

## Which diagnostic criteria of metabolic syndrome are predictors of cardiovascular diseases in elderly populations?

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### ABSTRACT

**Introduction:** Metabolic syndrome (MetS) is one contributing factor to cardiovascular diseases (CVD). Although there have been several reports showing MetS to be a risk factor for CVD, there are limited data available on which of the diagnostic criteria for MetS carries the greatest risk for CVD in the elderly population. This study thus aimed to evaluate these criteria in terms of risk of CVD in this population.

**Methods:** This was a retrospective cohort study conducted at three referral hospitals in Thailand. The study period was between January 1, 2007 and December 31, 2016. Eligible patients were identified whether presence of MetS or not at the beginning of study and followed until the end of study. The primary outcome of study was presence of CVD. Predictors for CVD were analyzed by Cox proportional-hazards regression.

**Results:** During the study period, there were 1080 patients who met the study criteria, 253 (23.42%) of whom had CVD. There were five factors significantly associated with CVD occurrence including age, smoking, SBP, FPG, and HDL-c. The two factors with the highest adjusted hazard ratio were FPG and SBP at 2.92 and 2.34, respectively.

**Conclusions:** The three MetS criteria including SBP, FPG, and HDL-c may be predictors for cardiovascular diseases in elderly populations. Physician may need to focus on these particular factors of MetS in terms of CVD prevention in elderly patients.

### Introduction

The prevalence of cardiovascular diseases (CVD) are increasing, resulting in disability and death, particularly in elderly populations [1–4]. It is predicted that by 2030, 35% of the population will suffer from cardiovascular diseases [5,6]. In Europe, mortality from CVD is higher than from any other conditions (46%), and it is higher in females than in males (51% vs 42%) [7]. Cardiovascular disease is also the leading cause of mortality in Central Asia, a risk that increases with age [8]. The expected total cost of treatment for cardiovascular diseases in 2030 is 1044 billion USD [9].

Metabolic syndrome (MetS) is one contributing factor to CVD. A study from Iran found that metabolic syndrome increased the risk for

CVD by 1.97 times in males and 2.25 times in females [10]. A study from the US in an elderly population (age 44–84 years) found that metabolic syndrome increased the risk of cardiovascular diseases by 1.71 times [11]. Although there have been several reports showing MetS to be a risk factor for CVD [10–12], there are limited data available on which of the diagnostic criteria for MetS carries the greatest risk for CVD in the elderly population. Additionally, elderly population is vulnerable to CVD complications, morbidity, and mortality. A mortality rate of non-ST segment elevation myocardial infarction in elderly patients was increasing by age and up to 45.5% [13]. This study thus aimed to evaluate which criterion of MetS was related with CVD in this population. Knowing these predictors may be beneficial or change in medical care of the elderly patients.

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## Methods

This was a retrospective cohort study conducted at three referral hospitals in north (Maharat Nakhon Chiang Mai Hospital), northeast (Khon Kaen Regional Hospital), and central (Saraburi Regional Hospital) Thailand. The study period was between January 1, 2007 and December 31, 2016. The inclusion criteria were age over 60 years and no evidence of cardiovascular disease. Patients for whom there were no data of cardiovascular disease at the end of study were excluded. Eligible patients were identified whether presence of MetS or not at the beginning of study and followed until the end of study. The primary outcome of study was presence of CVD. The study protocol was approved by the institutional review board (042/2559).

Metabolic syndrome was defined by the presence of at least three out of the five diagnostic criteria proposed by the National Cholesterol Education Program–Adult Treatment Panel 3 (NCEP ATP III) and the World Health Organization (WHO) [14,15]. These included body mass index  $\geq 25 \text{ kg/m}^2$ , high density lipoprotein-cholesterol (HDL-c)  $\leq 40 \text{ mg/dL}$  in males or  $\leq 50 \text{ mg/dL}$  in females, triglyceride  $\geq 150 \text{ mg/dL}$ , hypertension or blood pressure  $\geq 130/85 \text{ mmHg}$ , and diabetes or fasting plasma glucose  $\geq 110 \text{ mg/dL}$ . Note that waist circumference was substituted by body mass index due to limited data of waist circumference and by the diagnostic criterion by the American Association of Clinical Endocrinologists or AACE [16]. Cardiovascular diseases were diagnosed by attending physicians and coded based on the International Classification of Diseases and Related Health Problems (ICD10), as follows: I20 - I25 Ischemic heart diseases or I60 - I69 Cerebrovascular diseases.

