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ORIGINAL ARTICLE

The Correlation between Serum Lipoprotein(a) and Risk of Mortality in Patients on Peritoneal Dialysis

Ling-Cang Xu [1, 2], Fang-Fang Zhou [1, 2], Meng Li [1, 2], Zhi-Wei Dai [1, 2], Hai-Xue Lin [1, 2], Bei-Xia Zhu [1, 2], Qun Luo [1, 2]

[1] *Department of Nephrology, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang Province, China*
[2] *Ningbo Institute of Life and Health Industry, University of Chinese Academy of Sciences, Ningbo, Zhejiang Province, China*

SUMMARY

Background: **Patients with peritoneal dialysis commonly have severe disorders of lipid metabolism, with particularly severe changes in serum lipoprotein(α) [Lp(α)]. Serum Lp(α) may play a role in the risk of mortality in peritoneal dialysis patients. The aim was to investigate the correlation between high serum Lp(α) levels and all-cause mortality and death from cardiovascular events and infection in peritoneal dialysis patients.**

Methods: **Three hundred and ninety-two patients with end-stage kidney disease who started peritoneal dialysis treatment between March 1, 2007 and May 31, 2020, were selected. Clinical data of all enrolled patients after 3 months of peritoneal dialysis were collected. Based on the median value of serum Lp(α) level, all enrolled patients were divided equally into a high serum Lp(α) level group (> 275.95 mg/L, n = 196) and a low serum Lp(α) level group (< 275.95 mg/L, n = 196). SPSS25.0 statistical software was used to analyze the factors affecting serum Lp(α) levels and the correlation between high serum Lp(α) levels and all-cause mortality and death from cardiovascular events and infection in peritoneal dialysis patients.**

Results: **Binary multivariate logistic regression analysis showed that higher low-density lipoprotein (LDL) levels (OR = 1.614, 95% CI: 1.261 - 2.068, p = 0.000) and high Body Mass Index (BMI) levels (OR = 1.063, 95% CI: 1.004 - 1.126, p = 0.036) were the risk factors for the high serum Lp(α) levels. High serum albumin levels (OR = 0.959, 95% CI: 0.927 - 0.991, p = 0.014) and high parathyroid hormone levels (OR = 0.999, 95% CI: 0.997 - 1.000, p = 0.010) were protective factors for the high serum Lp(α) levels. The cumulative survival of patients in the high serum Lp(α) level group was lower in death from cardiovascular events as shown by Kaplan-Meier survival analysis (Log-rank test χ^2 = 4.348, p = 0.037). Multivariate Cox regression analysis showed that high serum Lp(α) levels were an independent risk factor for death from cardiovascular events in peritoneal dialysis patients (HR = 1.002, 95% CI: 1.001 - 1.003, p = 0.001).**

Conclusions: **The occurrence of high serum Lp(α) levels in peritoneal dialysis patients was positively associated with LDL and BMI, and negatively associated with serum albumin and parathyroid hormone levels. High serum Lp(α) levels were related to the risk of death from cardiovascular events in peritoneal dialysis patients.**
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Correspondence:
Qun Luo
Department of Nephrology
Hwa Mei Hospital
University of Chinese Academy of Sciences
No. 41, Northwest Street
Ningbo
Zhejiang Province, 315010
China
Phone/Fax: + 86 574-83870217
Email: luoqun@ucas.ac.cn

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INTRODUCTION

Peritoneal dialysis (PD) is an effective renal replacement therapy for patients with end-stage kidney disease. It uses the peritoneum as a biological dialysis membrane relying on diffusion, convection, and ultrafiltration to remove retained metabolites, correct electrolytes, acid-base imbalances, and remove excess water. Compared with hemodialysis, it has the advantages of low cost, simple operation, low impact on hemodynamics, good residual kidney function protection, etc. [1,2]. Therefore, this technique is frequently employed in clinical practice; however, the long-term clinical prognosis of PD patients remains poor, and the factors influencing their prognosis are complex. In addition, cardiovascular disease (CVD) is the leading cause of death in PD patients, accounting for approximately 40% of mortality in dialysis patients worldwide [3,4]. Therefore, studying the risk factors that lead to death from CVD in PD patients and providing active and effective interventions will be beneficial in improving PD patients' survival rates.

Patients with PD commonly have severe disorders of lipid metabolism [5-8], with particularly extreme changes in serum lipoprotein(α) [Lp(α)], triglycerides, and high-density lipoprotein. Serum Lp(α) is a lipoprotein with a specific structure synthesized by the liver, consisting primarily of proteins, lipids, and sugars. Its lipid composition is similar to that of low-density lipoprotein (LDL). The apolipoprotein it contains is covalently bound by apolipoprotein A (Apo A) and apolipoprotein B100 (Apo B100) with disulfide bonds [9-11]. The precise mechanism of its action on blood vessels is unknown. However, *in vitro* and animal studies have demonstrated that serum Lp(α) can penetrate the intima, causing thrombosis, inflammation, and the formation of foam cells [12].

