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Effect of Low Body Mass Index on the Clinical Outcomes of Japanese Patients With Acute Myocardial Infarction

— Results From the Prospective Japan Acute Myocardial Infarction Registry (JAMIR) —

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Background: Acute myocardial infarction (AMI) patients with low body mass index (BMI) exhibit worse clinical outcomes than obese patients; however, to our knowledge, no prospective, nationwide study has assessed the effect of BMI on the clinical outcomes of AMI patients.

Methods and Results: In this multi-center, prospective, nationwide Japanese trial, 2,373 AMI patients who underwent emergent percutaneous coronary intervention within 12 h of onset from the Japanese AMI Registry (JAMIR) were identified. Patients were divided into the following 4 groups based on their BMI at admission: Q1 group (BMI <18.5 kg/m^2, n=133), Q2 group (18.5≤BMI<25.0 kg/m^2, n=1,424), Q3 group (25.0≤BMI<30.0 kg/m^2, n=672), and Q4 group (30.0 kg/m^2≤BMI, n=144). The primary endpoint was all-cause death, and the secondary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. The median follow-up period was 358 days. Q1 patients were older and had lower prevalence of coronary risk factors. Q1 patients also had higher all-cause mortality and higher incidence of secondary endpoints than normal-weight or obese AMI patients. Multivariate analysis showed that low BMI (Q1 group) was an independent predictor for primary endpoint.

Conclusions: AMI patients with low BMI had fewer coronary risk factors but worse clinical outcomes than normal-weight or obese patients.

Key Words: Acute myocardial infarction; Coronary risk factors; Low body mass index; Obesity paradox

Obesity is associated with the development of cardiovascular disease and coronary risk factors,[1–5] but obese patients with cardiovascular disease have better clinical outcomes than underweight patients. This phenomenon has been termed the "Obesity Paradox", and has been reported by several studies worldwide.[6–10] In contrast, a large cohort study in the US reported that patients with acute myocardial infarction (AMI) who have a low body mass index (BMI) had a higher prevalence of frailty and higher mortality than normal-weight patients.[11] Moreover, O'Brien et al reported that underweight patients

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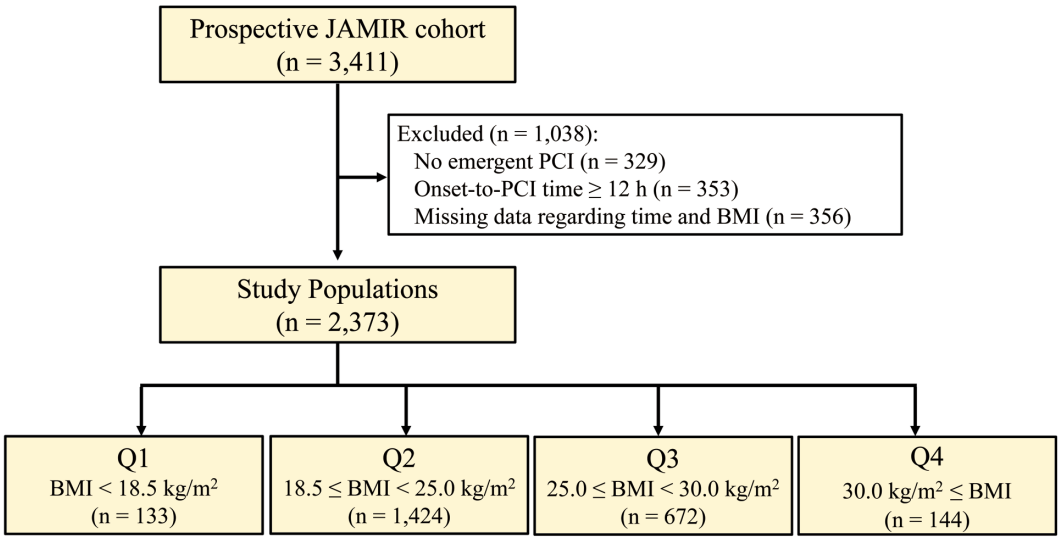

Figure 1. Study flowchart. BMI, body mass index; JAMIR, Japan Acute Myocardial Infarction Registry; PCI. percutaneous coronary intervention.

