

Association of cystatin C levels with metabolic syndrome incidence: a nested case-control study with propensity score matching

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Abstract

Objective: Metabolic syndrome (MetS) involves multiple metabolic disorders and seriously affects human health. Identification of key biological factors associated with MetS incidence is therefore important. We explored the association between MetS and the biochemical profiles of Chinese adults in Shenyang City in a nested case-control study.

Methods: We included adult participants who underwent physical examination at our hospital for 2 consecutive years. Participants' biochemical profiles and other MetS components were tested and monitored continuously. Propensity score matching was used to adjust confounding factors between participants with and without MetS. We analyzed the association between incidence of MetS and the biochemical profiles of participants.

Results: Of 5702 participants who underwent physical examination between 1 January 2017 and 1 December 2018, 538 had confirmed newly developed MetS. After successfully matching 436 pairs of participants, mean cystatin C (Cys-C) level was significantly higher in the MetS group than in the non-MetS group. Logistic regression analysis indicated that age (years) and γ -glutamate transpeptidase, creatinine, uric acid, and Cys-C levels were significantly associated with MetS incidence; among these, the odds ratio of Cys-C was highest (3.03; 95% confidence interval, 1.02–9.00).

Conclusions: Cys-C levels were significantly associated with the incidence of MetS among Chinese adults.

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Keywords

Metabolic syndrome, biochemical profile, propensity score matching, nested case-control study, cystatin C, Chinese adults

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Introduction

Metabolic syndrome (MetS) refers to a pathological state in which a cluster of metabolic disorders, involving multiple organic compounds such as carbohydrates, proteins, and fats, coexist in one individuals. This complex metabolic disorder syndrome seriously affects human health. The current global incidence of MetS is 10% to 40% and is steadily increasing.¹ Approximately 110 million Chinese adults have MetS. The prevalence of MetS is higher in urban than in rural areas and higher in eastern regions than in central and western regions. The incidence of MetS increases with increasing age of the population.^{2,3} An analysis of the prevalence of MetS components showed that dyslipidemia and overweight/obesity were the most prevalent, followed by hypertension and abnormal blood glucose levels.³ MetS is an independent risk factor for cardiovascular disease (CVD), diabetes mellitus, and chronic kidney disease and is also closely related to all-cause mortality.⁴⁻⁷ As a major challenge to public health, MetS is still managed poorly owing to no convenient risk assessment standards or scientifically proven, personalized interventional schemes being available, which renders personalized disease management difficult.

Cystatin C (Cys-C), a low-molecular-weight cysteine protease inhibitor involved in vascular extracellular matrix remodeling,⁸ is an established biomarker of glomerular filtration⁹ and early renal dysfunction¹⁰ and is also a predictive

marker of CVD.^{11,12} In the present study, we sought to examine the association between MetS and the biochemical profiles of an adult Chinese cohort. MetS is an important risk factor of CVD, so it is speculated that Cys-C may be related to metabolic syndrome; however, there are few related studies at present; most existing research has been case-control studies with limited sample sizes. To circumvent this shortcoming, propensity score matching (PSM) have frequently been used to eliminate selection bias and uneven distribution of factors, serving as an ideal approach to evaluating interventional effects on MetS using non-randomized control data.¹³⁻¹⁶ In this nested case-control study, we used PSM to investigate the correlation between MetS and Cys-C, to provide a reference for further development of health management strategies in MetS.

Methods

Study participants and sampling

This was a nested case-control study. In 2017, a total of 10,856 individuals visited Shengjing Hospital for a regular physical examination (PE). In this study, we excluded patients with MetS found on physical examination. People without MetS were followed up for 1 year (N=7122). In 2018, individuals who developed MetS during the second physical examination were recorded. The PE was performed by a team of board-certified health care

providers. The inclusion criteria were individuals who received at least two PEs during the designated study period, with completion of all required data collection at each visit. Data collected during each of two PE visits included body weight, blood pressure, routine blood indexes, fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and liver function and kidney function indexes. A comprehensive disease history was also taken. We excluded those participants who had confirmed (1) metabolic disorders such as obesity, hyperlipidemia, hypertension, or diabetes, (2) disease complications such as angina pectoris, myocardial infarction, cerebral infarction, and gastric cancer, (3) a positive history of coronary bypass surgery, coronary stenting, or major gastrectomy, and (4) complications associated with inflammatory diseases including acute and chronic infectious diseases, transplant rejection, immune disorders, and use of immunosuppressive drugs. Figure 1 presents a flowchart describing the selection of the study population.

