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Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients

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Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients.

Background. Although hypocholesterolemia is common in chronic hemodialysis patients, its effect on survival has not been studied in a large patients population.

Methods. A cohort of chronic hemodialysis patients (N = 1167) was prospectively followed from January 1991 to January 2001. The survival impact of this cohort, who were divided according to different baseline levels of serum cholesterol, were calculated with the multivariate Cox proportional hazard analysis after adjusting for baseline clinical and laboratory variables.

Results. During the study period, 567 (48.6%) patients died. The mean (SD) baseline level of serum cholesterol was 171.0 (40.8) mg/dL and ranged from 76 to 378 mg/dL. The five-year survival rate was highest (0.812) in the subgroup that had a serum cholesterol range of 200 to 219 mg/dL and was lowest (0.608) in the subgroup with serum cholesterol values of <140 mg/dL. The five-year survival rate was 0.735 in the subgroup with serum cholesterol of ≥220 mg/dL. Serum cholesterol was a significant predictor of death with an adjusted hazards ratio (95% confidence interval) was 0.939 (0.891 to 0.989). In a subgroup of patients with serum albumin values ≥4.5 g/dL (N = 128), the adjusted hazards ratio was even greater at 1.370 (1.105 to 1.692). Other than sex, body mass index and serum albumin were significant determinants of baseline levels of serum cholesterol.

Conclusions. Hypocholesterolemia was an independent predictor of death in patients on chronic hemodialysis. This impact of hypercholesterolemia on survival was only evident in a subgroup of patients whose serum albumin was more than 4.5 g/dL.

Cardiovascular disease is a common cause of death in chronic hemodialysis patients [1, 2] and hypercholesterolemia is a conventional risk factor of cardiovascular disease in the general population [3, 4]. However, serum cholesterol is often low in dialysis patients, probably because of malnutrition and chronic inflammation [5, 6]. Previous reports have noted a significant association between low serum cholesterol and mortality in the general population [7] and in dialysis patients [8, 9]. We have previously observed a higher prevalence of cerebral hemorrhage in both the general population [10] and chronic dialysis patients who have low serum cholesterol [11]. Few studies have examined the role of serum cholesterol in the prognosis of chronic dialysis patients. For this purpose, we studied a cohort of chronic hemodialysis patients over a ten-year period.

In the present study, we examined the significance of baseline levels of serum cholesterol for the prognosis of chronic hemodialysis patients after adjusting for confounding variables such as age, sex, presence of diabetes mellitus, duration of dialysis, serum albumin, and body mass index. We also looked at the determinants of baseline levels of serum cholesterol.

Key words: hypoalbuminemia, hypercholesterolemia, dialysis, serum cholesterol, risk factors in HD, Japan and hemodialysis.

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METHODS

Cohort of chronic hemodialysis patients

Patients (N = 1243) who were on chronic hemodialysis in January 1991 were prospectively followed until January 2001 (10 years).

Chronic hemodialysis patients were defined as those who survived for at least one month while on a regularly scheduled dialysis treatment. The Okinawa Dialysis Study (OKIDS) registry contains the records of all dialysis patients who have resided in Okinawa since 1971, and details of this registry have been published before [11–13]. The registry includes patient name, sex, birth date, start date of dialysis, primary renal disease, and other pertinent data. The dialysis regimen in Okinawa is similar to that in other parts of Japan [11–13]. The medical policy and health care systems for dialysis therapy in Japan were reviewed recently [14]. More than 83% of the patients in our OKIDS registry underwent dialysis three times per week. The dialysis period per session was 3.0 to 3.5 hours in 5.2%, 3.5 to 4.0 hours in 57.0%, 4.0 to 5.0 hours in 10.0%, and more than 5.0 hours in 27.8%. The median blood flow rate was 200 mL/min. A bicarbonate solution was used as the dialysate in all units.

Dialyzer reuse is exceptional in Japan. The baseline laboratory values were obtained before routine hemodialysis in January 1991 [6, 13]. Laboratory and clinical data including body weight, height, blood pressure, blood urea nitrogen (BUN), serum creatinine, total cholesterol, triglyceride, total protein, serum albumin, and uric acid were filed in the computer registry. In a subgroup of patients, data for C-reactive protein (CRP; $N = 158$) also were available [15]. Body height was measured within six months of the start of the study and body mass index (BMI) was defined as the ratio of weight to height squared (kg/m^2). Causes of death were noted as infection, dialysis withdrawal, cardiac, sudden death, vascular, and others. Death associated with withdrawal occurred in patients who had severe cachexia or malnutrition or who were hemodynamically unstable and thus unable to undergo regular dialysis.

