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ORIGINAL ARTICLE

Correlation between Apolipoprotein A1 and the Occurrence and Prognosis of Cardiovascular Events in Peritoneal Dialysis Patients

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SUMMARY

Background: **This study investigates the value of apolipoprotein A1 in assessing the occurrence and prognosis of cardiovascular events in peritoneal dialysis patients.**
Methods: **A retrospective analysis was conducted based on the clinical information of 80 end-stage renal disease patients who underwent peritoneal dialysis at Zhuji People's Hospital Zhejiang Province from January 2015 to December 2016. Based on the median value of apolipoprotein A1, patients were evenly distributed as either High Apolipoprotein A1 Group (H-ApoA1, > 1.145g/L, n = 40) or Low Apolipoprotein A1 Group (L-ApoA1, < 1.145g/L, n = 40).**
Results: **When compared with the H-ApoA1 group, the L-ApoA1 group patients were observed to have higher BMI, total Kt/V, hemoglobin, AKP, glycated hemoglobin, HOMA-IR, HDL levels, while simultaneously having lower total Ccr, triglycerides, total cholesterol, LDL, CRP levels ($p < 0.05$). Further analysis found that the all-cause mortality rate, cardiovascular death rate, and cardiovascular event rates were significantly higher in L-ApoA1 group patients than the H-ApoA1 group ($p < 0.05$); no statistical significance was found for mortality rates due to infection, abandon treatment, tumor, failure, gastrointestinal bleeding or undetermined reasons between the two groups ($p > 0.05$). In addition, the median all-cause mortality and median occurrence of cardiovascular events of L-ApoA1 group patients were observed to be shorter than the H-ApoA1 group ($p < 0.05$), and apolipoprotein A1 is a risk factor for all-cause mortality rate and cardiovascular occurrence end-point events ($p < 0.05$).**
Conclusions: **Peritoneal dialysis patients with a reduced level of apolipoprotein A1 have a poorer prognosis and more severe cardiovascular events.**
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INTRODUCTION

End-stage renal disease (ESRD) is a final outcome for many acute and chronic kidney diseases because 10% - 30% of kidney disease patients advance into this chronic stage annually. It has become a global public health concern [1,2]. Various renal replacement therapies such as hemodialysis, peritoneal dialysis, and renal transplant are the main treatment approaches for managing ESRD [3]. Peritoneal dialysis uses the peritoneum (a biological

and permeable membrane) to remove a portion of small or medium molecular solutes and electrolytes from the body and retains cells and proteins within [4]. Clinical research has found that peritoneal dialysis has several unique advantages, such as ease of operation, broad ranges of application, and it does not require any special equipment. Because peritoneal dialysis can be performed at home, it has a smaller impact on the patient's life. In addition, peritoneal dialysis does not require the entire body to be exposed to anticoagulants and is also suitable for dialysis patients who have a high tendency to bleed [5-7]. As peritoneal dialysis treatment is widely and rapidly becoming the main choice of therapy for ESRD patients, there is an increased awareness to study the quality of life and prognosis of peritoneal dialysis patients.

Currently, there is a demonstrated increase in the survival rates of ESRD patients with further in-depth research on the technique and management of peritoneal dialysis. However, cardiovascular diseases remain as the leading cause of death and major complications for ESRD patients and accounts for 36.9% of the total mortality rate in ESRD patients [8]. Oymak O et al. found that ESRD patient groups have a significantly higher mortality rate than that found in the normal population and that from all of the various causes of mortality in ESRD patients, deaths due to cardiovascular diseases have been shown to be the most significant [9]. Out of the various cardiovascular diseases that ESRD patients develop, such as stroke, peripheral vascular disease, and atrial fibrillation, clinical studies have shown that coronary heart disease and myocardial ischemia are the most severe [10-12]. The occurrence and development of cardiovascular diseases generally elevates the morality rate of patients and results in poor clinical outcome. Therefore, it is critical to identify risk factors that would influence the survival of ESRD patients and correspondingly adopt appropriate measures to improve the prognosis of ESRD patients.

Apolipoprotein is a type of protein that combines and transports blood lipids to various parts of the body for metabolism and further use. Recent studies have found an important role of apolipoprotein A1 in activating lecithin cholesterol acyltransferase [13,14]. Serum levels of apolipoprotein A1 are closely related to the occurrence and development of hyperlipidemia, atherosclerosis, neuro-cardiovascular diseases and others. Many clinical studies show that apolipoprotein A1 is able to better predict the occurrence of cardiovascular diseases [15,16]. For example, in a 10-year follow-up study by Empana JP et al. it was found that total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein, cholesterol, triglyceride, and apolipoprotein A1 are substantially predictive of coronary heart disease [17]. However, related studies on apolipoprotein A1 and the occurrence and prognosis of cardiovascular events in peritoneal dialysis patients are limited.

This study is a single-center study that investigated and analyzed the occurrence, risk factor, and prognosis of cardiovascular events in peritoneal dialysis patients to provide clinicians with vital insights to manage variable risk factors and to improve the cardiovascular status in peritoneal dialysis patients, thereby improving the patients' prognosis and survival rates.