Ethical issues

Our study was approved by the medical ethics committee of Shengjing Hospital of China Medical University (2017PS42K). This was a retrospective study, with no direct intervention. All patient data were anonymous, and participants' information and privacy were fully protected. Therefore, the institutional review board waived the requirement for written informed consent from participants.

Research methods

Demographic and laboratory parameters. During each visit, general demographics parameters such as height, body weight, body mass index (BMI), and blood pressure were recorded. For routine blood testing, venous blood was withdrawn from

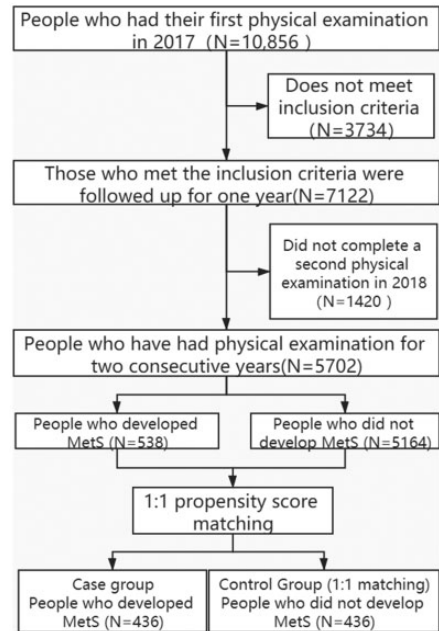


Figure 1. Flowchart of study population.

participants in the morning after a 12-hour overnight fast. Details of the routine blood indexes examined are listed in Table 1. All laboratory biochemical profiles assessed are listed in Table 2. All tests were performed using standard techniques with the corresponding standard reagents in the Clinical Laboratory Department in the same hospital. Specifically, blood glucose was measured using the glucose oxidase method, TG was measured enzymatically, and HDL-C was measured with a direct method.

Criteria for MetS diagnosis. Following the criteria established in 2004 by the Chinese Society of Diabetes of the Chinese Medical Association, MetS was confirmed if a participant presented at least three or all of the following four conditions: (1) overweight or obesity, with BMI ≥ 25.0 kg/m²; (2) hyperglycemia with FPG ≥ 6.1 mmol/L and/or 2-hour postprandial blood glucose

Table 1. Comparison of routine blood index profiles in participants with and without MetS (before and after PSM).

Characteristic	Before PSM			After PSM				
	With MetS Without MetS			With MetS Without MetS				
	(N=538)	(N=5164)	t	p	t	p		
White blood cell count, 10 ⁹ /L	6.78±1.68	6.42±1.6	-4.84	0	6.82±1.68	6.8±1.77	-0.22	0.83
Neutrophilic granulocytes, %	55.89±7.7	55.96±7.92	0.19	0.85	55.89±7.64	55.59±8.11	-0.56	0.58
Lymphocytes, %	35.58±7.49	35.48±7.56	-0.28	0.77	35.48±7.35	35.71±7.84	0.45	0.65
Monocytes, %	6.23±1.82	6.22±1.81	-0.16	0.87	6.26±1.85	6.35±1.86	0.66	0.51
Eosinophils, %	2.17±1.55	2.21±1.84	0.56	0.58	2.23±1.61	2.21±1.61	-0.25	0.80
Basophils, %	0.12±0.21	0.11±0.2	-0.11	0.91	0.11±0.22	0.13±0.21	0.71	0.48
Neutrophil count, 10 ⁷ /L	3.83±1.24	3.64±1.23	-3.4	0	3.86±1.26	3.83±1.34	-0.25	0.80
Lymphocyte count, 10 ⁷ /L	2.37±0.65	2.24±0.61	-4.74	0	2.38±0.65	2.38±0.69	-0.01	1.00
Monocyte count, 10 ⁷ /L	0.42±0.16	0.4±0.14	-3.67	0	0.42±0.16	0.43±0.16	0.20	0.84
Eosinophil count, 10 ⁷ /L	0.15±0.12	0.14±0.13	-1.05	0.29	0.15±0.12	0.15±0.12	-0.42	0.68
Basophil count, 10 ⁷ /L	0.01±0.01	0.01±0.01	-0.85	0.39	0.01±0.01	0.01±0.01	0.59	0.56
Red blood cell count, 10 ¹² /L	4.88±0.42	4.77±0.45	-5.66	0	4.91±0.41	4.87±0.42	-1.33	0.18
Hemoglobin, g/L	149.17±13.59	143.72±15.19	-7.99	0	150.12±13.05	148.52±13.96	1.7	0.08
Hematocrit, %	43.24±3.44	42.04±3.86	-6.96	0	43.41±3.33	43.13±3.54	1.20	0.22
Mean corpuscular volume, fL	88.69±3.94	88.25±4.22	-2.32	0.02	88.61±3.9	88.31±4.1	-1.12	0.27
Mean hemoglobin content, pg	30.58±1.63	30.15±1.76	-5.43	0	30.63±1.56	30.51±1.66	1.1	0.13
Mean hemoglobin concentration, g/L	344.76±10.98	341.54±10.7	-6.62	0	345.71±10.4	344.32±10.08	-2.00	0.05
RDW-CV, %	12.82±0.63	12.87±0.85	1.29	0.19	12.79±0.59	12.81±0.67	0.24	0.81
RDW-SD, %	41.33±2.46	41.27±2.64	-0.49	0.62	41.23±2.45	41.14±2.62	-0.50	0.62
Platelet count, 10 ⁹ /L	215.9±53.27	225.98±51.9	4.27	0	214.88±51.22	219.29±47.83	1.31	0.18

