Original Paper

Association of very Low-density Lipoprotein Cholesterol with All-cause and Cardiovascular Mortality in Peritoneal Dialysis

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Key Words

Cardiovascular disease • End-stage kidney disease • Mortality • Peritoneal dialysis

Abstract

Background/Aims: Cardiovascular disease (CVD) is the leading cause of death in dialysis patients. Little is known about the relationship between very low-density lipoprotein cholesterol (VLDL-C) and cardiovascular mortality in these patients. **Methods:** A total of 1324 incident patients who began continuous ambulatory peritoneal dialysis (CAPD) therapy at our hospital between January 1, 2005, and September 30, 2014, with baseline serum VLDL-C values were investigated. The associations of the VLDL-C levels with all-cause and cardiovascular mortality were assessed. **Results:** The mean age of the cohort was 50.2 ± 14.8 years, and the mean VLDL-C level was 33.6 ± 18.0 mg/dl. One hundred sixty-five (12.5%) patients died during the study period. Multivariable models revealed that the high VLDL-C group was associated with significantly higher all-cause (HR, 2.08, 95% CI, 1.13 to 3.29, $P = 0.002$) and cardiovascular mortality (HR, 1.92, 95% CI, 1.18 to 4.29, $P = 0.013$) compared with the low VLDL-C group even after adjusting for various covariates. Using the VLDL-C level as a continuous variable, the hazard ratios (HRs) of all-cause and cardiovascular mortality associated with a 10-mg/dl increase in VLDL-C level were 1.12 (95% CI, 1.02 to 1.26, $P = 0.025$) and 1.11 (95% CI, 1.02 to 1.22, $P = 0.029$), respectively. VLDL-C was associated more strongly to all-cause (e.g., Akaike information criteria of 1990.205 vs. 1994.451) and cardiovascular (e.g., Akaike information criteria of 984.146 vs. 985.634) mortality than triglyceride (TG) levels. **Conclusions:** An elevated VLDL-C level is an independent risk factor for all-cause and cardiovascular mortality in peritoneal dialysis (PD) patients.

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Introduction

Cardiovascular diseases (CVDs) are recognized as the major cause of mortality in dialysis patients and are responsible for 40% to 50% of deaths; this rate is ten to 30 times higher than that in the general population [1-4].

Dyslipidemia is often observed in patients with end-stage renal disease (ESRD) [5] and is characterized by abnormal concentrations and compositions of plasma lipoproteins. Studies in the general population have revealed that reductions in total cholesterol and LDL-C levels are effective in reducing cardiovascular events and mortality [6-8]. Unfortunately, several epidemiological surveys and randomized clinical trials have failed to show a beneficial effect of lipid-lowering therapy in terms of reducing CVD in dialysis patients despite significant reductions in LDL-C levels [9-12]. These findings suggest that the accelerated atherosclerosis and CVD in most dialysis patients may not be due to elevated LDL-C levels. Elevated serum triglyceride (TG) levels are associated with an increased risk of CVD, but this relationship is ambiguous because it becomes attenuated after adjusting for HDL-C and LDL-C [13]. However, recent genetic studies have provided additional evidence in favor of a causal and independent association between triglyceride-rich lipoproteins and CVD [14, 15]. Thus, focus is shifting to alternative measures of TGRL metabolism as potential causal biomarkers of CVD risk [16]. Very low-density lipoprotein (VLDL) is the most atherogenic TGRL particles, and the measurement of VLDL-C is relatively straightforward and captures distinct aspects of the TGRL and serum TG [17]. A large cross-sectional study (Penn Diabetes Heart Study (PDHS)) found that higher VLDL-C levels were associated with increasing coronary artery calcification (CAC) after adjusting for numerous traditional CV risk factors in patients with type 2 diabetes [18].

Peritoneal dialysis treatment may further exacerbate lipoprotein abnormalities, and high levels of VLDL-C may lead the peripheral artery atherosclerosis [19, 20]. However, it is unclear whether VLDL-C level is an independent risk for mortality in PD patients. Therefore, a longitudinal cohort study was conducted to assess whether the VLDL-C level was useful in predicting the all-cause and cardiovascular mortalities in PD patients.

