Increased levels of serum Hcy and UA as well as the thickness of carotid intima-media correlates with the severity of coronary artery lesions

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Abstract

Background: To investigate the correlation between serum homocysteine (Hcy) and uric acid (UA) levels as well as the carotid intima-media thickness (IMT) and the severity of coronary artery lesions in elderly patients with coronary heart disease (CHD). Methods: A total of 156 elderly patients (≥60 years old) with CHD in the study group ; 54 patients with normal coronary artery were selected as the control group. The study group were further divided into low (≤20 points, n=72), middle (21-39 points, n=56) and high (≥40 points, n=28) score groups according to SYNTAX score. Serum Hcy and UA levels, IMT, Gensini and Sullivan scores were measured and analyzed by Pearson correlation. The risk factors for CHD and the correlation were analyzed by single factor analysis and logistic regression. Results: SYNTAX scores showed that the levels of serum Hcy, UA, and the IMT in middle [(20.03 ± 7.88) μmol/L, (326.34 ± 79.34) μmol/L, (1.26 ± 0.07) mm)] and high score [(28.98 ± 8.04) μmol/L, (456.67 ± 98.34) μmol/L, (1.33 ± 0.08) mm] groups were significantly higher compared to the low score group [(11.34 ± 6.83) μmol/L, (206.78 ± 77.45) μmol/L, (1.19 ± 0.05) mm)], while the high score group had the highest levels (all $P < 0.001$). Serum Hcy, UA levels and the IMT were positively correlated with SYNTAX and Sullivan scores (all $P < 0.001$). Additionally, male gender, smoking, history of hypertension, systolic pressure, pulse pressure, Hcy, UA, IMT, and BMI independently correlated with the severity of CHD (all $P < 0.05$). Conclusions: The serum levels of Hcy and UA and the IMT in patients with CHD were significantly elevates, and positively correlated with the severity of coronary artery lesions, which may serve as diagnostic indicators.

Background

Coronary heart disease (CHD) is a common disease of the human circulatory system. It is caused by many factors including the person's lifestyle, dietary habits, heredity, and so on. Coronary atherosclerotic heart disease, the most common type of CHD, is caused by coronary atherosclerotic stenosis, which leads to necrosis of the myocardium due to the insufficient blood supply. In addition, broadly speaking, the stenosis of the lumen caused by extensive inflammation and embolism also lead to CHD [1]. For a long time, the "gold standard" for evaluating the severity of coronary artery lesions has been the coronary angiography, but it is too traumatic to be suitable for elderly patients. However, most CHD patients are middle-aged and elderly. Therefore, it is important to identify and develop appropriate non-invasive tests and indicators for the clinical evaluation of CHD severity.

In recent years, it has been shown that the severity of CHD coronary artery lesions is related to the levels of serum homocysteine (Hcy) and uric acid (UA) and the carotid intima-media thickness (IMT) [2]. Hcy is a sulfur-containing amino acid produced during methionine metabolism and is significantly associated with the severity of coronary artery lesions. It plays an important role in the development of cardiovascular diseases such as atherosclerosis, aneurysms, and myocardial infarction. Hcy can promote hypertrophy and the proliferation of neutrophils, which can directly damage vascular endothelial cells and their function, thereby, increasing the risk of cardiovascular disease.

UA is one of the most important water-soluble endogenous antioxidants in the human body and acts as an important component of the cardiovascular structure [3]. UA can aggravate atherosclerosis by promoting renal tubule reabsorption of sodium ions. Some studies have shown that UA is an independent risk factor and an independent predictor of coronary atherosclerosis [4]. It is also suggested that UA has a protective effect due to its free radical scavenging effect which is 10 times better compared to other anti-oxidants [5]. It can chelate metal ions and inhibit the Fenton reaction. It can, hence, prevent cardiovascular damage by oxidative stress and thus play a protective role. Lowering UA level may, hence, improve the prognosis of CHD patients with acute myocardial infarction.

A previous study found that when coronary atherosclerosis occur, the IMT increases [6]. IMT can be easily and noninvasively measured to observe atherosclerosis in patients with CHD and is a good indicator of the severity of coronary artery lesions.

