The Obesity-Mortality Paradox in Patients With Heart Failure in Taiwan and a Collaborative Meta-Analysis for East Asian Patients

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A global heart failure (HF) registry suggested that the inverse association between body mass index (BMI) and all-cause mortality differed by race, particularly stronger in Japanese patients at 1-year follow-up. Whether this finding was consistent across all East Asian populations was unknown. In a multicenter prospective study in Taiwan, we enrolled 1,301 patients hospitalized for systolic HF from 2013 to 2014 and followed up the mortality after their discharge for a median of 1-year period. Cox proportional hazard regression analyses were used to assess the association of BMI with all-cause mortality. The results showed that BMI was inversely associated with all-cause mortality (hazard ratio and 95% CI per 5-kg/m^2 increase: 0.75 [0.62 to 0.91]) after adjusting for demographics, traditional risk factors, HF severity, and medications at discharge. Subsequently, we sought previous studies regarding the BMI association with mortality for East Asian patients with HF from Medline, and a random-effect meta-analysis was performed by the inverse variance method. The meta-analysis including 7 previous eligible studies (3 for the Chinese and 4 for the Japanese cohorts) and the present one showed similar results that BMI was inversely associated with all-cause mortality (hazard ratio 0.65 [0.58 to 0.73], $I^2 = 37\%$). In conclusion, our study in Taiwan and a collaborative meta-analysis confirmed a strong inverse BMI-mortality association consistently among East Asian patients with HF. **(Am J Cardiol 2016;118:1011−1018)**

Obesity is a well-known risk factor of incident cardiovascular disease (CVD) and mortality in the general population.[1] However, several epidemiologic studies have revealed that overweight or obesity defined as greater body mass index (BMI) was associated with better survival in patients with established CVD.[2−4] Since 2001, the inverse association between BMI and mortality has been investigated in patients with heart failure (HF), and most studies were conducted in the Western countries.[5,6] Until 2010, 2 Japanese registries emerged to examine the BMI association while the results were conflicting.[7,8] In 2014, Shah et al[9] performed a 1-year prospective global registry to explore the obesity paradox in HF and revealed that the inverse association was stronger in subjects with older age, nondiabetes, recent onset HF, or systolic HF. In addition, the study showed a racial difference where the inverse BMI association with mortality was stronger in Japanese patients than European and American patients (each 5-kg/m^2 increase in BMI, hazard ratios [HRs] 0.53 and 0.91, respectively). Since previous studies for the Japanese patients were not consistent and the sample size of the Japanese cohort in the global acute HF registry was relatively small (n = 645), more evidence for a stronger inverse BMI association with mortality across all East Asian populations with HF are needed. Therefore, we investigated the association between BMI and mortality in a systolic HF cohort in Taiwan and sought previous studies for East Asian patients from Medline to perform a meta-analysis.

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See page 1017 for disclosure information.

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Methods

The Taiwan Society of Cardiology-Heart Failure with Reduced Ejection Fraction (TSOC-HFrEF) registry was a multicenter study aimed to prospectively investigate the prognosis of patients with systolic HF in Taiwan. The registry was conducted in 22 medical centers and enrolled patients hospitalized for acute worsening HF, whose echocardiographic left ventricular ejection fraction were <45%. BMI was defined as body weight (kg)/square of height (m^2). Hypertension was defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl or the use of hypoglycemic medications. Dyslipidemia was defined as fasting low-density lipoprotein cholesterol ≥130 mg/dl, or high-density lipoprotein cholesterol <40 mg/dl in men or <50 mg/dl in women, or the use of lipid-lowering medications. The baseline data were obtained on admission and/or at discharge including demographic parameters, cause of HF, co-morbidities, clinical status, electrocardiographic and echocardiographic findings, laboratory data, interventional, and medical treatments. The participants were divided to 4 groups by BMI categories at discharge: <20.5 kg/m^2 (underweight), 20.5 to 24.0 kg/m^2 (normal weight), 24.1 to 27.4 kg/m^2 (overweight), and ≥27.5 kg/m^2 (obesity), according to the guidelines of the Department of Health in Taiwan and the results from the Eastern Taiwan integrated health care delivery system of Coronary Heart Disease (ET-CHD) registry.[4]