Materials and Methods

Study Population

All incident patients who began CAPD therapy at the First Affiliated Hospital of Zhejiang University in China between January 1, 2005, and September 30, 2014, were investigated. The exclusion criteria were an age below 18 years at the initiation of PD therapy, transfer from hemodialysis therapy or failed kidney transplantation, a follow-up of less than 90 days, and the recovery of renal function. This study was performed in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University. All participants provided informed consent before enrollment.

Data Collection

Clinical data were collected from our regularly updated computerized records and reviews of the patients' medical and nursing notes. Baseline demographic and clinical data, including gender, age, body mass index (BMI), cause of ESRD, blood pressure, lipid-lowering therapy, prior history of hemodialysis (HD), and comorbid conditions (history of angina, myocardial infarction, cerebrovascular disease, chronic pulmonary disease, diabetes, peripheral vascular disease and malignancy), were collected. The Charlson comorbidity index (CCI) was calculated according to presence of each comorbidity [21]. The collected biochemical data included baseline very low-density lipoprotein cholesterol (VLDL-C), triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, serum albumin, uric acid, phosphates, calcium, alkaline phosphatase (ALP), potassium, C-reactive protein and parathyroid hormone. All of the biochemical parameters were assessed in the center

laboratory of our hospital. Specially, VLDL-C was measured as a transformation of cholesterol particle. The dialysis dose (Kt/V) was calculated based on 24-h dialysate collection using PD Adequest software (Baxter Healthcare). Residual renal function was calculated as the mean of the urea and creatinine clearance and adjusted for 1.73 m² of body surface area from a 24-h urine collection.

The primary outcome of interest was all-cause mortality, and cardiovascular (CV) mortality was considered as the secondary outcome of interest. Cardiovascular death was defined as death caused by acute myocardial infarction, atherosclerotic heart disease, arrhythmia, cardiomyopathy, congestive heart failure, or cerebrovascular events [22] as determined by the PD nurses and professors after comprehensive analyses of the patients' medical records. Survival status was censored on March 31, 2015, for the patients who were still on PD therapy at our center.

Statistical analysis

The participants were divided into the following 3 groups based on the VLDL-C level tertiles: low (< 24.4 mg/dl), middle (22.4-37.5 mg/dl), and high (> 37.5 mg/dl). The patient characteristics are presented for each group. Continuous variables are presented as the means and the standard deviations or the medians with the interquartile ranges, and categorical variables are presented as frequencies with percentages. Differences between groups were examined with one-way ANOVA, Kruskal-Wallis, or chi-square tests as appropriate. The correlations between VLDL-C and continuous variables were assessed by Pearson's correlation analysis, and categorical variables were evaluated using Spearman's R test. A multiple linear regression model was used to identify the determinants of VLDL-C level.

