Predictive Value of Small Dense Low-density Lipoprotein Cholesterol and Remnant-like Particle Cholesterol for Cardiovascular Events in Chinese Elder Diabetes Mellitus Patients

Li Xu
Department of general surgery, Suzhou Ninth People's Hospital, Nantong University, Suzhou, China.
Feifei Lu
Affiliated Hospital of Nantong University
Jingfen Lu
Affiliated Hospital of Nantong University
Yan Xu
Affiliated Hospital of Nantong University
Nuoer Chen
Affiliated Hospital of Nantong University
Xuewen Zhou
Affiliated Hospital of Nantong University
Jianhong Xu
Affiliated Hospital of Nantong University
Hao Shen (shenhaojyk@126.com)
Department of Blood Transfusion and Clinical Laboratory Medicine, Suzhou Ninth People's Hospital, Nantong University, Suzhou, China.

Research

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Abstract

Background

As a subcomponent of lipoprotein cholesterol (LDL-C), small dense LDL-C (sdLDL-C) have been suggested to be a better predictor of cardiovascular diseases(CVD). This research was to evaluate the predictive of the sdLDL-C in cardiovascular events (CVs) in Chinese elder type 2 diabetes mellitus(DM) patients.

Methods

Serum sdLDL-C measured by homogeneous method was compared in 386 consecutive type 2 DM patients between December 2014 and December 2016. Finally, 92 type 2 DM patients had CVs during the 48-month follow-up period. Receiver operating characteristic (ROC) curves were used for assess the predictive value of baseline parameters to major CVs.

Results

Ninety-two CVs occurred during the study period.The ROC curve manifested that sdLDL-C in the study population had a matchable discriminatory power (AUC for sdLDL-C was 0.7366, P = 0.003). In addition, kaplan-Meier event-free survival curves displayed a obvious increase of CVs risk for sdLDL-C ≧ 26 mg/dL (log-rank = 9.10,P = 0.003). This phenomenon had analogous

results

in patients who received statins at baseline (log rank = 7.336，P = 0.007).The study discovered that the increase in HbA1c, glucose, LDL-C, sdLDL-C, non-HDL-C and ApoB and the decrease in ApoA1 were obviously interrelated with heightened CVs risk through Cox regression analysis. Multivariate analysis demonstrated that the increase of sdLDL-C and HbA1c was obviously correlated with CVs. The results of the study indicated that sdLDL-C (per 10 mg/dL) was a increased risk for CVs in the multivariate model (HR 1.281, 95% CI 1.225–16.032; P < 0.01).

Conclusion

The consequences demonstrated that sdLDL-C was more effective than RLP-C in predicting the future CVs of Chinese elder type 2 DM patients

Background

Type 2 diabetes mellitus (DM) patients are more likely to have cardiovascular disease (CVD) in part owing to dyslipidemia characterized by elevated low-density lipoprotein cholesterol (LDL-C), small dense LDL-C(sdLDL-C) and remnant lipoprotein cholesterol (RLP-C) in serum[1, 2]. Moreover, prior research had discovered that higher sdLDL-C and RLP-C levels are interrelated with elevated risk of CVD events [3–5].

Cross-sectional studies have shown that sdLDL-C concentration is closely related to the severity of cardiovascular disease and is independent of classic coronary risk factors[6].Moreover, another study had revealed that a higher RLP-C concertration as a risk factor for cardiovascular events (CVs) independent of other risk factors in diabetic patients [7].However, very little studies in the past have assessed the relationship between sdLDL-C and RLP-C and CVs in Chinese elder type 2 diabetes mellitus(DM) patients.

SdLDL-C levels could be easily detected through automated analysis[8]. But these methods have not yet been impressed on large number of type 2 DM patients, especially among the Chinese elder population. The study attempted to investigate whether sdLDL-C can predict CVs in Chinese elder type 2 DM patients.

