Serum albumin is a strong predictor of death in chronic dialysis patients

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Serum albumin is a strong predictor of death in chronic dialysis patients. We examined the predictive value of various clinical variables in assessing survival in chronic hemodialysis patients ($N = 1,243$, 524 females, 719 males) who were under treatment with hemodialysis as of January 1991 in Okinawa, Japan and who were followed up until April 1992. Basal clinical data such as sex, starting date of dialysis, primary renal disease, blood pressure, blood chemistry values, and dialysis prescription data obtained just prior to dialysis were registered at the start of the study. As of the end of April 1992, 104 had died, 16 were transplant recipients, and five had been transferred. Those who died had significantly lower levels of total protein, serum albumin, total cholesterol, triglyceride, BUN, serum creatinine, body weight, body height, diastolic blood pressure, and duration of hemodialysis than those who survived. Older patients and those with diabetes mellitus had a poorer prognosis. A forward stepwise logistic procedure by SAS was used to determine the predictive value of the above clinical variables. With the addition of laboratory variables, the predictive value of diabetes was lost, as the diabetic patients had low serum levels of albumin and creatinine. The standardized coefficient was -0.380 ($P = 0.0001$) at age of entry, 0.316 ($P = 0.0001$) for serum albumin, 0.280 ($P = 0.0001$) for serum creatinine, 0.138 ($P = 0.043$) for body mass index (BMI), and -0.139 ($P = 0.016$) for male sex. The prescribed dialysis dose (M^2 hr per week) was significantly correlated with serum creatinine ($r = 0.48$, $P = 0.0001$), serum albumin ($r = 0.135$, $P = 0.0001$) and BMI ($r = 0.275$, $P = 0.0001$). Serum albumin was found to be a strong predictor of death in chronic hemodialysis patients. Causes of low serum albumin should be carefully evaluated if underlying illness is not evident.

Several retrospective studies of survival in patients receiving maintenance hemodialysis have been conducted [1–3]. However, no predictors of mortality other than age at start of dialysis and diabetes mellitus have been identified. Measurement of predialysis BUN and KT/V has been used to monitor the amount of dialysis [4, 5] and, consequently, the use of short dialysis was introduced. Short dialysis may result in underdialysis and is associated with poor outcome [6, 7]. In fact, the reported frequency of underdialysis is high, especially in those on shortened dialysis [8]. However, the use of shortened dialysis was based on the result obtained in the National Cooperative Dialysis Study of well patients [9]. These findings do not apply to the older and sicker patients who are currently increasingly accepted for dialysis [10] and who are possibly malnourished. Lowrie and Lew [4] and others [5] have shown that nutritional status is a good predictor of mortality in dialysis patients. However, the role of dialysis prescription has not been fully evaluated [4]. We therefore conducted a short-term prospective study to identify the nutritional and dialysis prescription factors useful in assessing the risk of mortality in patients receiving maintenance hemodialysis.

We were able to follow a large number of chronic hemodialysis patients. A retrospective analysis of the patients' survival and a description of the demographics of the population have been presented previously [11]. We found that age at the start of dialysis, the year starting dialysis, and the presence of diabetes mellitus were significant prognostic factors. However, since these factors are not subject to modification with treatment, we designed a short-term prospective study to detect those factors, if any, which are clinically controllable. The results may be useful in the formulation of therapeutic strategies which would interdict the abnormalities precipitating death in patients receiving chronic hemodialysis.

Methods

Between 1971 and 1990, we registered a total of 1,982 patients who had survived at least one month on scheduled maintenance dialysis in Okinawa, Japan [11]. Patients who died ($N = 605$), underwent renal transplant ($N = 75$), were transferred ($N = 23$) and were placed on CAPD ($N = 36$) were subsequently excluded. Therefore, a total of 1,243 patients (524 females, 719 males) were receiving maintenance hemodialysis as of January 1991, the start of the study period. By the end of the study period, April 1992, 104 patients had died, 16 had undergone renal transplantation, and five had been transferred. Analysis was conducted using data for the 1,222 patients (515 females, 707 males) who had not received renal transplantation or been transferred.

