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Prognostic Impacts of Metabolic Syndrome in Patients With Chronic Heart Failure

– A Multicenter Prospective Cohort Study –

Soichiro Tadaki, MD; Yasuhiko Sakata, MD, PhD; Yutaka Miura, MD, PhD; Satoshi Miyata, PhD; Masanori Asakura, MD, PhD; Kazunori Shimada, MD, PhD; Takeshi Yamamoto, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Toshiaki Kadokami, MD, PhD; Satoshi Yasuda, MD, PhD; Toshiro Miura, MD, PhD; Shin-ichi Ando, MD, PhD; Masafumi Yano, MD, PhD; Masafumi Kitakaze, MD, PhD; Hiroyuki Daida, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: Metabolic syndrome (MetS) is involved in the increased risk of atherosclerotic cardiovascular diseases. We have previously reported that the prevalence of MetS is more than 2-fold greater in patients with chronic heart failure (CHF) than in the general population in Japan. However, the prognostic impact of MetS in CHF patients remains to be elucidated.

Methods and Results: In the present nationwide, large-scale clinical study in Japan, we enrolled 4,762 patients with Stage C/D CHF. The prevalence of MetS by the definition of the Japanese Committee for the Diagnostic Criteria in 2005 was 41.3% (50.6% in males, 21.5% in females). MetS was characterized by higher prevalence of males, obesity and lifestyle-related comorbidities, including glucose intolerance, dyslipidemia and hypertension. Multivariate Cox hazard analysis showed that MetS was associated with increased incidence of the composite of all-cause death and atherosclerotic events in males (hazard ratio [HR] 1.28; 95% confidence interval [CI] 1.06–1.54, P=0.011) but not in females (HR 1.23, 95% CI 0.87–1.75, P=0.241). Among the components of MetS, over waist circumference and glucose intolerance were significantly associated with increased incidence of the composite endpoint (HR 1.23, P=0.038, and HR 1.29, P<0.001, respectively) in males but not in females.

Conclusions: The results indicate that MetS only has a negative prognostic impact in male CHF patients. (*Circ J* 2016; **80:** 677–688)

Key Words: Chronic heart failure; Metabolic syndrome; Obesity; Prognosis; Sex differences

The prevalence of metabolic disorders, such as diabetes mellitus (DM), dyslipidemia and hypertension, and chronic heart failure (CHF) has been rapidly increasing over the past decades in Japan, along with westernization of lifestyles and the rapid aging of society.[1–4] Metabolic syndrome (MetS) is a pathological condition with a clustering of metabolic components and is substantially involved in the increased risk of atherosclerotic cardiovascular diseases in the general population in general[1,5–11] and patients with coronary artery disease in particular.[12–17] We have previously reported that the prevalence of MetS in patients with CHF is more than 2-fold greater than in the general population in Japan.[18] However, the prognostic impact of MetS in CHF patients remains to be elucidated. Furthermore, although sex differences may exist in the prevalence of MetS,[18–21] little is known about sex differences in the prognostic impact of MetS.

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Since our first report on the prevalence and clinical signifi-

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Department of Cardiovascular Medicine and Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai (S.T., Y.S., Y.M., S.M., H.S.); Cardiovascular Division of Internal Medicine, National Cerebral and Cardiovascular Center, Suita (M.A., S.Y., M.K.); Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo (K.S., H.D.); Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube (T.Y., T.M., M.Y.); Department of Internal Medicine Division of Cardio-Vascular Medicine, Kurume University School of Medicine, Kurume (Y.F.); and Division of Cardiovascular Medicine, Saiseikai Futsukaichi Hospital, Chikushino (T.K., S.A.), Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Hiroaki Shimokawa, MD, PhD, Professor and Chairman, Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: shimo@cardio.med.tohoku.ac.jp

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cance of MetS in Japanese patients with CHF in a nationwide, large-scale study,[18] we have prospectively followed up the patients for 5 years, and now have enough data to analyze the prognostic impact of MetS in this population. In the present study, we thus aimed to elucidate the prognostic impact of MetS with a special reference to sex differences in Japanese CHF patients.[18,22]

Methods

Study Design

Between September 2006 and December 2010, we successfully enrolled 10,470 patients with cardiovascular diseases from 6 institutes in Japan.[18,22] After excluding 11 patients without data to determine the stage of CHF and 5,697 Stage A/B patients, we finally enrolled 4,762 consecutive patients with symptomatic CHF (Stage C/D). HF was diagnosed by the Framingham Criteria[23] and the stages of CHF by the ACCF/AHA guidelines.[24] We prospectively collected the following data from the medical records of participating hospitals by use of web data collection system (Fujitsu Systems East, Tokyo, Japan):[18,22] (1) baseline demographic data (eg, age, sex, height, body mass index [BMI], body weight, waist circumference, systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, lipid profile and fasting plasma glucose), (2) laboratory data including levels of B-type natriuretic peptide (BNP) and echocardiographic data such as left ventricular ejection fraction (LVEF), (3) coronary risk factors (hypertension, DM and dyslipidemia), (4) other medical history (admissions for HF, stroke, atrial fibrillation, ischemic heart disease, hypertensive heart disease, cardiomyopathy, valvular heart disease, and congenital heart disease), (5) non-pharmacological treatments (pacemaker implantation, implantable cardioverter defibrillator, cardiac resynchronization therapy, percutaneous coronary intervention, radiofrequency catheter ablation, coronary artery bypass grafting and valvular surgery), (6) medications (angiotensin-