Methods

Subjects and study design

This research includes 418 consecutive patients aged ≥ 65 years with Type 2 DM at Suzhou Ninth People's Hospital, Suzhou, China, between December 2014 and December 2016,all of these studies had no history of CVD. DM was identified according to 2009 American diadetes Association criteria for diabetes diagnosis[9]. The body mass index (BMI), estimate of glomerular filtration rate (eGFR) and smoking(current smokers and at least one cigarette per day)were recorded. The diagnosis of hypertension was based on a hypertension or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and/or use of antihypertensive medications within 2 weeks of enrollment[10]. The diagnostic criterion for dyslipidemia was defined as the fasting srum lipid levels as follows LDL-C ≥ 140 (mg/dl), high-density lipoprotein cholesterol (HDL-C) < 40 (mg/dl) or triglyceride (TG) ≥ 150 (mg/dl) and/or the current use of lipid-lowering medication[11].

Exclusion criteria were : age ≥ 90 years (n = 2), presence of malignancy (n = 3), known thyroid disorders (n = 3), lost of blood examination data (n = 6), infectious disease (n = 7), lost during follow-up (n = 7) and severe hepatic and nephrotic disease (n = 4). Finally, 386 patients (mean age of 72.7 ± 5.4 year, range from 65 to 86 years) were effectively included in the study. All parameters were measured for subjects yearly during the follow-up, Clinical and laboratory data was collated between September and November 2019. The endpoints were: (1)CVD death, (2) the date of the first occurrence of CVs, and (3) the patient visit to the Suzhou Ninth People's Hospital for the last time,Table 1 shows the CVs.

Table 1
Cardiovascular events

Cardiovascular events	Number(n = 92)
Cardiovascular death	8
acute coronary syndrome	13
hospitalization for heart failure	26
any revascularization	36
stroke	9

Laboratory measurements

The blood samples were collected after 12 hours of fasting in the morning. After collection, the samples were centrifuged immediately and stored at -80°C until assay within the same day. High-sensitivity C-reactive protein(hsCRP),HDL-C, Hemoglobin A1c (HbA1c), LDL-C, TG,, fasting blood glucose, apolipoprotein A-I（ApoA-I）, apolipoprotein B（ApoB）and lipoprotein (a) were detected through standard biochemical tests as earlier report[12]. The sdLDL-C[5] and RLP-C[13]were discovered by a detergent-based fully-automatic homogeneous method(Denka Seiken kit).

Statistical analyses

All statistical analyses were performed using the SAS9.1 solftware package. The Chi-square test was used to analyze classification variables. Wilcoxon test for abnormal distribution parameters and independent sample t-test was used for normal distribution parameters to compare the baseline characteristics of CVs group and non-CVs group. Correlation coefficients between sdLDL-C and various parameters were ditermind by Spearman's rank analysis. Kaplan-meier method was used to compare the occurrence of CVs above or below the median sdLDL-C level, differents were assessed with log-rank test. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were used for determining the ability of sdLDL-C, HbA1c, and RLP-C to predict CVs. Cox regression and multivariate Cox regression analysis were employed to regulate these independent predictors. All statistical analyses were double-tailed, statistically significant was considered at the level $P < 0.05$.

Results

This study included 269 males (69.7%) and 117 (30.3%) females. The age of these persons was 65 years or older. They received follow-ups ranging from 20 to 48 months, with an average of 28 months. At baseline the patients with CVs had obviously higher BMI and were more likely to be under calcium channel blockers and insulin therapy compared with non-CVs patients (Table 2). A comparison of laboratory findings (Table 3) manifested the levels of glucose, HbA1c,LDL-C, non-HDL-C, sdLDL-C, RLP-C, ApoB and ApoA-1 in the CVs group were significantly different from those of the non-CVs group. There

was no significantly difference in TG, hsCRP, HDL-C, eGFR, sdLDL-C /LDL-C ratioand lipoprotein (a) between the two groups.

