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Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss

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Abstract

The aim of this study was to investigate the association between the non-high-density lipoprotein cholesterol (non-HDL-C) with sudden sensorineural hearing loss (SSHL) and the predictive value of non-HDL-C for SSHL.

A total of 324 patients with SSHL and 972 well-matched controls were enrolled from 2009 to 2012 in Korea. The association of serum non-HDL-C with the risk of SSHL was evaluated using multivariate regression analysis, smooth curve fitting after adjusting for potential confounders. The discrimination ability of non-HDL-C in predicting SSHL was determined by calculating the area under the curve (AUC), and its clinical usefulness was evaluated by decision curve analysis. This was a secondary analysis of a case–control study.

There was a non-linear relationship between the serum non-HDL-C and the incidence of SSHL. After adjustment for potential confounders, the incidence of SSHL rose significantly with ascending quartiles of serum non-HDL-C (using Q1 as the reference group, the OR [95% CI] of Q2, Q3, and Q4 were 4.34 [2.43–7.74], 7.08 [3.99–12.56], and 20.88 [11.86–36.75], respectively [*P* for trend <.0001]). The discrimination ability of serum non-HDL-C in predicting SSHL was 0.747 (95% CI, 0.717–0.776), and the AUC was 0.733 (95% CI, 0.705–0.777) in the internal validation.

Elevated serum non-HDL-C was strongly associated with increased risk of SSHL, and it may play a role as a useful biomarker in predicting the risk of SSHL.

Abbreviations: AUC = area under the curve, BMI = body mass index, CHD = coronary heart disease, CI = confidence interval, CRF = chronic renal failure, CVD = cardiovascular disease, DCA = decision curve analysis, DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, SSHL = sudden sensorineural hearing loss, TC = total cholesterol, TG = triglycerides.

Keywords: lipid, non-high-density lipoprotein cholesterol, prediction, sudden sensorineural hearing loss

1. Introduction

As an audiologic emergency disease, sudden sensorineural hearing loss (SSHL) is characterized by a rapid decline in hearing.[1] According to clinical practice guideline, SSHL is defined as sudden hearing loss of more than 30 dB measured over at least three consecutive frequencies of pure tone audiometry and maintaining for at least 72 h.[2] The estimated prevalence of SSHL ranges from 5 to 30 cases per 100,000 people a year, and it has a higher prevalence in unilateral SSHL than in bilateral SSHL.[3,4] Notably, ~40% to 70% of the SSHL patients fail to recover within 2 weeks,[5] and 13% of those who exhibit spontaneous recovery will inevitably experience recurrent episode of SSHL.[6,7]

The underlying pathogenesis of SSHL, however, has not been fully elaborated. Reportedly, autoimmune diseases, blood vessel disorders, and viral infections may be related to developing SSHL.[3,8,9] Nevertheless, for the majority of patients with SSHL, the etiology is still unclear, which is namely idiopathic SSHL. In the last few decades, several studies have reported that there is an association between lipid profiles and risk of SSHL.[3,10,11] Generally, the cochlea is supplied by one to several terminal arteries with no collateral circulation. The current explanation for the "lipid hypothesis" is that elevated blood lipid increases blood viscosity and contributes to atherosclerosis of the vessels supplying to the cochlea, and thus may result in hearing impairment.[12] In contrast, as a multi-components lipid parameter, the non-high-density lipoprotein cholesterol (non-HDL-C) has showed great value in predicting the risk for

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In the previously published article [11], Lee et al. has clearly stated that the study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital. Verbal informed consent was obtained from all participants.

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cardiovascular disease (CVD).[13] Therefore, we made a hypothesis that the non-HDL-C associates with the risk of SSHL and has potential to predict SSHL.

In the present study, we investigated the specific association between the non-HDL-C with the risk of SSHL, and the predictive value of non-HDL-C for SSHL was also analyzed based on a case–control study.

2. Materials and methods

2.1. Study design and ethics statement

This was a secondary analysis of a large-scale case–control study.[11] A total of 324 patients with unilateral SSHL were consecutively collected at a University-affiliated hospital in Korea between 2009 and 2012, and 972 well-matched participants were collected from the Korea National Health and Nutrition Examination Survey (KNHANES) as controls (three controls per case) between 2009 and 2010. In the previously published article,[11] Lee et al. have clearly stated that the study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital. Verbal informed consent was obtained from all participants after being fully informed of the pertinent study information (purpose, procedures, potential benefits, and alternatives to participation).

