Including selective metabolic components in current diagnostic criteria does not improve discriminative validity for metabolic syndrome: a risk score approach

Huan-Cheng Chang

Sheng-Pyng Chen and Hao-Jan Yang

Abstract

Objective: To examine whether including additional metabolic components to the current five-marker system can improve the discriminative validity for diagnosing metabolic syndrome (MetS).

Methods: This longitudinal cohort study included data from subjects that had completed at least three health examinations during a 5-year period. The study outcome was the onset of MetS. Sociodemographic and biochemical variables were recorded for all subjects so that the adjusted relative risks (ARRs) could be calculated for 11 metabolic components. Risk scores for the development of MetS based on the ARR values were determined. The sums of the risk scores of different component combinations were used to conduct a receiver operating characteristic (ROC) curve analysis of MetS diagnosis.

Results: A total of 3368 individuals with complete data was analysed. The ARRs of the 11 metabolic components were all statistically significant. According to ROC analysis, although good discriminative validity (area under the curve [AUC] range, 0.954–0.976) could be achieved for MetS diagnosis by using either all 11 or combinations of six metabolic components (the five current components plus one extra component), the current five metabolic components used for diagnosis had the best discriminative validity (AUC = 0.977).

1Department of Community Medicine, Division of Family Medicine, Landseed Hospital, Tao-Yuan
2Department of Health Care Management, Chang Gung University, Tao-Yuan
3Department of Public Health, Chung Shan Medical University, Taichung
4Department of Family and Community Medicine, Chung Shan Medical University Hospital, Taichung

Corresponding author:
Hao-Jan Yang, Department of Public Health, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Road, Taichung 40201.
Email: hjyang@csmu.edu.tw
Conclusion: The current five metabolic components used for the diagnosis of MetS still represent the best combination with the highest discriminative validity.

Keywords
Metabolic syndrome, diagnostic criteria, risk score, receiver operating characteristic curve analysis

Date received: 17 August 2018; accepted: 12 December 2018

Introduction
Diagnosis of the metabolic syndrome (MetS) by the current medical community usually adopts the standard of using the five markers suggested by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III): waist circumference (waist), fasting glucose (FG), blood pressure, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C). However, due to the rather complex mechanisms involved in the development of MetS, increasing numbers of studies have suggested that other physical or biochemical factors that are closely associated with MetS should also be incorporated into the MetS diagnostic criteria. For example, MetS is closely associated with other chronic diseases such as cardiovascular disease (CVD) and type 2 diabetes mellitus, which in turn are linked to cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, two important metabolic components. In addition, for many patients, MetS takes the form of hepatic steatosis, a condition not only linked to TG levels but also to LDL-C levels. These data demonstrate that cholesterol and LDL-C are also important for MetS diagnosis.

Hepatic steatosis can also lead to abnormal liver function, so including two common liver function markers, namely glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT), as diagnostic markers for MetS would appear to be a rational idea. In particular, raised GPT levels are regarded as a result of insulin resistance and considered to be a better diagnostic marker for MetS than fasting blood glucose.

Some researchers suggest that uric acid (UA) and/or hyperuricaemia should be considered as MetS markers because epidemiology studies showed that hyperuricaemia acts as either a correlate or an independent risk factor for MetS. However, other studies have argued that hyperuricaemia is only a manifestation of CVD and that the use of medications to lower UA levels does not prevent the development of CVD. Therefore, the role of UA in MetS diagnosis remains to be clarified.

Recent studies have shown that in East Asian countries, body mass index (BMI) and waist circumference both have good discriminative ability for MetS, yet there are insufficient solid data to refer to in order to tell which marker is better for predicting MetS. Therefore, the present study used large-scale community follow-up survey samples to perform a comprehensive analysis of the MetS predictability of a variety of biomarkers, especially focusing on blood lipid markers, liver function markers and uric acid. This present study also compared the discriminative ability of...
waist circumference and BMI in predicting MetS, in the hope of offering references for future revisions to the MetS diagnostic criteria.

A risk score (RS)-based analysis was successfully applied to identify the factors used to predict type 2 diabetes mellitus, but has never been used in MetS studies. Because the factors associated with MetS are more multivariate and complex than those for other CVD, using an RS-based analysis to identify potential predictors and combining the analysis with receiver operating characteristic (ROC) curve analysis can effectively enable identification of markers with higher discriminative validity and help identify the best combination for diagnosis.

**Subjects and methods**

**Participants**

Using multi-stage probability proportional to size sampling strategy, this longitudinal cohort study randomly invited residents who were ≥30 years of age with a registered household in Pingzhen District, Taoyuan City, Taiwan to undertake free health examinations in the Department of Community Medicine, Landseed Hospital, Tao-Yuan, Taiwan annually for 5 consecutive years between 2007 and 2011. These subjects were known as the ‘Landseed Cohort’. For sample consistency and data integrity, only those who completed at least three health examinations in the 5-year period were included in the study. In addition, to understand the causality between metabolic components and MetS, subjects that were diagnosed with MetS at the first health examination were excluded from the study.