Table 1. Baseline Clinical Characteristics of CHF Patients by MetS

	(–) MetS (n=2,681)	(+) MetS (n=1,885)	P value
Age (years)	70.0±0.2	67.2±0.3	<0.001
Sex (male)	1,533 (57.2%)	1,571 (83.3%)	<0.001
Height (cm)	157.0±0.2	162.4±0.2	<0.001
Weight (kg)	54.4±0.2	69.2±0.3	<0.001
BMI (kg/m^2)	22.0±0.1	26.2±0.1	<0.001
WC (cm)	79.2±0.2	93.5±0.2	<0.001
BP (mmHg)			
Systolic	124.0±0.4	129.5±0.4	<0.001
Diastolic	70.6±0.2	74.2±0.3	<0.001
Heart rate (beats/min)	72.5±0.3	72.3±0.3	0.594
TG (mg/dl)	114.4±1.4	151.8±2.6	<0.001
Total cholesterol (mg/dl)	182.2±0.7	184.4±0.9	0.051
HDL cholesterol (mg/dl)	53.9±0.3	48.7±0.4	<0.001
LDL cholesterol (mg/dl)	104.2±0.7	106.3±0.9	0.056
Fasting blood glucose (mg/dl)	112.8±0.7	126.2±1.0	<0.001
BNP (pg/ml)	127.0 (49.6–272.1)	82.9 (32.1–193.5)	<0.001
LVEF (%)	56.6±0.3	57.2±0.3	0.183
≥50%	1,738 (67.2%)	1,283 (70.8%)	0.011
Components of MetS			
Over-WC	286 (10.7%)	1,885 (100%)	<0.001
Dyslipidemia	1,746 (67.6%)	1,690 (90.4%)	<0.001
Glucose intolerance/DM	1,133 (43.9%)	1,276 (68.9%)	<0.001
Hypertension	1,930 (72.2%)	1,761 (93.4%)	<0.001
Medical history			
HT	1,914 (71.5%)	1,753 (93.0%)	<0.001
DM	622 (23.3%)	781 (41.5%)	<0.001
DL	1,703 (63.6%)	1,662 (88.2%)	<0.001
CRF	80 (3.0%)	64 (3.4%)	0.440
Stroke	479 (17.9%)	363 (19.3%)	0.230
AF	1,091 (40.8%)	590 (31.5%)	<0.001
IHD	1,059 (39.5%)	1,035 (54.9%)	<0.001
HHD	226 (8.4%)	241 (12.8%)	<0.001
CM	544 (20.3%)	359 (19.0%)	0.308
VHD	845 (31.5%)	300 (15.9%)	<0.001
CHD	56 (2.1%)	18 (1.0%)	0.003
HF admission	1,504 (56.3%)	932 (49.7%)	<0.001

(Table 1 continued the next page.)

	(–) MetS (n=2,681)	(+) MetS (n=1,885)	P value
Non-medical therapy			
PMI	228 (8.5%)	124 (6.6%)	0.018
ICD	71 (2.6%)	30 (1.6%)	0.018
CRT	43 (1.6%)	20 (1.1%)	0.156
PTCA	683 (25.5%)	739 (39.2%)	<0.001
RFCA	48 (1.8%)	36 (1.9%)	0.823
CABG	209 (7.8%)	207 (11.0%)	<0.001
Valvular surgery	306 (11.4%)	99 (5.2%)	<0.001
Medications			
ACEI/ARB	1,822 (68.8%)	1,489 (80.3%)	<0.001
β-blocker	1,255 (50.3%)	1,015 (56.3%)	<0.001
Statin	820 (31.0%)	918 (49.0%)	<0.001
NYHA class			<0.001
I	546 (20.4%)	462 (24.5%)	
II	1,791 (66.9%)	1,245 (66.1%)	
III	308 (11.5%)	170 (9.0%)	
IV	33 (1.2%)	6 (0.3%)	
NYHA III/IV	341 (12.7%)	176 (9.3%)	<0.001
Stage of heart failure			0.006
C	2,616 (97.6%)	1,861 (98.7%)	
D	65 (2.4%)	24 (1.3%)	

Results are mean±standard error (SE) or median (25th percentile/75th percentile). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CM, cardiomyopathy; CRF, chronic renal failure; CRT, cardiac resynchronization therapy; DL, dyslipidemia; DM, diabetes mellitus; HDL, high-density lipoprotein; HF, heart failure; HHD, hypertensive heart disease; HT, hypertension; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MetS, metabolic syndrome; NYHA, New York Heart Association; PMI, pacemaker implantation; PTCA, percutaneous transluminal coronary angioplasty; RFCA, radiofrequency catheter ablation; TG, triglyceride; VHD, valvular heart disease; WC, waist circumference.

converting enzyme inhibitor [ACEI], angiotensin-receptor blocker [ARB], β-blocker, and statin), and (7) New York Heart Association (NYHA) HF class. The primary endpoint was a composite of all-cause death and atherosclerotic cardiovascular events, including acute myocardial infarction (AMI), stroke, unstable angina pectoris requiring hospitalization, and endovascular interventions or coronary artery bypass grafting for stable coronary artery disease, peripheral arterial disease and carotid artery disease. The secondary endpoints included each component of the primary endpoint, such as all-cause death and atherosclerotic events. The study protocol was approved by the ethical committee of each institute and the present study was prospectively conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent.

Definition of MetS

In the present study, we primarily employed the definition of MetS used by the Japanese Committee for the Diagnostic Criteria of MetS in April 2005 (the original Japanese criteria), which defined MetS as 2 or more metabolic abnormalities (dyslipidemia, glucose intolerance/DM and hypertension) in addition to the waist circumference criterion (≥85 cm in male and 90 cm in female).[25] Dyslipidemia was defined as use of lipid-lowering drugs and/or elevated lipid levels, triglycerides (TG) ≥150 mg/dl and/or high-density lipoprotein (HDL) cholesterol <40 mg/dl. Glucose intolerance/DM was diagnosed by the use of antidiabetic drugs and/or fasting glucose ≥110 mg/dl. Hypertension was diagnosed by the use of antihypertensive drugs and/or systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg. In addition to these original Japanese criteria,[25] we examined 2 other criteria of MetS to validate the results: (1) the modified Japanese criteria, in which MetS was defined as 2 or more metabolic abnormalities (dyslipidemia, glucose intolerance/DM and hypertension) in addition to the waist circumference criterion for Asians recommended by the International Diabetes Federation (IDF) (≥90 cm in male and 80 cm in female),[26] and (2) the modified National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP) III criteria,[27] which defined MetS as 3 or more metabolic disorders among the following 5 abnormalities: elevated TG (≥150 mg/dl), reduced HDL cholesterol (<40 mg/dl in male and 50 mg/dl in female, respectively), glucose intolerance/DM, hypertension and over waist circumference modified for Asians by the IDF (≥90 cm in male and 80 cm in female) (**Table S1**).[26]

