RESEARCH ARTICLE

Distinguish different Chinese medicine types of metabolic syndrome by combining body mass index and uric acid

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Abstract

Objective: To provide clinical support for traditional Chinese medicine classification of metabolic syndrome patients.

Methods: The retrospective study was conducted at Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, and Sichuan Provincial Hospital of Chinese Medicine, Chengdu, China, and comprised data of metabolic syndrome patients having visited the two hospitals between January and December 2017. The patients were divided into 2 groups based on the different types of Chinese medicine. Group1 had Qi-Yin deficiency and group 2 had phlegm-blood stasis. Various laboratory tests related to metabolic syndrome were conducted, analysed and compared in both the groups.

Results: Of the 263 patients, 173(66%) were in group 1 and 90(34%) were in group 2. Body mass index and blood uric acid level had statistical significance between the groups ($p<05$) .The sensitivity was over 90% and the accuracy was 60%.

Conclusion: Body mass index and blood uric acid level were found to be the two independent factors to distinguish between different types of metabolic syndrome.

Keywords: Metabolic syndrome, Body mass index, Blood uric acid, Traditional Chinese medicine. (JPMA 70: 993; 2020) DOI: https://doi.org/10.5455/JPMA.5519

Introduction

Metabolic syndrome (MS) is a cluster of metabolic disorders including abdominal or central obesity, impaired glucose tolerance (IGT), elevated plasma glucose or diabetes mellius (DM), elevated blood pressure (BP) or hypertension (HTN) and dyslipidaemia.[1] Of all these conditions, insulin resistance (IR) is the common pathophysiological basis of MS.[2] Generally, the diagnosis of MS is often confirmed by some essential factors, like elevated waist circumference (WC), elevated triglycerides (TG), reduced high density lipoprotein (HDL), elevated BP and elevated fasting blood glucose (FBG).[3] Patients with MS are prone to some critical diseases. It has been proven that MS is associated with increased risk of cardiovascular disease (CVD),[4] chronic kidney disease (CKD),[5] type 2 DM (T2DM)[6] etc.

In China, rapid economic growth as well as social and cultural changes have reconstructed people's lifestyle and increased the incidence of many chronic diseases, including MS. A study in 2009 showed that the overall age-standardised prevalence of the MS was about 21.3% in China.[7] The high morbidity indicated that there was an urgent need to develop national strategies for the prevention, detection and treatment of obesity and MS in China.

Different from Western medicine, tradition Chinese medicine (TCM) believes that these human diseases are the results of the disorder of Qi-Yin deficiency, which includes blood, essence and fluid or six pathogens that attack human body including wind, cold, heat, dampness, dryness and fire.[8] The presentations of different diseases are named TCM patterns. A TCM pattern is considered a "pattern of disharmony" or "functional disturbance" within the functional entities of the TCM model of the body,[9] demonstrated by profiles of signs and symptoms indicated by patients through the four significant diagnostic procedures: inspection, auscultation and olfaction, inquiry and palpation.[10] In TCM terms, MS is closely associated with spleen, liver and kidney, and the core pathogenesis include phlegm and blood stagnation. Dysfunction of spleen transportation, uncontrolled distribution by liver and deficiency of kidney lead to dampness, phlegm and blood stagnation and then cause MS.[11] The therapeutic principles of MS are based on different patterns that are essential for the prognosis of patients. Consequently, clarifying the specific patterns of MS is the key to selecting the proper TCM treatment.

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However, to our knowledge, there are few studies exploring the differences among different patterns of MS in the view of clinical and laboratory results. The current study was planned to fill this gap in order to provide clinical support for TCM classification of MS patients.

