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The new definition of metabolic syndrome including hyperuricemia improves its prognostic value: results from NHANES database

Zhichao Zhang^{1†}, Yuanxin Pang^{2†}, Jun Shen³, Weihai Chen³, ChuanZhen Hao^{4*} and Zhijun Lei^{5*}

Abstract

Background Metabolic syndrome (MetS) is a significant global health issue that is strongly associated with an increased risk of cardiovascular disease (CVD). While MetS was initially proposed to identify more high-risk individuals and facilitate early management, hyperuricemia has not yet been included in its definition, despite its strong association with MetS. This study aims to explore the prognostic value of incorporating hyperuricemia into the definition of MetS.

Methods Data derived from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2018 were analyzed. The old version of MetS (MetS_{old}) aligned with NCEP-ATP III criteria, whereas the new version of MetS (MetS_{new}) included hyperuricemia as a sixth criterion. Baseline characteristics were compared between participants with and without MetS, and outcomes were assessed by multivariate analyses.

Results Among the 36,363 participants analyzed, 12,594 (34.6%) and 14,137 (38.9%) met MetS_{old} and MetS_{new} criteria respectively. Compared to MetS_{old}, MetS_{new} identified additional 1534 (4.24%) participants at metabolic risk. Both MetS_{old} and MetS_{new} were significantly associated with long-term all-cause and CVD mortality (all $P < 0.001$). Furthermore, the additional participants identified by MetS_{new} exhibited a similar risk of all-cause and CVD mortality as those meeting MetS_{old} criteria. MetS_{new} demonstrated enhanced identification and reclassification abilities compared to MetS_{old}, as evidenced by improvement in C-index, NRI and IDI.

Conclusions The inclusion of hyperuricemia in the MetS criteria could identify a larger proportion of individuals at metabolic risk, thereby facilitating early management to prevent long-term adverse events.

Keywords Metabolic syndrome, Hyperuricemia, Prognostic value, Mortality

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Introduction

Metabolic syndrome (MetS) is characterized by abdominal obesity, insulin resistance, hypertension, dysglycemia, and dyslipidemia [1]. It remains a significant global health issue and is associated with an increased risk of several chronic diseases, such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and certain malignant tumor [2–4]. Individuals with MetS share a 1.5-fold increased risk of CVD mortality compared to those without the syndrome [3]. The main mechanisms of MetS are insulin resistance and visceral adiposity [5]. The concept of MetS was firstly proposed in 1998 [6], aiming at identifying individuals at enhanced risk of CVD and mortality, thereby initiating early management to prevent adverse outcomes [7].

CVD is considered the leading cause of death all over the world, and an increasing number of risk factors have been identified as associated with CVD [8]. Among these factors, hyperuricemia, which indicates elevated levels of end-product of purine metabolism, has been linked to the incidence of gout and kidney stones. Furthermore, numerous clinical studies have demonstrated a significant association between increased serum uric acid levels and the incidence of T2DM [9, 10], hypertension [11, 12], heart failure [13, 14] and coronary artery disease [15, 16]. Both clinical and preclinical data suggest that hyperuricemia is related to insulin resistance [17, 18], a core mechanism of MetS. Additionally, a bidirectional relationship has been observed between MetS and hyperuricemia [19]. Despite the strong correlation between hyperuricemia and MetS, the former has not been included in the criteria for MetS, and few studies have reported the exact correlation between them as a whole and CVD. Accordingly, the present study, based on the National Health and Nutrition Examination Survey (NHANES) database (1999–2018), aims to investigate whether the inclusion of hyperuricemia into the definition of MetS could improve its ability to predict long-term prognosis.

Materials and methods

Study population

The present study was a prospective cohort study based on participants from the NHANES (1999–2018) database. Briefly, the NHANES is a cross-sectional survey designed to evaluate the health and nutrition status in the United States. In total, 97,446 participants were enrolled in NHANES during this period, and parameters for MetS and hyperuricemia were screened. The following participants were excluded: (1) age < 18 years old ($n = 40,432$); (2) lack of waist circumference data ($n = 5,798$); (3) lack of blood pressure ($n = 12,684$); (4) lack of high-density lipoprotein cholesterol (HDL-C) data ($n = 1,965$); (5) lack of triglyceride data ($n = 68$); (6) lack of blood glycemia information ($n = 70$); (7) lack of uric acid data ($n = 13$); and (8)

absence of follow-up information ($n = 53$). Ultimately, a total of 36,363 participants were remained in the final analysis, as illustrated in Fig. 1. Data on demographic variables (age, sex, race, body mass index (BMI), waist circumference), medical history (hypertension, DM and smoking status), and laboratory variables (fasting glucose, glycosylated hemoglobin (HbA1c), total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), HDL-C, serum creatinine (Scr) and uric acid) were collected.

Definitions

In the present study, hyperuricemia was defined as a uric acid level exceeding 7 mg/dl in males and 6 mg/dl in females [20]. According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria [21], the old version of MetS (MetS_{old}) was established when individuals presented with at least 3 of the followings: (1) waist circumference > 102 cm for males or > 88 cm for females; (2) blood pressure $\geq 130/85$ mmHg or the use of antihypertensive treatments; (3) fasting plasma glucose level ≥ 100 mg/dl; (4) fasting triglyceride level ≥ 150 mg/dl; (5) HDL-C level < 40 mg/dl for males or < 50 mg/dl for females. The new version of MetS (MetS_{new}) includes hyperuricemia as the sixth criterion. Participants meeting at least 3 of these six criteria were identified as having MetS_{new}.

