

Which Components of Metabolic Syndrome have a Greater Effect on Mortality, CVA and Myocardial Infarction, Hyperglycemia, High Blood Pressure or Both?

Abstract

Background: This study aims to evaluate the incidence of stroke, ischemic heart disease (IHD), and cardiovascular disease (CVD) mortality in clusters containing hypertension (HTN), clusters containing diabetes (diabetes mellitus [DM]), cluster with both HTN, DM, and cluster without HTN, DM in patients with metabolic syndrome (MetS). **Materials and Methods:** The association between MetS and outcomes was examined in 2257 patients with MetS that were divided into four groups includes patients with MetS with hyperglycemia (Cluster 1), patients with MetS with HTN (Cluster 2), patients with MetS with HTN and hyperglycemia (Cluster 3) and patients with MetS without HTN and hyperglycemia (Cluster 4). To assess the risk ratio and incidence of CVA, myocardial infarction, and mortality with the use multivariate Cox proportional hazards models. **Results:** As it shown the lowest prevalence of events was in Cluster 1 and against in Cluster 3 the prevalence of stroke with 34 (38.2%) cases and the prevalence of IHD and CVD mortality in Cluster 2 with, respectively, 168 (54.7%) and 51 patients (49%) had the most frequencies ($P < 0.001$), and hence that the lowest prevalence of events was seen in Cluster 1, but stroke in Cluster 3 with 34 cases (38.2%) and the prevalence of IHD and CVD mortality in Cluster 2, respectively, with 168 (54.7%) and 51 patients (49%) had the most frequencies ($P < 0.001$). **Conclusion:** More intensive changes in lifestyle and management protocols may be required in these patients for controlling the components of the syndrome, with the aim of preventing not only type II diabetes and CVD but also ischemic cerebrovascular events.

Keywords: Blood pressure, cardiovascular disease, diabetes mellitus, metabolic syndrome, mortality, myocardial infarction

Introduction

Metabolic syndrome (MetS) refers to the clustering of several risk factors that together increased the risk of cardiovascular diseases (CVD). The interrelated factors include obesity, hyperglycemia, dyslipidemia, and hypertension (HTN) and the presence of MetS increases the risk of CVD and type II diabetes.^[1,2]

In addition, it poses a significant risk of higher morbidity, mortality, and financial burden. The prevalence of MetS has been rising in both developed and developing countries, probably as a consequence of modern lifestyle and the overweight/obesity epidemic.^[3] Therefore, MetS is considered a public health, as well as a clinical problem. During the past decades, due to major lifestyle changes and aging population, the prevalence of MetS, CVD and other

chronic diseases has been increasing in Iran. Based on a national study, MetS has been diagnosed in 34.7%–37.4% of the Iranian population. Moreover, high incidence rates for almost all CVD and mortality have been reported in the Iranian population.^[4]

The etiology of MetS has not been clearly defined, thus the definition of MetS is not only based on etiology and pathology, but also on the predictors of CVD as a primary outcome of MetS. Its diagnostic criteria have been developed on the basis of best clustering of interrelated risk factors of CVD which occur simultaneously and can predict CVD events. Since there is no exclusive definition for MetS diagnosis, prevalence, incidence, and its association with an increased risk of CVDs depends on the used criteria.^[5] Each MetS component increases the risk of CVD, diabetes, and all-cause mortality.^[5-7] According to a study

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conducted by Gami *et al.*, the synergistic effects of these disorders increase the risk of further disease and mortality much more than the sum of the risk increases provided by each component. MetS increases total mortality from CVDs by 1.5–2.5 folds.^[7] Moreover, individuals with MetS are five times more likely to develop type 2 diabetes.^[6] The main causes of MetS remain to be determined. However, it seems that abdominal obesity and insulin resistance are the key components.^[7,8] Therefore, MetS is now an emerging health problem in the public and individual levels. Since programs for primary prevention of non-communicable diseases emphasize appropriate evaluation and management of the risk factors, gathering reliable information about the prevalence of MetS in various populations can be very effective in planning and use of preventive strategies for such diseases.^[9]

