Original Article

Impact of Metabolic Syndrome among Patients with and without Diabetes Mellitus on Long-Term Outcomes after Percutaneous Coronary Intervention

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Metabolic syndrome (MS) is highly prevalent and an established key risk factor for coronary artery disease, regardless of the presence or absence of diabetes mellitus (DM). Long-term follow-up studies have addressed the influence of MS with and without DM on the prognosis of patients undergoing percutaneous coronary intervention (PCI). We classified 748 consecutive patients who had undergone PCI into four groups as follows: neither DM nor MS, DM alone, MS alone, and both DM and MS. Post hoc analyses were conducted using prospectively collected clinical data. Multivariate Cox regression was used to evaluate the risk within each group for all-cause mortality and composite cardiac events (cardiac death, non-fatal acute coronary syndrome), adjusting for age, gender, body mass index, low-density lipoprotein (LDL) cholesterol level, hypertension, smoking, prior coronary artery bypass graft, presentation of acute coronary syndrome, left ventricular ejection fraction, multivessel disease, and procedural success. The progress of 321 (42.9%) patients with neither DM nor MS, 109 (14.6%) patients with DM alone, 129 (17.2%) patients with MS alone, and 189 (25.3%) patients with both DM and MS was followed up for a mean of 12.0±3.6 years. Patients with both DM and MS had significant risk for increased all-cause mortality (2.10 [1.19–3.70]). Patients with MS alone (2.14 [1.31–3.50]) and with both DM and MS (1.87 [1.18–2.96]) were at significant risk for increased cardiac events. In conclusion, the risk of cardiac events is significantly increased in patients with metabolic syndrome following PCI, irrespective of DM. (*Hypertens Res* 2008; 31: 235–241)

***Key Words*: coronary artery disease, hypertension, obesity, Japanese**

Introduction

The prevalence of metabolic syndrome (MS), a cluster of dyslipidemia, dysglycemia, hypertension and obesity, is increasing, and MS is regarded as a key risk factor for the development of coronary artery disease, even in the Japanese population (*1*). The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) Guidelines defined new criteria for MS in 2001 and proposed that MS be considered a target in the prevention of cardiovascular disease in addition to reducing low-density lipoprotein (LDL) cholesterol levels (*2*). The American Heart Association in conjunction with the National Heart, Lung and Blood Institute (AHA/NHLBI) subsequently proposed a set of MS criteria based on slight modifications to the NCEP-ATP III criteria (*3*). Diabetes mellitus (DM) is included in both the NCEP-ATP III and AHA/NHLBI definitions of MS. However, several investigators have shown that regardless of the presence or absence of DM, MS itself is associated with a risk for coronary artery

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Table 1. Baseline Patient Characteristics