Survival was analyzed using the Kaplan-Meier method, and the groups were compared using a log-rank test. The censored events included kidney transplantation, transfer to hemodialysis therapy, a move to another dialysis center, and loss to follow-up. The Cox proportional hazards regression model was used to assess the relationship between the VLDL-C levels and all-cause and cardiovascular mortalities after adjusting for several groups of covariates. Covariates with *P*-value < 0.2 in univariate models or for importance of concern were selected for multivariate Cox regression models. A competing risk regression model based on Fine and Gray was also used. The results are expressed as the hazard ratio (HR) and the 95% confidence interval (95% CI). Because plasma triglycerides and VLDL-C levels were highly correlated (Pearson *r* = 0.76), these parameters were not included in models together. To identify whether VLDL-C was associated with mortality independent of plasma triglycerides, we assessed the relationships of VLDL-C with all-cause and cardiovascular mortalities in adjusted models where patients were stratified in to those with high triglycerides (> 150 mg/dl) and low triglycerides (< 150 mg/dl). We also compared VLDL-C and TG association with mortality in Cox regression models using Akaike information criteria (AIC) and Bayesian information criteria (BIC) [23]. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc.) and SAS version 9.2 (SAS Institute Inc.). *P* < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 1529 patients initiated peritoneal dialysis at our center during the study period; 205 patients were excluded, and the remaining 1324 patients were included in the final analysis (Fig. 1). The mean age of the cohort was 50.2 ± 14.8 years, 55.7% of the patients were male, and the mean VLDL-C level was 33.6 ± 18.0 mg/dl. The baseline characteristics of the patients categorized by VLDL-C tertile are summarized in Table 1. The patients with higher VLDL-C levels were more likely to be female, exhibited higher prevalence of diabetes mellitus and previous HD, had higher Charlson comorbidity scores and rates of statin use, had higher hemoglobin, calcium, C-reactive protein, total triglycerides, total cholesterol, HDL-C, LDL-C and potassium levels, and had lower serum albumin and parathyroid hormone levels (*P* < 0.05). No significant differences were observed between the groups in terms of age, blood pressure, BMI, education level, residual GFR, total Kt/Vurea, serum uric acid, phosphate or ALP levels.

Factors associated with baseline VLDL-C levels

The results of correlation analyses are listed in Table 2. There was no correlation between age, residual GFR, serum phosphorus, CRP, total Kt/V urea and VLDL-C level. In contrast, baseline VLDL-C levels positively correlated with sex, Charlson comorbidity index score, BMI, hemoglobin, serum calcium, TG, LDL-C and ALP levels and negatively correlated with serum albumin, HDL-C, potassium and PTH levels. Multivariate linear regression analysis indicated that serum albumin ($\beta = -0.08$, $p < 0.001$), TG ($\beta = 0.73$, $p < 0.001$), HDL-C ($\beta = -0.24$, $p < 0.001$) and LDL-C ($\beta = 0.293$, $p < 0.001$) levels were independently associated with baseline VLDL-C levels.

Associations of the VLDL-C levels with all-cause and CV mortalities

The median follow-up period was 25.4 months (range from 3.1 to 125.2 months). During the study period, 165 (12.5%) patients died, 178 (13.4%) patients were transferred to HD, and 261 (19.7%) patients underwent kidney transplantati-

Table 1. Demographics and biochemical characteristics

	Low VLDL (451)	Middle VLDL (435)	High VLDL (438)	P
VLDL-C (mg/dL)	17.0±5.3	30.1±3.6	53.3±16.2	<0.001
Age	49.2±13.8	51.4±14.5	50.1±14.2	0.06
Male (%)	272(60.3)	247(56.8)	219(50.0)	0.007
Education				
Illiteracy and elementary (%)	176(39.0)	179(41.1)	175(40.0)	0.881
Secondary and higher (%)	275(61.0)	256(58.9)	263(60)	
BMI (kg/m ²)	21.4±7.9	21.5±3.0	21.8±3.3	0.524
Blood pressure				
Systolic (mmHg)	146(136-153)	145(131-156)	145(135-159)	0.379
Diastolic (mmHg)	89(81-96)	88(80-96)	89(81-97)	0.723
Diabetes mellitus (%)	45(10.0)	70(16.1)	73(16.7)	0.007
Charlson comorbidity score	3.2±1.4	3.6±1.6	3.6±1.5	<0.001
Baseline biochemistry				
Hemoglobin (g/dL)	8.2±1.6	8.2±1.7	8.5±1.7	<0.013
Albumin (g/dL)	3.74±0.52	3.67±0.55	3.62±0.59	0.009
Uric acid (mg/dL)	8.8±2.1	8.7±2.3	8.6±2.3	0.436
Calcium (mg/dL)	8.2±1.1	8.4±0.9	8.5±1.0	<0.001
Phosphate (mg/dL)	5.7±1.4	5.6±1.6	5.7±1.7	0.549
Triglycerides (mg/dL)	97.1±40.0	126.9±47.6	199.3±119.8	<0.001
Total cholesterol (mg/dL)	96.2±39.4	127.1±46.7	200.3±119.5	<0.001
HDL-C(mg/dL)	46.8±14.3	40.9±11.2	39.07±12.3	<0.001
LDL-C (mg/dL)	81.3±27.5	87.9±23.6	104.7±36.2	<0.001
Alkaline phosphatase (U/L)	76.1±56.8	76.4±40.1	77.3±49.3	0.940
Potassium (mmol/L)	4.6±0.8	4.5±0.7	4.5±0.7	0.071
Parathyroid hormone (pg/mL)	329(192-497)	279(153-437)	294(146-449)	<0.009
C-reactive protein	2.4 (1.2-6.1)	2.6 (1.3-8.6)	2.7 (1.1-8.9)	0.048
Residual GFR (mL/min/1.73 m ²)	6.8(5.1-8.6)	7.0(5.2-8.6)	6.8(5.0-8.7)	0.865
Lipid-lowering therapy (%)	23(5.1)	49(11.3)	67(10.5)	<0.001