Outcomes

The NHNAES database was linked to the death certificate records filed on the National Death Index (NDI). The data on mortality including the date and cause of death were extracted from the linked mortality files until December 31, 2019 (<https://www.cdc.gov/nchs/data-linkage/>). In the present study, the primary outcome was all-cause mortality, while the secondary outcome was CVD-mortality, defined as death resulting from heart diseases or cerebrovascular diseases.

Statistical analysis

Categorical data were presented as frequencies (percentages) and analyzed using chi-square test or Fisher's exact test. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of numerical variables. Normally distributed variables were summarized as mean \pm standard deviation (SD), with comparisons conducted by Student's *t*-test; Skewed variables were presented as median (25th–75th) and compared using the Mann-Whitney *U*-test. The event-free survival curves were plotted by Kaplan-Meier analysis and compared by log-rank test. Cox proportional model was employed to evaluate all-cause mortality, while competing risk analysis (Fine-Gray model) was utilized to assess CVD mortality. Multivariate analyses were conducted to adjust for

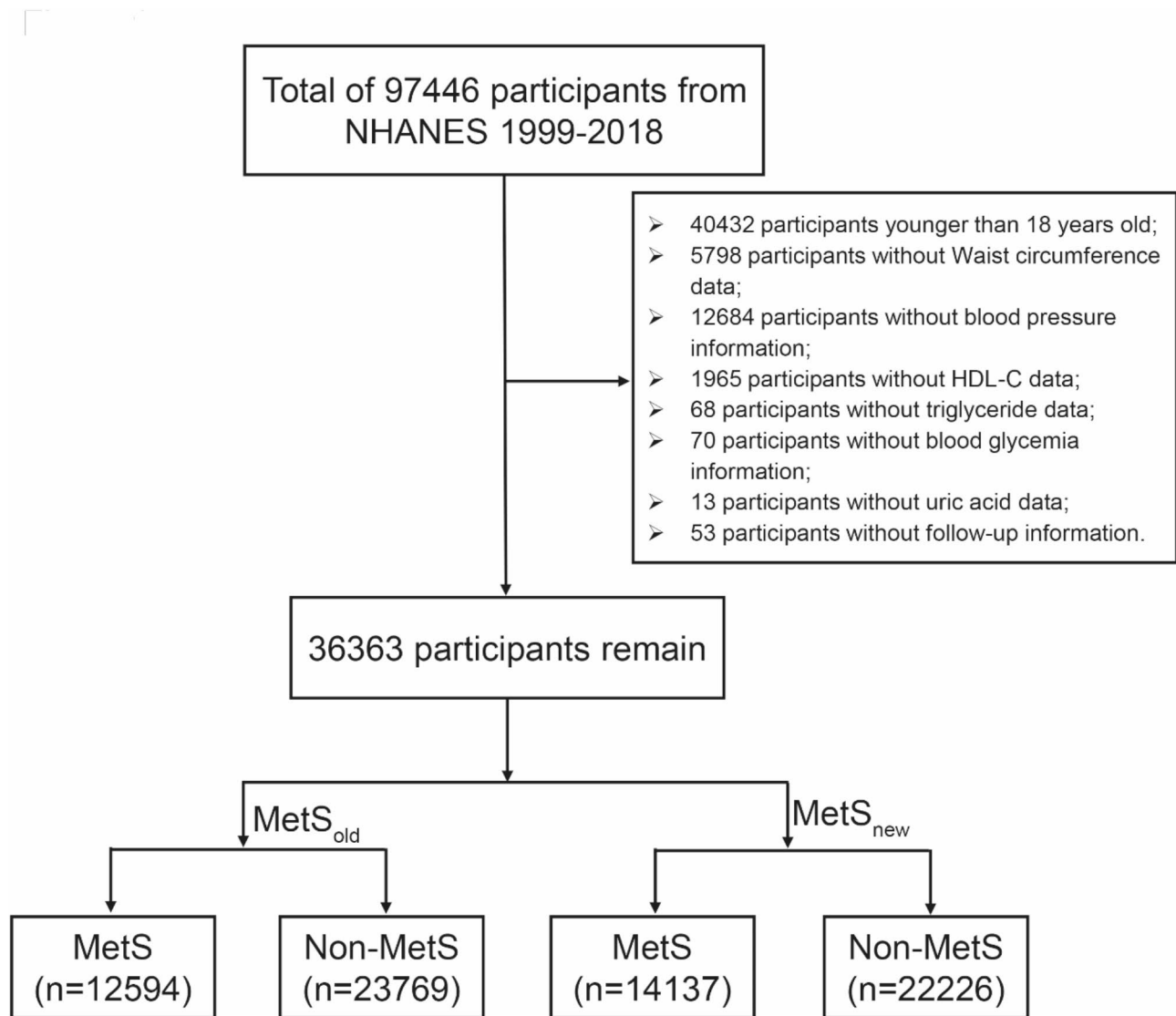


Fig. 1 The flow chart of the present study

Abbreviations: HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; MetS_{old}, the old version of MetS; MetS_{new}, the new version of MetS

confounding factors. **Model 1:** we adjusted for age, sex, race and current smoking status. **Model 2:** we adjusted for age, sex, race, current smoking status, BMI, LDL-C and Scr. Subgroup analysis were conducted to determine the association between hyperuricemia and outcomes across different components of MetS_{old}. We also calculated C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to clarify the identification and reclassification ability of MetS_{new} compared to MetS_{old}. A two-sided P value < 0.05 was thought to indicate a statistically significant difference. All data analyses were performed by R software (Version 4.0.5; R foundation for Statistical Computing Vienna, Austria).