Statistical Analysis

Continuous variables are shown as mean±standard error, and categorical variables as counts and percentages. Comparisons between groups were performed with Welch's t-test for continuous variables and Fisher's exact test for categorical variables. In the multivariate analysis for events, the Cox regression hazard model was utilized with the covariates such as sex (only in overall group), age, BMI, BNP, LVEF, SBP and DBP and heart rate. Cumulative incidence curves of the endpoints were estimated by Cox regression hazard models with the mean value of age, BMI, LVEF, SBP, DBP and heart rate, and the median value of BNP as covariates. Chronic renal failure was defined as serum creatinine ≥3.0 mg/dl. Statistical analyses were performed using the statistical computing software R

Table 2. Baseline Clinical Characteristics of CHF Patients by Sex

	Male			Female		
	(–) MetS (n=1,533)	(+) MetS (n=1,571)	P value	(–) MetS (n=1,148)	(+) MetS (n=314)	P value
Age (years)	69.0±0.3	66.4±0.3	<0.001	71.4±0.4	71.7±0.7	0.712
Height (cm)	162.8±0.2	164.7±0.2	<0.001	149.3±0.2	150.5±0.4	0.006
Weight (kg)	58.3±0.2	70.4±0.3	<0.001	49.1±0.3	63.0±0.7	<0.001
BMI (kg/m^2)	22.0±0.1	25.9±0.1	<0.001	22.0±0.1	27.8±0.3	<0.001
WC (cm)	80.1±0.2	92.7±0.2	<0.001	78.0±0.3	97.5±0.4	<0.001
BP (mmHg)						
Systolic	122.8±0.5	129.0±0.5	<0.001	125.6±0.6	131.7±1.1	<0.001
Diastolic	70.5±0.3	74.5±0.3	<0.001	70.7±0.4	73.0±0.7	0.004
Heart rate (beats/min)	71.3±0.4	72.1±0.4	0.127	74.1±0.5	73.1±0.8	0.312
TG (mg/dl)	114.4±1.9	153.3±3.0	<0.001	114.3±1.9	144.3±4.1	<0.001
Total cholesterol (mg/dl)	177.4±0.9	182.9±1.0	<0.001	188.6±1.1	191.7±2.3	0.205
HDL cholesterol (mg/dl)	52.2±0.4	48.4±0.4	<0.001	56.1±0.5	50.4±0.8	<0.001
LDL cholesterol (mg/dl)	101.7±0.9	105.4±0.9	0.004	107.5±1.1	110.6±2.2	0.191
Fasting blood glucose (mg/dl)	113.5±1.0	126.9±1.1	<0.001	111.7±1.1	122.6±2.1	<0.001
BNP (pg/ml)	128.4 (48.0–273.0)	76.1 (29.9–181.0)	<0.001	125.5 (51.4–268.3)	116.5 (51.1–257.3)	0.735
LVEF (%)	54.2±0.4	56.4±0.4	<0.001	59.9±0.5	61.4±0.8	0.131
≥50%	916 (62.1%)	1,043 (69.1%)	<0.001	822 (74.1%)	240 (79.7%)	0.042
Components of MetS						
Over-WC	234 (15.3%)	1,571 (100%)	<0.001	52 (4.5%)	314 (100%)	<0.001
Dyslipidemia	974 (65.9%)	1,402 (90.0%)	<0.001	772 (70.0%)	288 (92.3%)	<0.001
Glucose intolerance/DM	651 (44.0%)	1,061 (68.8%)	<0.001	482 (43.7%)	213 (68.9%)	<0.001
Hypertension	1,069 (70.0%)	1,461 (93.0%)	<0.001	861 (75.1%)	300 (95.5%)	<0.001
Medical history						
HT	1,063 (69.5%)	1,454 (92.6%)	<0.001	851 (74.2%)	299 (95.2%)	<0.001
DM	369 (24.2%)	641 (40.9%)	<0.001	253 (22.1%)	140 (44.9%)	<0.001
DL	950 (62.1%)	1,375 (87.6%)	<0.001	753 (65.6%)	287 (91.4%)	<0.001
CRF	60 (3.9%)	53 (3.4%)	0.444	20 (1.7%)	11 (3.5%)	0.073
Stroke	287 (18.8%)	309 (19.8%)	0.523	192 (16.8%)	54 (17.3%)	0.865
AF	621 (40.6%)	508 (32.5%)	<0.001	470 (41.1%)	82 (26.4%)	<0.001
IHD	742 (48.4%)	897 (57.1%)	<0.001	317 (27.6%)	138 (43.9%)	<0.001
HHD	113 (7.4%)	181 (11.5%)	<0.001	113 (9.8%)	60 (19.1%)	<0.001
CM	321 (20.9%)	307 (19.5%)	0.348	223 (19.4%)	52 (16.5%)	0.255
VHD	381 (24.9%)	241 (15.3%)	<0.001	464 (40.4%)	60 (19.1%)	<0.001
CHD	21 (1.4%)	15 (1.0%)	0.317	35 (3.0%)	3 (1.0%)	0.043
HF admission	859 (56.2%)	771 (49.3%)	<0.001	645 (56.4%)	161 (51.6%)	0.140
Non-medical therapy						
PMI	95 (6.2%)	102 (6.5%)	0.769	133 (11.6%)	22 (7.0%)	0.022
ICD	49 (3.2%)	28 (1.8%)	0.015	22 (1.9%)	2 (0.6%)	0.136
CRT	27 (1.8%)	20 (1.3%)	0.304	16 (1.4%)	0 (0%)	0.031
PTCA	492 (32.1%)	647 (41.2%)	<0.001	191 (16.6%)	91 (29.0%)	<0.001
RFCA	31 (2.0%)	29 (1.8%)	0.795	17 (1.5%)	7 (2.2%)	0.326
CABG	154 (10.0%)	181 (11.5%)	0.184	55 (4.8%)	26 (8.3%)	0.025
Valvular surgery	131 (8.5%)	91 (5.8%)	0.003	175 (15.2%)	8 (2.5%)	<0.001
Medications						
ACEI/ARB	1,072 (70.9%)	1,243 (80.6%)	<0.001	750 (66.1%)	246 (78.8%)	<0.001
β-blocker	774 (51.2%)	844 (54.1%)	0.104	481 (42.4%)	171 (54.8%)	<0.001
Statin	461 (30.5%)	757 (48.5%)	<0.001	359 (31.7%)	161 (51.6%)	<0.001
NYHA class			0.003			0.618
I	356 (23.3%)	417 (26.6%)		190 (16.6%)	45 (14.3%)	
II	1,009 (65.9%)	1,026 (65.4%)		782 (68.1%)	219 (70.0%)	
III	147 (9.6%)	123 (7.8%)		161 (14.0%)	47 (15.0%)	
IV	18 (1.2%)	4 (0.3%)		15 (1.3%)	2 (0.6%)	
NYHA III/IV	165 (10.8%)	127 (8.1%)	0.012	176 (15.3%)	49 (15.7%)	0.930
Stage of heart failure			0.025			0.175
C	1,495 (97.5%)	1,550 (98.7%)		1,121 (97.6%)	311 (99.0%)	
D	38 (2.5%)	21 (1.3%)		27 (2.4%)	3 (1.0%)	

Results are mean±standard error (SE) or median (25th percentile/75th percentile). Abbreviations as in Table 1.