The baseline characteristics and MetS diagnostic criteria of all eligible patients were recorded. The studied variables included age, sex, occupation, area of residence (urban or rural), current smoking, current alcohol consumption, body mass index (BMI), and blood pressure. Area of residence was defined according to the patient's home address, with the main districts of Chiang Mai, Khon Kaen, or Saraburi being classified as urban and all other areas as rural. The patients were followed up on and censored for any of the above cardiovascular diseases until the end of the study.

**Sample size calculation.** A previous study found that among the MetS criteria, HDL-c had the least effect on CVD at 1.3 times resulting in the largest sample size [17]. The estimated sample size for a Cox proportional model with a power of 80% and confidence of 95% was 1080 subjects. The required sample size in each hospital was calculated based on the proportions of the total number of MetS patients in all three hospitals (317 out of 8480 patients from Chiang Mai, 415 out of 11,082 patients from Khon Kaen, and 348 out of 9307 patients from Saraburi).

**Statistical analysis.** All eligible patients were censored and divided into two groups: cardiovascular disease and non-cardiovascular disease. Descriptive statistics were used to compare the differences between the two groups. Normality of numerical variables were examined. Student *t* test was used to compare differences between two groups for normally-distributed numerical variables, while Wilcoxon Rank Sum test was used for non-normally distributed numerical variables. Overall survival and survival probability were calculated using Kaplan-Meier survival analysis. Factors associated with cardiovascular disease were analyzed using Cox proportional-hazards regression. A univariate method was used to identify potential predictors for cardiovascular disease. MetS criteria and factors with a *p* value  $< 0.2$  were subsequently analyzed using stepwise multivariate method of Cox regression analysis to define independent predictors for CVD. A receiver operating characteristic (ROC) curve of the final model by Cox survival analysis was created. All statistical analyses were performed using STATA (College Station, Texas, USA).

## Results

During the study period, there were 1080 patients who met the study criteria, 253 (23.42%) of whom had CVD. Diastolic blood pressure and

**Table 1**

Baseline characteristics of elderly patients categorized by presence of any cardiovascular disease.

Factors	No CVD n = 827	CVD n = 253	p value
Mean (SD) age, years	67.93 (6.75)	67.99 (6.28)	0.566
Male sex	297 (35.91)	97 (38.34)	0.502
Occupation			0.385
Government official	147 (17.78)	37 (14.62)	
Farmer	116 (14.03)	32 (12.65)	
Employee	84 (10.16)	35 (13.83)	
Merchant	57 (6.89)	26 (10.28)	
Unemployed	423 (51.15)	123 (48.62)	
Area of residence			0.456
Rural	520 (62.88)	166 (65.61)	
Urban	307 (37.12)	87 (34.39)	
Alcohol consumption	155 (18.85)	50 (19.48)	0.715
Smoking	158 (19.20)	73 (28.85)	0.001
Mean (SD) BMI, $\text{kg/m}^2$	24.80 (3.83)	25.10 (4.00)	0.830
Mean (SD) SBP, mmHg	136.82 (15.52)	138.60 (15.17)	0.111
Mean (SD) DBP, mmHg	75.26 (9.87)	77.29 (8.78)	$< 0.001$

Note. Data presented as number (percentage) unless indicated otherwise; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

**Table 2**

Laboratory results and metabolic syndrome criteria of elderly patients categorized by presence of any cardiovascular disease.

