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Prognostic Impact of Diabetes Mellitus on Clinical Outcomes in Lean Patients With Acute Myocardial Infarction

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Abstract. *Background/Aim: Little is known about the impact of diabetes mellitus (DM) on clinical outcomes in lean patients with acute myocardial infarction (AMI). We conducted this study to evaluate the impact of DM on clinical outcomes in AMI patients based on body mass index (BMI) level. Patients and Methods: A total of 1,282 consecutive AMI patients who underwent emergent percutaneous coronary intervention within 24 hours from onset were retrospectively studied. The patients were divided into 2 groups based on BMI: Underweight group (BMI <18.5 kg/m^2, n=61) and non-Underweight group (BMI ≥18.5 kg/m^2, n=1,221). The primary endpoint was all-cause death, and the secondary endpoint was major adverse cardiovascular and cerebrovascular events. The median follow-up period was 3.8 (1.7-5.0) years. Results: The Underweight patients were older and included more females than the non-Underweight patients, and had a lower prevalence of coronary risk factors including DM. The primary and secondary endpoints were significantly higher in the Underweight patients (both p<0.05 by the Log-rank test). When divided by the presence of DM, the secondary endpoint was significantly higher in the non-Underweight patients with DM than in those without DM (p<0.05). However, there was no significant difference between Underweight patients with DM and those without DM. Multivariate analyses showed that DM was an independent predictor for the primary and secondary endpoints in non-Underweight patients, but not in Underweight patients. Conclusion: DM was associated with worse clinical outcomes in normal-weight or obese AMI patients, but not in underweight AMI patients.*

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Obese patients have a higher prevalence of diabetes mellitus (DM) and cardiovascular disease (CVD), which is significantly associated with increased mortality (1-4). On the other hand, previous studies have reported worse clinical outcomes in underweight CVD patients including acute myocardial infarction (AMI) compared to obese or normal-weight patients (5-8). However, the underlying mechanisms of the worse outcomes in underweight AMI patients is not yet determined.

Several studies reported that AMI patients with low body mass index (BMI) tend to have lower incidence of cardiovascular risk factors including DM regardless of poor clinical outcomes compared to obese patients (8-10). Also, underweight general populations with DM have been shown to be significantly associated with worse cardiovascular mortality (11). However, little is known about the impact of DM on clinical outcomes in AMI patients with low BMI. Therefore, the aim of this study was to evaluate the impact of DM on clinical outcomes in AMI patients based on BMI level.

Patients and Methods

Study population. Consecutive AMI patients who admitted to the Hirosaki University Hospital between January 2007 and January 2017 and who had emergent percutaneous coronary intervention (PCI) within 24 hours from symptom onset were evaluated in this retrospective study (Figure 1). We excluded the patients without BMI data at admission (n=13), and finally enrolled 1,282 patients. The diagnosis of AMI was established using the universal definition of myocardial infarction (MI) based on clinical symptoms, changes in electrocardiographic readings, and the elevation of cardiac biomarkers (12). Patient management, including the choice of antiplatelet drugs or PCI procedures, was at the discretion of the treating physician.

BMI was calculated as body weight (kg) divided by the square of height (m^2) at the time of AMI presentation. We divided the patients into 2 groups according to baseline BMI as follows: Underweight group (BMI <18.5 kg/m^2, n=61) and non-Underweight group (BMI

≥18.5 kg/m^2, n=1,221) as per the World Health Organization (WHO) criteria (13) (Figure 1). Patients' hospital records about the past medical history and the clinical data during hospitalization were reviewed. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or use of antihypertensive medication before admission. DM was defined as a hemoglobin A1c level ≥6.5%, antidiabetic medical treatment, or a presence of a history of DM. Dyslipidemia was defined as a total cholesterol level ≥220 mg/dl, a low-density lipoprotein (LDL) cholesterol level ≥140 mg/dl, a high-density lipoprotein (HDL) cholesterol level <40 mg/dl, or medical treatment for dyslipidemia. This study was conducted based on the ethical guidelines for medical research on humans in the Helsinki Declaration. The research protocol was approved by the Institutional Review Board of the Hirosaki University Graduate School of Medicine.

Study endpoints. The primary endpoint in the present study was all-cause death. The secondary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), which was a composite of cardiovascular death, non-fatal MI, non-fatal stroke, and re-hospitalization for heart failure. The median follow-up period was 3.8 (1.7-5.0) years.

Statistical analysis. Continuous variables were expressed as mean±standard deviation or median (interquartile range), whereas categorical variables were expressed as frequencies and percentages. We used one-way analysis of variance to compare continuous variables and the Tukey-Kramer test to determine the statistical significance of differences. We employed the Mann-Whitney *U*-test for nonparametric variables, and chi-square analysis for categorical variables. The Kaplan-Meier method was used to estimate primary and secondary endpoints, and the Log-rank test was used to compare 2 groups. Using the Cox proportional hazards regression, we performed multivariate analyses for the determinants of all-cause death and MACCE. The variables including age, male (sex), hypertension, dyslipidemia, and DM were used for analysis. The 95% confidence intervals (CIs) and hazard ratios (HRs) were calculated. Statistical significance was defined as a *p*-value of less than 0.05. JMP pro version 16 was used to conduct statistical analysis (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. We enrolled 1,282 patients with mean age of 66±12 years and 1,011 (79%) were men. Sixty-one patients (5%) were in the Underweight group and 1,221 (95%) were in the non-Underweight group. Baseline characteristics of the study population are shown in Table I. Patients in the Underweight group were older and there existed more females than those in the non-Underweight group. Non-Underweight patients had a higher prevalence of coronary risk factors, including DM, dyslipidemia, and current smoking habits. The prevalence of previous MI and stroke between the 2 groups were not different. The prevalence of Killip classification IV or multivessel disease was equivalent and left ventricular ejection fraction at the acute phase was not different between the 2 groups. Peak CPK and CPK-MB also did not differ between the 2 groups.