The prevalence of MetS is not only influenced by excess weight but also by ethnic predisposition, gender, age, race, cultural and lifestyle habits, and environmental factors; thus, its prevalence has large variations in different societies.^[10,11] Grundy reported that between 20% and 30% of the adult population in most countries have MetS,^[12] also it has been reported that Asians have an ethnic predisposition to MetS, and it is of special concern for Middle Eastern populations, which are predicted to experience the greatest global burden of diabetes by 2020.^[13] As a country in this region, Iran is expected to have one of the highest prevalence rates of MetS worldwide. The nationwide prevalence of MetS is reported to be 35.6% based on Adult Treatment Panel III (ATP III) criteria. In metropolitan Tehran, 42% of women and 24% of men have MetS, with a total age-standardized prevalence of 33.7%, and hence it is very important to have an overall estimation of its prevalence and outcomes in Iran.^[14] Sarrafzadegan *et al.* showed that HTN is more important than other risk factors include diabetes mellitus (DM) to predict CVD events in Iranian population as well as the definition and compare the impact of HTN and DM separately or together in MetS different cluster.^[15]

This study aims to evaluate the prevalence of stroke, ischemic heart disease (IHD), and CVD mortality of clusters containing HTN, clusters including hyperglycemia, cluster with both HTN, hyperglycemia and cluster without HTN, hyperglycemia in patients with MetS from 2001 to 2015 in Isfahan.

Materials and Methods

According to a unified definition (ATP III), the presence of three or more of the following risk factors results in diagnosis of MetS: (1) waist circumference of 102 cm or greater in men and 88 cm or greater in women; (2) systolic and diastolic blood pressures of 130 mmHg or greater and 85 mmHg or greater, respectively, or use of antihypertensive medication; (3) high-density lipoprotein cholesterol (HDL-C)

levels <40 mg/dL in men and <50 mg/dL in women or use of cholesterol medication; (4) triglyceride (TG) levels of 150 mg/dL or higher or use of lipid-lowering medication; and (5) fasting glucose level of 110 mg/dL or higher or use of medication.^[1,2]

Data collection was done based on previous information and documents of Isfahan Cardiovascular Research Center from 2001 to 2015 and then evaluating the prevalence of stroke, IHD, and CVD mortality in clusters containing hyperglycemia, clusters containing HTN, clusters containing both HTN and hyperglycemia and cluster without HTN, hyperglycemia in patients with MetS.

The Ethics Committee of Isfahan Cardiovascular Research Center approved the study. After obtaining informed written consent, a 30-min full structured interview was conducted by trained health professionals using a validated questionnaire including questions on demographic characteristics, socioeconomic status, behaviors, attitudes, skills, and knowledge about chronic non-communicable diseases, as well as related lifestyle behaviors (including smoking, physical activity, and nutritional habits).

Measurement of blood pressure and anthropometric parameters were carried out following standard protocols and using calibrated instruments. Body mass index was calculated as weight (kg) divided by height squared (m²). A 12-lead electrocardiogram was recorded at the primary health care centers for all participants. Fasting blood samples were obtained from all participants and were examined in central laboratory of Isfahan Cardiovascular Research Center with adherence to external national and international quality controls. Serum total cholesterol, TGs and fasting blood glucose were measured enzymatically, using an autoanalyzer (Eppendorf, Hamburg, Germany) and serum HDL-C was determined after precipitation of low-density and very low-density lipoproteins with dextran sulfate-magnesium. The most commonly used definitions for MetS are those provided by the World Health Organization (WHO), the National Cholesterol Education Program (NCEP) ATP III, the international diabetes federation, and the joint interim societies.^[16]

According to a unified definition, the presence of three or more of the following risk factors results in a diagnosis of MetS: (1) waist circumference of 102 cm or greater in men and 88 cm or greater in women; (2) systolic and diastolic blood pressures of 130 mm Hg or greater and of 85 mm Hg or greater, respectively, or use of antihypertensive medication; (3) HDL-C levels <40 mg/dL in men and <50 mg/dL in women or use of cholesterol medication; (4) TG levels of 150 mg/dL or higher or use of lipid-lowering medication; and (5) fasting glucose level of 110 mg/dL or higher or use of medication. According to the mentioned diagnostic criteria (NCEP-ATPIII), we detected 2257 MetS patients were divided into four groups:

Cluster 1 - Patients with MetS with hyperglycemia includes the four sub-groups:

- 1-1 FBS + TG + HDL
- 1-2 FBS + TG + WC
- 1-3 FBS + HDL + WC
- 1-4 FBS + HDL + WC + TG.