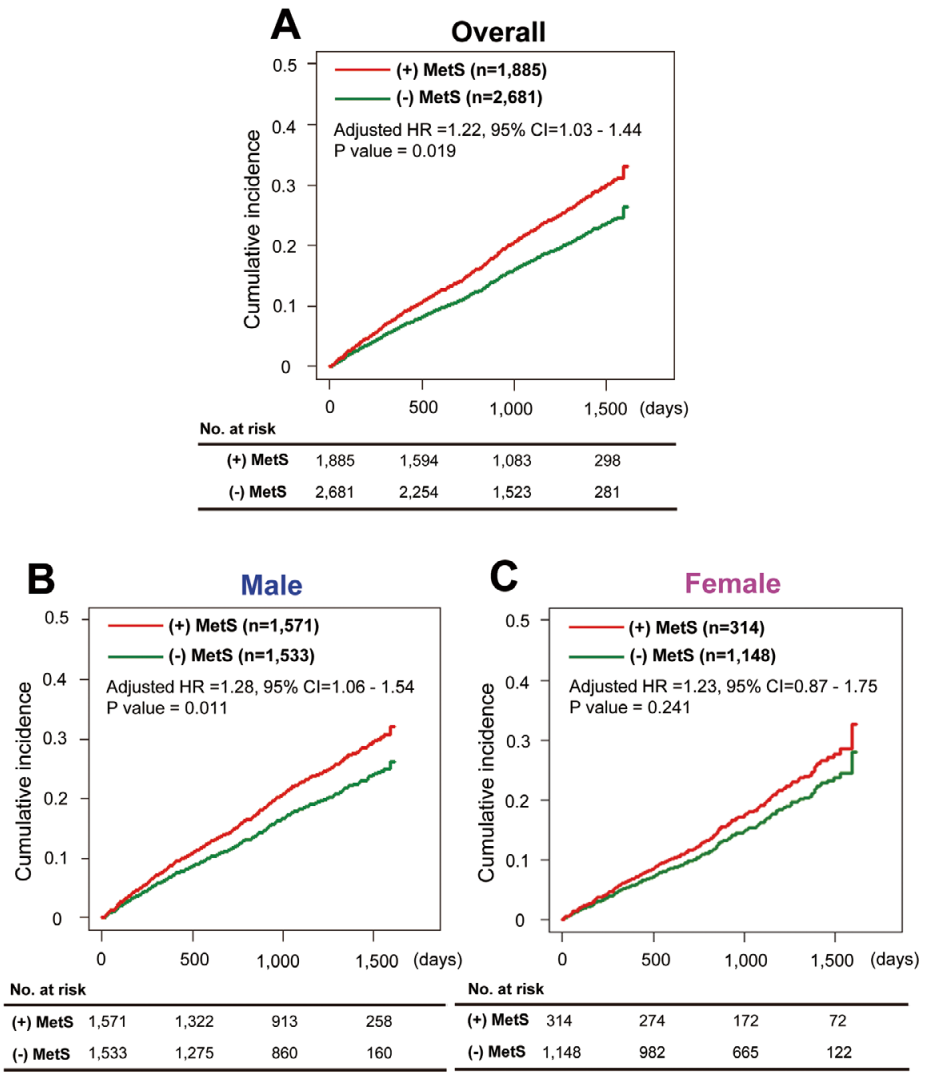

Figure 1. Cox regression incidence rate curves of the composite endpoint in CHF patients in (**A**) overall population, (**B**) males and (**C**) females. Hazard ratio (HR) and 95% confidence interval (95% CI) were obtained from multivariate Cox regression models. MetS, metabolic syndrome.

version 3.1.1 (http://www.r-project.org). P<0.05 and P value for interaction <0.1 were considered to be statistically significant.

Results

Characteristics of CHF Patients With and Without MetS

Among the 4,762 patients, 196 did not have enough information for the diagnosis of MetS and were excluded from the analysis. Among the remaining 4,566 patients, 1,885 (41.3%) had MetS and 2,681 (58.7%) did not. As shown in **Table 1**, the prevalence of males was 83.3% and 57.2% in patients with and without MetS, respectively. The patients with MetS were characterized by younger age, higher BMI, lower BNP levels and higher prevalence of over waist circumference, dyslipidemia, glucose intolerance/DM and hypertension, as compared with those without MetS. Furthermore, MetS patients were characterized by higher prevalence of ischemic heart disease, lower prevalence of atrial fibrillation, valvular heart disease, cardiomyopathy and congenital heart disease and prior history of HF admission, as compared with those without MetS.

Sex Differences in the Clinical Characteristics of CHF Patients With MetS

Table 2 shows the baseline clinical characteristics of CHF patients with and without MetS by sex. The prevalence of MetS was significantly higher in males compared with females (50.6 vs. 21.5%, P<0.001). In both sex groups, MetS patients were characterized by higher BMI, higher systolic and diastolic BP, and higher prevalence of over waist circumference, dyslipidemia, glucose intolerance/DM, hypertension, ischemic heart disease and hypertensive heart disease. In males, MetS patients, compared with those without it, were younger and had significantly higher levels of total cholesterol, LDL cho-