Results

Comparison of the incidence of MetS

A total of 36,363 patients were enrolled in the present study, of whom 12,594 (34.6%) and 14,137 (38.9%) met the diagnostic criteria for MetS_{old} and MetS_{new}, respectively. MetS_{new}, which was more sensitive than MetS_{old}, identified an additional 1,543 (4.24%) participants having MetS. These individuals fulfilled only two out of five components of the MetS_{old}'s criteria. The baseline characteristics of participants stratified by MetS_{old} and MetS_{new} criteria were presented in Tables 1 and 2, respectively. Individuals with MetS_{old} or MetS_{new} tended to be older ($P < 0.001$) and had higher BMIs ($P < 0.001$) as well as waist circumferences ($P < 0.001$) than those without either condition. A higher proportion of these participants were female ($P < 0.001$), Non-Hispanic White or

Table 1 Baseline characteristics of participants stratified by MetSold

	MetS n = 12,594	Non-MetS n = 23,769	Pvalue
Age, years	57.0(43.0–68.0)	40.0(26.0–57.0)	< 0.001
Sex, male	5770(45.8%)	11,860(49.9%)	< 0.001
BMI, Kg/m ²	31.3(28.0–35.8)	25.7(22.7–29.3)	< 0.001
Waist circumference, cm	107.2(99.1–116.8)	91.0(81.7–100.3)	< 0.001
Race			< 0.001
Mexican American	2505(19.9%)	4196(17.7%)	
Other Hispanic	1057(8.4%)	1741(7.3%)	
Non-Hispanic White	5501(43.7%)	9829(41.4%)	
Non-Hispanic Black	2448(19.4%)	5282(22.2%)	
Other Race	1083(8.6%)	2721(11.4%)	
Current smoker	2380(18.9%)	4561(19.2%)	0.511
Hypertension	9961(79.1%)	7364(31.0%)	< 0.001
Diabetes mellitus	7951(63.1%)	2838(11.9%)	< 0.001
Hyperuricemia	3501(27.8%)	2785(11.7%)	< 0.001
Fasting glucose, mg/dl	103(91–121)	89(83–95)	< 0.001
HbA1c, %	5.8(5.4–6.4)	5.3(5.1–5.6)	< 0.001
Total cholesterol, mg/dl	196.8(169.0–227.0)	187.1(162.0–215.0)	< 0.001
Triglyceride, mg/dl	181.9(129.2–256.8)	93.9(66.9–130.9)	< 0.001
LDL-C, mg/dl	110.0(85.0–137.0)	108.0(87.0–132.0)	< 0.001
HDL-C, mg/dl	42.9(36.0–49.9)	54.9(46.0–66.1)	< 0.001
Scr, mg/dl	0.85(0.70–1.01)	0.80(0.70–1.00)	< 0.001
Uric acid, mg/dl	5.70(4.70–6.70)	5.09(4.20–6.00)	< 0.001

Abbreviations: MetS, metabolic syndrome; MetS_{old}, the old version of metabolic syndrome; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Scr, serum creatinine

Mexican American ($P < 0.001$). Additionally, higher levels of fasting glucose, total cholesterol, triglyceride, LDL-C, Scr, uric acid, but a lower level of HDL-C were observed in participants with MetS_{old} or MetS_{new} (all $P < 0.001$). Unsurprisingly, patients with MetS_{old} or MetS_{new} were more likely to have hypertension ($P < 0.001$), diabetes mellitus ($P < 0.001$) and hyperuricemia ($P < 0.001$). Notably, participants who satisfied MetS_{new} had a greater percentage of hyperuricemia compared with those who met MetS_{old} (35.7% vs. 27.8%).

The association and prognostic impact of hyperuricemia on MetS

Consistent with previous studies [22], our analysis demonstrated a strong relationship between hyperuricemia and MetS (Supplementary Fig. 1). Regarding the predictive value of hyperuricemia, we further examined the association between hyperuricemia and long-term outcomes across different subgroups based on the