This study was approved by the Institutional Review Board of Landseed Hospital (no. LHIRB 15-003-B1). All subjects provided their written informed consent.

**Measures**

**Metabolic syndrome.** This study set the onset of MetS as the outcome. MetS was diagnosed according to the NCEP-ATP III criteria. However, in light of the differences between ethnicity, Taiwan’s National Health Agency engaged World Health Organization Expert Consultation in 2004 and proposed a revision of the waist standard, under which male and female waist circumferences needed to be ≥90 cm and ≥80 cm, respectively. The revised criteria were in line with those of International Diabetes Federation (IDF) recommended for Chinese ethnicity. Nevertheless, unlike the IDF criteria making waist the central and essential component, a subject was defined as having MetS with the presence of three or more of the following five components in this study: (i) raised TG (>110 mg/dl); (ii) reduced HDL-C (<40 mg/dl in males and <50 mg/dl in females); (iii) raised blood pressure (systolic blood pressure [SBP] ≥130 mmHg or diastolic blood pressure [DBP] ≥85 mmHg); (iv) raised FG (>100 mg/dl); (v) central obesity (waist circumference ≥90 cm in males and ≥80 cm in females).

**Potential predictors of MetS.** Each ‘Landseed Cohort’ subject underwent general physical examinations during the health examinations and blood and urine samples were collected for biochemical tests. A total of 31 markers were examined in this study. General examinations included height (cm), weight (kg), body fat (%), BMI (kg/m²), waist circumference (cm), hip circumference (cm), SBP (mm/Hg), DBP (mm/Hg) and bone mineral density (BMD). Urine tests included total protein (g/dl) and pH value. Blood tests included white blood cell count (WBC, 10⁶/mm³), red blood cell count (RBC, 10⁶/mm³), platelet count (*1000/μl), haemoglobin (Hb, pg),
haematocrit (HCT, %), mean corpuscular haemoglobin (MCH, pg), mean corpuscular-haemoglobin concentration (MCHC, %) and mean corpuscular volume (MCV, fl). Biochemical tests included FG (mg/dl), albumin (g/dl), globulin (g/dl), blood urea nitrogen (BUN, mg/dl), creatinine (mg/dl), UA (mg/dl), cholesterol (mg/dl), TG (mg/dl), HD-C (mg/dl), LDL-C (mg/dl), GOT (IU/l) and GPT (IU/l). Among them, BMI, SBP, DBP, TG, HDL-C and FG were selected according to MetS definition.1,23 The others were included based on previous studies such as BMD,24 WBC,25 Hb,26 HCT,27 UA,8,9 LDL-C4 and GPT.6,7 As each subject had at least three health examinations, this study used the marker data from the first examination for this analysis.

**Statistical analyses**

All statistical analyses were performed using the SAS® statistical package, version 9.4 (SAS Institute, Cary, NC, USA) for Windows®. Sociodemographic characteristics between subject groups with and without MetS were compared using \( \chi^2 \)-test. To evaluate the effects of different markers on MetS, Student’s \( t \)-test was applied to compare the differences in markers between subject groups with and without MetS. A \( P \)-value < 0.05 was considered statistically significant. Cohen’s \( d \) was used to evaluate the effect size (ES). The metabolic components selected based on ES were then divided into two groups: ‘normal’ and ‘abnormal’, according to general clinical standards. Multiple Poisson regression was applied, with the basic demographic variables as the control variables to evaluate the adjusted relative risk (ARR) of each metabolic component for MetS. The risk score (RS) of each metabolic component was then calculated based on their ARR. The RS was defined as 2, 3, 4 or 5 when the ARR fell between 1 and 2, 2 and 4, 4 and 15, or was >15, respectively.

To identify the best-fit model for predicting MetS using metabolic components, the present study proposed several potential combinations of metabolic components and retrieved the sum RS after summing the RSs of metabolic components in different combinations. The sum RS was then used to predict the future development of MetS. Model validation was performed using ROC curves and the applied area under the curve (AUC) was used as the indicator for model fitness, where a higher AUC indicated a better model.

**Results**

This longitudinal cohort study randomly selected 15,000 subjects aged ≥30 years from the 198,375 residents who registered their household in Pingzhen District, Taoyuan City, Taiwan and invited them for free health examinations annually for 5 consecutive years between 2007 and 2011. The ‘Landseed Cohort’ totalled 5,757 individuals from the 15,000 invited subjects. For sample consistency and data integrity, only those who completed at least three health examinations in the 5-year period (\( n = 3,644 \)) were included in the study. In addition, to understand the causality between metabolic components and MetS, subjects who were diagnosed with MetS at the first health examination (\( n = 276 \)) were excluded from the study. A total of 3,368 subjects, with a mean age of 63.03 years for males and 59.21 years for females, were included in the follow-up analysis, of whom 409 developed MetS.