Table 2
The clinical characteristics of the enrolled patients at baseline

Variables	Whole	CVs	non-CVs	P^a
	(*n* = 386)	(*n* = 92)	(*n* = 294)	
Characteristics				
Age (years)	72.7 ± 5.4	72.9 ± 5.2	72.8 ± 5.5	0.568
Male	269/386 (69.7)	65/92 (70.6)	204/294 (69.4)	0.818
BMI (kg/m^2)	23.6 ± 2.1	24.3 ± 2.3	23.4 ± 2.2	0.001
Cardiovascular disease risk factors				
Hypertension	270/386 (69.9)	64/92 (69.6)	206/294 (70.1)	0.927
Dyslipidemia	246/386 (90.2)	83/92 (90.2)	265/294 (90.1)	0.982
Smoking, current or former	246/386 (63.7)	59/92 (64.1)	187/294 (63.6)	0.927
Family history	82/386 (21.2)	21/92 (22.8)	61/294 (20.7)	0.671
medications				
Calcium-channel blocker	165/386 (42.7)	48/92 (52.2)	117/294 (39.8)	0.036
ACEI	212/386 (54.9)	56/92 (60.9)	156/294 (53.1)	0.189
ARB	172/386 (14.8)	40/92 (43.5)	132/294 (44.9)	0.943
β-blocker	114/386 (44.5)	27/92 (29.3)	87/294 (29.6)	0.964
Aspirin	347/386 (89.9)	84/92 (91.3)	263/294 (89.5)	0.608
Insulin	27/386 (7.0)	12/92 (13.0)	15/294 (5.1)	0.009
Statin	224/386 (58.0)	47/92 (51.1)	162/294 (55.1)	0.501

Data are presented as mean mean ± SD or the number and its percentage(%) percentage = the number of each individual category divided by n CVs cardiovascular, BMI body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker

[a]Indicates the comparison of mean or percentage between CVs group and non-CVs group

Table 3
The laboratory characteristics of the enrolled patients at baseline

Variables	Whole	CVs	non-CVs	P^a
	(n = 386)	(n = 92)	(n = 294)	
Triglycerides (mg/dL)	123.6 ± 71.3	134.5 ± 88.3	120.3 ± 63.2	0.097
LDL-C (mg/dL)	107.9 ± 30.5	116.7 ± 29.9	105.1 ± 29.8	0.001
sdLDL-C (mg/dL)	31.0 ± 12.1	36.2 ± 15.2	29.4 ± 16.8	0.001
HDL-C (mg/dL)	46.8 ± 15.1	44.2 ± 12.9	47.6 ± 15.1	0.052
Non-HDL-C (mg/dL)	129.3 ± 34.1	138.3 ± 35.5	126.5 ± 33.4	0.004
sdLDL-C/LDL-C	0.29 ± 0.11	0.31 ± 0.13	0.28 ± 0.16	0.102
RLP-C(mg/dL)	5.0 ± 3.1	5.6 ± 3.5	4.8 ± 2.7	0.022
Glucose (mg/dL)	114.9 ± 34.5	122.6 ± 46.4	112.5 ± 29.5	0.014
HbA1c (%)	6.38 ± 1.2	6.8 ± 1.3	6.25 ± 1.09	0.001
ApoA-I (mg/dL)	125.0 ± 25.3	119.3 ± 23.6	126.8 ± 27.1	0.018
ApoB (mg/dL)	86.1 ± 21.3	92.1 ± 21.6	84.2 ± 22.1	0.003
eGFR(mL/min/1.73 m^2)	69.9 ± 19.2	68.8 ± 14.1	70.3 ± 15.6	0.411
hsCRP(mg/dL)	0.54 ± 1.1	0.53 ± 1.3	0.55 ± 0.98	0.875
Lp (a) (mg/dL)	22.9 ± 24.1	25.1 ± 25.2	22.3 ± 24.1	0.401

Data are presented as mean mean ± SD. LDL-C, low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;RLP-C, remnant lipoprotein cholesterol;HbA1c, hemoglobin A1c; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; BNP, brain natriuretic peptide; eGFR, estimated glomerular fifiltration rate;hsCRP, high-sensitivity C-reactive protein;Lp (a), lipoprotein (a)

[a]Indicates the comparison of mean or percentage between CVs group and non-CVs group

In this study, first-time CVs were observed in 92 patients. (Fig. 1a) displayed a obvious increase of CVs risk for the median levels of sdLDL-C. This phenomenon had analogous results in patients who received statins at baseline(Fig. 1b). Cox regression analysis showed that increase in sdLDL-C and HbA1c revealed a higher risk for CVs. However, the elevated RLP-C level was not (Table 4).To determine whether sdLDL-C was an independent risk factor, we performed cox multivariate regression analysis.The models were built after adjustment age, gender and CVs risk factors. Model 1 including Glucose, HbA1c, LDL-C, Non-HDL-C,sdLDL-C, ApoA-I and ApoB and Model 2 only including sdLDL-C and HbA1c showed that just sdLDL-C and HbA1c remained significantly associated with the risk of CVs These results suggest that elevated Glucose and dyslipidemia might contribute to CVs.