with non-ST segment elevation myocardial infarction (NSTEMI) aged ≥65 years had worse mortality compared with those patients who were of normal weight.[12]

A previous single-center retrospective study conducted in Japan has shown that AMI patients with low BMI had worse all-cause mortality than those with high BMI.[13] Moreover, worse in-hospital mortality of AMI patients with low BMI was reported in a multi-center retrospective study.[14] However, to our knowledge, no studies in Japan have prospectively evaluated the effect of low BMI on AMI patients. Thus, this study evaluated the effect of BMI on patient clinical outcomes by conducting a post-hoc analysis of the prospective observational multi-center Japan AMI Registry (JAMIR) data.[15]

Methods

Study Population

The details of the JAMIR design have been published previously.[15] Briefly, consecutive patients presenting with spontaneous onset of AMI were enrolled in the period from December 2015 to May 2017 from 50 institutions to examine ischemic and bleeding events in Japanese patients with AMI and the association between these events and antiplatelet therapy. AMI was diagnosed as per the universal definition, with the allowance of the MONICA criteria, as per institutional settings.[16,17] We excluded patients who were admitted to the hospital ≥24 h after AMI onset, who had no return of spontaneous circulation on admission after out-of-hospital cardiopulmonary arrest, and those with AMI as a complication of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). We enrolled 3,411 patients to the JAMIR from 50 institutions in Japan. The current study excluded the following patients: 329 patients who did not undergo emergent PCI; 353 who did not undergo emergent PCI within 12 h of onset; and 356 for whom data on the time from onset to emergent PCI or if BMI information at admission were unavailable. Finally, 2,373 patients who underwent emergent PCI within 12 h of onset were included in the current analysis (**Figure 1**).

Patients were divided into the following 4 groups as per their BMI at admission as follows: Q1 group (BMI <18.5 kg/m^2, n=133), Q2 group (18.5 kg/m^2≤BMI<25.0 kg/m^2, n=1,424), Q3 group (25.0 kg/m^2≤BMI<30.0 kg/m^2, n=672), and Q4 group (30.0 kg/m^2≤BMI, n=144), as per the World Health Organization (WHO) criteria.[18] Patient management, including the choice of antiplatelet drugs, was at the discretion of the treating physician. Primary data were collected from the medical records of the patients. We collected information regarding patient demographics, medical history, ambulance use, details of coronary angiography and invasive therapy, cardiac medications, and outcomes. Investigators, clinical research coordinators, or local data managers at each study site registered the data using the JAMIR registration system. A follow-up study of the patients was performed 1 year after AMI onset, as per the medical information available at each study site. A letter that requested follow up was sent to the patients for whom medical information was unavailable at the study sites after 1 year because of hospital transfer or other reasons.

This study was conducted based on the ethical guidelines for medical research on humans in the Declaration of Helsinki. The research protocol was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M27-019-12) and local ethics committees or the local institutional review board at each study site, including Hirosaki University Hospital. Although informed consent was not obtained because of the observational nature of this registry, the study details were posted on a website and at the study sites (opt-out) to inform the subjects about the study design and timeline to ensure that they had the opportunity to refuse inclusion in this registry. In addition, the research secretariat confirmed compliance with opt-out procedures at each study site. This study