Outcomes of interest were (1) all-cause mortality; (2) cardiovascular mortality, defined as death of sudden cardiac death, ischemic heart disease, stroke, refractory HF, and lethal arrhythmia; and (3) noncardiovascular mortality. Patients were followed up at outpatient department for evaluating their clinical condition, laboratory, and imaging examinations every 6 months. The origin and the issue date of mortality were verified according to the medical record. The study complies with the Declaration of Helsinki that the jointed ethics committee has approved the protocol and that informed consent has been obtained from the subjects.

Characteristics of patients in each BMI group were compared using either analysis of variance or chi-square analysis and reported as mean ± SD or percent for continuous and categorical variables, respectively. The analysis used the time for follow-up at the patients' first enrollment (October 2013 to October 2014) with censoring at the occurrence of mortality or end of follow-up (February 1, 2015). Kaplan−Meier analysis was used to assess the association of BMI categories with mortality. Curves were compared using the log-rank test. Cox proportional hazard regression analyses were used to assess the multivariable association of BMI (as a continuous or categorical variable, respectively) with mortality, adjusting for potential confounders. In model 1, age, gender, and cause of HF were adjusted, and in model 2, demographic variables, co-morbidities, severity of HF, and medications at discharge were additionally adjusted. Stratified analyses exploring the association between BMI and all-cause mortality within age <65 and ≥65 years were performed. p Value <0.05 was used for as the criterion for variables to remain in the model 2. All statistical analyses were performed with SAS, version 9.2 (SAS Institute, Cary, North Carolina).

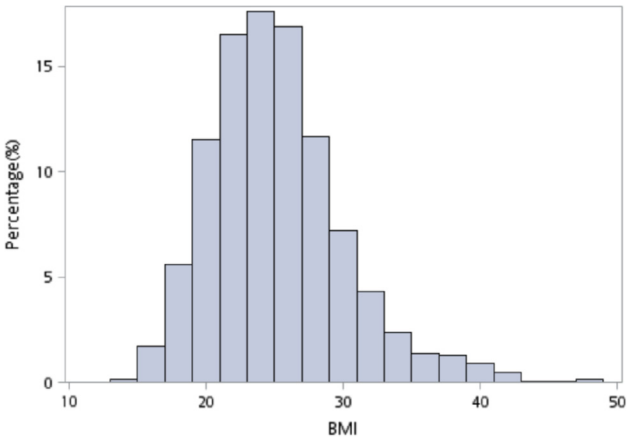

Figure 1. Distribution of baseline BMI among the total cohort of 1,301 patients with HF in Taiwan.

Subsequently, we sought previous studies evaluating the effect of BMI on the all-cause mortality among East Asian patients with HF from MEDLINE. The East Asian populations included those living in the territory of China, Japan, Mongolia, North Korea, South Korea, and Taiwan. We used keywords of body mass index, BMI, mortality, or the term of obesity paradox (or reverse epidemiology), and heart failure to search for the eligible studies written in English from 2000 to 2015. Two reviewers (GML and YHL) independently reviewed these papers and performed data extraction. Disagreements were resolved through consensus. Studies were required to report the association of BMI, treated as either a continuous variable or categorical variable, with mortality in patients with HF. A priori, we knew that not all studies, especially conducted in East Asian countries, would use the World Health Organization BMI classification system of <18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30.0 kg/m^2, respectively for underweight, normal, overweight, and obesity. To avoid eliminating studies with important data, we considered BMI levels within 2.5 kg/m^2 of standard levels to be acceptable. Studies comparing obese and nonobese were excluded unless outcomes in the normal BMI population alone were available. The primary outcome of interest was all-cause mortality.