Cluster 2 - Patients with MetS with HTN includes four sub-groups:

- 2-1 HTN + TG + HDL
- 2-2 HTN + TG + WC
- 2-3 HTN + HDL + WC
- 2-4 HTN + HDL + WC + TG.

Cluster 3 - Patients with MetS with HTN and hyperglycemia consists of seven sub-groups:

- 3-1 FBS + HTN + TG
- 3-2 FBS + HTN + HDL
- 3-3 FBS + HTN + WC
- 3-4 FBS + HTN + HDL + TG
- 3-5 FBS + HTN + WC + HDL
- 3-6 FBS + HTN + WC + TG
- 3-7 FBS + HTN + WC + TG + HDL.

Cluster 4 - Patients with MetS without HTN and hyperglycemia consists of one group:

- HDL + WC + TG.

After the baseline survey in 2001, the follow-up has been carried out every 2 years and continue until 2013 (totally 6 follow-ups was done). The reported events were checked with myocardial infarction (MI) and stroke registry database of the Surveillance Department, Isfahan Cardiovascular Research Center.^[15] Diagnosis of events was done by training persons and made the final decision on all of the 3 main events (stroke (fatal, non-fatal), IHD (fatal, non-fatal MI, USA, and sudden cardiac death) and CVD mortality).

Statistical analysis

All data were analyzed using SPSS for Windows software (SPSS Inc., Chicago, IL, USA; version 15). ANOVA was used for the comparison of means of independent groups and the Chi-square test or Fisher's exact test (if necessary) for the comparison of proportions and categorical variables. Cox proportional hazards modeling was used with time to the outcome as the dependent variable and the presence of defined risk factors as independent dichotomous variables for the calculation of hazard ratios and 95% confidence intervals. For all analyses, statistical significance was assessed at a level of 0.05 (two-tailed).

Results

In this study, 2257 patients with MetS were divided into 4 groups: 192 subjects (8.51%) were in the cluster with hyperglycemia, 1142 patients (50.59%) in the cluster with HTN (the largest group), 371 patients (16.43%) in the cluster with hyperglycemia and HTN and 552 patients (24.45%) in the cluster without hyperglycemia and HTN. According to Table 1 that shows the patients' demographic data 616 cases (27.3%) were male and 1641 cases (72.7%) were female with the mean age of 53.39 ± 11.53 years that reveal significant differences among the four clusters in age and sex ($P < 0.001$).

On the other hand, in each sex, the mean age of the patients in comorbid hyperglycemia and HTN cluster was more than the other clusters, and patients with MetS without HTN and hyperglycemia, had the lowest age, and hence the mean age was significantly different based on sex between the four clusters ($P < 0.001$) [Table 1].

Furthermore, 523 patients (23.2%) were lived in village that among them 293 cases (56.02%) had

Table 1: Distribution of demographic in patient with metabolic syndrome

Variables	Total (n=2257)	Cluster				P
		1 (n=192) Hyperglycemia	2 (n=1142) HTN	3 (n=371) Hyperglycemi + HTN	4 (n=552) Without hyperglycemia + HTN	
Gender; male	616 (27.3)	52 (27.1)	317 (27.8)	152 (41)	95 (17.2)	<0.001
Age at baseline	53.39±11.53	50.47±10.50	55.26±11.42	59.21±10.09	46.60±9.37	<0.001
Residential area (rural)	523 (23.2)	36 (18.8)	293 (25.7)	90 (24.3)	104 (18.8)	0.007
BMI	29.0±4.25	28.8±4.49	28.9±4.32	29.0±4.36	29.2±3.92	0.546
Total daily physical activity	719.4±497.4	755.4±529.6	711.1±497.3	658.5±469.7	764.9±500.1	0.009
Current smoking	300 (13.3)	30 (15.6)	143 (12.5)	62 (16.3)	65 (11.8)	0.093
Education level						
Illiterate	1013 (44.9)	74 (38.5)	558 (48.9)	206 (55.5)	175 (31.7)	<0.001
Primary school	774 (34.3)	77 (40.1)	372 (32.6)	106 (28.6)	219 (39.7)	
Greater than primary school	470 (20.8)	41 (21.4)	212 (18.6)	59 (15.9)	158 (28.6)	