The 5-year cumulative incidence rate of MetS was 12.14% (409/3,368) in the present study. Subjects with MetS were slightly older (\( \chi^2 = 22.94; P < 0.001 \)), more highly educated (\( \chi^2 = 28.04; P < 0.001 \)) and had a greater personal income (\( \chi^2 = 9.99; P = 0.007 \)) than those without MetS.
Males were more likely to have MetS than females ($\chi^2 = 9.18; P = 0.001$), but marital status was not associated with the occurrence of MetS.

The differences in all physical and biochemical variables between the MetS group and the non-MetS group are shown in Table 2. Of the 31 biomarkers included in the comparison, a total of 10 items had a medium effect size (i.e. Cohen’s $d \geq 0.5$). Among them, as weight and BMI were highly related markers, only BMI, which had a higher effect size, was included in the following analysis, even though both markers had reached or surpassed a medium effect size. Similarly, although hip circumference had a medium effect size, it was strongly related to waist circumference, so only waist circumference was included in the subsequent analysis. To better evaluate the effects of blood lipid and hepatic inflammatory markers, the analysis included cholesterol, LDL-C, GOT and GPT in further analyses, even though the four markers failed to attain a medium effect size. A total of 11 potential metabolic components were selected for further analysis.

According to the multiple Poisson regression model, all selected 11 metabolic components had significant effects on MetS (Table 3). The risk of developing MetS for subjects with central obesity was 20-times (ARR 19.60; 95% confidence interval [CI] 15.24, 25.22) greater than that for normal controls. Cholesterol had the smallest effect size, for which subjects with a higher cholesterol level were 1.35-times (ARR 1.35; 95% CI 1.13, 1.62) more likely to develop MetS than the normal controls. To balance the weights of each metabolic component,
Table 2. Distribution of physical and biochemical markers between subjects with and without metabolic syndrome.

| Biomarkers                                | Total sample $n = 3368$ | Metabolic syndrome | Metabolic syndrome $n = 409$ | No $n = 2959$ | Statistical significance | ES (d) |
|-------------------------------------------|-------------------------|--------------------|-------------------------------|--------------|--------------------------|--------|
|                            | Mean | SD    | Mean | SD    | Mean | SD    | t               |                           |            |
| Fasting glucose, mg/dl                  | 91.89 | 23.48 | 108.50 | 37.43 | 89.61 | 19.80 | 9.92 | $P < 0.0001$ | 0.51 |
| Creatinine, mg/dl                       | 0.97  | 0.39  | 1.05  | 0.40  | 0.96  | 0.39  | 4.61 | $P < 0.0001$ | 0.24 |
| Cholesterol, mg/dl                      | 200.37 | 35.86 | 206.10 | 39.48 | 199.60 | 35.27 | 3.16 | $P = 0.0017$ | 0.65 |
| Triglyceride, mg/dl                     | 126.22 | 108.53 | 231.10 | 183.30 | 111.70 | 83.90 | 12.99 | $P < 0.0001$ | 0.65 |
| High-density lipoprotein-cholesterol, mg/dl | 60.23 | 15.36 | 46.56  | 10.92 | 62.12  | 14.92 | -25.69 | $P < 0.0001$ | -1.42 |
| Low-density lipoprotein-cholesterol, mg/dl | 124.79 | 32.37 | 128.50 | 34.34 | 124.30 | 32.06 | 2.45 | $P = 0.0143$ | 0.12 |
| Systolic blood pressure, mm/Hg           | 123.57 | 19.13 | 136.50 | 18.81 | 120.30 | 17.79 | 15.87 | $P < 0.0001$ | 0.86 |
| Diastolic blood pressure, mm/Hg          | 75.03  | 11.68 | 83.17  | 12.04 | 73.01  | 10.67 | 15.20 | $P < 0.0001$ | 0.84 |
| Height, cm                               | 159.44 | 8.09  | 158.90 | 8.15  | 159.50 | 8.08  | -0.90 | NS           | -0.07 |
| Weight, kg                               | 61.19  | 15.78 | 67.09  | 11.42 | 60.65  | 16.02 | 6.21 | $P < 0.0001$ | 0.56 |
| Body mass index, kg/m²                   | 24.01  | 5.96  | 26.49  | 3.36  | 23.79  | 6.10  | 8.45 | $P < 0.0001$ | 0.80 |
| Waist circumference, cm                  | 80.75  | 10.41 | 90.22  | 8.39  | 78.41  | 9.49  | 24.09 | $P < 0.0001$ | 1.41 |
| Hip circumference, cm                    | 94.32  | 6.61  | 97.88  | 7.02  | 93.99  | 6.48  | 6.84 | $P < 0.0001$ | 0.55 |
| Body fat, %                              | 27.78  | 7.46  | 31.05  | 7.62  | 27.48  | 7.38  | 5.48 | $P < 0.0001$ | 0.47 |
| Haemoglobin, pg                          | 14.06  | 1.60  | 14.33  | 1.63  | 14.02  | 1.59  | 3.75 | $P = 0.0002$ | 0.19 |
| Haematocrit, %                           | 42.54  | 4.09  | 43.06  | 4.20  | 42.47  | 4.07  | 2.75 | $P = 0.0061$ | 0.14 |
| Mean corpuscular volume, fl              | 89.63  | 7.50  | 89.35  | 7.16  | 89.67  | 7.55  | -0.80 | NS           | -0.04 |
| Red blood cells, 10⁶/mm³                  | 4.77   | 0.54  | 4.84   | 0.54  | 4.76   | 0.54  | 2.78 | $P = 0.0054$ | 0.15 |
| White blood cells, 10⁶/mm³                | 5.84   | 1.60  | 6.36   | 1.66  | 5.77   | 1.57  | 7.04 | $P < 0.0001$ | 0.36 |
| Mean corpuscular haemoglobin, pg         | 29.62  | 2.97  | 29.74  | 2.86  | 29.60  | 2.99  | 0.90 | NS           | 0.05 |
| Mean corpuscular-haemoglobin concentration, % | 32.99 | 1.14  | 33.24  | 1.17  | 32.96  | 1.13  | 4.69 | $P < 0.0001$ | 0.24 |
| Platelets, *10⁶/μl                       | 248.52 | 59.81 | 246.50 | 63.20 | 248.80 | 59.33 | -0.74 | NS           | -0.04 |