HRs and 95% CIs were risk factors adjusted and retrieved from the studies for meta-analysis. If BMI was treated as a continuous variable for all-cause mortality, all the retrieved HRs and their corresponding CIs were converted to HRs associated with 5-kg/m^2 increase in BMI. When BMI levels were categorical, all the retrieved HRs and their CIs were converted into HRs using BMI: 18.5 to 23.9 kg/m^2 as reference group. RevMan (version 5.2) (Cochrane Author Support Tool; website: http://tech.cochrane.org) was used to perform random-effect meta-analysis of the converted HRs and their corresponding CIs by the inverse variance method for 5-kg/m^2 increase in BMI and BMI category, respectively. Heterogeneity was examined using the Higgins I^2 test.[10] Roughly, Higgins I^2 values of 25, 50, and 75% were interpreted as indicating low, moderate, and high heterogeneity.

Table 1
Baseline characteristics of patients with systolic heart failure According to body mass index at discharge

Variables	Body Mass Index (kg/m^2)				P-value
	<20.5 (N=195)	20.5-24.0 (N=384)	24.1-27.4 (N=370)	≥27.5 (N=352)	
Demographic					
Age (years)	72.2±15.0	67.1±14.5	64.7±13.9	55.8±15.2	<0.0001
Men	66.2%	67.5%	74.6%	79.0%	0.0007
Cause of heart failure					
Ischemic	42.1%	49.5%	48.7%	38.9%	0.12
Dilated cardiomyopathy	29.7%	30.0%	31.4%	40.1%	
Hypertensive	9.2%	5.0%	7.0%	8.5%	
Valvular	12.8%	11.2%	6.8%	5.7%	
Hypertension	32.3%	31.5%	32.2%	42.6%	0.0046
Diabetes mellitus	29.2%	41.9%	48.9%	48.9%	<0.0001
Dyslipidemia	16.4%	16.4%	19.7%	27.0%	0.0016
Chronic obstructive pulmonary disease	17.4%	13.0%	8.4%	8.5%	0.0023
Atrial fibrillation	29.7%	27.3%	27.0%	24.4%	0.5871
Prior myocardial infarction	28.7%	24.5%	26.5%	21.0%	0.1805
Prior stroke/ transient ischemic accident	10.3%	8.6%	10.0%	8.8%	0.8606
Current cigarette smoking	44.1%	46.1%	51.4%	57.7%	0.0036
Current alcohol consumption	25.6%	28.9%	34.6%	42.3%	<0.0001
Percutaneous coronary intervention	26.7%	28.4%	32.2%	24.7%	0.16
Coronary artery bypass grafting	6.7%	6.0%	4.9%	6.3%	0.80
Valvular surgery	6.2%	8.3%	5.4%	4.3%	0.12
Cardiovascular implantable electronic device	7.7%	11.7%	7.6%	9.4%	0.20
New York Heart Association functional class	2.3±0.7	2.3±0.7	2.1±0.7	2.1±0.7	0.008
Heart rate (beats/min)	80.5±15.1	80.1±14.0	79.9±14.6	80.9±17.0	0.80
Systolic blood pressure (mmHg)	118.8±18.5	116.6±18.4	120.2±18.2	121.9±19.7	0.001
Diastolic blood pressure (mmHg)	67.9±11.8	70.2±13.5	73.7±29.2	76.5±14.0	<0.0001
Estimated glomerular filtration rate (ml·min^{-1}·1.73m^2)	60.4±41.0	61.9±35.3	60.3±37.0	63.6±30.7	0.61
Hemoglobin (g/dl)	11.5±2.1	12.2±6.6	11.7±2.2	17.2±53.8	0.21
Left ventricular end-diastolic diameter (mm)	61.4±24.3	64.5±34.4	63.6±24.9	65.1±22.5	0.50
Left ventricular end-systolic diameter (mm)	50.2±16.7	53.6±24.9	54.5±34.6	55.1±19.4	0.20
Left ventricular ejection fraction	29.6±8.6%	28.3±8.6%	28.6±8.6%	27.8±9.0%	0.14
Medication use at discharge					
Angiotensin converting enzyme inhibitors	25.6%	24.5%	25.7%	29.8%	0.39
Angiotensin II receptor blockers	21.5%	33.3%	36.0%	41.8%	<0.0001
Beta-blockers	46.7%	58.6%	58.9%	69.0%	<0.0001
Calcium-channel blockers	12.3%	9.1%	14.6%	13.9%	0.10
Nitrates	34.4%	34.4%	36.8%	37.2%	0.81
Digitalis	29.7%	26.6%	25.4%	23.6%	0.45
Furosemides	74.9%	80.2%	78.7%	84.7%	0.038
Spironolactone	39.5%	46.9%	44.3%	55.1%	0.002
Anti-platelets	55.9%	58.9%	63.5%	54.0%	0.061
Anti-coagulants	22.6%	21.9%	17.8%	26.4%	0.051
Anti-arrhythmic agents	12.3%	15.9%	14.3%	17.1%	0.47