Abbreviations: VLDL-C, very low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; residual GFR, residual glomerular filtration rate; BMI, body mass index.

Fig. 1. Flow chart of the participants in the study cohort. PD, peritoneal dialysis.

Table 2. Correlation analysis between VLDL-C level and patient characteristics

	VLDL	Age	Sex	CCI	BMI	GFR	UA	Ca	P	Albumin	TG	CRP	HDL	LDL	Hb	K	ALP
Age	0.03																
Sex	0.10 ^b	0.01															
CCI	0.10 ^b	0.82 ^b	-0.01														
BMI	0.12 ^b	0.14 ^b	-0.19 ^b	0.10 ^b													
GFR	-0.01	0.15 ^b	-0.22 ^b	0.19 ^b	0.03												
UA	-0.04	-0.17 ^b	-0.18 ^b	-0.19 ^b	0.05	-0.08 ^a											
Ca	0.11 ^b	0.01	0.13 ^b	0.02	-0.002	0.17 ^b	-0.07										
P	0.001	-0.24 ^b	-0.05	-0.24 ^b	0.02	-0.48 ^b	0.20 ^b	-0.29 ^b									
Albumin	-0.08 ^a	-0.10 ^b	0.08 ^b	-0.19 ^b	0.02	-0.05	0.03	-0.30 ^b	0.03								
TG	0.73 ^b	-0.004	0.17 ^b	0.05	0.17 ^b	-0.01	-0.06 ^a	0.19 ^b	-0.04	0.05							
CRP	0.05	0.13 ^b	-0.15 ^b	0.12 ^b	-0.001	0.01	0.06	-0.02	-0.001	-0.15 ^b	0.003						
HDL	-0.28 ^b	-0.02	0.22 ^b	-0.04	-0.22 ^b	-0.002	-0.09 ^b	0.03	-0.03	0.08 ^b	-0.21 ^b	-0.10 ^b					
LDL	0.34 ^b	-0.02	0.15 ^b	0.03	0.07 ^b	-0.04	-0.08 ^b	0.04	0.07 ^b	-0.09 ^b	0.33 ^b	-0.01	0.25 ^b				
Hb	0.09 ^b	0.10 ^b	-0.11 ^b	0.06 ^a	0.12 ^b	-0.23 ^b	-0.03	0.29 ^b	-0.17 ^b	0.21 ^b	0.14 ^b	-0.09 ^b	-0.01	0.14 ^b			
K	-0.06 ^a	-0.06 ^a	-0.04	-0.05	0.03	-0.11 ^b	-0.02	0.02	0.19 ^b	0.07 ^b	-0.06 ^a	-0.03	0.004	0.05	-0.01		
ALP	0.05 ^a	0.18 ^b	0.03	0.15 ^b	-0.05	-0.01	-0.05	-0.12 ^b	-0.07 ^a	0.10 ^b	0.02	0.07 ^a	0.02	0.01	0.03	0.02	
PTH	-0.09 ^b	-0.13	0.14 ^b	-0.18 ^b	-0.06 ^a	-0.29 ^b	0.08 ^b	-0.32 ^b	0.24 ^b	0.11 ^b	-0.11 ^b	0.03	0.04	-0.10 ^b	-0.22 ^b	0.01	0.33 ^b

Abbreviations: VLDL-C, very low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; residual GFR, residual glomerular filtration rate. BMI, body mass index; CCI, Charlson comorbidity index; Hb, hemoglobin; UA, uric acid; ALP, alkaline phosphatase; CRP, C-reactive protein; TG, triglycerides; Ca, calcium; P, phosphate; K, potassium; PTH, Parathyroid hormone.