The most important characteristics of CHD are irreversibility, sudden death rate, and a slow disease progression. Therefore, early diagnosis and treatment of CHD is of great importance. What's more, the diagnosis of the severity of CHD mainly depends on the assessment of the severity of coronary artery lesions [7]. This diagnosis can help in appropriate treatment and prognosis of CHD. Hence, in the present study, we have explored the correlation between serum levels of Hcy and UA as well as the IMT, and the severity of coronary artery lesions in elderly patients with CHD.

Methods

General data

This study was approved by the Medical Ethics Committee of The Second Xiangya Hospital of Central South University. A total of 156 elderly patients who admitted in our hospital for CHD diagnosed by coronary angiography from September 2017 to August 2018 were enrolled as the study group for retrospective analysis. According to their SYNTAX scores, the study group was further sub-divided into three groups: low score (≤ 20 points, 72 cases), middle score (21-40 points, 56 cases), and high score (≥ 40 points, 28 cases) groups [8]. Another 54 healthy controls with normal coronary artery were enrolled as the control group and coronary angiography was performed at the same time. All patients and their families agreed to participate in the study and signed the informed consent document.

Inclusion criteria for study group: All patients: (1) met the diagnostic criteria of CHD according to the *Guidelines for Coronary Heart Disease*, and were diagnosed by coronary angiography [9]; (2) were aged from 61 to 88 years; (3) had no history of an operation, hormone use, use of immunosuppressive agents and antibiotics in the past six months; (4) had no history of gout and hyperuricemia.

Exclusion criteria: The following patients were excluded: (1) those with serious diseases of liver, kidney, brain, lung, and other basic organs; (2) those with acute and chronic infections; (3) those with malignant tumors, tuberculosis, and aneurysms; (4) those with diseases of blood, endocrine, and immune systems; and (5) those with lactation and pregnancy.

Sample collection

First of all, the imaging physicians with more than 5 years of working experience performed coronary angiography on the control group, and proved that there was no coronary artery disease. Secondly, after all the subjects (including the study group and the control group) were admitted to the hospital, 5 mL of fasting venous blood was collected from all study participants by examiner with more than 5 years of working experience and after 30 min of standing at room temperature was centrifuged at a speed of 3,000 rpm for 10 minutes. The serum was separated and used to determine the Hcy and UA levels in the blood. The serum Hcy level was measured using circulating enzyme method with Hcy detector (Shenzhen Ausa Pharma Co., Ltd.) according to the kit instructions (Shanghai Jimian Industrial Co., Ltd.). UA enzyme colorimetry was used to measure serum UA level by automatic biochemical analyzer according to kit instructions (Shanghai Xinfan Biotechnology Co., Ltd). Ultrasound doctors with more than 5 years working experience used VIVIVID7 ultrasound diagnostic device (Shenzhen Kaili Biomedical Science and Technology Co., Ltd.) to examine the neck vessels in the subjects in the supine position with the probe frequency ranging from 7.5 Hz to 12.0 Hz.

Observation parameters

Main parameters: (1) The levels of Hcy, UA and IMT: The levels of Hcy, UA and IMT were compared between the study group and control group as well as among the low, middle, and high score group. IMT was measured as the mean of thickness between the anterior and posterior walls of the carotid arteries, including bilateral carotid bifurcation, bilateral internal carotid artery, and the bilateral of the common carotid artery. A measurement of 0.9 mm $\leq$ IMT < 1.3 mm was considered as thickening while IMT $\geq$ 1.3 mm was considered as atheromatous plaque formation. (2) SYNTAX score: Pearson linear correlation was used to analyze the correlation between serum Hcy, UA level, IMT and SYNTAX score. All study group patients underwent coronary angiography by Judkins method in the catheter room of our hospital. According to the segmentation evaluation standard for the coronary artery image score of the American Heart Association [9]. Syntax integral is calculated by computer program. The algorithm includes 12 problems, the first three problems are the dominant type of coronary artery, the number of lesions and the number of vascular segments in lesions. The maximum number of lesions was 12. Each lesion was labeled with 1, 2, 3 and so on. Each lesion may involve one or more segments, and the integral of each lesion will be calculated by the involved segments. The last nine problems are the adverse characteristics of lesions. The integral of each lesion is obtained according to the adverse characteristics, and the sum of the integral of each lesion is the SYNTAX integral. The higher the score was, the greater the degree of coronary artery stenosis was.