Table 2 Baseline characteristics of participants stratified by MetSnew

	MetS n = 14,137	Non-MetS n = 22,226	Pvalue
Age, years	57.0(42.0–68.0)	39.0(26.0–56.0)	< 0.001
Sex, male	6665(47.1%)	10,965(49.3%)	< 0.001
BMI, Kg/m ²	31.2(27.8–35.7)	25.5(22.6–29.0)	< 0.001
Waist circumference, cm	107.2(99.1–116.8)	91.0(81.7–100.3)	< 0.001
Race			< 0.001
Mexican American	2691(19.0%)	4010(18.0%)	
Other Hispanic	1132(8.0%)	1666(7.5%)	
Non-Hispanic White	6163(43.6%)	9167(41.2%)	
Non-Hispanic Black	2892(20.5%)	4838(21.8%)	
Other Race	1259(8.9%)	2545(11.5%)	
Current smoker	2644(18.7%)	4297(19.3%)	0.139
Hypertension	10,938(77.4%)	6387(28.7%)	< 0.001
Diabetes mellitus	8277(58.5%)	2512(11.3%)	< 0.001
Hyperuricemia	5044(35.7%)	1242(5.59%)	< 0.001
Fasting glucose, mg/dl	101(90–118)	88(82–95)	< 0.001
HbA1c, %	5.7(5.4–6.3)	5.3(5.1–5.5)	< 0.001
Total cholesterol, mg/dl	196.8(169.5–227.0)	187.1(160.8–213.8)	< 0.001
Triglyceride, mg/dl	174.9(120.9–249.8)	92.9(65.9–127.9)	< 0.001
LDL-C, mg/dl	110.9(2.22–3.54)	107.1(86.0–131.8)	< 0.001
HDL-C, mg/dl	44.1(37.1–51.8)	54.9(46.0–66.1)	< 0.001
Scr, mg/dl	0.87(0.70–1.04)	0.80(0.70–0.98)	< 0.001
Uric acid, mg/dl	5.90(4.80–7.00)	4.90(4.10–5.80)	< 0.001

Abbreviations: MetS, metabolic syndrome; MetS_{new}, the new version of metabolic syndrome; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Scr, serum creatinine

components of MetS_{old} criteria (Fig. 2). As the number of MetS_{old} components increased, the forest plot illustrated a decreasing trend in the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. Notably, these associations became insignificant in subgroups with more than 3 components of MetS_{old}. We also observed a similar trend for CVD mortality. These results indicated that the prognostic value of hyperuricemia was mainly manifested in the early stages of MetS.

The association between MetS and long-term outcomes

Univariate and multivariate analyses were conducted to evaluate the risk of all-cause and CVD mortality. As demonstrated in Table 3; Fig. 3A–B, patients with MetS_{old} were significantly associated with an increased risk of all-cause mortality (Unadjusted HR:2.38, 95% CI:2.25–2.52, $P < 0.001$) and CVD mortality (Unadjusted HR:2.51, 95%CI:2.27–2.78, $P < 0.001$). Even after adjusting for confounding factors, the HRs and 95% CIs for all-cause (Adjusted HR:1.31, 95%CI:1.23–1.40, $P < 0.001$) and CVD

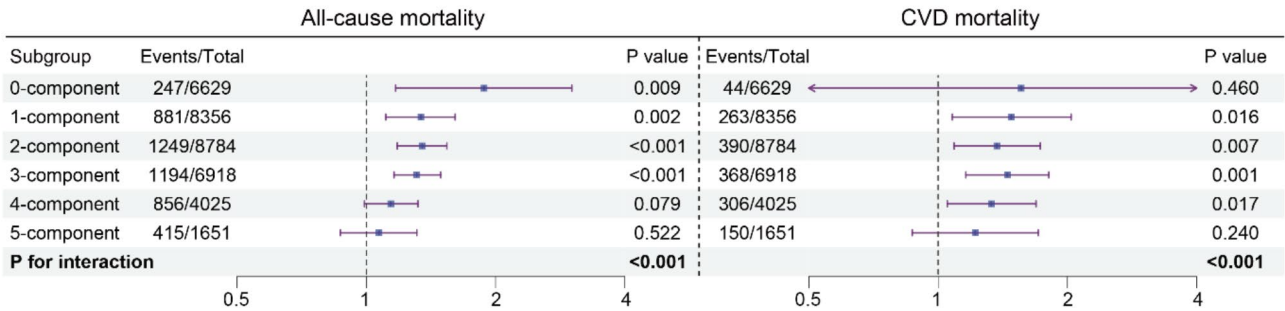


Fig. 2 The forest plot showed the HRs and 95% CIs of hyperuricemia for all-cause and CVD mortality in different components of MetS_{old}. Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; MetS_{old}, the old version of metabolic syndrome

Table 3 The association between long-term outcomes between MetS defined by MetSold and MetSnew

	Unadjusted		Adjusted for Model 1		Adjusted for Model 2	
	HR (95% CI)	Pvalue	HR (95% CI)	Pvalue	HR (95% CI)	Pvalue
MetS _{old}						
All-cause mortality	2.38(2.25–2.52)	<0.001	1.30(1.22–1.37)	<0.001	1.31(1.23–1.40)	<0.001
CVD mortality	2.51(2.27–2.78)	<0.001	1.39(1.26–1.54)	<0.001	1.28(1.15–1.44)	<0.001
MetS _{new}						
All-cause mortality	2.58(2.44–2.74)	<0.001	1.33(1.25–1.41)	<0.001	1.35(1.27–1.44)	<0.001
CVD mortality	2.81(2.53–3.11)	<0.001	1.47(1.32–1.63)	<0.001	1.36(1.21–1.53)	<0.001

Model 1: Adjusted for age, sex, race and current smoker;

Model 2: Adjusted for age, sex, race, current smoker, BMI, LDL-C and Scr;

Abbreviations: MetS, metabolic syndrome; MetS_{old}, the old version of MetS; MetS_{new}, the new version of MetS; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine

mortality (Adjusted HR:1.28, 95%CI:1.15–1.44, $P<0.001$) remained significant.

