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Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients

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Abstract

Background. The prognosis of chronic dialysis patients is poor, in part due to the high incidence of cardiovascular disease. Malnutrition, such as hypoalbuminaemia, has been shown to be a predictor of death in this group of patients, while serum C-reactive protein (CRP) is a predictor of myocardial infarction and sudden death. Thus, the aim of the present study was to determine of the relationship between CRP and serum albumin concentration, and the value of baseline CRP data in the prediction of death.

Methods. In one of the dialysis units in Okinawa, Japan, baseline CRP data was available ($n=163$, 95 men and 68 women) in January 1991. These patients were divided into two groups according to their baseline CRP levels, with group 1 consisting of CRP <10 mg/l ($n=128$) and group 2 of CRP $\geqslant 10$ mg/l ($n=35$), and then followed up until the end of 1997. Survival curves were calculated using the Kaplan–Meier method. The statistical significance of the relationship between CRP levels and the risk of death was evaluated by multiple logistic analysis with covariables such as age, sex, diabetes mellitus, serum albumin, and blood pressure.

Results. The mean (SD) level of serum albumin was 38 (3) g/l in group 1 and 36 (3) g/l in group 2 ($P<0.00001$). The 5-year survival rate was significantly poorer in group 2 (44.4%) than in group 1 (82.5%) ($P<0.0001$). Furthermore, the risk of death was significantly higher in group 2 (relative risk 3.48 (95% confidence interval 1.76–6.89), $P<0.0003$) by multivariate Cox proportional hazard analysis.

Conclusions. CRP is a significant predictor of death in chronic dialysis patients, independent of serum albumin and other possible confounders. Dialysis patients with high CRP levels should be carefully evaluated and monitored regardless of serum albumin concentrations in the normal range.

Introduction

The prognosis of patients on chronic dialysis is poor, due to the high incidence of cardiovascular disease such as stroke, sudden death, and cardiac failure [1]. Furthermore, dialysis patients are often associated with reduced immunity and have a high incidence of infection [2]. Recently, prior bacterial and viral infections have been shown to lead to cardiovascular disease [3]. The prognostic value of serum C-reactive protein (CRP) on the occurrence of myocardial infarction, sudden death, and stroke has been reported in the general population [4,5]. Consequently, CRP is a possible predictor of death in dialysis patients [6].

Malnutrition is prevalent in chronic dialysis patients [7,8]. Hypoalbuminaemia, which suggests the presence of malnutrition, has been shown to be a strong predictor of death in such patients [8]. Hypoalbuminaemia may take several weeks to develop, and treatment may be delayed. Due to rapid and sustained response to tissue injury, CRP has been used to evaluate disease activity. Hence, the measurement of CRP in chronic dialysis patients may establish the risk of death faster than the measurement of serum albumin.

The aim of the present study was to examine the relationship between CRP and serum albumin concentration, and the prognostic value of CRP in the chronic dialysis population. A better understanding of the pathophysiological mechanisms of death in chronic dialysis patients may result in new strategies for the treatment and prevention.

Subjects and methods

Patients

Data from the Okinawa Dialysis Study (OKIDS) was obtained through the collaboration of the physicians in charge of the dialysis unit in Okinawa, Japan [1]. All dialysis patients with end-stage renal disease and who had survived at least 1 month on dialysis were registered. Their medical records were reviewed, and if necessary further information was obtained from paramedical staff, patients, and patients'

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families. Chronic dialysis therapy was initiated in 1971 in Okinawa, with 39 units currently. Consisting of subtropical islands, Okinawa is situated in the southernmost part of Japan. The population is stable at around 1.2 million and has the longest life-span. More than 95% of patients with end-stage renal disease in Okinawa remain on chronic dialysis due to the shortage of organs for renal transplantation.

A cohort of 1243 chronic dialysis patients who were alive on 1 January 1991 was examined [8]. The mean age and duration of dialysis was 52.2 years and 61.9 months respectively. Two hundred and eleven subjects (17.0%) were diabetic. In most of the patients ($n=1041$, 83.7%), dialysis was performed three times a week. In 708 patients (57.0%), dialysis lasted 3.5–4.0 h per session [8]. Laboratory and clinical data including body weight, blood pressure, and blood chemistry were obtained before the regular haemodialysis session, in January, 1991. Body height was measured within 6 months of the start of the study. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). The cause of death was classified into six categories: infection, withdrawal, cardiac, sudden death, vascular, or others [1,9]. All patients were followed up until whichever of death, renal transplantation, transfer out of Okinawa, or the end of 1997came earliest. No patients were lost to follow-up.