Values are ±SD, unless otherwise noted.

MetS, metabolic syndrome; PSM, propensity score matching; SD, standard deviation; RDW, red blood cell distribution width; CV, coefficient of variation.

Table 2. Univariate analysis of blood biochemical profiles in participants with and without MetS before PSM.

Characteristic	With MetS (N=538)	Without MetS (N=5164)	t/χ^2	p
Age (years)	54.89±12.53	45.67±12.73	-16.00	0.00
Total protein (g/L)	72.67±4.6	71.84±4.34	-4.12	0.00
Sex, n				
Male	416	3112	60.11	0.01
Female	122	2052		
Albumin (g/L)	44.4±2.35	44.63±2.23	2.16	0.03
Albumin to globulin ratio	1.61±0.27	1.67±0.27	5.39	0.00
Aspartate aminotransferase (U/L)	25.65±10.82	23.37±11.42	-4.35	0.00
Alanine aminotransferase (U/L)	30.19±19.87	25.38±20.74	-5.11	0.00
γ -glutamate transpeptidase (U/L)	46.27±46.75	32.56±32.56	-6.58	0.00
Alkaline phosphatase (U/L)	83.86±24.81	77.06±22.12	-6.61	0.00
Prealbumin (mg/L)	0.3±0.06	0.29±0.05	-4.47	0.00
Cholinesterase (U/L)	9760.74±1973.94	9086.23±1863.89	-7.87	0.00
Total bilirubin (μ mol/L)	14.12±5.24	13.51±5.42	-2.43	0.02
Direct bilirubin (μ mol/L)	4.07±1.93	3.96±1.68	-1.41	0.16
Indirect bilirubin (μ mol/L)	10.03±3.65	9.55±3.97	-2.65	0.01
Total bile acid (μ mol/L)	3.39±3.39	3.18±3.52	-1.34	0.18
Urea (mmol/L)	5.7±1.18	5.28±1.24	-6.70	0.00
Creatinine (μ mol/L)	72.9±13.79	69.39±16.4	-4.27	0.00
Uric acid (μ mol/L)	384.72±87.69	346.88±93.83	-7.99	0.00
Cystatin C (mg/L)	0.78±0.21	0.69±0.18	-8.34	0.00

Values are \pm SD, unless otherwise noted.

MetS, metabolic syndrome; PSM, propensity score matching.

>7.8 mmol/L and/or diagnosed with and being treated for diabetes; (3) hypertension with systolic blood pressure/diastolic blood pressure \geq 140/90 mmHg and/or diagnosed with and being treated for hypertension and (4) dyslipidemia (fasting blood TG \geq 1.7 mmol/L and/or fasting blood HDL-C <0.9 mmol/L for men and <1.0 mmol/L for women).