Similarly, when stratifying the patients by the definition of MetS_{new}, the risk of all-cause mortality (Adjusted HR:1.35, 95%CI:1.27–1.44, $P<0.001$) and CVD mortality (Adjusted HR:1.36, 95%CI:1.21–1.53, $P<0.001$) were significantly higher in participants with MetS_{new} compared to those without, after full multivariable adjustment (Tables 3and Fig. 3C-D).

Comparisons of prognostic value between MetSold and MetSnew

Among the 36,363 participants included in this study, 4,842(13.3%) and 1,521(4.18%) individuals experienced all-cause and CVD death, respectively. Regardless of the criteria employed, individuals with MetS exhibited a higher likelihood of experiencing all-cause mortality (MetS_{old}:19.6% vs. 10.0%, $P<0.001$; MetS_{new}: 19.7% vs. 9.28%, $P<0.001$) and CVD mortality (MetS_{old}:6.54% vs. 2.93%, $P<0.001$; MetS_{new}:6.60% vs. 2.65%, $P<0.001$) compared to those without. Although there was no significantly numerical difference in all-cause and CVD mortality between participants identified by MetS_{old} and MetS_{new}, the inclusion of hyperuricemia in the definition of MetS allowed for the identification of an additional 315 patients with all-cause death and 109 individuals with CVD death respectively.

To evaluate the risk of all-cause and CVD mortality according to the MetS_{new} criteria compared with the MetS_{old} criteria, analyses were performed in the three subgroups: Group A(MetS_{old}–MetS_{new}–), Group B (MetS_{old}–MetS_{new}+), Group C (MetS_{old}+MetS_{new}+). Group A represented the absence of MetS based on the MetS_{old} and MetS_{new} criteria; Group B represented the absence of MetS according to the MetS_{old} criteria but the presence of MetS according to the MetS_{new} criteria; Group C represented the presence of MetS according to both the MetS_{old} and MetS_{new} criteria. The baseline characteristics of these groups were displayed in Supplementary Table 1. As illustrated in Fig. 4A-B, Kaplan-Meier curves indicated that participants in Group B and C had a similar risk of all-cause and CVD-mortality compared to those in Group A. These results were further supported by multivariable analyses, which demonstrated that compared to Group A, the adjusted HRs and 95%CIs for all-cause mortality [Group B vs. Group A:1.30(1.15–1.46), $P<0.001$; Group C vs. Group A:1.36(1.28–1.46), $P<0.001$] and CVD mortality [Group B vs. Group A:1.39(1.12–1.71), $P=0.002$; Group C vs. Group A:1.36(1.20–1.53), $P<0.001$] were still statistically significant (Table 4). These results indicated that the additional participants identified by MetS_{new} carried a comparable risk of all-cause and CVD mortality to those defined by traditional criteria (MetS_{old}).

