Predictors of Mortality in Hemodialysis Patients

Philip Goldwasser, Neal Mittman, Antoinette Antignani, Donna Burrell, Marie-Alex Michel, James Collier, and Morrell M. Avram

ABSTRACT

Serum biochemical measures suggestive of undernutrition have been reported to correlate with 1-yr mortality risk in prevalent groups of hemodialysis patients. The predictive power of these variables has not been reported in newly diagnosed patients or in patients whose dialysis prescription is guided by urea kinetics. The relationship of these predictors to mortality over periods of longer than 1 yr is also unreported. Therefore, the survival of 184 hemodialysis patients was examined for up to 44 months (1987 to 1991) with the Cox proportional hazards model. Baseline demographic, clinical, and biochemical parameters were used as independent variables. To adjust for bias in patient selection, the survival of patients with 12 months or less of prior dialysis at the time of enrollment ("new cases") was analyzed separately from that of patients with more than 1 yr of prior treatment ("long-standing cases"). Serum albumin was less than 3.5 g/dL in 31% of new cases and in 12% of long-standing cases. Adjusting for the other variables, low serum albumin was the strongest mortality risk predictor in both new and long-standing groups. Low serum cholesterol was an independent risk predictor in both groups. Diabetes and race were not significant predictors. Mean age at enrollment was nearly a decade higher for nonsurvivors than for survivors, in both new and long-standing groups. Yet, age was not an independent risk predictor in the Cox model for the new group because of an unexpectedly high death rate among young black men. Female gender, which was contounded by increased age, took the place of age in the model for the new group. For each model, there was good agreement between observed and predicted mortality for up to 24 months. To assess the influence of dialysis treatment time and dose (measured as pre-to-post treatment urea ratio) on risk, survival was examined in a subset of 139 patients monitored for up to 22 months, from 1989 to 1991, a period when the urea ratio was used routinely. Adjusting for the other variables, low serum albumin and cholesterol again independently increased risk. The urea ratio was also a significant independent predictor. The pattern of mortality by urea ratio was U shaped, with minimum risk for values between 2.5 and 3.4. Treatment time did not influence risk. It was concluded that baseline serum values of albumin and cholesterol strongly influence survival for up to 2 yr in new and long-standing hemodialysis patients. Because albumin and cholesterol are indices of visceral protein status, these findings suggest that visceral protein depletion is a major risk factor for mortality in hemodialysis patients, even when they are adequately dialyzed.

Key Words: Survival, ESRD, undernutrition, serum albumin, serum cholesterol, short hemodialysis

Despite the improvements in dialysis technology over the past decade, mortality in the ESRD population is high and has been rising (1-3). The increase in the prevalence of comorbid conditions as the result of changing patient selection does not adequately explain this trend (4,5). Although cardiovascular disease remains the most important cause of mortality in ESRD (6-12), recent studies have shown that atherosclerosis is not accelerated by ESRD (7-10,13,14). Furthermore, the lipid disturbances of dialysis patients bear either an inconsistent or no relationship to their vascular disease (14-17). Thus, new predictors of mortality risk in dialysis patients have been sought.

The National Cooperative Dialysis Study (NCDS) focused attention on the relationship between clinical outcome and urea kinetics, a mathematical approach that can be used to quantify both dialysis dose and protein intake (18). The NCDS demonstrated reduced morbidity in patients randomized to receive high urea clearances (i.e., treatments designed to maintain low BUN levels) in the context of adequate protein intake. In contrast, studies that examined
cases were examined separately. To determine the
enrolled into the study once a
quantify and guide dialysis prescription.

tum of demographic, clinical, and biochemical va-
the Cox proportional hazards model to determine the
independent relationship to mortality risk of a spec-
tations and, in particular, to newly diagnosed
Last, the influence of biochemical risk fac-
tors on survival for periods longer than 1 yr has not
been reported.

