Whether the combination of ApoB/ApoA1 ratio and non-HDL/HDL ratio can better predict cardiovascular risks and severity of coronary stenosis in Chinese patients with acute myocardial infarction

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Research Article

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Abstract

Background: Acute myocardial infarction (AMI) is an important cause of death globally. To investigate the value of combining apolipoprotein B/apolipoprotein A1 (APoB/APoA1) and non-high-density lipoprotein/high-density lipoprotein (non-HDL/HDL) ratio in AMI.

Methods: Patients admitted within 24 hours after the onset of AMI symptoms were included and divided into AMI group (*n*=364) and non-AMI group (*n*=152) according to coronary angiography. After an overnight fast, laboratory data were obtained and calculated. Gensini score was obtained to evaluate the coronary stenosis degree. Multivariate logistic regression, Spearman's rank correlation analysis and Receiver operating characteristics (ROC) curve analysis were used.

Results: Male ratios, patients with smoking and drinking history, ApoB/ApoA1 ratio and non-HDL/HDL ratio were higher in AMI group (*P*<0.001). ApoB/ApoA1 and non-HDL/HDL ratio were positively related with Gensini score (r=0.507, P<0.001 r=0.187, P<0.001). The association of ApoB/ApoA1 ratio with AMI was stronger than non-HDL/HDL ratio (OR=11.870, 95%CI: 5.735-24.565 vs. OR=2.168, 95%CI: 1.685-2.788). Patients in the top quartile of ApoB/ApoA1 distribution had higher risk of AMI (OR=8.929, 95%CI: 4.800-16.610) compared with those in the bottom, which was the same in non-HDL/HDL (OR=1.346, 95%CI: 1.126-1.610). Area under ROC curve of ApoB/ApoA1 ratio combined with non-HDL/ HDL ratio was the largest but no much higher than ApoB/ApoA1 ratio (0.838 vs 0.833), which was the same with sensitivity and specificity (71.2% and 85.1% vs. 68.1% and 83.5%).

Conclusions: ApoB/ApoA1 and non-HDL/HDL ratio were strongly associated with AMI. However, combination of these two have no much greater impact on AMI than that individual contribution of ApoB/ApoA1 ratio.

Introduction

Coronary heart disease (CHD) is the leading cause of death globally, which accounts for approximately one-third of all deaths in 2019 [1]. The costs burden, the morbidity and mortality rate have risen rapidly in the last decades especially in the developing countries because of CHD [2, 3]. In Asia, most countries are experiencing the serious challenges from CHD as increasing cholesterol levels mainly due to the improvement of living standards. While in China, CHD accounts for 22% of total cardiovascular deaths in urban areas and 13% in rural areas [4–6]. Moreover, the deaths of CHD ranked first worldwide in 2019 [1]. The conditional risk factors such as hypertension, smoking, hyperlipidemia, obesity and diabetes were important for prevention of AMI. Therefore, new and sturdy risk factors of CHD are still interest of studies.

The causal link between lipid abnormalities and CHD is well established. Both the AMORIS and INTERHEART study uncovered apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio as the strongest indicator in evaluation the risk of fatal myocardial infarction, for it might be the best marker of the balance of atherogenic and anti-atherogenic particles [7, 8]. Non-high-density lipoprotein (non-HDL) is a measure of both low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) that contained

triglyceride (TG)-rich atherogenic particles and recommended as second-line treatment goal [9, 10]. Previous studies showed that LDL/HDL ratio TC/HDL ratio had a positive association with an increased risk of CHD [11], and the level of non-HDL was associated with the risk of AMI events [12].

The joint effects of lipids on CHD have been examined in several studies [13, 14]. However, whether APoB/APoA1 ratio and non-HDL/HDL ratio have combined utility for predicting the risk and severity of AMI is unclear, especially in Chinese patients. Therefore, we retrospectively evaluate the predicting value of the combined measurements of APoB/APoA1 ratio and non-HDL/HDL ratio in suspected AMI patients with typical symptoms.