Results

The TSOC-HFrEF registry enrolled overall 1,450 patients; 149 patients were excluded because of loss to follow-up, resulting in 1,301 patients (90%) for analysis. Figure 1 shows the distribution of the BMI levels at discharge among the total cohort. The median BMI level was 24.6 kg/m^2, respectively, ranging from 13.9 to 52.7 kg/m^2.

Table 1 lists the baseline profiles of patients with HF according to the BMI levels. Patients with lower BMI levels had older age, more proportion of women, and greater New York Heart Association functional classes. On the contrary, patients with higher BMI levels had higher prevalence of co-morbidities, including diabetes mellitus, hypertension, dyslipidemia, and current cigarette smoking, and were more frequently prescribed by angiotensin receptor blockers, β blockers, anticoagulation agents, spironolactone, or loop diuretics at discharge. With regard to the proportion of invasive cardiovascular procedures, renal functions, hemoglobin concentrations, and left ventricular ejection fraction, there were no differences among 4 groups.

Table 2 lists that the mortality was 16.0%, 10.2%, and 5.8%, respectively for all-cause, cardiovascular, and noncardiovascular origins during a 1-year follow-up period after discharge. The all-cause mortality, cardiovascular and noncardiovascular mortality increased with decreasing BMI categories (Figure 2). In the model

Table 2
Hazard ratios for the mortality according to body mass index

Cause of mortality	Body mass index, kg/m^2				
	Categorical				Continuous Per +5 kg/m^2
	<20.5	20.5-24.0	24.1-27.4	≥27.5	
All-cause	50 (25.6%)	48 (12.5%)	46 (12.4%)	28 (8.0%)	172 (16.0%)
Crude	2.13* (1.43-3.17)	1	1.00 (0.69-1.56)	0.57 (0.35-0.92)	0.66* (0.55-0.78)
Model 1	1.92* (1.28-2.87)	1	1.04 (0.69-1.56)	0.71 (0.44-1.16)	0.75* (0.61-0.90)
Model 2	1.89* (1.25-2.85)	1	0.99 (0.66-1.49)	0.72 (0.44-1.19)	0.75* (0.62-0.91)
Cardiovascular	33 (16.9%)	25 (6.5%)	33 (8.9%)	19 (5.4%)	110 (10.2%)
Crude	2.66* (1.58-4.50)	1	1.37 (0.81-2.31)	0.81 (0.45-1.48)	0.72* (0.58-0.89)
Model 1	2.42* (1.43-4.12)	1	1.41 (0.83-2.38)	0.96 (0.52-1.77)	0.80 (0.63-1.01)
Model 2	2.48* (1.45-4.26)	1	1.38 (0.81-2.34)	1.03 (0.55-1.92)	0.82 (0.65-1.04)
Non-cardiovascular	17 (8.7%)	23 (6.0%)	13 (3.5%)	9 (2.6%)	62 (5.8%)
Crude	1.48 (0.79-2.78)	1	0.61 (0.31-1.19)	0.32* (0.14-0.75)	0.56* (0.41-0.76)
Model 1	1.32 (0.70-2.49)	1	0.64 (0.32-1.26)	0.43* (0.14-0.75)	0.66* (0.47-0.91)
Model 2	1.22 (0.64-2.34)	1	0.57 (0.28-1.14)	0.41* (0.17-0.98)	0.66* (0.47-0.92)