We compiled an extensive database from 1987 to
1991 in the course of performing a serial survey of
lipoproteins in dialysis patients (24). In a preliminary
analysis of the database, we reported that, compared
with survivors, nonsurvivors had lower mean baseline
values of cholesterol, apolipoprotein B, albumin,
and creatinine (25). We now extend this initial report
with an analysis of the survival of 184 HD patients
monitored for up to 44 months (1987 to 1991) using
the Cox proportional hazards model to determine the
independent relationship to mortality risk of a spec-
trum of demographic, clinical, and biochemical vari-
able, including apoproteins. To adjust for survivor
bias in patient selection, new and long-standing
cases were examined separately. To determine the
influence of dialysis dose and treatment time on
mortality risk, survival was analyzed in a subset of
139 patients monitored for up to 22 months (1989 to
1991), when urea kinetics was routinely used to
count and guide dialysis prescription.

METHODS

Patients

All hemodialysis outpatients at The Long Island
College Hospital were enrolled into the study once a
year as annual cohorts. One hundred ninety-eight
patients ultimately enrolled over a 3-yr period: 88 in
June 1987, 37 in April 1988, 48 in April 1989, and
25 in February 1990. Upon enrollment, clinical and
laboratory data were collected. Survivors of each an-
nual cohort were restudied annually at the same time
as new patients were enrolled. This resulted in mul-
tiple data for many patients. Survival was recorded
up to February 1, 1991. Fourteen patients who
switched between HD and continuous ambulatory
peritoneal dialysis (CAPD) were excluded from the
analysis.

Clinical Data

Clinical data included age, gender, race, etiology of
ESRD, duration of ESRD and total months on dia-
lysis, estimated dry weight, length of dialysis treat-
ment (hours), dialyzer membrane, dialysate, total
heparin dose, mean predialysis blood pressure (of
three consecutive treatments), diabetic status before
uremia, and medications. The racial composition of
the population was black (54.6%), white (29.5%), and
Hispanic (15.9%). There were 52.1% women. Thirty-
seven percent of the patients were diabetic. On study
entry, mean age was 58.5 ± 15.6 (SD) yr (range, 18
to 87) and mean prior months on dialysis was 35.7 ±
43.0 (range, 0 to 230). The causes of ESRD were:
hypertensive nephrosclerosis (36.4%), diabetes mel-
itus (31.5%), chronic glomerulonephritis (10.3%),
polycystic disease (6.5%), obstruction (3.3%), human
immunodeficiency virus-related (1.1%), miscella-
neous (7.6%), and unknown (3.3%).

Description of Dialysis Prescription

HD prescription was evolving during the 4-yr stud-
ed. In 1987, the population was treated with acetate
(85%) or bicarbonate (15%) dialysis on largely con-
ventional membranes (Table 1) with Cobe Centry 2
or Centry 2Rxn machines (Cobe, Lakewood, CO). In
1988, a small number of patients were being treated
with shorter, high-efficiency, or high-flux prescrip-
tions and 62% of the population received bicarbonate
dialysis. Beginning in 1989, all treatments were per-

<table>
<thead>
<tr>
<th>TABLE 1. Membranes prescribeda</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Membranes Prescribed</td>
</tr>
<tr>
<td>CUPRO SCE CA PAN HP</td>
</tr>
<tr>
<td>1987  59  23  4</td>
</tr>
<tr>
<td>1988  77  1  13  1</td>
</tr>
<tr>
<td>1989  35  34  56  1</td>
</tr>
<tr>
<td>1990  15  39  70  10</td>
</tr>
</tbody>
</table>

a Abbreviations: CUPRO, cuprophane; SCE, saponified cellulose; CA, cellulose acetate; PAN, polycrionitrile; HP, hemophane.
formed on Cobe Centrasytem 3 machines with bicarbonate bath and volumetric control of ultrafiltration, and dialysis prescription was guided, in part, by the goal of achieving a value of ≥2.5 for the ratio of pretreatment BUN to 5-min posttreatment BUN (26–28). The posttreatment BUN was drawn 5 min after treatment in order to minimize the problem of spuriously low post-BUN values that result from graft recirculation and from the disequilibrium between intracellular and extracellular fluid spaces. The majority of the patients were receiving erythropoietin therapy in 1990.