Statistical analysis and PSM

All data were analyzed using IBM SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Normally distributed data were expressed as $\bar{X} \pm$ standard deviation (SD). Comparisons between the groups were performed using independent sample t -tests. Categorized variables were expressed either as a rate or composition ratio, when

appropriate, and comparisons between participants with or without MetS were performed using the chi-square test. PSM was implemented using the PSM extension procedure in IBM SPSS. Specifically, taking MetS status in the second year as the dependent variable and various other covariates as independent variables, the propensity score was estimated using logistic regression, and matching was performed using a 1:1 nearest neighbor method. Matching factors included white blood cell count, lymphocyte count, monocyte count, red blood cell count, hemoglobin, hematocrit, mean hemoglobin content, mean hemoglobin concentration, and platelet count. Each participant with new-onset MetS, defined as the disease group (New MetS group), was matched with an individual without MetS with the most similar propensity

score, defined as the normal group (Non MetS group). This process ensured goodness-of-fit of the matching results by defining the caliper of PSM, and then comparing the change in the SD of the covariates between participants with and without new-onset MetS prior to and after matching. The closer to 0 the SD after matching, the more satisfactory the matching result. When an absolute value of the SD was less than 0.1 (10%), the balance of the variables between the groups was considered good. Values $p < 0.05$ (two-sided) were considered statistically significant. Predictors of MetS were determined using multivariate regression analysis. The association between the variables and the incidence of MetS was represented with the odds ratio (OR) and 95% confidence interval (CI).

Results

A total of 5702 people completed two PEs between 1 January 2017 and 1 December 2018. Of the 5702 participants, 3527 were men and 2175 were women, with a mean age of 45.67 ± 12.74 years.

Routine blood index profiles in participants with and without new-onset MetS prior to matching

For all participants examined during the observational period, regardless of sex, 538 out of 5702 participants were confirmed to have newly developed MetS, with an overall prevalence of 9.4%. As shown in Table 1, routine blood index profiles including white blood cell count, lymphocyte count, monocyte count, red blood cell count, hemoglobin, hematocrit, mean hemoglobin content, mean hemoglobin concentration, and platelet count, were compared prior to matching. The results indicated a significant difference in each parameter between participants with and without newly developed MetS.

Routine blood index profiles in participants with and without new-onset MetS after matching

By defining participants without newly developed MetS as the reference for matching purposes, we performed PSM for a total of 436 pairs that were matched successfully. We excluded 102 participants with newly developed MetS and PSM was not performed owing to a lack of some blood biochemical profiles. Unbalanced covariates between participants with and without new-onset MetS were balanced after matching (Table 1). Absolute values of the SDs were adequately controlled within 10.0%, as expected, and the balance of the covariates was also significantly improved with PSM, which was indicative of the high quality of the matching. After matching, no statistical significance was identified between participants with and without newly developed MetS.

Univariate analysis of blood biochemical profiles in participants with and without new-onset MetS

Prior to matching, the complete blood biochemical profiles between the two groups were significantly different for each of the following components: albumin, albumin to globulin ratio, aspartate aminotransferase, alanine aminotransferase, γ -glutamate transpeptidase, alkaline phosphatase, prealbumin, cholinesterase, total bilirubin, indirect bilirubin, urea, creatinine, uric acid, and Cys-C ($p < 0.05$) (Table 2). This indicated an association with MetS for a wide range of blood biochemical profiles. However, after PSM matching, the magnitude of the association was reduced in a few parameters such as aspartate aminotransferase, alanine aminotransferase, and prealbumin. Albumin, albumin to globulin ratio, γ -glutamate transpeptidase, alkaline phosphatase, cholinesterase, total bilirubin,

Table 3. Univariate analysis of blood biochemical profiles in participants with and without MetS after PSM.