Secondary parameters: (1) Sullivan score: Pearson linear correlation analysis was used to analyze the correlation between serum Hcy, UA level, IMT and Sullivan score. Sullivan score method was used to

calculate the proportion of atherosclerotic plaque in the coronary artery. The higher the score, the higher the proportion of atherosclerotic plaque in the coronary artery. (2) Univariate analysis: The general data of study group and control group were included in the single factor analysis, including gender, body mass index (BMI), history of smoking, alcohol consumption, hypertension, diabetes and cardiovascular diseases, systolic, diastolic and pulse pressure, Hcy, UA, and IMT. (3) Logistic regression analysis: Logistic regression analysis was used to analyze the correlation between multiple factors and severity of coronary artery lesions, with the integral of coronary stenosis degree as the dependent variable, Hcy, UA, IMT thickening as the independent variables.

Statistical methods

All data in this study were analyzed by SPSS21.0 statistical software. The level of each observation index was expressed as the mean ± standard deviation (± sd) and analyzed using F-test. All count data were expressed as percentages (n, %) and analyzed using a χ^2 test. Pearson linear correlation analysis was used to analyze the correlation between serum Hcy, UA level as well as IMT and Gensini score, Sullivan score. The general data of study group and control group were included in the single factor analysis. Logistic regression analysis was used to analyze the correlation of multiple factors and severity of coronary artery lesions. The integral of coronary stenosis was taken as the dependent variable while Hcy, UA, and IMT were taken as independent variables. Differences were considered significant when $P < 0.05$.

Results

General data comparison among low, middle and high score groups

There was no significant difference in the general data among the three groups ($P > 0.05$). See Table 1 for details.

Comparison of Hcy and UA levels and IMT among low, middle and high score groups

The serum Hcy and UA levels and the IMT in the middle and high score groups were significantly higher compared to the low score group (all $P < 0.001$), while the same parameters in the high score group were significantly higher compared to the middle score group (all $P < 0.001$). See Table 2 and Figure 1 for details.

Correlation of serum Hcy, UA level and IMT with SYNTAX score

Pearson correlation analysis showed that serum Hcy and UA levels and IMT were positively correlated with SYNTAX score in the study groups (r = 0.476, 0.517, 0.528; P < 0.001), respectively. See Table 3 and Figure 2 for details.

Correlation of serum Hcy and UA levels and IMT with Sullivan integral

Pearson correlation analysis showed that serum Hcy and UA levels and IMT were positively correlated with Sullivan integral in the study groups (r = 0.587, 0.563, 0.617; P < 0.001), respectively. See Table 4 and Figure 3 for details.

Univariable analysis of general data in the experimental and control groups

Univariable analysis of the general data showed that male gender, BMI, history of smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, and IMT significantly correlated with CHD in the study groups (all P < 0.05). See Table 5 for details.

Logistic regression analysis of the correlation between multivariate factors and CHD

Based on assignment table (Table 6), logistic regression analysis showed that male gender, smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, IMT, and BMI independently correlated with the severity of CHD in the study groups (all P < 0.05). See Table 7 for details.

Discussion

There are many risk factors for developing CHD in the elderly among which age is the most significant, followed by carotid plaque formation. In addition, B-complex vitamins, gender, obesity, smoking, and alcohol can affect the severity of coronary artery disease by influencing the level of serum Hcy and UA [10]. In recent years, with the increasing incidence and mortality of CHD in the elderly, the improvement of therapeutic efficacy has been the heat spot. Under the circumstances of slow progression and high risk of late stage, the key to the effective management of CHD is timely and effective diagnosis. Studies have shown that the main method to assess the severity of CHD in patients is to evaluate the severity of coronary artery lesions, and hence, it is important to find suitable non-invasive, low-cost evaluation markers [11].