Patients and Methods

The retrospective study was conducted at Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, and Sichuan Provincial Hospital of Chinese Medicine, Chengdu, China, and comprised data of metabolic syndrome patients having visited the two hospitals between January and December 2017. The data studied related to diagnosed MS patients aged 16-70 years with definite TCM patterns of Qi-yin deficiency (QD) or Phlegm-blood stasis (PS)). Using Chinese Diabetes Society (CDS) diagnostic criteria,[12] 3 or all of the following 4 components are diagnosed as MS:[13,14] body mass index (BMI) >25.0kg/m^2;[15] FBG >6.1mmol/L or oral glucose tolerance test (OGTT-2h) >7.8mmol/L or diagnosed diabetics under treatment; systolic BP (SBP) >140mmHg or diastolic BP (DBP) >90mmHg[16] or currently taking antihypertensive drugs; and dyslipidemia where the cut-off value was taken as TG >1.7mmol/L or fasting HDL <0.9mmol/L for males and <1.0mmol/L for females.

TCM divides people's physique into 9 basic types:[17] peace and quality (type A), qi deficiency (type B), yang deficiency (type C), Yin deficiency (D type), phlegm-turbid (E type), damp heat (F type), blood stasis (G type), gas stagnation (H type) and special enamel (type I). For the purpose of the current study, the patients were divided into QD and PS groups. QD is characterised by fatigue, shortness of breath, spontaneous sweating, thirst and more drinking, dry stool, reddish tongue coating, weak or thin veins. PS is characterised by bloating, fatigue, limb pain, chest pain, dark tongue, sputum, string pulse or deep and unsmooth pulse. Baseline characteristics and results of various laboratory tests were obtained from the medical records after approval was obtained by the institutional ethics committees of the two hospitals.

Data was analysed using SPSS 24 and MedCalc 11.4.2.0 (bvba, Belgium). Prism 7.00 a (GraphPad Software Inc., USA) was used to generate graphs. Each variable was represented as median with interquartile range (IQR). Normality and homogeneity of data were evaluated by Kolmogorov-Smirnov test. Student t-test or Mann-Whitney test was applied to compare the differences of continuous variables. Pearson Chi-square test was employed to evaluate statistical differences of categorical variables. Logistic regression models were used to calculate hazard ratio (HR) and 95% confidence interval (CI). The correlation was evaluated by the Spearman correlation coefficient. Receiver operating characteristics (ROC) curves and area under ROC (AUROC) were calculated to evaluate the differentiating power of markers, and DeLong test was applied to compare the different AUROC values. Sensitivity, specificity, Youden index, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative LR (-LR), odds ratio (OR) and Kappa (K) value were calculated by 2 × 2 table in SPSS 24. Two-tailed $p<0.05$ was defined as statistically significant.

Results

Of the 690 medical records evaluated, 263(38%) represented the study sample; 173(66%) in the QD group and 90(34%) in the PS group Baseline demographics of the two groups were comparable, and only BMI in the PS group was significantly higher than in the QD group

Table-1: Characteristics of patients in two groups (N=263).

