



Correlation between small and dense low-density lipoprotein cholesterol and cardiovascular events in Beijing community population

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Abstract

The relationship between small dense low-density lipoprotein cholesterol (sdLDL-C) and different cardiovascular events has been observed in several large community studies, and the results have been controversial. However, there is currently no cross-sectional or longitudinal follow-up study on sdLDL-C in the Chinese hypertension population. We analyzed the association of plasma sdLDL-C levels with major adverse cardiovascular events in 1325 subjects from a longitudinal follow-up community-based population in Beijing, China. During the follow-up period, a total of 191 subjects had MACEs. Cox regression analysis showed that sdLDL-C is a major risk factor for MACEs independent of sex, age, BMI, hypertension, diabetes, smoking, SBP, DBP, FBG, eGFR in the general community population (1.013 (1.001–1.025, $P < .05$)), but the correlation disappeared after adjusting for TC and HDL-C in Model 3. Cox analysis showed that hypertension combined with high level of sdLDL-C was still the risk factor for MACEs (2.079 (1.039–4.148)). Our findings in the Chinese cohort support that sdLDL-C is a risk factor for major adverse cardiovascular events in hypertension subjects.

1 | BACKGROUND

The incidence of coronary heart disease (CHD) is increasing; CHD affects the health and quality of life of patients and is even life threatening. CHD is affected by a variety of risk factors, such as sex, age, family history, smoking history, hypertension, diabetes, and dyslipidemia.¹ Currently, it is recognized that dyslipidemia is the main target of CHD treatment; in particular, low-density lipoprotein cholesterol (LDL-C) plays an important role in the formation of atherosclerosis. The higher the level of LDL-C is, the greater the

possibility of atherosclerosis is. At present, LDL is taken as the primary target for intervention. However, many patients with normal LDL-C levels will still develop cardiovascular disease.^{2,3} Therefore, further studies on LDL subgroups have found that small dense low-density lipoprotein cholesterol (sdLDL-C) has a stronger atherogenic effect.^{4–6} However, the data on the relationship between sdLDL-C and CHD worldwide are still limited. Therefore, the purpose of this study is to explore the relationship between sdLDL-C and major adverse cardiovascular events (MACEs) and its role in predicting MACEs.

Abbreviations: DBP, diastolic blood pressures; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; SBP, systolic blood pressures; sdLDL-C, small dense low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Xiaona Wang and Liang Wang contributed equally to this study

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2 | METHODS

2.1 | Subjects

The research was conducted in the Pingguoyuan community in Beijing, China. A public recruitment announcement was first published on the community bulletin board with the consent of the community management committee. The subjects voluntarily participated in the study, which aimed to recruit community residents. Initially, all the subjects received physical examinations at the community medical center. From September 2007 to January 2009, a total of 1828 subjects aged ≥ 18 years were recruited. Bedridden patients, or patients suffering from mental disorders or severe systemic diseases (including myocardial infarction, coronary artery disease, cerebrovascular events, severe liver insufficiency, severe renal insufficiency, immune system diseases, endocrine and metabolic disorders [except for type 2 diabetes]) were excluded from this study. In the end, 1680 subjects were enrolled in this study, and the enrolled subjects were followed up for a second time between September 2017 and October 2018 via a face-to-face questionnaire by two cardiovascular physicians. An average follow-up time of 9.5 years (8.7-10.5 years) was completed by 1325 subjects, during which 191 (including 84 deaths) major adverse cardiovascular events (MACEs) occurred, and 355 subjects were lost to follow-up. We followed up their families over the phone to get the data.

The proportion of subjects lost to follow-up was approximately 21.1%, and the follow-up rate was 78.9%. The entire protocol of this study was approved by the ethics committee of the PLA General Hospital, and each subject signed an informed consent form.