	Neither DM nor MS (n=321)	DM alone (n=109)	MS alone (n=129)	Both DM and MS (n=189)
Age, years*	58.2±10.3	62.4±8.8†	58.2±10.5	60.0±9.3
Male, *n* (%)	287 (89.4)	93 (85.3)	109 (84.5)	162 (85.7)
BMI, kg/m²*	22.5±2.5	22.3±1.9	25.1±2.4†	24.9±2.7†
FBG, mg/dL*	88.3±9.2	113.7±37.5†	94.4±11.7	120.2±45.2†
Hypertension, *n* (%)*	183 (57.0)	53 (48.6)	100 (77.5)†	149 (78.8)†
Systolic BP, mmHg*	128.0±17.8	125.7±16.0	133.4±18.0**	137.8±19.4†
Diastolic BP, mmHg*	74.3±13.4	73.1±12.0	77.6±13.8**	78.7±12.3†
Lipid profile				
LDL-c, mg/dL	135.7±38.7	128.8±41.4	143.5±42.2	137.3±48.7
HDL-c, mg/dL*	46.0±13.2	48.0±10.4	36.4±9.7†	38.3±11.6†
Triglyceride, mg/dL*	123.5±51.2	115.6±52.9	203.8±117.8†	189.7±98.8†
Current smoker, *n* (%)	248 (77.3)	82 (75.2)	100 (77.5)	149 (78.8)
Family history, *n* (%)	103 (32.1)	43 (39.5)	46 (35.7)	67 (35.5)
Medications				
Nitrates, *n* (%)	286 (89.1)	104 (95.4)	116 (89.9)	166 (87.8)
Nicorandil, *n* (%)	66 (20.6)	15 (13.8)	23 (17.8)	36 (19.1)
ACE inhibitors, *n* (%)	19 (5.9)	6 (5.5)	13 (10.1)	20 (10.6)
β-Blockers, *n* (%)	75 (23.4)	22 (20.2)	42 (32.6)**	47 (24.0)
CCB, *n* (%)*	78 (24.3)	22 (20.2)	54 (41.9)†	67 (35.5)†
Aspirin, *n* (%)	227 (70.7)	82 (75.2)	88 (68.2)	131 (73.2)
Warfarin, *n* (%)	127 (38.8)	42 (38.5)	41 (31.8)	80 (42.3)
Statins, *n* (%)	99 (30.8)	46 (42.2)**	36 (27.9)	62 (32.8)
Procedure				
ACS, *n* (%)	94 (29.2)	36 (33.0)	36 (27.9)	50 (26.5)
Previous CABG, *n* (%)	54 (16.8)	26 (23.9)	27 (20.9)	28 (14.8)
Multivessel disease, *n* (%)*	135 (42.1)	63 (57.8)†	71 (55.0)**	112 (59.3)†
Procedural success, *n* (%)	283 (88.2)	95 (87.2)	109 (84.5)	166 (87.8)
LVEF %, %	67.5±10.1	65.7±12.6	68.2±11.3	65.5±13.1

Data are means±SD unless otherwise indicated. *$p<0.01$ across groups. **$p<0.05$ compared with neither DM nor MS. †$p<0.01$ compared with neither DM nor MS. MS, metabolic syndrome; DM, diabetes mellitus; BMI, body mass index; FBG, fasting blood glucose; BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ACE, angiotensin converting enzyme; CCB, calcium channel blockers; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction.

disease (*4*–*6*). Therefore, MS has been established as a new target for the primary prevention of coronary artery disease, independently of DM. Furthermore, several studies have shown a relationship between MS and the prognosis of patients with coronary artery disease, or of patients following percutaneous coronary intervention (PCI) (*7*–*9*). However, little is known about the impact of MS with and without DM in such patients (*8*). In particular, the impact of MS with and without DM among Asians has not been investigated. Therefore, we examined whether MS affects the long-term prognosis of Japanese patients with and without DM who had undergone PCI to treat coronary artery disease.

Methods

Participants and Data Collection

We analyzed data from 748 consecutive Japanese patients who had undergone PCI at Juntendo University Hospital, Japan between January 1984 and December 1992. The indications for all PCI comprised objective evidence of myocardial ischemia (positive stress test) or ischemic symptoms associated with significant angiographic stenosis. Demographic data including age, gender, and body mass index (BMI), coronary risk factors (blood pressure, total cholesterol, LDL cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, fasting plasma glucose level, smoking history, family history of coronary artery disease), medication use,