Table 1. Patient Characteristics

	Q1 group (n=133)	Q2 group (n=1,424)	Q3 group (n=672)	Q4 group (n=144)	P value
Age, years	78±11	69±12	63±13	56±13	<0.001
Male sex, n (%)	71 (53)	1,112 (78)	567 (84)	122 (85)	<0.001
BMI, kg/m^2	17.3±1.1	22.3±1.7	27.0±1.4	33.2±4.2	<0.001
Coronary risk factors, n (%)					
Hypertension	69 (52)	1,016 (71)	491 (73)	114 (79)	<0.001
Dyslipidemia	66 (50)	970 (68)	503 (75)	114 (79)	<0.001
Diabetes mellitus	30 (23)	477 (34)	244 (36)	69 (48)	<0.001
Current smoker	35 (26)	605 (43)	333 (50)	77 (54)	<0.001
Atrial fibrillation, n (%)	19 (14)	105 (7)	28 (4)	6 (4)	<0.001
Previous MI, n (%)	9 (7)	138 (10)	55 (8)	11 (8)	0.47
Previous PCI, n (%)	12 (9)	168 (12)	70 (10)	17 (12)	0.66
Previous CABG, n (%)	3 (2)	40 (3)	14 (2)	0 (0)	0.18
PAD, n (%)	5 (4)	61 (4)	16 (2)	1 (1)	0.037
Multi-vessel or LMT, n (%)	64 (48)	615 (43)	267 (40)	57 (40)	0.21
Killip classification, n (%)					<0.001
I	79 (59)	1,143 (80)	544 (81)	111 (77)	
II	16 (12)	119 (8)	42 (6)	18 (13)	
III	7 (5)	60 (4)	34 (5)	4 (3)	
IV	31 (23)	102 (7)	52 (8)	11 (8)	
STEMI, n (%)	114 (86)	1,181 (83)	576 (86)	127 (88)	0.19
Door-to-device time, min	80 [60–122]	66 [50–92]	65 [50–89]	68 [53–95]	<0.001
Culprit lesion, n (%)					
LMT	4 (3)	28 (2)	14 (2)	2 (1)	0.78
RCA	44 (33)	536 (38)	242 (36)	66 (46)	0.11
LAD	69 (52)	689 (48)	334 (50)	68 (47)	0.81
LCx	20 (15)	203 (14)	93 (14)	17 (12)	0.85
Bypass graft	0 (0)	6 (1)	2 (1)	0 (0)	1.0
Unknown	0 (0)	1 (1)	0 (0)	0 (0)	1.0
Final TIMI grade 3, n (%)	124 (93)	1,310 (92)	620 (92)	127 (88)	0.38
Max CPK (mg/dL)	1,777 [902–3,429]	1,593 [664–3,405]	2,004 [729–3,889]	2,726 [1,007–4,804]	<0.001
Max CPK-MB (mg/dL)	150 [73–347]	158 [66–327]	194 [72–373]	242 [89–438]	<0.001
Blood chemistry at admission, mg/dL					
Total cholesterol	182±46	191±51	201±46	204±49	<0.001
Triglyceride	84±45	129±112	163±119	212±224	<0.001
LDL-cholesterol	110±40	118±37	127±39	127±36	<0.001
HDL-cholesterol	52±16	48±13	45±12	42±10	<0.001
Glucose	177±77	174±73	176±72	193±89	0.045
Creatinine	1.0±0.9	1.1±1.3	1.0±1.0	1.0±0.4	0.19
LVEF at acute phase (%)	48±14	52±12	52±12	53±13	0.011
Medication during hospitalization, n (%)					
Aspirin	132 (99)	1,406 (99)	667 (99)	144 (100)	0.52
Clopidogrel	24 (18)	227 (16)	93 (14)	19 (13)	0.42
Prasugrel	115 (86)	1,231 (86)	598 (89)	132 (92)	0.16
Oral anticoagulant	22 (17)	185 (13)	77 (11)	15 (10)	0.32
ACEI	67 (50)	782 (55)	365 (54)	86 (60)	0.47
ARB	32 (24)	397 (28)	182 (27)	38 (26)	0.80
β-blocker	79 (59)	954 (67)	445 (66)	106 (74)	0.09
Statin	113 (85)	1,330 (93)	623 (93)	133 (92)	0.01
Proton pump inhibitor	121 (91)	1,320 (93)	625 (93)	131 (91)	0.74

Data are presented as mean±standard deviation values, n (%), or median values and interquartile ranges. Q1 group: BMI <18.5 kg/m^2; Q2 group: 18.5≤BMI<25.0 kg/m^2; Q3 group: 25.0≤BMI<30.0 kg/m^2; and Q4 group: 30.0 kg/m^2≤BMI. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CPK, creatinine phosphokinase; CPK-MB, creatinine phosphokinase-MB; HDL, high-density lipoprotein; LAD, left ascending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