Methods

Study population

The study population comprised of 516 patients (including 386 men and 130 women, age range 31–92 years old) with typical clinical manifestations (chest pain or chest stuffiness) within 24 hours after the onset of symptoms who were admitted to the Department of Cardiology, Zhongnan Hospital, Wuhan University from 1 March 2013 to 31 October 2015. AMI was diagnosed based on the clinical, electrocardiographic, biochemical and coronary angiography criteria. Patients with severe valvular disease, myocarditis, cardiomyopathy, acute or chronic inflammatory diseases, renal insufficiency, hepatic dysfunction and malignancy were excluded from this study. Then the suspected patients were divided into AMI group (n = 364) and non-AMI group (n = 152).

Clinical variables

The clinical and demographical data were taken from cases records: vital signs, height, weight, age, gender, blood pressure, cardiovascular risk factors, smoking and drinking history, hypertension, diabetes mellitus, hypercholesterolemia, and medication use was obtained at baseline. body mass index(BMI)was calculated.

Blood lipid detection

The venous blood was drawn from the antecubital vein on the first morning after admission and then delivered to the department of Clinical Laboratory of Zhongnan Hospital for lipid detection and other biochemical criterion. ApoB/ApoA1 ratio and non-HDL /HDL ratio were calculated. We analyzed ApoB/ApoA1 ratio and non-HDL/HDL ratio in quartiles, respectively.

Gensini score assessment

Coronary angiography data were acquired from catheter room by 3 interventional cardiovascular physicians who did not know any information about the patients. The severity of coronary stenosis were calculated based on the classic Gensini Score system [15, 16].

Statistical Analysis

Continuous parametric variables are presented as mean ± standard deviation (mean ± SD). Discrete variables are presented as number and relative frequencies per category (*n*, %). Parametric variables were compared by Student t-test or Mann-Whitney test between groups. Proportions were compared by the chi-square test. Spearman's rank correlation was used for bivariate correlations. Multivariate logistic regression analysis was used to identify the predictive value of independent factors for the presence of AMI. Receiver operating characteristics (ROC) curves were used to quantify the overall prognostic accuracy of the Gensini score and lipids profile. The area under the receiver operating characteristics curve (AUC) was a summary measure over criteria and cut-point choices. All statistical analysis was carried out with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) for Windows. Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics of study population

516 patients were included in this study, Table 1 summarized the baseline characteristics of all patients. There were more male patients in AMI group than non-AMI group ($P < 0.001$). However, there were no significant differences in terms of age, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP) ($P > 0.05$). Patients in AMI group had higher percentage of smoking and drinking habits ($P < 0.001$), but no obvious differences in history of hypertension, hypercholesterolemia and diabetes mellitus ($P > 0.05$). The Gensini score in AMI group was much higher than non-AMI group ($P < 0.001$). In AMI group, level of LDL ($P = 0.010$), APoB/APoA1 ratio ($P < 0.001$) and non-HDL /HDL ratio ($P < 0.001$) were higher than non-AMI group with lower HDL ($P < 0.001$) and APoA1 ($P < 0.001$).