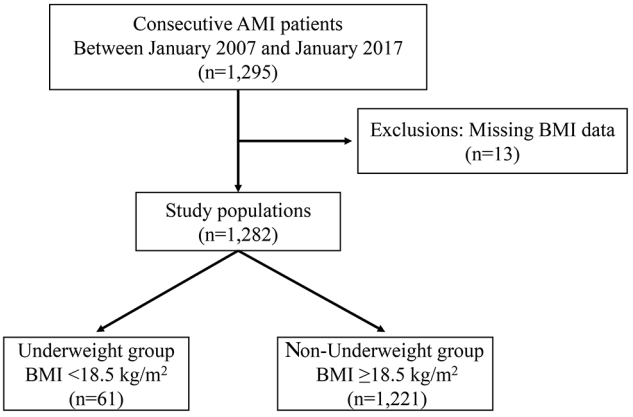

Figure 1. *Study flow chart. AMI: Acute myocardial infarction, BMI: body mass index.*

With respect to PCI procedures, final TIMI flow ≥2 or time to reperfusion were not different between the 2 groups. Renal function was decreased in the Underweight patients.

Clinical outcomes. The Kaplan-Meier curves for the primary and secondary endpoints between the 2 groups (BMI <18.5 kg/m^2 *vs*. BMI ≥18.5 kg/m^2) are compared, as shown in Figure 2, and the details of the clinical outcomes are shown in Table II. The primary endpoint, defined as all-cause death, was significantly higher in Underweight patients (p<0.05 by the Log-rank test) (Figure 2A). Moreover, the secondary endpoint, defined as MACCE, was also significantly higher in Underweight patients (p<0.05 by the Log-rank test) (Figure 2B). Among the secondary endpoints, the frequency of cardiovascular death (21% *vs*. 9%, p<0.05) and re-hospitalization for heart failure (15% *vs*. 7%, p<0.05) were significantly higher in Underweight patients (Table II). To evaluate the impact of DM on the clinical outcomes, we performed the Kaplan-Meier estimates for the primary and secondary endpoints between the 2 groups (patients with DM *vs*. those without DM) according to BMI level at admission (Figure 3 and Figure 4). The incidence of all-cause death tended to be higher in the Underweight patients with DM (p=0.067 by the Log-rank test) and in the non-Underweight patients with DM (p=0.075 by the Log-rank test) compared with those without DM, respectively, although these were not statistically significant (Figure 3A and 3B). The incidence of MACCE was significantly higher in non-Underweight patients with DM than in those without DM (p<0.05 by the Log-rank test) (Figure 4B). However, there was no significant difference between Underweight patients with DM and without DM (p=0.33 by the Log-rank test) (Figure 4A).

Predictor for the clinical outcomes. Multivariate analyses for the primary and secondary endpoints are shown in Table

Table I. *Patient characteristics*.

	All patients (n=1,282)	Underweight (n=61)	Non-Underweight (n=1,221)	*p*-Value
Age, years	66±12	77±9	65±12	<0.05
Male, n (%)	1,011 (79)	39 (64)	972 (79)	<0.05
BMI, kg/m^2	24±4	17±1	24±3	<0.05
Coronary risk factors, n (%)				
Diabetes mellitus	627 (49)	20 (33)	607 (49)	<0.05
Dyslipidemia	1,029 (80)	37 (60)	992 (81)	<0.05
Hypertension	939 (73)	44 (72)	895 (73)	0.88
Current smoker	527 (41)	15 (24)	512 (42)	<0.05
Previous MI, n (%)	124 (10)	6 (10)	118 (10)	1.00
Previous stroke, n (%)	120 (9)	9 (14)	111 (9)	0.17
Killip classification 4, n (%)	88 (7)	6 (10)	82 (7)	0.30
LVEF, %	46±10	45±11	46±10	0.08
STEMI, n (%)	1,213 (95)	57 (93)	1,156 (94)	0.57
Multi-vessel disease, n (%)	660 (51)	36 (59)	624 (51)	0.24
LMT lesion, n (%)	126 (10)	9 (15)	117 (10)	0.19
Time to reperfusion, min	286 (195-450)	325 (215-430)	285 (194-450)	0.43
Final TIMI flow ≥2, n (%)	1,233 (96)	59 (96)	1,174 (96)	1.00
Blood chemistry at admission				
eGFR, ml/min/1.73m^2	72 (55-87)	63 (37-84)	72 (55-87)	<0.05
HbA1c, %	6 (5.7-6.7)	5.9 (5.5-6.2)	6 (5.7-6.8)	<0.05
Glucose, mg/dl	146 (119-195)	131 (114-157)	148 (119-196)	<0.05
Triglyceride, mg/dl	101 (64-159)	64 (46-97)	103 (66-162)	<0.05
LDL-cholesterol, mg/dl	120 (97-143)	103 (79-131)	120 (98-144)	<0.05
HDL-cholesterol, mg/dl	45 (38-53)	50 (41-61)	45 (38-53)	<0.05
Peak CPK, IU/l	2,441 (1,096-4,453)	2,183 (884-3,312)	2,469 (1,102-4,463)	0.16
Peak CPK-MB, IU/l	242 (111-450)	227 (107-402)	242 (111-451)	0.92