CRP was measured occasionally, but not routinely in every unit. However, CRP data from January 1991 was available for all patients in one of the units ($n=163$, 95 men and 68 women). Blood was drawn before starting regular dialysis of the week. CRP was measured by turbimetric immunoassay. The tentative normal range was <6 mg/l. Since in Japan, results of CRP measurement are expressed as mg/dl, therefore more than 1.0 mg/dl is usually accepted as abnormally high value. Using of this method, the distribution of CRP was skewed and 12 (7.4%) patients registered '0' values. Mathematical transformation of CRP was not performed; instead the patients were divided into two groups: group 1, CRP <10 mg/l, and group 2, CRP $\geqslant 10$ mg/l. The clinical conditions and possible causes of elevated CRP levels were investigated by reviewing medical records.

Statistical analysis

Categorical variables were compared using the χ^2 tests. Continuous variables were compared using Student's *t*-test. Kaplan–Meier plots were used to calculate patient survival. The univariate and multivariate Cox proportional hazards analysis were used to determine the relative risk of death. The covariates included were age, sex, diabetes mellitus, year starting dialysis, diastolic blood pressure, and serum albumin, all of which were shown as predictors of death in this cohort. The dependent variable in this model was binary, that is, survival or mortality at the end of the observation period. Data are expressed as the mean SD. Statistical analysis was performed with the SAS software package using the OKIDS database.

Results

A comparison of the clinical and laboratory variables between the groups is shown in Table 1. Group 2 had a higher mean age, proportion of women, and incidence of diabetes mellitus than group 1. However, antihypertensive drugs were used less frequently in group 2 than in group 1 patients. The mean serum creatinine was lower in group 2 despite no differences in either dose of dialysis or body mass index. The serum albumin concentration was lower in group 2 than group 1.

Table 1. Baseline characteristics of chronic dialysis patients by baseline serum C-reactive protein (CRP)

	CRP (mg/l)		
	<10 ($n=128$)	$\geqslant 10$ ($n=35$)	*P*
M/F	80/48	15/20	<0.037
Diabetes mellitus	17 (13.3%)	11 (31.4%)	<0.0117
Age (years)	50.5 (14.5)	59.7 (12.8)	<0.0006
Dose of dialysis, m^2h/w	19.2 (5.4)	19.3 (5.8)	NS
Duration of dialysis (months)	76.1 (52.8)	68.4 (43.3)	NS
Body mass index (kg/m^2)	21.5 (3.0)	22.3 (3.4)	NS
Smoker	38 (29.7%)	6 (17.1%)	NS
Drinker	32 (25.0%)	6 (17.1%)	NS
Antihypertensive drugs	64 (50.0%)	8 (22.9%)	<0.0036
Blood pressure (mmHg)			
Systolic	147 (24)	144 (22)	NS
Diastolic	76 (12)	74 (12)	NS
Mean arterial	100 (14)	97 (14)	NS
Biochemistry*			
Serum urea concentration (mol/l)	32 (5)	32 (7)	NS
Serum creatinine (μmol/l)	1257 (279)	1084 (251)	<0.0008
Total protein (g/l)	65 (3)	65 (4)	NS
Serum albumin (g/l)	38 (3)	36 (3)	<0.00001
Serum uric acid (μmol/l)	513 (85)	520 (117)	NS
Plasma total cholesterol (mmol/l)	4.59 (0.96)	4.48 (1.11)	NS

*Mean (SD), NS denotes not significant.