Biochemical Data
Upon enrollment, baseline blood work was drawn immediately before the first treatment of the week from the arteriovenous access. A multiphasic biochemistry screen was obtained for each patient with the SMAC autoanalyzer (Technicon, Tarrytown, NY). High-density lipoprotein cholesterol was measured on the DuPont ACA (DuPont, Wilmington, DE) by use of an assay from EM Diagnostic Systems (Gibbstown, NJ). Apoproteins A-I and B were measured by immunoturbidimetric assays (Isolab Inc., Akron, OH). Appropriate blanks were used to correct for turbidity in samples. Parathyroid hormone (PTH) was measured with the Allegro intact PTH assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Study Design
We examined patient survival using a proportional hazards model based on the data recorded on initial enrollment. Patients were classified as “new” cases if their time on dialysis before initial enrollment was 12 months or less; otherwise, they were considered to be “long-standing” cases. The patients were monitored for up to 44 months. Survival times of the new and long-standing groups were analyzed separately. The groups are described in Table 2.

In a separate analysis, we examined the survival of the subset of patients on whom data were collected in 1989 or 1990, when clinical dialysis prescription was routinely designed to achieve a pretreatment to posttreatment BUN ratio of 2.5 or more. There were 139 patients with complete data. This group included 62 patients who initially enrolled in April 1989 (N = 44) and February 1990 (N = 18), as well as 77 survivors from the cohorts that enrolled in 1987 (N = 48) and 1988 (N = 29). For the latter 77 patients, the biochemical data collected in April 1989 were used in this analysis.

Data Analysis
Survival was analyzed by use of the Cox proportional hazards model (29,30) with baseline age, race, gender, diabetes, duration of ESRD, BUN, creatinine, albumin, cholesterol, high density lipoprotein-cholesterol (HDL-C), apoproteins A-I and B, calcium, and PTH as independent variables. Treatment time and BUN ratio were also used as independent variables in the Cox analysis of the 1989 to 1991 subset. The variables chosen reflected our previous experience as well as reports in the literature. Variables were selected for the final models by a backward stepwise approach. The proportional hazard assumption was tested by plotting baseline hazards across strata. If the hazards were parallel among the strata, the variable was modeled as a covariate; otherwise, the analysis was stratified. The fit of the models was assessed by comparing predicted survival with that of the observed probabilities of survival for selected subgroups of patients. Observed survival was computed by the Kaplan-Meier method (31). Data presented include the regression coefficients, the relative risk ratios and their 95% confidence intervals (CI), and the actual P values for the risk ratios. The relative risk reflects the level of risk associated with a variable, assuming other factors are held constant. Albumin was treated as a categorical variable with clinically relevant breakdowns. Cholesterol was treated as either a continuous variable or a categorical variable. The BUN ratio was treated as a categorical variable.

For selected analyses, the unpaired t test, the χ² test, and Pearson's correlation coefficient (r) were used.

RESULTS
New Cases
The model for the new cases is presented in Table 3. Adjusting for the other variables in the model,
patients with a serum albumin below 3.5 g/dL were at a 3.5-fold increased mortality risk relative to patients with albumin values between 3.5 and 3.9 g/dL (P = 0.025) and at a nearly 10-fold risk relative to patients with serum albumin values of 4.0 g/dL or more (P = 0.004). Serum albumin was less than 3.5 g/dL in 31% of the new cases.

When modeled as a continuous variable, each reduction in baseline serum cholesterol of 1 mg/dL increased the risk of death by 1% (P < 0.06). Alternatively, when treated as a categorical variable, a cholesterol value below 120 mg/dL was associated with a fourfold increase in risk relative to values of 200 mg/dL or more (relative risk, 4.0; 95% CI, 0.96 to 16.67; P = 0.056). The low-cholesterol group was also at twofold greater risk compared with patients with values between 120 and 199 mg/dL, although this difference was not statistically significant (relative risk, 2.12; 95% CI, 0.60 to 7.69; P = 0.25).