(continued)
| Biomarkers                                      | Total sample n = 3368 | Metabolic syndrome n = 409 | No n = 2959 | t   | Statistical significance | ES (d) |
|------------------------------------------------|------------------------|----------------------------|-------------|-----|--------------------------|--------|
|                                                | Mean   | SD   | Mean   | SD   | Mean   | SD   |             |               |
| Blood urea nitrogen, mg/dl                     | 14.92  | 4.82 | 16.30  | 6.53 | 14.73  | 4.50 | 4.70        | P < 0.0001    | 0.24        |
| Uric acid, mg/dl                              | 5.68   | 1.51 | 6.45   | 1.55 | 5.57   | 1.48 | 11.16       | P < 0.0001    | 0.57        |
| Total protein, g/dl                           | 7.54   | 0.41 | 7.62   | 0.41 | 7.53   | 0.41 | 3.88        | P = 0.0001    | 0.22        |
| Albumin, g/dl                                 | 4.49   | 0.26 | 4.52   | 0.25 | 4.48   | 0.26 | 2.37        | P = 0.0176    | 0.16        |
| Globulin, g/dl                                | 3.06   | 0.36 | 3.10   | 0.38 | 3.05   | 0.36 | 2.74        | P = 0.0062    | 0.13        |
| Glutamic-oxaloacetic transaminase, IU/l       | 24.19  | 12.38| 27.70  | 17.36| 23.71  | 11.44| 4.51        | P < 0.0001    | 0.23        |
| Glutamic-pyruvic transaminase, IU/l           | 25.56  | 19.79| 33.22  | 23.30| 24.50  | 19.01| 7.24        | P < 0.0001    | 0.37        |
| pH value                                       | 6.00   | 0.82 | 5.84   | 0.73 | 6.02   | 0.83 | -4.72       | P < 0.0001    | -0.25       |
| Bone mineral density                          | -0.76  | 1.03 | -0.84  | 1.16 | -0.75  | 1.02 | -0.93       | NS            | -0.08       |

Student’s t-test was applied to compare the differences in markers between subject groups with and without MetS; NS, no significant between-group difference (P ≥ 0.05). ES, effect size: d = 0.2 refers to a small effect size; d = 0.5 refers to a medium effect size; and d = 0.8 refers to a large effect size.
Table 3. Adjusted relative risk (ARR) and risk score (RS) of selected metabolic components for metabolic syndrome according to the multiple Poisson regression model.