Cox regression model was used in the analysis adjusting for the covariates including age, gender, and primary cause of heart failure in model 1; and age, gender, a history of previous myocardial infarction, hypertension, diabetes, dyslipidemia, current smoking status, current alcohol intake, chronic obstructive pulmonary disease, New York Heart Association functional class, and medications with angiotensin II receptor blockers, β blockers, loop diuretics, spironolactone, antiplatelet agents (aspirin or clopidogrel), and anticoagulation agents (warfarin or dabigatran) in model 2.

Data were presented as hazard ratio (95% CI).

* p Value <0.05.

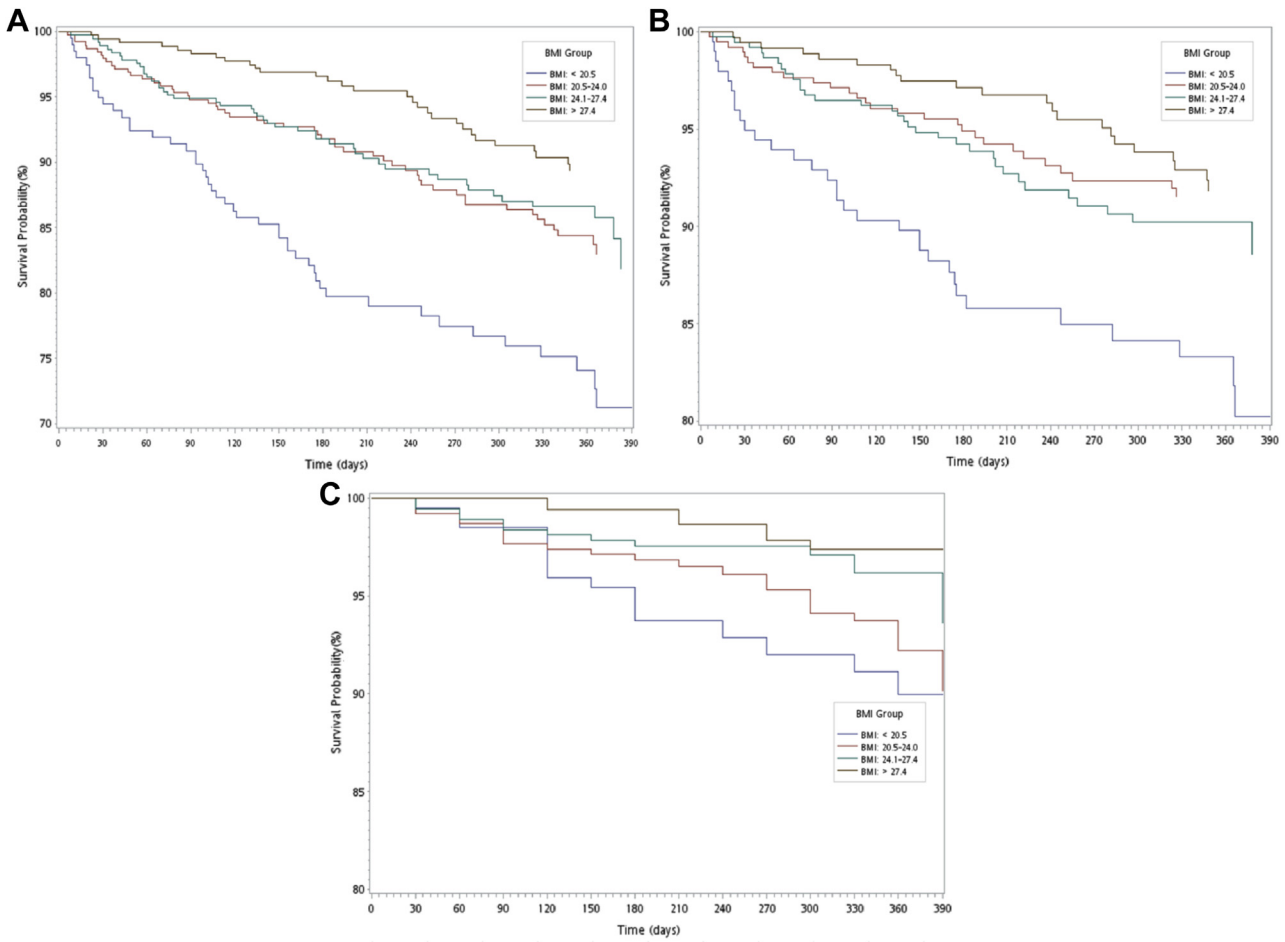

Figure 2. Kaplan−Meier event-free curves for all-cause mortality *(A)*, cardiovascular mortality *(B)*, and noncardiovascular mortality *(C)*, based on BMI categories at discharge: <20.5 kg/m^2 *(blue lines)*, 20.5 to 24.0 kg/m^2 *(green lines)*, 24.1 to 27.4 kg/m^2 *(red lines)*, and >27.4 kg/m^2 *(brown lines)*; Log-rank tests: p values were <0.0001, <0.0001, and 0.0016, respectively.

Table 3
Hazard ratios for the mortality according to body mass index by age <65 and ≥65 years

Cause of mortality	Body mass index per +5-kg/m^2	
	Age <65 years (n=693)	Age ≥65 years (n=658)
All-cause	11.1%	18.8%
Crude	0.75 (0.58-0.96)*	0.76 (0.60-0.97)*
Model 1	2.68 (0.10-69.6)	0.79 (0.62-1.02)
Model 2	0.82 (0.62-1.08)	0.77 (0.60-1.00)*
Cardiovascular	7.8%	11.7%
Crude	0.88 (0.66-1.16)	0.78 (0.58-1.06)
Model 1	0.95 (0.71-1.28)	0.82 (0.60-1.11)
Model 2	0.98 (0.71-1.33)	0.77 (0.56-1.06)