All the medical records were reviewed by one of us (K.I.) and the following data were obtained: date of birth, sex, date of start of dialysis, laboratory and clinical data, dialysis prescription, and status as of April 1992. The laboratory values were obtained before routine hemodialysis in January 1991. Laboratory and clinical data included body weight, height, blood pressure, total protein, serum albumin, total cholesterol, triglyceride, BUN, serum creatinine, and uric acid. Body height was measured within six months of the start of the study. Body mass index (BMI) was defined as the ratio of weight to height squared (kg/m^2). In addition, dialysis prescription data, such as type of

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Table 1. Characteristics of the patients and dialysis prescription

Number of patients	
Total	1,243
Males	719
Females	524
Age at January 1991, *years*	
Mean ± SEM	52.2 ± 0.4
Range	13 to 91
Duration of hemodialysis treatment, *months*	
Mean ± SEM	61.9 ± 1.4
Range	1 to 233
Original renal disease	
Chronic glomerulonephritis	839 (67.5%)
Diabetes mellitus	211 (17.0%)
Hypertensive nephrosclerosis	59 (4.7%)
Polycystic kidney disease	29 (2.3%)
Lupus nephritis	23 (1.9%)
Others	82 (6.6%)
Frequency of dialysis per week	
once	11 (0.9%)
twice	191 (15.4%)
thrice	1041 (83.7%)
Duration of dialysis, *hours per session*	
<3.0	0
3.0–3.5	65 (5.2%)
3.5–4.0	708 (57.0%)
4.0–5.0	125 (10.0%)
5.0≤	345 (27.8%)
Dialyzer membrane area (*square meter, m²*)	
<1.0	60 (4.8%)
1.0–1.4	434 (34.9%)
1.5–1.9	534 (43.0%)
2.0≤	215 (17.3%)
Dose of dialysis, *m² hr per week*	
<10	139 (11.2%)
10–15	289 (23.2%)
15–20	349 (28.1%)
20–25	244 (19.6%)
25–30	134 (10.8%)
30≤	88 (7.1%)

Table 2. Comparison of clinical variables between patients who died and those who survived

Clinical variables	Died $N = 104$	Survived $N = 1,118$	P value
Age, *years*	65.2 (1.2)	52.2 (0.4)	0.0001
Duration of HD, *months*	45.3 (4.2)	63.4 (1.5)	0.0001
Dose of HD, *m² hr/W*	15.6 (0.5)	18.5 (0.2)	0.0001
Body height, *meters*	1.53 (0.01)	1.57 (0.03)	0.003
Body weight, *kg*	48.7 (0.9)	53.4 (0.3)	0.0001
Body mass index, *kg/m²*	20.6 (2.6)	21.7 (0.1)	0.001
Systolic blood pressure, *mm Hg*	153.8 (2.6)	151.3 (0.7)	NS
Diastolic blood pressure, *mm Hg*	77.0 (1.2)	81.3 (0.4)	0.001
Total protein, *g/dl*	6.3 (0.1)	6.5 (0.1)	0.0001
Serum albumin, *g/dl*	3.5 (0.1)	3.9 (0.1)	0.0001
Total cholesterol, *mg/dl*	158.8 (3.9)	171.9 (1.2)	0.001
Triglyceride, *mg/dl*	131.3 (8.3)	165.1 (3.5)	0.0003
BUN, *mg/dl*	78.9 (2.2)	86.4 (0.6)	0.001
Serum creatinine, *mg/dl*	10.4 (0.3)	13.4 (0.1)	0.0001
Serum uric acid, *mg/dl*	7.9 (0.2)	8.3 (0.1)	NS
Smoker, %	17.3	23.8	NS
Drinker, %	10.6	21.5	0.009
Antihypertensives, %	56.7	51.7	NS
Diabetes mellitus, %	35.6	15.3	0.0001

Parentheses denote SEM. NS, not significant.

dialyzer, blood flow rate, duration and frequency of dialysis were obtained. The cause of death was classified into the six categories: infection, withdrawal, cardiac, sudden death, vascular, or other [6, 11]. No patients were lost to follow-up.