Data shown n (%) or mean±SD. Cluster 1: MetS (hyperglycemia): FBS + TG + HDL; DFBS + TG + WC; FBS + HDL + WC; FBS + HDL + WC + TG, Cluster 2: MetS (HTN): HTN + TG + HDL; HTN + TG + WC; HTN + HDL + WC; HTN + HDL + TG + WC, Cluster 3: MetS (hyperglycemi + HTN): FBS + HTN + TG; FBS + HTN + HDL; FBS + HTN + WC; FBS + HTN + HDL + TG; FBS + HTN + WC + HDL; FBS + HTN + WC + TG; FBS + HTN + WC + TG + HDL, Cluster 4: MetS (Without hyperglycemia + HTN): HDL + WC + TG. HTN: Hypertension, HDL: High-density lipoprotein, FBS: Fasting blood sugar, TG: Triglyceride, WC: Waist circumference, MetS: Metabolic syndrome, SD: Standard deviation, BMI: Body mass index

HTN ($P = 0.007$). The mean of the patients' body mass index was $29.0 \pm 4.25 \text{ kg/m}^2$ with no significant difference in the four clusters ($P = 0.546$). Physical activity in Cluster 4 with neither hyperglycemia nor HTN was higher than the other clusters ($P = 0.009$). In general, 13.3% of the patients were smoked that their frequency was similar among the four clusters ($P = 0.093$). Finally, 1013 patients (44.9%) were illiterate and only 470 ones (20.8%) had an education higher than the primary school which comparing the four clusters showed that the patients in no hyperglycemia and HTN cluster had the highest level of education ($P < 0.001$) [Table 1].

The highest significant mean of the age of events was seen generally and also on gender in cluster III (cluster includes hyperglycemia and HTN) ($P < 0.001$) [Table 2].

Furthermore, stroke has been occurred in 89 patients (3.94%), IHD in 307 patients (13.60%) and CVD mortality in 104 patients (4.61%), and hence that in Cluster 1, 7 patients (7.9%) had stroke, 22 patients (7.2%) had IHD and in 5 (4.8%) ones CVD mortality has happened. As it shown the lowest prevalence of events was in Cluster 1 and against in Cluster 3 the prevalence of stroke with 34 (38.2%) cases and the prevalence of IHD and CVD mortality in Cluster 2

with respectively 168 (54.7%) and 51 patients (49%) had the most frequencies ($P < 0.001$), so that the lowest prevalence of events was seen in Cluster 1, but Stroke in Cluster 3 with 34 cases (38.2%) and the prevalence of IHD and CVD mortality in Cluster 2, respectively, with 168 (54.7%) and 51 patients (49%) had the most frequencies ($P < 0.001$).

The prevalence of each events was not significantly different based on phenotype of each cluster ($P > 0.05$); for example, the considered phenotype in Cluster 1 had no significant role in the prevalence of stroke and only the type of cluster can play a significant role in the incidence of mentioned events [Table 3 and Figure 1].

The Hazard ratio of cardiovascular events in each clusters showed it was higher in MetS patients of Cluster 4 with comorbid diseases such as hyperglycemia, HTN, and the both than the subjects without these diseases. In fact, the Hazard risk of these complications will be higher in these hypertensive patients with hazard ratio of 1.94 (1.24–2.64) and both hyperglycemia and HTN with hazard ratio of 3.99 (2.86–5.57) can have a significant role in the probable prevalence of cardiovascular events ($P < 0.001$). On the other hand, the risk of cardiovascular events has been decreased with controlling the age, but it would

Table 2: Comparison mean of age at event in patients with metabolic syndrome

Patients	Cluster	(Mean±SD)*	P
In all patients	Hyperglycemia (n=28)	59.8±11.4 ^c	<0.001
	HTN (n=201)	65.2±11.5 ^d	
	Both (n=116)	68.3±9.82 ^{a,d}	
	Without hyperglycemia and HTN (n=50)	55.5±9.05 ^{b,c}	
In females	Hyperglycemia (n=20)	62.6±11.8 ^d	<0.001
	HTN (n=132)	65.7±11.5 ^d	
	Both (n=58)	67.1±9.04 ^d	
	Without hyperglycemia and HTN (n=39)	55.0±9.11 ^{a,b,c}	
In males	Hyperglycemia (n=8)	52.9±6.50 ^b	<0.001
	HTN (n=69)	64.4±11.5 ^{a,c}	
	Both (n=58)	69.4±10.5 ^{a,b,d}	
	Without hyperglycemia and HTN (n=11)	57.1±9.09 ^c	