The following details were collected: gender, age, weight, body mass index (BMI), coexisting diseases (hypertension, diabetes mellitus [DM], stroke, coronary heart disease [CHD], and chronic renal failure [CRF]). Blood lipid variables included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-DL-C (LDL-C), and non-HDL-C (calculated as subtracting HDL-C from TC). Blood lipid profiles were measured between 6 and 8 AM in all the participants after an overnight fast.[11] All the patients with SSHL in the present study were unilateral SSHL and fulfilled the audiometric criterion of SSHL.[11]

2.2. Statistical analyses

Descriptive statistics were used to summarize baseline characteristics and blood lipid profiles. Continuous data were presented as mean ± standard deviation, and categorical data were expressed as the number and the percentage. Unpaired *t* test or Kruskal–Wallis rank sum test, Pearson chi-squared test or the Fisher's exact test was performed between the SSHL group and the non-SSHL group, as appropriate. Multivariate regression analysis was used to evaluate the relationship between serum non-HDL-C and the risk of SSHL, and both the crude model and the adjusted models were presented. Multicollinearity test was performed for the selection of variables. Adjusted criteria were as the following[14]: adjust I: variables produced a change in the regression coefficient ≥10%, either after introduction them into the basic model or removing them from the completed model, or the regression coefficient of the co-variables yielded *P*-value < .1; adjust II: variables were included in criteria I and variables that were considered to need adjustment judged by clinical significance. The area under the curve (AUC) was calculated to determine the discrimination ability of non-HDL-C in predicting SSHL, and a nomogram was constructed to facilitate applications. Additionally, decision curve analysis (DCA) was used for evaluating the clinical usefulness of non-HDL-C in predicting SSHL. All analyses were performed using R software (version 3.5.1). $P < .05$ was considered statistically significant.

3. Results

In the present study, a total of 324 SSHL patients and 972 controls with normal hearing were recruited. No significant difference in participant demographic characteristics was observed between the SSHL group and the non-SSHL group (Table 1). However, the blood lipid profiles (TG, TC, HDL-C, and non-HDL-C) were significantly higher in the SSHL group than in the non-SSHL group (Table 2, $P < .05$). Moreover, DM, CRF, and BMI were found to be positively correlated with SSHL as assessed by univariate analysis (Table 2, $P < .05$).

During the process of screening variables that need to be adjusted, variables of weight, TC, and HDL-C were removed from multicollinearity test. Variables of DM, CRF, and BMI were selected based on the criterion of adjust I, while age and gender were also adjusted according to the criterion of adjust II. A non-linear relationship was observed between the non-HDL-C and the risk of SSHL in smooth curve fitting after adjusting for confounders based on adjust II (including DM, CRF, BMI, age, and gender) (Fig. 1). Both in the unadjusted model and in the adjusted models, the incidence of SSHL increased significantly with increasing concentration of serum non-HDL-C (Table 3). In multivariate regression analysis, using Q1 as the reference group, the OR (95% CI) of Q2, Q3, and Q4 of serum non-HDL-C were 4.34 (2.43–7.74), 7.08 (3.99–12.56), and 20.88 (11.86–36.75), respectively (P for trend <.0001) after adjusting for the potential confounders (Table 3, adjust II).

Table 1

Baseline characteristics and blood lipid profiles of the participants.

Variables	Participants with SSHL	
	Yes (n = 324)	No (n = 972)
Age (year)	49.6 ± 16.5	48.8 ± 14.7
Gender, n (%)		
Male	162 (50.0)	452 (46.5)
Female	162 (50.0)	520 (53.5)
BMI (kg/m^2)	23.9 ± 3.3	23.3 ± 3.2
Weight (kg)	63.8 ± 11.6	61.7 ± 11.1
Coexisting diseases		
Hypertension, n (%)		
No	253 (78.09)	797 (82.00)
Yes	71 (21.91)	175 (18.00)
DM, n (%)		
No	283 (87.35)	886 (91.15)
Yes	41 (12.65)	86 (8.85)
CHD, n (%)		
No	318 (98.15)	955 (98.25)
Yes	6 (1.85)	17 (1.75)
CRF, n (%)		
No	318 (98.15)	971 (99.90)
Yes	6 (1.85)	1 (0.10)
Stroke, n (%)		
No	316 (97.53)	959 (98.66)
Yes	8 (2.47)	13 (1.34)
Blood lipids		
TG (mg/dL)	122.8 ± 77.2	109.6 ± 65.3
TC (mg/dL)	192.8 ± 33.9	183.5 ± 34.9
HDL-C (mg/dL)	57.6 ± 15.3	54.3 ± 13.0
LDL-C (mg/dL)	110.7 ± 35.6	107.2 ± 31.2
Non-HDL-C (mg/dL)	160.5 ± 35.9	129.1 ± 33.1

BMI = body mass index, CHD = coronary heart disease, CRF = chronic renal failure, DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss, TC = total cholesterol, TG = triglycerides.