MATERIALS AND METHODS

Study population

A retrospective analysis was conducted based on the clinical information of 80 ESRD patients who underwent peritoneal dialysis at Zhuji People's Hospital Zhejiang Province from January 2015 to December 2016. All patients included in this study received dialysis treatments for at least 3 months and had a regular follow-up. Patients' information such as age, height, weight, and BMI, as well as their laboratory parameters, such as albumin, C-reactive protein, triglycerides, and hemoglobin were recorded accordingly. Based on the median value of apolipoprotein A1 levels, patients were evenly distributed as the High Apolipoprotein A1 Group (H-ApoA1, > 1.145 g/L, n = 40) or the Low Apolipoprotein A1 Group (L-ApoA1, < 1.145 g/L, n = 40). For the clinical information of patients included in this study, refer to Table 1. Exclusion criteria included: (1) patients with a predicted life span of less than 3 months; (2) patients undergoing acute infection, experiencing an unstable clinical condition or having an unstable clinical condition of cardiovascular diseases; (3) patients with incomplete clinical information; (4) patients who dropped out due to unknown reasons; (5) peritoneal dialysis turned hemodialysis or renal transplant patients; (6) pregnant patients or patients with a malignant tumor. All patients included in this study are at least 18 years old. This study was approved by the ethics committee of Zhuji People's Hospital Zhejiang Province.

Continuous ambulatory peritoneal dialysis

According to K/DOQI guideline (2006), ISPD guideline (2006) and NICE guideline (2011): Peritoneal dialysis patients received a daily dose of 6 - 10 L for a total dwell time for 10 - 12 hours, a dwell time of 4 - 6 hours each time, exchanged for 3 - 4 times during the day and exchanged once during the night. For each patient, the dialysis prescription is personalized to achieve optimum liquid volume balance and solute removal. Peritoneal dialysis patients' total Kt/V (urea clearance index) is at least 1.7 or their CCR (creatinine clearance rate) is at least 50 L/(1.73 m^2).

Measurement of indicators

General information collected included age, gender, history of diabetes, calcium carbonate, calcitriol, and history of using lipid-lowering drugs. Height and body mass were measured according to the standard measurement protocol. Body mass index (BMI) was calculated ac-

cordingly.

Blood pressure measurement for peritoneal dialysis patients: the intradialytic blood pressure, based on a mean blood pressure value, was derived from 3 separate measurements taken from patients after they were allowed to rest in a quiet condition for 10 minutes. Based on clinical characteristics, the causes of ESRD for the patients were affirmed. After fasting for 8 hours, 5 mL of peripheral venous blood was collected in the morning from all ESRD patients. Standard clinical laboratory methods were employed to measure hemoglobin, serum iron, transferrin, transferrin saturation (TSAT), alkaline phosphatase (AKP), calcium, phosphorus, intact parathyroid hormone (iPTH), albumin, prealbumin, C-reactive protein (CRP), glycated hemoglobin, insulin, and lipid levels (including low density lipoprotein (LDL), triglycerides, high density lipoprotein (HDL)).

Insulin resistance was evaluated using the homeostasis model: HOMA-IR = Fasting Serum Insulin (U/L) x Fasting Serum glucose (mmol/L)/22.5; total Kt/V = (Residual renal Kt + Peritoneal Kt) x 7/V, the calculated results were further divided based on actual body-surface area and further adjusted by 1.73; Peritoneal Kt = (Parotid-fluid urea nitrogen/Blood urea nitrogen) x 24 hours dialysis solution discharge; Residual renal Kt (mL/minute) = (urinary urea nitrogen/blood urea nitrogen) x 24 hours urine volume. An apolipoprotein A1 assay kit (Immunoturbidimetry, Kuake Bioscience Technology, Zhejiang, Approval number: Zhejiang Food and Drug Administration (approved) 2013 No. 2400574) was used to measure the levels of apolipoprotein A1 in patients' serum, wherein the assay was performed strictly in accordance to the instructions provided in the assay kit.

Follow-up

Peritoneal dialysis patients' follow-up period and prognosis were collected, the start point of the follow-up was when peritoneal dialysis patient first undergoes the peritoneal dialysis, the end point of the follow-up was the time of death. Causes of death and cardiovascular events of patients were recorded. Endpoint events include (1) all-cause mortality rate: all types of causes resulting in patient's death, (2) cardiovascular events: coronary artery events, carotid plaque formation, neurocardiovascular diseases, and peripheral arterial disease. Coronary artery events: typical angina symptoms, electrocardiogram dynamics ST-T changes or at least a three-fold increase in myocardial markers; Neuro-cardiovascular diseases: brain infarction or brain hemorrhage as verified by CTorMRI; Peripheral arterial disease: exhibit symptoms of intermittent limping and/or experience of leg pain during resting state, stenosis of blood vessels identified by angiography; Carotid plaque formation as verified by carotid ultrasound; Congestive heart failure: as verified by clinical manifestation, pulmonary signs, chest X-ray or echocardiography. (3) Cardiovascular death: deaths caused by cardiovascular events.