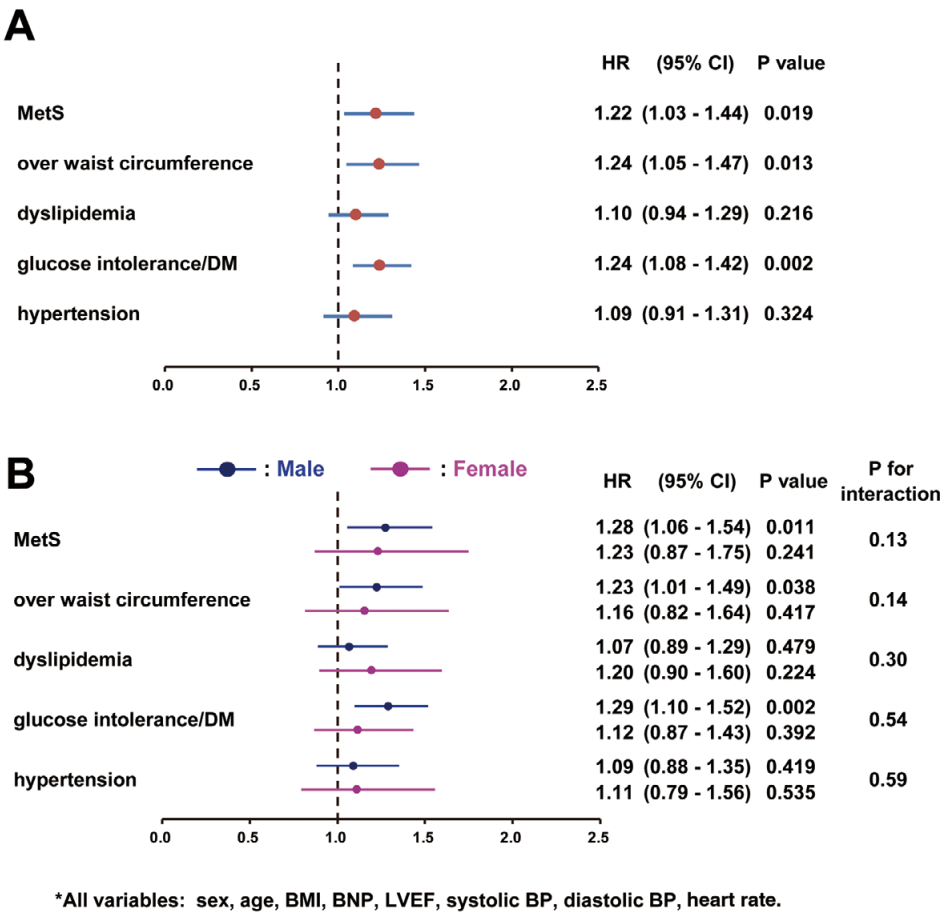

Figure 2. Forest plots of adjusted hazard ratio (HR) and 95% confidence interval (95% CI) according to the MetS components for composite endpoints in (**A**) overall population, (**B**) males and females. BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; DM, diabetes mellitus; LVEF, left ventricular ejection fraction MetS, metabolic syndrome.

lesterol and LVEF and lower BNP levels and NYHA class. In contrast, female CHF patients with MetS, as compared with those without it, had comparable age, BNP levels and NYHA classes. In addition, female CHF patients with MetS less frequently received non-pharmacological treatments, such as pacemaker implantation and cardiac resynchronization therapy, and more frequently underwent coronary artery bypass grafting. As for medications, MetS patients of both sexes were more likely to be treated with renin-angiotensin system inhibitors, such as ACEI and ARB, and statins, while female MetS patients were more likely to be treated with β-blockers than males.

Prognostic Impact of MetS in CHF Patients by Sex

During the follow-up period of 3.2±1.1 years, 1,171 patients (24.6%) experienced the composite endpoint (820 males (25.4%) vs. 351 females (22.8%), P<0.001). The cumulative incidence curves and multivariate Cox hazard models revealed that MetS was significantly associated with increased incidence of the composite endpoint in CHF patients (hazard ratio (HR) 1.22; 95% CI 1.03–1.44, P=0.019), particularly males (HR 1.28; 95% CI 1.06–1.54, P=0.011), but not females (HR 1.23; 95% CI 0.87–1.75, P=0.241) (**Figure 1**). Analysis for the secondary endpoints showed that MetS had significant prognostic impact in the overall population and males (but not in females) for atherosclerotic events but not for all-cause death (**Figure S1**). Among the MetS components, over waist circumference and glucose intolerance/DM were significantly associated with an increased composite endpoint, which was particularly evident in males but not in females (**Figure 2**). The cumulative incidence rate curves revealed that glucose intolerance/DM had a significant association with increased incidence of the composite endpoint regardless of the presence or absence of over waist circumference in the overall population and in males but not in females (**Figure 3**).

It was also shown that MetS had significant prognostic impact for atherosclerotic events but not for all-cause death (**Figure 4**), which was particularly evident in males (**Figure S2**). In contrast, in females, MetS had no significant impact for all-cause death or atherosclerotic events (**Figure S2**). The multivariate analysis demonstrated that among the MetS components, only glucose intolerance/DM had a significant association with increased incidence of all-cause death (**Figure 4**), which was evident in males but not in females (**Figure S2**). In contrast, in both the overall population and males, over waist circumference, dyslipidemia and glucose intolerance/DM were

