Non-high-density Lipoprotein Cholesterol May Predict the Cardio-cerebrovascular Risk in Patients on Maintenance Hemodialysis

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Abstract

Background

Non-high-density lipoprotein cholesterol (non-HDL-C) may be an independent risk factor for cardio-cerebrovascular disease (CVD); however, the cutoff level in patients on maintenance hemodialysis (MHD) is unknown.

Methods

We performed a multicenter retrospective study of MHD patients treated at 10 dialysis centers in Guangdong Province from July 1, 2016, to April 1, 2017. We collected laboratory test data and recorded CVD complications and outcomes.

Results

A total of 1,288 patients were enrolled; the non-HDL-C interquartile range was 2.76 (2.24–3.45) mmol/L. Over a median follow-up time of 23 months, 142 patients developed CVD. The non-HDL-C level was a principal risk factor for such events ($P < 0.05$; area under the curve 0.822, 95% confidence interval 0.800–0.842). The maximum Youden index was 0.549 and the best cutoff > 3.39 mmol/L.

Conclusion

Higher baseline non-HDL-C levels are associated with an increased risk of CVD in MHD patients. Thus, non-HDL-C effectively predicts CVD.

Background

Chronic kidney disease (CKD) is associated with significant morbidity and mortality. Globally, in 2017, 1.2 million people (95% uncertainty interval [UI] 1.2 to 1.3 million) died of CKD [1]. End-stage renal disease (ESRD) has become a major public health problem given increased life expectancies worldwide [2]. More than 2.5 million people are on renal replacement therapy; the number is projected to double by 2030 [3]. Such patients are at high risk of cardio-cerebrovascular disease (CVD), which independently predicts a need for dialysis [4, 5]. Attempts to reduce CVD in ESRD patients have usually been extensions of strategies employed for general populations [6]. Dyslipidemia in ESRD patients, and frequent changes in lipid and lipoprotein levels, greatly contribute to CVD development [6]. Certain dyslipidemia patterns increase the risk of atherosclerotic vascular disease in general populations. It thus seems likely that dyslipidemia increases the CVD risk in ESRD patients. Such dyslipidemia is characterized by high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels [8]. However, prior studies evaluating associations between specific lipid and lipoprotein levels and CKD were limited in terms of scope and generalizability [8]. Although some studies suggested no, or an inverse, association between low-density lipoprotein cholesterol (LDL-C) levels and the CVD risk in patients on maintenance hemodialysis (MHD), the effects of lipid levels remain unknown. We thus performed a multicenter cross-sectional study of 1,876 dialysis patients. The trends, and the effects of confounding factors, were validated and adjusted by dividing patients into quartiles (1/4, 3/4). We seek to improve the definition and prevention of, and therapy for, dyslipidemia in dialysis patients.

Methods

Study Design and Participants

This retrospective study was performed at 10 hospitals in South Guangdong Province, including Shenzhen Traditional Chinese Medicine Hospital, Dongguan People's Hospital, The First people's Hospital of Zhaoqing, The Second People's Hospital of Futian District Shenzhen, Baoan Central Hospital of Shenzhen, Tungwah Hospital of Sun Yat-sen University, Guangzhou Hospital of Integrated Traditional and West Medicine, Shunde Hospital of Southern Medical University, The Sixth Affiliated Hospital of Sun Yat-sen University and Huizhou Municipal Central Hospital. The Sixth Affiliated Hospital of Sun Yat-sen University served as the coordinating hospital. All hospital laboratories adhered to the Blood Purification Standard Operating Procedure of Guangdong and had passed the quality and competence tests of the Guangdong Medical Association [11].

Demographic and dialysis-related data were collected using Epidata Entry ver. 3.1.1203.2006. We included 1,876 patients who underwent regular hemodialysis from July 2016 to July 2017. Additional inclusion criteria were: (1) at least 2 dialysis days/ week, and (2) dialysis duration ≥ 3 months. The exclusion criteria were: (1) missing baseline or follow-up data (especially lipid data), (2) CVD or death, and/or (3) a tumor.

Biochemical Analysis

Blood samples were drawn at MHD commencement and analyzed locally. For all patients, the fasting plasma glucose, serum albumin, hemoglobin, potassium, total cholesterol (TC), HDL-C, TG, LDL-C, blood urea nitrogen, uric acid, white blood cell, platelet, creatinine, calcium, phosphate, and parathyroid hormone (PTH) levels, and the parameter Kt/V (a measure of the efficacy of hemodialysis), were measured at regular but different intervals. The body mass index (BMI) for each patient was calculated as the post-dialysis body weight divided by the square of the height.