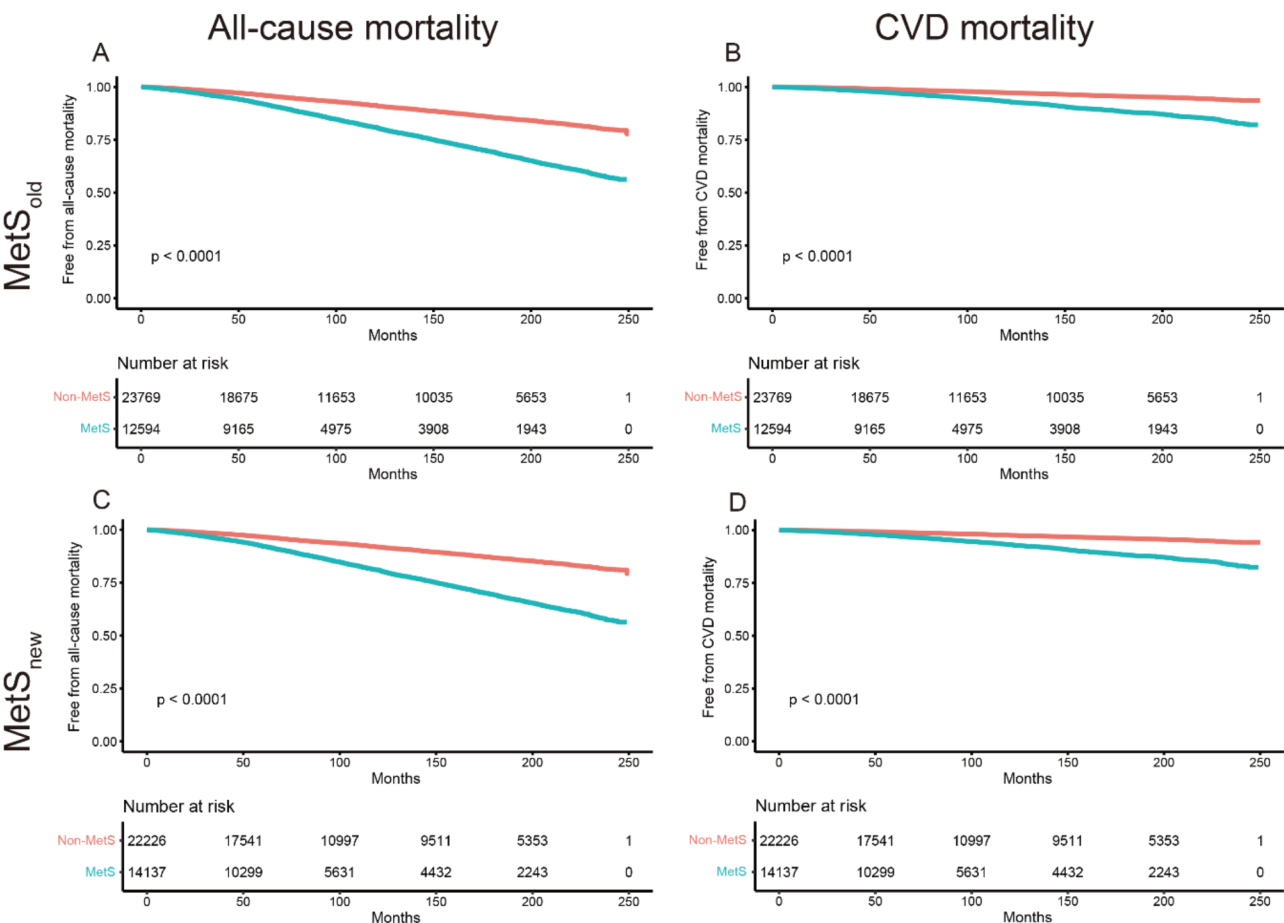


Fig. 3 The risk of all-cause and CVD mortality in MetS_{old} (A and B) or MetS_{new} (C and D) participants compared to those without. Abbreviations: CVD, cardiovascular disease; MetS, metabolic syndrome; MetS_{old}, the old version of MetS; MetS_{new}, the new version of MetS

Subsequently, we compared the prognostic value of MetS_{old} and MetS_{new}. For all-cause mortality, the C-index of MetS_{new} was significantly higher than that of MetS_{old} (0.607 vs. 0.594, $P < 0.001$), indicating that MetS_{new} outperforms MetS_{old} in distinguishing individuals who will experience all-cause mortality from those who will not (Table 5). Moreover, MetS_{new} demonstrated better reclassification performance than MetS_{old}, with an NRI of 0.023 (95% CI: 0.016–0.034, $P < 0.001$) and an IDI of 0.545 (95% CI: 0.053–0.637, $P < 0.001$) (Table 5). These results suggested that MetS_{new} substantially improved the predictive accuracy of all-cause mortality compared to MetS_{old}. Similar patterns were observed for CVD mortality, with MetS_{new} outperforming MetS_{old} (Table 5).

Discussion

Based on the NHANES (1999–2018) database, the major findings of this study are as follows: (1) the inclusion of hyperuricemia in the criteria of MetS identified an additional 4.24% participants at metabolic risk; (2) both MetS_{old} and MetS_{new} were significantly associated with

an increased risk of all-cause and CVD mortality; (3) the additional 4.24% participants identified by MetS_{new} exhibited a similar risk of all-cause and CVD mortality as those who met MetS_{old} criteria; (4) MetS_{new} demonstrated enhanced prognostic value compared to MetS_{old}.

The concept of MetS was first introduced by the World Health Organization (WHO) in 1998, with the aim of identifying individuals at an increased risk of developing CVD [6]. Since then, several diagnostic criteria have been proposed for clinical definition of MetS, including those from NCEP-ATP III [1], the International Diabetes Federation (IDF) [23], and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [24] etc. Among these, the NCEP-ATP III has been the most widely used in clinical practice. The application of different diagnostic criteria has led to varying estimates of MetS prevalence globally [25, 26]. Furthermore, the predictive value of various criteria shows significant differences. Several studies have demonstrated that the NCEP-ATP III criteria is superior to other criteria in predicting CVD events [27–29]. In contrast, a retrospective