Factors	No CVD n = 827	CVD n = 253	p value
FPG, mg/dL	127.98 (49.61)	132.44 (34.81)	$< 0.001$
Serum Cr, mg/dL	1.34 (0.76)	1.51 (1.54)	0.613
eGFR*, ml/min/1.73 $\text{m}^2$	48.19 (14.32)	48.97 (13.63)	0.652
Total cholesterol, mg/dL	200.80 (57.67)	203.69 (80.41)	0.142
Triglyceride, mg/dL	151.29 (87.37)	149.86 (78.90)	0.358
HDL-c, mg/dL	48.52 (12.00)	43.34 (13.53)	$< 0.001$
LDL-c, mg/dL	118.40 (42.78)	88.77 (27.03)	0.007
Metabolic syndrome, n (%)	342 (41.34)	134 (52.96)	0.001
Metabolic syndrome criteria			0.003
1 item	188 (22.73)	50 (19.76)	
2 items	297 (5.91)	69 (27.27)	
3 items	223 (26.96)	100 (39.53)	
4 items	98 (11.85)	26 (10.28)	
5 items	21 (2.54)	8 (3.16)	

Note. FPG: fasting plasma glucose; Cr: creatinine; eGFR: estimated glomerular filtration rate; HDL-c: high density lipoprotein cholesterol; \* measured by using CKD-EPI formula.

smoking status were baseline characteristic that differed significantly between the two groups (Table 1). The CVD group had significantly higher diastolic blood pressure than the non-CVD group (77.29 mmHg vs 75.26 mmHg; *p* value 0.001), while smokers were more frequently found in CVD group than the non-CVD group (28.85% vs 19.20%; *p* value 0.001). Laboratory test results for FPG, HDL, and LDL also differed significantly between the CVD and non-CVD groups (FPG = 132 and 127 mg/dL, respectively; HDL-c = 43 vs 48 mg/dL, respectively; LDL-c = 88 vs 118 mg/dL, respectively; Table 2).

According to the study flow (Fig. 1), MetS gave relative risk of CVD of 1.429 (95% confidence interval of 1.143, 1.786). MetS was also diagnosed in a significantly greater proportion of patients in the CVD group (52.96% vs 41.34%; *p* value  $< 0.001$ ) than in the non-CVD group, as shown in Table 2. The numbers of metabolic syndrome criteria also differed between the two groups, with higher percentages of patients exhibiting two, three or five criteria in the CVD group (Table 2). The non-MetS group had a longer CVD-free duration at 108 months (95% CI 105–110) than the MetS group (103 months with 95% CI 100–106), as shown in Table 3 and Fig. 2 (*p* 0.001).

There were five factors significantly associated with CVD occurrence including age, smoking, SBP, FPG, and HDL-c (Table 4). The two factors with the highest adjusted hazard ratio were FPG and SBP at 2.92 and

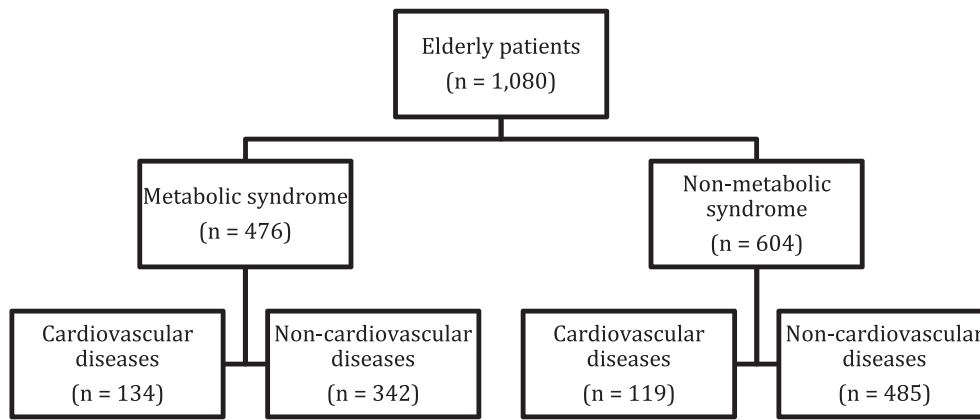


Fig. 1. Study flow of elderly patients with and without metabolic syndrome and occurrence of cardiovascular diseases by a retrospective cohort study.

Table 3

Numbers of elderly patients with and without metabolic syndrome and occurrence of cardiovascular disease (CVD) by time.