Patients demographics determined at the start of the study are shown in Table 1. The mean (SEM) age was 52.2 (0.4) years, ranging from 13 to 91 years old. The mean duration of hemodialysis treatment was 61.9 (1.4) months, ranging from one to 233 months. The original renal diseases were chronic glomerulonephritis ($N = 839$, 67.5%), diabetic nephropathy ($N = 211$, 17.0%), hypertensive nephropathy ($N = 59$, 4.7%), polycystic kidney disease ($N = 29$, 2.3%), lupus nephritis ($N = 23$, 1.9%), and other ($N = 82$, 6.6%). One thousand forty-one patients (83.7%) were dialyzed three times per week, 191 patients (15.4%) two times per week, and 11 patients (0.9%) once a week. The duration of dialysis (hours per session) was 3.0 to 3.5 hours in 65 patients (5.2%), 3.5 to 4.0 hours in 708 (57.0%), 4.0 to 5.0 hours in 125 (10.0%), and more than five hours in 345 (27.8%). The median hours per session was 3.5 to 4.0 hours. The dialyzer membrane area used (m²) was <1.0 m² in 60 patients (4.8%), 1.0 to 1.4 m² in 434 (34.9%), 1.5 to 1.9 m² in 534 (43.0%), and more than 2.0 m² in 215 (17.3%) (range, 0.7 to 2.2 m²; mean, 1.48 m²) The weekly dialysis dosage, calculated as (frequency of dialysis) × (duration of dialysis) × (dialyzer

membrane area) was as <10 m² hrs in 139 patients (11.2%), 10 to 15 m² hrs in 289 (23.2%), 15 to 20 m² hrs in 349 (28.1%), 20 to 25 m² hrs in 244 (19.6%), 25 to 30 m² hrs in 134 (10.8%), and more than 30 m² hrs in 88 (7.1%) (range, 3.3 to 33.0 m² hrs; median, 15 to 30 m² hrs). The mean (SEM) blood flow rate was 188.3 (0.7) ml/min, ranging from 100 to 300 ml/min, and the median blood flow rate was 200 ml/min. Data regarding smoking and drinking habits and the use of antihypertensive drugs were also obtained.

Student's *t*-test and the chi square test were used to compare data for those who died with that for those who survived. Variables found to be significant were entered into the logistic analysis model using a SAS package [11]. The dependent variable in this model was binary, that is, survival or mortality at the end of the observation period. A variable was deleted from the model if it did not meet the 5% significance level. Pearson correlation coefficients were calculated to examine the relationship between the pertinent clinical variables. Data are expressed as mean ± SEM.

Results

In the 104 patients who died, the cause of death was infection in 16.3%, withdrawal in 16.3%, cardiac in 28.0%, sudden death in 7.7%, vascular in 16.3%, and other in 15.4%.

Table 2 shows values of clinical variables in the patients that died and those that survived. In the deceased group, age was greater and duration of hemodialysis was shorter, while the dose of dialysis was lower than that in the survival group. Body height, weight, and BMI were significantly lower in the former group. There was no difference between the groups in systolic blood pressure, but diastolic blood pressure was slightly lower in the deceased group. Total protein, serum albumin, total cholesterol, triglyceride, BUN, and serum creatinine were also lower in the deceased group. The percentage of smokers and ex-smokers was slightly lower in deceased group. The percentage of drinkers and ex-drinkers was significantly lower in the

Table 3. Results of the logistic analysis

Variables	Stand. coef.	Chi-square	P
Age in 1991, *years*	−0.3799	26.53	0.0001
Sex (male = 1)	−0.1386	4.51	0.0336
Body mass index, *kg/m²*	0.1378	4.07	0.0437
Serum albumin, *g/dl*	0.3161	22.26	0.0001
Serum creatinine, *mg/dl*	0.2797	13.21	0.0003

Abbreviation Stand coef is standardized coefficient.

deceased group. More than 50% of all patients were prescribed antihypertensive drugs. The percentage of diabetic patients was significantly higher in the deceased group (35.6% vs. 15.3%, $P < 0.0001$ by chi-square test).

Table 3 summarizes the results of the logistic analysis. In addition to age and male sex, the laboratory variables of serum albumin, serum creatinine, and body mass index were found to be significant predictors of death. The prognostic value of diabetes mellitus was lost with the addition of laboratory variables, since the diabetics had low levels of serum albumin and creatinine. Weekly dialysis schedule *per se* and dose of dialysis were not significantly associated with mortality in chronic dialysis patients.

The association between relative risk of death and serum albumin, creatinine, and BMI values is summarized in Table 4. The serum albumin values for all patients were distributed as follows: less than 3.5 g/dl in 16.9%; 3.5 to 3.9 g/dl in 41.1%; 4.0 to 4.4 g/dl in 30.6%; and 4.5 g/dl and over in 11.4%. The crude death rate in each albumin range was 22.3%, 7.6%, 4.3%, and 2.2%, respectively. The serum creatinine values in all patients were distributed as follows: less than 10 mg/dl in 17.4%; 10 to 14.9 mg/dl in 52.0%; 15.0 to 19.9 mg/dl in 29.0%; and 20 mg/dl and over in 1.6%. The crude death rate in each creatinine range was 18.8%, 9.0%, 1.1%, and 0%, respectively. The relative risk of death was lower in patients with higher levels of serum creatinine. The body mass index was distributed as follows: less than 21 kg/m² in 46.6%; 21 to 23.9 kg/m² in 33.4%; and 24 kg/m² and over in 20.0%. The relative risk of death was lower in patients with higher BMI.