In addition, serum calcium levels and patient gender were significant predictors (Table 3). Each 1-mg/dL increase in baseline serum calcium was associated with an 80% increase in mortality risk (P = 0.027). Women were at a fourfold increased risk compared with men (P < 0.04). Age did not appear in the model, although the mean age of nonsurvivors was almost 10 yr older than that of survivors (66.9 ± 13.5 versus 57.2 ± 15.4; P = 0.08). On further analysis, the explanation for the exclusion of age from the model was the occurrence of three deaths with a mean age of 35 among black men. When, for example, survival was examined using the white patients only, age was a highly significant mortality predictor. Additionally, the mean age of the women in the entire group was 10 yr older than that of the men (65.0 ± 12.7 versus 55.1 ± 17.3; P = 0.006). Thus, the higher risk associated with female gender indirectly reflects the influence of age on risk.

The fit of the model is shown in Figure 1. For patients with serum albumin below 3.5 g/dL, there was good agreement between the observed survival and that predicted by the model at 12 (50 versus 59%) and at 24 months (17 versus 21%). Similarly, for patients with albumin ≥3.5 g/dL, observed survival was in good agreement with predicted survival at 12 (86 versus 90%) and at 24 months (76 versus 73%).

Long-standing Cases

Table 4 shows the results of the proportional hazards model for the survival of 108 long-standing cases, with complete data monitored for up to 44 months. Low serum albumin was again the strongest mortality risk predictor. Increased age and decreased serum cholesterol were also significant predictors.

Serum albumin was less than 3.5 g/dL in approximately 12% of cases. Albumin values below 3.5 g/dL were associated with a sevenfold increase in risk compared with higher values (P = 0.001). There was little difference in risk between the 3.5 to 3.9 range and the ≥4.0 g/dL range for albumin. As a continuous variable, each reduction of 1 mg/dL in baseline serum cholesterol was associated with a nearly 1% increase in risk (P < 0.04). Alternatively, as a categorical variable, cholesterol values below 120 mg/dL were associated with a twofold to threefold increase in risk compared with values of 200 mg/dL or more (relative risk, 2.56; 95% CI, 0.99 to 6.67; P = 0.053). The mortality risk associated with the low-cholesterol group was similar to the risk of patients with values of 120 to 199 mg/dL (relative risk, 1.17; 95% CI, 0.48 to 2.44; P = 0.852).

Relative risk was increased by 4% per year for each additional year of age at the time of study entry (P = 0.001). Gender did not appear in the model. The mean age of women was, again, significantly higher than that of men (61.9 ± 13.7 versus 52.3 ± 15.8; P = 0.001). Diabetes increased risk by nearly 50%, but this was not statistically significant. Omitting diabetes from the model did not affect the coefficients of the other predictors in Table 4.

The fit of the model for long-standing patients is

**TABLE 3. Proportional hazards analysis of 67 new cases studied over 44 months**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>2.24</td>
<td>9.8 (2.04-46.57)</td>
<td>0.004</td>
</tr>
<tr>
<td>(vs 4.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>1.23</td>
<td>3.4 (1.16-10.09)</td>
<td>0.025</td>
</tr>
<tr>
<td>(vs 3.5-3.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Women (vs</td>
<td>1.38</td>
<td>4.0 (1.14-13.85)</td>
<td>0.031</td>
</tr>
<tr>
<td>White Men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Women (vs</td>
<td>1.53</td>
<td>4.6 (1.34-15.93)</td>
<td>0.016</td>
</tr>
<tr>
<td>White Men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>0.57</td>
<td>1.8 (1.07-2.94)</td>
<td>0.027</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>-0.01</td>
<td>0.99 (0.98-1.00)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Figure 1. Actual and predicted survival for new patients by serum albumin (alb) level (in grams per deciliter). obs, observed; pred, predicted.
shown in Figure 2. For patients with serum albumin below 3.5 g/dL, there was good agreement between observed and predicted survival at 12 (33 versus 40%) and at 24 months (8 versus 12%). Similarly, for patients with albumin ≥3.5 g/dL, observed survival was in good agreement with predicted survival at 12 (88 versus 88%) and at 24 months (71 versus 75%).