Characteristic	With MetS (N=436)	Without MetS (N=436)	<i>t</i> / χ^2	<i>p</i>
Age (years)	53.62±11.89	43.89±11.07	-12.49	0.00
Total protein (g/L)	72.76±4.67	72.45±4.5	-0.99	0.32
Sex, n				
Male	347	302	12.20	0.01
Female	89	134		
Albumin (g/L)	44.48±2.4	44.91±2.23	2.75	0.01
Albumin to globulin ratio	1.61±0.27	1.66±0.26	3.02	0.00
Aspartate aminotransferase (U/L)	26.03±11.26	25.56±25.95	-0.34	0.74
Alanine aminotransferase (U/L)	31.06±20.45	29.83±38.26	-0.58	0.56
γ -glutamate transpeptidase (U/L)	47.91±48.66	37.45±34.13	-3.65	0.00
Alkaline phosphatase (U/L)	82.99±23.2	79.42±24.11	-2.20	0.03
Prealbumin (mg/L)	0.3±0.06	0.3±0.06	-1.39	0.17
Cholinesterase (U/L)	9802.04±1960.31	9331.16±1953.4	-3.53	0.00
Total bilirubin (μ mol/L)	14.31±5.31	13.45±5.11	-2.43	0.02
Direct bilirubin (μ mol/L)	4.13±2	4.03±1.74	-0.78	0.43
Indirect bilirubin (μ mol/L)	10.17±3.68	9.42±3.58	-3.02	0.00
Total bile acid (μ mol/L)	3.47±3.52	3.27±3.25	-0.84	0.40
Urea (mmol/L)	5.7±1.18	5.34±1.13	-4.60	0.00
Creatinine (μ mol/L)	72.9±13.79	70.68±16.32	-2.16	0.03
Uric acid (μ mol/L)	384.72±87.69	358.24±99.52	-4.15	0.00
Cystatin C (mg/L)	0.78±0.21	0.7±0.16	-5.83	0.00

Values are \pm SD, unless otherwise noted.

MetS, metabolic syndrome; PSM, propensity score matching.

indirect bilirubin, urea, creatinine, uric acid, and Cys-C were still significantly different between participants with and without new-onset MetS ($p < 0.05$) (Table 3).

Multivariate logistic regression analysis of risk factors for metabolic syndrome

In multivariate logistic regression analysis, we used the presence or absence of MetS as the corresponding variable; age, albumin to globulin ratio, albumin, γ -glutamate transpeptidase, alkaline phosphatase, cholinesterase, total bilirubin, indirect bilirubin, urea, creatinine, uric acid, and Cys-C levels as continuous independent variables; and sex as a binary independent variable. The results showed that age and γ -glutamate transpeptidase, creatinine, uric acid, and Cys-C level were all associated with

MetS; the highest OR value was for Cys-C with 3.03 (95% CI, 1.02–9.00; Table 4).

Discussion

We performed a comprehensive analysis of the relationship of MetS and a variety of common blood biomarkers using the PSM method in this nested case-control study of an adult Chinese population in a metropolitan setting. We found a MetS prevalence of 9.4% during 2 years of observation and identified multiple factors potentially linked with the development of MetS.

Most previous studies^{17–19} that have assessed the risk factors of MetS have been based on reviews of hospital case data. The balance between case and control groups is often insufficient, and it is difficult to exclude the impact of various

Table 4. Multivariate logistic regression analysis of predictors for metabolic syndrome.

Variable	β	SE	Wald chi-square	p	Exp(B)	95% CI
Age (years)	0.075	0.007	102.320	0	1.078	1.062–1.094
γ -glutamate transpeptidase (U/L)	0.006	0.002	9.479	0.002	1.006	1.002–1.010
Creatinine (μ mol/L)	-0.016	0.007	5.310	0.021	0.984	0.971–0.998
Uric acid (μ mol/L)	0.003	0.001	10.526	0.001	1.003	1.001–1.005
Cystatin C (mg/L)	1.109	0.555	3.985	0.046	3.030	1.02–9.000
Constant	-4.758	0.533	79.644	0	0.009	

SE, standard error; CI, confidence interval.

confounding factors on the results. PSM has been widely used in recent years.^{20,21} This statistical method can effectively balance differences between groups, reduce the effects of confounding, and yield results similar to those of a randomized controlled study.²² After confirmation of their hematological parameters and other clinical data, a total of 436 participants were diagnosed with newly developed MetS. After balancing the baseline characteristics of these 436 pairs of participants, thereby reducing the potential bias generated by confounding factors, we further examined a series of biochemical parameters and their potential correlation with the development of MetS.

After matching, we analyzed 19 variables in univariate analysis, including albumin level and albumin to globulin ratio. The results showed that albumin, albumin to globulin ratio, γ -glutamate transpeptidase, alkaline phosphatase, cholinesterase, total bilirubin, indirect bilirubin, urea, creatinine, uric acid, and Cys-C levels were significantly associated with metabolic syndrome. Further, multivariate analysis showed that age and γ -glutamate transpeptidase, creatinine, uric acid, and Cys-C levels were risk factors for MetS.