2.2 | Clinical data collection

Medical history was collected by cardiovascular specialists with unified training. All the subjects were investigated to determine the following: cardiovascular history, hypertension history, diabetes history, family history, smoking history, drinking history, and medication history. A standardized questionnaire was used to investigate the subjects' name, sex, nationality, age, education level, occupation, marital status, family address, contact information, and other information. Blood pressure, height, weight, and waist and hip circumference were measured by trained doctors. When measuring the height and weight, shoes, socks, and caps were removed, and the height measurements were accurate to 1 cm, and the weight meter measurements were accurate to 0.1 kg. To measure the waist and hip circumference, any coat was removed and belts were loosened, and the tape measure was placed between the upper part of the hip bone and the lower part of the chest. The measurements were made while the subject was exhaling and their abdomen was relaxed, and the readings were accurate to 1 cm. Prior to measuring their blood pressure, the subjects rested in a sitting position for 5 minutes. Then, blood pressure was measured twice with an interval of 1-2 minutes, and the mean value was calculated.

Key messages

This study was granted an exemption from requiring ethics approval by Chinese PLA General Hospital Ethics Committee because this study was a retrospective observational study.

Blood was drawn from subjects with an empty stomach by specially trained nurses. Patients who had not been diagnosed with diabetes mellitus were examined by an oral glucose tolerance test (OGTT). Fasting blood glucose and postprandial blood glucose, serum TC, TG, HDL-C, LDL-C, and uric acid (UA) were measured with a Roche Diagnostics GmbH kit (Mannheim, Germany) using a Roche 6000 automatic biochemical analyzer (Roche 6000). Serum creatinine (CR) was determined by a Roche enzyme assay kit on the Hitachi 7600 automatic analyzer (Hitachi, Tokyo, Japan). The sdLDL "Seiken" kit (Denka Seiken Co. Ltd, Tokyo, Japan) was used to detect the plasma sdLDL levels on the Hitachi 7180 automatic biochemical analyzer (Hitachi, Japan) [6]. According to the standards of the WHO lipid reference laboratory, all the blood samples were analyzed in the same laboratory.

2.3 | Definition of variables

Smoking is defined as smoking at least 1 cigarette a day for at least 1 year. Exercise is defined as at least 1 hour of each exercise performed 3 to 5 times a week. Hypertension is defined as mean systolic blood pressure (SBP) ≥ 140 mmHg and/or mean diastolic blood pressure (DBP) ≥ 90 mmHg, and/or regular use of antihypertensive drugs. Diabetes is defined as intravenous fasting blood glucose level ≥ 7.1 mmol/L, and/or 2 hours after eating blood glucose level ≥ 11.1 mmol/L, or use of hypoglycemic drugs or insulin. BMI = weight(kg) / height²(m²); non-HDL-C = TC(mmol/L)-HDL-C(mmol/L); eGFR = $141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018$ [female] (or $\times 1.159$ [male]); Scr is blood creatinine (mg/dL); κ values are as follows: 0.7 for women and 0.9 for men; α is -0.329 for women and -0.411 for men.

The definition of MACE comprised nonfatal myocardial infarction, newly diagnosed CHD (identified by coronary artery imaging or receiving coronary revascularization), stroke (ischemic or hemorrhagic), and cardiovascular mortality.

2.4 | Statistical analyses

The categorical variables are expressed as numbers and percentages, and the continuous variables are expressed as the mean \pm standard deviation or median (quartile). t test was used for normally distributed data, while the nonparametric Mann-Whitney U test was used for non-normally distributed data, and the chi-square test was used for classified data. For the comparison between groups, analysis of variance was used

when the data were homogeneous, and Kruskal-Wallis test was used for the comparison between groups when the data were not normally distributed or the variance was not uniform. The quartiles of the sdLDL-C levels were labeled as Q1 (<27.6ng/ml), Q2 (27.6ng/ml ≤ Q2<37.7ng/ml), Q3 (37.7ng/ml ≤ Q3<53.37ng/ml), and Q4(≥53.37ng/ml). The subjects were divided into four groups according to whether or not they had hypertension: H4: high levels of sdLDL-C (Q3 and Q4) and hypertension; H3: high levels of sdLDL-C (Q3 and Q4) and nonhypertensive; H2: hypertensive and low levels of sdLDL-C(Q1 and Q2); H1: low levels of sdLDL-C(Q1 and Q2) and nonhypertensive. Spearman correlation analysis and multiple linear regression analysis were used to evaluate the correlation between the plasma sdLDL-C levels and biomarkers. The relationship between the sdLDL-C levels and MACEs was analyzed by Cox proportional hazard regression model. Kaplan-Meier survival curves indicating cumulative incidence of major adverse cardiovascular events (MACEs). SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) was used for statistical analysis; $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of the study population