Dialysis Prescription and Mortality

The influence of treatment time and BUN ratio on survival, adjusting for baseline clinical, demographic, and biochemical data, was examined in 139 patients monitored for up to 22 months from 1989 to 1991, when the BUN ratio was routinely used clinically. The group is described in Table 5. The mean treatment time was 3 h, 8 min, with a range from 2 h to 4 h, 15 min (Table 6). The mean BUN ratio was 2.58, equivalent to a urea reduction of 61.2% per treatment. The BUN ratio correlated directly with treatment time (r = 0.30; P < 0.001) and age (r = 0.24; P < 0.005) and inversely with estimated dry weight (r = −0.52; P < 0.0001), but it was not correlated with serum albumin or cholesterol. On initial exploration, the pattern of mortality by BUN ratio appeared to be U shaped (Table 7). Consequently, the BUN ratio was treated as a categorical variable in the Cox analysis.

The proportional hazards model is shown in Table 8. The significant independent risk predictors were age, low serum cholesterol and serum albumin <3.5 g/dL, female gender, and BUN ratio. Treatment time.

TABLE 4. Proportional hazards analysis of 108 long-standing cases studied over 44 months

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient</th>
<th>Relative Risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>1.98</td>
<td>7.24 (3.35–15.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>1.04 (1.02–1.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>−0.007</td>
<td>0.993 (0.987–0.999)</td>
<td>0.032</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.40</td>
<td>1.49 (0.83–2.65)</td>
<td>0.180</td>
</tr>
</tbody>
</table>

TABLE 5. Description of 139 patients studied from 1989 to 1991

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>58.5 ± 15.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of ESRD</td>
<td>48.5 ± 50.4</td>
</tr>
<tr>
<td>White</td>
<td>26.6%</td>
</tr>
<tr>
<td>Black</td>
<td>54.0%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19.4%</td>
</tr>
<tr>
<td>Male</td>
<td>49.6%</td>
</tr>
<tr>
<td>Female</td>
<td>50.4%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>36.0%</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>64.0%</td>
</tr>
<tr>
<td>Dialysis Hours</td>
<td>3.13 ± 0.44</td>
</tr>
<tr>
<td>BUN Ratio</td>
<td>2.58 ± 0.57</td>
</tr>
<tr>
<td>Dry Weight (lbs)</td>
<td>145 ± 36</td>
</tr>
</tbody>
</table>

TABLE 6. Twenty-two-month crude mortality rate by treatment time

<table>
<thead>
<tr>
<th>Time</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>N</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.00–2.50</td>
<td>2.45±0.14</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>2.67–2.75</td>
<td>2.73±0.03</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>3.59±0.25</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>3.25–3.75</td>
<td>3.45±0.12</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>4.00–4.25</td>
<td>4.02±0.06</td>
<td>15</td>
<td>47</td>
</tr>
</tbody>
</table>

TABLE 7. Twenty-two-month crude mortality rate by BUN ratio

<table>
<thead>
<tr>
<th>BUN Ratio</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>N</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.90</td>
<td>1.65 ± 0.22</td>
<td>13</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>1.90–2.49</td>
<td>2.26 ± 0.16</td>
<td>57</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>2.50–3.39</td>
<td>2.87 ± 0.25</td>
<td>57</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>≥3.40</td>
<td>3.72 ± 0.31</td>
<td>12</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

* Mortality rate by BUN Ratio category: P < 0.02 by χ².
* Exact ranges are: 1.13–1.89, 1.91–2.49, 2.50–3.38, and 3.45–4.37.
prior months on dialysis, estimated dry weight, and diabetic status were not significant independent predictors. Compared with the reference category (BUN ratio, 2.50 to 3.39), risk increased by approximately 70% (relative risk, 1.71; 95% CI, 0.83 to 3.53; \( P = 0.14 \)) for cases with BUN ratio values of 1.90 to 2.49 and nearly fivefold (relative risk, 4.78; 95% CI, 1.53 to 14.9; \( P = 0.008 \)) for BUN ratio values below 1.90.