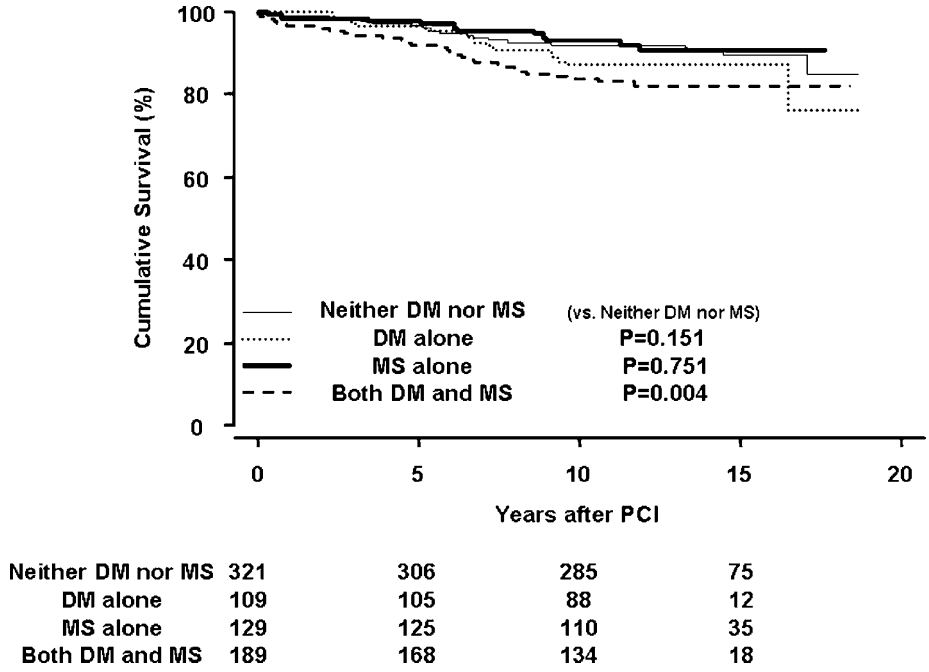

Fig. 1. *Cumulative survival (all-cause death). No significant differences in survival between patients with MS alone and those having neither DM nor MS (log-rank test, p = 0.751). Survival rates between patients with both DM and MS and those having neither DM nor MS significantly differed (log rank test, p = 0.004). MS, metabolic syndrome; DM, diabetes mellitus; PCI, percutaneous coronary intervention.*

and intervention procedures were prospectively collected in the database at our institution. Blood samples were obtained early in the morning after an overnight fast. Plasma glucose and serum triglyceride, total and HDL cholesterol were directly measured and LDL cholesterol was calculated using the Friedewald formula ([total cholesterol] − [HDL cholesterol] − [triglyceride/5]) when the triglyceride value was ≤400 mg/dL. When the triglyceride value was >400 mg/dL (n=13), LDL cholesterol was directly measured in stored serum samples. Blood pressure was measured at the time of admission for elective patients or a few days after admission for emergency patients. Outcome data, including death and cardiac events, were collected by serial contact (every 5 years) with the patients or their families until September 2002 and assessed from the medical records of patients who had died and of those who continued to be followed up at our hospital. Information about the circumstances and date of death was obtained from the families of patients who died at home, and details of the cardiac events or the cause of death were supplied by other hospitals or clinics where patients had been admitted. Mortality data were categorized according to the cause of death, such as death from all causes or cardiac death due to coronary artery disease, cardiogenic shock, and sudden death. Composite cardiac events included the incidence of cardiac death and of non-fatal acute coronary syndrome, including acute myocardial infarction and unstable angina pectoris. Patients were classified based on the presence or absence of MS at baseline using the modified AHA/NHLBI definition (*3*), with the exception that obesity was defined as BMI ≥25 kg/m^2 based on the established Japanese criteria for obesity (*10*), rather than based on waist circumference as in the AHA/NHLBI definition. The other MS criteria were the same as those by AHA/NHLBI: triglycerides ≥150 mg/dL; HDL cholesterol <40 mg/dL for men, <50 mg/dL for women; blood pressure ≥130/85 mmHg or treatment with antihypertensive medications; and fasting blood glucose ≥100 mg/dL or treatment with oral hypoglycemic drugs or insulin injection. Patients who had 3 of these 5 criteria were regarded as having MS. Furthermore, patients in each group with and without MS were divided into two subgroups according to the presence or absence of DM using the following definition: fasting plasma glucose level ≥126 mg/dL (*11*) or treatment with oral hypoglycemic drugs or insulin injection. We separated the patients into four groups as follows: neither DM nor MS, DM alone, MS alone, and both DM and MS. Each patient was further categorized based on the presence of coronary risk factors using the following criteria: hypertension was defined as systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or treatment with antihypertensive medications. A current smoker was defined as one who smoked at the time of PCI or who had quit smoking within 1 year before PCI.

