Survival by Time of Day of Hemodialysis in an Elderly Cohort

Donald L. Bliwise, PhD
Nancy G. Kutner, PhD
Rebecca Zhang, MS
Kathy P. Parker, PhD, RN

Context Patients with end-stage renal disease (ESRD) typically undergo hemodialysis (HD) during the morning or afternoon, with time of treatment generally based on space availability or patient preference. No studies have investigated variation in patient survival as a function of the time of day when they receive dialysis.

Objective To investigate the association of elderly patients’ HD treatment shift with their continued survival, controlling for well-established HD-related mortality risk factors.

Design, Setting, and Participants An 11-year follow-up cohort study conducted among 242 ESRD patients aged 60 years or older who underwent HD at 58 dialysis facilities in Georgia either during a morning shift (n = 167) or an afternoon shift (n = 75) and who completed baseline (1998) and follow-up (1991) interviews.

Main Outcome Measure Mortality from all causes occurring through July 7, 1999, as verified by death-certificate reviews, and compared by morning- vs afternoon-shift HD.

Results Morning-shift HD patients survived significantly longer than afternoonshift patients (median survival, 941 days vs 470 days; P < .001). A Cox proportional hazards model indicated that the morning shift was protective (relative risk, 0.71; 95% confidence interval, 0.53-0.95) independent of age, race, sex, body mass index, functional status, diabetic ESRD, cardiovascular comorbidity, weekly hours of dialysis, and months of dialysis.

Conclusions Possible explanations for differential survival in association with morning- vs afternoon dialysis include salutary effects of sleep in the morning or less efficient biochemical exchange during afternoon dialysis. Results from this cohort study may warrant prospective observational studies and randomized clinical trials that systematically alter the time of day at which HD is administered.

JAMA. 2001;286:2690-2694 www.jama.com

©2001 American Medical Association. All rights reserved.
hort, 3 patients who underwent home HD, 42 who underwent peritoneal dialysis, and 1 who recovered renal function were ineligible for this analysis. Thus, we did not use an intent-to-treat analysis. Of the remaining 303 patients treated by in-center HD, 24 could not be included in this analysis because their dialysis shift changed after the study began, 4 could not be included because insufficient information was available about their dialysis shift times at baseline or follow-up, and 33 could not be included because of missing data on other variables included in the multivariable analyses. Thus, 242 patients were available for inclusion in this analysis. Two of these patients (morning shift) experienced failed transplants and did not receive dialysis for only a few days.

Determination of Dialysis Shift and Medical History

Time of day for HD was recorded at baseline (1988) and follow-up (1991) patient interviews. Patients whose in-center HD was initiated between 6:00 and 11:00 AM were considered to have undergone morning dialysis (n = 167). Patients whose in-center dialysis was initiated between 11:30 AM and 4:00 PM were considered to have undergone afternoon dialysis (n = 75). The HD patients included and excluded in the shift analyses reported here did not have different demographic or health-status characteristics, except that included patients were more likely to be male. Between included and excluded patients, there was no significant difference in poststudy survival or months of dialysis before study entry.

A comprehensive interview and a review of medical records were conducted for all patients at the beginning of the study and for patients participating in the 3-year follow-up. Characteristics of HD (months of dialysis before study entry and number of hours of dialysis per week) were confirmed by the dialysis facility, as was history of diabetes mellitus as a primary cause of ESRD. Cardiovascular disease was defined as a history of myocardial infarct, stroke, and treated or untreated hypertension. Body mass index (BMI; computed as weight in kilograms divided by height in meters squared) and serum albumin levels were also recorded. For further analyses, BMI was dichotomized at more than 23 kg/m² vs less than 23 kg/m², according to the median of the study population. Months of dialysis before study entry and hours of dialysis per week were dichotomized at the median of the distribution for each (36 months and 10.5 hours, respectively). Functional status was assessed on the basis of interview questions determining to what extent patients were capable of simple activities (eg, climbing stairs or walking around the block) and sedentary during the daytime. Functional impairment was classified according to Guttman scaling as most severe, moderately severe, least severe, or none. Patients’ vital status was monitored from the baseline interview in 1988 (beginning of the study) to July 7, 1999. Death certificates were obtained to determine causes of death.

Data Analyses

The primary analysis used in this study was the Cox proportional hazards model, in which continued survival in days after the beginning of the study was modeled by using a variety of demographic and health predictors. Two patients who received successful transplants were censored at the date of transplant, and the only patient who survived was censored as of the study’s ending date, July 7, 1999. Binary variables were coded 1 for age at least 70 years, male sex, black race, BMI more than 23 kg/m², HD for at least 36 months, HD at least 10.5 hours weekly, higher functional status (ie, least severe or no functional impairment), diabetes as the primary cause of ESRD, and the presence of cardiovascular comorbidity. Referent categories were coded 0 for younger age, female sex, white race, lower BMI, fewer months of HD, fewer hours of HD each week, lower functional status, absence of diabetes as the cause of ESRD, and absence of cardiovascular comorbidity. Because our previous work indicated that race, sex, and BMI had a significant interaction effect on survival (ie, higher BMI was protective in black men and women and in white men), a 2- and 3-way interaction terms for these variables were included in the model. The effect of dialysis shift was examined by using afternoon shift as the referent category. Examination of proportionality assumptions in the Cox model indicated no significant time × risk factor interactions for any variable in the model. Data were analyzed by using SAS Version 8 (SAS Institute, Cary, NC).