A BUN ratio above 3.40 (\( N = 12 \)) was associated with a twofold to threefold increase in risk (relative risk, 2.56; 95% CI, 0.97 to 7.03; \( P = 0.07 \)). This subgroup had a high mortality rate as the result of wasting illnesses, including three cancer-related deaths. When the patients were ranked by BUN ratio, the mean dry weight of the 12 patients with the highest BUN ratio values was significantly lower than the mean dry weight of the next 12 patients (106 ± 18 versus 125 ± 19; \( P = 0.021 \)).

**DISCUSSION**

Serum biochemical measurements suggestive of malnutrition have been reported to correlate with 1-yr mortality risk in cross-sectional studies of hemodialysis patients (19,22,23). However, cross-sectional studies lead to many potential biases. For example, selection bias would be important if patients who died quickly differed systematically from those who survived. There may also be a confounding bias between prior treatment and biochemical markers, comorbidities, and demographic parameters on future survival. Although some of the same biases can exist in studies of newly diagnosed cases, they are less likely to occur. Using a proportional hazards model to study survival for up to 44 months, we found that low albumin and cholesterol are independent predictors of mortality risk in both "new" patients, *i.e.*, in their first year of dialysis, and in "long-standing" patients, *i.e.*, those who have survived the high attrition associated with the first year on maintenance HD. The demonstration of the importance of biochemical risk predictors confirms and extends the observations of Lowrie and Lew's cross-sectional study of 1-yr survival in a much larger group using logistic regression (23).

In addition to the biochemical risk predictors, demographic parameters were significant predictors of increased risk. Age was associated with mortality in both new and long-standing cases but was statistically significant only in the long-standing cases. This anomaly occurred because of a disproportionately high death rate among young black men in the new group. Female gender was associated with increased risk in new patients. This in part resulted from the older age of the female patients. Given the disparity in age between men and women and the exclusion of age from the model because of the anomaly of three young male deaths, female gender is partly acting as a proxy for age in the final model. In other populations, where these disparities do not exist, the influence of female gender would be expected to be less. Thus, other studies have reported either no influence of gender or increased risk for men (23,32-36). Similar to Lowrie and Lew, we found no influence of race or diabetes on mortality risk (23). The majority of nondiabetic patients in our study had hypertensive nephrosclerosis. Although the etiology of renal failure was not used as an independent variable in our analysis, this parameter did not contribute significantly to the model reported by Lowrie and Lew except for polycystic disease, which was associated with reduced risk, and multiple myeloma, which was associated with increased risk (23).

Low serum albumin is clearly the single most important risk predictor in HD patients, new or long standing. Others have found low albumin to be an adverse risk factor in acute and chronic nonrenal settings (37-40) and even in healthy individuals (41-43). A recently published multivariate study of survival over 9 yr in 7,735 healthy men in the United Kingdom showed that a baseline serum albumin below 4 g/dL was associated with increased all-cause and cardiovascular mortality over the entire 9 yr (41).