Data are presented as mean±standard deviation, n (%), or median and interquartile ranges. Underweight group: BMI <18.5 kg/m^2, and non-Underweight group: BMI ≥18.5 kg/m^2. BMI: Body mass index; MI: myocardial infarction; LVEF: left ventricular ejection fraction; STEMI: ST elevation myocardial infarction; LMT: left main trunk; TIMI: thrombolysis in myocardial infarction; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CPK: creatine phosphokinase; CPK-MB: creatine phosphokinase myocardial isoform.

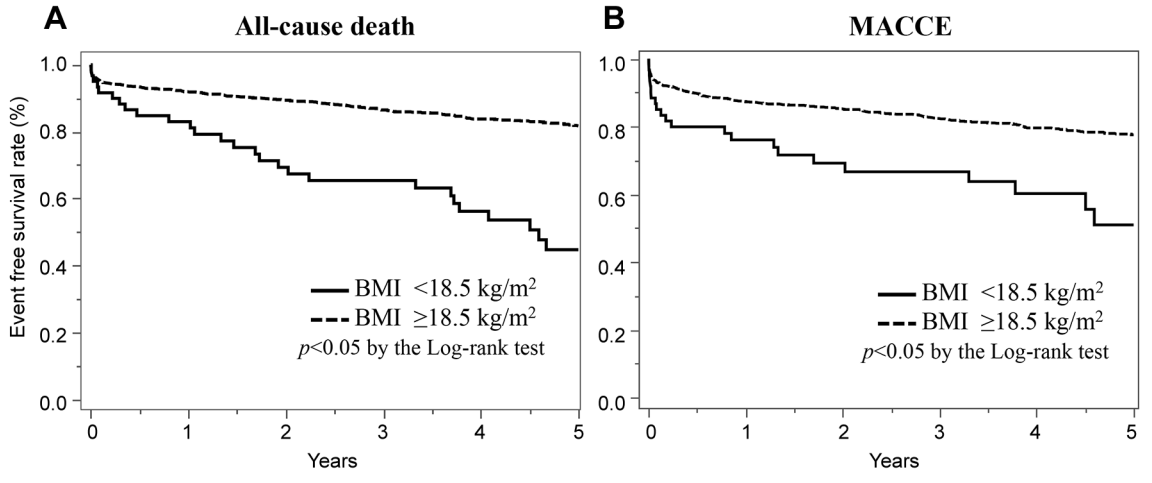

Figure 2. *Comparison of the Kaplan-Meier curves for the clinical outcomes between patients with BMI <18.5 kg/m^2 and BMI ≥18.5 kg/m^2. (A) All-cause death. (B) MACCE: a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and re-hospitalization for heart failure. BMI: Body mass index, MACCE: major adverse cardiovascular and cerebrovascular events.*

III and Table IV. Age and DM were an independent predictor for all-cause death and MACCE in all study patients. Male (sex) was an independent predictor for all-cause death, but not for MACCE. Hypertension and dyslipidemia were not an independent predictor for both all-cause death and MACCE. Moreover, when analyzed by BMI category, age was an independent predictor for all-cause death both in non-Underweight patients and in Underweight patients, whereas male (sex) and DM were independent predictors only in non-Underweight patients. Similarly, age and DM was an independent predictor for MACCE in the non-Underweight patients, whereas none of them was in the Underweight patients.

Table II. *Clinical outcomes according to BMI at admission.*

	Underweight (n=61)	Non-Underweight (n=1,221)	*p*-Value
Primary endpoint			
All-cause death, n (%)	31 (51)	221 (18)	<0.05
Secondary endpoints			
Cardiovascular death, n (%)	13 (21)	105 (9)	<0.05
Non-fatal MI, n (%)	3 (5)	65 (5)	1.00
Non-fatal stroke, n (%)	4 (7)	71 (6)	0.78
Re- hospitalization for heart failure, n (%)	9 (15)	83 (7)	<0.05

Data are presented as n (%). Underweight group: BMI <18.5 kg/m^2, and non-Underweight group: BMI ≥18.5 kg/m^2. BMI: Body mass index; MI: myocardial infarction.

Discussion

Major findings. In the present study, we showed that underweight AMI patients were associated with worse all-cause death and MACCE compared to normal-weight or obese AMI patients. Furthermore, our results revealed that DM was a significant predictor for all-cause death and MACCE in normal-weight or obese AMI patients, but not in underweight AMI patients.