All patients were followed-up until death, renal transplantation, transfer outside of Okinawa, or January 1, 2001. Seventy-six patients were excluded from the study: 61 for renal transplantation, 14 transferred outside Okinawa, and one for whom serum cholesterol data was unavailable. Therefore, 1167 patients, 680 men and 487 women, were enrolled in the present study. No patients were lost to follow-up.

Statistical analysis

The unpaired *t* test and the chi square test were used to analyze differences in discrete variables between the groups. Survival curves were calculated by the Kaplan-Meier method. Cox proportional hazard analysis was done to examine the significance of baseline level of serum cholesterol as a predictor of prognosis for survival after adjusting for confounding variables with an SAS model. Determinants of baseline levels of serum cholesterol were examined by multivariate logistic analysis. Data are expressed as mean (SD). *P* values less than 0.05 were considered statistically significant.

RESULTS

Demographics of the cohort of chronic hemodialysis patients are summarized in Table 1. The number of deaths was 567 (48.6%) over ten years.

Baseline serum cholesterol levels were distributed as shown in Figure 1. The mean ± SD level of serum cholesterol was 171.0 ± 40.8 mg/dL and ranged from 76 to 378 mg/dL.

Several pertinent results are summarized by subgroups of the baseline serum cholesterol levels in Table 2. Serum triglyceride levels increased in all groups with increases in the serum cholesterol level except for the baseline 200 to 219 mg/dL group. However, the mean levels of serum albumin remained constant, and the baseline levels of serum cholesterol and serum albumin were not significantly associated.

Table 1. Demographics of the study patients

Number of patients	1167
Men	680 (58.3%)
Age at start of study *years*	
Mean	52.6
SD	14.6
Range	15 to 92
Duration of dialysis *months*	
Mean	62.8
SD	50.8
Range	1 to 233
Primary renal disease	
Chronic glomerulonephritis	776 (66.5%)
Diabetes mellitus	208 (17.8%)
Systemic lupus erythematosus	18 (1.5%)
Polycystic kidney disease	28 (2.4%)
Nephrosclerosis	58 (5.0%)
Others	79 (6.8%)
Outcome	
Alive	600 (51.4%)
Dead	567 (48.6%)

The study period was from January 1991 to January 2001.

The ten-year mortality rate as differentiated by subgroup of serum cholesterol level is shown in Figure 2. The mortality rate was lowest (35.9%) at the baseline serum cholesterol level of 200 to 219 mg/dL and the highest (57.2%) at the serum cholesterol of less than 140 mg/dL. The survival curves by baseline level of serum cholesterol are shown in Figure 3. The five-year survival rates were 60.8%, 68.3%, 69.7%, 78.5%, 81.2%, and 73.5% from the lowest to the highest levels of baseline serum cholesterol, respectively. The survival rate was best in the subgroup with a serum cholesterol range of 200 to 219 mg/dL.

The distribution of causes of death is shown in Table 3. Cardiovascular death such as death due to a cardiac event plus sudden death was highest (35.5%) in the group of the highest level of baseline serum cholesterol (≥220 mg/dL). In contrast, cerebrovascular death was highest (22.4%) in the lowest level of baseline serum cholesterol (<140 mg/dL).

Results of the multivariate Cox proportional hazards analysis are summarized in Table 4. The hazards ratio (95% confidence interval; 95% CI) for subgroups according to serum cholesterol levels was 0.939 (0.891 to 0.989), which was significant ($P = 0.0180$). With the lower serum cholesterol levels the mortality rate was high, and significant even after adjusting for serum albumin, BMI, and other variables. The adjusted hazard ratio (95% CI) was 0.997 (0.996 to 0.999) for every mg/dL of serum cholesterol.