**TABLE 8. Proportional hazards analysis of 139 cases studied over 22 months**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient</th>
<th>Relative Risk (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.030</td>
<td>1.030 (1.005-1.057)</td>
<td>0.018</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>-0.010</td>
<td>0.990 (0.983-0.996)</td>
<td>0.012</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL (vs ≥ 3.5)</td>
<td>0.819</td>
<td>2.268 (1.114-4.623)</td>
<td>0.024</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>-0.939</td>
<td>0.391 (0.181-0.843)</td>
<td>0.016</td>
</tr>
<tr>
<td>Dialysis Hours</td>
<td>0.378</td>
<td>1.456 (0.680-3.133)</td>
<td>0.34</td>
</tr>
<tr>
<td>Months on Dialysis</td>
<td>0.005</td>
<td>1.005 (0.999-1.010)</td>
<td>0.11</td>
</tr>
<tr>
<td>BUN Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.90 (vs 2.50-3.39)</td>
<td>1.564</td>
<td>4.778 (1.527-14.939)</td>
<td>0.008</td>
</tr>
<tr>
<td>1.90-2.49 (vs 2.50-3.39)</td>
<td>0.538</td>
<td>1.713 (0.829-3.532)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥3.40 (vs 2.50-3.39)</td>
<td>0.938</td>
<td>2.555 (0.971-7.029)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
This finding continued to be true after excluding "early" (first 5 yr) mortality. An inverse relationship between serum albumin and risk of coronary death was also found in the subjects monitored in the Multiple Risk Factor Intervention Trial (42). In that study, serum albumin values of less than 4.4 g/dL were associated with a more than threefold increased risk relative to values above 4.7 g/dL. Because the patients in some of these studies were in apparent good health, some have speculated that low albumin level directly contributes to increased mortality, e.g., by reducing the capacity of the serum to bind potential toxins (44–46).

Low serum cholesterol has also been linked with increased noncardiovascular mortality in many groups, including healthy populations (47). Minimum risk was associated with serum cholesterol between 188 and 225 mg/dL in the Honolulu Heart Program study of 7,479 middle-aged men (48). Reduced serum cholesterol increased risk of death for most noncardiac causes, even after excluding early (5 to 10 yr) deaths from the analysis. A study of elderly women monitored over 5 yr found that minimum mortality risk was associated with serum cholesterol of 270 mg/dL (49). The increased risk with lower levels was not accounted for by cancer deaths (49). As with serum albumin, some have speculated that reduced serum cholesterol directly contributes to mortality risk, e.g., by reducing the cholesterol content of cell membranes (47). Nevertheless, in a population with chronic illness, it is likely that reduced serum levels of albumin and cholesterol are also indirect markers of the risk due to malnutrition or to subclinical or overt comorbid conditions (43,50).

Both serum albumin and serum cholesterol levels may be depressed in states of advanced malnutrition. In the early stages of chronic primary and secondary protein-energy malnutrition, whether because of decreased intake or increased requirements, an adaptive increase in muscle breakdown occurs that contributes to the preservation of the amino acid supply for the synthesis of visceral proteins such as albumin and lipoproteins (51). When malnutrition is more sustained or severe, this adaptation becomes inadequate and the concentrations of the serum proteins fall (51). Malnutrition is known to be highly prevalent in dialysis patients (19,52–54). The association of low serum albumin and cholesterol with increased mortality is compatible with the view that advanced malnutrition is the primary marker of mortality in HD patients and possibly its primary cause (19). Protein intake was not quantified in this study. However, even if decreased protein intake were demonstrated, assignment of a primary role in HD mortality to decreased protein intake would be confounded by the prevalence in these patients of many disturbances that both accelerate catabolism and decrease intake. For example, dialysis patients are prone to fluid overload, which can result in hepatic congestion and anorexia, directly and indirectly leading to impaired synthesis of proteins (55). At the same time, extreme states of heart failure are associated with elevated levels of tumor necrosis factor (56). HD itself can be catabolic (57,58). HD is associated with a loss of free amino acids and increased levels of interleukin-1 and tumor necrosis factor (59,60). Blood membrane contact has been shown to engender accelerated muscle protein degradation when cuprophane membranes are used, but not when "biocompatible" membranes such as polyacrylonitrile are used (58). Dietary intake may be reduced when dialysis is performed with cuprophane compared with polyacrylonitrile (61). The acidosis of uremia also contributes to negative nitrogen balance (59,62). Finally, uremic patients are extremely susceptible to negative nitrogen balance and wasting when an intercurrent illness occurs (63).