Association between BMI and cardiovascular disease. Adipocytes secrete a variety of hormones. Some have effects on renin-angiotensin-aldosterone system activation, sympathetic nerve activation, and dysregulation of insulin growth factor, all of which are known as triggers for metabolic diseases including DM and CVD (14, 15). On the other hand, several adipocytes are reported to have cardioprotective effects, which may be inhibited by excess body fat (16, 17). The WHO defined obesity as "excess body fat that is detrimental to health", which is known to be an important CVD risk factor, causing 3 million deaths worldwide (1-4). BMI has been reported to be an important predictor for cardiovascular mortality (18-20). However, even if patients have a normal-BMI, an increased fatness might not be ruled out because BMI does not reflect the body composition such as fat and muscle (21-23). As a result, several studies reported that BMI might be an inadequate marker for general adiposity (14). However, BMI is easily calculated by body weight and height, and therefore many studies employed BMI as a simple and economical index of obesity.

It has been reported that low BMI patients with CVD including AMI have worse clinical outcomes compared to obese or normal-weight patients (5-10, 24, 25), which is consistent with our findings. Underweight patients might be affected by non-cardiac death due to comorbidities, such as cancer, and pneumonia. Although these comorbidities might be one of the reasons for worse mortality in underweight patients, the underlying mechanisms of the worse outcomes in underweight AMI patients is not yet determined.

Impact of DM on clinical outcomes in underweight AMI patients. Consistent with previous reports, DM was shown to be one of the independent risk factors for MACCE in AMI patients in the present study. Many epidemiological studies have shown that DM is associated with obesity and is an independent risk factor for CVD (26-28). On the other hand, Underweight patients have been previously shown to be older and have less traditional CVD risk factors, such as DM compared to normal-weight or obese patients (9, 10, 29). Nevertheless, worse all-cause death and MACCE were found in underweight AMI patients compared to normal-weight or obese AMI patients in our study. This is consistent with previous reports showing that non-cardiac death such as cachexia, malnutrition, and malignancy, as well as cardiac deaths, are more common in the older underweight patients (30-32).

DM and underweight have been shown to be associated with worse mortality in general populations (22). Compared to non-diabetics, underweight diabetics were shown to be significantly higher risk of all-cause death only in younger age groups (<65 years). Nilsson *et al*. also reported that cardiac death and all-cause mortality were significantly increased in non-obese DM patients with BMI <25 kg/m^2 (11). In our study, the incidence of all-cause death and MACCE in Underweight AMI patients with BMI <18.5 kg/m^2 did not differ between those with DM and without DM, indicating that DM is an independent predictor for all-cause death and MACCE only in the normal-weight or obese AMI patients, but not in the Underweight AMI patients.

Characteristics of the elderly DM patients. In an aging society, the aging of DM patients is also increasing (33, 34). Although the life expectancy of DM patients is generally shorter than that of non-DM patients (35), it has been reported that the relative risk of mortality in DM patients

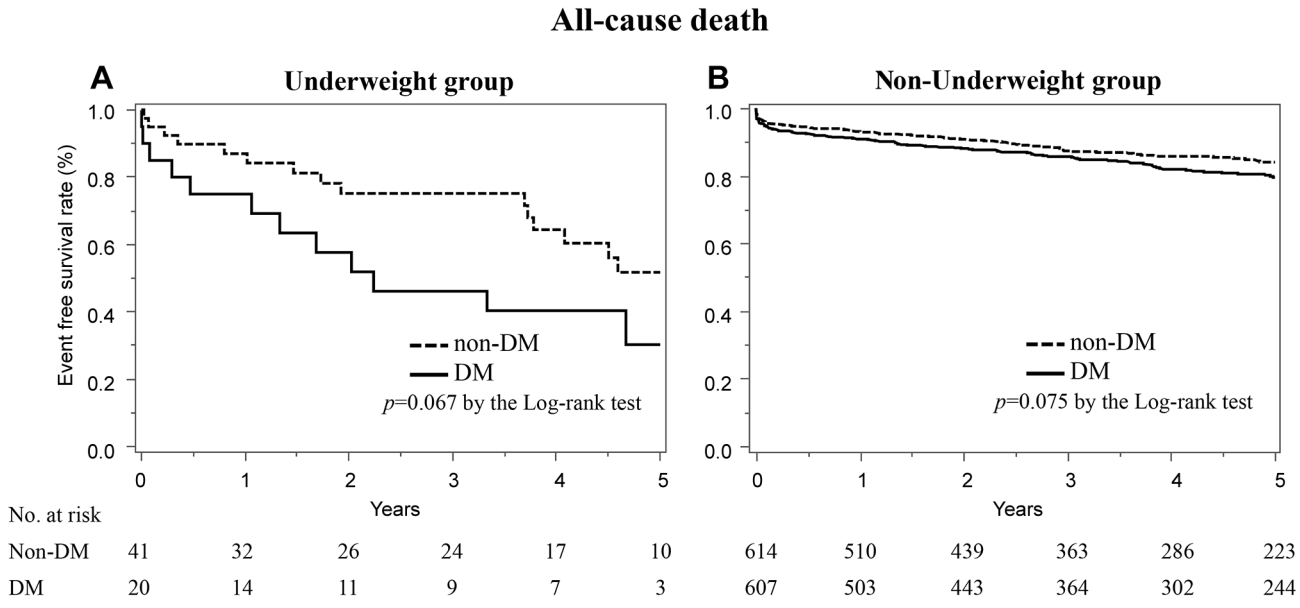

Figure 3. *Comparison of Kaplan-Meier curves for all-cause death between 2 groups (DM vs. non-DM patients) in the Underweight group (BMI <18.5 kg/m^2) (A) and in the non-Underweight group (BMI ≥18.5 kg/m^2) (B). DM indicates diabetes mellitus.*