Table 2

Univariate analysis of possible influencing factors of the risk of SSHL.

Variables	Statistics	Developing SSHL	
		OR (95% CI)	*P*
Age (year)	49.0 + 15.2	1.00 (1.00, 1.01)	0.3803
Gender, n (%)			
Male	614 (47.4)	Ref.	
Female	682 (52.6)	0.87 (0.68, 1.12)	0.2750
BMI (kg/m^2)	23.5 + 3.2	1.06 (1.02, 1.10)	0.0036
Weight (kg)	62.2 + 11.3	1.02 (1.01, 1.03)	0.0043
Hypertension, n (%)			
No	1050 (81.0)	Ref.	
Yes	246 (19.0)	1.28 (0.94, 1.74)	0.1208
DM, n (%)			
No	1169 (90.2)	Ref.	
Yes	127 (9.8)	1.49 (1.01, 2.22)	0.0471
CHD, n (%)			
No	1273 (98.2)	Ref.	
Yes	23 (1.8)	1.06 (0.41, 2.71)	0.9033
CRF, n (%)			
No	1289 (99.5)	Ref.	
Yes	7 (0.5)	18.32 (2.20, 152.76)	0.0072
Stroke, n (%)			
No	1275 (98.4)	Ref.	
Yes	21 (1.6)	1.87 (0.77, 4.55)	0.1689
TG (mg/dL)	112.9 + 68.7	1.00 (1.00, 1.00)	0.0033
TC (mg/dL)	192.1 + 39.0	1.02 (1.02, 1.03)	<0.0001
HDL-C (mg/dL)	55.2 + 13.7	1.02 (1.01, 1.03)	0.0002
LDL-C (mg/dL)	108.1 + 32.4	1.00 (1.00, 1.01)	0.0955
Non-HDL-C (mg/dL)	137.0 + 36.5	1.03 (1.02, 1.03)	<0.0001

BMI = body mass index, CHD = coronary heart disease, CRF = chronic renal failure, DM = diabetes mellitus, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss, TC = total cholesterol, TG = triglycerides.

With regard to the discrimination ability of serum non-HDL-C in predicting SSHL, The AUC was 0.747 (95% CI, 0.717–0.776) (Fig. 2A). With a cut-off value of 155.5 mg/dL, serum non-HDL-C yielded an accuracy of 75.08%, a specificity of 82.20%, a sensitivity of 53.70%, a positive predictive value of 50.14%, and a negative predictive value of 84.19% in predicting SSHL (supplemental material: Table 1, http://links.lww.com/MD/D789). In the internal validation using the bootstrapping method (resampling = 500), the AUC achieved 0.733 (95% CI, 0.705–0.777) (Fig. 2B). To provide individuals with a quantitative tool to predict the probability of SSHL, a nomogram was constructed (Fig. 3). In addition, The DCA (Fig. 4) showed that when the threshold probability of an individual was <60%, application of this model to predict SSHL would add net benefit when compared with the strategy of either treat-all or treat-none.