Data Collection and Measures

General information, medical histories, and laboratory data were collected by physicians. All patients were asked about CVD complications and underwent blood tests every 3 months. The data were stored in Excel format. The study adhered to the principles of the Declaration of Helsinki. The work was approved by the Human Research Ethics Committees of the involved hospitals. Investigators or persons authorized by the investigators explained the benefits and risks of trial participation to each patient, or their legal representatives or notaries. Written informed consent was obtained from each patient. Trial data were stored in a safe in the office of the first author, who performed all statistical analyses.

Baseline and Outcome Data

Patient sex, age, and independence (or not) were recorded. Outcomes were assessed from baseline until discharge (i.e., the end of intervention) (Table 1). The primary outcomes were CVDs, including myocardial infarction, acute left heart failure, non-myocardial acute coronary syndrome, cerebral infarction, and cerebral hemorrhage. The pre-specified secondary outcomes were the association of the non-HDL-C level with CVD and the predictive utilities of the LDL-C, TC, and non-HDL-C levels.

Statistical Analyses

Patients were compared by age and sex. We divided the patients into four groups by the baseline non-HDL-C quartiles. SPSS software ver. 25.0 (Chicago, IL, USA) was used for all analyses. Continuous variables that were normally distributed are shown as means $\pm$ standard deviations and were compared employing a one-way analysis of variance. Continuous variables that were not normally distributed are shown as Mean values (quartiles 1, 3) and

compared with the aid of the Kruskal-Wallis test. Categorical variables are expressed as frequencies (proportions) and were compared using the chi-squared test. The Kaplan-Meier method was employed to calculate cumulative survival and draw survival curves; the log-rank test was used to explore significance. The relationship between the non-HDL-C level and CVDs was analyzed via Cox's proportional hazard regression and the results expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The area under the receiver operator curve (AUC) and the 95% CI were used to evaluate the predictive utility of the non-HDL-C level in terms of various endpoints. The AUC ranged from 0.5 (indicating randomness) to 1.0 (complete dependence). The maximum Youden index was used to determine the optimal non-HDL-C cutoff for each endpoint. A two-sided $\alpha \leq 0.05$ was taken to indicate significance.

Results

Participant characteristics

A total of 1,288 patients aged 59.85 ± 15.06 years were enrolled; 766 males (59.5%) and 522 females (40.5%). The non-HDL-C interquartile range was 2.76 (2.24–3.45) mmol/L. Age; pre-dialysis weight; and the levels of white and red blood cells and platelets, serum creatinine and albumin, ferritin, and blood calcium differed among the four quartiles (all $P < 0.05$). After a median follow-up of 14 months, 142 patients had experienced CVD. Patients in the non-HDL-C ≥ 3.45 mmol/L group exhibited a higher CVD rate (31.7%) than the other groups (Figure 2). Univariate Cox's regression showed that age and the levels of white blood cells, platelets, blood glucose, TC, TG, non-HDL-C, and total blood protein were risk factors for CVD (all $P < 0.05$, Tables 2 and 3). The Kaplan-Meier survival curve revealed a positive correlation between the non-HDL-C level and CVD incidence (HR 1.102, 95% CI 1.070–1.134, $P < 0.001$). The ROC curves suggested that, compared to the TC (AUC 0.710, 95% CI 0.684–0.735), TG (AUC 0.777, 95% CI 0.753–0.799), and LDL-C (AUC 0.583, 95% CI 0.753–0.799) levels, the non-HDL-C level (AUC 0.822, 95% CI 0.800–0.842) better predicted CVD (Figure 4). The maximum Youden index was 0.549, and the corresponding non-HDL-C cutoff 3.39 mmol/L. Next, the non-HDL-C level was included in a Cox regression using the quartiles as categorical variables. Single-factor regression showed that, after adjusting for age and sex using the Q1 group as a reference, Q2 (HR 0.041, 95% CI 0.018–0.094, $P < 0.001$), Q3 (HR 0.070, 95% CI 0.035–0.138, $P < 0.001$), and Q4 (HR 0.224, 95% CI 0.142–0.354, $P < 0.001$) were at higher risks of CVD; the risks were not affected by diabetes status, dialysis duration, BMI, anticoagulant type, or systolic or diastolic blood pressure. After further adjustment for hemoglobin, serum albumin, and blood uric acid and creatinine levels, the Kt/V, average ultrafiltration rate, and platelet and serum urea nitrogen levels, the risk proportions remained different (and statistically significant) ($P < 0.001$, Table 3). Thus, the non-HDL-C level was associated with an increased risk of CVD in MHD patients.