| Selected metabolic components | Total sample | Metabolic syndrome | 95% confidence interval | RS |
|------------------------------|--------------|--------------------|-------------------------|----|
|                              | $n = 3368$   | Yes $n = 409$      | No $n = 2959$           |    |
| Waist circumference, cm      |              |                    |                         |    |
| Abnormal (male ≥ 90; female ≥ 80) | 450 13.36  | 344 84.11          | 106 3.58                | 19.60 15.24 25.22 5 |
| Normal (male < 90; female < 80) | 2918 86.64  | 65 15.89           | 2853 96.42              | 1.00 1          |
| Body mass index, kg/m²       |              |                    |                         |    |
| Abnormal (≥ 24)              | 773 22.95   | 334 81.66          | 439 14.84               | 10.58 8.33 13.43 4 |
| Normal (<24)                 | 2595 77.05  | 75 18.34           | 2520 85.16              | 1.00 1          |
| Triglyceride, mg/dl          |              |                    |                         |    |
| Abnormal (≥ 150)             | 723 21.47   | 317 77.51          | 406 13.72               | 10.22 8.22 12.72 4 |
| Normal (<150)                | 2645 78.53  | 92 22.49           | 2553 86.28              | 1.00 1          |
| Blood pressure, mmHg         |              |                    |                         |    |
| Abnormal (SBP ≥ 130; DBP ≥ 85) | 193 5.73    | 190 46.45          | 3 0.10                  | 7.46 6.36 8.75 4 |
| Normal (SBP < 130; DBP < 85) | 3175 94.27  | 219 53.55          | 2956 99.90              | 1.00 1          |
| High-density lipoprotein     |              |                    |                         |    |
| cholesterol, mg/dl           |              |                    |                         |    |
| Abnormal (male < 40; female < 50) | 323 9.59    | 122 29.83          | 201 6.79                | 3.74 3.12 4.47 3 |
| Normal (male ≥ 40; female ≥ 50) | 3045 90.41  | 287 70.17          | 2758 93.21              | 1.00 1          |
| Fasting glucose, mg/dl       |              |                    |                         |    |
| Abnormal (≥ 100)             | 506 15.02   | 117 28.61          | 389 13.15               | 2.46 2.04 2.98 3 |
| Normal (<100)                | 2862 84.98  | 292 71.39          | 2570 86.85              | 1.00 1          |

(continued)
Table 3. Continued.

| Selected metabolic components | Total sample | Metabolic syndrome |
|------------------------------|--------------|--------------------|
|                              | n = 3368     | Yes n = 409        | No n = 2959        |
| Uric acid, mg/dl             |              |                    |
| Abnormal (male ≥7; female ≥6) | 863 25.62    | 188 45.97          | 675 22.81          |
| Normal (male <7; female <6)  | 2505 74.38   | 221 54.03          | 2284 77.19         |
| Glutamic-pyruvic transaminase, IU/l | | | |
| Abnormal (>40)               | 366 10.87    | 94 22.98           | 272 9.19           |
| Normal (≤40)                 | 3002 89.13   | 315 77.02          | 2687 90.81         |
| Glutamic-oxaloacetic transaminase, IU/l | | | |
| Abnormal (>40)               | 168 4.99     | 46 11.25           | 122 4.12           |
| Normal (≤40)                 | 3200 95.01   | 363 88.75          | 2837 95.88         |
| Low-density lipoprotein cholesterol, mg/dl | | | |
| Abnormal (>130)              | 1363 40.47   | 197 48.17          | 1166 39.41         |
| Normal (≤130)                | 2005 59.53   | 212 51.83          | 1793 60.59         |
| Cholesterol, mg/dl           |              |                    |
| Abnormal (>200)              | 1579 46.88   | 223 54.52          | 1356 45.83         |
| Normal (≤200)                | 1789 53.12   | 186 45.48          | 1603 54.17         |

ARR: Adjusted risk ratio; 95% confidence interval; RS: Risk score.
the RSs were calculated based on the ARR values and recorded as 2, 3, 4 or 5 when the ARR fell between 1 and 2, 2 and 4, 4 and 15, or was >15, respectively. Based on this rule, subjects with higher waist circumference values had their RS recorded as 5; those with higher BMI, TG and BP scored 4; those with abnormal HDL-C, FG, UA, GPT and GOT values had their RS recorded as 3; those with abnormal LDL-C and cholesterol scored 2; and those with normal values had their RS recorded as 1.

The ROC analysis using the selected 11 metabolic components to discriminate MetS showed that the discriminative validity of waist circumference was the highest, especially among women (AUC = 0.87; Table 4). TG, HDL-C, BMI, FG and BP also had good discriminative validity (AUC range, 0.74–0.85), whereas UA, GPT, GOT, cholesterol and LDL-C did not have good discriminative ability for MetS (AUC ≤ 0.71). This suggests that the five markers used as the current diagnostic criteria for MetS have the best discriminative ability of all metabolic components. BMI was not a match for waist circumference even though it showed good discriminative validity. In addition, according to the ROC analysis results in this current study, the optimal cut-off values of the current five markers were very close to the recommended values, and only the optimal cut-off value of HDL-C was lower than recommended.

To identify the best metabolic component combinations, this study used the current five-marker system as the basis and added one metabolic component at a time to form six combinations of six metabolic components each. After summing the RS of each metabolic component, a ROC analysis for MetS was performed and the results were compared with the current five-marker system. These current results showed that although the six combinations of six components all had good discriminative validity (AUC range, 0.967–0.976), they were still not as effective as the current five-marker system (AUC = 0.977; Table 5).