High serum Lp(α) levels have been shown in studies to be an independent risk factor for atherosclerosis, coronary heart disease, stroke, and death from CVD [10,13], and serum Lp(α) may also play a role in death from CVD in dialysis patients [14]. In the previous study, lipoproteins with a lower risk of serious infection have been identified in hemodialysis patients [15]. Moreover, high serum Lp(α) levels were found to be a risk factor for all-cause mortality in type 2 diabetic hemodialysis patients [16]. In one another study, the PD patients were found to have significantly higher serum Lp(α) levels than hemodialysis patients [17]. However, there are few studies on the correlation between high serum Lp(α) levels and all-cause mortality, and death from CVD and infection in PD patients. Therefore, in our study, serum Lp(α) levels in PD patients will be analyzed to investigate their correlation with all-cause mortality, CVD death, and infection-related mortality in PD patients.

MATERIALS AND METHODS

General information

Before collecting data, we estimated the sample size by the two-sided test with G Power 3.1. In this two-sided test, we set as effect size = 0.5, $\alpha = 0.05$, and $1\text{-}\beta = 0.9$, then found that it was 174. Our sample size met the statistical requirements. This study was conducted retrospectively and included patients who started PD treatment with an indwelling peritoneal dialysis tube at the Department of Nephrology, Hwa Mei Hospital, University of Chinese Academy of Sciences, from March 1, 2007, to May 31, 2020. Inclusion criteria included: age $\geq$ 18 years, duration of PD treatment $\geq$ 3 months, and regular follow-up. Exclusion criteria included: patients who received indwelling peritoneal dialysis tubing in other hospitals, patients who underwent hemodialysis for more than 3 months before PD, previous history of renal transplantation, death or CVD within 3 months after PD, patients with chronic liver disease and severe liver function abnormalities, patients with combined pregnancy or malignancy, patients treated with blood transfusion within 3 months before the study, and patients with incomplete clinical data. This study was approved by the Ethics Committee of Hwa Mei Hospital, University of Chinese Academy of Sciences, (No. PJ-KY-NBEY-2016-016-01). Written informed consent was waived because this study was retrospective in nature.

Data collection

All patients were followed up until death, transfer to renal transplantation, transfer to hemodialysis treatment, and transfer to other dialysis centers, lost to follow-up, or as of October 31, 2020, via outpatient clinics, telephone, and WeChat. Baseline clinical data were collected from all enrolled patients 3 months after dialysis, including demographics: gender, age, causes of renal failure, history of smoking, history of alcohol consumption, systolic blood pressure, diastolic blood pressure, heart rate, body mass index (BMI), hypertension, diabetes, heart disease, cerebrovascular disease, laboratory biochemical parameters: serum Lp(α), complete blood count, sodium, potassium, chloride, calcium, bicarbonate, fasting glucose and glycated hemoglobin, hemoglobin, serum albumin, alkaline phosphatase, blood creatinine, urea nitrogen, uric acid, blood phosphorus, C-reactive protein, total serum bilirubin, aspartate aminotransferase, alanine aminotransferase, parathyroid hormone, high-density lipoprotein, low-density lipoprotein (LDL), triglycerides, total cholesterol, 24-hours urine output, and estimated glomerular filtration rate (eGFR), and dialysis-related data: Kt/V, normalized protein catabolic rate, erythropoietin dose and peritoneal equilibra-

tion test. eGFR was calculated by referring to the CKD-EPI formula. All laboratory biochemical indices were obtained from the same laboratory, and serum Lp(α) levels were determined by immunoturbidimetric assay. In addition, information on the clinical transition and cause of death of patients was recorded. The diagnosis of death determined that CVD factors were the direct cause of death, which was determined jointly by the supervising physician and the supervising nurse. Based on the median values of serum Lp(α) levels collected, all enrolled patients were equally divided into high and low serum Lp(α) level groups.

Statistical methods

SPSS25.0 software was used to analyze the data statistically, and the mean ± standard deviation ($\bar{x} \pm s$) was used for measurement data that conformed to a normal distribution, and the *t*-test was used for comparison between two groups; measurement data that did not conform to normal distribution were expressed as $M(_{P25\text{-}P75})$. The Mann-Whitney U test was used for comparison between the two groups; the count data was expressed as a rate (%), and the χ^2 test was used for comparison between the two groups; the factors influencing high serum Lp(α) levels were analyzed by binary multivariate logistic regression, the survival prognosis of the two groups was compared by Kaplan-Meier survival analysis. The correlation between high serum Lp(α) levels with all-cause mortality and CVD mortality in PD patients was analyzed by multivariate Cox regression. $p < 0.05$ was considered a statistically significant difference.