Statistical analysis

For this study, data were analyzed using the statistical package, SPSS 22.0. Quantitative data were presented as mean ± standard deviation and analyzed using chi-squared test or Fisher's exact test. Count data were presented as n (%) and analyzed using chi-squared test. The conditions of patients' end-point event occurrences are analyzed using the Kaplan-Meier method and log-rank test. One-factor analysis and a multi-factor Cox proportional hazards regression model were employed to analyze the risk factors involved in the occurrence of end-point events. A statistical value of $p < 0.05$ is considered to be statistically significant.

RESULTS

Comparison of clinical information

This study retrospectively analyzed related clinical information of 80 peritoneal dialysis patients. Based on the median value of apolipoprotein A1, patients were evenly distributed into the High Apolipoprotein A1 group (H-ApoA1, > 1.145 g/L, n = 40) or the Low Apolipoprotein A1 group (L-ApoA1, < 1.145 g/L, n = 40). Apolipoprotein A1 levels in H-ApoA1 group patients are determined to be 1.44 ± 0.21 g/L and is substantially higher than the L-ApoA1 group (0.92 ± 0.16 g/L, $p < 0.05$). From the analysis of the clinical information (Table 1), L-ApoA1 group patients were observed to have relatively higher BMI, total Kt/V, hemoglobin, AKP, glycated hemoglobin, HOMA-IR, HDL levels, while having relatively lower total CCR, triglycerides, total cholesterol, LDL, CRP levels ($p < 0.05$) as compared with the H-ApoA1 group. On the contrary, no significant differences were observed for other clinical parameters, such as gender proportions, age, ESRD causes, biomarkers of iron metabolism, calcium phosphorus product, iPTH, calcium carbonate, calcitriol, and use of a lipid-lowering drug ($p > 0.05$).

Follow-up outcome

During the follow-up period, 37 patients died and 30 patients experienced cardiovascular events. Among the deceased patients, 24 patients died due to heart attack or coronary artery disease whereas 14 patients died from infections. The all-cause mortality rate, cardiovascular death rate, and cardiovascular events rate were observed to be lower in H-ApoA1 group patients than in the L-ApoA1 group ($p < 0.05$); no significant differences were noted between the two groups for mortality rate caused by infections, abandon treatment, tumor, failure, gastrointestinal bleeding or undetermined reasons ($p > 0.05$) (Table 2 and Table 3).

Survival analysis and endpoint events risk factor analysis

Statistical analysis has found that the median all-cause mortality rate period and median cardiovascular events occurrence period are longer in H-ApoA1 group pa-

Table 1. Comparison of clinical information between the two patient groups.

Indices		L-ApoA1 Group (n = 40)	H-ApoA1 Group (n = 40)
Age (years)		68.73 ± 11.12	66.35 ± 10.28
Male [n (%)]		17 (42.50)	21 (52.50)
Disease cause [n (%)]	Glomerulus nephritis	21 (52.50)	19 (47.50)
	Diabetes	12 (30.00)	16 (40.00)
	High blood pressure	2 (5.00)	1 (2.50)
	Others	5 (12.50)	4 (10.00)
Systolic blood pressure (mmHg)		132.25 ± 14.64	132.68 ± 15.35
Diastolic blood pressure (mmHg)		79.45 ± 10.94	76.23 ± 15.17
Mean arterial pressure (mmHg)		93.88 ± 11.06	95.5 ± 9.84
BMI (kg/m^2)		23.97 ± 3.36	20.46 ± 1.99 *
Total Kt/V		2.3 ± 0.34	2 ± 0.25 *
Total CCR (L/week)		68.93 ± 2.74	77.9 ± 3.5
D/P		0.67 ± 0.11	0.67 ± 0.09
Dialysis period (months)		56.28 ± 6.7	55.93 ± 7.93
Calcium carbonate usage rate [n (%)]		13 (32.50)	13 (32.50)
Calcitriol usage rate [n (%)]		12 (30.00)	12 (30.00)
Lipid-lowering drug usage rate [n (%)]		14 (35.00)	15 (37.50)
Hemoglobin (g/L)		83.1 ± 7.45	76.42 ± 11.18 *
Serum iron (μmol/L)		11.4 ± 5.84	12.15 ± 4.68
Transferrin (g/L)		1.77 ± 0.47	1.74 ± 0.47
Ferritin (ng/mL)		13.25 ± 4.83	12.78 ± 4.77
TSAT (%)		29.4 ± 4.77	30.85 ± 4.94
AKP (U/L)		99.03 ± 24.6	85.13 ± 26.11 *
Adjusted calcium (mmol/L)		2.26 ± 0.41	2.25 ± 0.45
Phosphorus (mmol/L)		1.42 ± 0.34	1.42 ± 0.34
iPTH (pg/mL)		223.12 ± 33.38	236.15 ± 35.67
CRP (mg/L)		2.75 ± 0.25	3.63 ± 0.64
Albumin (g/L)		31.42 ± 5.14	32.03 ± 3.55
Prealbumin (g/L)		286.97 ± 81.32	281.65 ± 74.81
Glycated hemoglobin (%)		6.52 ± 0.73	5.7 ± 0.63 *
Serum insulin (pmol/L)		13.28 ± 5.68	13.52 ± 5.46
HOMA-IR		3.05 ± 0.41	2.02 ± 0.33
Triglycerides (mmol/L)		0.96 ± 0.13	1.65 ± 0.24 *
Total cholesterol (mmol/L)		3.67 ± 1.12	4.67 ± 1.31 *
HDL (mmol/L)		1.22 ± 0.11	0.97 ± 0.16 *
LDL (mmol/L)		1.81 ± 0.41	2.83 ± 0.39 *