The observations in our study showed that the serum Hcy level in the CHD group was significantly higher than in the control group, indicating that the serum Hcy level was an independent risk factor for CHD. The study also showed that the level of serum Hcy in high and middle score groups was significantly higher than in the low score group and that in the high score group was even higher compared to the middle

score group. This indicated that the level of serum Hcy was positively correlated with Gensini score i.e. the severity of coronary lesions. The higher the level of serum Hcy, the more serious the coronary lesions. Hcy is produced in the liver and other organs by the methionine metabolic cycle. There are two ways, methionine and cysteine. Normally, Hcy has a lower serum concentration of about 8 μmol/L [12]. Hcy induces coronary artery disease by damaging proteins through oxidative stress, resulting in the decrease or inactivation of enzymes and enzyme receptors, along with the decrease in nitric oxide synthesis, and subsequently impairs endothelial function, ultimately hindering vascular expansion. Besides, Hcy is an important factor in promoting thrombosis. Under its increased expression, the blood is in an hypercoagulable state, which causes a large number of platelets to adhere and aggregate together. At the same time, Hcy induces lumen stenosis by stimulating the proliferation of vascular smooth muscle cells, and also results in an imbalance in the lipid, carbohydrate and protein metabolism, leading to the formation of lipid deposition plaques [13, 14]. Various studies have found that there is a significant correlation between high serum Hcy level and CHD [15]. Wang et al. also found the significant correlation between serum Hcy level and severity of coronary artery disease [16]. These previous results are consistent with the observations in this study [17, 18].

This study showed that the serum UA levels in the study group was significantly higher compared to the control group. Also, the serum UA level in high and middle score groups was significantly higher compared to the low score group, while high score group had the highest serum UA level. This indicated that serum UA is an independent risk factor for CHD and was positively correlated with the severity of coronary artery disease. UA is a water-soluble antioxidant distributed in the human cardiovascular system which is normally stable in the serum. It is produced by purine metabolism by the oxidation of hypoxanthine to xanthine under the action of enzymes and finally to UA. Under normal circumstances, its serum level is stable [19]. Some studies have pointed out that serum UA levels in the elderly diagnosed with CHD show significant changes, suggesting that it has a certain correlation with coronary artery disease [20]. In elderly coronary artery disease, UA level increases as a result of increasing production but slow metabolism. Studies have shown that elevated serum UA level can lead to sympathetic excitation and renal hemodynamic changes. To be specific, UA promotes the re-absorption of sodium through the proximal convoluted tubules of the glomeruli and accelerates the production of endothelin in blood, thus inducing CHD and also aggravating the severity of coronary artery disease, which was consistent with this research[21, 22].

In this study, IMT in the study group was significantly higher compared to the control group. IMT in middle and high score groups was significantly higher compared to the low score group whereas IMT in the high score group was significantly higher compared to the middle score group, indicating that IMT is significantly correlated with the severity of coronary artery disease. IMT is an important visual index for evaluating the severity of coronary artery disease. A study has shown that IMT correlates with the severity of coronary artery disease and greater the IMT, more serious is the CHD [23]. One of the pathological basis for developing CHD in the elderly is endothelial damage, which leads to lipid deposition under the intima of the vessel, promotes inflammation and plaque formation, and eventually thickens smooth

muscle and hardens the vessel wall, leading to increased IMT [24]. These results were consistent with those of the above studies [25].

Pearson correlation analysis showed that serum Hcy, UA level and IMT positively correlated with SYNTAX and Sullivan score, respectively. Logistic regression analysis showed that male gender, smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, IMT, and BMI were independently associated with the severity of CHD. The innovation of this study lies in the use of serum detection indicators in the diagnosis of CHD, which is non-invasive, easy to operate and low-cost. It is expected to be widely used in clinical practice, and its application prospect has a promising future. The greatest disadvantage of this study is the small sample size.

Conclusions

In conclusion, the levels of serum Hcy and UA and IMT in patients with CHD were significantly elevated, and the increase positively correlated with the severity of coronary artery lesions. They can be used as diagnostic indices for evaluating the severity of CHD in clinical settings.

Abbreviations

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness; CHD, coronary heart disease; BMI, body mass index

Declarations

Ethical approval and consent to participate

This study was approved by the Medical Ethics Committee of The Second Xiangya Hospital of Central South University. All patients and their families agreed to participate in the study and signed the informed consent document.

Consent for publication

Not applicable.

Availability of data and materials

The analysed data sets generated during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CMT contributed to the study concepts, study design, definition of intellectual content, literature research and data acquisition in addition to preparing and editing the manuscript. JML contributes to the manuscript review and guaranteed the integrity of the entire study. FX contributed to data and statistic analysis. CMT carried out the clinical studies. FX and YZZ did experimental studies. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work.