### Table 4. Receiver operating characteristic curve analysis of selected metabolic components for metabolic syndrome.

| Selected metabolic components                                      | Area under the curve | Optimal cut-off point |
|--------------------------------------------------------------------|-----------------------|-----------------------|
| Waist circumference, cm³                                          |                       |                       |
| Female                                                             | 0.87                  | 79.49                 |
| Male                                                               | 0.84                  | 89.48                 |
| Triglyceride, mg/dlap                                            | 0.85                  | 150.35                |
| High-density lipoprotein cholesterol, mg/dlap                    |                       |                       |
| Female                                                             | 0.85                  | 29.05                 |
| Male                                                               | 0.80                  | 23.63                 |
| Body mass index, kg/m²                                            | 0.80                  | 25.07                 |
| Fasting glucose, mg/dlap                                          | 0.76                  | 100.10                |
| Blood pressure, mmHg³                                            |                       |                       |
| Systolic                                                           | 0.75                  | 127.97                |
| Diastolic                                                          | 0.74                  | 85.02                 |
| Uric acid, mg/dl                                                  |                       |                       |
| Female                                                             | 0.71                  | 5.30                  |
| Male                                                               | 0.63                  | 6.90                  |
| Glutamic-pyruvic transaminase, IU/l                               | 0.66                  | 26.00                 |
| Glutamic-oxaloacetic transaminase, IU/l                           | 0.59                  | 27.04                 |
| Cholesterol, mg/dl                                                | 0.55                  | 225.96                |
| Low-density lipoprotein cholesterol, mg/dl                        | 0.54                  | 133.95                |

*Current metabolic component used for diagnosing metabolic syndrome.
Even by including all 11 metabolic components into the analysis (AUC = 0.954), the results were not as effective as the current five-marker system or the six-marker combinations. Replacing waist circumference with BMI resulted in a drop in discriminative validity compared with the existing five-marker system (AUC = 0.950).

**Discussion**

Unlike some cross-sectional studies based on undiagnosed MetS data that could only provide temporal relationships, this current study adopted a longitudinal approach to examine the discriminative ability of 11 physical and biochemical metabolic markers selected from a variety of potential components for the development of MetS, based on their associated RSs using a ROC curve analysis in a 5-year follow-up community cohort study. Although several studies in the Han Chinese population have used a similar design as the present study, they mainly focused on middle-to-upper class people living in urban areas whose findings may not be representative of the general population. These previous studies also examined the relationship between MetS and single or few biomarkers, without taking current diagnostic components into account. Not adjusting for the five diagnostic components results in a failure to further understand the contribution of individual markers in discriminating MetS in addition to the diagnostic criteria. Moreover, the relationships between study markers and MetS were more likely to be confounded by the diagnostic components.

Using the five markers used for current MetS diagnosis as the basis, the present study added one of six other metabolic markers (BMI, UA, GPT, GOT, cholesterol and LDL-C) to the diagnosis and found no increase in discriminative ability compared with the original five-marker system. Moreover, by replacing waist circumference with BMI, the current results showed that the predictability of waist circumference was greater. These current results suggest that despite the association between many physical and biochemical markers and MetS, the current five-marker diagnostic

---

**Table 5.** Receiver operating characteristic curve analysis of metabolic syndrome by using the sum of risk scores of combinations of selected metabolic components.

| Combinations of selected metabolic components | Area under the curve | Optimal cut-off point | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|-----------------------------------------------|----------------------|-----------------------|-------------|-------------|--------------------------|---------------------------|
| Current five items*                           | 0.977                | 11.000                | 0.917       | 0.931       | 0.68                     | 0.99                      |
| Current five items with waist circumference replaced by BMI | 0.950                | 10.000                | 0.927       | 0.846       | 0.49                     | 0.99                      |
| Current five items plus GOT                   | 0.976                | 12.000                | 0.926       | 0.925       | 0.66                     | 0.99                      |
| Current five items plus GPT                   | 0.975                | 12.000                | 0.936       | 0.918       | 0.65                     | 0.99                      |
| Current five items plus cholesterol           | 0.975                | 12.000                | 0.941       | 0.901       | 0.60                     | 0.99                      |
| Current five items plus LDL-C                 | 0.974                | 12.000                | 0.932       | 0.905       | 0.61                     | 0.99                      |
| Current five items plus UA                    | 0.969                | 12.000                | 0.936       | 0.889       | 0.57                     | 0.99                      |
| Current five items plus BMI                   | 0.967                | 12.001                | 0.946       | 0.843       | 0.49                     | 0.99                      |
| All 11 items                                  | 0.954                | 19.999                | 0.903       | 0.861       | 0.51                     | 0.98                      |

*Including waist circumference, triglyceride, high-density lipoprotein cholesterol, fasting glucose and blood pressure. BMI, body mass index; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; LDL-C, low-density lipoprotein cholesterol; UA, uric acid.
system still represents the best combination for predicting the disease, and that adding other elements to the current diagnosis was unnecessary. This was particularly true for markers like UA, liver function markers (GPT and GOT) and other blood lipid markers (cholesterol and LDL-C).