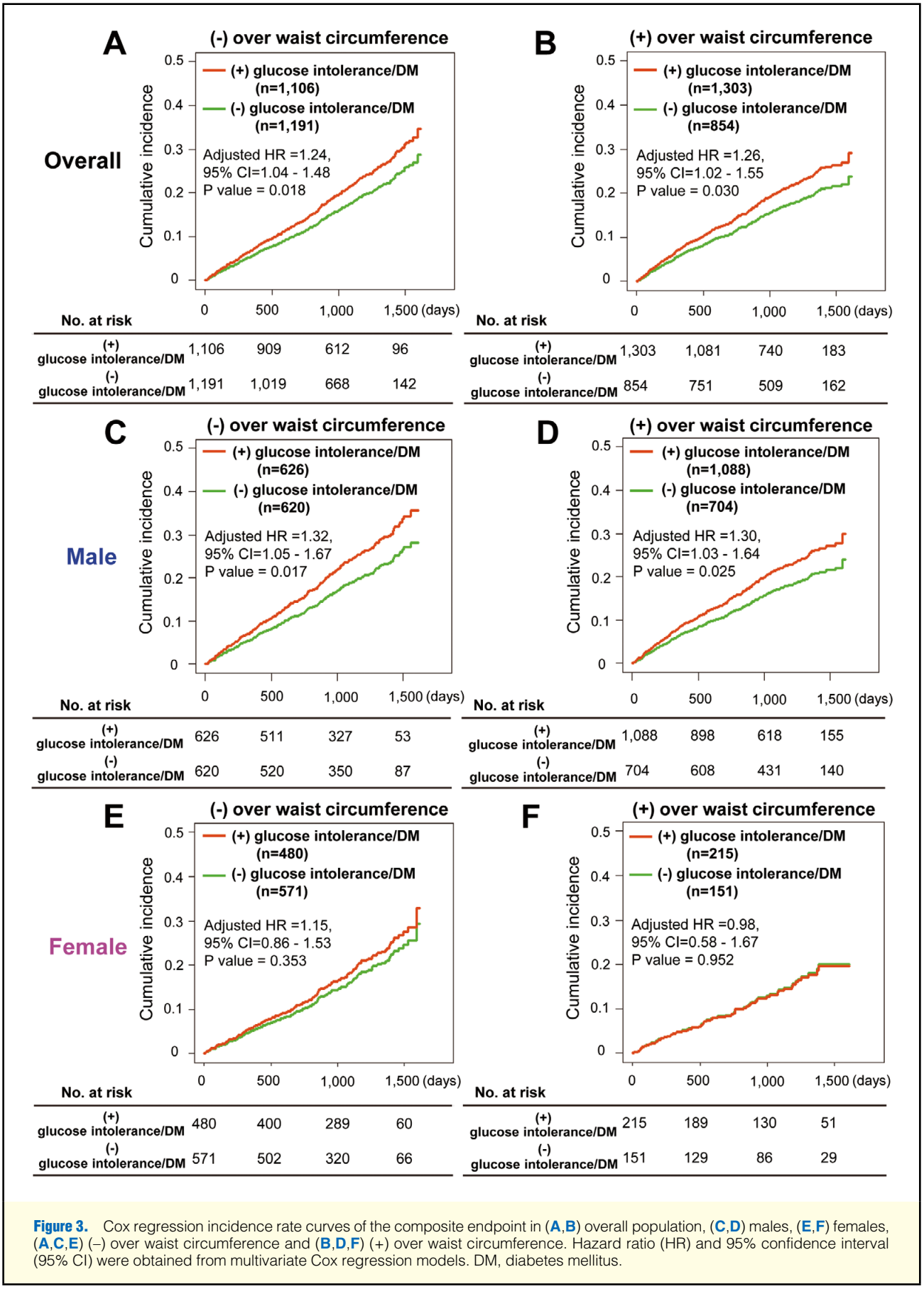

Figure 3. Cox regression incidence rate curves of the composite endpoint in (**A**,**B**) overall population, (**C**,**D**) males, (**E**,**F**) females, (**A**,**C**,**E**) (–) over waist circumference and (**B**,**D**,**F**) (+) over waist circumference. Hazard ratio (HR) and 95% confidence interval (95% CI) were obtained from multivariate Cox regression models. DM, diabetes mellitus.

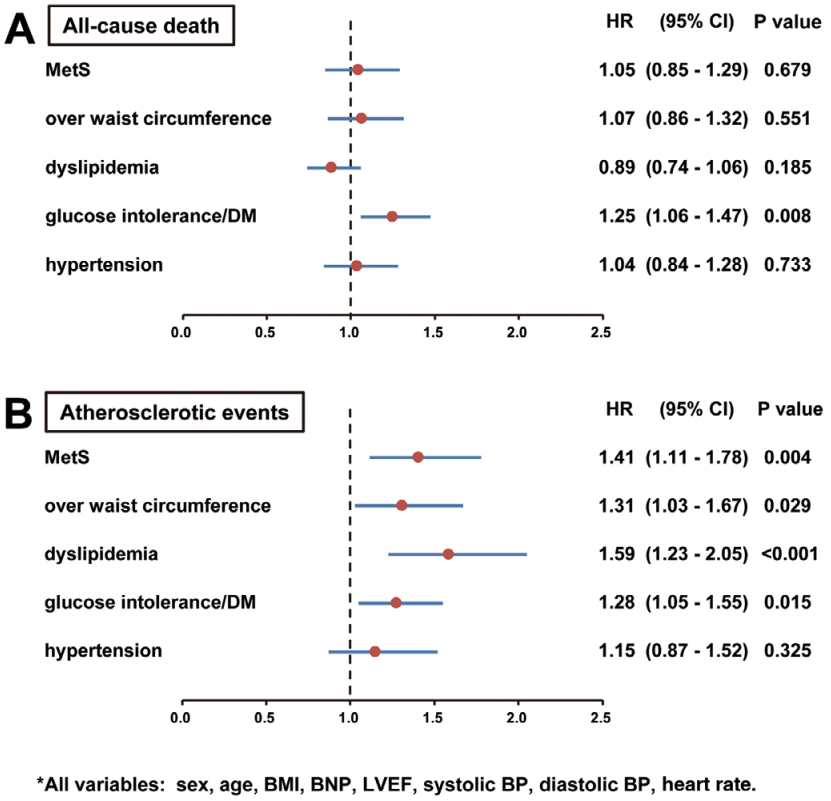

Figure 4. Forest plots of adjusted hazard ratio (HR) and 95% confidence interval (95% CI) according to the MetS components for (**A**) all-cause death and (**B**) atherosclerotic events. BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; DM, diabetes mellitus; LVEF, left ventricular ejection fraction MetS, metabolic syndrome.

significantly associated with increased incidence of atherosclerotic events, while in females only dyslipidemia had a significant association with an increased incidence of atherosclerotic events but not with that of all-cause death (Figures 4,S2).

Evaluation of Prognostic Impact of MetS by 3 Different Definitions

Finally, we evaluated the prognostic impact of MetS in CHF patients by using 3 different definitions. When defined by the original Japanese criteria or by the modified Japanese criteria, MetS had a significant association with increased incidence of the composite endpoint in the overall population and males, whereas it had no impact when defined by the modified NCEP-ATP III criteria (Figure 5). MetS defined by all 3 criteria had no significant association with the incidence of the composite endpoint in females. In contrast, MetS in any of the criteria had no significant association with the incidence of all-cause death in the overall population or both sexes, whereas it had a significant association with increased atherosclerotic events in all the criteria in the overall population and both sexes, except for the original Japanese criteria in females (Figure 5).