Table 1
Baseline characteristics of AMI group and non-AMI group

	AMI (n = 364)	non-AMI (n = 152)	P
Age(years)	61.95 ± 12.17	58.70 ± 11.82	0.254
Male [n (%)]	300 (82.42%)	86(56.58%)	0.000***
BMI (kg/m^2)	23.90 ± 1.91	24.44 ± 2.41	0.090
SBP (mmHg)	130.57 ± 23.69	133.03 ± 19.45	0.066
DBP (mmHg)	77.28 ± 15.41	80.11 ± 11.76	0.070
HR (beats/minute)	77 ± 4.2	74 ± 9.2	0.234
Temperature (°C)	36.3 ± 0.16	36.4 ± 0.28	0.155
SPO_2 (%)	97.7 ± 1.40	98.7 ± 1.41	0.000***
Smoking [n (%)]	220(60.4%)	39(25.66%)	0.000***
Drinking [n (%)]	147(40.4%)	30(19.73%)	0.000***
Hypertension [n (%)]	197(54.1%)	85(55.92%)	0.742
Hypercholesterolemia [n (%)]	192(52.7%)	77(50.66%)	0.710
Diabetes mellitus [n (%)]	82(22.5%)	25(16.45%)	0.208
Gensini score	56.53 ± 0.14	3.57 ± 0.02	0.000***
TC(mmol/L)	4.86 ± 0.95	4.83 ± 0.94	0.520
TG(mmol/L)	1.85 ± 1.25	1.52 ± 0.49	0.388
LDL(mmol/L)	3.00 ± 0.85	2.64 ± 0.63	0.010*
HDL(mmol/L)	1.03 ± 0.23	1.28 ± 0.30	0.000***
APoA1 (g/L)	1.13 ± 0.21	1.27 ± 0.24	0.000***
APoB (g/L)	0.89 ± 0.25	0.85 ± 0.22	0.133
APoB/ApoA1	0.81 ± 0.26	0.33 ± 0.10	0.000***
Non-HDL/HDL	3.90 ± 1.58	2.91 ± 0.64	0.000***

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; APoA1, apolipoprotein A1; APoB, apolipoprotein B; non-HDL/HDL, (total cholesterol minus high-density lipoprotein cholesterol)/high-density lipoprotein cholesterol.

Compared to non-AMI group:*P<0.05;***P<0.001.

Association of ApoB/ApoA1 ratio and non-HDL/HDL ratio with AMI

In multivariate logistic regression analysis, many blood lipid indices such as APoB/APoA1 ratio and non-HDL/HDL ratio were significantly associated with the risk of AMI after adjusting for covariates (including gender, age, BMI, hypertension, diabetes, smoking, SBP and DBP). APoB/APoA1 ratio (OR 11.870, 95%CI: 5.735–24.565) showed the most obvious relationship with AMI, followed by ApoB (OR: 4.266, 95%CI: 1.465–12.422) and non-HDL/HDL (OR 2.168, 95%CI: 1.685–2.788, Table S1).

In further quartiles analysis, patients in top quartile of ApoB/apoA1 had a higher percentage with AMI (80.49% VS 19.51%, $\chi^2 = 82.37$, $P < 0.001$). A similar trend also appeared in top quartile of non-HDL/HDL (85.53% VS 14.47%, $\chi^2 = 47.22$, $P < 0.001$, Fig. 1). After adjusting for covariates, patients in top quartile of ApoB/ApoA1 ratio had the strongest association with the risk of AMI compared to the value in the lowest quartile (OR: 8.929, 95%CI: 4.800-16.610). The same was true for the non-HDL/HDL ratio subgroup (OR: 1.346, 95% CI: 1.126–1.610) in top quartile (Table 2).

Table 2
Logistic regression analysis for association of the quartile groups of APoB/APoA1 and non-HDL/HDL with AMI

APoB/APoA1 Quartiles (min-max)	**OR (95%CI), P**	**non-HDL/HDL Quartiles (min-max)**	**OR (95%CI), P**
Q1 (< 0.51)	Ref	Q1 (< 0.2.86)	Ref
Q2 (0.51–0.73)	2.126(1.726–2.620), 0.000	Q2 (2.86–3.50)	1.003(0.596–1.691), 0.990
Q3 (0.73–0.91)	2.958(2.162–4.048), 0.000	Q3 (3.50–4.40)	1.183(0.911–1.536), 0.207
Q4 (≥ 0.91)	8.929(4.800-16.610), 0.000	Q4 (≥ 4.40)	1.346 (1.126–1.610), 0.001

APoA1, apolipoprotein A1; APoB, apolipoprotein B; non-HDL/HDL, (total cholesterol minus high-density lipoprotein cholesterol)/high-density lipoprotein cholesterol; CI, confidence interval; OR, odds ratio.