Table 2 shows a comparison of the causes of death, and age and dialysis duration at death between the groups. In the high CRP patients (group 2), cardiac death was the main cause of death, whereas in group 1, the causes of death were widely distributed among the

Table 2. Causes of death and mean age and haemodialysis duration at death by baseline serum C-reactive protein (CRP)

	CRP (mg/l)	
	<10 ($n=28$)	$\geqslant 10$ ($n=20$)
Causes of death		
Infection	4 (14.3%)	3 (15.0%)
Withdrawal	9 (32.1%)	1 (5.0%)
Cardiac	3 (10.7%)	11 (55.0%)
Sudden death	3 (10.7%)	1 (5.0%)
Vascular	8 (28.6%)	2 (10.0%)
Other	1 (3.6%)	2 (10.0%)
Age at death, years		
Mean (SD)	67.8 (15.2)	69.1 (9.7)
Range	38 ~ 89	48 ~ 84
HD duration at death, months		
Mean (SD)	97.2 (49.6)	85.0 (48.5)
Range	26 ~ 251	6 ~ 172

HD, haemodialysis.

six categories. No differences in mean age or dialysis duration were observed between the groups.

Figure 1 shows the survival curves for groups 1 and 2 calculated by the method of Kaplan and Meier during the study period, from 1991 to 1997. As a whole, the patients' survival rate was 95.7% in the first 12 months and 74.4% at 60 months. The prognosis was significantly poorer in group 2 (5-year survival rate of 44.4%) than in group 1 (5-year survival rate of 82.5%, $P<0.0001$).

Patient outcomes and serum albumin concentration according to the quartiles of baseline CRP are shown in Table 3. The mortality rate was higher in the high CRP patients (group 2) the in other three groups. There was a weak inverse correlation between CRP and serum albumin ($r=0.30$, $P<0.0001$).

The results of Cox proportional hazard analysis are summarized in Table 4. Considering age, diabetes mellitus, and other predictors of death, CRP remained an independent, significant predictor of death (relative risk 3.48 (95% CI 1.76–6.89), $P<0.0003$). Similarly, if we compare the CRP groups between <6 mg/l and >6 mg/l, the hazard was 12.96 (2.65–63.42, $P<0.0016$).

Medical conditions at the time of CRP measurement are summarized in Table 5. Eighteen patients (11.0%) were hospitalized at the time of CRP measurement, others were ambulatory and were not exhibiting any clinical signs of overt heart failure or severe hypertension. Most cases of infection were mild and only one patient was hospitalized. No patients were not sick enough to be hospitalized. Four patients hospitalized for the repair of the arteriovenous fistula and five patients had recent surgery for the blood access before the CRP determination. Other medical conditions included: skin eruption in four patients, confusion in two, congestive heart failure in two, and chest pain, gangrene, gastrointestinal bleeding, haemorrhoid, and worsening of systemic lupus erythematosus and multiple myeloma.

Table 6 showed the serial determinations of CRP since January 1991.

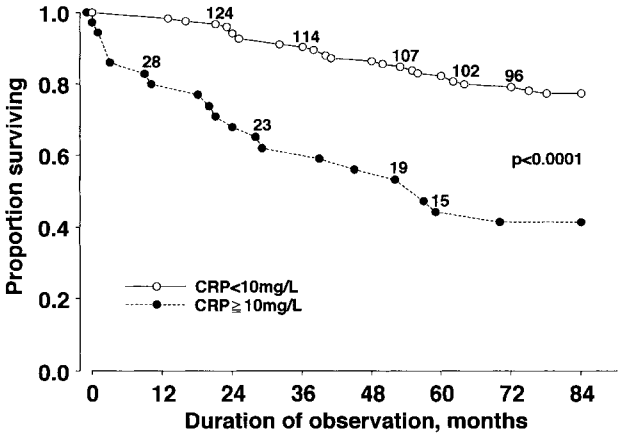

Fig. 1. Survival curves calculated by Kaplan–Meier method according to baseline CRP concentration.

Table 3. Number of patients, death, and renal transplantation and mean (SD) levels of serum albumin by the baseline serum CRP

	CRP (mg/l)			
	0–1	2–3	4–9	⩽10
Number of				
Patients	40	46	42	35
Death	3	14	11	20
Renal transplantation	3	3	1	1
Serum albumin (g/l)				
Mean	39	39	37	36
SD	2	3	4	3

Table 4. Risk ratio (95% confidence interval) of death by baseline CRP

Variable	Risk ratio (95% CI)	*P*
CRP only	3.45 (1.93–6.17)	<0.0001
CRP plus sex, age, DM, year starting dialysis, diastolic blood pressure, serum albumin	3.48 (1.76–6.89)	<0.0003