Table 5 shows the Pearson correlation coefficients for dialysis dosage and several clinical variables. There was a significant positive correlation between the dialysis dosage and serum creatinine, BMI, and duration of dialysis. There was a negative correlation between dialysis dosage and age.

As shown in Figure 1, there was a significant correlation between dialysis dosage and serum creatinine ($r = 0.482$, $P = 0.0001$).

Discussion

The annual overall mortality rate of patients in our dialysis registry was about 7% [11], which is lower than others [12–14], but not the lowest [15]. It is possible that differences among patient groups in the percentage of diabetic patients, age at entry, dialysis prescription, and other clinical conditions may contribute to these results [16]. Of the laboratory variables, serum levels of albumin and creatinine and body mass index were found to have significant predictive value (Table 3). Other variables, such as total cholesterol, serum uric acid, BUN, total protein, and blood pressure, had no significant predictive value.

While a number of other laboratory variables, such as CO_2, potassium, phosphate, and calcium, may contribute to survival [4], these were considered to have less predictive value than BUN or total cholesterol.

High serum creatinine was associated with low risk of death, but was also associated with high dialysis dosage. While increased dialysis may lead to greater patient body mass and generation of creatinine, it is also possible that physicians consider serum creatinine value and provide dialysis at greater doses to better nourished patients. If albumin and creatinine values rather than diabetes mellitus were applied as predictors of mortality risk, it might be found that the extremely high mortality associated with diabetes mellitus is related as much to undernutrition as it is to diabetes mellitus *per se* [17].

In the Diaphane collaborative study [1], better survival was found in patients dialyzed three times a week than in those dialyzed twice a week. Prolonged and slow dialysis was associated with 75% survival at 10 years [15]. Underdialysis may trigger a feedback mechanism decreasing the dietary intake of nutrients [4], thereby reducing the levels of serum albumin, and, eventually, of creatinine and body mass index. Lean patients have a poorer prognosis among both dialysis patients [1] and hypertensive patients [18], although leanness *per se* was not considered to be an independent risk factor [18]. However, we could not exclude the possibility that patients already had these clinical characteristics before starting hemodialysis therapy and that they were not improved despite adequate dialysis. Uremia *per se* [19] and the current practice of prescribing a low-protein diet to retard the progression of renal failure may cause malnutrition [20].

Comorbid conditions such as vascular disease, ischemic heart disease, malignancies, and chronic obstructive pulmonary disease are risk factors of mortality in dialysis patients [10]. Of the 123 patients (9.9%) in our group who were hospitalized due to multiple reasons, 29 (24%) died during the study period. This rate is significantly higher (chi square value 42.6, $P < 0.0001$) than that of patients who were ambulatory at the start of study (6.7%).

We did not assess the intake of protein in this study. Protein intake was assumed to be prescribed as recommended, 1.0 to 1.4 g/kg [21, 22], which is lower than that of the general population in Okinawa [23]. However, it is reported that poor compliance with dietary and medical advice is quite common in adult chronic hemodialysis patients [24]. If so, a large number of dialysis patients may be malnourished, even though they are ambulatory and their condition stable [4]. Of the patients in our registry, 58% were hypoalbuminemic (<4.0 g/dl); 2.8% severely hypoalbuminemic (<3.0 g/dl); Lowrie and Lew [4] reported 66% and 2.0%, respectively. It has been suggested that the dietary protein intake is affected by the dialysis dosage and can be increased with more intense dialysis [25, 26]. Therefore, physicians should be aware of the possibility of inadequate dialysis treatment as well as of underlying illness which reduces appetite [27].