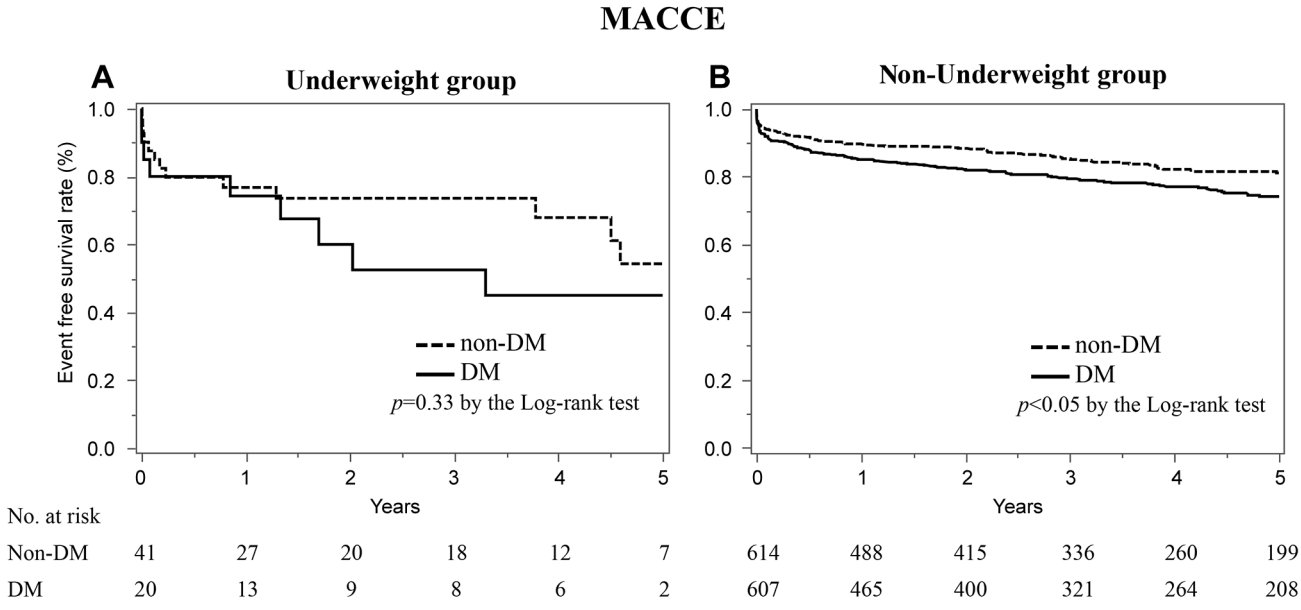

Figure 4. *Comparison of Kaplan-Meier curves for MACCE between 2 groups (DM vs. non-DM patients) in the Underweight group (BMI <18.5 kg/m^2) (A) and in the non-Underweight group (BMI ≥18.5 kg/m^2) (B). DM indicates diabetes mellitus, MACCE: major adverse cardiovascular and cerebrovascular events.*

decreases with aging (36). Zoungas *et al*. reported that an increase in the duration of DM had a greater impact on worse clinical outcomes than an increase in age. Since the duration of DM is expected to be longer in DM patients with a younger onset of disease, it is conceivable that the majority of high-risk DM patients may be excluded from the older DM group as a result (37). In other words, the surviving elderly patients with DM might have been a low-risk group with a short duration of DM. These previous studies are consistent with the present study showing that

Table III. *Adjusted hazard ratios for the primary endpoint.*

	Adjusted HR (95% CI)	*p*-Value
Primary endpoint		
All patients		
Age	1.07 (1.05-1.08)	<0.05
Male (sex)	1.48 (1.06-2.07)	<0.05
Diabetes mellitus	1.48 (1.13-1.95)	<0.05
Dyslipidemia	0.76 (0.56-1.03)	0.08
Hypertension	0.98 (0.72-1.33)	0.91
Underweight		
Age	1.06 (1.01-1.13)	<0.05
Male (sex)	0.78 (0.34-1.79)	0.56
Diabetes mellitus	2.07 (0.93-4.62)	0.07
Dyslipidemia	1.23 (0.53-2.85)	0.63
Hypertension	2.14 (0.77-5.94)	0.14
Non-Underweight		
Age	1.07 (1.05-1.08)	<0.05
Male (sex)	1.58 (1.10-2.29)	<0.05
Diabetes mellitus	1.48 (1.10-1.99)	<0.05
Dyslipidemia	0.77 (0.55-1.07)	0.12
Hypertension	0.91 (0.66-1.27)	0.58

Primary endpoint was defined as all-cause death. Underweight group: BMI <18.5 kg/m^2, and non-Underweight group: BMI ≥18.5 kg/m^2. BMI: Body mass index; HR: hazard ratio; CI: confidence interval.