RESULTS

Demographic and medical characteristics of the 242 patients as a function of shift are shown in Table 1. On average, HD patients who underwent morning dialysis survived more than a year longer than patients who underwent afternoon dialysis (Figure). Patients who were dialyzed in the morning were more likely to be black and have higher BMI, but there were no other statistically significant differences between the 2 groups.

According to the Cox regression model, univariate tests of association with patients’ continued survival in days after the beginning of the study are summarized in Table 2. Black race, higher BMI, absence of cardiovascular comorbidity, higher functional status, and morning dialysis shift were significantly associated with HD patients’ continued survival (all P < .05).

Table 2 presents the results of the multivariable Cox model predicting survival as related to demographic and health variables, as well as time of day of dialysis. As we have reported elsewhere, the interaction of race, sex, and BMI affects survival in this population. Higher functional status also predicted patients’ continued survival. Additionally, consistent with the data shown in Tables 1 and 2, the protective effect for patients’ survival of the morning shift was sustained in this multivariable model. Analysis of death certificates indicated no differences be-
Survival by Time of Day of Hemodialysis in an Elderly Cohort

tween morning- and afternoon-shift patients for any cause of death including cardiovascular (eg, cardiac arrest or cerebrovascular accident; 55% vs 47%), infectious (eg, sepsis or pneumonia; 13% vs 17%), or other causes (eg, malignancy, hyperkalemia, or elective withdrawal from dialysis; 32% vs 36%; \( P = .47 \)). Review of death certificates indicated that only 3 patients voluntarily withdrew from HD treatment; all 3 were treated on a morning shift.

Usual weight gain between dialysis treatments was examined as an indicator of compliance with dialysis regimen.\(^9\) Between morning- and afternoon-shift patients, there was no significant difference in interdialytic weight gain (mean [SD] gain, 2.06 [1.06] kg vs 1.97 [1.02] kg, respectively; \( P = .81 \)). Analysis of changing comorbidities for individuals surviving to the 3-year follow-up and reinterviewed indicated that, although patients at follow-up had lower functional status, lower BMI, and greater cardiovascular comorbidity, these patterns occurred equally for morning- and afternoon-shift patients. There was also no significant difference in hours of weekly dialysis throughout the 3 years for individuals dialyzed in the morning vs the afternoon.

Both morning- and afternoon-shift patients showed a trend for decreased albumin levels throughout the 3 years preceding follow-up (0.11 g/dL vs 0.70 g/dL, respectively), but the extent of this decrease did not significantly differentiate patients in the 2 shifts (\( P = .19 \)).

**COMMENT**

The risk factors we examined did not account for the higher survival rate of elderly ESRD patients undergoing HD who were dialyzed during the morning. There may be other selection factors that lead ESRD patients to be assigned to or to select morning shift, but they remain unidentified.

If the time of day of dialysis significantly affects survival, some speculation regarding putative mechanisms that underlie the effect may not be premature. For example, biochemical clearance may be optimized during morning-shift HD. In a group of 124 patients representing 4 shifts, Mattana et al\(^11\) reported that HD patients who were dialyzed late in the day had relatively higher levels of potassium and phosphorus than those undergoing HD earlier in the day, implying less effective dialysis, perhaps owing to interaction with the evening meal. Although we did not have our population’s laboratory data on hyperkalemia or hyperphosphatemia and therefore were unable to test this hypothesis, the possibility exists that some impairment of biochemical clearance might have hastened mortality in patients being dialyzed in the afternoon shift.

Optimization of medical interventions by introduction of treatments at

---

**Table 1.** Patient Demographic, Treatment, and Health Status Characteristics by Hemodialysis (HD) Treatment Shift

<table>
<thead>
<tr>
<th></th>
<th>Morning Shift (n = 167)</th>
<th>Afternoon Shift (n = 75)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) survival, d‡</td>
<td>941 (360-1806)</td>
<td>470 (190-1021)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median months receiving HD before entering study</td>
<td>36</td>
<td>34</td>
<td>.79</td>
</tr>
<tr>
<td>Functional status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unimpaired</td>
<td>13</td>
<td>7</td>
<td>.22</td>
</tr>
<tr>
<td>Least impaired</td>
<td>11</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>31</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Severely impaired</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Median dialysis, h/wk</td>
<td>10.5</td>
<td>10.5</td>
<td>.26</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.9 (5.4)</td>
<td>69.1 (6.0)</td>
<td>.17</td>
</tr>
<tr>
<td>Black, %</td>
<td>65.3</td>
<td>41.3</td>
<td>.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>52.7</td>
<td>50.7</td>
<td>.77</td>
</tr>
<tr>
<td>BMI &gt;23 kg/m(^2), %</td>
<td>57.5</td>
<td>55.7</td>
<td>.004</td>
</tr>
<tr>
<td>Serum albumin, mean (SD), g/dL§</td>
<td>3.8 (0.5)</td>
<td>3.9 (0.8)</td>
<td>.88</td>
</tr>
<tr>
<td>Diabetic ESRD, %</td>
<td>29.3</td>
<td>25.3</td>
<td>.52</td>
</tr>
<tr>
<td>Cardiovascular comorbidity, %</td>
<td>46.7</td>
<td>50.7</td>
<td>.57</td>
</tr>
</tbody>
</table>