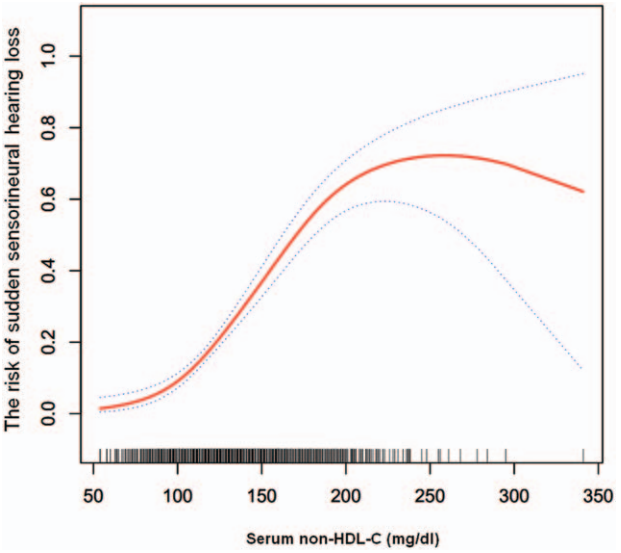

Figure 1. The smooth curve fitting shows a non-linear relationship between serum non-HDL-C concentrations and the risk of SSHL after adjusting the potential confounding factors (gender, age, DM, CRF, and BMI). Dotted lines represent the upper and lower 95% CI. BMI = body mass index, CI = confidence interval, CRF = chronic renal failure, DM = diabetes mellitus, HDL-C = high density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss.

4. Discussion

The present study showed that elevated serum non-HDL-C level is associated with increased risk of SSHL. Furthermore, our results revealed that serum non-HDL-C has the potential to be a useful biomarker in predicting the risk of SSHL.

Nowadays, due to the dilemmas in the field of prevention and treatment, SSHL remains a huge clinical and public health-challenge.[11] Despite several etiological risk factors have been proposed (e.g., autoimmune diseases, vascular diseases, and viral infection), most patients with SSHL could not be contributed to a clear etiology, and therefore they may experience ineffective treatment or recurrent episode of SSHL.[3,8,9] In the last few decades, based on the theory that abnormal blood supply of the cochlea may contribute to hearing impairment and blood viscosity could be affected by blood lipid concentration,[12] "lipid hypothesis" has been proposed by a number of studies.[3,10,11] Therefore, SSHL, at least to some extent, may represent the disorder metabolism of lipids. In a cohort study,

Table 3

Multivariate regression analysis of quartiles of serum non-HDL-C with the risk of SSHL.

Quartiles of serum non-HDL-C (mg/dL)	n	Developing SSHL OR (95% CI) *P*-value		
		Unadjusted	Adjust I*	Adjust II†
Q1 (≦111)	315	Reference	Reference	Reference
Q2 (112–127)	332	4.21 (2.37, 7.47) <0.0001	4.18 (2.35, 7.44) <0.0001	4.34 (2.43, 7.74) <0.0001
Q3 (128–158)	325	6.62 (3.78, 11.59) <0.0001	6.31 (3.59, 11.11) 0.0004	7.08 (3.99, 12.56) 0.0004
Q4 (159–341)	324	18.69 (10.80, 32.33) <0.0001	18.23 (10.48, 31.73) <0.0001	20.88 (11.86, 36.75) <0.0001
P for trend		<0.0001	<0.0001	<0.0001

BMI = body mass index, CRF = chronic renal failure, DM = diabetes mellitus, HDL-C = high density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss.
* Adjust I adjust for: DM, CRF, and BMI.
† Adjust II adjust for: gender, age, DM, CRF, and BMI.