Combination of ApoB/ApoA1 ratio and non-HDL/HDL ratio in predicting AMI

For further investigation, all patients were divided into other four groups according to ApoB/ApoA1 ratio and non-HDL/HDL ratio as follows: Group 1: low ApoB/ApoA1 ratio and low non-HDL/HDL ratio; Group 2: low ApoB/ ApoA1 ratio and high non-HDL/HDL ratio; Group 3: high ApoB/ApoA1 ratio and low non-HDL/HDL ratio; Group 4: high ApoB/ApoA1 ratio and high non-HDL/HDL ratio. The incidence of AMI was higher in Group3 and Group4 than in Group1 (78.57% and 79.79% *VS* 65.99%, $P < 0.05$). When combining

high ApoB/ApoA1 ratio and high non-HDL/HDL ratio in group4, patients had the highest risk of AMI (79.79%, Fig. 1).

Correlations of ApoB/ApoA1 and non-HDL/HDL *with Gensini score*

In Spearman's rank correlation analysis as showed in Table S2, TC, LDL, ApoB ApoB/ApoA1 and non-HDL/HDL were significantly positive associations with higher score while HDL and ApoA1 showed significantly negative associations ($P < 0.05$). Among all these factors associated with coronary stenosis, the ApoB/ApoA1 ratio and non-HDL/HDL ratio demonstrated the first two ($r = 0.507$, $P < 0.001$;$r = 0.187$, $P < 0.001$ $P < 0.001$).

ROC curves in quantifying prognostic accuracy of Gensini score and lipids profile with AMI

The AUC of ROC curve was used to determine the predictive values of lipids profile. Combination of APoB/APoA1 ratio and non-HDL/HDL ratio manifested the largest ROC area than other lipids index (0.838, $P < 0.001$), which is not much greater than APoB/APoA1 ratio alone (0.833, $P < 0.001$, Fig. 2). The sensitivity and specificity of combination of APoB/APoA1 ratio and non-HDL/HDL ratio were superior but not significant to those of each as a predictor alone (71.2% VS 68.1% and 67%, 85.7% VS 83.5% and 71.4%).(Table S3).

Discussion

This study verified the different characteristics between AMI and non-AMI patients among with typical clinical manifestations. Patients with higher APoB/APoA1 ratio and non-HDL/HDL ratio, especially the former, had higher risk of AMI. They both had significantly positive associations with Gensini score, which indicated the severity of the coronary stenosis. When combining these two parameters, it did not show much greater impact when revealing cardiovascular risks on AMI than that expected from the individual contribution.

In the present study, the traditional risk factors such as male, smoking and drinking history were different between AMI and non-AMI group, which was verified by other studies [8]. CHD refers to the hardening, narrowing and rupture of coronary arteries caused by excessive accumulation of cholesterol substances in the artery walls. Its root reason is known as atherosclerosis, while atherogenic dyslipidemia plays a key role in this process. Atherogenic dyslipidemia consisted of abnormal aggregation of lipoproteins, including elevated levels of TC, ApoB and LDL particles, and decreased levels of HDL particles and ApoA1 [17, 18], which were founded in our study as well.

Interestingly, we found that oxygen saturation in AMI group was lower than non-AMI group (97.7 ± 1.40 *VS* 98.7 ± 1.41, $P < 0.001$) which may indicate the utility of oxygen therapy. However, it is controversial in previous studies and calls for further investigations [19, 20]. Lipids profile including APoB/APoA1 ratio and non-HDL/HDL ratio were significantly and independently associated with an increasing risk of AMI

and APoB/ APoA1 ratio was the most obvious related factors, which was in accordance with previous studies [21, 22].

We also found that the relative risk of AMI in top quartile subgroup compared with bottom subgroup was 8.929 for APoB/ APoA1 ratio and 1.346 for non-HDL/HDL ratio, which indicated that the higher values of these two ratios were better predictors of AMI, the results were similar to the UKPDS [23]. Furthermore, our study found that APoB/APoA1 ratio and non-HDL/HDL ratio had the first and second strongest associations with Gensini score, respectively, which indicated the severity of the coronary stenosis.

Our analysis also discovered high APoB/APoA1 ratio and high non-HDL/HDL ratio combination might enhance their ability to predict the incidence of AMI (n = 75, 79.79%). APoB/APoA1 ratio (AUC = 0.833) was more useful in predicting a greater risk of AMI than non-HDL/HDL ratio (AUC = 0.728), ApoB (AUC = 0.551) and other lipids profile. The differences between APoB, APoB/APoA1 ratio and non-HDL/HDL ratio in predicting the risk of AMI were probably associated with the essences of these lipids profile. ApoB was present in atherogenic lipoproteins including LDL, intermediate-density lipoprotein and very-low-density lipoprotein, its level indicated the number of atherogenic lipoprotein particles. ApoA1 was a major constituent of HDL, an anti-atherogenic apolipoprotein appeared to reverse the cholesterol transport [24, 25]. The ratio of APoB/APoA1 could represent the balance between the atherogenic and anti-atherogenic lipoproteins, and maybe a good predictor of AMI [7]. Non-HDL could be calculated by simply subtracting HDL from TC, which comprised all the cholesterol contained in LDL, VLDL and IDL. Thus, it was the cholesterol in the atherogenic particles and has been recommended as a target, especially in patients with high non-fasting TG levels by the National Cholesterol Education Program guidelines (NCEP ATP III 2002) [26]. It has often been used as a surrogate measure of circulating atherogenic lipoproteins, the increases in the non-HDL/HDL ratio was as strongly associated with the risk of AMI, which was shown in previous studies [27, 28]. In a study among obese Indian men, ApoB/ApoA1 ratio and non-HDL/HDL ratio were elevated significantly and were more prone to develop cardiovascular diseases [29].

It has been reported that the severity of coronary stenosis was a valuable predictor for future cardiovascular events. But the relationship between APoB/APoA1 ratio, non-HDL/HDL ratio with Gensini score were less investigated. It is reported that APoB/APoA1 ratio was significantly associated with the multi-branches and Gensini score in the CHD patients [30]. Similarly, high atherogenic lipid levels also enhanced the risk the fibrinogen induced coronary atherosclerosis [31]. In our study, the correlation between APoB, LDL, APoB/APoA1 ratio, non-HDL /HDL ratio and Gensini score was significantly obvious.

Studies have investigated the joint effects of different lipids, and the results vary [13, 32]. A ten-year follow-up showed no greater impact on CHD than their individual contributions when combing triglycerides (TGs), total cholesterol (TC) and high density lipoprotein cholesterol (HDLC) [14]. To our knowledge, no previous studies have explored the value of combination of ApoB/ApoA1 ratio and non-HDL/HDL ratio in predicting the risk of AMI. When combining the APoB/APoA1 ratio and non-HDL/HDL ratio, the predictive value (AUC = 0.838) was higher than any individual parameters but no much greater than APoB/APoA1 ratio alone (AUC = 0.833). Furthermore, its sensitivity (71.2%) and specificity (85.7%)

increased, but only a limited improvement relative to APoB/APoA1 ratio. The notion that the combination confers unexpected levels of risk is unsubstantiated by our data.

Limitations

Our study has some limitations. The patients were accepted in Zhongnan Hospital, thus the generalizability of our findings to other populations requires caution. The study was a retrospective analysis, the bias in data selection and in the analysis was unavoidable. The sample size of our study was limited in terms of the incidence of AMI, additional large longitudinal studies in diverse settings are needed to confirm our findings.

Conclusion

We verified the different characteristics between AMI and non-AMI patients with typical clinical manifestations and demonstrated that ApoB/ApoA1 ratio and non-HDL/HDL ratio were superior to other lipid profiles to predict AMI. But their combination did not show significant better contribution than applying ApoB/ApoA1 ratio alone. The study affirmed the ApoB/ApoA1 ratio as a relatively specific and sensitive property to predict cardiovascular risks, and provided guidance for clinical assessment of AMI.