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Tables

Table 1 General data comparison (± sd, *n* (%))

Group	Low score group (n = 28)	Middle score group (n = 28)	High score group (n = 28)	F	P
Gender (male/female)	55/17	42/14	22/6	0.243	0.912
Average age (year)	71.91 ± 13.82	71.21 ± 14.12	73.32 ± 14.11	0.831	0.312
BMI (kg/m^2)	24.43 ± 2.34	24.35 ± 2.31	24.65 ± 2.37	0.217	0.918
Type of CHD (n, %)					
Stable type	30 (41.67)	23 (41.07)	11 (39.29)	0.047	0.977
Unstable type	19 (26.39)	15 (26.79)	8 (28.57)	0.05	0.976
Acute cardiac infarction	23 (31.94)	18 (32.14)	9 (32.14)	0.001	1.000
Co-morbidities (n, %)					
Hypertension	40 (55.56)	31 (55.36)	16 (57.14)	0.267	0.987
Diabetes	29 (40.28)	24 (42.86)	11 (39.29)	0.128	0.937
Hyperlipidaemia	43 (59.72)	34 (60.71)	17 (60.71)	0.016	0.992
Heart failure	40 (55.56)	33 (58.93)	16 (57.14)	0.011	0.912

BMI, body mass index; CHD, coronary heart disease.

Table 2 Comparison of Hcy and UA levels and IMT (± sd)

Group	Low score group (n = 28)	Middle score group (n = 28)	High score group (n = 28)
Hcy (μmol/L)	11.34 ± 6.83	20.03 ± 7.88$^{***, ###}$	28.98 ± 8.04***
UA (μmol/L)	206.78 ± 77.45	326.34 ± 79.34$^{***, ###}$	456.67 ± 98.34***
IMT (mm)	1.19 ± 0.05	1.26 ± 0.07$^{***, ###}$	1.33 ± 0.08***

***P < 0.001, compared with low score group; $^{###}$P < 0.001, compared with high score group.

Table 3 Correlation of serum Hcy, UA level and IMT with SYNTAX score

Group	Correlation coefficient	Statistic	P
Hcy	0.476	10.069	0.000
UA	0.517	10.091	0.000
IMT	0.528	10.031	0.000

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 4 Correlation of serum Hcy and UA levels and IMT with Sullivan score

Group	Correlation coefficient	Statistic	P
Hcy	0.587	10.031	0.000
UA	0.563	10.043	0.000
IMT	0.617	10.034	0.000

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 5 Univariable analysis of general data

Group	Control group (n = 54)	Study group (n = 150)	P	χ^2
Male (n, %)	23 (42.59)	119 (76.28)	0.000	24.254
BMI (kg/m^2)	30.21 ± 4.13	24.32 ± 2.12	0.000	10.033
Smoking (n, %)	33 (61.11)	60 (38.46)	0.004	8.340
Drinking (n, %)	10 (18.52)	21 (13.46)	0.367	0.815
Hypertension history (n, %)	10 (18.52)	105 (67.31)	0.000	38.545
Diabetes history (n, %)	8 (14.81)	16 (10.26)	0.364	0.823
CVD history (n, %)	12 (22.22)	35 (22.44)	0.974	0.001
Systolic pressure (mmHg)	122.21 ± 8.32	135.32 ± 11.34	0.000	9.033
Diastolic pressure (mmHg)	76.34 ± 5.43	75.34 ± 8.32	0.317	1.005
Pulse pressure (mmHg)	45.43 ± 10.32	60.12 ± 12.32	0.000	8.560
Hcy (μmol/L)	7.59 ± 0.46	21.03 ± 7.66	0.000	21.801
UA (μmol/L)	155.33 ± 47.79	363.35 ± 85.31	0.000	22.057
IMT (mm)	0.81 ± 0.05	1.28 ± 0.07	0.000	53.317

BMI, body mass index; CVD, cardiovascular disease; Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 6 Univariable analysis of general data

Index	Assignment	
	0	1
Gender	Female	Male
Body mass index (kg/m^2)	≥26	<26
Smoking	No	Yes
Hypertension history	No	Yes
Systolic pressure (mmHg)	≤128	>128
Pulse pressure (mmHg)	≤52	>52
Hcy (μmol/L)	≤11	>11
UA (μmol/L)	≤190	>190
IMT (mm)	≤1	>1

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 7 Logistic regression analysis of the correlation between multivariate factors and CHD