Discussion

The novel findings of the present study are that (1) MetS has prognostic impact in male Japanese patients with CHF but not females; (2) among the MetS components, over waist circumference and glucose intolerance/DM have prognostic impact; and (3) among the current 3 definitions of MetS, the Japanese and Asian definitions effectively delineate the CHF patients at risk. To the best of our knowledge, this is the first study demonstrating the prognostic impact of MetS in CHF patients.

Prevalence and Characteristics of MetS in CHF Patients

In the present study, the prevalence of MetS was 41.3% in patients with Stage C/D CHF. MetS was noted in 50.3% and 21.5% of male and female patients, respectively, both of which were higher than in the general population (≈20% in males and ≈10% in females).[6,19,28] It is highly possible that MetS and CHF form a vicious cycle, in which activation of the sympathetic nervous system and renin-angiotensin system appears to be involved.[29] However, it was also noteworthy that patients with MetS had lower NYHA class and lower BNP levels as compared with those without it. In addition, the prevalence of atrial fibrillation was lower in patients with MetS, which is inconsistent with previous reports in the general population.[30,31] This discrepancy in the prevalence of atrial fibrillation could be explained by the younger age and less severe HF status in patients with MetS as compared with those without it.

Sex Differences in the Prevalence and Characteristics of CHF Patients With MetS

In the present study, we found that the prevalence of MetS in CHF patients was significantly higher in males than in females,

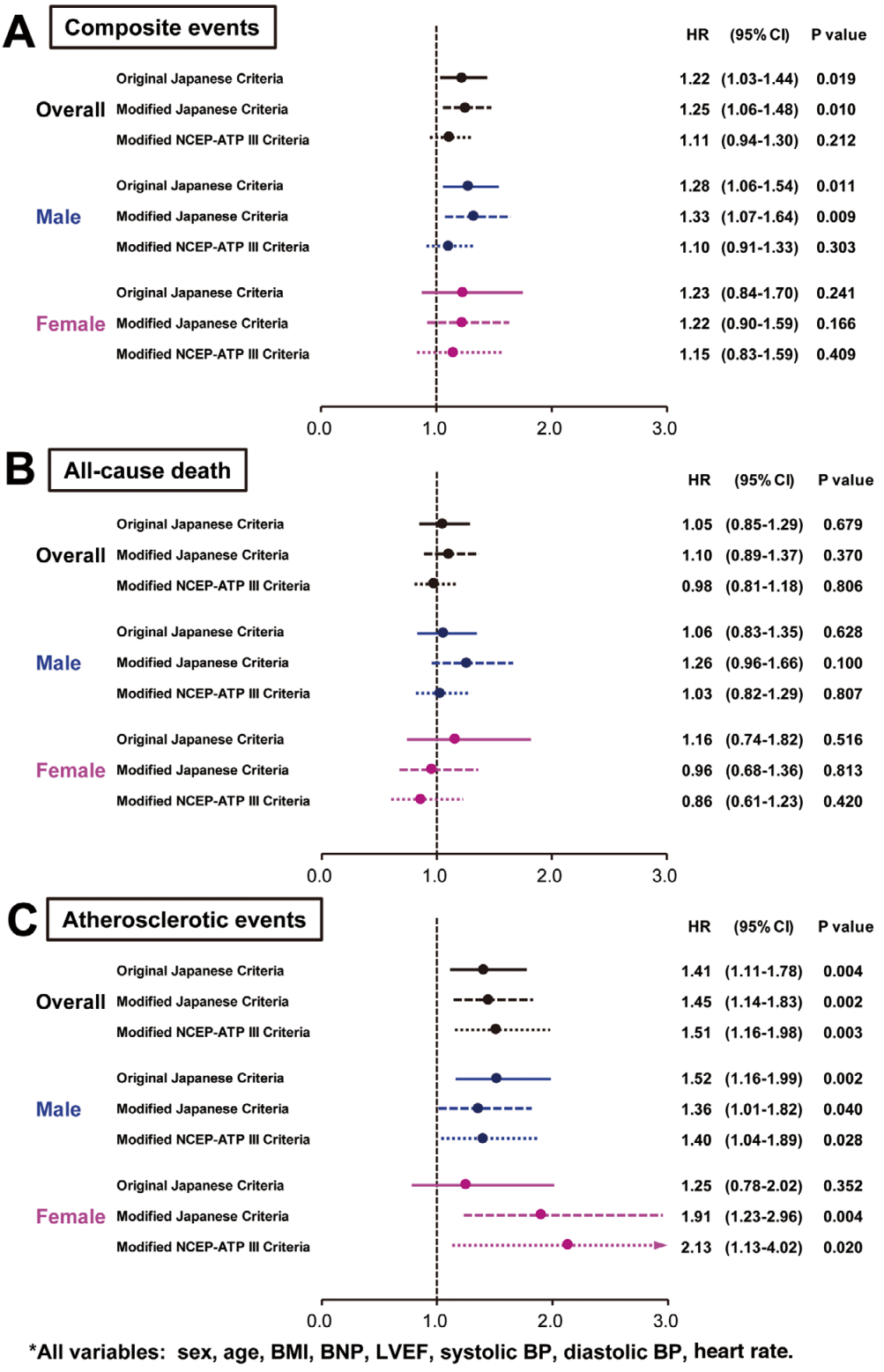

Figure 5. Forest plots of adjusted hazard ratio (HR) and 95% confidence interval (95% CI) according to the MetS criteria for (**A**) composite endpoint, (**B**) all-cause death and (**C**) atherosclerotic events. BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fraction; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III.

a consistent finding with previous studies of the general populations in Japan,[6,19,28] but inconsistent with those in Western populations.[32,33] For example, it was reported that the prevalence of MetS, as defined by the NCEP-ATP Ⅲ criteria, was higher in females than in males (32.1 vs. 19.9%) in the European population of the MORGAM Study.[32] One possible explanation for this difference between Caucasians and Japanese populations in the prevalence of MetS in females could be the difference in the prevalence of central obesity in females. Furthermore, it should be pointed out that the lower prevalence of abdominal obesity in Japanese female population is related, at least in part, to the waist circumference cut-off points in the Japanese criteria (85 cm for males and 90 cm for females).[25] This notion was also confirmed in the Tanno and Sobetsu Study, a cohort study of the general population in the Hokkaido area, Japan.[28] Thus, it is possible that the cut-off point of 90 cm for females may have underdiagnosed central obesity in the Japanese population. This sex difference in the definition of abdominal obesity should be taken into consideration when evaluating the prevalence of MetS in the Japanese population using the Asian criteria of the IDF (90 cm for men and 80 cm for women).[26,34]