RESULTS

Baseline demographic and clinical characteristics of patients

According to the screening criteria, 392 patients were enrolled in this study between March 1, 2007, and May 31, 2020. Based on the median value of serum Lp(α) levels in all enrolled patients, patients were equally divided into a high serum Lp(α) level group (> 275.95 mg/L, n = 196) and a low serum Lp(α) level group (< 275.95 mg/L, n = 196). The age of the patients was 57.50 (47.00, 70.00) years, and 225 (57.40%) were male.

Comparison of baseline information between groups

In comparison to the low serum Lp(α) level group, the high serum Lp(α) level group had a higher proportion of male patients, higher levels of bicarbonate, glycated hemoglobin, LDL, total cholesterol, and C-reactive protein, and lower levels of heart rate, serum albumin, and aspartate aminotransferase ($p < 0.05$). In addition, age, causes of renal failure, smoking history, alcohol history, systolic blood pressure, diastolic blood pressure, BMI, percentage of patients with hypertension, percentage of patients with diabetes mellitus, percentage of patients with heart disease, percentage of patients with cerebrovascular disease, complete blood count, sodium, potassium, chloride, calcium, fasting glucose, hemoglobin, alkaline phosphatase, blood creatinine, urea nitrogen, uric acid, blood phosphorus, total serum bilirubin, alanine aminotransferase, parathyroid hormone, high-density lipoprotein, triglycerides, 24-hours urine volume, eGFR, Kt/V, normalized protein catabolic rate, erythropoietin dose and peritoneal equilibration test in both groups had no statistically significant differences ($p > 0.05$) (Table 1).

Results of binary multivariate logistic regression analysis of factors associated with high serum lipoprotein(α) levels

High LDL levels (OR = 1.614, 95% CI: 1.261 - 2.068, p = 0.000) and high BMI levels (OR = 1.063, 95% CI: 1.004 - 1.126, p = 0.036) were risk factors for the occurrence of high serum Lp(α) levels. High serum albumin levels (OR = 0.959, 95% CI: 0.927 - 0.991, p = 0.014) and high parathyroid hormone levels (OR = 0.999, 95% CI: 0.997 - 1.000, p = 0.010) were protective factors for the development of high serum Lp(α) levels (Table 2).

Survival analysis of all-cause mortality, CVD death, and infection-related mortality in patients with different serum lipoprotein(α) levels

The follow-up period of this study was up to October 31, 2020. Among them, 71 (18.11%) patients died, 12 (3.06%) patients received renal transplantation, 41 (10.46%) patients were transferred to hemodialysis, 51 (13.01%) patients were transferred to other dialysis centers, 5 (1.28%) patients were lost to follow-up, and the remaining 212 (54.08%) patients continued to be followed up in our center. Of the 71 patients who died, 44 (61.97%) died due to cardiovascular disease (CVD), 10 (14.08%) died due to infection, 1 (1.41%) died due to gastrointestinal bleeding causes, 5 (7.04%) died due to malnutrition, and 11 (15.49%) died due to other causes. Survival curves of patients in different serum Lp(α) level groups showed that cumulative all-cause mortality at years 1, 3, and 5 after PD initiation was 5.61% (11/196), 13.27% (26/196), and 17.35% (34/196) in patients in the high serum Lp(α) level group, and 5.10% (10/196), 9.18% (18/196), and 10.71% (21/196) in the low serum Lp(α) level group, respectively. The comparison between groups showed no statistically significant difference in cumulative survival between the two groups in terms of all-cause mortality (log-rank test $\chi^2 = 2.325$, p = 0.127) (Figure 1). Cumulative CVD mortality at years 1, 3, and 5 after PD initiation was 4.08% (8/196), 8.16% (16/196), and 11.22% (22/196) in patients in the high serum Lp(α) level group and 3.06% (6/196), 5.10% (10/196), and 5.61% (11/196) in the low serum Lp(α) level group, respectively. In terms of CVD deaths, patients in the high serum Lp(α) level group had a lower cumulative survival rate (log-rank test $\chi^2 = 4.348$, p = 0.037) than those in the low serum Lp(α) level group (Figure 2). There are 4 and 6 patients who died for in-

Table 1. Comparison of baseline information between groups.