Time, months	No metabolic syndrome group			Metabolic syndrome group		
	Total	CVD	% CVD free	Total	CVD	% CVD free
24	565	39	93	442	37	92
36	548	14	91	421	19	88
60	524	16	88	393	19	84
120	451	45	80	308	54	72

2.34, respectively (Table 4). The area under the ROC curve of the Cox survival model for cardiovascular disease was 71.24% (95% confidence interval of 65.90%-76.57%) as shown in Fig. 3.

Discussion

This study found that patients with metabolic syndrome were more likely to develop cardiovascular disease compared to those without (52.96% vs 41.34%; p value 0.001), as shown in Table 1 [10–12]. Elderly MetS patients may increase risk of CVD from shorten telomere. A previous study found that MetS had a high risk of shorter telomere by three times (p 0.01) [18] which leads to atherosclerosis and CVD [19]. However, only three of the five diagnostic criteria for MetS were independent predictors for CVD in the elderly including SBP, FPG, and HDL-c (Table 4). Neither BMI nor triglyceride levels were significant predictors

according to univariate analysis and multivariate analysis, respectively. Note that the survival model had the ROC curve in the acceptable range [20] indicating good model.

As has been previously reported, SBP, FPG, and low HDL-c were significant predictors for CVD in adults and elderly patients [21,22], as well as smoking and advanced age [23,24]. In this study, participants over 80 years of age were not included in the final model for cardiovascular prediction due to the small number of these patients. The mean age of the population in this study was approximately 70 years (Table 1). Increasing FPG as an indicator of CVD may be related to telomere shortening. Type 2 DM with myocardial infarction had significantly higher FPG (175 vs 93 mg/dL; p < 0.01) and shortening of telomere (0.30 vs 0.53; p 0.005) than control group [25].

There are two explanations as to why BMI was not a significant factor for CVD in this study. First, the population in this study was not extremely obese, with an average BMI of approximately 25 kg/m<sup>2</sup> (Table 1). Second, the effect of BMI on cardiovascular risk has been shown to exhibit a U-shaped curve, with patients with extremely low and extremely high BMI being most at risk [23]. Similarly, the triglyceride levels of the patients in this study were quite low at 150 mg/dL, resulting in their having no association with cardiovascular diseases. The results of this study imply that SBP, FPG, and HDL-c were strong predictors for cardiovascular diseases in elderly patients with slightly high body mass indices and normal triglyceride levels.

The main limitation of this study was its retrospective design, meaning that some parameters may not be equally distributed between

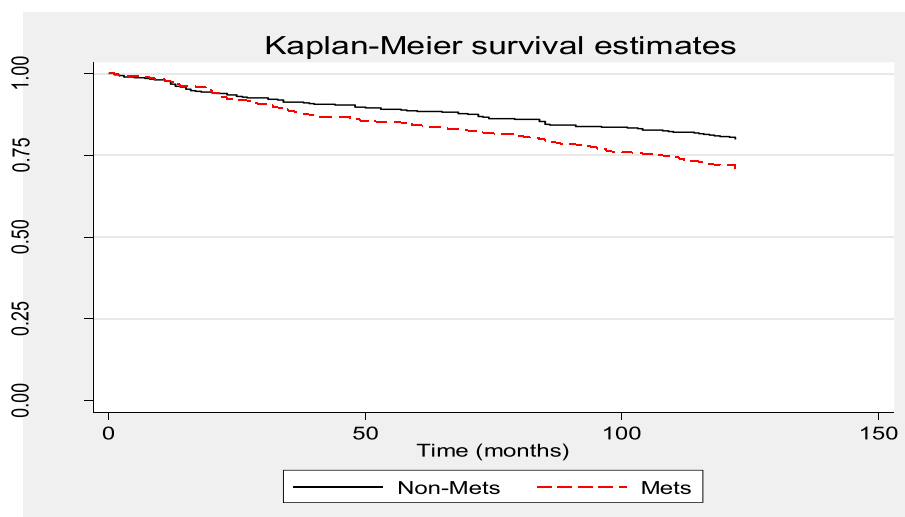


Fig. 2. Kaplan-Meier survival estimates for cardiovascular disease in elderly patients categorized by presence of metabolic syndrome (Mets) with a p value of 0.001.