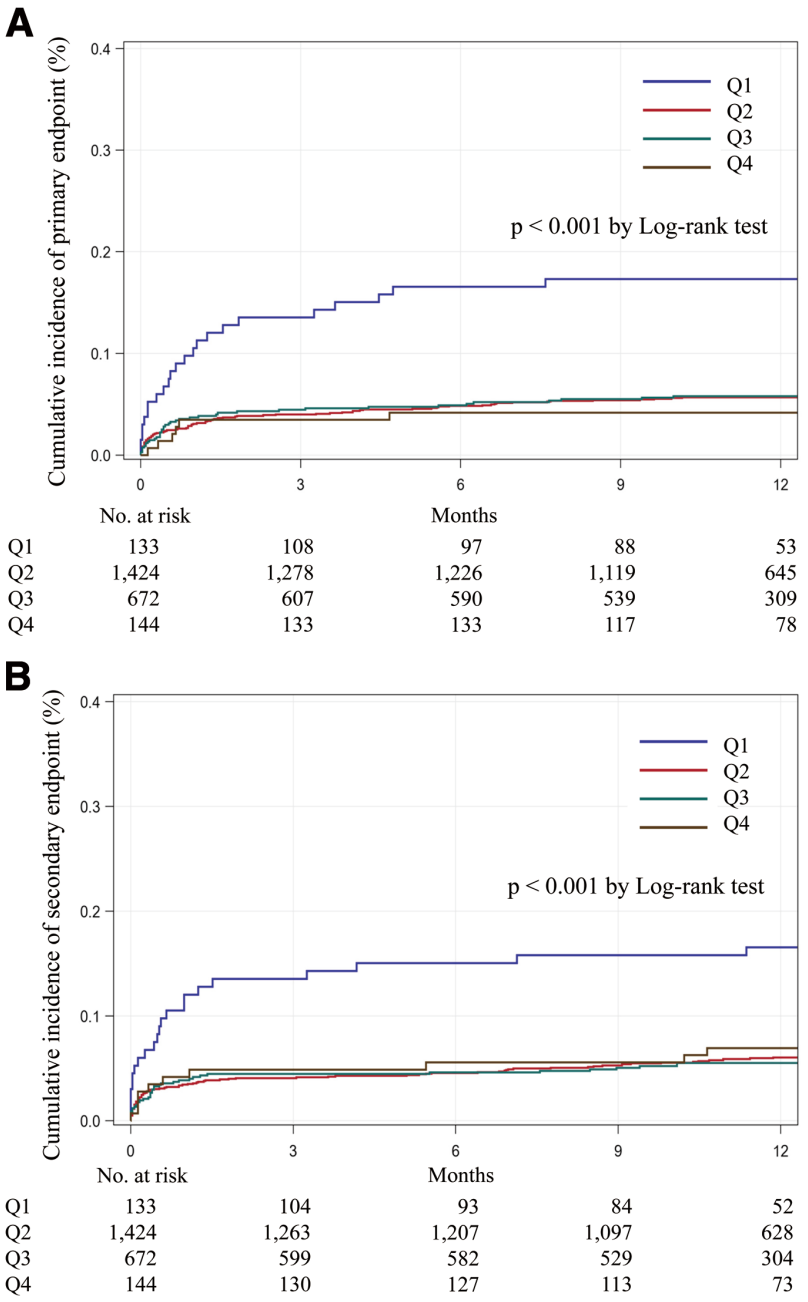

Figure 2. Kaplan-Meier curves for the clinical outcomes among the 4 groups: Q1 group (BMI <18.5 kg/m^2, blue line), Q2 group (18.5 kg/m^2≤BMI<25.0 kg/m^2, red line), Q3 group (25.0 kg/m^2≤BMI <30.0 kg/m^2, green line), and Q4 group (30.0 kg/m^2≤BMI, brown line). (**A**) All-cause death (primary endpoint). (**B**) A composite of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke (secondary endpoint).

was registered with the Japanese UMIN Clinical Trials Registry (UMIN000019479).

Study Endpoints

The primary endpoint in the present study was all-cause death. The secondary endpoint was a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. Type 3 or 5 bleeding based on Bleeding Academic Research Consortium (BARC) criteria[19] was evaluated. The median follow-up period of this study was 358 (286–398) days.