Effects of serum cholesterol on survival were further analyzed in relation to the baseline levels of serum albumin (Table 5). The adjusted hazards ratio (95% CI) for those with serum albumin levels of 3.5 to 3.9 g/dL was 0.911 (0.839 to 0.989), which suggests an inverse relation-

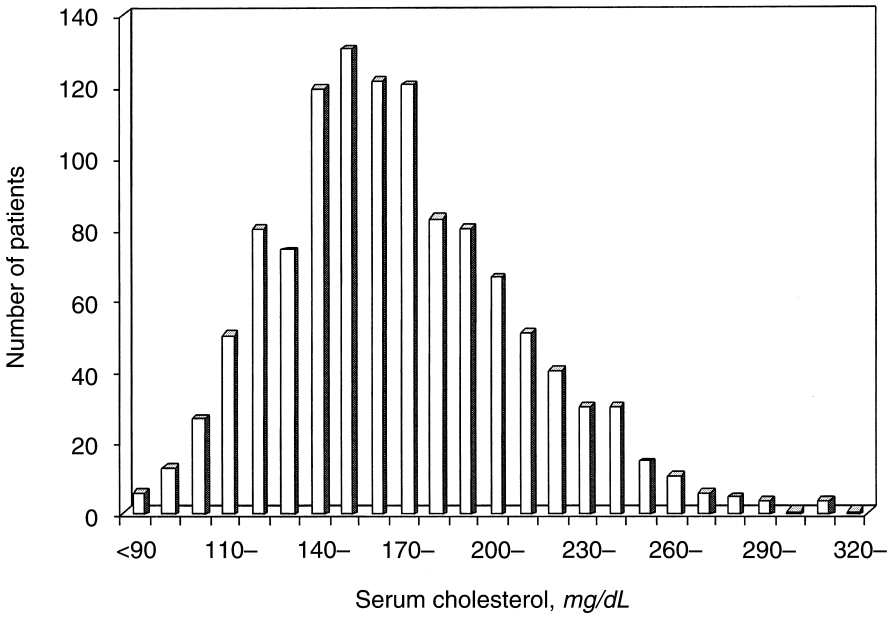

Fig. 1. Distribution of baseline levels of serum cholesterol. Baseline data were obtained before a regular hemodialysis session in January 1991.

Table 2. Mean (SD) levels of serum cholesterol, triglyceride, and albumin, and body mass index (BMI) at the baseline grouped by serum cholesterol subgroup

	Baseline levels of serum cholesterol *mg/dL*					
	<140 *N* = 250	140–159 *N* = 249	160–179 *N* = 241	180–199 *N* = 163	200–219 *N* = 117	≥220 *N* = 147
Serum cholesterol *mg/dL*						
Mean	121.2	149.5	169.0	189.0	208.6	246.4
SD	13.1	5.9	5.6	5.7	5.6	24.8
Range	76–139	140–159	160–179	180–199	200–219	220–378
Serum triglyceride *mg/dL*						
Mean	108.8	130.3	150.9	202.0	191.3	238.1
SD	55.5	70.8	86.3	129.1	119.6	131.9
Range	15–424	22–538	37–591	39–964	52–773	52–924
Serum albumin *g/dL*						
Mean	3.8	3.9	3.9	3.9	3.9	3.9
SD	0.5	0.5	0.5	0.4	0.4	0.5
Range	2.0–5.3	2.5–5.1	2.5–6.0	2.8–5.1	2.9–4.9	2.8–5.3
BMI kg/m^2						
Mean	20.9	21.2	21.3	22.5	22.2	22.8
SD	2.9	3.0	3.0	3.5	3.2	3.5
Range	15.2–33.4	14.3–32.1	14.6–31.0	14.2–35.2	16.6–37.7	14.9–34.0

ship between death risk and the level of serum cholesterol. However, in the subgroup of patients with serum albumin ≥4.5 g/dL, the adjusted hazards ratio was 1.370 (1.109 to 1.692, $P = 0.0034$), suggesting that there is a positive relationship between death risk and level of serum cholesterol. In this group of patients, hypercholesterolemia was a significant risk factor for death.

Determinants of serum cholesterol were analyzed by multivariate logistic analysis (Table 6). Other than sex, BMI and serum albumin were significant determinants of serum cholesterol. Hypocholesterolemia was associated with significantly higher levels of serum CRP and a higher prevalence of high CRP (Table 7).