N	Phlegm-blood stasis 179	Qi-yin Deficiency 90	P value
Age, years	59.00(50.00-67.00)	62.00(52.00-66.00)	0.353
Gender, male	48(53.3%)	85(49.7%)	0.578
BMI, kg/m^2	26.43(24.53-29.03)	25.15(23.00-27.42)	0.002
Waistline	93.50(91.00-99.00)	94.00(88.50-99.00)	0.336
Waist/Hipline	0.95(0.92-0.98)	0.96(0.90-0.98)	0.672
SBP, mmHg	142.00(130.80-154.00)	140.50(130.00-152.80)	0.533
DBP, mmHg	80.00(71.00-92.00)	82.00(75.00-89.00)	0.945
TG, mmol/L	2.02(1.35-2.55)	2.00(1.43-2.81)	0.543
TC, mmol/L	5.02(4.02-5.95)	4.74(4.03-5.78)	0.481
HDL-C, mmol/L	0.99(0.89-1.14)	0.97(0.86-1.12)	0.312
LDL-C, mmol/L	3.24(2.52-4.00)	3.13(2.60-3.81)	0.544
ALT, U/L	20.00(14.40-31.00)	19.80(13.00-31.00)	0.475
AST, U/L	19.00(14.65-27.00)	20.00(15.00-27.00)	0.833
ALP, U/L	74.00(59.00-92.00)	70.00(56.00-89.50)	0.337
GGT, U/L	30.00(23.00-55.00)	29.00(19.00-45.00)	0.130
TBIL, μmol/L	8.90(6.60-11.90)	8.75(6.35-12.23)	0.618
TBA, μmol/L	3.50(2.10-6.20)	3.20(2.10-5.40)	0.571
Urea, mmol/L	5.34(4.06-6.56)	5.34(4.36-6.56)	0.598
Cr, μmol/L	72.00(60.00-80.00)	67.00(56.00-85.00)	0.503
FBG, mmol/L	8.35(6.14-12.08)	8.80(6.49-13.04)	0.105
BHBA, mmol/L	0.08(0.05-0.12)	0.10(0.05-0.20)	0.198
HbA1c, %	8.00(6.80-10.20)	8.20(6.70-10.30)	0.960
C peptide, nmol/L	0.52(0.35-0.75)	0.47(0.33-0.79)	0.710
BUA, μmol/L			
Male	400.00(351.00-471.00)	368.00(307.00-419.00)	0.024
Female	406.00(347.00-496.00)	365.00(290.30-444.00)	0.024
eGFR, ml/min/1.73m^2	96.77(71.01-107.70)	95.54(76.03-107.00)	0.914

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; TBIL: Total bilirubin; TBA: Total bile acid; Cr: Creatinine; FBG: Fasting blood glucose; BHBA: Beta hydroxybutyric acid ; HbA1c: Glycated haemoglobin; BUA: Blood uric acid; eGFR: Estimated glomerular filtration rate.

Table-2: Univariate and multivariate logistic regression analysis of factors related to Qi-yin deficiency (QD) and Phlegm-blood stasis (PS).

Variables	Univariate analysis			Multivariate analysis		
	HR (95% CI)	β	P value	HR (95% CI)	β	P value
Gender, male	0.87(0.52-1.44)	-0.182	0.578	0.90(0.54-1.49)	-0.108	0.674
Age(y)	1.01(0.99-1.04)	0.014	0.201	1.01(0.98-1.03)	0.006	0.654
BMI (kg/m2)	0.90(0.84-0.97)	-0.102	0.005	0.89(0.82-0.91)	-0.120	0.006
Waist/Hipline	0.04(0.00-86.12)	3.329	0.410			
SBP (mmHg)	1.00(0.98-1.01)	0.003	0.680			
DBP (mmHg)	1.00(0.99-1.02)	0.003	0.590			
TG (mmol/L)	1.08(0.91-1.28)	0.074	0.359			
TC (mmol/L)	0.95(0.80-1.14)	-0.052	0.600			
HDL-C (mmol/L)	0.81(0.33-1.98)	-0.224	0.643			
LDL-C (mmol/L)	0.96(0.78-1.19)	-0.042	0.730			
ALT (U/L)	0.99(0.98-1.00)	-0.010	0.060	1.00(0.98-1.01)	-0.005	0.540
AST (U/L)	0.99(0.97-1.00)	-0.012	0.154			
ALP (U/L)	1.00(0.99-1.01)	0.003	0.525			
GGT (U/L)	1.00(0.99-1.00)	-0.006	0.068	1.00(0.99-1.01)	-0.006	0.086
TBIL(μmol/L)	0.99(0.94-1.04)	-0.008	0.722			
TBA (μmol/L)	0.98(0.92-1.04)	-0.021	0.521			
Urea (mmol/L)	1.03(0.90-1.17)	0.033	0.691			
Cr (μmol/L)	1.00(0.99-1.01)	0.001	0.970			
FBG (mmol/L)	1.01(0.97-1.06)	0.012	0.544			
BHBA (mmol/L)	2.50(0.49-12.83)	0.910	0.272			
HbA1c (%)	1.02(0.90-1.15)	0.007	0.818			
Cpeptide (nmol/L)	1.02(0.47-2.24)	0.012	0.954			
BUA (μmol/L)	1.00(0.99-1.00)	-0.004	0.004	1.00(0.99-1.00)	-0.004	0.014
eGFR (ml/min/1.73m^2)	1.00(0.10-1.01)	0.002	0.546			