As compared to H-ApoA1 group, * - $p < 0.05$.

tients than in the L-ApoA1 group ($p < 0.05$) (Figure 1). From the analysis of risk factors of all-cause mortality rate and occurrence of cardiovascular events, one-factor Cox regression analysis identified that age, BMI, CRP, total cholesterol, HDL, and apolipoprotein A1 are risk factors for all-cause mortality rate and end-point events of cardiovascular occurrence, respectively ($p < 0.01$). As the number of end-point events is relatively limited, multi-factor Cox regression analysis which included these variables identified that apolipoprotein A1 is a risk factor for all-cause mortality rate and end-point events cardiovascular occurrence ($p < 0.05$) (Table 4).

Table 2. Follow-up outcome between the two patient groups.

Grouping	All-cause mortality rate	Cardiovascular death	Cardiovascular events
H-ApoA1 group (n = 40)	13 (32.5)	4 (10.00)	9 (22.50)
L-ApoA1 group (n = 40)	24 (60.00)	11 (27.50)	21 (52.50)
χ^2	6.084	4.021	7.680
p-value	0.014	0.045	0.006

Table 3. Causes of mortality between the two patient groups.

Cause of death	H-ApoA1 group (n = 13)	L-ApoA1 group (n = 24)	χ	p-value
Cardiovascular events	4 (30.77)	11 (45.83)	4.021	0.045
Infection	2 (15.38)	4 (16.67)	0.721	0.396
Abandon treatment	1 (7.69)	2 (8.33)	0.346	0.556
Tumor	1 (7.69)	1 (4.17)	0	1
Failure	2 (15.38)	3 (12.50)	0.213	0.644
Gastrointestinal bleeding	1 (7.69)	2 (8.33)	0.346	0.556
Undetermined	1 (7.69)	1 (4.17)	0	1

Table 4. One-factor analysis of end-point events and risk factors in peritoneal dialysis patients.

Variable	All cause mortality rate			Cardiovascular events		
	Wald	HR (95% CI)	p-value	Wald	HR (95% CI)	p-value
One-factor analysis						
Age (year)	41.229	1.099 - 1.195	0.000	34.443	1.102 - 1.215	0.000
Male [n (%)]	0.60	0.584 - 1.995	0.806	0.248	0.583 - 2.474	0.619
Systolic blood pressure (mmHg)	49.641	1.090 - 1.166	0.000	43.294	1.111 - 1.216	0.000
Diastolic blood pressure (mmHg)	2.147	0.961 - 1.006	0.143	0.936	0.961 - 1.014	0.333
Mean arterial pressure (mmHg)	0.365	0.961 - 1.021	0.546	0.000	0.965 - 1.036	0.998
BMI (kg/m^2)	37.449	0.587 - 0.760	0.000	34.524	0.586 - 7.66	0.000
Total Kt/V	0.578	0.566 - 3.638	0.447	0.760	0.554 - 4.647	0.383
Total CCR (L/week)	3.231	0.891 - 1.005	0.072	4.299	0.862 - 0.996	0.038
D/P	0.182	0.018 - 13.030	0.670	0.016	0.028 - 58.980	0.899
Peritoneal dialysis duration (months)	0.278	0.947 - 1.032	0.598	2.095	0.916 - 1.013	0.148
Calcium carbonate use rate [n (%)]	0.245	0.045 - 1.621	0.621	1.181	0.321 - 1.385	0.277
Calcitriol use rate [n (%)]	0.007	0.525 - 2.017	0.933	0.000	0.458 - 2.182	0.998
Lipid-lowering drug use rate [n (%)]	0.193	0.464 - 1.628	0.661	0.182	0.411 - 1.771	0.670
Hemoglobin (g/L)	1.133	0.985 - 1.051	0.287	2.757	0.994 - 1.071	0.097
Serum iron (μmol/L)	0.314	0.925 - 1.044	0.575	1.508	0.890 - 1.027	0.219
Transferrin (g/L)	0.036	0.468 - 1.867	0.849	0.141	0.383 - 1.917	0.708
Ferritin (ng/mL)	0.124	0.927 - 1.054	0.725	0.014	0.925 - 1.072	0.907
TSAT (%)	0.617	0.915 - 1.038	0.432	1.111	0.891 - 1.035	0.292
AKP (U/L)	0.940	0.983 - 1.006	0.332	0.345	0.982 - 1.010	0.557

Table 4. One-factor analysis of end-point events and risk factors in peritoneal dialysis patients (continued).