Statistical Analyses

Baseline continuous variables are presented as mean±standard deviation values or median and interquartile range, as per data distribution. Categorical variables are presented as percentages. One-way analysis of variance and the Kruskal-Wallis test were used to compare continuous variables, and the chi-squared test was performed to compare dichotomous variables. Kaplan-Meier curves for primary (all-cause death) and secondary (a composite of cardiovascular death, non-fatal MI, and non-fatal stroke) outcomes were analyzed using the Log-rank test. Multivariate Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of low BMI (<18.5 kg/m^2) on the primary and secondary outcomes. Age (≥75 years), male sex, hypertension, diabetes mellitus, dyslipidemia, history of smoking, and Killip classification ≥II were included in the models as

Table 2. Clinical Outcomes of the Study Patients

	Q1 group (n=133)	Q2 group (n=1,424)	Q3 group (n=672)	Q4 group (n=144)	P value
All-cause death	25 (19)	85 (6)	39 (6)	6 (4)	<0.001
Cardiovascular death	16 (12)	45 (3)	21 (3)	3 (2)	<0.001
Non-fatal MI	3 (2)	32 (2)	12 (2)	5 (3)	0.58
Non-fatal stroke	3 (2)	11 (1)	3 (1)	1 (1)	0.16
BARC Type 3 or 5 bleeding	10 (8)	71 (5)	25 (4)	3 (2)	0.096

Data are presented as n (%). Q1 group: BMI <18.5 kg/m^2; Q2 group: 18.5≤BMI<25.0 kg/m^2; Q3 group: 25.0≤BMI<30.0 kg/m^2; Q4 group: 30.0 kg/m^2≤BMI. BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.

Table 3. Adjusted HRs for Primary and Secondary Endpoints

	Adjusted HR (95% CI)	P value
(A) Primary endpoint		
BMI <18.5 kg/m^2	1.71 (1.09–2.69)	0.021
Age ≥75 years	2.23 (1.56–3.19)	<0.01
Male sex	1.21 (0.82–1.78)	0.34
Hypertension	0.74 (0.52–1.04)	0.078
Diabetes mellitus	1.39 (1.00–1.94)	0.054
Dyslipidemia	0.60 (0.43–0.83)	<0.01
Current smoker	0.87 (0.60–1.26)	0.46
Killip classification ≥II	4.87 (3.51–6.76)	<0.01
(B) Secondary endpoint		
BMI <18.5 kg/m^2	1.60 (1.00–2.58)	0.052
Age ≥75 years	1.97 (1.39–2.78)	<0.01
Male sex	1.46 (0.98–2.18)	0.061
Hypertension	0.75 (0.53–1.04)	0.087
Diabetes mellitus	1.11 (0.79–1.54)	0.56
Dyslipidemia	0.74 (0.53–1.02)	0.066
Current smoker	0.75 (0.52–1.07)	0.109
Killip classification ≥II	3.64 (2.65–4.99)	<0.01

Primary endpoint was defined as all-cause death. Secondary endpoint was defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

confounding factors. The level of significance was set at P<0.05. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics of the Patients

Patient characteristics were compared among the 4 groups (**Table 1**). Average age significantly increased with decreasing BMI. There were fewer male patients in the Q1 group than in the other groups. The prevalence of coronary risk factors, including hypertension, dyslipidemia, diabetes mellitus, and current smoking increased with increasing BMI. More patients in the Q1 group had atrial fibrillation, and the prevalence of previous MI, previous PCI, and previous CABG was comparable in the 4 groups. There were more patients with Killip classification IV and low left ventricular ejection fraction (LVEF) at admission in Q1 group, although the severity of coronary artery disease, including the culprit lesion and the prevalence of final Thrombolysis in Myocardial Infarction (TIMI) grade 3 after emergent PCI was not significantly different among the 4 groups. The door-to-device time in the Q1 group was longer than that in other groups; however, the maximum creatinine phosphokinase (CPK) and maximum CPK-MB levels were lower in the Q1 group than those for obese patients. The serum creatinine levels of the 4 groups were comparable. In terms of medications used during hospitalization, the use of cardioprotective agents, such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), β-blockers, and antithrombotic agents, were comparable among the 4 groups; however, the use of statins was less common in the Q1 group.