*‡*IQR indicates interquartile range; BMI, body mass index; and ESRD, end-stage renal disease. \( P \) values reflect Wilcoxon test and \( \chi^2 \) test probabilities for continuous and categorical variables, respectively.

†Three patients were censored: 2 at the date of receipt of transplant (both morning shift) and 1 still alive at the end of study observation period (July 7, 1999; morning shift).

§Serum albumin data obtained for a subset of the study group (\( n = 135 \)).

---

**Figure.** Kaplan-Meier Survival Curves for Elderly Patients Undergoing Dialysis During Morning and Afternoon Shift

Median survival was 941 days on morning shift (interquartile range, 360-1806) and 470 days on afternoon shift (interquartile range, 190-1021). The log-rank \( P = .002 \).
specific times of day is not without precedent. For example, nocturnal administration of calcitriol reduced dialysis patients’ risk of hypercalcemia.13 Perhaps the most dramatic examples of temporal optimization of treatment are from chemotherapy.14,15 In metastatic colorectal carcinoma, for example, antitumor activity was maximized and adverse effects minimized by the administration of 5-fluorouracil and leucovorin during the early morning.16 Similar time-of-day susceptibility to best chemotherapeutic response has been noted for renal cell carcinoma.17 Although the mechanisms underlying these chemotherapeutic observations are undoubtedly different from those observed in our study, these results suggest that simple manipulations of when treatments are instituted profoundly affect health, which assumes increasing importance as more frequent and longer dialysis treatment is more widely implemented.18

Sleep during HD, which is common, may also contribute to the continued survival of patients treated in the morning. Individuals undergoing HD in the morning are sleepier than those being dialyzed at other times of day,19 and the notion that sleep is vital for health and that loss of sleep hastens morbidity and mortality has been borne out amply by numerous epidemiologic human studies and experimental animal studies. For example, studies from well-defined populations suggest that chronic short sleep may be a harbinger for all causes of mortality.20,21 In experimentally sleep-deprived animals, sleep loss has been associated with compromised thermoregulatory, immunologic, and, perhaps most relevant for the current discussion, protein metabolic functions.22,23 Data such as these imply that sleep during morning dialysis may represent a beneficial compensatory response to sleep loss imposed by early waking times. This explanation assumes differences in the quantity or quality of intradialytic sleep as a function of the time of day. This hypothesis remains to be verified polysomnographically.

As a final caveat, our data indicating apparently protective effects of morning dialysis were seen in an elderly cohort. Whether younger patients undergoing HD would derive similar benefit remains unclear. For example, age-dependent sleep pattern changes that occur in elderly individuals might predispose them to the early-morning arising required for morning dialysis, and their increased tendency to nap might also enhance the likelihood of their sleeping during the procedure.24,25 To test this hypothesis, studies examining the differential effect of HD shift in younger populations would be required, and polysomnographic studies18 documenting the amount and quality of sleep occurring on various shifts would also be necessary. Randomized clinical trials may be required to determine definitively whether morning shift is protective for any age group. In the interim, further observational studies using larger databases such as the United States Renal Data System should investigate whether dialysis shift, independent of cumulative hours of weekly dialysis or duration of dialysis treatment,26 significantly affects dialysis outcomes, including patients’ survival.

### Author Contributions

Study concept and design: Bliwise, Kutner, Parker.
Analysis and interpretation of data: Bliwise, Kutner, Zhang, Parker.
Drafting of the manuscript: Bliwise, Kutner.
Critical revision of the manuscript for important intellectual content: Bliwise, Kutner, Zhang, Parker.
Statistical expertise: Zhang.
Obtained funding: Kutner.
Administrative, technical, or material support: Kutner.
Study supervision: Kutner.

### Funding/Support

This study was supported by National Institutes of Health grants AG05909 (Dr Kutner), DK42949 (Dr Kutner), AG10643 (Dr Bliwise), AG06066 (Dr Bliwise), NS53545 (Dr Bliwise), and NR04340 (Dr Parker).

### Acknowledgment

Tess Bowles, MEd, assisted with the data preparation and Laura-Beth Straight, MDiv, assisted with word processing.
REFERENCES


Soundness of understanding is connected with freedom of enquiry; consequently, opinion should, as far as public security will admit, be exempted from restraint.

—William Goodwin (1756-1836)