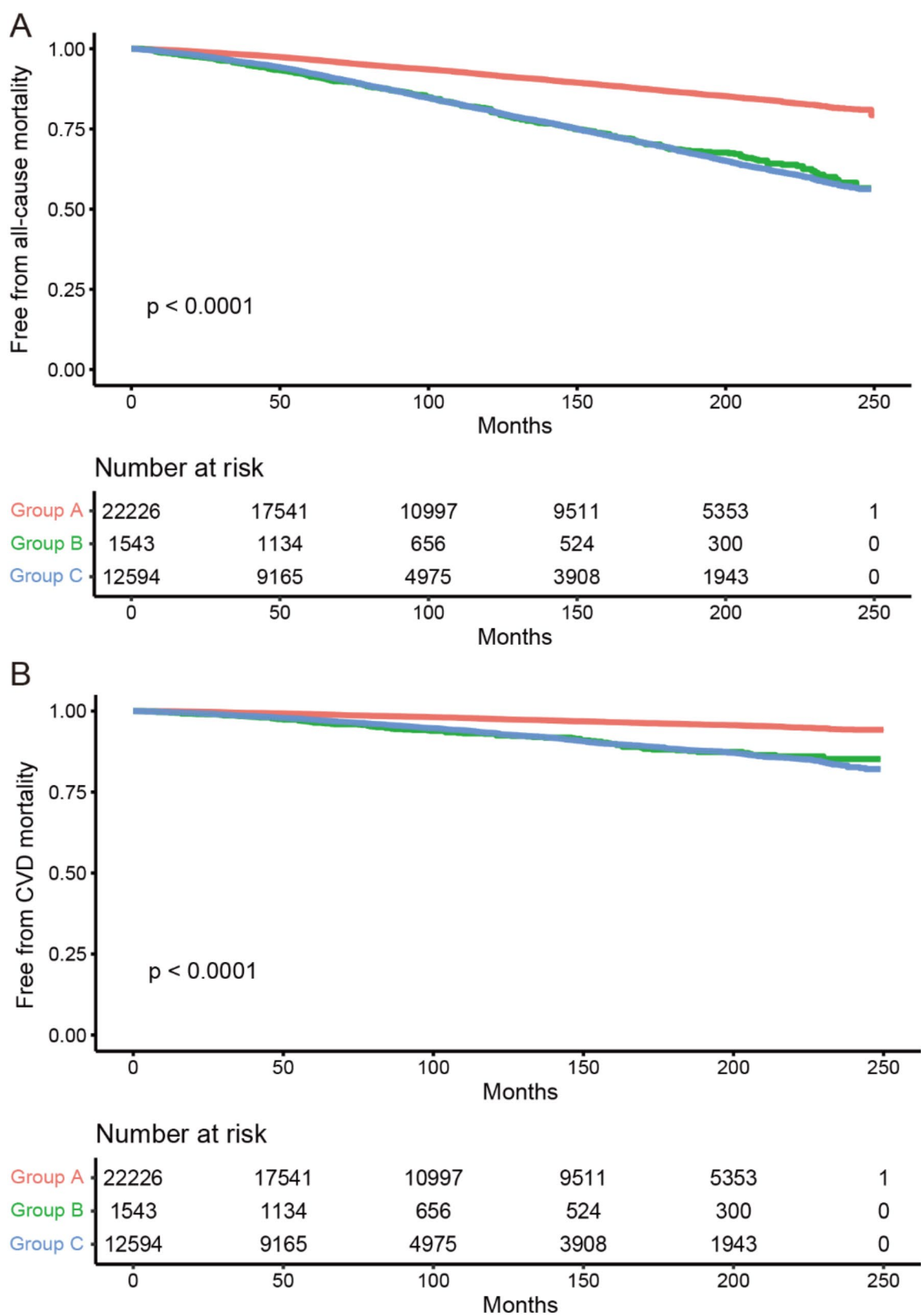


Fig. 4 The risk of all-cause and CVD mortality in different subgroups. Group A: MetS_{old}-MetS_{new}⁻, Group B: MetS_{old}-MetS_{new}⁺, Group C: MetS_{old}+MetS_{new}⁺ Abbreviations: CVD, cardiovascular disease; MetS_{old}, the old version of metabolic syndrome; MetS_{new}, the new version of metabolic syndrome

Table 4 The HR (95%CI) for all-cause mortality and CVD mortality in different subgroups

	Unadjusted		Adjusted for Model 1		Adjusted for Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality						
Group A	1.00	-	1.00	-	1.00	-
Group B	2.54(2.25–2.86)	< 0.001	1.28(1.14–1.45)	< 0.001	1.30(1.15–1.46)	< 0.001
Group C	2.59(2.44–2.75)	< 0.001	1.34(1.26–1.42)	< 0.001	1.36(1.28–1.46)	< 0.001
CVD mortality						
Group A	1.00	-	1.00	-	1.00	-
Group B	2.87(0.34–3.52)	< 0.001	1.48(1.21–1.82)	< 0.001	1.39(1.12–1.71)	0.002
Group C	2.80(2.52–3.11)	< 0.001	1.47(1.32–1.64)	< 0.001	1.36(1.20–1.53)	< 0.001

Group A: MetS_{old}-MetS_{new}-, Group B: MetS_{old}-MetS_{new}+, Group C: MetS_{old}+MetS_{new}+
Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; MetS, metabolic syndrome; MetS_{old}, the old version of MetS; MetS_{new}, the new version of MetS

Table 5 Comparison of prognostic ability for all-cause and CVD mortality between MetSold and MetSnew

	C-index	P value	NRI	P value	IDI	P value
All-cause mortality						
MetS _{old}	0.594(0.586–0.601)					
MetS _{new}	0.607(0.600–0.614)	< 0.001	0.023(0.016–0.034)	< 0.001	0.545(0.053–0.637)	< 0.001
CVD mortality						
MetS _{old}	0.602(0.589–0.615)					
MetS _{new}	0.617(0.605–0.630)	< 0.001	0.011(0.006–0.015)	0.004	0.608(0.046–0.649)	0.004

Abbreviations: CVD, cardiovascular disease; MetS_{old}, the old version of metabolic syndrome; MetS_{new}, the new version of metabolic syndrome; NRI, net reclassification improvement; IDI, integrated discrimination improvement

cross-sectional study found that IDF criteria is more effective in assessing the risk of hepatosteatosis and fibrosis [30]. The major difference among these criteria lies in the varying cut-off value of each component. However, it remains unclear whether integrating additional metabolic risk factors could both identify more individuals at metabolic risk and enhance predictive value.

The core pathophysiology process of MetS is insulin resistance, which is related to a higher risk of CVD [31–33]. Additionally, a growing number of metabolic risk factors, such as low serum bilirubin levels [34], non-alcoholic fatty liver disease (NAFLD) [35], sarcopenia [36, 37] and hyperuricemia, have been linked to the rising incidence of CVD. Among these factors, hyperuricemia has garnered significant attention due to its rising prevalence and associated comorbidities as more people adopt a Western lifestyle [38]. Uric acid, the final product of purine metabolism, can lead to gout when present at elevated levels. Preclinical evidence suggests that hyperuricemia may induce inflammatory cytokines production, endothelia dysfunction, reactive oxygen species (ROS) production, triggering inflammation response and vascular injury [39–42]. Furthermore, accumulating evidence has proved that patients with hyperuricemia, particularly those with gout [43], have a higher incidence of MetS [19, 44]. A previous study also demonstrated a linear association between uric acid levels and indices of insulin resistance (fasting C-peptide, fasting insulin and HOMA-insulin resistance) [45].