Indicators	High serum lipoprotein(α) level group (n = 196)	Low serum lipoprotein(α) level group (n = 196)	$t/\chi^2/Z$	p
Gender (male, % of cases)	123 (62.76)	102 (52.04)	4.601 [b]	0.032
Age (years)	59.00 (49.00, 70.00)	56.00 (45.25, 70.00)	-1.305 [c]	0.192
Causes of renal failure			3.578 [b]	0.311
Chronic glomerulonephritis	98	106		
Diabetic nephropathy	34	31		
Hypertensive nephrosclerosis	27	34		
Others	37	25		
Smoking history (cases, %)	45 (22.96)	37 (18.88)	0.987 [b]	0.320
History of alcohol consumption (cases, %)	28 (14.29)	20 (10.20)	1.519 [b]	0.218
Systolic blood pressure (mmHg)	150.00 (130.00, 168.00)	143.00 (130.00, 160.00)	-1.814 [c]	0.070
Diastolic blood pressure (mmHg)	80.00 (70.00, 90.00)	80.00 (70.00, 90.75)	-0.344 [c]	0.731
Heart rate (beats/min)	78.00 (72.00, 82.00)	78.00 (74.00, 86.00)	-1.977 [c]	0.048
BMI ($^{kg/m2}$)	22.45 (20.89, 24.60)	22.03 (19.53, 24.24)	-1.686 [c]	0.092
Hypertension (cases, %)			2.979 [b]	0.225
Primary	113 (57.65)	104 (53.06)		
Renal	65 (33.16)	63 (32.14)		
Diabetes mellitus (cases, %)	62 (31.63)	57 (29.08)	0.302 [b]	0.583
Heart disease (cases, %)	42 (21.43)	34 (17.35)	1.045 [b]	0.307
Cerebrovascular disease (cases, %)	23 (11.73)	19 (9.69)	0.427 [b]	0.514
White blood cell count ($\times 10^9$/L)	6.30 (4.90, 7.60)	5.80 (4.83, 7.00)	-1.452 [c]	0.147
Neutrophil count ($\times 10^9$/L)	4.20 (3.10, 5.29)	3.90 (3.02, 4.88)	-1.790 [c]	0.074
Lymphocyte count ($\times 10^9$/L)	1.20 (0.90, 1.55)	1.20 (0.93, 1.60)	-0.128 [c]	0.898
Monocyte count ($\times 10^9$/L)	0.48 (0.30, 0.60)	0.45 (0.34, 0.58)	-0.810 [c]	0.418
Eosinophil count ($\times 10^9$/L)	0.17 (0.08, 0.29)	0.17 (0.10, 0.31)	-0.952 [c]	0.341
Basophil count ($\times 10^9$/L)	0.03 (0.02, 0.04)	0.02 (0.01, 0.04)	-1.247 [c]	0.212
Erythrocyte count ($\times 10^9$/L)	3.42 (3.02, 3.98)	3.61 (2.96, 4.02)	-0.977 [c]	0.328
Platelet count ($\times 10^9$/L)	179.00 (139.25, 225.25)	172.00 (137.00, 202.75)	-1.635 [c]	0.102
Sodium (mmol/L)	140.90 (139.20, 142.98)	141.20 (139.63, 143,30)	-1.590 [c]	0.112
Potassium (mmol/L)	4.23 (3.81, 4.81)	4.14 (3.68, 4.70)	-0.655 [c]	0.513
Chloride (mmol/L)	101.14 ± 4.87	102.02 ± 4.38	-1.887 [a]	0.060
Calcium (mmol/L)	2.08 ± 0.23	2.01 ± 0.23	-1.026 [a]	0.306
Phosphorus (mmol/L)	1.36 (1.14, 1.58)	1.31 (1.13, 1.50)	-1.352 [c]	0.176
Bicarbonate (mmol/L)	24.30 (22.43, 26,40)	23.40 (21.30, 25.88)	-2.261 [c]	0.024

Table 1. Comparison of baseline information between groups (continued).

Indicators	High serum lipoprotein(α) level group (n = 196)	Low serum lipoprotein(α) level group (n = 196)	$t/\chi^2/Z$	p
Fasting glucose (mmol/L)	4.87 (4.34,5.76)	5.03 (4.53, 5.97)	-1.721 [c]	0.085
Glycated hemoglobin (%)	5.50 (5.10,6.00)	5.35 (4.90, 5.88)	-2.149 [c]	0.032
Serum albumin (g/L)	31.82 ± 6.13	33.39 ± 6.15	-2.531 [a]	0.012
Alkaline phosphatase (IU/L)	74.50 (57.50, 93.75)	84.67 (59.00, 100.75)	-0.862 [c]	0.389
Blood creatinine (μmol/L)	605.95 (481.38, 803.65)	637.30 (470.05, 820.73)	-0.597 [c]	0.551
Urea nitrogen (mmol/L)	18.35 ± 6.11	18.36 ± 5.79	-0.018 [a]	0.986
Uric acid (μmol/L)	400.95 (342.08, 452.75)	391.10 (327.18, 452.73)	-0.514 [c]	0.607
Blood phosphorus (mmol/L)	1.36 (1.14, 1.58)	1.31 (1.13, 1.50)	-1.352 [c]	0.176
C-reactive protein (mg/L)	3.50 (1.40, 10.32)	2.11 (0.87, 5.89)	-3.180 [c]	0.001
Total serum bilirubin (μmol/L)	5.20 (3.73, 6.50)	5.20 (3.90, 6.38)	-0.358 [c]	0.721
Aspartate aminotransferase (IU/L)	17.00 (13.00, 23.00)	19.00 (14.00, 25.00)	-2.270 [c]	0.023
Alanine aminotransferase (IU/L)	14.00 (10.00, 20.75)	15.00 (10.00, 24.00)	-1.355 [c]	0.175
Parathyroid hormone (pg/mL)	194.90 (120.35, 327.83)	214.05 (140.80, 377.55)	-1.711 [c]	0.087
Low-density lipoprotein (mmol/L)	2.42 (1.98, 3.12)	2.23 (1.72, 2.70)	-3.480 [c]	0.001
High-density lipoprotein (mmol/L)	1.14 (0.90, 1.37)	1.09 (0.89, 1.38)	-0.912 [c]	0.362
Triglycerides (mmol/L)	1.28 (0.90, 1.91)	1.28 (0.83, 1.97)	-0.074 [c]	0.941
Total cholesterol (mmol/L)	4.31 (3.71, 5.15)	4.08 (3.41, 4.83)	-2.566 [c]	0.010
24h urine volume (mL)	1,000.00 (662.50, 1,337.50)	1,000.00 (800.00, 1,250.00)	-0.174 [c]	0.862
eGFR (mL/min per 1.73m^2)	6.92 (5.38, 9.15)	6.57 (5.13, 9.07)	-1.036 [c]	0.300
Kt/V	1.89 (1.77, 1.98)	1.88 (1.75, 2.01)	-0.279 [c]	0.780
nPCR (g/kg/d)	0.95 ± 0.18	0.96 ± 0.17	-0.565 [a]	0.572
Peritoneal equilibration test			1.557 [b]	0.669
High transporter	27	20		
High-average transporter	81	87		
Low-average transporter	73	71		
Low transporters	15	18		
Erythropoietin (cases, %)	142 (72.45%)	131 (66.84%)	1.460 [b]	0.227
Erythropoietin dose (IU/Week)	10,000 (6,000, 10,000)	6,000 (6,000, 10,000)	-1.495 [c]	0.135