Variable	All cause mortality rate			Cardiovascular events		
	Wald	HR (95% CI)	p-value	Wald	HR (95% CI)	p-value
Adjusted Calcium (mmol/L)	0.130	0.441 - 1.758	0.719	0.179	0.524 - 2.725	0.673
Phosphorus (mmol/L)	0.014	0.355 - 2.501	0.905	0.281	0.445 - 4.097	0.596
iPTH (pg/mL)	0.086	0.993 - 1.010	0.769	0.100	0.989 - 1.008	0.752
CRP (mg/L)	23.155	2.322 - 7.390	0.000	18.912	2.213 - 8.149	0.000
Albumin (g/L)	0.966	0.897 - 1.037	0.326	1.136	0.877 - 1.039	0.286
Prealbumin (g/L)	0.018	0.996 - 1.004	0.893	0.151	0.994 - 1.004	0.698
Glycated hemoglobin (%)	0.261	0.749 - 1.637	0.609	1.929	0.882 - 2.089	0.165
Serum insulin (pmol/L)	0.00	0.947 - 1.057	0.984	0.895	0.967 - 1.101	0.344
HOMA-IR	32.495	3.601 - 13.791	0.000	31.131	4.619 - 24.221	0.000
Triglycerides (mmol/L)	9.880	1.781 - 12.047	0.002	5.559	1.242 - 10.555	0.018
Total cholesterol (mmol/L)	0.372	0.851 - 1.359	0.542	0.025	0.744 - 1.285	0.873
HDL (mmol/L)	13.038	0.006 - 0.215	0.000	8.581	0.007 - 0.371	0.003
LDL (mmol/L)	1.457	0.469 - 1.197	0.227	3.243	0.350 - 1.045	0.072
Apolipoprotein A1	28.426	0.001 - 0.048	0.000	28.450	0.000 - 0.012	0.000
Multi-factor analysis						
Age	3.317	0.996 - 1.101	0.069	0.800	0.963 - 1.105	0.371
Systolic blood pressure	1.769	0.977 - 1.127	0.183	3.867	1.000 - 1.235	0.049
BMI	11.631	0.416 - 0.789	0.001	1.129	0.543 - 1.199	0.288
CRP	0.116	0.185 - 3.275	0.733	2.163	0.546 - 69.493	0.141
HOMA-IR	1.922	0.619 - 16.476	0.166	1.760	0.505 - 34.874	0.185
HDL	7.507	0 - 0.101	0.006	5.179	0.000 - 0.243	0.023
Apolipoprotein A1	18.167	0 - 0.001	0.000	17.216	0.000 - 0.000	0.000

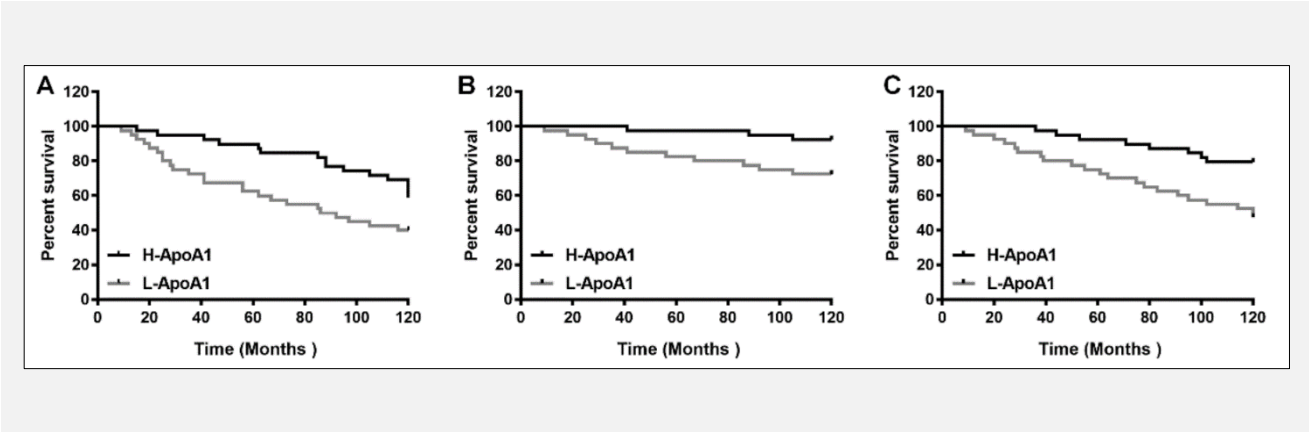

Figure 1. Survival analysis.

(A) All-cause mortality rate, (B) Cardiovascular death, (C) Cardiovascular events.