Discussion

An elevated cholesterol level is an independent risk factor for coronary heart disease (CHD). LDL-C is the principal laboratory parameter used for CVD management [11]. The National Lipid Association Expert Panel concluded that elevated levels of non-HDL-C and LDL-C are the root causes of atherosclerosis because the processes underlying elevation thereof contribute to most clinical CHD events [13, 14]. To reduce the risk of ischemic events in CHD patients, the fasting level of LDL-C should be controlled to < 1.4 mmol/L (the primary target) and that of non-HDL-C to < 2.2 mmol/L (the secondary target) according to 2019 European guidelines.

Serum LDL-C, TG, HDL-C, and non-HDL-C levels are associated with the risk of atherosclerotic CVD and other CV events [13, 14]. Serum β -trace protein and β 2-microglobulin, and a composite of these markers with the eGFRcr and eGFRcys rates, were also independently associated with the risk of ESRD and all-cause mortality [16].

The non-HDL-C level is obtained by subtracting the HDL-C level from the TC level, and serves as a comprehensive measure of atherogenic lipids, including LDL-C, lipoprotein (a), intermediate-density lipoprotein, and very LDL remnants [17], and a marker of cardiovascular risk [18]. In 2018, the global age-standardized mean non-HD-C level was 3.3 mmol/L (range 3.2–3.4 mmol/L) for women and 3.3 mmol/L (range 3.3–3.4 mmol/L) for men [18], but the figures for dialysis patients remain unclear.

Over a median follow-up of 14 months, 142 of our patients developed CVD. Univariate Cox's regression showed that age; anticoagulant type; and white blood cell, platelet, blood sugar, TC, TG, non-HDL-C, and total blood protein levels were risk factors for CVD (all $P < 0.05$). The Kaplan-Meier survival curve revealed a positive correlation between the non-HDL-C level and CVD incidence. The ROC curves suggest that, relative to TC (AUC 0.710, 95% CI 0.684–0.735), TG (AUC 0.777, 95% CI 0.753–0.799), LDL-C (AUC 0.583, 95% CI 0.753–0.799), and other indicators, non-HDL-C (AUC 0.822, 95% CI 0.800–0.842) better predicted CVD in MHD patients. The Youden index maximum was 0.549, corresponding to a non-HDL-C cutoff of 3.39 mmol/L.

Compared to overseas large-scale studies [19], the LDL-C reductions that we observed were greater. Takahiro [20] found that the non-HDL-C level predicted mortality and was minimally affected by the fasting or serum TG level. Meta-analyses and large prospective studies found that the on-treatment levels of non-HDL-C better predicted CVD than LDL-C levels [21]. The non-HDL-C level is a simple predictor of risk in patients on and off statins; there is no need for a fasting blood sample [22]. When post-prandial LDL-C and non-HDL-C goals were re-evaluated using the non-fasting cut-off points, the percentage attainments did not differ in the fasting and non-fasting states. It has been suggested that the clinical benefit afforded by controlling the non-HDL-C level is better than that available by controlling the LDL-C level [24]. Non-HDL-C assessment is better than LDL-C evaluation when exploring the percentage attainments of non-fasting lipid levels that improve the coronary health of dialysis patients [23].

The strengths of our study include the large sample size and the involvement of 10 provincial dialysis centers; this enhances the generalizability of our findings. Also, all researchers strictly followed standard operating procedures. Transdermal dialysis was simple, associated with good patient acceptance. The dropout rate was only 3.5% and the exit rate 4.0%. The principal limitation is that the retrospective design may be associated with observer and/or performance bias; also, the follow-up time was short.

Conclusions

In conclusion, possible CVD events in MHD patients require attention. We found that higher serum non-HDL-C levels were associated with a greater risk of CVD. Additional clinical studies are required.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Airong Qi, Shunmin Li conceived and designed the research methods. Denggui Luo, Yueming Luo, Yanhong Zou analysed the data. Yuanzhao Xu, Bo Fu, Dong Yang, Jun Yang, Cai Xu and Shuyi Ling collected the data.

Denggui Luo, Yueming Luo and Yanhong Zou wrote the original draft. Airong Qi and Shunmin Li reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was reviewed and approved by the hospital's Human Research Ethics Committee (No. K2020-029-01). The investigator or a person authorized by the investigator was responsible for disclosing the benefits and risks of trial participation to each patient, the patient's legal representative, or a notary witness. Written informed consent was obtained from each patient for participation in the trial.