Table 4
Predictors for cardiovascular events according to Cox,s proportional hazard analysis

variable	Univariate model Multivariate model		
	HR 95%CI	Model 1	Model 2
HR 95%CI	HR 95%CI		
Age	1.065 (1.136–1.624)**	1.034(1.015–1.583)*	1.089(1.025–1.590)**
Men	0.801 (0.456–1.564)	0.771 (0.469–1.693)	0.774 (0.501–1.763)
LDL-C (per 10 mg/dL)	1.103 (1.093–1.347)**	1.135 (0.857–1.432)	-
sdLDL-C (per 10 mg/dL)	1.285 (1.145–19.033)**	1.276 (1.201–16.664)**	1.281 (1.225–16.032)**
Non-HDL-C (per 10 mg/dL)	1.089 (1.038–1.945)**	1.131 (0.955–1.836)	-
RLP-C	1.165 (0.873–2.055)	-	-
Glucose	1.107 (1.066–1.208)*	0.996 (0.905–1.202)	-
HbA1c	1.305 (1.13–2.312)***	1.321 (1.142–2.406)**	1.225 (1.152–2.412)**
ApoA-I (per 10 mg/dL)	0.889(0.762–0.941)**	0.892 (0.798–1.042)	-
ApoB (per 10 mg/dL)	1.125 (1.095–2.055)**	0.796 (0.718–1.944)	-

*P < 0.05,**p < 0.01,***p < 0.001.LDL-C, low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;RLP-C, remnant lipoprotein cholesterol;HbA1c, hemoglobin A1c; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; BNP, brain natriuretic peptide

Spearman's correlation analysis between sdLDL-C and various parameters are shown in the Table 5. These result suggest that the level of sdLDL-C exhibited significant positive correlations with triglyceride and RLP-C than LDL-C. These result suggest that sdLDL-C might the major factor among LDL-C contribute to CVs.

Table 5
Spearman’s correlation of LDL-C and sdLDL-C to patient characteristics

Variables	LDL-C		sdLDL-C	
	r	P	r	P
age	-0.194	0.009	-0.164	0.025
Triglycerides	0.171	0.018	0.323	0.001
HDL-C	-0.029	0.702	-0.363	0.001
Non-HDL-C	0.563	0.001	0.588	0.001
RLP-C	0.406	0.011	0.521	0.001
HbA1c	0.024	0.802	0.061	0.431
ApoA-I	-0.035	0.704	-0.301	0.001
ApoB	0.622	0.001	0.623	0.001
Lp (a)	0.252	0.008	0.027	0.831
LDL-C, low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;RLP-C, remnant lipoprotein cholesterol;HbA1c, hemoglobin A1c; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B;Lp (a), lipoprotein (a)				
(a) (b)				

We performed the ROC analysis in order to test the discriminatory power of sdLDL-C for the cardiovascular events(Fig. 2). The result indicate that the AUC of the sdLDL-C has a strong discriminating power against CVs, and its optimal cut-off value is 36.2 mg/dL(AUC = 0.736, P = 0.003) than HbA1C and RLP-C.

Discussion

Diabetes mellitusis patients are often accompanied by dyslipidemia, which is the major contollable risk factor associated with cardiovascular disease(CVD) events. Dyslipidemia has been confirmed as one of the principal processes underlying CVD, while sdLDL-C is considered as an emerging risk factor for CVD. Indeed, about 70% of elder type 2 DM patients die from CVD [14–16].

To the best of our knowledge, few study have investigated on the influence of sdLDL-C levels on the onset of CVs in Chinese elderly type2 DM patients.