*In each part of patients, according to results of *post hoc* test, similar letters (a, b, c, d) indicate insignificantly and dissimilar letters indicate significantly. HTN: Hypertension, SD: Standard deviation

Table 3: Prevalence of events in cluster of metabolic syndrome

Cluster	Events					
	Stroke (n=89)	P	IHD (MI, SCD, USA) (n=307)	P	CVD mortality (n=104)	P
1	7/89 (7.9)	<0.001	22/307 (7.2)	<0.001	5/104 (4.8)	<0.001
2	33/89 (37.1)		168/307 (54.7)		51/104 (49)	
3	34/89 (38.2)		82/307 (26.7)		44/104 (42.3)	
4	15/89 (16.9)		35/307 (11.4)		4/104 (3.8)	

Data shown n/N (%). Cluster 1: MetS (hyperglycemia): FBS + TG + HDL; FBS + TG + WC; FBS + HDL + WC; FBS + HDL + WC + TG, Cluster 2: MetS (HTN): HTN + TG + HDL; HTN + TG + WC; HTN + HDL + WC; HTN + HDL + TG + WC, Cluster 3: MetS (hyperglycemia + HTN): FBS + HTN + TG; FBS + HTN + HDL; FBS + HTN + WC; FBS + HTN + HDL + TG; FBS + HTN + WC + HDL; FBS + HTN + WC + TG; DM + HTN + WC + TG + HDL, Cluster 4: Mets (without hyperglycemia + HTN): HDL + WC + TG. MI: Myocardial infarction (ST elevation, non-ST elevation), USA: Unstable angina, SCD: Sudden cardiac death, IHD: Ischemic heart disease, CVD: Cardiovascular disease, HTN: Hypertension, HDL: High-density lipoprotein, FBS: Fasting blood sugar, TG: Triglyceride, WC: Waist circumference, MetS: Metabolic syndrome, DM: Diabetes mellitus

be still significant ($P < 0.001$). Sex-based evaluation of these events showed that the hazard ratio in both sexes in Clusters 2 and 3 was notably and significantly higher than Cluster 4, but controlling the age in each sexes reduces the hazard ratio of events in Cluster 2, but Cluster 3 keeps its significant role in increasing the risk of events ($P < 0.001$). In other words, it seems that both hyperglycemia and HTN can be more dangerous in the prevalence of cardiovascular events in MetS and increases the probability of these events [Table 4].

Discussion

The MetS leads to variety of disorders which is resulted from an abnormality in metabolism pathways which cause HTN as a common symptom, insulin resistance and

hyperglycemia, hyperinsulinemia, and also dyslipidemia. The sedentary life which results in reducing physical activity, aging, genetic issues, abdominal obesity, and insulin resistance seems to be the main reasons of the syndrome. Involvement of immune system is also reported to have an active role in MetS development.^[17,18]

The results showed that the HTN cluster was the most common in MetS. In this study, MetS was more common in men than women. In some studies, MetS has been proposed as one of the most important risk factors for type 2 diabetes and CVD,^[19-22] however, other investigations did not observe this association.^[23] Furthermore, some studies have pointed to the high prevalence of MetS in elderly >40 years.^[24] In line with this study, the prevalence of the syndrome was higher in women than men while the contrary has been