Index	OR	95% CI	P
Male	10.22	1.23-70.32	0.000
Body mass index	9.21	2.21-61.24	0.000
Smoking	10.23	2.21-31.22	0.000
Hypertension history	9.32	1.12-33.42	0.000
Systolic pressure	11.33	2.21-32.33	0.000
Pulse pressure	11.35	2,22-32.22	0.000
Hcy	10.88	1.38-71.43	0.000
UA	11.21	2.13-61.13	0.000
IMT	12.35	5.08-31.02	0.000

CHD, coronary heart disease; OR, odds ratio; CI,confidence interval; Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Figures

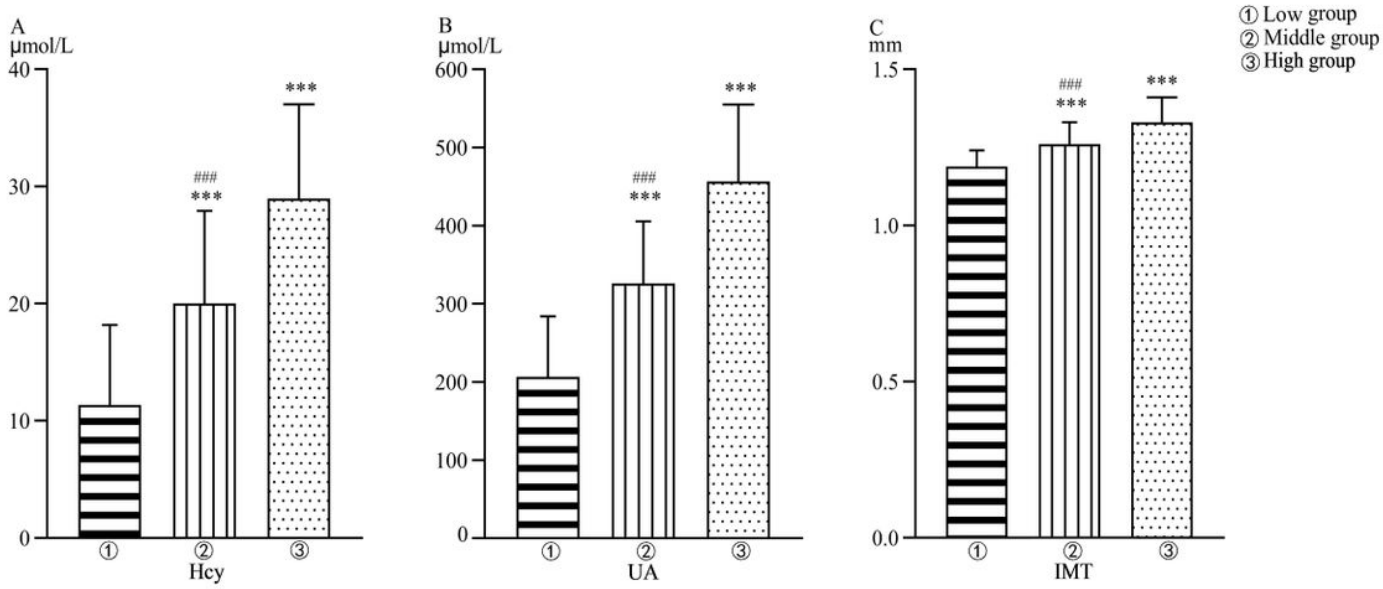

Figure 1

Comparison of Hcy(A), UA (B) and IMT (C) levels among low, middle and high groups. Compared with the low group, ***P < 0.001; compared with the high group, ###P < 0.001. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness

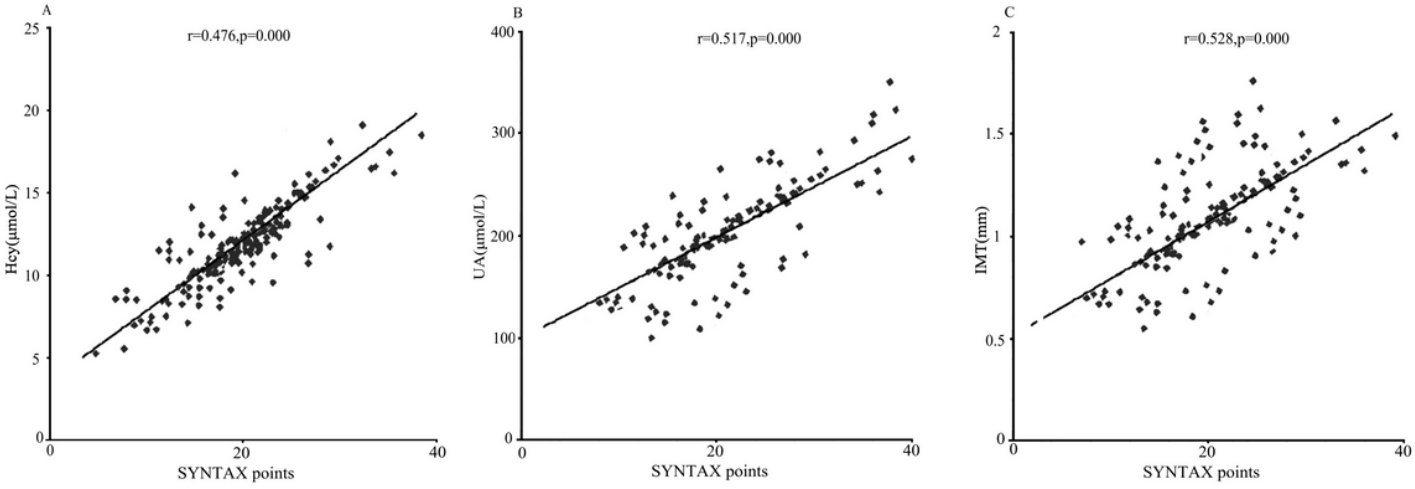

Figure 2

Correlation between serum Hcy (A), UA (B) levels and IMT (C) and SYNTAX score. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness

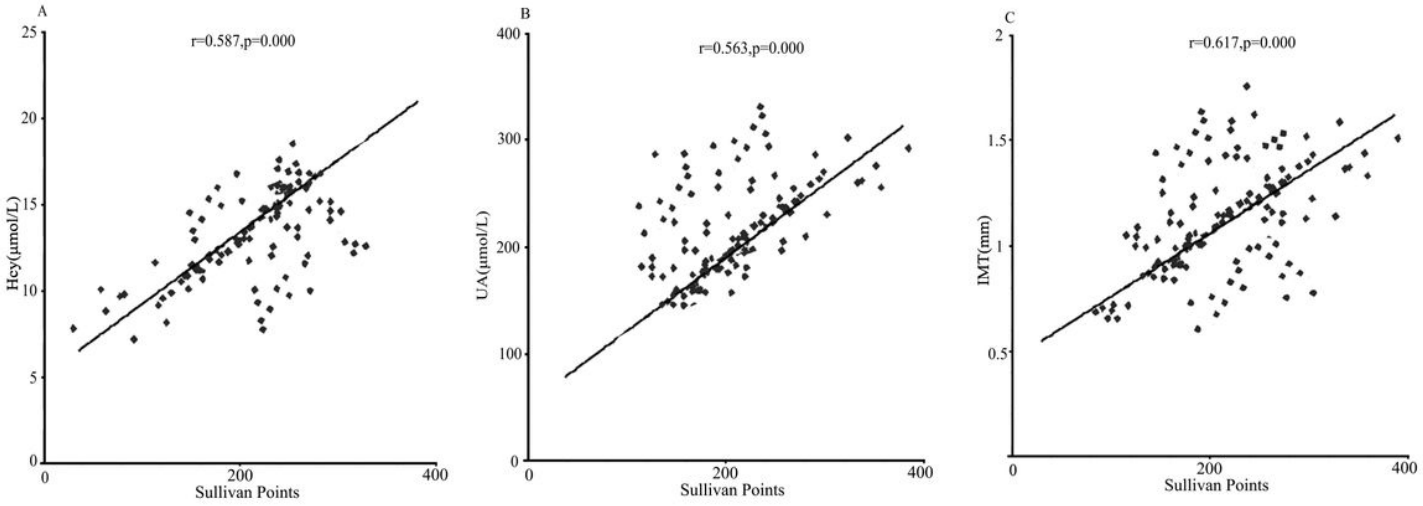

Figure 3

Correlation between serum Hcy (A), UA (B) levels and IMT (C) and Sullivan scores. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness