciable effects on mortality IDRs or *P* of the PLMSI predicting survival time were found.

Survival curves for patients grouped by PLMSIs less than 20 and greater than 20 were also found to be significantly different by exact log-rank test ($P = 0.007$). The 20-month survival rate for patients in the group with PLMSI greater than 20 was 50%, whereas the group with PLMSI less than 20 showed a 20-month survival rate of 90% (Fig 2). Survival curves for APLMSI less than 10 and 10 to 40 were found to be significantly different from the survival curve for APLMSI greater than 80 (Fig 3).

A limited number of Spearman correlations were also performed to better understand the relationship between duration of dialysis and other variables. Duration of dialysis was correlated only with PLMSI ($r = 0.42$; $P < 0.02$) and APLMSI ($r = 0.44$; $P < 0.01$). Duration of dialysis was not correlated with a measure of sleep. PLMSI and APLMSI were also correlated with hematocrit (PLMSI, $r = -0.36$; $P < 0.05$ and APLMSI, $r = -0.36$; $P < 0.05$).

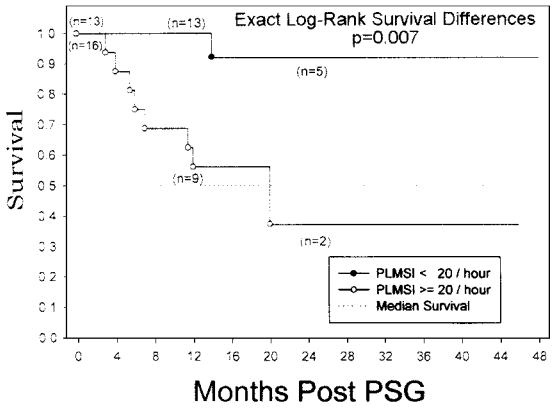

Fig 2. Kaplan-Meier survival curves comparing patients with PLMSI of 20 or greater per hour (n = 16) versus patients with PLMSI less than 20 per hour (n = 13). The unadjusted difference in survival was statistically significant (exact log-rank test, *P* = 0.007). Differences remained significant controlling for group differences in mean length of time undergoing dialysis, age RDI, URR, albumin, sex, coronary artery disease, and diabetes. Abbreviation: PSG, polysomnography.

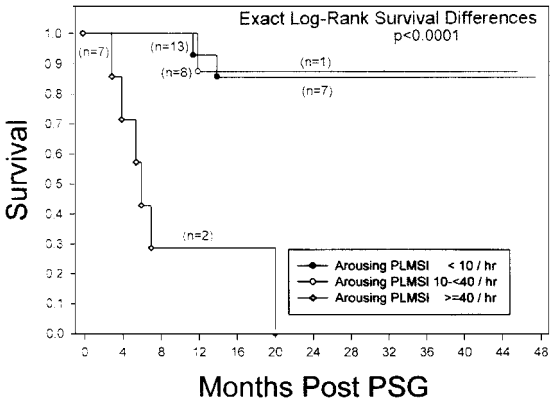

Fig 3. Kaplan-Meier survival curves comparing patients with an APLMSI of 40 or greater (n = 7), 10 to less than 40 (n = 8), and less than 10 (n = 14) per hour of sleep. The unadjusted differences among survival curves were statistically significant (exact log-rank test, *P* < 0.0001). Differences remained significant controlling for group differences in mean length of time undergoing dialysis, age RDI, URR, albumin, sex, coronary artery disease, and diabetes. Abbreviation: PSG, polysomnography.

DISCUSSION

This report presents evidence for potentially new predictors of mortality in patients with ESRD who report problems with sleep and daytime alertness. All statistical procedures performed found that in this group of patients with ESRD, only PLMSI, APLMSI, and total arousals per hour of sleep differed significantly between surviving and deceased groups and significantly predicted death. The Kaplan-Meier curves suggest that with greater numbers of PLMS, there is a greater risk for death within a shorter period of time. PLMSI greater than 20 or APLMSI greater than 40 predicted mortality. When all patients were divided into two groups by PLMSI less than or more than 20, the 20-month survival rate was 50% for those with a PLMSI of 20 or greater versus greater than 90% survival for those with a PLMSI less than 20 ($P = 0.0008$; Fig 2). APLMSI was six times greater in the deceased than survivor group ($P = 0.00006$).

More thoroughly researched risk factors, such as URR, albumin level, and hematocrit, were not found to be independent predictors of mortality in this relatively small, select group of patients. Controlling for their effects in the estimation of relative mortality rates in the PLMSI and APLMSI categories reduced the size of the overall effect of PLMSI and APLMSI, but did not

prevent them from reaching statistical significance. The reduction in the size of the statistical effect, however, suggests that the relationship between PLMSI and APLMSI with other established risk factors, such as serum albumin level, URR, and hematocrit, as well as duration of dialysis (months), may be more complicated than is evident in this study. High numbers of PLMS may reflect dialytic inadequacy or persistence of an abnormal uremic milieu, including anemia. Correction of anemia in such patients has been reported to reduce PLMS and APLMS by approximately one half.[36] PLMS may be secondary to or act as a marker of cerebral and/or peripheral dysfunction in patients with ESRD induced by other, perhaps multiple, pathological processes present in renal failure or secondary to dialysis. This hypothesis is lent support by reports that successful renal transplantation markedly improves ESRD-related sleep disorders, including PLMS.[24,25]

An alternate hypothesis of the relationship between PLMS and mortality in this population considers the possible effects of chronic, severe sleep fragmentation and sleep deprivation. Sleep was severely disrupted, particularly in the deceased group. Total arousals from sleep were significantly greater than in the deceased group. Chronic sleep fragmentation has a variety of well-described consequences, including the cardiovascular sequelae of circadian disruption and loss of nocturnal dipping of blood pressure, resulting in increased hypertensive burden and left ventricular hypertrophy.[37-39] Sleep deprivation has also been implicated as a source of impaired immune function.[40-42] The trend for patients with increased duration of dialysis (months) to have a greater PLMSI (and consequently greater mortality risk) could represent longer exposure of those patients to the effects of chronic sleep disruption.

Further support for the relationship between PLMS, APLMS, and mortality can be found in the recent report that restless legs syndrome (RLS) is associated with increased mortality in a population similar to that described here.[43] RLS and PLMS are hypothesized to have similar causes and respond to treatment with similar medication. A primary report of RLS is associated with a finding of PLMS in 80% of patients in the general population.[44] However, PLMS may occur in the absence of RLS in the general population. Coleman et al[29] noted a primary finding of RLS in only 8 of 53 patients with a primary diagnosis of PLMS. In our own clinical practice, only 2% of all patients with a primary diagnosis of PLMS also report severe RLS (Benz and Pressman, unpublished data). Thus, PLMS may occur independently of RLS and result from factors independent of RLS. Additionally, RLS is characterized by subjective sensations primarily in the lower limbs that occur during wakefulness before sleep and are inferred to be present by history alone. RLS severity, therefore, cannot be quantified in the same objective manner as PLMS.

An initial working hypothesis for this study was that sleep apnea was likely to be the main risk factor for mortality in this group. Obstructive sleep apnea is reported to be associated with increased morbidity and mortality in the general population.[20,21] The failure of sleep apnea in patients with ESRD to predict mortality may be explained by several factors.

First, sleep apnea of ESRD is often reported to be of the rarer central type, not the obstructive type found in patients previously reported to have increased morbidity and mortality. Kimmel et al[16] reported that 7 of 26 patients with ESRD studied had predominantly central sleep apnea, and Mendelson et al[26] found that 5 of 11 dialysis patients had between 53% and 90% central apneas. Central sleep apnea is not related to obesity and is often associated with less nocturnal hypoxemia.[45] Thus, the effect of obesity-related obstructive sleep apnea on mortality in the general population may not necessarily be extrapolated to patients with ESRD.

Second, sleep apnea may require a much longer time before increased mortality becomes evident. He et al[20] reported that statistically significant increased mortality in sleep apnea patients in the same age range as our patients was not evident for at least 7 years after the initial sleep study. Thus, sleep apnea may not be a significant risk factor for mortality in the majority of patients with ESRD. Longer studies or larger sample sizes may be needed to correctly assess the impact of sleep apnea on patients with ESRD.

One potential limitation of this study is that patients were not randomly selected. Rather, all had reported problems regarding sleep or daytime sleepiness and all had been referred to a sleep disorder center for evaluation. A majority

of surveyed patients with ESRD have complaints about their sleep, and asymptomatic patients have been noted to have PLMS without their knowledge.[9,10,12,13] However, a definitive study of the incidence of sleep disorders in a large random sample of patients with ESRD has not been published. This leaves open the question of precisely how common sleep disorders are in this population.

Mortality rates for patients with ESRD remain unacceptably high. This appears to be especially true for dialysis patients in the United States whose survival time is less than that of many other technologically advanced countries.[46] Efforts to reduce the mortality rate have been the subject of numerous publications, consensus panels, and multicenter studies, including the National Institutes of Health HEMO Study. Total fiscal Medicare, state, and private-payer budgets for the ESRD population now exceed $13 billion annually, stimulating demand for improved outcome.[1] Barrett et al[3] recently concluded that predictors of short survival time in ESRD have largely proven inadequate. Determining predictors of mortality is the first step in ultimately understanding inadequacy of therapy and focusing on beneficial interventions. PLMSI and APLMSI, as well as the total number of arousals per hour of sleep, represent potential novel predictors of mortality in patients with ESRD. Further study is indicated to delineate the relationships between chronic renal failure, sleep disorders, and mortality to improve the long-term outcome of this high-risk population.

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