**Table 4**

Predictors of cardiovascular disease in elderly patients by clinical and metabolic syndrome factors.

Factors	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)
Age, years		
60–69	1	1
70–79	1.42 (1.10, 1.85)	1.64 (1.02, 2.64)
≥80	0.88 (0.48, 1.63)	Not included
SBP, mmHg		
<130	1	1
≥130	1.97 (1.43, 2.72)	2.34 (1.10, 4.95)
FPG, mg/dL		
<110	1	1
≥110	2.80 (1.83, 4.27)	2.92 (1.63, 5.23)
HDL-c, mg/dL		
>40 (M), >50 (F)	1	1
≤40 (M), ≤50 (F)	3.35 (2.21, 5.09)	1.83 (1.09, 3.09)
Smoking		
Non-smoker	1	1
Smoker	1.58(1.20, 2.07)	1.67(1.00, 2.77)

*Note.* SBP: systolic blood pressure; FPG: fasting plasma glucose; HDL-c: high density lipoprotein cholesterol; model was adjusted for triglyceride and diastolic blood pressure.

both groups such as LDL-c level as this was not a randomized controlled trial. Another limitation is that the patients in this study were mainly from rural area (66.51%) with history of alcohol consumption of 18.98% and smoking of 21.39%. Therefore, the results of this study may not apply to all elderly populations. Body mass index was used instead of waist circumference in this study due to limited data. However, body mass index was one criterion for MetS by the AACE and both variables are highly correlated with a correlation of 0.75 [26]. Finally, there is no intervention or evaluation of physical function in the participants [27–29].

In conclusion, SBP, FPG, and HDL-c may be predictors for cardiovascular diseases in elderly populations. Physician may need to focus on these particular factors of MetS in terms of CVD prevention in elderly patients.

## CRedit authorship contribution statement

**Arinrada Ladla:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft. **Pramote Tongkrajai:** Conceptualization, Methodology, Supervision. **Sompong Srisaenpang:** Conceptualization, Methodology, Supervision. **Penprapa Siviroj:** Conceptualization, Methodology, Supervision. **Surakrant Yutthakasemsunt:** Conceptualization, Methodology, Supervision. **Somsak Tiangkao:** Conceptualization, Methodology, Supervision. **Verajit Chotmongkol:** Conceptualization, Methodology, Supervision. **Kittisak Sawanyawisuth:** Supervision, Writing - original draft, Writing - review & editing.

## Declaration of Competing Interest

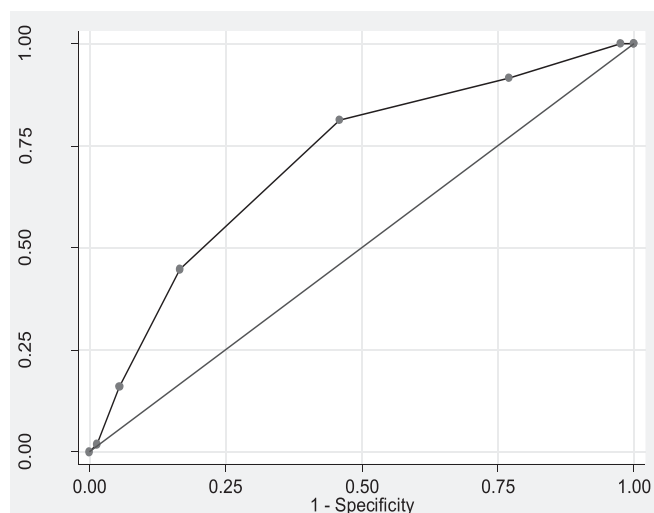
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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*Note.* Area under the ROC curve: 71.24% (95% confidence interval of 65.90%–76.57%).

**Fig. 3.** A receiver operating characteristic (ROC) curve of the Cox survival model for cardiovascular disease in elderly patients. *Note.* Area under the ROC curve: 71.24% (95% confidence interval of 65.90%–76.57%).

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