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; TBIL: Total bilirubin; TBA: Total bile acid; Cr: Creatinine; FBG: Fasting blood glucose; BHBA: Beta hydroxybutyric acid ; HbA1c: Glycated haemoglobin; BUA: Blood uric acid; eGFR: Estimated glomerular filtration rate.

Table-3: Efficacy of blood uric acid (BUA) and body mass index (BMI)and their combination in differentiating patients of Phlegm-blood stasis (PS) and Qi-Yin Deficiency (QD) at calculated cut-off value.

Indexes	Sensitivity	Specificity	Youden	Accuracy	PPV %	NPV %	+LR	-LR	OR	K
BMI	72.2%	47.9%	0.20	56.9%	44.9	74.5	1.39	0.58	2.38	0.18
BUA	78.4%	45.5%	0.24	57.6%	45.8	78.1	1.44	0.48	3.02	0.21
1 positive	96.9%	26.1%	0.23	52.3%	43.5	93.5	1.31	0.12	11.04	0.18
2 positive	53.6%	67.3%	0.21	62.2%	49.1	71.2	1.64	0.69	2.38	0.21
Combination*	90.6%	34.5%	0.25	53.6%	41.6	87.7	1.38	0.27	5.08	0.20

*Combination = 0.004*ln BUA + 0.12*ln BMI

PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; OR: Odds ratio; K: Kappa value.

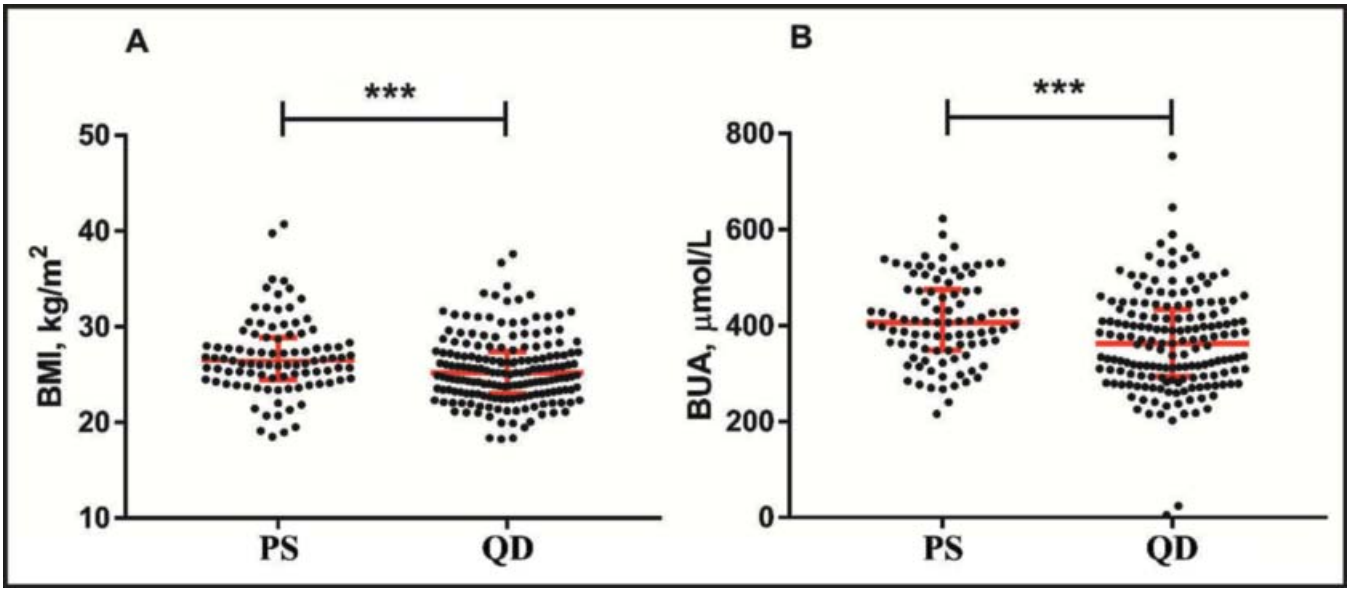
(p=0.002) (Table-1; Figure-1a).