Clinical Outcomes

The Kaplan-Meier curves of the 4 groups (Q1, Q2, Q3 and Q4) are presented in **Figure 2**, and the details of the clinical outcomes at 1 year are shown in **Table 2**. The primary endpoint, defined as all-cause mortality, was significantly higher in the Q1 group than the other 3 groups (P<0.001 by the log-rank test). Moreover, the secondary endpoint, defined as a composite of cardiovascular death, non-fatal MI, and non-fatal stroke, was also significantly higher in the Q1 group than the other 3 groups (P<0.001 by the log-rank test). Most clinical events occurred within 3 months from the onset of AMI onset. All-cause and cardiovascular deaths were more common in the Q1 group; however, the prevalence of non-fatal MI and non-fatal stroke was comparable among the 4 groups.

Type 3 or 5 bleeding based on the BARC criteria[19] was common in the Q1 group, followed by Q2, Q3, and Q4, although it was not significant (8%, 5%, 4%, and 2%, respectively; P=0.096) (**Table 2**). We evaluated the association between all-cause death and bleeding events by performing a multivariate analysis (**Supplementary Table**). BARC type 3 or 5 bleeding was an independent predictor for the primary endpoint (HR: 5.04, 95% CI: 3.34–7.60, P<0.01).

Predictors of the Clinical Outcomes

In order to determine whether low BMI is a predictor of the clinical outcomes of AMI patients who underwent emergent PCI, we performed a multivariate analysis (**Table 3**). Low BMI (Q1 group), older age and Killip classification ≥II were independent predictors for the primary endpoint. Similarly, low BMI tended to be associated with greater risk for the secondary endpoint, and older age and Killip classification ≥II were independent predictors for the secondary endpoint. In contrast, hypertension and dyslipidemia tended to be inversely associated with the primary and secondary endpoints. Sex, diabetes mellitus and

current smoking were not independent predictors for the primary or secondary endpoints.

Discussion

JAMIR is a multi-center, nationwide, prospective observational study that was conducted with Japanese patients who had AMI. In the present study, we found that AMI patients with low BMI had worse clinical outcomes even though they had fewer coronary risk factors. Further, patients with low BMI had a higher prevalence of Killip classification IV and lower LV function than those with a normal-weight or obesity. Moreover, low BMI was an independent predictor for clinical outcomes. To the best of our knowledge, this is the first report to evaluate the effect of low BMI on the clinical outcomes of AMI patients using a nationwide prospective registry in Japan. These results are in agreement with the findings reported by the previous single-center[13] and multi-center retrospective[14] studies conducted in Japan.

In the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH), AMI patients with low BMI had fewer coronary risk factors, higher B-type natriuretic peptide levels, higher prevalence of Killip classification IV, and lower LVEF than obese patients.[20] These patients had high mortality, which is consistent with the findings in the present study. Moreover, higher in-hospital mortality has been reported for AMI patients with low BMI in the China Acute Myocardial Infarction (CAMI) registry,[21] wherein patients in the low-BMI group were older and had a lower prevalence of coronary risk factors and higher prevalence of Killip classification IV. These studies, as well as our trial, suggest that the clinical characteristics of AMI patients in Asian countries were similar, and the effect of low BMI on the clinical outcomes of AMI patients was confirmed in both Asian and Western populations.

Hypertension and dyslipidemia are known as risk factors for the development of coronary artery disease in the general populations;[22] however, several studies have shown that in-hospital mortality is inversely associated with the conventional coronary risk factors in AMI patients, such as hypertension, smoking, dyslipidemia, and diabetes.[23,24] These results support our findings that hypertension and dyslipidemia tend to be inversely associated with the primary or secondary endpoints. There might be several explanations for this. AMI patients with few coronary risk factors were given fewer evidence-based medications for secondary prevention. Statin use was less frequent in low-BMI patients with few coronary risk factors compared with overweight or obese patients with multiple coronary risk factors in our study. However, patients with multiple coronary risk factors before AMI onset might be more likely to receive optimal medical therapy to prevent the development of coronary artery disease, such as ACEIs, ARBs, β-blockers, antithrombotic agents, and statins. This optimal medical therapy before hospitalization might improve the clinical outcomes of AMI patients with multiple coronary risk factors. Further studies are needed to investigate the underlying mechanisms of the inverse association between coronary risk factors and the clinical outcomes of AMI patients.