Numerous studies have indicated that both hyperuricemia and MetS are significantly associated with CVD and long-term outcomes. However, it remains unclear whether the combination of these two factors can improve prognostic ability. A study from rural Northeast China found that the combination of hyperuricemia and MetS was an independent predictor of left ventricular hypertrophy [42]. Another study involving 9589 subjects reported that elevated serum uric acid levels were related to higher CVD mortality risk, regardless of the presence of MetS, providing an NRI of 7.1% for CVD mortality over the diagnosis MetS [46]. However, these studies did not consider hyperuricemia and MetS as a combined entity. Interestingly, our present analysis is the first to add hyperuricemia as the sixth criterion of MetS to explore its prognostic impact on long-term all-cause and CVD mortality. The results align with prior studies that have shown hyperuricemia to be associated with poor prognosis [47–49]. We found that MetS_{new} (which includes hyperuricemia as the sixth criterion) can identify more individuals at metabolic risk and predict higher risks of all-cause and CVD death. Additionally, we discovered that while the incidence of hyperuricemia increased, its prognostic impact declined as the components of MetS increased. This finding suggested that hyperuricemia may be beneficial for detecting individuals at metabolic risk in the early stages of MetS. The probable reason behind this phenomenon may be that hyperuricemia promote the development and progression of MetS during the

early phase, while becoming a concomitant factor in the advanced stages of MetS.

Despite the simplicity and practicality of the NCEP-ATP III criteria in clinical settings, its effectiveness in identifying individuals at elevated risk for CVD remains uncertain. Our results surprisingly demonstrated that the additional participants identified by the MetS_{new} criteria had similar long-term prognosis as patients with MetS defined by MetS_{old}. This indicated that the traditional definition of MetS is not sufficiently robust. Efforts have been made to enhance the prognostic capability of MetS. Clarissa Elysia Fu et al. illustrated that the NAFLD increased the incidence of CVD and mortality [35]. Several studies have suggested that incorporating NAFLD into the definition of MetS could help identify a greater proportion of participants at higher metabolic risk [50, 51]. Additionally, a study involving 533 healthy Japanese women indicated that coexistence of MetS and sarcopenia could also increase the risk of CVD [52]. While MetS was related to a long-term prognosis regardless of the criteria adopted in their study, they did not demonstrate that the new criterion was superior to the traditional one in predicting long-term all-cause or CVD mortality. In our study, we evaluated multiple statistical indices (C-index, INR and IDI), which showed that MetS_{new} improved the integrated discriminatory and reclassification abilities compared to MetS_{old}. The strength of our analysis lies in the inclusion of hyperuricemia in the new definition, which can identify an additional 4.24% of individuals with the similar risk of long-term all-cause and CVD mortality.

The present analysis assessed the prognostic capability of hyperuricemia as a sixth criterion of MetS, based upon the NHANES (1999–2018) database. However, several limitations exist. Although previous studies have implied a U-shaped association between serum uric acid level and risk of mortality, we focused solely on hyperuricemia (> 7 mg/dl in men and > 6 mg/dl in women) in our analysis [53]. Moreover, we defined hyperuricemia according to the serum uric acid level, which means that individuals receiving uric acid-lowering medications may have been excluded from our study. Thirdly, the participants from the NHANES (1999–2018) database just reflect the demographic of the United States.

Conclusion

In conclusion, the present study found that incorporating hyperuricemia into the definition of MetS identified additional participants at metabolic risk and improve the prognostic ability for long-term all-cause and CVD mortality. This inclusion is beneficial to early management to prevent poor prognosis.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IDI	Integrated discrimination improvement
LDL-C	Low-density lipoprotein cholesterol
MetS	Metabolic syndrome
MetS _{new}	The new version of MetS
MetS _{old}	The old version of MetS
NAFLD	Non-alcoholic fatty liver disease
NCEP-ATP III	National Cholesterol Education Program's Adult Treatment Panel III
NDI	National Death Index
NHANES	National Health and Nutrition Examination Survey
NRI	Net reclassification improvement
ROS	Reactive oxygen species
Scr	Serum creatinine
SD	Standard deviation
T2DM	Type 2 diabetes mellitus

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12872-025-04529-7>.

Supplementary Material 1

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Author contributions

All authors made a significant contribution to the work reported. Zhijun Lei developed the main idea of the study. Zhijun Lei, Zhichao Zhang and Yuanxin Pang designed the study, analyzed data and drafted the manuscript. Zhijun Lei, Zhichao Zhang, Yuanxin Pang, Weihai Chen, ChuanZhen Hao and Jun Shen reviewed and revised the manuscript. All the authors read and approved the final manuscript.

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Data availability

NHANES data is available publicly at <https://www.cdc.gov/nchs/nhanes/index.htm>.

Declarations

Ethics approval and consent to participate

The data in our study derived from NHANES (1999–2018) database. The NHANES research was approved and agreed to by the NCHS Research Ethics Review Committee. All participants signed written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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