This study initially enrolled 1680 subjects, with an average follow-up time of 9.5 years (8.7-10.5 years). For various reasons, 355 subjects were lost to follow-up. A successful follow-up rate of 78.9% (1325 subjects) was achieved. One hundred ninety-one cases of

MACEs occurred. In the end, the data of 1325 subjects were used in the analysis of this study, including the data of 642 males (48.5%) and 683 females (51.5%), and these subjects had an average age of 58.99 ± 11.28 years. A stratified analysis was made according to whether MACEs occurred and the baseline characteristics and laboratory data of the study population were statistically analyzed as shown in Table 1. There were differences in age, sex, smoking, diabetes, SBP, HDL-C, LDL-C, eGFR, and sdLDL-C between the patients with MACEs and those without MACEs ($P < .05$). The main characteristics of the population with MACEs were as follows: advanced age, male, smoking, diabetes, higher levels of SBP, LDL-C, and sdLDL-C, and lower levels of HDL-C and eGFR.

3.2 | Correlation analysis of baseline sdLDL-C and other indicators

In the univariate model, the baseline sdLDL-C level was positively correlated with age, BMI, SBP, DBP, TC, TG, LDL, FBG, and UA ($P < .05$). Multiple linear regression analysis showed that TG, LDL-C and circulating sdLDL-C levels were positively correlated ($P < .05$) (Table 2).

3.3 | Correlation analysis of sdLDL-C and major adverse cardiovascular events

During the follow-up period, a total of 191 subjects had MACEs. Cox regression analysis showed that sdLDL-C was the main risk factor for

TABLE 1 Baseline characteristics and laboratory test results of subjects

	All subjects (n = 1325)	Non-Mace (n = 1134)	Mace (n = 191)	
Age (岁)	58.99 ± 11.28	57.95 ± 11.15	65.90 ± 9.57	<0.001
Male(n (%))	642 (48.5)	508 (44.8)	102 (53.4)	<0.001
BMI (kg/m ²)	25.48 ± 3.44	25.44 ± 3.36	25.70 ± 3.95	0.353
Smoking(n (%))	359 (27.1)	286 (25.2)	62 (32.5)	<0.001
Diabetes(n (%))	232 (17.5)	177 (15.6)	44 (23.0)	<0.001
Hypertension(n (%))	680 (51.32%)	569 (50.18%)	111 (58.11%)	<0.001
SBP (mmHg)	119.63 ± 17.55	118.62 ± 17.33	126.46 ± 17.55	<0.001
DBP (mmHg)	76.55 ± 11.22	76.65 ± 11.27	75.85 ± 10.87	0.389
TC (mmol/L)	5.02 ± 0.93	5.01 ± 0.92	5.0769 ± 0.95	0.424
TG (mmol/L)	1.5 (1.1, 2.1)	1.5 (1.1, 2.11)	1.6 (1.2, 2.4)	0.228
HDL-C (mmol/L)	1.37 ± 0.37	1.39 ± 0.35	1.25 ± 0.43	<0.001
LDL-C (mmol/L)	2.92 ± 0.72	2.89 ± 0.71	3.09 ± 0.73	0.001
FBG (mmol/L)	5.38 ± 1.66	5.34 ± 1.62	5.63 ± 1.87	0.067
eGFR(ml/min/1.73 m ²)	94.17 ± 14.35	95.11 ± 13.91	87.10 ± 15.63	<0.001
UA (mmol/L)	293.87 ± 76.59	292.40 ± 75.55	304.08 ± 82.99	0.066
sdLDL-C(mg/dl)	40.25 ± 19.55	40.16 ± 19.45	42.89 ± 20.43	0.035

Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fast blood glucose; eGFR, estimated glomerular filtration rate;UA, uric acid; sdLDL-C, small dense low-density lipoprotein cholesterol