DISCUSSION

The present study showed that hypocholesterolemia is an independent predictor of death in chronic hemodialysis patients. This is true even after adjusting for other possible confounders affecting baseline levels of serum cholesterol such as age [16], BMI, and serum albumin. Hypocholesterolemia is common in the chronic dialysis population; however, the mechanisms are not well delineated. Cytokinemia, which may be related to impaired removal of substances or to exposure of dialysis patients to an occult chronic inflammation, is one of the causes of hypocholesterolemia [5]. Declining serum cholesterol

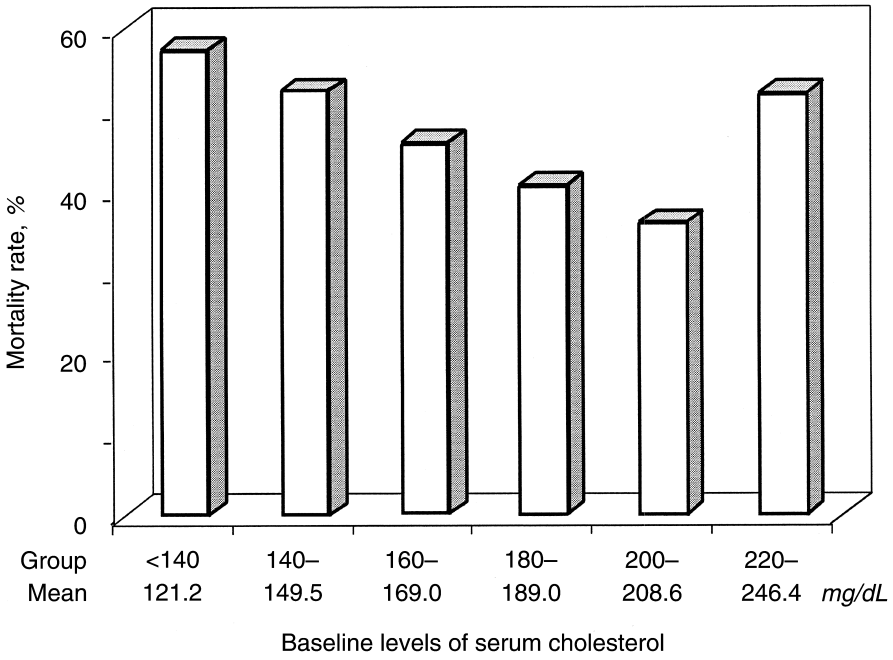

Fig. 2. Relationship between mortality rate and subgroups of baseline levels of serum cholesterol. Baseline data were obtained before regular hemodialysis session in January 1991.

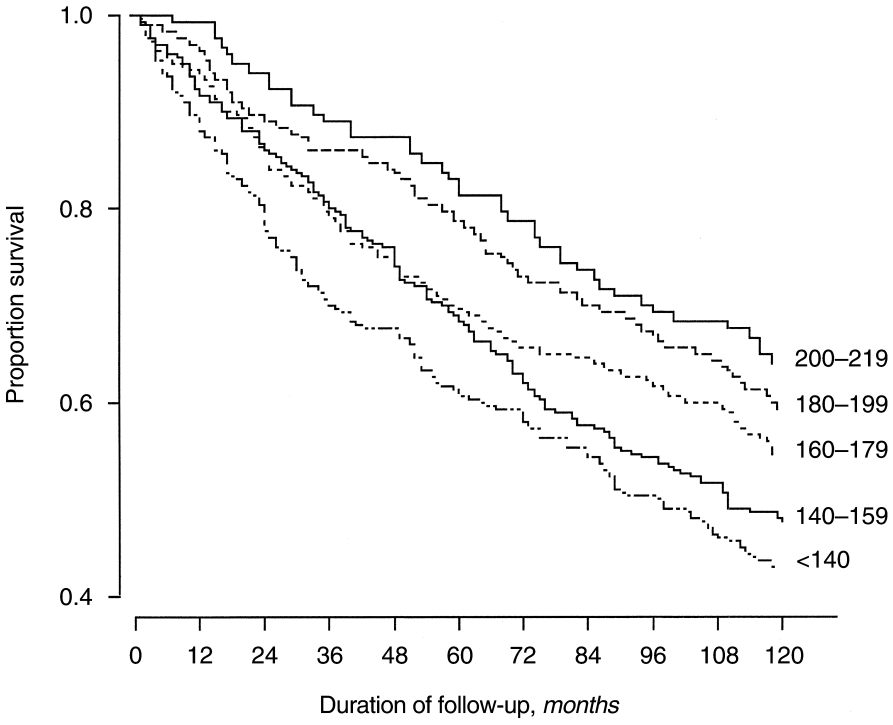

Fig. 3. Survival curves based on the baseline groups divided by serum cholesterol level.

levels in chronic dialysis patients may be an indicator of either declining health or dietary, metabolic, and other clinical abnormalities similar to those associated with old age [7]. Serum cholesterol level has been used an indicator of energy intake [17]. In our dialysis population, the mean level of serum cholesterol was significantly lower than that of the general population in our region [3, 10].