Table IV. *Adjusted hazard ratios for the secondary endpoints.*

	Adjusted HR (95% CI)	*p*-Value
Secondary endpoints		
All patients		
Age	1.05 (1.04-1.06)	<0.05
Male (sex)	1.00 (0.75-1.34)	1.00
Diabetes mellitus	1.47 (1.12-1.94)	<0.05
Dyslipidemia	0.75 (0.55-1.02)	0.59
Hypertension	1.00 (0.73-1.37)	0.47
Underweight		
Age	1.05 (0.99-1.10)	0.06
Male (sex)	0.52 (0.21-1.30)	0.16
Diabetes mellitus	1.68 (0.71-3.96)	0.24
Dyslipidemia	0.49 (0.20-1.17)	0.11
Hypertension	0.92 (0.36-2.39)	0.87
Non-Underweight		
Age	1.05 (1.03-1.06)	<0.05
Male (sex)	1.08 (0.79-1.47)	0.65
Diabetes mellitus	1.49 (1.14-1.94)	<0.05
Dyslipidemia	1.05 (0.75-1.45)	0.79
Hypertension	1.15 (0.84-1.57)	0.38

Secondary endpoint was defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and re-hospitalization for heart failure. Underweight group: BMI <18.5 kg/m^2, and non-Underweight group: BMI ≥18.5 kg/m^2. BMI: Body mass index; HR: hazard ratio; CI: confidence interval.

DM did not have a significant impact on poor clinical outcomes in the underweight AMI patients.

Kirkman *et al.* reported that the incidence of DM increases with aging up to 65 years, however after 65 years, both the incidence and the prevalence of DM decrease. Therefore, elderly diabetic patients can be divided into two groups: those with incidental DM diagnosed after age 65 years, and those with longer duration of DM (38). For elderly-onset DM, the mechanism of insulin resistance is thought to be due to changes in body composition, decreased lean body mass, and decreased physical activity, suggesting that there might be different characteristics from middle aged-onset DM (39, 40). The duration of DM treatment might be complexly associated with clinical outcomes, therefore the impact of DM on clinical outcomes of the elderly diabetic patients were not simply evaluated.

Study limitations. There are certain limitations in the present study. First, although the clinical variables were adequately adjusted, the results might be influenced by unknown variables. Second, we reported worse clinical outcomes in underweight AMI patients, however, obese patients may often develop hypertension, DM, and dyslipidemia in the long-term period, eventually leading to poor clinical outcomes. Third, these results were derived from only limited numbers of underweight AMI patients by a single-center retrospective study and might therefore not be generalizable to other populations. Although the mechanisms of the less prognostic impact of DM on the underweight AMI patients are undetermined, it is possible that the shorter observation period may have influenced the results. Fourth, since we only collected the BMI data at admission, any change in the BMI was not evaluated. Accordingly, the impact of BMI change on the clinical outcomes was not discussed (20). Fifth, there was no information about the physical examination, such as waist circumference to determine the degree of visceral fat accumulation. Finally, there was a paucity of medical information about the treatment of DM, which might have influenced the results. Although this retrospective study had these limitations, our results might contribute to partly explain the underlying mechanisms for worse clinical outcomes in underweight AMI patients. Further larger-scale prospective studies are clearly warranted.

Conclusion

Underweight AMI patients had worse clinical outcomes compared to normal-weight or obese AMI patients. DM was associated with worse clinical outcomes in normal-weight or obese AMI patients, but not in underweight AMI patients. Further studies are required to seek for the mechanisms for worse clinical outcomes in underweight AMI patients.

Conflicts of Interest

Dr. Tomita received research funding from Japan Lifeline Co., Ltd. and Speakers' Bureau/Honorarium from Bayer, Daiichi-Sankyo, Bristol-Myers Squibb, and AstraZeneca. The rest of the Authors have no relevant disclosures.

Authors' Contributions

Conception: Misato Hamadate, and Hirofumi Tomita. Study design: Misato Hamadate, Hiroaki Yokoyama, and Hirofumi Tomita. Data collection and processing: Misato Hamadate, Hiroaki Yokoyama, Shuntaro Sakai, Shun Shikanai, Yuya Sorimachi, Ken Yamazaki, Kazutaka Kitayama, Naotake Miura, and Takashi Yokota. Article writing: Misato Hamadate. Critical review: Hiroaki Yokoyama and Hirofumi Tomita.

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References

1 Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R and Milani RV: Obesity and prevalence of cardiovascular diseases and prognosis-the obesity paradox updated. Prog Cardiovasc Dis *58(5)*: 537-547, 2016. PMID: 26826295. DOI: 10.1016/j.pcad.2016.01.008

2 Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M and Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index): National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. Lancet *377(9765)*: 557-567, 2011. PMID: 21295846. DOI: 10.1016/S0140-6736(10)62037-5

3 Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ and Comparative Risk Assessment Collaborating Group: Selected major risk factors and global and regional burden of disease. Lancet *360(9343)*: 1347-1360, 2002. PMID: 12423980. DOI: 10.1016/S0140-6736(02)11403-6

4 Hubert HB, Feinleib M, McNamara PM and Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation *67(5)*: 968-977, 1983. PMID: 6219830. DOI: 10.1161/01.cir.67.5.968

5 Ades PA and Savage PD: The obesity paradox: perception *vs*. knowledge. Mayo Clin Proc *85(2)*: 112-114, 2010. PMID: 20118385. DOI: 10.4065/mcp.2009.0777

6 Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F and Lopez-Jimenez F: Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet *368(9536)*: 666-678, 2006. PMID: 16920472. DOI: 10.1016/S0140-6736(06)69251-9