TABLE 2 Correlation analysis of baseline sdLDL-C and other indicators

	Baseline sdLDL-C(ng/ml)			
	r	P	β	P
age (岁)	0.118	<0.001	0.001	0.992
male (%)	-0.027	0.409	-4.346	0.095
BMI (kg/m ²)	0.113	0.001	0.048	0.637
smoking (%)	-0.017	0.613	-0.181	0.839
diabetes (%)	0.057	0.081	2.096	0.203
SBP (mmHg)	0.073	0.026	0.003	0.054
DBP (mmHg)	0.141	<0.001	0.007	0.874
TC (mmol/L)	0.533	<0.001	0.244	0.862
TG (mmol/L)	0.432	<0.001	5.821	<0.001
HDL-C (mmol/L)	-0.206	<0.001	-2.668	0.155
LDL-C (mmol/L)	0.535	<0.001	12.976	<0.001
FBG (mmol/L)	0.112	0.001	0.152	0.712
eGFR(ml/min/1.73m ²)	0.062	0.060	2.798	0.102
UA (mmol/L)	0.146	<0.001	0.012	0.151

Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fast blood glucose; eGFR, estimated glomerular filtration rate; UA, uric acid; sdLDL-C, small dense low-density lipoprotein cholesterol

MACEs (Table 3). The hazard ratio of the highest quartile (> 52.2 ng/ml) to the lowest quartile (\leq 25.18 ng/ml) of sdLDL-C was 1.008, and the 95% CI was 1.004-1.019 ($P < .05$). Model 1, which substituted sex and age into the equation, derived a hazard ratio between the highest quartile and the lowest quartile of sdLDL-C that was 1.014, and the 95% CI was 1.003-1.026 ($P < .05$). Model 2 substitutes traditional cardiovascular risk factors into the equation, and the results show that sdLDL-C is a major risk factor for MACEs independent of sex, age, BMI, hypertension, diabetes, smoking, SBP, DBP, FBG, eGFR in the general community population (1.013 (1.001–1.025, $P < .05$)), but the correlation disappeared after adjusting for TC and HDL-C in Model 3.

3.4 | Correlation analysis of sdLDL-C and major adverse cardiovascular events in hypertensive population

Cox analysis was performed based on whether the subjects were hypertensive (Table 4). The results showed that when other risk factors were not adjusted, hypertension and high levels of sdLDL-C were risk factors for MACEs in the elderly population (2.604 (1.369–4.953, $P < .01$)). Model 1, adjusted for sex and age, showed that sdLDL-C is a risk factor for MACEs (2.539 (1.333-4.835, $P < .01$)). Model 3, adjusted for sex, age, BMI, diabetes, smoking, SBP, DBP,

TABLE 3 Cox proportional hazards models analysis for associations between baseline sdLDL-C levels and MACE

	HR (95% CI)			
	Unjust	Model 1	Model 2	Model 3
Q1	1	1	1	1
Q2	1.005 (0.962-1.049)	1.009 (0.967-1.953)	1.007 (0.964-1.052)	1.007 (0.958-1.059)
Q3	1.008 (0.986-1.031)	1.018 (0.994-1.042)	1.018 (0.994-1.043)	1.022 (0.993-1.052)
Q4	1.008 (1.004-1.019)*	1.014 (1.003-1.026)*	1.013 (1.001-1.025)*	1.005 (0.989-1.021)

Note: Models are defined as follows: model 1 = adjusted for age and sex; model 2 = adjusted for model 1 + presence of BMI, hypertension, diabetes, smoking, SBP, DBP, FBG, eGFR; model 3 = adjusted for model 2 + TC, HDL-C

MACE, major adverse cardiovascular event.