A significant impact of hypocholesterolemia was previously suggested in both the general population [7] and dialysis patients [8, 9]. A low level of serum cholesterol may indicate the existence of malnutrition and is often associated with a low level of serum albumin. Actually, serum albumin level was strongly associated with serum cholesterol level in our dialysis patients (Table 6) and

Table 3. Causes of death according to the baseline levels of serum cholesterol

	Serum cholesterol *mg/dL*						
Cause of death	<140 *N* = 250	140–159 *N* = 249	160–179 *N* = 241	180–199 *N* = 163	200–219 *N* = 117	≥220 *N* = 147	Total *N* = 1167
Infection	23.1%	19.2%	17.3%	16.7%	19.0%	18.4%	19.4%
Withdrawal	21.0%	20.0%	13.6%	22.7%	14.3%	17.1%	18.5%
Cardiac	18.2%	28.5%	23.6%	28.8%	26.2%	27.6%	24.7%
Sudden death	4.2%	3.8%	5.5%	3.0%	7.1%	7.9%	4.9%
Cerebrovascular	22.4%	12.3%	20.0%	15.2%	11.9%	14.5%	16.9%
Others	11.2%	16.2%	20.0%	13.6%	21.4%	14.5%	15.5%
Number of deaths	143	130	110	66	42	76	567

The total percentage may not be 100% because of rounding.

Table 4. Results of multivariate Cox proportional hazards analysis of risk of death in chronic hemodialysis patients

Variables	Hazard ratio	95% CI	*P* value
Men vs. women	1.321	1.111–1.571	0.0016
Age *years*	1.060	1.052–1.067	<0.0001
DM vs. non-DM	2.271	1.863–2.767	<0.0001
Serum albumin *g/dL*	0.624	0.514–0.757	<0.0001
BMI kg/m^2	0.971	0.945–0.998	0.0364
HD duration *months*	1.028	1.005–1.051	0.0156
Serum cholesterol[a]	0.939	0.891–0.989	0.0180

Abbreviations are: CI, confidence interval; DM, diabetes mellitus; BMI, body mass index; HD, hemodialysis. The hazards ratio was calculated after adjusting for other variables in this Table. Observation period was from January 1991 to January 2001.

[a] Serum cholesterol was grouped into 6 groups as in Table 2

Table 5. Multivariate Cox proportional hazards analysis relating to the risk of death categorized by serum albumin subgroup of total cholesterol (TC)

S_{Alb} level	Mortality rate %	TC *mg/dL mean (SD)*	Hazards ratio	95% CI
<3.5 *g/dL* (*N* = 200)	70.0	163.1 (45.1)	0.912	0.827–1.006
3.5–3.9 *g/dL* (*N* = 482)	53.7	171.5 (38.6)	0.911[a]	0.839–0.988
4.0–4.4 *g/dL* (*N* = 354)	35.9	172.9 (40.8)	0.949	0.844–1.068
≥4.5 *g/dL* (*N* = 128)	31.3	176.2 (41.1)	1.370[b]	1.109–1.692

The effect of total cholesterol was evaluated in each subgroup related to baseline levels of serum albumin (S_{Alb}). The hazards ratio was calculated after adjusting for sex, age, presence of diabetes mellitus, body mass index, and duration of dialysis.

[a] $P = 0.0249$, [b] $P = 0.0034$

Table 6. Determinants of baseline levels of serum cholesterol examined by multivariate logistic analysis

Variables	Odds ratio	95% CI	*P* value
Men vs. women	0.472	0.381–0.586	<0.0001
Age *years*	0.999	0.992–1.007	NS
DM vs. non-DM	0.929	0.696–1.239	NS
Serum albumin *g/dL*	1.627	1.293–2.047	<0.0001
BMI kg/m^2	1.138	1.101–1.176	<0.0001
HD duration *months*	1.002	1.000–1.004	NS

Abbreviations are: DM, diabetes mellitus; BMI, body mass index; HD, hemodialysis. The odds ratio was calculated including variables in this Table.