^a Correlation is significant at the 0.05 level (2-tailed); ^b, Correlation is significant at the 0.01 level (2-tailed)

on. Among the 165 deaths, 42 deaths (20 due to CV events) occurred in the lowest tertile group, whereas 49 (24 due to CV events) and 74 (40 due to CV events) deaths occurred in the middle and highest tertiles, respectively.

The Kaplan-Meier survival curves for all-cause and CV mortalities for the patients with the different VLDL-C levels are illustrated in Fig. 2. All-cause and CVD mortalities vary significantly between the three groups (long-rank test $P < 0.001$). The patients in the high VLDL-C group exhibited the lowest patient and cardiovascular survival rates.

Table 3 displays the hazard ratios (HRs) of all-cause and cardiovascular mortality that were associated with the different VLDL-C levels while considering the low VLDL-C group as the reference. According to the multivariable Cox proportional hazards model

Fig. 2. Kaplan-Meier survival curves for the patients with different VLDL-C levels. The cumulative mortality curves for (A) all-cause mortality and (B) CV mortality based on the VLDL-C level tertiles at baseline are shown.

Table 3. Relationships between the tertiles, continuous VLDL-C and all-cause and CV mortalities

	Tertile 2		Tertile 3		Continuous VLDL-C	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause mortality						
Model 1	1.42 (0.94-2.13)	0.101	2.46 (1.68-3.60)	<0.001	1.17 (1.10-1.25)	<0.001
Model 2	1.16 (0.77-1.77)	0.476	2.07 (1.40-3.06)	<0.001	1.13 (1.05-1.21)	0.001
Model 3	1.08 (0.71-1.64)	0.73	2.02 (1.36-2.99)	<0.001	1.11 (1.03-1.19)	0.004
Model 4	1.12 (0.73-1.72)	0.611	2.08 (1.13-3.29)	0.002	1.12 (1.02-1.26)	0.025
CV mortality						
Model 1	1.46 (0.80-2.64)	0.214	2.03 (1.64-4.81)	<0.001	1.15 (1.09-1.26)	<0.001
Model 2	1.14 (0.63-2.01)	0.67	1.99 (1.22-3.64)	0.008	1.13 (1.07-1.24)	0.006
Model 3	1.11 (0.60-2.05)	0.74	1.97 (1.26-3.80)	0.006	1.13 (1.03-1.24)	0.008
Model 4	1.20 (0.64-2.24)	0.57	1.92 (1.18-4.29)	0.013	1.11 (1.02-1.22)	0.029

Note: The reference group was the VLDL-C tertile 1 group. Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; VLDL-C, very low-density lipoprotein cholesterol. Model 1, Unadjusted. Model 2. Adjusted for age, gender, education level and Charlson comorbidity score. Model 3. Adjusted for the model 2 covariates and hemoglobin, serum albumin, uric acid, alkaline phosphatase, C-reactive protein, residual glomerular filtration rate. Model 4. Adjusted for the model 3 covariates plus high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and lipid-lowering therapy.

analysis, the high VLDL-C group was associated with significantly higher all-cause (Model 4; HR, 2.08, 95% CI, 1.13 to 3.29, $P = 0.002$) and CV mortality compared with the low VLDL-C group even after adjusting for various covariates (Model 4; HR, 1.92, 95% CI, 1.18 to 4.29, $P = 0.013$). Using the VLDL-C level as a continuous variable, the HRs for all-cause and cardiovascular mortalities associated with a 10-mg/dl increase in the VLDL-C level were 1.12 (95% CI, 1.02 to 1.26, $P = 0.025$) and 1.11 (95% CI, 1.02 to 1.22, $P = 0.029$), respectively.