The present study also revealed sex differences in the clinical characteristics of CHF patients with MetS; male CHF patients with MetS, as compared with those without it, were younger and had lower NYHA class, whereas female CHF patients with MetS, as compared with those without it, had comparable age and HF severity. In addition, some other sex differences were noted in terms of clinical background and treatments. It is conceivable that sex differences in the hormonal regulation of body fat distribution and adipocyte size and function may explain the sex differences in the clinical characteristics of CHF patients with MetS.[20,35]

Prognostic Impact of MetS in Patients With CHF

It has been reported that MetS is associated with a worse prognosis in patients with ischemic heart disease[12–17] and in those with stroke.[36] In the present study, MetS was associated with increased incidence of the composite endpoint of all-cause death and atherosclerotic events. However, MetS had a significant prognostic impact on atherosclerotic events but not on all-cause death as an individual secondary endpoint. This finding may be clinically significant because MetS has been considered to be a risk of cardiovascular events and death.[33,37] For example, in their meta-analysis of 87 studies (n=951,083), Mottillo et al demonstrated that MetS was significantly associated with increased risk of all-cause mortality (relative risk [RR]: 1.58), myocardial infarction (RR: 1.99) and stroke (RR: 2.27).[37] However, in the secondary prevention setting of Japanese patients with AMI, Nakatani et al reported that the impact of MetS, defined by the modified NCEP-ATP Ⅲ criteria, was not associated with increased cardiac death but was associated with increased non-fatal myocardial infarction,[15] a finding consistent with the present study. Thus, the prognostic impact of MetS on mortality may differ between Caucasians and Japanese populations and between the primary and secondary prevention settings of cardiovascular disease in the current era.

Sex Differences in the Prognostic Impact of MetS in CHF Patients

The present study demonstrated that the prognostic impact of MetS in CHF patients was evident in males but not in females. This finding has significant importance because there have been few reports regarding the sex differences in the prognostic impact of MetS in patients with cardiovascular diseases. Several explanations are possible for these sex differences. First, sex differences in the clinical characteristics of MetS patients regarding age, HF severity and treatments may explain the differences. Second, it is possible that MetS is underdiagnosed in Japanese females with the original Japanese criteria, in which the presence of over waist circumference is mandatory for the diagnosis. Third, waist circumference does not necessarily reflect the extent of visceral obesity, as men are likely to store the visceral fat, whereas women have subcutaneous fat.[38,39]

Nonetheless, it was reported in a meta-analysis that the prognostic impact of MetS in females was equivalent or even greater than in males in European populations without known cardiovascular disease (36 cohorts from 10 countries in the MORGAM Study).[32] It is possible that the discrepancy in the prognostic impact of MetS in females between the MORGAM Study and the present study could be caused by the difference in ethnicity (Caucasians vs. Japanese) and/or the participants (general population vs. CHF patients).

Influence of Over Waist Circumference and Glucose Intolerance/DM on the Prognostic Impact in CHF Patients

The present study demonstrated that among the 4 MetS components, over waist circumference and glucose intolerance/DM were associated with increased composite endpoint in male CHF patients. Thus, it is possible that these components of MetS have synergistic effects, at least in males. However, Cox regression incidence curves showed that glucose intolerance/DM had almost comparable prognostic impact for the composite endpoint regardless of over waist circumference in males. In contrast, in females, glucose intolerance/DM again had no prognostic impact regardless of over waist circumference. Thus, the prognostic impact of glucose intolerance/DM may be independent of accumulation of visceral fat in male CHF patients, warranting further studies to elucidate the mechanisms involved in the prognostic impact of glucose intolerance/DM in CHF patients with MetS.

Influence of MetS Criteria on Prognostic Impact of MetS

In the present study, we primarily used the 2005 definition of the Japanese Committee for the Diagnostic Criteria of MetS[25] as the original Japanese criteria and found that MetS was associated with increased risk of the composite endpoint and atherosclerotic events in CHF patients. Because it has been occasionally questioned whether the original Japanese criteria are appropriate to evaluate cardiovascular risks in Japanese patients with metabolic disorders, we compared 3 different MetS criteria to evaluate the prognostic impact of MetS in CHF patients. As a result, we found that the prognostic impact of MetS on the composite endpoint was insignificant in males when defined by the modified NCEP-ATP Ⅲ criteria[27] and that the prognostic impact of MetS on the atherosclerotic events was insignificant in females when defined by the original Japanese criteria.[25] These results indicate that caution should be paid when extrapolating the results from one MetS criterion to those with another one. Because both age and sex especially are known to influence the prevalence of MetS and its prognostic impact,[32] several criteria should be used to validate the results obtained.

Study Limitations

First, because the present results were primarily obtained using the Japanese criteria,[25] we need to be cautious in generalizing our findings to other cohorts using with different MetS crite-

ria. Second, because we focused on the prognostic impact of MetS in Japanese CHF patients in the present study, the impact of MetS on other cardiovascular diseases remains to be examined in future studies. Third, in the present study, the etiologies of stroke were unknown and thus it is possible that thromboembolic stroke caused by atrial fibrillation was included in atherosclerotic events. Fourth, because there are no upper limits of the extent of diabetes, dyslipidemia or hypertension in the current MetS criteria, we were unable to exclude the influence of a more severe status of those abnormalities, although this point may be out of the scope of the present study.

Conclusions

In the present study, we were able to demonstrate that MetS has a negative prognostic impact in male CHF patients but not in females, suggesting the importance of a sex-specific approach to the management of metabolic disorders in these patients.

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Conflict of Interest Statement

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Supplementary Files

Supplementary File 1

Table S1. The current 3 criteria of metabolic syndrome

Figure S1. Cox regression incidence rate curves for (**A**,**C**,**E**) all-cause death and (**B**,**D**,**F**) atherosclerotic events in patients with chronic heart failure in (**A**,**B**) overall population, (**C**,**D**) males and (**E**,**F**) females.

Figure S2. Forest plots of adjusted hazard ratio (HR) and 95% confidence interval (95% CI) according to the MetS components and sexes for (**A**) all-cause death and (**B**) atherosclerotic events.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0942