Participants with MetS had higher serum uric acid levels than those in the normal group, consistent with previous findings.^{23,24} Zhang et al.²⁵ reported that a higher serum uric acid (SUA) level (within the normal range) is an independent risk

factor for the incidence of MetS. However, the exact biological mechanism underlying the association between SUA and MetS remains unclear. Zhu et al.²⁶ found that the key pathophysiological mechanism of MetS is an increase in uric acid level, which can directly inhibit insulin receptor substrate-1 and Akt insulin signal transduction and induce insulin resistance. An increase in SUA level can lead to endothelial dysfunction and reduce the production of nitric oxide, which is necessary for insulin to stimulate glucose uptake.^{24,27} Therefore, increases in SUA level can lead to insulin resistance and hyperinsulinemia. SUA may be a biomarker of incident MetS. In this study, multiple regression analysis showed that the OR of uric acid was not particularly high; further studies are needed to elucidate the details of this relationship.

Our results showed that Cys-C levels in the MetS group were significantly higher than those in the normal control group. After adjusting for other related confounding factors, we found that age and γ -glutamate transpeptidase, creatine, uric acid, and Cys-C levels were all related to MetS. The OR of Cys-C (3.03, 1.02–9.00) was the highest among all factors. The specific pathophysiological mechanism of Cys-C and MetS currently remains unclear. The following factors may be involved in this mechanism. The first is renal function damage. Cys-C is a biomarker of early renal

function damage. Hypertension and hyperglycemia in MetS are the main risk factors in chronic kidney disease. Additionally, high TG and low HDL-C levels (both clinical values that are often neglected) are also risk factors of renal function damage.²⁸ MetS can cause renal function damage and increase Cys-C levels; in turn, renal function damage can induce insulin resistance, increasing the risk of MetS or accelerating the progression of MetS, thereby generating a vicious circle. The second factor is cytotoxic effects. Studies^{29,30} have shown that Cys-C is involved in cell apoptosis and induces toxicity in cells, leading to an increased risk of CVD. The third factor is an oxidative stress mechanism. Oxidative stress is significantly increased in patients with MetS, which could stimulate Cys-C mRNA synthesis and increase Cys-C levels.³¹ Finally, Cys-C is closely linked to inflammation-related and procoagulant factors,³² including homocysteine, C-reactive protein, interleukin-6, tumor necrosis factor- α , intercellular adhesion molecule-1, and fibrinogen. Cys-C and its degradation products can activate phagocytic functions and promote inflammation. A chronic inflammatory response is an important pathogenic pathway in MetS.^{33,34} In addition, Cys-C levels are significantly associated with insulin resistance³⁵ and hypermetabolism.³⁶

There are several limitations in the study. First, although the main finding was generated by analyzing a relatively large data set, all data were collected from a single metropolitan medical center. Further studies should include multiple centers, especially those in underserved areas with respect to health care services. Second, the follow-up time was only 1 year. Statistical analysis of the cumulative incidence rate was not available. The follow-up time should be increased in future studies. However, in addition to taking advantage of the dynamic power of PSM for data analysis as a

strength of this study, another important strength is its novelty in the Chinese population.

As the prevalence of MetS is increasing rapidly in populations worldwide, particularly among young people, our approach can be adjusted to help determine the most effective prevention and management of MetS in different settings. Additionally, the disparity in medical care systems between urban and rural areas calls for even more implementation of readily available and easy testing methods. Given that Cys-C is assessed in nearly all community- or hospital-based settings, use of Cys-C levels can have a potent impact on improving early detection in patients with MetS.

In conclusion, Cys-C was found to be closely associated with MetS. The findings of our study showed that serum Cys-C level has important theoretical and clinical importance in the prevention of MetS. Cys-C levels are generally stable and independent of sex, age, and other factors. Monitoring the dynamic changes in Cys-C levels may help predict the occurrence, development, and prognosis of MetS.

Author contributions

DP conceptualized and designed the study, created the instrument for data collection, drafted the initial manuscript, and reviewed and revised the manuscript. TY collected data, performed data analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be responsible for the accuracy of all aspects of the work.

Declaration of conflicting interest

The authors declare that they have no conflicts of interest.

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