DISCUSSION

While peritoneal dialysis is an important approach of renal replacement therapy in ESRD patients, it is also common for peritoneal dialysis patients to also develop cardiovascular diseases [18,19]. Presently, the correlation between risk factors and the occurrence of cardiovascular events in ESRD patients remains unclear and cardiovascular prognosis reports related to peritoneal dialysis patients are limited. Multiple studies have demonstrated that apolipoprotein A1 levels are strongly related to the occurrence and development of cardiovascular events and are good predictors of poor prognosis of cardiovascular diseases [20-22]. Therefore, this study investigates the value of apolipoprotein A1 to assess the occurrence and prognosis of cardiovascular events in peritoneal dialysis patients. Our findings demonstrated that differences of apolipoprotein A1 levels in ESRD patients who received peritoneal dialysis are related to BMI, total Kt/V, hemoglobin, AKP, glycated hemoglobin, HOMA-IR, HDL, total CCR, triglycerides, total cholesterol, LDL, and CRP levels. Prognosis analysis found that L-ApoA1 group patients have relatively higher all-cause mortality rate, cardiovascular death rate, cardiovascular events rate, and a shorter median all-cause mortality rate period and median cardiovascular events occurrence period. Analysis of the risk factors of end-point events of ESRD peritoneal dialysis patients found that apolipoprotein A1 is a risk factor for all-cause mortality rate and occurrence of cardiovascular events. Therefore, peritoneal dialysis patients with relatively lower levels of apolipoprotein A1 generally have a poorer prognosis and experience more severe cardiovascular events.

Chen et al. found that an increase in apolipoprotein B/apolipoprotein A1 ratio is independently related to the all-cause mortality rate and cardiovascular events in peritoneal dialysis patients. Patients with a relatively higher ratio of apolipoprotein B/apolipoprotein A1 are prone to diabetes, while BMI, tKt/V, eGFR, N/L, hemoglobin, TG, CHOL, LDL, Lp(a) levels are significantly elevated while HDL is significantly reduced [23]. When compared with H-ApoA1 group patients, a retrospective analysis conducted on the clinical information from 60 ESRD peritoneal dialysis patients found that L-ApoA1 group patients possess relatively higher BMI, total Kt/V, hemoglobin, AKP, glycated hemoglobin, HOMA-IR, and HDL levels alongside relatively lower total Ccr, triglycerides, total cholesterol, LDL, and CRP levels, which is similar to the findings of Qinkai Chen et al. Relevant factors of apolipoprotein A1 is found to be highly related to ESRD peritoneal dialysis patient deaths and the occurrence of cardiovascular events. Apolipoprotein A1 is a major apolipoprotein which resembles high-density lipoprotein, wherein the levels of apolipoprotein A1 is closely related and high-density lipoprotein. Moreover, the expression of apolipoprotein A1 may highly affect serum levels of high-density lipoprotein [24,25]. Additional studies have found that apolipoprotein A1 is a cofactor of lecithin cholesterol acyltransferase that enables said acyltransferase to remove excess cholesterol in tissues and combines it with high-density lipoprotein, thereby playing an important role in facilitating reverse cholesterol transport to the liver [26, 27]. Abnormal levels of apolipoprotein A1 directly affects blood lipid metabolism in patients. Therefore, we speculate that the singular use of apolipoprotein A1 levels, instead of using apolipoprotein B/apolipoprotein A1 ratio, can similarly be employed to predict end-point events of ESRD peritoneal dialysis patients. Subsequently, we investigated the value of serum apolipoprotein A1 levels in predicting all-cause mortality rate, the occurrence of cardiovascular events, and cardiovascular death in ESRD peritoneal dialysis patients.

Our analysis has identified that the all-cause mortality rate, cardiovascular death rate, and cardiovascular events rate of L-ApoA1 group patients are substantially higher than H-ApoA1 group patients. Furthermore, the median all-cause mortality rate period and median period of cardiovascular events that occurred in L-ApoA1 group patients are shorter than H-ApoA1 group patients. This indicates that L-ApoA1 ESRD peritoneal dialysis patients have a poorer prognosis. Increasing apolipoprotein A1 levels will also be advantageous in lowering the mortality rate of patients and prolonging survival time while increasing their quality of life. Findings from further analysis conducted on the cause of death of peritoneal dialysis patients identified that various causes of mortality in L-ApoA1 patients, such as infection, abandon treatment, tumor, failure, gastrointestinal bleeding, and undetermined reasons, is generally higher or similar to L-ApoA1 patients, but no statistical significance was observed. The number of included ESRD peritoneal dialysis patients is relatively limited and is a possible reason behind the lack of statistical significance for the aforementioned analysis, thus the statistical significance cannot be clearly elucidated with the limited sample size.