Furthermore, previous studies concerning the elevated levels of RLP-C and sdLDL-C have been associated with CVs[17–19]. In the present study, Spearman's correlation analysis between sdLDL-C and various parameters are shown in the Table 5. These result suggest that the level of sdLDL-C exhibited significant positive correlations with triglyceride and RLP-C than LDL-C. These result suggest that sdLDL-C might the

major factor among LDL-C contribute to CVs. We performed the ROC analysis in order to test the discriminatory power of sdLDL-C for the cardiovascular events(Fig. 2). The result indicate that the AUC of the sdLDL-C has a strong discriminating power against CVs, and its optimal cut-off value is 36.2 mg/dL(AUC = 0.736, P = 0.003) than HbA1C and RLP-C.

Moreover,kaplan-Meier event-free survival curve displayed a obvious increase of CVs risk for the median levels of sdLDL-C(Fig. 1a). This phenomenon had analogous results in patients who received statins at baseline(Fig. 1b). Cox regression analysis showed that increase in sdLDL-C and HbA1c revealed a higher risk for CVs. However, the elevated RLP-C level was not (Table 4).To determine whether sdLDL-C was an independent risk factor, we performed cox multivariate regression analysis.The models were built after adjustment age, gender and CVs risk factors. Model 1 including Glucose, HbA1c, LDL-C, Non-HDL-C,sdLDL-C, ApoA-I and ApoB and Model 2 only including sdLDL-C and HbA1c showed that just sdLDL-C and HbA1c remained significantly associated with the risk of CVs These results suggest that elevated Glucose and dyslipidemia might contribute to CVs.

Indeed, sdLDL-C levels has the ability to predict CVD better than total LDL-C[18].In addition, the Québec Cardiovascular Study has shown that sdLDL-C is interrelated with an raised risk of CAD in men.[6, 7] On the other hand, remnant lipoproteins are rich in TG and the main components include VLDL in the fasting state [20].Obviously, the current study not only confirmed the sdLDL-C concentrations was an independent risk predictor for CVs, but also provided novel information concerning the role of RLP-C in predicting CVs in diabetic patients[21–24].

The limitations of this study mainly include: First, this cohort study is so small that it inevitably leads to a bias to fully observe the results and/or severity of CAD. Second, the effects of statin therapy needs further investigation. Finally, the comparison of the predictive ability of sdLDL-C for CVs to the patient subgroup needs further research. In future research, we will strive to solve these issues.

Conclusion

The consequences demonstrated that sdLDL-C was more effective than RLP-C in predicting the future CVs of elderly diabetic patients.

Abbreviations

DM
diabetes mellitus;
CVs
cardiovascular events;
CVD
cardiovascular diseases;
sdLDL-C

small dense low-density lipoprotein cholesterol;
RLP-C
remnant lipoprotein cholesterol;
LDL-C
low-density lipoprotein cholesterol;
HDL-C
high-density lipoprotein cholesterol;
HbAlc
hemoglobin A1c;21–24
Apo
apolipoprotein;
Lp (a)
lipoprotein (a);
ROC curves
receiver operating characteristic curves

Declarations

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Ethics approval and consent to participate

This study was approved by the Committee on Human Research of Suzhou Ninth People's Hospital. All patients signed a dedicate informed consent.

Availability of data and materials

Unfortunately, the initial data cannot be shared as it contains confidential information.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

Authors' contributions

XL and LFF planned the study and wrote the manuscript. LJF, XY and YHL contributed to data collection and enrolled patients. CNE and ZXW performed the flow mediated dilatation test. XJH and SH supervised the study and reviewed/edited the manuscript.