Because VLDL-C and TG values were highly correlated (Pearson $r = 0.76$), their inclusion in Cox models together can

Table 4. Comparison of VLDL-C and TG association with mortality in Cox models using AIC and BIC

	All-cause mortality		CV mortality	
	VLDL-C	TG	VLDL-C	TG
AIC	1990.205	1994.451	984.146	985.634
BIC	1989.850	1994.054	983.701	985.147

Model includes age, gender, education level, Charlson comorbidity score, hemoglobin, serum albumin, uric acid, alkaline phosphatase, C-reactive protein, residual glomerular filtration rate, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and lipid-lowering therapy. Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; CV, cardiovascular; HR, hazard ratio; VLDL-C, very low-density lipoprotein cholesterol; TG, triglycerides.

Table 5. Association of VLDL-C with mortality stratified by TG levels

	All-cause mortality		CV mortality	
	HR (95% CI)	P Value	HR (95% CI)	P Value
TG > 150mg/dl	1.21 (1.04-1.42)	0.015	1.29 (1.04-1.59)	0.018
TG < 150mg/dl	1.10 (1.01-1.22)	0.043	1.09 (0.96-1.25)	0.17

Model includes age, gender, education level, Charlson comorbidity score, hemoglobin, serum albumin, uric acid, alkaline phosphatase, C-reactive protein, residual glomerular filtration rate, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and lipid-lowering therapy. Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; VLDL-C, very low-density lipoprotein cholesterol; TG, triglycerides

lead to excess collinearity and potential spurious results. Thus, we compare VLDL-C and TG association with all-cause and CV mortality in Cox models using AIC and BIC scores. The result showed that both AIC and BIC scores were consistently lower for VLDL-C (Table 4). This indicated that VLDL-C performed better than TG in predicting all-cause and CV mortality when other confounders were held equal. Furthermore, stratified analysis also showed that VLDL-C had stronger association with all-cause and CV mortality in patients with TG > 150 mg/dl than those with TG < 150 mg/dl (Table 5).

Discussion

To our knowledge, no prior studies have examined the relationship between serum VLDL-C level and mortality in PD patients. In this retrospective study, we demonstrated that higher VLDL-C levels were associated with higher all-cause and cardiovascular mortalities even after adjusting for several potential confounders (e.g., demographic characteristics, the Charlson comorbidity score, and laboratory parameters). VLDL-C levels associated with higher mortality risk in patients with high TG levels suggesting possible potential value for VLDL-C in risk prediction beyond serum TG.

Epidemiological and genomic studies have suggested that TGRLs are causally relevant to atherosclerotic CVD [14, 15, 24-26]. The results from a large study that included 73,513 participants revealed that a 1 mmol/l (39 mg/dl) increase in TGRL was associated with a 2.8-fold increase in the causal risk for ischemic heart disease independent of reduced HDL-C [16]. Takeichi et al [27] and Kugiyama et al [28] also found that elevated TGRL levels are associated with increased risks of CVD. VLDLs are the major component and atherogenic particles of TGRL in the circulation. A PDHS study that examined VLDL-C as an alternative marker of TGRL demonstrated that VLDL-C levels are positively associated with increased coronary artery calcification in patients with type 2 diabetes even after adjusting for traditional risk factors [18]. Laakso et al. also reported that higher VLDL-C levels are associated with an increased risk of CVD in diabetic patients [29]. In dialysis, Kanda et al reported that VLDL-C is associated with peripheral artery disease (diagnosed using the ankle-brachial index) in PD patients with controlled LDL-C levels [20]. In the present study, similar results were observed; we found that elevated VLDL-C levels were associated with increased risks of all-cause and CV mortalities in patients treated with peritoneal dialysis independent of HDL-C, LDL-C and triglyceride levels.