* $P < .05$

TABLE 4 Cox proportional hazards models analysis for associations between baseline sdLDL-C levels and MACE in hypertension

	HR (95% CI)			
	Unjust	Model 1	Model 2	Model 3
H1	1	1	1	1
H2	1.117 (0.470-2.653)	1.288 (0.543-3.056)	1.251 (0.521-3.004)	1.361 (0.515-3.596)
H3	1.799 (0.911-3.553)	2.003 (1.007-3.985)*	1.898 (0.953-3.778)	2.079 (1.039-4.148)*
H4	2.604 (1.369-4.953)**	2.539 (1.333-4.835)**	2.734 (1.423-5.250)**	2.601 (1.122-6.027)*

Note: Models are defined as follows: model 1 = adjusted for age and sex; model 2 = adjusted for model 1 + presence of BMI, diabetes, smoking, SBP, DBP, FBG, eGFR; model 3 = adjusted for model 2 + TC, HDL-C

MACE, major adverse cardiovascular event.

** $P < .01$;

* $P < .05$

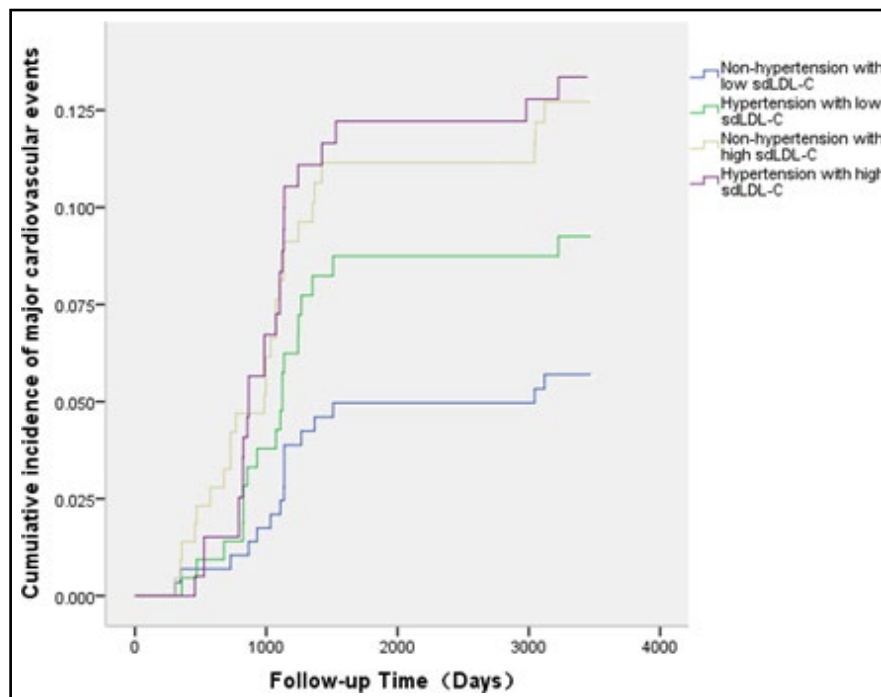


FIGURE 1 Risk for cardiovascular events by baseline sdLDL-C level. Kaplan-Meier survival curves indicating cumulative incidence of major adverse cardiovascular events across baseline sdLDL-C categories. Groups are indicated by colors; $P < .001$

TC, HDL-C, FBG, eGFR, showed that hypertension combined with high level of sdLDL-C was still the risk factor for MACEs (2.601 (1.122-6.027, $P < .01$)). The data suggest that sdLDL-C is an independent risk factor for major adverse cardiovascular events in people with hypertension (Figure 1).

4 | DISCUSSION

LDL-C plays an important role in the occurrence and outcome of atherosclerosis and cardiovascular diseases. Reasonable application of statins can play a positive role in preventing cardiovascular events,^{7,8} but there are also many clinical studies that have found that the risk of cardiovascular disease (CVD) is reduced to less than 30% after the application of statin lipid-lowering drugs. There may be other important risk factors to be considered.⁹⁻¹¹ The occurrence and development of atherosclerosis (AS) are not only related to the total amount of cholesterol, but may also be closely related to its heterogeneity.¹² According to the size and density, LDL can be divided into different subtypes, including large and light LDL (large buoyant low-density lipoprotein, lbLDL), intermediate-density LDL (intermediate-density lipoprotein, IDL), and small and dense LDL (small dense low-density lipoprotein, sdLDL). Many scholars believe that sdLDL has a stronger atherogenic effect than other LDL subtypes, as shown by different methodological studies, and sdLDL levels may have more predictive value for cardiovascular disease than LDL-C.