TG, total cholesterol (TC), HDL, LDL and FBG had no significant difference between the groups (p>0.05). Also, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TBIL) and total bile acid (TBA) were not statistically different (p>0.05). Only blood uric acid (BUA) values between male and female subjects were significantly different in both the groups (p=0.024) (Figure-1b).

In univariate analysis, only BMI and BUA were considerably related to different TCM patterns (p<0.05)).

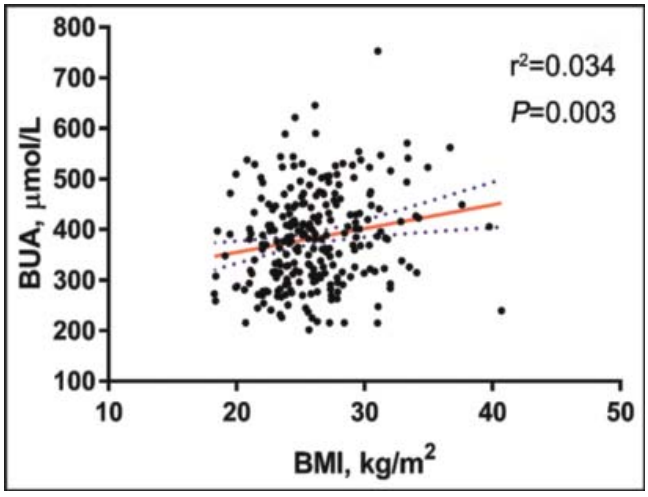
In multivariable analysis, age and gender were enrolled as confounding factors, and after adjusting for the two factors, BMI and BUA were finally selected as the two markers that could differentiate between QD and PS (p<0.05) (Table-2).

There was no significant correlation between BMI and BUA and the two were independent factors in



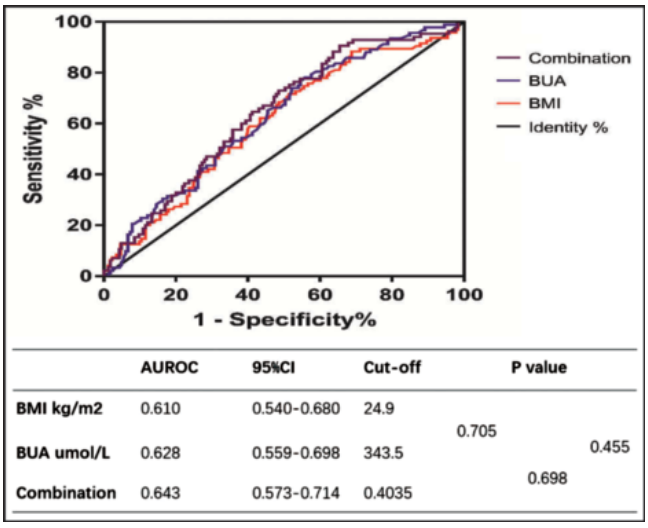
*** means P<0.01

Figure-1: Levels of blood uric acid (BUA) and body mass index (BMI) in different traditional Chinese medicine (TCM) patients (Qi-Yin deficiency [QD] and phlegm-blood stasis [PS] groups).