Several mechanisms have been proposed to explain why VLDL may be causally related to progression of atherosclerosis and CVD. VLDL is synthesized in the liver and serves as a vehicle that is responsible for the redistribution of triglycerides from liver to the peripheral tissues. Each VLDL particle contains a single molecule of apolipoprotein B100 and has a hydrophobic core that consists primarily of triglycerides and a small amount of cholesterol esters [30, 31]. The sizes of the VLDL particles vary depending on the quantity of triglycerides carried in the particle. Large VLDL particles are secreted from patients with hypertriglyceridemia and may contain 5 to 20 times more cholesterol than LDL. Unlike LDL, VLDL remnants rapidly penetrate the arterial wall, increase endothelial inflammation and facilitate the infiltration of monocytes, which results in foam cell formation and atherosclerosis [32, 33]. Normally, VLDL particles are hydrolyzed by lipoprotein lipase (LPL) and hepatic lipase (HL) in the plasma. Eisenberg et al and Mekki et al reported that the activities of LPL and HL are strongly decreased in patients with nephrotic syndrome and chronic renal failure, which results in hypertriglyceridemia and impaired clearance of the atherogenic, cholesterol-enriched remnants of VLDLs, which can rapidly penetrate the arterial wall and contribute cholesterol to atherosclerotic lesions [34-36]. Additionally, VLDL plays an important role in myocardial energetic and function by acting as a metabolic substrate. VLDL is taken up by both LPL and VLDL receptors in the myocardium [30]. Perman *et al.* demonstrated that hypoxia and ischemia up-regulate the expression of the VLDL receptor in an animal model, which leads to lipid accumulation in the myocardium and an increased risk of mortality following myocardial infarction [37]. Hepatic VLDL overproduction has been reported to be related to insulin resistance [38]. Adiels *et al* [39] and Gill *et al* [40] reported that in patients with metabolic syndrome or type 2 diabetes, insulin-resistant states and the loss of insulin-mediated suppression of apoB100 secretion lead to increased production of large VLDL-1 particles. Hypersecretion of large VLDL-1 particles, which contain more cholesterol, results in higher levels of remnant particles and small dense LDLs and lower levels of HDL that may contribute to the progression of vascular endothelial injury and atherosclerosis [41-43]. In peritoneal dialysis, glucose absorption and protein loss from the dialysate further aggravate

the metabolic abnormalities and insulin resistance. Prinsen et al reported that the VLDL-1 apoB100 pool size is increased in PD patients due to increased VLDL-1 apoB100 synthesis in combination with reduced VLDL-1 apoB100 catabolism, which inevitably results in the formation of atherogenic small dense LDL particles that may contribute to the progression of atherosclerosis [19]. Thus, the potential mechanisms mentioned above may contribute to the associations between elevated VLDL-C levels and the increases in all-cause and CV mortalities. VLDL-C is thus potentially a novel therapeutic target in dialysis patients. Our study further revealed that higher VLDL levels were associated with higher all-cause and cardiovascular mortalities in PD patients.

Our study has several limitations. First, it was a retrospective study performed in a single center; therefore, our findings only reveal associations and not causation due to the observational nature of the study. Second, only baseline data were used in our analysis. We did not investigate the influence of changes in VLDL-C levels during the observation period on the mortality of PD patients. Third, only PD patients were included in our study; thus, no extrapolation is possible to patients on hemodialysis or non-dialysis-dependent CKD patients. Despite its limitations, the present study is the first to investigate the association of VLDL-C with mortality in dialysis patients. The relationship between the VLDL-C level and mortality was examined using both a traditional Cox regression model and a competing-risk regression model, and our results were robust to adjustments for multiple risk factors and potential confounders.

Conclusion

Our study revealed that elevated VLDL-C levels are independently associated with higher risks of all-cause and cardiovascular mortalities in peritoneal dialysis patients. Further studies are needed to identify the underlying mechanisms and investigate whether VLDL can serve as a potential new therapeutic target for improving the survival of PD patients with dyslipidemia.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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