Consent for publication

All of the participants agreed and provided written informed consent.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1 Baseline MHD patient characteristics according to Non-HDL-C quartile

characteristic	Non-HDL-C Quartile				<i>p</i> -value
	Q1<2.24	2.24≤Q2≤2.76	2.76≤Q3≤3.45	Q4≥3.45	
	n=314	n=323	n=326	n=325	
Age (years)	57.89±14.17	59.84±15.09	59.47±15.51	62.86±15.07	<0.001
Gender					0.469
male, n (%)	185(58.9%)	194(60.1%)	184(56.4%)	203(62.5%)	
female, n (%)	129(41.1%)	129(39.9%)	142(43.6%)	122(37.5%)	
Dialysis time(months)	28.11(14.09-65.67)	25.17(11.56-53.33)	23.90(9.50-50.40)	26.47(7.99-47.01)	
BMI (kg/m ²)	19.71(14.50-25.00)	19.71(0.00-23.55)	19.59(0.00-24.72)	22.52(16.51-27.77)	<0.001
Cause of ESRD, n (%)					<0.001
primary glomerulonephritis	177(56.4%)	161(50.0%)	164(50.5%)	120(36.9%)	
diabetic nephropathy	65(20.7%)	68(21.1%)	68(20.9%)	87(26.8%)	
hypertensive nephropathy	19(6.1%)	12(3.7%)	12(3.7%)	18(5.5%)	
Anticoagulant type, n (%)					0.136
low molecular weight heparin	282(89.8%)	274(84.8%)	276(84.9%)	271(83.4%)	
unfractionated heparin	30(9.6%)	42(13.0%)	41(12.6%)	42(12.9%)	
Dialysis vascular access, n (%)					0.033
AVF	268(85.4%)	277(85.8%)	278(85.3%)	262(80.6%)	
AVG	3(1.0%)	2(0.6%)	6(1.8%)	6(1.8%)	
TCC	30(9.6%)	37(11.5%)	24(7.4%)	31(9.5%)	
NCC	13(4.1%)	7(2.2%)	18(5.5%)	26(8.0%)	
Mean UFV(L)	2.43(1.93-3.00)	2.40(1.65-2.93)	2.23(1.66-2.84)	2.30(1.71-3.16)	0.788
Systolic pressure (mmHg)	146.35±18.99	145.72±21.37	146.71±20.86	145.37±20.77	0.838
Diastolic pressure (mmHg)	82.84±11.89	82.50±12.49	84.68±10.09	84.17±10.21	0.814
Diabetes, n (%)	59(18.8%)	63(19.5%)	77(23.7%)	71(21.8%)	0.404

FPG (mmol/L)	4.35±1.81	6.99±3.02	4.86±1.25	7.42±2.84	0.058
Tc (mmol/L)	4.40±1.28	3.87±0.42	5.20±1.25	5.32±0.24	<0.001
Tg (mmol/L)	3.36±2.85	0.81±0.25	1.67±1.55	3.09±2.75	<0.001
LDL-C (mmol/L)	2.88(2.40-3.70)	2.06(1.83-2.33)	1.69(1.39-2.66)	2.02(1.54-2.41)	<0.001
Alb (g/L)	22.04±17.71	42.75±1.89	31.74±16.65	37.75±3.09	<0.001
Cr (μmol/L)	554.36±563.53	1082.75±161.16	937.10±654.46	1194.25±307.89	<0.001
BUN(μmol/L)	27.18(22.64-34.00)	27.40(22.80-33.90)	26.18(22.18-32.43)	26.97(22.00-34.12)	0.638
Ua (μmol/L)	266.60±211.82	458.75±35.85	465.30±271.41	547.25±133.98	<0.001
Total Kt/V	1.33(1.12-1.60)	1.32(1.18-1.50)	1.32(1.18-1.48)	1.37(1.12-1.76)	0.029
WBC (10 ⁹ /L)	4.72±1.44	6.40±1.45	6.15±2.53	7.00±1.31	0.035
Hb (g/L)	128.27±34.91	99.00±12.02	107.00±41.59	90.25±26.53	<0.001
Plt (10 ⁹ /L)	131.90±51.11	23.17±2.92	30.83±22.22	24.84±4.37	<0.001
K (mmol/L)	5.31(4.62-6.40)	5.15(4.50-5.70)	5.05(4.60-5.62)	5.40(4.63-7.00)	0.084
Ca (mmol/L)	2.20(2.08-2.36)	2.16(2.00-2.32)	2.15(2.04-2.31)	2.31(2.12-2.76)	0.012
PTH (pg/ml)	167.60(38.65-403.60)	260.96(75.05-585.33)	234.41(72.90-624.25)	233.93(79.03-587.40)	0.009
P (mmol/L)	6.80±5.89	1.79±0.47	3.56±2.83	2.46±0.44	<0.001