7 Nikolsky E, Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Negoita M, Lansky AJ and Mehran R: Impact of body mass index on outcomes after primary angioplasty in acute myocardial infarction. Am Heart J *151(1)*: 168-175, 2006. PMID: 16368312. DOI: 10.1016/j.ahj.2005.03.024

8 Yokoyama H, Tomita H, Honda S, Nishihira K, Kojima S, Takegami M, Asaumi Y, Yamashita J, Saji M, Kosuge M, Takahashi J, Sakata Y, Takayama M, Sumiyoshi T, Ogawa H, Kimura K, Yasuda S and JAMIR Investigators: 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). Circ J, 2021. PMID: 34803127. DOI: 10.1253/circj.CJ-21-0705

9 Champagne-Langabeer T, Kim J, Bower JK, Gardner A, Fowler R and Langabeer JR 2nd: Obesity, treatment times, and cardiovascular outcomes after ST-elevation myocardial infarction: findings from mission: lifeline North Texas. J Am Heart Assoc *6(9)*: e005827, 2017. PMID: 28939712. DOI: 10.1161/JAHA.117.005827

10 Kim HT, Jung SY, Nam JH, Lee JH, Lee CH, Son JW, Kim U, Park JS, Shin DG, Her SH, Chang KY, Ahn TH, Jeong MH, Rha SW, Kim HS, Gwon HC, Seong IW, Hwang KK, Chae SC, Kim KB, Cha KS, Oh SK, Chae JK and KAMIR-NIH registry investigators: Clinical implication of 'Obesity paradox' in elderly patients with acute myocardial infarction. Heart Lung Circ *30(4)*: 481-488, 2021. PMID: 33012675. DOI: 10.1016/j.hlc.2020.08.013

11 Nilsson G, Hedberg P and Öhrvik J: Survival of the fattest: unexpected findings about hyperglycaemia and obesity in a population based study of 75-year-olds. BMJ Open *1(1)*: e000012, 2011. PMID: 22021724. DOI: 10.1136/bmjopen-2010-000012

12 Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD and Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Glob Heart *7(4)*: 275-295, 2012. PMID: 25689940. DOI: 10.1016/j.gheart.2012.08.001

13 Nuttall FQ: Body mass index: Obesity, BMI, and health: a critical review. Nutr Today *50(3)*: 117-128, 2015. PMID: 27340299. DOI: 10.1097/NT.0000000000000092

14 Lavie CJ, Arena R, Alpert MA, Milani RV and Ventura HO: Management of cardiovascular diseases in patients with obesity. Nat Rev Cardiol *15(1)*: 45-56, 2018. PMID: 28748957. DOI: 10.1038/nrcardio.2017.108

15 Pi-Sunyer FX: The obesity epidemic: pathophysiology and consequences of obesity. Obes Res *10 Suppl 2*: 97S-104S, 2002. PMID: 12490658. DOI: 10.1038/oby.2002.202

16 Ghantous CM, Azrak Z, Hanache S, Abou-Kheir W and Zeidan A: Differential role of leptin and adiponectin in cardiovascular system. Int J Endocrinol *2015*: 534320, 2015. PMID: 26064110. DOI: 10.1155/2015/534320

17 Hajer GR, van Haeften TW and Visseren FL: Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J *29(24)*: 2959-2971, 2008. PMID: 18775919. DOI: 10.1093/eurheartj/ehn387

18 Ortega FB, Sui X, Lavie CJ and Blair SN: Body mass index, the most widely used but also widely criticized index: Would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality? Mayo Clin Proc *91(4)*: 443-455, 2016. PMID: 26948431. DOI: 10.1016/j.mayocp.2016.01.008

19 Lacey B, Yeap BB, Golledge J, Lewington S, McCaul KA, Norman PE, Flicker L, Almeida OP and Hankey GJ: Body mass index and vascular disease in men aged 65 years and over: HIMS (health in men study). J Am Heart Assoc *6(12)*: e007343, 2017. PMID: 29180456. DOI: 10.1161/JAHA.117.007343

20 Eilat-Adar S, Eldar M and Goldbourt U: Association of intentional changes in body weight with coronary heart disease event rates in overweight subjects who have an additional coronary risk factor. Am J Epidemiol *161(4)*: 352-358, 2005. PMID: 15692079. DOI: 10.1093/aje/kwi045

21 Scuteri A, Najjar SS, Morrell CH, Lakatta EG and Cardiovascular Health Study: The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. Diabetes Care *28(4)*: 882-887, 2005. PMID: 15793190. DOI: 10.2337/diacare.28.4.882

22 Coutinho T, Goel K, Corrêa de Sá D, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee SH, Kim YJ, Thomas R, Roger VL, Somers VK and Lopez-Jimenez F: Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol *57(19)*: 1877-1886, 2011. PMID: 21545944. DOI: 10.1016/j.jacc.2010.11.058

23 Romero-Corral A, Somers VK, Sierra-Johnson J, Jensen MD, Thomas RJ, Squires RW, Allison TG, Korinek J and Lopez-Jimenez F: Diagnostic performance of body mass index to detect obesity in patients with coronary artery disease. Eur Heart J *28(17)*: 2087-2093, 2007. PMID: 17626030. DOI: 10.1093/eurheartj/ehm243