Table 2. Risk for All Cause Mortality and Cardiac Event in Patients with DM Alone, MS Alone, and Both DM and MS

	Incidence (%)	Unadjusted			Adjusted		
		HR	95% CI	*p*	HR	95% CI	*p*
All-cause death							
Neither DM nor MS	30/321 (9.4)	1.00			1.00		
DM alone	15/109 (13.8)	1.55	0.83–2.88	0.169	1.29	0.68–2.43	0.435
MS alone	11/129 (8.5)	0.90	0.45–1.79	0.753	0.88	0.42–1.85	0.734
Both DM and MS	32/189 (16.9)	2.06	1.25–3.39	0.005	2.10	1.19–3.70	0.011
Cardiac event							
Neither DM nor MS	47/321 (14.6)	1.00			1.00		
DM alone	20/109 (18.3)	1.30	0.77–2.02	0.320	1.25	0.73–2.14	0.410
MS alone	35/129 (27.1)	1.97	1.27–3.05	0.002	2.14	1.31–3.50	0.001
Both DM and MS	46/189 (24.3)	1.79	1.19–2.69	0.005	1.87	1.18–2.96	0.008

DM, diabetes mellitus; MS, metabolic syndrome; HR, hazard ratio; CI, confidence interval; HRs and 95% CIs were adjusted for age, gender, body mass index, low-density lipoprotein cholesterol level, hypertension, smoking, prior coronary artery bypass graft, presentation of acute coronary syndrome, left ventricular ejection fraction, multivessel disease, and procedural success.

Statistical Analysis

Continuous variables are expressed as the means±SD and were compared using one-way ANOVA with Dunnett's test. Categorical data are tabulated as frequencies and ratios (%), and were compared using the χ^2 test. Survival and cardiac event-free survival were analyzed using Kaplan-Meier estimation with the log-rank test. Multivariate Cox proportional-hazards regression adjusted for age, gender, BMI, LDL cholesterol level, presence or absence of hypertension, current smoking, previous history of coronary artery bypass graft, acute coronary syndrome, left ventricular ejection fraction, multivessel disease, and procedural success (defined as residual stenosis <50% after PCI) determined risks for all-cause death and composite cardiac events in MS patients with or without DM. A *p*-value of <0.05 was considered statistically significant. All data were analyzed using Dr. SPSS II for Windows (SPSS Inc., Chicago, USA).

Results

Baseline and clinical event data were fully documented during the follow-up period (mean follow-up, 12.0±3.6 years) for all 748 enrolled patients. Most patients were middle-aged, non-obese males who were treated with nitrates and aspirin, and had single vessel disease with normal left ventricular contraction. Simple balloon angioplasty was applied since stents were not yet available at the time of the PCI procedures. Among the 748 patients, 298 (39.8%) had DM at the time of PCI. None of the patients who underwent PCI during the study period had type 1 diabetes. Overall, 321 (42.9%) patients had neither DM nor MS, 109 (14.6%) patients had DM alone, 129 (17.2%) had MS alone, and 189 (25.3%) had both MS and DM. In patients with MS alone, 49 (38.0%) revealed impaired fasting glucose (*i.e.*, fasting blood glucose ≥100 mg/dL). Table 1 shows the baseline characteristics of these groups. With respect to coronary risk factors, patients with MS alone were more comparable to those with both DM and MS than to those without MS. The two groups of patients without MS were similar, regardless of the presence or absence of DM. The diabetic groups included older patients and the group with both DM and MS included patients who most frequently had multivessel disease.