Table 7. Serum levels of C-reactive protein (CRP) grouped by serum cholesterol level in January 1991

	Serum cholesterol *mg/dL*			
	<160	160–199	≥200	Total
Number of patients	55	68	35	158
CRP *mg/dL*				
Mean	1.3[a]	0.5	1.2	0.9
SD	1.9	0.7	2.3	1.7
% with high CRP	29.1[b]	13.3	22.9	20.9

High CRP was defined as CRP ≥ 1.0 mg/dL.

[a] $P < 0.007$, [b] $P < 0.03$ compared to serum cholesterol of 160–199 mg/dL

in other studies [17]. Patients with hypoalbuminemia have a poor prognosis for survival [8, 13, 18], and they often have high CRP levels, suggesting chronic inflammation [19, 20]. In our study, a higher prevalence of elevated CRP was observed in patients with hypocholesterolemia (Table 7). Therefore, hypocholesterolemia may be another surrogate marker of health status of chronic dialysis patients. Malnutrition may contribute to a poor prognosis by aggravating pre-existing heart failure and increasing the susceptibility to infection [20].

Hypercholesterolemia is a conventional risk factor for cardiovascular events [3, 21, 22]. In our dialysis patients, serum cholesterol was also an independent, positive predictor of high risk for death in a subgroup of patients with high serum albumin ≥4.5 g/dL, suggesting that the higher the serum cholesterol the greater the risk of death (Table 5). Death from cardiovascular events was more prevalent in patients with high levels of serum cholesterol than in those with low levels (Table 3).

Recently, we observed a significant association between coronary artery calcification and dyslipidemia in chronic hemodialysis patients [23]. Dialysis patients often have altered lipid and lipoprotein profiles, a condition known as uremic dyslipidemia. Such abnormalities may be an important factor for accelerated atherosclerosis in dialysis patients [24, 25]. Unfortunately, lipid profiles such as high density lipoprotein (HDL)-cholesterol and lipoprotein(a) were not available in the present study.

The long-term survival rate for the group of dialysis

patients who had suffered acute myocardial infarction (AMI) was lower than that of the general population in both our series [26] and a group of US patients [27]. However, the incidence of AMI is much lower in Japan than in the United States. This difference cannot be attributed to the differences in basal serum cholesterol level between the populations of these two countries [28]. Changes in lifestyle and dietary habits have greatly influenced the mortality ratio from coronary heart disease and stroke [29].

There are some limitations to the present study results. First, the serum cholesterol values in the present study were obtained cross sectionally and thus, they may not represent the true status of each patient. However, as a whole, the serum cholesterol values were distributed normally in our cohort of patients (Fig. 1). Less than 10% of our patient population received 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the use of which began in August 1989 [3, 10]. Second, patients with low serum cholesterol levels are a heterogenous group comprising those with (*1*) lifelong low serum cholesterol levels and low coronary disease risk and (*2*) greater-than-usual decreases in serum cholesterol level and a high mortality rate [7]. Factors affecting the serum cholesterol level such as dietary intake amount, physical activity, and metabolic and hormonal factors were not examined in the present study. The rapid decrease in deaths due to stroke in Japan was explained, at least partly, by an increase in serum cholesterol contributing to the longevity of the Japanese population [30, 31]. With a longer duration of treatment, more patients become institutionalized [32], and the prevalence of various disorders may result in increased risk for hypocholesterolemia. Finally, further prospective studies are needed to establish a target level of serum cholesterol that will reduce the risk of mortality in the dialysis population. Cholesterol lowering drugs may only be indicated in patients with hypercholesterolemia when the serum albumin level is normal ($\geq$4.5 g/dL). Of course, patients with hypocholesterolemia should be evaluated for the underlying causes of hypocholesterolemia such as malnutrition and inflammation [17, 20], and should be encouraged to increase their energy intake and physical activity, if possible.

In summary, the present study documents the significant association between serum cholesterol level and the prognosis for survival in a cohort of chronic hemodialysis patients. A U-shaped curve phenomenon was observed between the death rate and the level of serum cholesterol. In addition to hypoalbuminemia and low BMI, hypocholesterolemia is an important clinical parameter of health status of chronic hemodialysis patients.

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