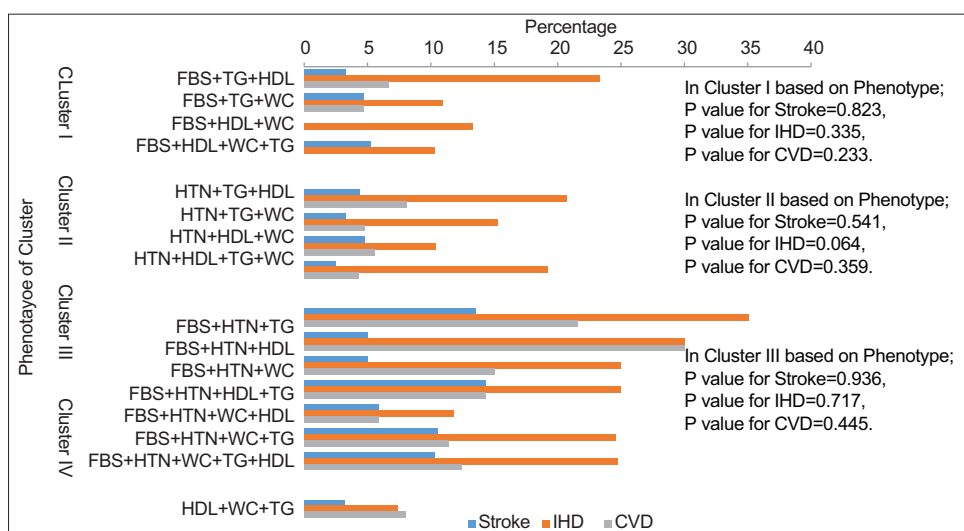


Figure 1: A prevalence of events in cluster of metabolic syndrome based on phenotype

Table 4: Hazard ratio (95% confidence interval) of developing cardiovascular events according to metabolic syndrome

Sex	Cluster	Crude model		Cluster	Age adjusted model	
		HR (95% CI)	P		HR (95% CI)	P
Male	1	1.55 (0.62-3.85)	0.346	1	1.47 (0.59-3.66)	0.407
	2	2.21 (1.17-4.18)	0.014	2	1.74 (0.91-3.34)	0.092
	3	4.59 (2.41-8.77)	<0.001	3	3.11 (1.58-6.12)	0.001
	4	Reference	-	4	Reference	-
Female	1	1.55 (0.90-2.67)	0.107	1	1.32 (0.77-2.27)	0.310
	2	1.80 (1.26-2.57)	0.001	2	1.27 (0.88-1.85)	0.193
	3	3.38 (2.25-5.08)	<0.001	3	2.20 (1.45-3.65)	<0.001
	4	Reference	-	4	Reference	-
Total	1	1.57 (0.98-2.49)	0.056	1	1.37 (0.86-2.18)	0.177
	2	1.94 (1.42-2.64)	<0.001	2	1.41 (1.02-1.95)	0.033
	3	3.99 (2.86-5.57)	<0.001	3	2.57 (1.81-3.64)	<0.001
	4	Reference	-	4	Reference	-

Cluster 1: MetS (hyperglycemia): FBS + TG + HDL; FBS + TG + WC; FBS + HDL + WC; FBS + HDL + WC + TG, Cluster 2: MetS (HTN): HTN + TG + HDL; HTN + TG + WC; HTN + HDL + WC; HTN + HDL + TG + WC, Cluster 3: MetS (hyperglycemia + HTN): FBS + HTN + TG; FBS + HTN + HDL; FBS + HTN + WC; FBS + HTN + HDL + TG; FBS + HTN + WC + HDL; FBS + HTN + WC + TG; DM + HTN + WC + TG + HDL, Cluster 4: MetS (without hyperglycemia + HTN): HDL + WC + TG. HR: Hazard ratio, CI: Confidence interval, HTN: Hypertension, HDL: High-density lipoprotein, FBS: Fasting blood sugar, TG: Triglyceride, WC: Waist circumference, MetS: Metabolic syndrome, DM: Diabetes mellitus

found in other reports which was estimated similar incidence in both sexes or slightly higher in men.^[14,25]

Phenotypical assessment of sex distribution in each of the four clusters showed that in males with hyperglycemia and/or HTN, high TG and low HDL phenotype were common. In addition, more abdominal circumference was seen in females. In other words, perhaps the female with MetS had a worse clinical characteristics situation than males.

New findings have reported that MetS could better identify other disorders such as CVD and type 2 diabetes, due to having the common symptoms, which includes metabolism dysfunction of glucose, obesity, dyslipidemia (high TG, low HDL), insulin resistance, and elevated blood pressure.^[23]

A number of studies have indicated that MetS, whether defined by NCEP criteria or those of WHO, is a risk factor for both type 2 diabetes^[26,20] and CVD.^[25,27-28]

IHD incidence with 13.6% had the highest prevalence and then CVD mortality risk (4.61%) and stroke (3.94%). Therefore, it might be said that HTN in patients with MetS can be a warning to cardiovascular events. Consistent with our findings, the study of National health and nutrition examination reported that MetS according to the ATP III criteria was the main univariate predictor of coronary events, but in multivariate analysis, HTN, and diabetes remained predictors of coronary heart disease while MetS did not remain a predictor for CHD anymore. The study also concluded that the risk of cardiovascular events was due to the components of MetS, particularly low HDL cholesterol, and high blood pressure.^[29]

In this regards, it can be stated that this syndrome, in fact, is the heterogeneous components that its complications are might be more or less appear in individuals.^[30] For example, High blood sugar and HTN in our population were the strong predictors of CVD. However, a lot of people, who were classified as MetS, may not have any of these risk factors. In fact, it is more likely that most of the increased prevalence of CVD events is in associated with cardiovascular risk factors.