24 Yano Y, Kario K, Ishikawa S, Ojima T, Gotoh T, Kayaba K, Tsutsumi A, Shimada K, Nakamura Y, Kajii E and JMS Cohort Study Group: Associations between diabetes, leanness, and the risk of death in the Japanese general population: the Jichi Medical School Cohort Study. Diabetes Care *36(5)*: 1186-1192, 2013. PMID: 23250802. DOI: 10.2337/dc12-1736

25 Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB and Milani RV: An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis *61(2)*: 142-150, 2018. PMID: 29981771. DOI: 10.1016/j.pcad.2018.07.003

26 Sakurai M, Saitoh S, Miura K, Nakagawa H, Ohnishi H, Akasaka H, Kadota A, Kita Y, Hayakawa T, Ohkubo T, Okayama A, Okamura T, Ueshima H and NIPPON DATA90 Research Group: HbA1c and the risks for all-cause and cardiovascular mortality in the general Japanese population: NIPPON DATA90. Diabetes Care *36(11)*: 3759-3765, 2013. PMID: 23877989. DOI: 10.2337/dc12-2412

27 Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration: Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. Lancet Diabetes Endocrinol *6(7)*: 538-546, 2018. PMID: 29752194. DOI: 10.1016/S2213-8587(18)30079-2

28 Kannel WB and McGee DL: Diabetes and cardiovascular risk factors: the Framingham study. Circulation *59(1)*: 8-13, 1979. PMID: 758126. DOI: 10.1161/01.cir.59.1.8

29 Yokoyama H, Higuma T, Endo T, Nishizaki F, Hanada K, Yokota T, Yamada M, Okumura K and Tomita H: Prognostic impact of body mass index and culprit lesion calcification in patients with acute myocardial infarction. Heart Vessels *34(12)*: 1909-1916, 2019. PMID: 31144097. DOI: 10.1007/s00380-019-01439-5

30 Fukuoka S, Kurita T, Dohi K, Masuda J, Seko T, Tanigawa T, Saito Y, Kakimoto H, Makino K and Ito M: Untangling the obesity paradox in patients with acute myocardial infarction after primary percutaneous coronary intervention (detail analysis by age). Int J Cardiol *289*: 12-18, 2019. PMID: 30665801. DOI: 10.1016/j.ijcard.2019.01.011

31 Angerås O, Albertsson P, Karason K, Råmunddal T, Matejka G, James S, Lagerqvist B, Rosengren A and Omerovic E: Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J *34(5)*: 345-353, 2013. PMID: 22947610. DOI: 10.1093/eurheartj/ehs217

32 Nigam A, Wright RS, Allison TG, Williams BA, Kopecky SL, Reeder GS, Murphy JG and Jaffe AS: Excess weight at time of presentation of myocardial infarction is associated with lower initial mortality risks but higher long-term risks including recurrent re-infarction and cardiac death. Int J Cardiol *110(2)*: 153-159, 2006. PMID: 16043245. DOI: 10.1016/j.ijcard.2005.06.040

33 Diabetes UK: Us, diabetes and a lot of facts and stats. Available at: https://www.diabetes.org.uk/resources-s3/2019-11/facts-stats-update-oct-2019.pdf [Last accessed on August 18, 2021]

34 Melzer D, Tavakoly B, Winder RE, Masoli JA, Henley WE, Ble A and Richards SH: Much more medicine for the oldest old: trends in UK electronic clinical records. Age Ageing *44(1)*: 46-53, 2015. PMID: 25103030. DOI: 10.1093/ageing/afu113

35 Bardenheier BH, Lin J, Zhuo X, Ali MK, Thompson TJ, Cheng YJ and Gregg EW: Disability-free life-years lost among adults aged ≥50 years with and without diabetes. Diabetes Care *39(7)*: 1222-1229, 2016. PMID: 26721810. DOI: 10.2337/dc15-1095

36 Gu K, Cowie CC and Harris MI: Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes Care *21(7)*: 1138-1145, 1998. PMID: 9653609. DOI: 10.2337/diacare.21.7.1138

37 Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, Heller S, Marre M, Patel A, Poulter N, Williams B, Chalmers J and ADVANCE Collaborative group: Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia *57(12)*: 2465-2474, 2014. PMID: 25226881. DOI: 10.1007/s00125-014-3369-7

38 Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, Huang ES, Korytkowski MT, Munshi MN, Odegard PS, Pratley RE and Swift CS: Diabetes in older adults. Diabetes Care *35(12)*: 2650-2664, 2012. PMID: 23100048. DOI: 10.2337/dc12-1801

39 Tamura Y, Omura T, Toyoshima K and Araki A: Nutrition management in older adults with diabetes: a review on the importance of shifting prevention strategies from metabolic syndrome to frailty. Nutrients *12(11)*: 3367, 2020. PMID: 33139628. DOI: 10.3390/nu12113367

40 Ogama N, Sakurai T, Kawashima S, Tanikawa T, Tokuda H, Satake S, Miura H, Shimizu A, Kokubo M, Niida S, Toba K, Umegaki H and Kuzuya M: Association of glucose fluctuations with sarcopenia in older adults with type 2 diabetes mellitus. J Clin Med *8(3)*: 319, 2019. PMID: 30845785. DOI: 10.3390/jcm8030319

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