Table 5. Medical conditions of patients by baseline CRP

	Infection	Arthralgia	Shunt trouble	Other
CRP<10 mg/l, $n=128$	31 (24.2%)	36 (28.1%)	6 (4.7%)	7 (5.5%)
CRP⩾10 mg/l, $n=35$	13 (37.1%)	7 (20.0%)	3 (8.6%)	7 (20.0%)
P value	0.127	0.334	0.372	0.007

Discussion

Cardiovascular mortality is high in a population on chronic dialysis. In particular, acute myocardial infarction is more common in winter than summer [10]. This is also true in Okinawa [11], and is partly

Table 6. Follow-up determinations of CRP

Time	All		CRP<10 mg/l		CRP⩾10 mg/l	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1991						
Jan.	163	10.2 (19.9)	128	3.0 (2.3)	35	37.0 (30.3)
Feb.	155	9.4 (19.5)	123	5.4 (12.7)	32	24.9 (30.6)
Mar.	152	9.3 (17.6)	121	5.2 (10.8)	31	25.5 (27.6)
Aug.	148	8.1 (23.8)	120	2.5 (7.4)	28	32.1 (45.9)
1992						
Mar.	136	11.7 (18.0)	110	8.2 (8.7)	26	26.5 (33.7)
Aug.	134	8.4 (15.8)	110	5.2 (7.1)	24	22.8 (30.8)
Dec.	127	11.6 (25.3)	105	7.6 (16.1)	22	30.5 (45.6)

n denotes number of patients.

explained by the greater incidence of respiratory infection in the winter months. One study has shown that a period of about 2 weeks after acute respiratory infection is associated with an increased risk of acute myocardial infarction in the general population [12].

The potential or hidden causes of tissue damage can be easily detected by measuring C-reactive protein, and since CRP responds very rapidly to tissue injury it has consequently become one of the best laboratory indicators for monitoring disease activity [4,5]. Infection and tissue injury, if diagnosed in the early phases, can be treated accordingly by antibiotics, or anti-inflammatory drugs. Patients with high CRP levels thereafter are believed to suffer from multiple insults. Uraemia *per se* or poorly dialysed patients may show delayed recovery from tissue damage and anorexia. Blood-access failure or miss-puncture may underlie these cases. Dialysis equipment, such as the biocompatible membrane dialyser, may also contribute to this damage [13]. Thus, the nutritional state of such patients may deteriorate quite rapidly. However, if detected in the early phase, intradialysis parenteral nutritional support may help rectify this situation [14].

Hypoalbuminaemia has been reported to be a strong predictor of death, particularly for cardiovascular death, in chronic dialysis patients [8,15]. The causes of hypoalbuminaemia are multifactorial, and may well include infection and other tissue damage. Studies have shown that the synthesis of albumin is normal in dialysis patients if the calorie intake is in the normal range [16].

Chronic dialysis patients have multiple symptoms that may aggravate atherosclerosis. Unfortunately, changes of the atherogenic risk factors such as Lp(a), fibrinogen, HDL-C, and others were not examined in this study. It is quite common to see disturbed lipoprotein metabolism in dialysis population. Even in normotensive dialysis patients, the incidence of stroke is higher than that of the general population [17]. However, whether dialysis *per se* accelerates atherosclerosis remains debatable [18], since the acceptance of sicker patients for dialysis has increased recently [1]. It is intriguing that high CRP levels appear to be enhancing atherosclerosis [19] or indication of ongoing vascular damage [20].

Results showed that even a single determination of CRP is predictive of the prognosis of dialysis patients. Therefore, regular check of CRP may be helpful to detect early sign of tissue damage or asymptomatic inflammation. If it stays at high levels, further work-up is warranted. Obtaining the time-average values of CRP for the analysis may be biased, since the high CRP patients will die soon (Table 6). For the Cox regression models the use of baseline determination is recommended over the use of time-averaged values in prospective studies [21].

In summary, the present study showed that high CRP levels are a strong predictor of death in chronic dialysis patients, and strongly supports recent findings [20], but contradict another report [22]. Due to the rapid response to tissue injury, CRP is a more sensitive marker than serum albumin. Further investigation is necessary to establish the significance of this observation for improving outcomes in a larger patient population.

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