Astor et al. found that higher levels of serum apolipoprotein A1 are accompanied by lower incidence rates of chronic kidney disease with increased eGFR levels, as estimated by the chronic kidney disease epidemiology collaboration equation [28]. Collective research from Bhargava A et al. and others have found that the accumulation of apolipoprotein A-IV in the high-density lipoprotein of ESRD patients is reflective of an impaired reverse cholesterol transport mechanism, which is considered to be a major factor contributing to the high incidence rate of atherosclerosis in these patients [29,30]. Correspondingly, we included serum levels of apolipoprotein A1 into the Cox proportional hazard regression model to assess the risk factors leading to the occurrence of end-point events. Our study has found that serum apolipoprotein A1 levels are a risk factor for the all-cause mortality rate and the occurrence of cardiovascular events in ESRD peritoneal dialysis patients, regardless of whether a one-factor or a multi-factor Cox proportional hazard regression model was used, even

when adjusted with the inclusion of other variables. Therefore, it will be advantageous to measure serum apolipoprotein A1 levels and a combination of other prognostic biomarkers for effectively establishing a treatment approach and improving the patient's prognosis.

This study is a retrospective, single-center, and relatively small study with certain limitations. Firstly, this study's findings only describe the relationship between serum apolipoprotein A1 levels and prognosis, as well as its relationship with clinical information, but lacks in-depth mechanistic investigations on how serum apolipoprotein A1 levels affect prognosis. Furthermore, as the number of cardiovascular deaths in this study is relatively limited, this study is unable to investigate the risk factors behind cardiovascular deaths in peritoneal dialysis patients. In order to improve the value of apolipoprotein A1 for evaluating prognosis, it is vital for subsequent studies to adopt a large scale and multi-center clinical study and to provide mechanistic investigations on the impact of apolipoprotein A1 levels on the prognosis of peritoneal dialysis patients.

In summary, this study assessed the relationship between serum levels of apolipoprotein A1 in peritoneal dialysis patients and their prognosis. Patients with low apolipoprotein A1 levels are found to have a higher all-cause mortality rate, cardiovascular events occurrence rate, and death rate; therefore, low levels of apolipoprotein A1 are considered risk factors for all-cause mortality rate and occurrence of cardiovascular events. Apolipoprotein A1 could be an effective biomarker to stratify potential risk factors of peritoneal dialysis patients. Determination of apolipoprotein A1 levels will be advantageous for formulating corresponding treatments and improving the prognosis of peritoneal dialysis patients.

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This retrospective study is approved by the Ethics Committee of Zhuji People's Hospital Zhejiang Province (No. 2021. 1215).

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Supplemental material for this manuscript can be obtained from the corresponding author.

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This is not a prospective study.

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The authors declared no conflict of interest.

References:

1. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs. Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 2019;321:69-79. (PMID: 30418475)

2. Kim K, Son HE, Ryu JY, et al. C1q nephropathy in adults is a form of focal segmental glomerulosclerosis in terms of clinical characteristics. PLoS One 2019;14:e0215217. (PMID: 31002691)

3. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med 2018;379:1431-42. (PMID: 30304656)

4. Shao Q, Xia Y, Zhao M, et al. Effectiveness and Safety of Peritoneal Dialysis Treatment in Patients with Refractory Congestive Heart Failure due to Chronic Cardiorenal Syndrome. Biomed Res Int 2018;2018:6529283. (PMID: 29888270)

5. Cao XY, He YN, Zhou JH, et al. Safety, Effectiveness, and Manipulability of Peritoneal Dialysis Machines Made in China: A Randomized, Crossover, Multicenter Clinical Study. Chin Med J (Engl) 2018;131:2785-91. (PMID: 30511680)

6. Hu S, Ming P, Qureshi AR, Lindholm B, Bo Y, Yang H. Peritonitis: Episode Sequence, Microbiological Variation, Risk Factors and Clinical Outcomes in a North China Peritoneal Dialysis Center. Kidney Blood Press Res 2018;43:1573-84. (PMID: 30347399)

7. Cho Y, Buchel J, Steppan S, et al. Longitudinal Trend in Lipid Profile of Incident Peritoneal Dialysis Patients is Not Influenced by the Use of Biocompatible Solutions. Perit Dial Int 2016;36: 146-53. (PMID: 26429421)

8. Borrelli S, Chiodini P, De Nicola L, et al. Prognosis and determinants of serum PTH changes over time in 1-5 CKD stage patients followed in tertiary care. PLoS One 2018;13:e0202417. (PMID: 30138402)

9. Kocyigit I, Unal A, Gungor O, et al. Effects of dialysis solution on the cardiovascular function in peritoneal dialysis patients. Intern Med 2015;54:3-10. (PMID: 25742886)

10. Roberts MA, Pilmore HL, Ierino FL, et al. The rationale and design of the Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Feasibility Study. Nephrology (Carlton) 2015;20:140-7. (PMID: 25382452)

11. Yoon CY, Park J, Seo C, et al. Low Dentin Matrix Protein 1 Is Associated With Incident Cardiovascular Events in Peritoneal Dialysis Patients. J Bone Miner Res 2016;31:2149-58. (PMID: 27390906)

12. Liu Y, Ma X, Zheng J, Jia J, Yan T. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis patients: a meta-analysis of randomised controlled trials. BMC Nephrol 2017;18:206. (PMID: 28666408)

13. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. N Engl J Med 2019;380:1022-32. (PMID: 30865796)