Obesity is a complex disorder that is usually associated with many other metabolic abnormalities; however, obesity might exert some cardioprotective effects in a special setting. Adipose tissue plays an important role in the production of various hormones and cytokines, including adiponectin that exerts a cardioprotective effect against systemic atherosclerosis or inflammation.[25,26] These factors might be involved in the protective mechanisms in obese patients, although BMI may not necessarily be associated with fat distribution or adipose tissue function. In an insulin-insensitive rat model of dietary obesity, a protective effect of obesity against ischemia-reperfusion injury with 45 min of left anterior descending artery occlusion and 120 min of reperfusion was confirmed.[27] The authors of this paper concluded that cardioprotection by obesity might occur via the modulation of reperfusion injury salvage kinase signaling.

In contrast, low BMI is a marker of systemic illness, inflammation, or cancer.[6] Low BMI patients might be affected by non-cardiac mortality owing to comorbidities such as cancer, chronic obstructive pulmonary disease, and pneumonia. These comorbidities are suggested to cause worse mortality in low-BMI patients. A prior study has reported that frailty is associated with adverse outcomes for older AMI patients.[28] Bucholz et al also reported that AMI patients with low BMI had a higher prevalence of frailty and poor nutritional status, and higher mortality than those of a normal weight.[11] Moreover, they demonstrated that AMI patients with low BMI had worse mortality even in a subset of patients without significant comorbidity or frailty. These findings indicate that it is still unclear whether lower BMI itself has an effect on mortality or if it just reflects several confounding factors; further studies are therefore needed.

A recent report from the Japanese nation-wide Cardiovascular Intervention and Therapeutics (CVIT) registry found that antiplatelet therapy was associated with increased risk of bleeding, especially in AMI patients with low BMI.[29] In this study, the incidence of BARC type 3 or 5 bleeding tended to be higher in the low BMI group, although there were no differences in the antiplatelet therapy between the low BMI group and the other 3 groups. The bleeding events were related to worse mortality for our subjects, and it might be one of the reasons for the worse clinical outcomes for low BMI patients compared with normal-weight or obese patients. Meta-analysis on 81,553 patients with acute coronary syndrome enrolled in 8 large randomized clinical trials showed that underweight patients were associated with increased risk of mortality and bleeding compared with those with a higher BMI,[30] which was consistent with our study results.

Study Limitations

There are certain limitations to our study. First, the clinical variables were adequately adjusted; however, the comparative results might be influenced by undetermined variables, such as poor nutrition and physical frailty. We did not collect data regarding frailty or nutrition status, therefore, we could not evaluate the association between low BMI and frailty. Second, the association between low BMI and worse clinical outcomes found in the present study could be attributable to the relatively short-term follow-up duration. Obese patients may often develop hypertension, dyslipidemia, and diabetes mellitus in the long-term period, eventually leading to poor clinical outcomes. Therefore, larger-scale, prospective, and longer-term observational studies involving a national population are clearly warranted. Third, hypertension and dyslipidemia tend to be

inversely associated with adverse events in this study. This might be related to selection bias and the observational design of the study, as has been described and discussed before.[31] Differential selection from an underlying population cohort into a study data set can reverse the direction of observed associations, making a deleterious factor appear protective. As it was reported that approximately 30% of AMI cases end in death prior to hospitalization,[32] the patients with more cardiovascular risk factors were more likely to be excluded in this study. Fourth, the optimal cut-off point of BMI for obesity was not determined in Asian populations. Although we divided the populations using the WHO classification, there were more populations with low BMI in Asia than in Western countries. Fifth, the present Japanese AMI cohort included a limited number of patients with extremely high BMI (≥40 kg/m^2), although a previous AMI study in a Western country demonstrated higher mortality not only in underweight patients but also in patients with extremely high BMI (U-shaped relationship between BMI and mortality).[33] Sixth, we only collected the BMI data at the time of study registration; any change in the BMI was not evaluated, therefore, we could not discuss the effect of BMI change on the clinical outcomes. Finally, these results were derived from only Japanese populations, and therefore might not be generalizable to other populations.

Conclusions

The nationwide JAMIR study demonstrated that AMI patients with low BMI had fewer coronary risk factors but worse clinical outcomes than normal-weight or obese patients.

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IRB Information

This study was conducted based on the ethical guidelines for medical research on humans in the Declaration of Helsinki. The research protocol was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M27-019-12) and local ethics committees or the local institutional review board at each study site, including Hirosaki University Hospital.

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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