Note: [a] *t*-value, [b] χ^2-value, [c] *Z*-value.
BMI - body mass index, eGFR - estimated glomerular filtration rate, nPCR - normalized protein catabolic rate.

Table 2. Results of binary multivariate logistic regression analysis of factors associated with high serum lipoprotein(α) levels.

Indicators	B	S. E	Wald	p	OR (95% CI)
BMI	0.061	0.029	4.411	0.036	1.063 (1.004 - 1.126)
Serum albumin	-0.042	0.017	6.029	0.014	0.959 (0.927 - 0.991)
Parathyroid hormone	-0.001	0.001	6.635	0.010	0.999 (0.997 - 1.000)
Low-density lipoprotein	0.479	0.126	14.398	0.000	1.614 (1.261 - 2.068)

Table 3. Results of Cox regression analysis of the association between serum lipoprotein(α) levels and all-cause mortality.

Influencing Factors	B	SE	Wald	p	HR (95% CI)
Age	0.108	0.014	57.098	0.000	1.114 (1.084 - 1.146)
Drinking	0.926	0.369	6.278	0.012	2.524 (1.223 - 5.206)
Heart rate	0.044	0.012	12.407	0.000	1.045 (1.020 - 1.071)
BMI	-0.101	0.038	7.038	0.008	0.904 (0.839 - 0.974)
Albumin	-0.178	0.029	36.704	0.000	0.837 (0.790 -0.887)
Uric acid	0.002	0.001	4.326	0.038	1.002 (1.000 -1.004)
Blood phosphorus	1.806	0.415	18.968	0.000	6.089 (2.701 - 13.727)
CRP	0.019	0.006	9.892	0.002	1.019 (1.007 - 1.031)
Total bilirubin	-0.158	0.079	4.034	0,045	0.854 (0.732 - 0.996)
Glutathione aminotransferase	0.020	0.009	5.540	0.019	1.020 (1.003 - 1.038)
Low-density lipoprotein	-0.523	0.215	5.927	0.015	0.593 (0.389 - 0.903)
Triglyceride	0.195	0.107	3.289	0.070	1.215 (0.984 - 1.499)
Total cholesterol	0.469	0.196	5.748	0.017	1.599 (1.089 - 2.346)
eGFR	0.132	0.028	22.025	0.000	1.141 (1.080 - 1.206)
Erythrocyte count	-0.671	0.193	12.041	0.001	0.511 (0.350 - 0.747)

Table 4. Results of Cox regression analysis of the association between serum lipoprotein(α) levels and CVD mortality.