Values are expressed as mean ± SD, median and interquartile range, or number (percentage) as appropriate. BMI Body mass index, ESRD end-stage renal disease, AVF Autogenous arteriovenous fistula, AVG Arteriovenous graft, TCC Tunnel-cuffed catheter, NCC Non-cuffed catheter, UFV Ultrafiltration volume, CVD Cardiovascular disease, FPG Fasting plasma glucose, Tc Total cholesterol, Tg Triglycerides, LDL-c Low density lipoprotein cholesterol, Alb Albumin, Cr Creatinine, BUN Blood urea nitrogen, Ua Uric acid, Hb Hemoglobin, Plt Platelets, Pth Parathyroid hormone.

Table 2 The association of Non-HDL-C with CVD in the study cohort

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Age	1.022 (1.011-1.034)	<0.001	1.020 (1.009-1.032)	<0.001
Gender	0.938 (0.665-1.323)	0.714		
BMI	0.992 (0.981-1.004)	0.196		
Total KT/V	0.989 (0.977-1.002)	0.098		
WBC	1.078 (1.044-1.114)	<0.001	1.083 (1.040-1.128)	<0.001
Plt	1.005 (1.003-1.007)	<0.001	1.005 (1.002-1.007)	<0.001
Hb	1.000 (0.997-1.004)	0.952		
FPG	1.037 (1.007-1.067)	0.015	1.026 (0.999-1.054)	0.061
K	0.996 (0.989-1.003)	0.996		
Ca	0.996 (0.989-1.003)	0.278		
P	0.983 (0.912-1.060)	0.664		
Ua	1.001 (1.000-1.002)	0.057		
Cr	1.000 (1.000-1.001)	0.303		
Alb	1.008 (0.990-1.026)	0.380		
Tc	1.053 (1.020-1.087)	0.002		
Tg	1.080 (1.049-1.111)	<0.001	1.094 (1.056-1.133)	<0.001
LDL-c	0.996 (0.991-1.002)	0.194		
HDL-c	0.068 (0.038-0.120)	<0.001		
Non-HDL-c	1.092 (1.061-1.124)	<0.001	1.124 (1.087-1.161)	<0.001
Diabetes	1.048 (0.702-1.563)	0.819		

Table 3 Cox regression analysis of different levels of Non-HDL-C and cardiovascular and cerebrovascular events

Variable	Model 1		Model 2		Model 3	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Continuous variable						
Non-HDL-C (mmol/L)	1.102 (1.070-1.134)	<0.001	1.135 (1.094-1.177)	<0.001	1.266 (1.020-1.572)	0.033
Categorical variables						
Q1	Reference		Reference		Reference	
Q2	0.041 (0.018-0.094)	<0.001	0.036 (0.016-0.084)	<0.001	0.023 (0.003-0.176)	<0.001
Q3	0.070 (0.035-0.138)	<0.001	0.060 (0.030-0.119)	<0.001	0.056 (0.013-0.246)	<0.001
Q4	0.224 (0.142-0.354)	<0.001	0.175 (0.109-0.282)	<0.001	0.238 (0.104-0.545)	0.001

Model 1: Adjusted for age and gender

Model 2: Adjusted for model 1 covariates and diabetes, dialysis time, BMI, anticoagulant type, systolic blood pressure and diastolic pressure

Model 3: Adjusted for model 2 covariates and hemoglobin, serum albumin, uric acid, serum Cr, Kt/V, Mean UFV, Platelets, Blood urea nitrogen

All variables with a confirmed P-value < 0.05

Figures

Figure 1

Flow chart of the participants in the study cohort.

Figure 2

The comparison of CVD events between each group

Number at risk

Non-HDL-C < 2.24	314	314	314	314	314	311	311	286	1
2.24 ≤ Non-HDL-c < 2.76	323	323	323	323	322	312	309	238	1
2.76 ≤ Non-HDL-c < 3.45	326	326	325	324	322	286	274	187	0
Non-HDL-c ≥ 3.45	325	325	321	320	320	259	243	194	2

Figure 3

Kaplan–Meier curves of MHD patients with different levels of Non-HDL-C cardiovascular mortality

Variable	AUC	SE	95% CI
Tg	0.777	0.0198	0.753 – 0.799
LDL-c	0.583	0.0262	0.555 – 0.610
Tc	0.710	0.0228	0.684 – 0.735
Non-HDL-c	0.822	0.0188	0.800 – 0.842

Figure 4

ROC curve chart of the predictive effect of LDL-C, TC and Non-HDL-C on CVD events in MHD patients