Blood pressure was not found to be a significant predictive factor in our short-term prospective study, in contrast to the findings in previous studies of dialysis patients [1, 15, 28] and the general population [29–31]. Since the mean duration of hemodialysis at the start of study was 61.9 months, the hypertensive patients at risk may have died before study enrollment.
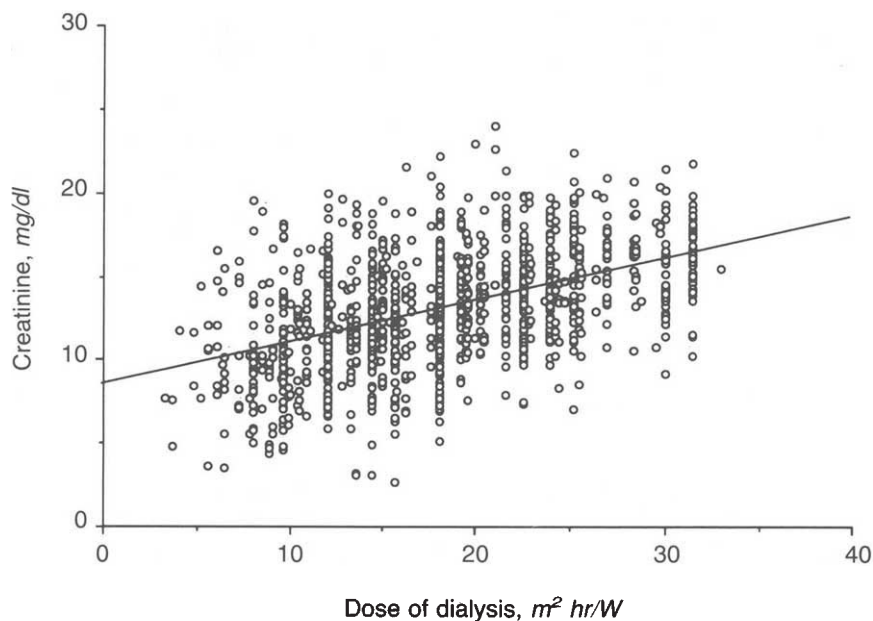
Fig. 1. *Correlation between serum creatinine and dialysis dosage.* The correlation was significant ($r = 0.469$, $P < 0.001$).

Table 4. Crude risk ratios and relative death risks

Variables	Patients		Risk of death	Relative death risk		
	Exposed	Died		To index	95% C.I.	P
Albumin, *g/dl*						
<3.5	206	46	0.223	1.00		
3.5–3.9	501	38	0.076	0.40	0.22–0.58	0.0001
4.0–4.4	373	16	0.043	0.27	0.12–0.41	0.0001
4.5–	139	3	0.022	0.24	0.06–0.48	0.001
Creatinine, *mg/dl*						
<10.0	213	40	0.188	1.00		
10.0–14.9	635	57	0.090	0.59	0.34–0.84	0.006
15.0–	373	4	0.011	0.12	0.03–0.21	0.0001
Body mass index *kg/m²*						
<21.0	570	60	0.105	1.00		
21.0–23.9	408	30	0.074	0.98	0.54–1.42	0.596
24.0–	244	14	0.057	0.79	0.35–1.22	0.177

Index risk is the death risk if albumin, creatinine, and BMI are <3.5 g/dl, <10.0 mg/dl, and <21.0 kg/m². C.I. denotes confidence interval.

Table 5. Correlation between the dose of dialysis and the several clinical variables

Clinical variables	r	P
Serum creatinine, *mg/dl*	0.482	0.0001
Duration of dialysis, *months*	0.349	0.0001
Age, *years*	−0.333	0.0001
Body mass index, *kg/m²*	0.275	0.0001
Serum albumin, *g/dl*	0.135	0.001

The Pearson correlation coefficient (r) and P values are shown in this Table.

In fact, the reported peak period of vulnerability (hazard) for cardiac death is the first four years [6]. Recently it has been reported that there is little effect of systolic or diastolic hypertension on the short-term survival of hemodialysis patients [32]. However, in our study, about 45% of all deaths were related to cardiac and vascular events that suggested underlying atherosclerosis [33–35].

Of the significant predictors of death, serum albumin and BMI are correctable. The dosage of dialysis can be increased by either prolonging the duration of dialysis treatment or using a larger dialyzer membrane area. In our experience, however, patients are very reluctant to agree to prolongation of the treatment time [36].

In summary, we demonstrated in this short-term prospective study that serum levels of albumin and creatinine and the BMI are significant predictors of death in maintenance hemodialysis patients. The dialysis dosage was significantly correlated with each of these laboratory and clinical variables. The dialysis prescription should carefully be adjusted in such high-risk patients. However, the effect of increasing dialysis dosage on patients survival rate remains to be determined.

Acknowledgments

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