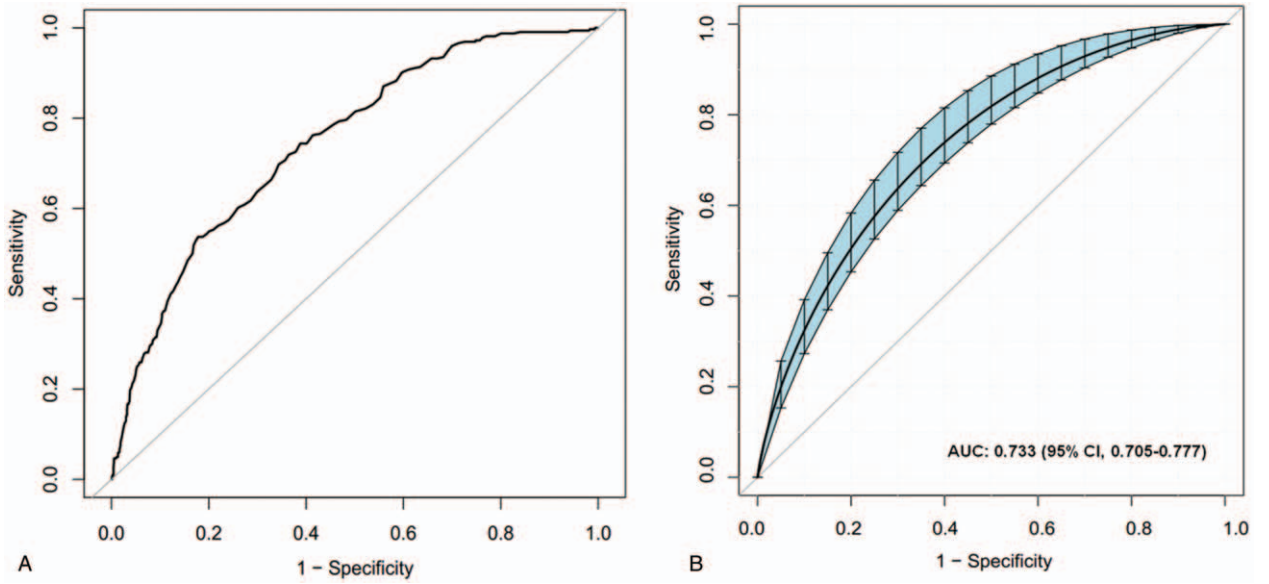

Figure 2. The discriminatory ability of serum non-HDL-C in predicting SSHL. The AUC was 0.747 (95% CI, 0.717–0.776) of serum non-HDL-C in predicting SSHL (A), and it was 0.733 (95% CI, 0.705–0.777) in the internal validation using the bootstrapping method (resampling = 500) (B). AUC = area under the curve, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss.

Ballesteros et al.[10] reported that lipid profile positively correlated with the development of SSHL. Similarly, in a case–control study, Aimoni et al.[3] pointed out that hypercholesterolemia was strongly associated with the risk of SSHL. Moreover, Lee et al.[11] demonstrated that TG and TC were associated with the prevalence of SSHL and the prognosis of SSHL.

Non-HDL-C is calculated by subtracting HDL-C from TC,[15] namely that it mainly contains TG, LDL-C, very-LDL-C, and intermediate-DL-C, and chylomicron remnants.[16,17] Recently, non-HDL-C has been recommended as an important target in patients with CVD in the revised National Cholesterol Education Program guidelines.[13] In addition, several prospective cohort studies have revealed that non-HDL-C is an independent risk factor for mortality in individuals free of CVD.[18] Moreover, with the advantage of maintaining relative stability regardless of whether it is tested on a non-fasting status or not, Non-HDL-C will be more convenient in application than LDL-C and TG.[19]

In the present study, we found that elevated serum non-HDL-C level was strongly associated with an increased incidence of SSHL. After adjusting for potential confounding risk factors (gender, age, DM, CRF, and BMI), the strength of this association did not change. It seems that when serum non-HDL-C level exceeds 250 mg/dL, the risk of SSHL declines (Fig. 1); however, no statistically significant differences were observed for this trend. Only 8 cases of serum non-HDL-C level was >250 mg/dL in this study population, which may affect the curve fitting in Figure 1. Furthermore, we analyzed the predictive role of serum non-HDL-C for SSHL. Although the discrimination ability of serum non-HDL-C in predicting SSHL was moderate (AUC: 0.747), non-HDL-C showed a good accuracy (75.08%) and specificity (82.20%). We also constructed a nomogram to quantify the risk of SSHL based on serum non-HDL-C concentration, which is easy to use and its clinical usefulness was supported by DCA. DCA is a novel method, which can offer insight into clinical consequences on the basis of threshold probability, and the net benefit could be derived from DCA.[20,21] Specifically, the DCA showed that if the threshold probability of an individual is <60%, using the nomogram based on serum non-HDL-C in the present study to predict SSHL will add more benefit than either the treat-all strategy or the treat-none strategy. Besides, serum non-HDL-C is widely available and inexpensive, suggesting that serum non-HDL-C may be suitable for initial screening high-risk individuals with SSHL in healthcare settings, such as primary healthcare and occupational health institutions.

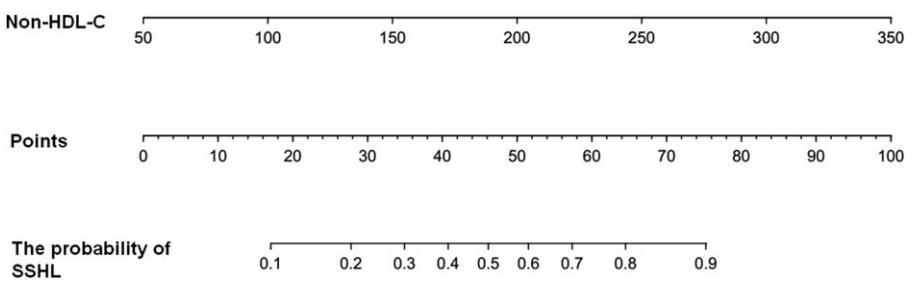

Figure 3. The nomogram based on the serum non-HDL-C for predicting SSHL. First, find point for serum non-HDL-C of an individual on the middle rule; then the corresponding predicted probability of developing SSHL could be found on the lowest rule. HDL-C = high density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss.