14. Gibson CM, Kerneis M, Yee MK, et al. The CSL112-2001 trial: Safety and tolerability of multiple doses of CSL112 (apolipoprotein A-I [human]), an intravenous formulation of plasma-derived apolipoprotein A-I, among subjects with moderate renal impairment after acute myocardial infarction. Am Heart J 2019;208:81-90. (PMID: 30580130)

15. Gurbel PA, Tantry US, D'Andrea D, et al. Evaluation of potential antiplatelet effects of CSL112 (Apolipoprotein A-I [Human]) in patients with atherosclerosis: results from a phase 2a study. J Thromb Thrombolysis 2018;45:469-76. (PMID: 29582212)

16. Gille A, D'Andrea D, Tortorici MA, Hartel G, Wright SD. CSL112 (Apolipoprotein A-I [Human]) Enhances Cholesterol Efflux Similarly in Healthy Individuals and Stable Atherosclerotic Disease Patients. Arterioscler Thromb Vasc Biol 2018;38:953-63. (PMID: 29437574)

17. Canoui-Poitrine F, Luc G, Bard JM, et al. Relative Contribution of Lipids and Apolipoproteins to Incident Coronary Heart Disease and Ischemic Stroke: The PRIME Study. Cerebrovasc Dis 2010;30:252-9. (PMID: 20664258)

18. Nataatmadja MS, Johnson DW, Pascoe EM, et al. Associations Between Peritoneal Glucose Exposure, Glucose Degradation Product Exposure, and Peritoneal Membrane Transport Characteristics in Peritoneal Dialysis Patients: Secondary Analysis of the balANZ Trial. Perit Dial Int 2018;38:349-55. (PMID: 30087174)

19. Tsai S, Zhao H, Wu B, Zuo L, Wang M. Serum Magnesium Abnormality and Influencing Factors of Serum Magnesium Level in Peritoneal Dialysis Patients: A Single-Center Study in Northern China. Blood Purif 2018;45:110-7. (PMID: 29241212)

20. Gille A, Duffy D, Tortorici MA, Wright SD, Deckelbaum LI, D'Andrea DM. Moderate Renal Impairment Does Not Impact the Ability of CSL112 (Apolipoprotein A-I [Human]) to Enhance Cholesterol Efflux Capacity. J Clin Pharmacol 2019;59:427-36. (PMID: 30452776)

21. Capodanno D, Mehran R, Gibson CM, Angiolillo DJ. CSL112, a reconstituted, infusible, plasma-derived apolipoprotein A-I: safety and tolerability profiles and implications for management in patients with myocardial infarction. Expert Opin Investig Drugs 2018;27:997-1005. (PMID: 30376729)

22. Wei XB, Chen XJ, Li YL, et al. Apolipoprotein A-I: A favorable prognostic marker in infective endocarditis. J Clin Lipidol. 2018; 12:498-505. (PMID: 29339066)

23. Zhan X, Chen Y, Yan C, et al. Apolipoprotein B/apolipoprotein A1 ratio and mortality among incident peritoneal dialysis patients. Lipids Health Dis 2018;17:117. (PMID: 29776362)

24. Bodde MC, Hermans MPJ, Jukema JW, et al. Apolipoproteins A1, B, and apoB/apoA1 ratio are associated with first ST-segment elevation myocardial infarction but not with recurrent events during long-term follow-up. Clin Res Cardiol 2019 May; 108(5):520-38. (PMID: 30298424)

25. Lagerstedt JO, Dalla-Riva J, Marinkovic G, et al. Anti-ApoA-I IgG antibodies are not associated with carotid artery disease progression and first-time cardiovascular events in middle-aged individuals. J Intern Med 2019;285:49-58. (PMID: 30028049)

26. Liu M, Mei X, Herscovitz H, Atkinson D. N-terminal mutation of apoA-I and interaction with ABCA1 reveal mechanisms of nascent HDL biogenesis. J Lipid Res 2019;60:44-57. (PMID: 30249788)

27. Tortorici MA, Duffy D, Evans R, et al. Pharmacokinetics and Safety of CSL112 (Apolipoprotein A-I [Human]) in Adults With Moderate Renal Impairment and Normal Renal Function. Clin Pharmacol Drug Dev 2019 Jul;8(5):628-36. (PMID: 30240132)

28. Goek ON, Kottgen A, Hoogeveen RC, Ballantyne CM, Coresh J, Astor BC. Association of apolipoprotein A1 and B with kidney function and chronic kidney disease in two multiethnic population samples. Nephrol Dial Transplant 2012;27:2839-47. (PMID: 22287661)

29. Qu J, Ko CW, Tso P, Bhargava A. Apolipoprotein A-IV: A Multifunctional Protein Involved in Protection against Atherosclerosis and Diabetes. Cells 2019;8:319. (PMID: 30959835)

30. Dai Y, Shen Y, Li QR, et al. Glycated Apolipoprotein A-IV Induces Atherogenesis in Patients With CAD in Type 2 Diabetes. J Am Coll Cardio 2017;70:2006-19. (PMID: 29025558)