Whether sdLDL-C is a risk factor for CAD independent of other traditional lipid indicators is still controversial. A case-control

study¹³ enrolled 109 nonfatal myocardial infarction patients and 121 control patients and found that sdLDL-C was independently associated with the risk of myocardial infarction even after adjusting for risk factors such as age, sex, and weight. In a Japanese prospective study,¹⁴ 2034 patients without cardiovascular disease were followed for an average 11.7 years. The results showed that an increased level of sdLDL-C was associated with an increased risk of CVD. For every 10 mg/dL increase in sdLDL-C, the risk of CVD increased by 1.21 (95% CI: 1.12-1.31). Other studies found that sdLDL-C is a risk factor for CAD in people with diabetes,¹⁵ kidney disease,¹⁶ hypertension patients with poor controlled hypertension,¹⁷ and liver transplants.¹⁸ Other research has shown that sdLDL-C has a stronger relationship with cIMT progression than LDL-C.¹⁹ The ARIC study²⁰ included a total of 11,419 patients followed for 11 years and found that sdLDL-C is a risk factor for coronary heart disease, but after adjusting for LDL-C, apo B, and TC, the predictive value of sdLDL-C is weakened or disappears. Some scholars²¹ believe that in patients after myocardial infarction, sdLDL is associated with a reduced risk of all-cause death and noncardiovascular death. In this study, we found that after adjusting for confounding factors (sex, age, BMI, hypertension, diabetes, smoking, TC, HDL-C, FBG, eGFR), the circulating sdLDL-C level was not an independent risk factor for MACEs. To further explore the relationship between sdLDL-C and MACEs in patients with hypertension, it was observed that sdLDL-C was an independent risk factor for MACE (2.079 (1.039-4.148, $P < .05$)).

LDL-C is the main lipid risk factor for the development of AS, and sdLDL-C is considered to be the main LDL-C component that causes

AS. Very low-density lipoprotein (VLDL), which is rich in triglycerides secreted by the liver, is defatted by lipoprotein lipase, and the remaining triglycerides in VLDL are transferred to LDL particles through cholesterol ester transfer protein. sdLDL is the product of LDL particles defatted by liver lipase.^{22,23} The half-life of sdLDL is longer than that of lbLDL (3.10 days vs. 1.95 days),²⁴ and it is more prone to oxidation reactions. Therefore, sdLDL is more effective in causing atherosclerosis than LDL-C, especially in people with metabolic syndrome, obesity, and diabetes.²⁵⁻²⁹ sdLDL-C can participate in atherosclerosis through a variety of mechanisms. Because of its smaller particles, sdLDL-C is more likely to penetrate the endothelial barrier and migrate to the blood vessel wall and is more likely to be oxidized. The decrease in clearance rate increases the possibility of chemical modification in plasma,^{30,31} which is considered to facilitate progression of the atherosclerotic plaque. sdLDL-C can also participate in inflammation by activating immune cells and participate in the development of coronary heart disease.³² In addition, sdLDL-C is related to the presence of macrophages in plaques, which may be related to unstable arterial plaques.³³

Increasing numbers of studies have confirmed the value of sdLDL-C in CVD risk prediction. sdLDL-C has been listed as one of the newly discovered important cardiovascular risk factors in the adult treatment group of the National Cholesterol Education Program (NCEP).³⁴ Apparently, cholesterol- and LDL-lowering compounds are also effective in the reduction of sdLDL levels. In addition, improving the lipid profile, especially reducing triglyceride levels, adopting an appropriate regimen, and changing one's lifestyle, can decrease sdLDL levels.³⁵ In this study, we reported a direct relationship between plasma sdLDL levels and MACEs in a large sample community population. However, since this is a community-based study, it is limited by race, ethnicity, and geographical location.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

XW and PY designed the study; RC, XY, WX, LW, and YZ participated in acquisition of data; XW and PY researched and evaluated the literature; XW undertook the statistical analysis and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL

The study was approved by the ethics committee of the People's Liberation Army General Hospital, and each subject provided informed written consent.

DATA AVAILABILITY STATEMENT

Not applicable.

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