Red line: regression curve; Dashed line: 95% confidence interval (CI).

Figure-2: Correlation of levels of blood uric acid (BUA) and body mass index (BMI).



	AUROC	95%CI	Cut-off	P value	
BMI kg/m2	0.610	0.540-0.680	24.9	0.705	
BUA umol/L	0.628	0.559-0.698	343.5		0.455
Combination	0.643	0.573-0.714	0.4035	0.698	

Figure-3: Comparison of reciver operating characteristic (ROC) curves of markers in differentiating different patterns. Cut-off values were calculated by Youden index.[37]

terms of distinguishing between different TCM types of MS (Figure-2).

There was no significant difference among BMI, BUA and the combination of the two, but the combination was slightly better than BMI and BUA alone (Figure-3).

The sensitivity was over 90% and the accuracy was 60% (Table-3).

Discussion

MS is a complicated syndrome owing to the coexistence of a variety of diseases. In recent years, basic and clinical researches on the TCM theory in the treatment of diseases have progressed a lot.[18] And TCM is thought to be beneficial to manage and treat MS patients, especially the disorder of glucose and lipids. However, the first and most important thing in TCM treatment of MS is to locate the

relevant TCM pattern.

Huang et al. reported that Qi Deficiency Syndrome and Kidney Deficiency Syndrome are the two main TCM patterns in women MS patients[19] leading to a poor quality of life.

Furthermore, they concluded that, except for BMI, WC and hip circumstance (HC), there was no difference in most biochemical parameters between different TCM patterns.

In our study, QD and PS were the main patterns for MS patients. We analysed the differences in the results of various laboratory tests between the two groups and found that only the difference in BMI and BUA values was statistically significant. A previous study in Japan recommended setting the cut-off value 23.0-24.9 kg/m^2 for BMI to prevent MS.[20] Our results showed that BMI cut-off value 24.9 kg/m^2 could differentiate PS from QD in MS patients in China.

BUA, an inert metabolic end-product of purine metabolism, is often viewed as a bystander in the process of MS.[21,22] Although it could be commonly seen elevated in MS patients, BUA has not been enrolled as a diagnostic criterion for MS. However, BUA has been recently incriminated in various chronic diseases and pathological procedures, like CVDs,[23] DM nephropathy[24,25] and liver diseases.[26] A large number of clinical studies[21,27-30] have shown that with the increase in the level of BUA, the incidence of MS is increasing. In addition, many researches have revealed the association between elevated levels of BUA and HTN,[31] hypertriglyceridemia[32] and IR.[33] All these abnormalities were typical presentations of MS. As for the underline mechanisms, a study revealed the association between serum uric acid (SUA) and apolipoprotein E (ApoE) allele, impairing the glycolytic pathway, which finally triggers MS.[34] Therefore, BUA values have been widely studied as risk predictors of MS.[35,36] In our study, BUA was not only associated with MS, but also an independent indicator in distinguishing between different TCM patterns in MS patients. By using the cut-off value of 343.5 μmol/L, BUA could detect 78.4% of patients in the PS group.

Furthermore, we analysed the combination of BMI and BUA in three ways (one positive, two positive and combination through a distinguishing model). The results showed that the sensitivity could increase by about 20% after combining BMI and BUA, and the accuracy was almost 60%. Although specificity was not satisfactory, it was sufficient to distinguish between TCM patterns.

To our knowledge, this was the first study comparing TCM patterns in the light of basic laboratory tests. And the results showed BMI and BUA can do the job in MS patients. However, the study was limited by the fact that it had a small sample size and focussed on only two TCM patterns while leaving out cases of all other patterns.

Conclusion

BMI and BUA were two indices that were different in PS and QD groups of MS patients.

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Conflict of Interest: None.

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