Overall, 88 patients (11.8%) died from all causes, and 148 cardiac events (19.8%) occurred during follow-up. Figure 1 shows the Kaplan-Meier estimates for survival with respect to all-cause death. The survival rate differed significantly between patients with both DM and MS and those having neither condition (log-rank test, $p=0.004$), although patients with DM alone and those with MS alone did not differ significantly from those who had neither DM nor MS. Cox proportional hazard regression analysis to adjust for baseline covariates showed that the presence of both DM and MS was significantly associated with increased all-cause mortality (hazard ratio [HR], 2.10; 95% confidence interval [CI], 1.19–3.70; $p=0.011$) (Table 2). Other independent predictors for all-cause mortality were age (HR, 1.05; 95% CI, 1.03–1.08; $p<0.001$), hypertension (HR, 1.89; 95% CI, 1.10–3.24; $p=0.021$) and left ventricular ejection fraction (HR, 0.98; 95% CI, 0.96–0.99; $p=0.003$).

The Kaplan-Meier curve shows that patients with MS alone and those with both DM and MS had lower cardiac event-free survival rates than those having neither DM nor MS (log-rank test, $p=0.002$ and $p=0.004$ for patients with MS alone and with both DM and MS, respectively; Fig. 2). Multivariate analysis revealed that both MS with and MS without DM were significantly associated with an increased risk of cardiac events (HR, 1.87; 95% CI, 1.18–2.96; $p=0.008$ with both DM and MS; HR, 2.14; 95% CI, 1.31–3.50; $p=0.002$ with MS alone). Table 2 summarizes the results of multivariate Cox proportional hazards regression analysis. Other independent predictors for cardiac events were a history of coronary artery

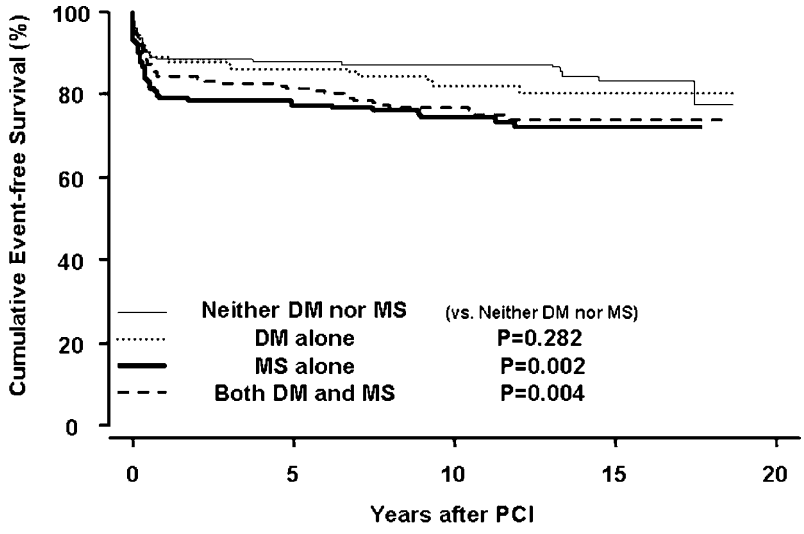

Fig. 2. *Cumulative event-free survival for cardiac events. Event-free survival between patients with MS alone and those having neither DM nor MS differed significantly (log rank test: p=0.002). Patients with both DM and MS and patients having neither condition also differed significantly (log rank test, p=0.004). MS, metabolic syndrome; DM, diabetes mellitus; PCI, percutaneous coronary intervention.*

bypass graft (HR, 1.72; 95% CI, 1.12–2.64, $p=0.013$), presentation of acute coronary syndrome (HR, 14.0; 95% CI, 9.53–20.6; $p<0.001$), left ventricular ejection fraction (HR, 0.98; 95% CI, 0.95–0.99; $p=0.004$), multivessel disease (HR, 1.52; 95% CI, 1.04–2.21, $p=0.031$) and procedural success (HR, 0.65; 95% CI, 0.42–0.99; $p=0.049$).

Discussion

Analysis of long-term follow-up (≥10 years) data obtained from our institution revealed an association between MS and future cardiac morbidity in groups without DM at the baseline examination. Separating the patients into groups based on the presence or absence of DM revealed an independent risk of cardiac events associated with MS.