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Figures

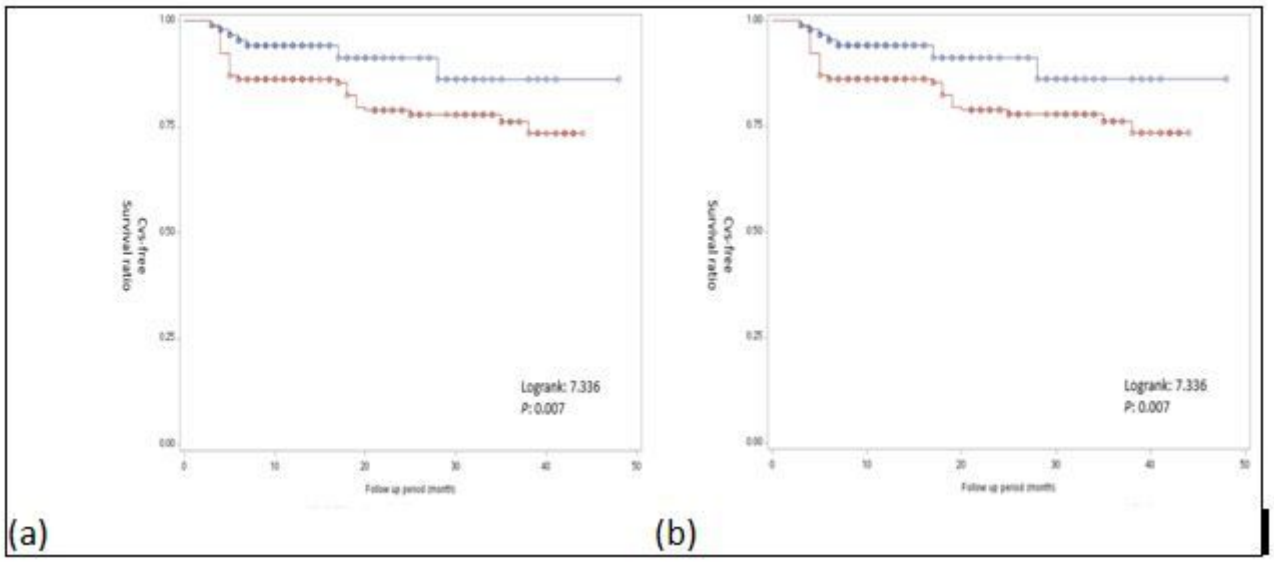

Figure 1

The Kaplan–Meier eventfree survival of patients stratifified by the median small dense low-density lipoprotein cholesterol (sdLDL-C) concentration (26 mg/dL). (a) All patients, (b) patients treated with statins The Kaplan–Meier eventfree survival of patients stratifified by the median small dense low-density lipoprotein cholesterol (sdLDL-C) concentration (26 mg/dL). (a) All patients, (b) patients treated with statins

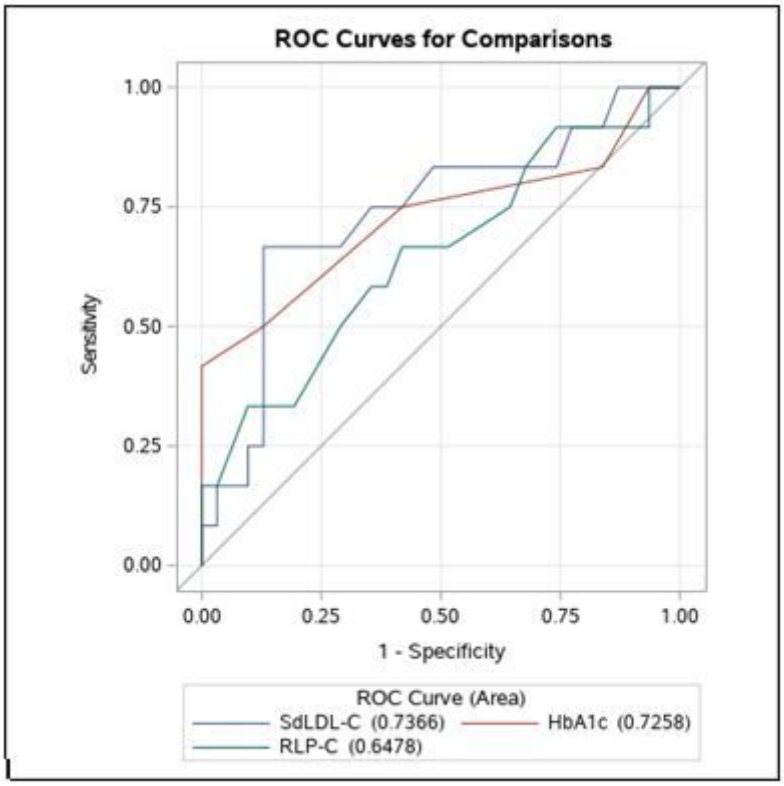

Figure 2

Receiver operating characteristic curves showed discriminatory power of SdLDL-C, HbA1C and RLP-C on cardiovascular events Receiver operating characteristic curves showed discriminatory power of sdLDL-C, HbA1C and RLP-C on CVs