Influencing Factors	B	SE	Wald	p	HR (95% CI)
Lipoprotein(a)	0.002	0.001	10.814	0.001	1.002 (1.001 - 1.003)
Age	0.105	0.021	23.816	0.000	1.110 (1.065 - 1.158)
Smoking	1.244	0.478	6.758	0.009	3.469 (1.358 - 8.860)
Diabetes	1.433	0.391	13.443	0.000	4.193 (1.949 - 9.021)
Heart disease	2.268	0.426	28.320	0.000	9.655 (4.189 - 22.256)
Hemoglobin	-0.035	0.009	14.984	0.000	0.966 (0.949 - 0.983)
Urea nitrogen	-0.140	0.037	14.286	0.000	0.870 (0.809 - 0.935)
Uric acid	0.008	0.002	14.738	0.000	1.008 (1.004 - 1.012)
Blood phosphorus	2.228	0.606	13.513	0.000	9.283 (2.830 - 30.453)
CRP	0.028	0.008	12.601	0.000	1.029 (1.013 - 1.045)
Total bilirubin	-0.298	0.120	6.154	0.013	0.742 (0.586 - 0.939)
Triglyceride	0.379	0.141	7.246	0.007	1.460 (1.108 - 1.924)
High-density lipoprotein	1.345	0.483	7.755	0.005	3.840 (1.490 - 9.898)
Glycated hemoglobin	-0.505	0.221	5.244	0.022	0.604 (0.392 - 0.930)
Kt/V	-2.620	0.757	11.995	0.001	0.073 (0.017 - 0.321)

Table 5. Results of Cox regression analysis of the association between serum lipoprotein(α) levels and infection-related mortality.

Influencing Factors	B	SE	Wald	p	HR (95% CI)
Age	0.065	0.032	4.277	0.039	1.067 (1.003 - 1.135)
Drinking	1.726	0.694	6.176	0.013	5.616 (1.440 - 21.900)
Albumin	-0.196	0.053	13.869	0.000	0.822 (0.741 - 0.911)

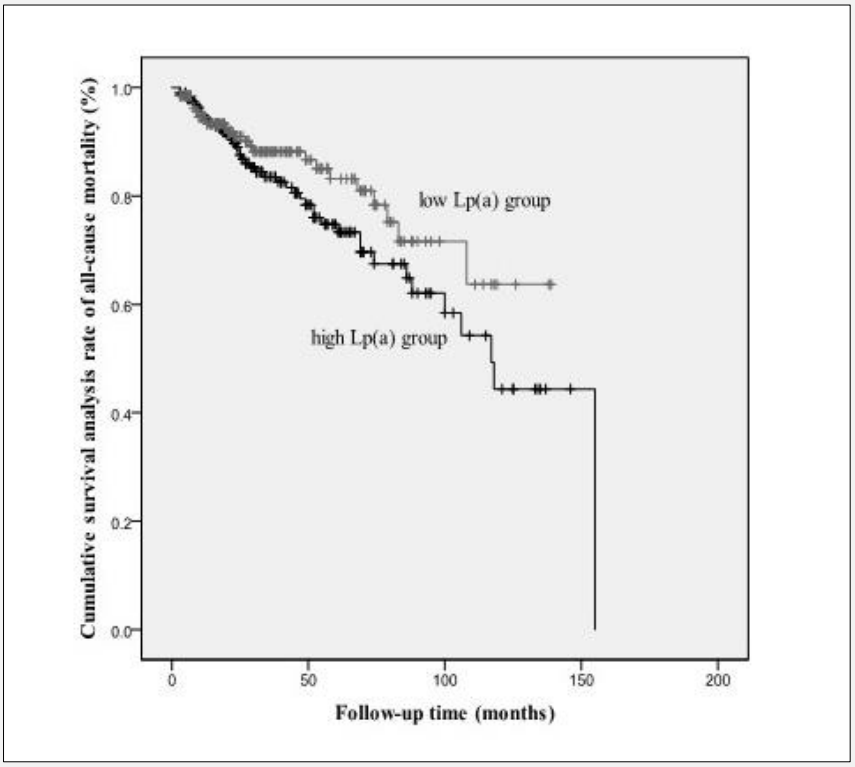

Figure 1. Kaplan-Meier survival analysis of all-cause mortality in patients with different serum lipoprotein(α) levels.

fection in the low and high serum Lp(α) level group, respectively. There is no significant statistical difference between both groups (log-rank test χ^2 = 0.170, p = 0.680) (Figure 3).

Predictive value of serum lipoprotein(α) levels on prognosis of PD patients

After adjusting for patient demographics and important laboratory indicators, a multivariate Cox regression analysis showed that high serum Lp(α) levels were not an independent risk factor for all-cause mortality in PD patients (Table 3). However, high serum Lp(α) levels were an independent risk factor for CVD death in PD patients (HR = 1.002, 95% CI: 1.001 - 1.003, p = 0.001) (Table 4). For infection-related mortality, the results showed that high serum Lp(α) levels were not an independent risk factor in PD patients (Table 5).

DISCUSSION

In this study, we found that high LDL levels and high BMI levels were risk factors for the occurrence of high serum Lp(α) levels. In contrast, high serum albumin and parathyroid hormone levels were protective factors against the development of high serum Lp(α) levels.