It is worth noting that the optimal cut-off values obtained in this current study via the ROC curve analysis of the five markers used for current MetS diagnosis were consistent with the ATP III or IDF criteria. The consistent optimal cut-off values and high AUC demonstrated the suitability and good discriminative ability of waist circumference, TG, BP, HDL-C and FG for MetS diagnosis. Only the optimal cut-off value of HDL-C (female ≥29 mg/dl; male ≥24 mg/dl) was lower than the current clinical standard (female ≥50 mg/dl; male ≥40 mg/dl). What accounts for the lower optimal cut-off value for HDL-C in this current study compared with the current clinical standard might be the older age of the Landseed Cohort (mean of 63.03 years for males; mean of 59.21 years for females). Mean HDL-C levels decrease with increasing age and the role played by HDL-C in cardiovascular protection is, to a great extent, regulated by TG and LDL-C. As a result, in this current study, HDL-C levels needed to reduce to a relatively low level to show a negative effect on MetS in this older aged sample. However, this hypothesis requires further validation through future studies as no similar finding has been reported in previously published research.

In addition, the present study replaced waist circumference with BMI as the MetS diagnostic criteria and found that whether compared against each other or evaluated by combining the other four markers, the ROC curve analysis results all showed that waist circumference had a higher discriminative ability for MetS than BMI. This result was consistent with some of the previous studies conducted using ROC curve analysis, which have demonstrated that the predictability of waist circumference is superior to BMI concerning CVD-related outcomes. For example, the Third National Health and Nutrition Examination Survey in the United States indicated that waist circumference surpassed BMI in predicting risk aspects of CVDs. A previous study demonstrated that compared with BMI, central obesity (waist circumference) was a better discriminative marker for predicting hypertension, type 2 diabetes, and dyslipidaemia.

A limitation of this study was the relatively old age of the sample, thus the study cohort differed from the demographic structure of the general population. As a result, the effects of different markers on MetS might be impacted. As this study used follow-up survey data from a single community, the generalizability of its results would require further validation by future studies.

In conclusion, considering the above limitation, this study confirmed that the current five-marker system has the best discriminative validity for MetS diagnosis, and although other physical and biochemical markers were likely capable of predicting MetS, their discriminative ability as diagnostic criteria is limited.

Acknowledgements
The authors are indebted to all the participants for their dedicated collaboration.

Declaration of conflicting interest
The authors declare that there are no conflicts of interest.

Funding
This work was supported by the collaborative projects between Chung Shan Medical University and Landseed Hospital (CSMU-LSH-103-01).
ORCID iD
Hao-Jan Yang http://orcid.org/0000-0002-9565-0799

References
1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.
2. McCracken E, Monaghan M and Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol 2018; 36: 14–20.
3. Suchday S, Bellehsen M, Friedberg JP, et al. Clustering of cardiac risk factors associated with the metabolic syndrome and associations with psychosocial distress in a young Asian Indian population. J Behav Med 2014; 37: 725–735.
4. Torres do Rego A, Perez de Isla PL, Saltijeral Cerezo A, et al. Cholesterol control according to the presence of metabolic syndrome in coronary and diabetic patients. Relationship with non-alcoholic fatty liver disease. Eur J Intern Med 2014; 25: 438–443.
5. Kawamoto R, Tabara Y, Kohara K, et al. Relationships between lipid profiles and metabolic syndrome, insulin resistance and serum high molecular adiponectin in Japanese community-dwelling adults. Lipids Health Dis 2011; 10: 79.
6. Angelico F, Del Ben M, Conti R, et al. Insulin resistance, the metabolic syndrome, and nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2005; 90: 1578–1582.
7. Abe Y, Kikuchi T, Nagasaki K, et al. Usefulness of GPT for diagnosis of metabolic syndrome in obese Japanese children. J Atheroscler Thromb 2009; 16: 902–909.
8. Onat A, Uyarel H, Hergenc G, et al. Serum uric acid is a determinant of metabolic syndrome in a population-based study. Am J Hypertens 2006; 19: 1055–1062.
9. Reimann M, Schutte AE, Malan L, et al. Hyperuricaemia is an independent factor for the metabolic syndrome in a sub-Saharan African population: a factor analysis. Atherosclerosis 2008; 197: 638–645.
10. Choi HK and Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007; 120: 442–447.
11. Rho YH, Woo JH, Choi SJ, et al. Association between serum uric acid and the Adult Treatment Panel III-defined metabolic syndrome: results from a single hospital database. Metabolism 2008; 57: 71–76.
12. Sun D, Li S, Zhang X, et al. Uric acid is associated with metabolic syndrome in children and adults in a community: the Bogalusa Heart Study. PLoS One 2014; 9: e89696.
13. Chen D, Zhang H, Gao Y, et al. Cross-sectional and longitudinal associations between serum uric acid and metabolic syndrome: results from Fangchenggang Area Male Health and Examination Survey in China. Clin Chim Acta 2015; 446: 226–230.
14. Hu G, Qiao Q, Tuomilehto J, et al. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004; 164: 1066–1076.
15. Lippi G, Montagnana M, Franchini M, et al. The paradoxical relationship between serum uric acid and cardiovascular disease. Clin Chim Acta 2008; 392: 1–7.
16. Feig DI, Kang DH and Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008; 359: 1811–1821.
17. Oda E. Uric acid lowering therapy for prevention of cardiovascular disease requires further evidence to be validated. J Lab Precis Med 2017; 2: 66.
18. Cheong KC, Ghazali SM, Hock LK, et al. The discriminative ability of waist circumference, body mass index and waist-to-hip ratio in identifying metabolic syndrome: variations by age, sex and race. Diabetes Metab Syndr 2015; 9: 74–78.
19. Satoh H, Kishi R and Tsutsui H. Body mass index can similarly predict the presence of multiple cardiovascular risk factors in
middle-aged Japanese subjects as waist circumference. *Intern Med* 2010; 49: 977–982.