Abbreviations

APoB/ APoA1	apolipoprotein B/apolipoprotein A1
non-HDL/HDL	non-high-density lipoprotein/high-density lipoprotein
AMI	acute myocardial infarction
CHD	Coronary heart disease
LDL, VLDL	low-density lipoprotein, very-low-density lipoprotein
TG	triglyceride
BMI	body mass index
ROC, AUC	receiver operating characteristics, operating characteristics curve
SBP, DBP	systolic blood pressure, diastolic blood pressure
TC, HDLC	total cholesterol, high density lipoprotein cholesterol

Declarations

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Availability of data and materials

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

Authors' contributions

Jianlei Cao and Xiaoqing Jin participated in study design, data arrangement, data analysis and article writing. These authors contribute equally as co-authors. Yi Jiang participated in data arrangement, article writing and revision. Haoyue Xu and Yaqi Liu participated in study design, data analysis, article revision. Wenlin cheng participated in data analysis and article revision. Chao Zhang participated in data arrangement, analysis and article revision. Xiaoyan Wu participated in study design and conduct, data arrange, and article revision. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Zhongnan Hospital (IRB number: 2021053). Consent of patients has been waived.

Conflicts of interest

There are no conflicts of interest.

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Figures

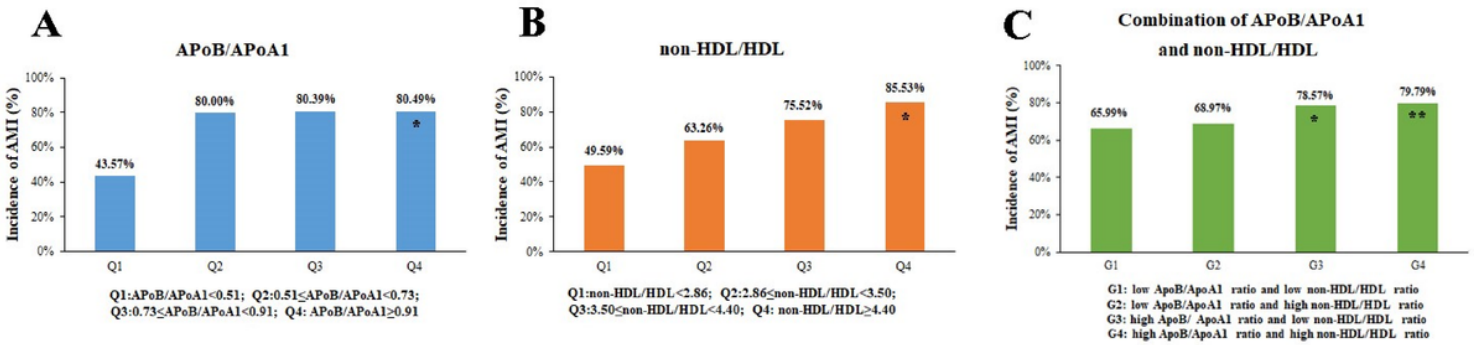

Figure 1

Pearson Chi-Square test for relationship of the quartile groups of APoB/APoA1 ratio, non-HDL/HDL ratio with AMI and the combination of these two ratio in predicting AMI.

(A). The relationship of the quartile groups of APoB/APoA1 ratio with AMI compared to non-AMI group;
(B). The relationship of the quartile groups of non-HDL/HDL ratio with AMI compared to non-AMI group;
(C). Combination of APoB/APoA1 and non-HDL/HDL in predicting AMI compared to group 1.

APoA1, apolipoprotein A1; APoB, apolipoprotein B; non-HDL/HDL, (total cholesterol minus high-density lipoprotein cholesterol)/high-density lipoprotein cholesterol. *P<0.05, **P<0.01.