Short treatment time has been linked to mortality risk in studies of dialysis patients receiving treatments that are largely unguided by urea kinetics (23,32). These studies provided indirect evidence that inadequate dialysis increases mortality risk. The direct correlation between treatment time and BUN ratio observed in our study supports this view. In the study of Lowrie and Lew (23), short treatment time was a significant, independent predictor only if the serum biochemical values were not used in the logistic model. This suggests that short, inadequate dialysis may lead to undernutrition, which in turn, increases mortality risk.

We examined the relationship to 22-month mortality risk of serum biochemistry values, treatment time, and dialysis dose (the BUN ratio). Visceral protein status (serum albumin and cholesterol) and dialysis dose were found to be independent predictors of mortality risk. Thus, biochemical markers of undernutrition are important risk predictors, even in patients receiving adequate dialysis by generally accepted criteria (26–28). Conversely, the delivered dose of dialysis is an independent risk predictor, even after adjustment for serum albumin and cholesterol.

Except for a paradoxical increase in risk with very high BUN ratio values (discussed below), risk was inversely related to the BUN ratio. This inverse relationship is in agreement with the findings of other survival studies that have appeared in abstract form, reviewed recently by Hakim et al. (64). Because a single measurement of the BUN ratio was used, our study may underestimate the slope of this relationship for several reasons. First, the effect of regression-to-the-mean for single measurements of a risk factor has been shown to result in underestimation of the slope of the risk gradient ("regression dilution bias") (65). Second, monthly physician interventions during the study wound tend to be selective. Patients
with the lowest initial ratio values would be more likely to receive increases in their dialysis dose, which would tend to reduce the risk associated with low initial values. Additionally, patients who "fail to thrive" because of an unsuspected comorbid condition may empirically receive increases in their dialysis dose, thus diminishing the apparent benefit associated with higher dialysis doses.

The third reason is that comorbidity and its associated weight loss may confound the relationship of BUN ratio to risk. This possibility is suggested by the strong inverse correlation observed between weight and BUN ratio. The BUN ratio is a measure of the delivered dose of dialysis normalized to the body urea space ($V_u$). If patients who are dying are losing weight (hence, $V_u$) without a compensatory reduction in their absolute dialysis dose, they would tend to have rising BUN ratio values over time. The effect of this trend would be to diminish the apparent risk associated with low BUN ratio values and to mask the benefit or even increase the risk associated with higher values. Thus, the paradoxical increase in relative risk observed in 12 patients with very high values of the BUN ratio (>3.4) was the result of a high prevalence of several wasting conditions, as suggested by the very low mean weight for the group and by examination of the causes of death. The increase in mortality is also compatible with the hypothesis that a very high delivered dose of dialysis is detrimental, e.g., by causing depletion of amino acids and other nutrients (58,59), especially in patients who are already nutritionally depleted. However, this cannot be proved because severe comorbidity confounded the cases that received very high dialysis doses in this study.

Short treatment time was not a risk predictor in this study. This in part reflects the inclusion in the model of a more direct measure of dialysis dose, the BUN ratio. Additionally, it is possible that physicians allocated longer treatment times to patients with comorbid conditions such as heart disease. This would tend to confound any relationship between short time and risk. In any event, recent studies have established the safety of short treatment times in populations such as ours that received bicarbonate dialysis via volumetrically accurate equipment with attention to urea kinetics (66,67).

In summary, decreased levels of serum albumin and cholesterol were found to be independent predictors of mortality risk in both new and long-standing HD patients over at least 2 yr. In patients receiving dialysis quantified by the BUN ratio, serum levels of albumin and cholesterol and the dialysis dose, but not treatment time, predicted mortality risk. These observations are compatible with the view that protein-energy malnutrition is the main cause of mortality in HD patients even when they are receiving adequate dialysis. Further research should be directed to assessing more sensitive nutritional markers and to targeting high-risk groups for therapeutic trials with interventions that lessen catabolism, improve dietary intake, and correct comorbid conditions.

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