According to both the NCEP-ATP III and AHA/NHLBI definitions for MS, patients with DM simultaneously satisfied the criterion for high blood glucose (*2*, *3*, *12*). Hence, many of our patients with MS also had DM and most of the diabetic patients were classified as having MS among the population in which the type 2 DM resulted from obesity. Furthermore, the risk for increased mortality and morbidity of cardiovascular disease in patients with MS is associated with significant overlaps with DM, which is an established risk factor for a poor prognosis following PCI (*13–15*). From this viewpoint, risk assessment is warranted in patients with MS alone, DM alone, or both MS and DM. Nigam *et al*. reported that Western populations of patients with MS alone and with DM alone had a higher risk for cardiovascular mortality and morbidity than patients with neither of these conditions (*8*). However, it remains controversial whether such risks are also prevalent among Asians, who differ considerably from non-Asians in terms of obesity-related features (*16–18*). In addition, the risk for patients with both DM and MS was not described in their study. Here, we examined the risk among Asian patients with MS alone, DM alone and with both MS and DM. The results showed that patients with MS alone were at significantly increased risk for cardiac events, which was compatible with the findings reported by Nigam *et al*. (*8*). Furthermore, the risk for both all-cause mortality and incidence of cardiac events was increased among patients with both MS and DM. These results indicated that MS is important in patients irrespective of DM and that aggressive and multifactorial intervention is required for the secondary prevention of cardiac mortality and morbidity.

However, we did not find a significant risk for either all-cause mortality or cardiac events among patients with DM alone. These results contradicted those of Nigam *et al*., who identified a significantly higher risk in patients with DM alone than in those with MS (*8*). We cannot specifically explain this discrepancy, although ethnic differences might be involved in the risk of MS and DM. Of course, the relatively small number of patients and differences in patient characteristics between our study and the report by Nigam *et al*. (*8*)

also affected these results. During this study period, diabetic patients with more complex or more advanced lesions were predominantly referred for coronary artery bypass graft (CABG) in Japan, and therefore, diabetic patients included in this investigation might have had a lower risk than those described by Nigam *et al*. (*8*). Patients with DM alone also had the lowest BMI, were the least hypertensive and smoked the least among the four groups, which might have biased the results. These patients were most frequently treated with statins, which are associated with a better long-term outcome after PCI. This also affected the finding that the outcome was not significantly different between patients with DM alone and those having neither MS nor DM. The findings of this study should be interpreted with caution from this viewpoint.

The present study included several other limitations. Firstly, we used BMI to classify individuals as obese because waist circumference was not measured. Recent clinical studies show that most subjects identified as having MS based on the BMI would also have been diagnosed as obese according to waist circumference cut-off points (*19*, *20*). It is worth noting that, in the present study, we used BMI $\geq$25 kg/m^2 as the cut-off point for obesity, which differs from recent clinical trials of Western populations, which applied a cut-off of BMI $\geq$30 kg/m^2. We selected BMI $\geq$25 kg/m^2 as the cut-off for obesity based on the results of a study on the relationship between BMI, visceral fat area or waist circumference and obesity in the Japanese population (*10*).

Secondly, balloon angioplasty was the sole PCI for all patients. It is difficult to determine whether the improvement in clinical outcome was due in part to the recent increase in the use of stents, the recent improvements in operator skills in PCI, and/or recent improvement of adjunctive drug therapy. Therefore, further investigation is needed to clarify whether MS would affect the outcome in this era of stent implantation.

Thirdly, crossover among the four groups during follow-up was not considered. For example, data about new onset diabetes—particularly among patients with MS alone—were not available. These might have affected the results, and hence, analysis of diabetic status during follow up is warranted.

In conclusion, having MS at the time of PCI was associated with an increased incidence of cardiovascular events for over 10 years after the procedure. The association of MS with poor outcomes was significant regardless of the presence or absence of DM and was independent of other potential confounders on multivariate analysis. The present study showed the clinical importance of MS, irrespective of DM, for the secondary prevention of coronary artery disease, and highlights the need to treat each MS component, even when impairment is mild.

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