On the other hand, occurrence evaluation of any cardiovascular events based on each phenotype suggested that aforementioned events by event- or pheno-type of each subgroup were not being different. In other words, the risk of cardiovascular events is relatively high in people with hyperglycemia and/or HTN and the phenotype cannot be influenced in the occurrence of these events.^[31]

The current study has expanded on the results of Rachas *et al.* which suggested that the different MetS definitions did not add any information to the risk factor-based model for prediction of CVD prevalence and mortality events, a finding that could have originated from pooling weak components, that is, WC, TGs and HDL-C with the

powerful components, such as high BP and high fasting plasma glucose, in the MetS concept.^[3]

The results of these analyses demonstrated that the effect of the MetS on either all-cause or CVD mortality in the patients with prevalent CVD from the SAHS population is primarily driven by the inclusion of diabetes in the definition of the MetS. Both the NCEP and the WHO accept diabetes as one of the criteria defining the MetS, in the latter case as a surrogate for insulin resistance.^[3,32,33] This is somewhat paradoxical since diabetes is also considered to be an outcome of MetS.^[34,20] It is unusual to consider a condition to be the both element and outcome of a syndrome. Since diabetes is itself a well-recognized and strong CVD risk factor,^[27,35] it is not surprising that a condition which includes diabetes as part of its definition would be associated with increased CVD mortality, and it is also not unreasonable to expect that it might be associated with increased all-cause mortality as well.

Continuing basic research into the origins and pathogenesis of this syndrome is clearly indicated, since such research may shed light on the mechanisms whereby such a large number of diabetes and CVD risk factors tend to cluster in individuals. Moreover, a better understanding of MetS etiology would quite likely facilitate the emergence of a more scientifically based and less arbitrary definition of the condition. Furthermore, if a specific therapy for MetS were to emerge, this would provide an impetus to develop appropriate diagnostic criteria to identify individuals who might benefit from such therapy. For example, insulin sensitizing agents might someday become standard treatment for non-diabetic individuals with MetS that, most of them are insulin resistant. Before such treatment could be routinely recommended, however, clinical trials would be needed to establish its efficacy. In the meantime, therapy for the MetS is merely the therapy for its various components and whether a given component occurs in isolation or in combination with other components as in the MetS, makes little if any difference to how it is treated.^[36]

Finally, the risk of cardiovascular events in patients with metabolic diseases which also had hyperglycemia and/or high blood pressure was higher than that of both in those without the above-mentioned disorders. Moreover, the ratio of the risk of these events in males was more than females and age can also increase the possibility of the events occurrence. In general, we can say that the probability of cardiovascular events occurred in males was more than females gender and age have a key role in aggregating these conditions. Unlike our study, Mozaffarian *et al.* showed that MetS did not predict higher mortality in the absence of HTN or altered glucose metabolism.^[37] Another investigation stated that despite similar increase risk of ischemic stroke between the genders, the increase risk trend was more for women (OR = 2.10 vs. 1.39 for women

and men, consequently). Furthermore, women are more vulnerable to CVDs.^[38,39]

Conclusion

According to our findings, MetS increases the morbidity rate, which should be checked and overviewed in MI and CVD patients. The study has several limitations. First, the information about changing of MetS related factors was not available. Second, the data of ischemic stroke or TIA were gathered from the participant hospitals and minor stroke was not admitted to the hospital or registered to the other nonparticipant hospital, and these data would have been missed.

Further investigation is required in other cohorts to determine whether the hyperglycemia and/or HTN have a direct effect on MetS and evaluation of MetS increases on the risk of ischemic stroke both genders, as in the present cohort. MetS should be distinguished meticulously, especially in patients with previous thrombotic diseases. The protocol should be more intensive to control the possible changes of MetS' factors. We think that our aim in the study designed with the similar protocol may better to focus on type 2 diabetes as well as ischemic cerebrovascular events.

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Conflicts of interest

There are no conflicts of interest.

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