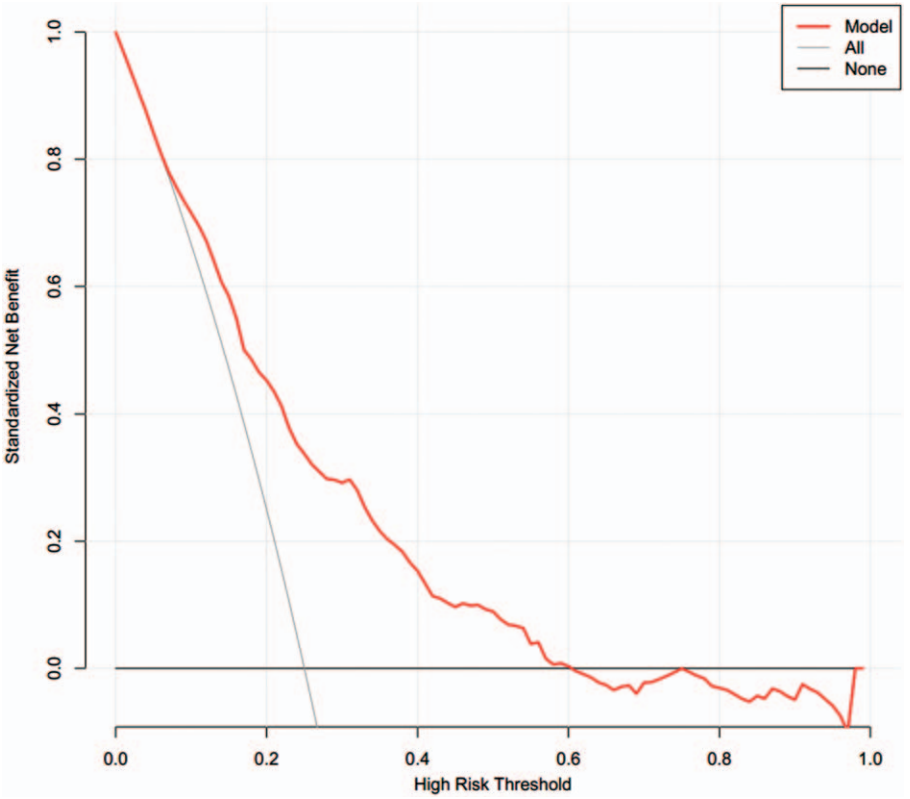

Figure 4. The DCA of the predictive value of serum non-HDL-C for SSHL. The red solid line represents the performance of serum non-HDL-C in predicting SSHL. It shows that when the high risk threshold of developing SSHL is <60%, application of serum non-HDL-C in predicting SSHL in the present study would add more net benefit than either the treat-all or the treat-none strategy. DCA = decision curve analysis, HDL-C = high density lipoprotein cholesterol, SSHL = sudden sensorineural hearing loss.

Nevertheless, some limitations of the present study are worth noting. First, this study was a single-center observational study and only the internal validation was performed; therefore, whether the results could be applied to other regions needs further independent validation. Secondly, although the participants recruited in the present study were matched,[11] several potential confounders may also need to be adjusted, such as audiological factors (hearing loss degree and configuration), brain trauma and noise exposure, as well as lipid-lowering drugs use and smoking status, which were not available from the original data.

5. Conclusions

Our results showed that serum non-HDL-C level positively correlated with increased incidence of SSHL. Moreover, serum non-HDL-C has the potential to be a useful predictor for SSHL, which may help improve early evaluation and management of the risk of SSHL.

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Conceptualization: Saibin Wang.
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Funding acquisition: Saibin Wang, Yibin Pan.
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Methodology: Saibin Wang.
Project administration: Saibin Wang.
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Supervision: Yibin Pan.
Writing – original draft: Saibin Wang.
Writing – review & editing: Saibin Wang.

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