20. Sung KC, Ryu S and Reaven GM. Relationship between obesity and several cardiovascular disease risk factors in apparently healthy Korean individuals: comparison of body mass index and waist circumference. *Metabolism* 2007; 56: 297–303.

21. Lindström J and Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care* 2003; 26: 725–731.

22. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157–163.

23. International Diabetes Federation. *The IDF consensus worldwide definition of the metabolic syndrome*. Brussels, Belgium: IDF Communications, 2016, pp.10–11.

24. Bilić-Čurčić I, Makarović S, Mihaljević I, et al. Bone mineral density in relation to metabolic syndrome components in post-menopausal women with diabetes mellitus type 2. *Acta Clin Croat* 2017; 56: 58–63.

25. Meng W, Zhang C, Zhang Q, et al. Association between leukocyte and metabolic syndrome in urban Han Chinese: a longitudinal cohort study. *PLoS One* 2012; 7: e49875.

26. Wu S, Lin H, Zhang C, et al. Association between erythrocyte parameters and metabolic syndrome in urban Han Chinese: a longitudinal cohort study. *BMC Public Health* 2013; 13: 989.

27. Lohsoonthorn V, Jiamjarasrungsi W and Williams MA. Association of hematological parameters with clustered components of metabolic syndrome among professional and office workers in Bangkok, Thailand. *Diabetes Metab Syndr* 2007; 1: 143–149.

28. Mohan V, Sandeep S, Deepa M, et al. A diabetes risk score helps identify metabolic syndrome and cardiovascular risk in Indians - the Chennai Urban Rural Epidemiology Study (CURES-38). *Diabetes Obes Metab* 2007; 9: 337–343.

29. Lin JW, Chang YC, Li HY, et al. Cross-sectional validation of diabetes risk scores for predicting diabetes, metabolic syndrome, and chronic kidney disease in Taiwanese. *Diabetes Care* 2009; 32: 2294–2296.

30. Zhang W, Chen Q, Yuan Z, et al. A routine biomarker-based risk prediction model for metabolic syndrome in urban Han Chinese population. *BMC Public Health* 2015; 15: 64.

31. Ferrara A, Barrett-Connor E and Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984–1994. *Circulation* 1997; 96: 37–43.

32. Wilson PW, Anderson KM, Harris T, et al. Determinants of change in total cholesterol and HDL-C with age: the Framingham study. *J Gerontol* 1994; 49: M252–M257.

33. Bartlett J, Predazzi IM, Williams SM, et al. Isolated Low High-Density Lipoprotein Cholesterol a Cardiovascular Disease Risk Factor? New Insights From the Framingham Offspring Study. *Circ Cardiovasc Qual Outcomes* 2016; 9: 206–212.

34. März W, Kleber ME, Scharnagl H, et al. HDL cholesterol: reappraisal of its clinical relevance. *Clin Res Cardiol* 2017; 106: 663–675.

35. Welty FK. How do elevated triglycerides and low LDL-cholesterol affect inflammation and atherothrombosis? *Curr Cardiol Rep* 2013; 15: 400.

36. Janssen I, Katzmarzyk PT and Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; 79: 379–384.

37. Zhu S, Heymsfield SB, Toyoshima H, et al. Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors. *Am J Clin Nutr* 2005; 81: 409–415.

38. Lee CM, Huxley RR, Wildman RP, et al. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol* 2008; 61: 646–653.