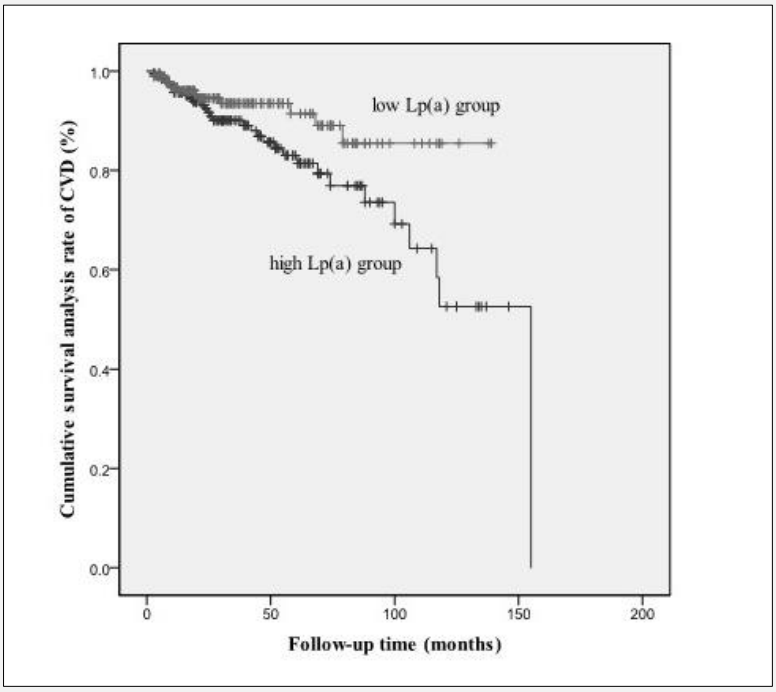

Figure 2. Kaplan-Meier survival analysis of CVD deaths in patients with different serum lipoprotein(α) levels.

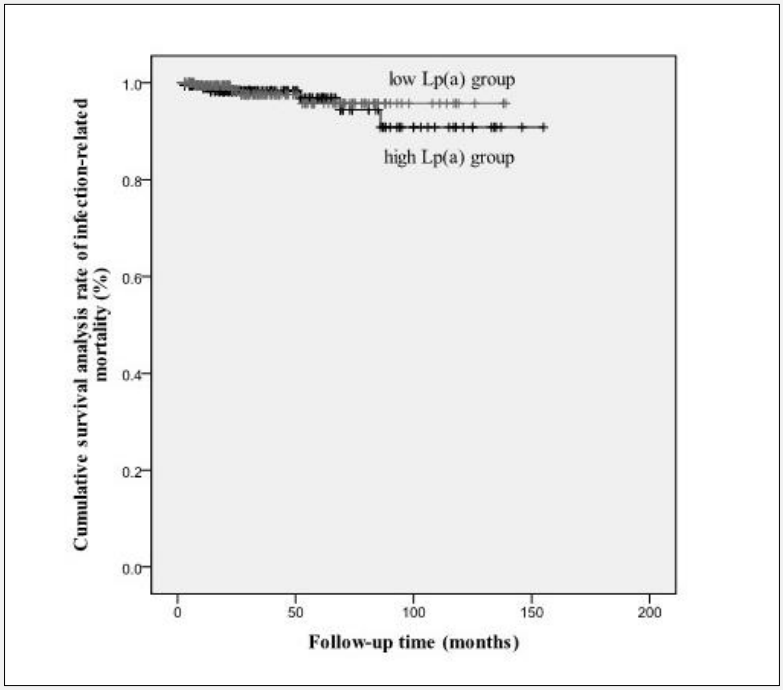

Figure 3. Kaplan-Meier survival analysis of infection-related mortality in patients with different serum lipoprotein(α) levels.

Studies have shown that high serum Lp(α) and high LDL are often present together in PD patients [8,18]. Our study also found that the group with high serum Lp(α) levels had higher LDL levels and that high LDL levels were a risk factor for the occurrence of high serum Lp(α) levels. This may be because serum Lp(α) and LDL have similar lipid compositions, and increased LDL synthesis by the liver may be accompanied by increased serum Lp(α) synthesis. Obese people have higher serum Lp(α) levels compared to normal-weight people [19]. Zhou H et al. [20] found that serum Lp(α) levels were significantly higher in the high BMI group compared to the normal BMI group in PD patients and the difference was statistically significant ($p = 0.032$). This is in line with the findings of the current study, in which we found that having a high BMI is a risk factor for having high serum Lp(α) levels. Our study also found that patients in the high Lp(α) level group had relatively low albumin levels and that high serum albumin levels were a protective factor for the occurrence of high serum Lp(α) levels. Other researchers have discovered that patients with PD have elevated serum Lp(α) levels due to a decrease in serum albumin levels. The exact mechanism is unknown, but it is speculated that it may be due to a partial loss of albumin from the peritoneal fluid as a result of PD, which induces an increase in hepatic synthesis of serum Lp(α), but not a decrease in catabolism that causes high serum Lp(α) levels [21, 22]. High parathyroid hormone levels were also found to be a protective factor against the development of elevated serum Lp(α) levels in this study. Still, the underlying mechanisms are unknown and require further investigation and validation.