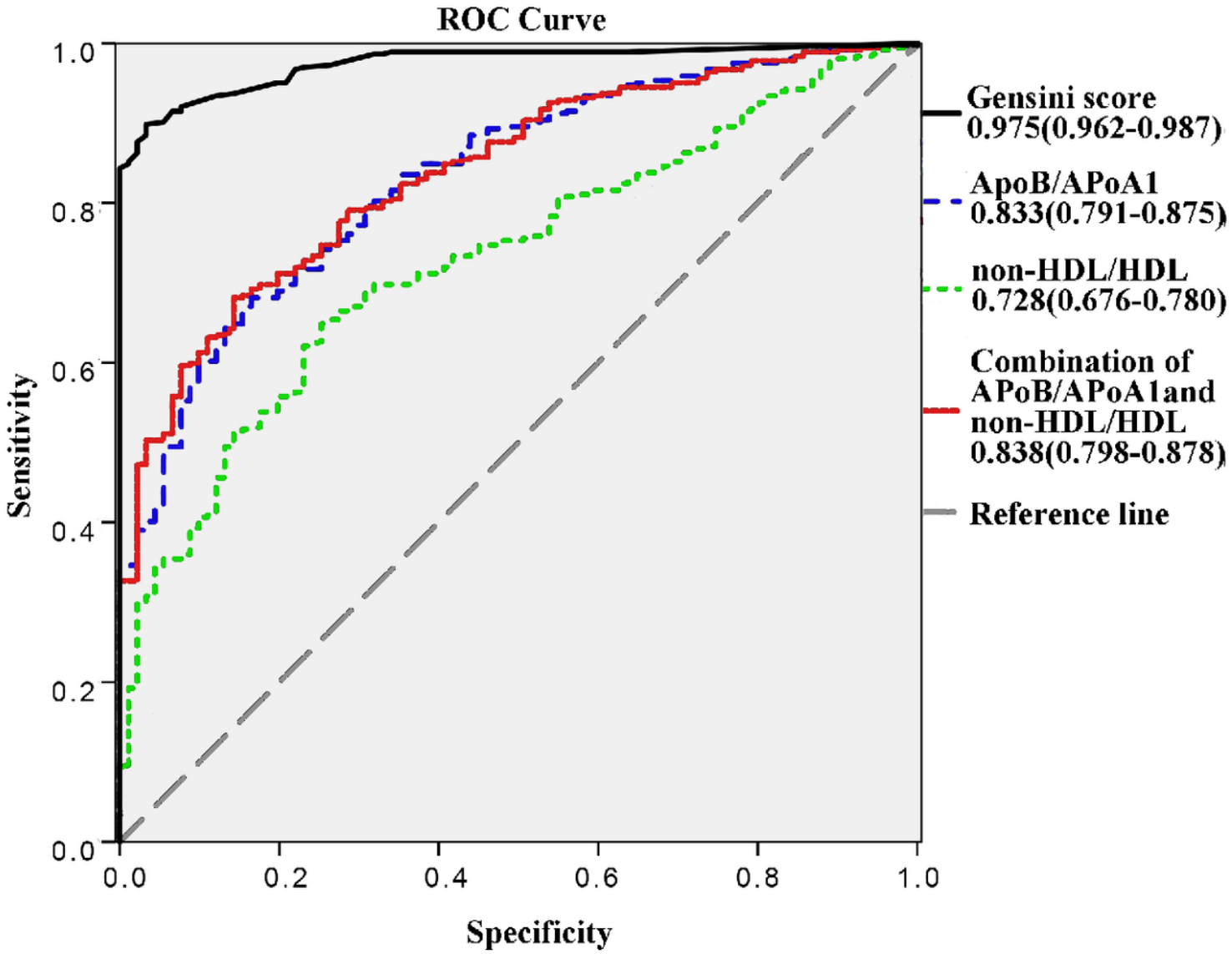

Figure 2

Area under the receiver operating characteristics curve for AMI.

APoA1, apolipoprotein A1; APoB, apolipoprotein B; non-HDL/HDL, (total cholesterol minus high-density lipoprotein cholesterol)/high-density lipoprotein cholesterol.

Supplementary Files

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- Additionalfiles.docx