This study found that the cumulative survival rate for CVD death was lower in the group with high serum Lp(α) levels than in the group with low serum lipoprotein(a) levels. This also indicates that serum Lp(α) level affects the CVD mortality rate of PD patients. Zhong Z et al. [23] divided 1,492 PD patients into high, medium, and low serum Lp(α) level groups and found that the high serum Lp(α) group had a lower cumulative survival rate in terms of CVD deaths than the other two groups (log-rank test $p = 0.001$), which was consistent with the results of our study. However, in terms of all-cause mortality, they discovered that the high serum Lp(α) level group had a lower cumulative survival rate than the other two groups (log-rank test $p = 0.013$). In contrast, our study did not find a difference in cumulative survival between the two groups in terms of all-cause mortality. Different exclusion criteria, sample size, and follow-up time of our enrolled PD patients could explain the disparity in study results.

In both the general population and patients with chronic kidney disease, serum Lp(α) levels are an independent risk factor for CVD death [24]. High serum Lp(α) levels were also an independent risk factor for CVD death in patients with PD in our study. When combined with the pathophysiological properties of serum Lp(α), we can explain the association between elevated serum Lp(α) levels and CVD death in PD patients as follows: (1) structural analysis of atherosclerotic vascular tissues, which revealed that serum Lp(α) is directly involved in atherosclerotic plaque formation [11,23,25]. (2) Serum Lp(α) promotes the migration of inflammatory cells (e.g., monocytes) to the vessel wall and the secretion of inflammatory cytokines (e.g., interleukin-1), which accelerates vascular atherosclerosis indirectly [11,26,27]. (3) Apolipoprotein A, one of the components of serum Lp(α), shows homology with fibrinolytic enzyme and can compete for its binding site, weakening fibrinolysis and thus causing thrombosis; (4) serum Lp(α) can also promote coagulation by binding and inhibiting tissue factor pathway inhibitors (significant coagulation regulators) [11]. As a result, we conclude that elevated serum Lp(α) levels represent the formation of vascular atherosclerosis and thrombosis, which may also provide favorable evidence that elevated serum Lp(α) levels are an independent risk factor for CVD mortality in patients with PD. Hopewell JC et al. [28] discovered that high serum lipoprotein (a) was associated with the risk of developing coronary artery disease in a study of 995 patients with coronary artery disease and 998 normal patients. Furthermore, researchers have found a genetic link between serum Lp(α) and coronary heart disease [29,30]. However, Gault MH et al. [31] found that serum Lp(α) levels were not a risk factor for coronary heart disease in PD and hemodialysis patients by analyzing 52 hemodialysis patients, 58 PD patients, and 56 controls. The reason for this result may be related to the small sample size of their study, the inclusion criteria of the study population, and differences in population ethnicity [32]. More studies have shown that serum Lp(α) levels are an independent risk factor for cardiovascular disease in dialysis patients [14,33], which is also consistent with our study. However, high serum Lp(α) levels were not found to be an independent risk factor for all-cause mortality in PD patients in our study. Zhong Z et al. [23] found that both low and high serum Lp(a) levels are risk factors for all-cause death and that a high Lp(a) level is an independent predictor of CV death in PD patients. The reasons for the inconsistency between the results of Zhong Z et al. [23] and our study could be due to different inclusion/exclusion criteria for study subjects, the different confounding factors for correction, and also the fact that factors such as dietary habits of PD patients in different regions can affect all-cause mortality in patients [32], which also fully illustrates the complexity of the causes affecting all-cause mortality in PD patients.

This study has the following limitations: (1) the study data are from a single center and are retrospective studies that can only determine correlations; (2) the levels of each index were selected for analysis after three months of PD treatment, and the effect of dynamic changes in serum Lp(α) levels during dialysis on PD patients was not assessed; and (3) because it was a retrospective study, it was not possible to assess whether lowering serum lipoprotein(a) levels could reduce CVD

death in patients, and the mechanisms by which serum lipoprotein(a) levels affect the occurrence of CVD death in PD patients have not been investigated. Therefore, we anticipate that a multicenter, large clinical study combined with a mechanistic study of serum Lp(α) levels on the prognosis of PD patients would be more beneficial in demonstrating the effect of elevated serum lipoprotein(a) levels on the prognosis of PD patients.

CONCLUSION

In conclusion, this study investigated the correlation between high serum Lp(α) levels and all-cause mortality, CVD death and infection-related mortality in PD patients, and the results showed that the high serum Lp(α) levels in PD patients were positively associated with LDL and BMI, and negatively associated with serum albumin and parathyroid hormone levels. High serum Lp(α) levels were associated with the risk of CVD death in PD patients, but high serum Lp(α) levels were not significantly associated with the risk of all-cause death and infection-related mortality in PD patients. Therefore, serum Lp(α) level can be an important indicator to monitor the risk of CVD death in PD patients in clinical practice.

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Declaration of Interest:
The authors declared that they have no conflicts of interest with regard to this work.

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