Non-cardiovascular	3.3%	7.1%
Crude	0.49 (0.29-0.82)*	0.74 (0.50-1.09)
Model 1	0.53 (0.30-0.94)*	0.77 (0.52-1.14)
Model 2	0.53 (0.31-0.92)*	0.79 (0.53-1.19)

Cox regression model was used in the analysis adjusting for the covariates including age, gender, and primary cause of heart failure in model 1; and age, gender, a history of previous myocardial infarction, hypertension, diabetes, dyslipidemia, current smoking status, current alcohol intake, chronic obstructive pulmonary disease, New York Heart Association functional class, and medications with angiotensin II receptor blockers, β blockers, loop diuretics, spironolactone, antiplatelet agents (aspirin or clopidogrel), and anticoagulation agents (warfarin or dabigatran) in model 2.

Data were presented as hazard ratio (95% CI).

* p Value <0.05.

Table 4
Cohort studies evaluating the effect of body mass index on the all-cause mortality in East Asian patients with heart failure during 2000 to 2015

Study (Country)	Subject registry (systolic HF, %)	Study period (mean years)	Sample size (n)	Age (years)	Sex (male, %)
Nochioka et al. [7] (Japan)	CHART (41.5%)	2000-2005 (3.4 years)	972	68.2	65.2
Hamaguchi et al. [8] (Japan)	JCARE-CARD (68%)	2004-2006 (2.1 years)	2,488	70.5	60.2
Kaneko et al. [14] (Japan)	Shinken database (100%)	2004-2012 (3.1 years)	404	63.0	81.2
Shah et al. [9] (Japan)	GREAT network From ATTEND (53.4%)	2007-2011 (1 year)	645	73.3	58.0
Takiguchi et al. [15] (Japan)	Single center study (49.7%)	2009-2012 (2 years)	648	65.9	60.3
Xu et al. [11] (China)	Single center study (100%)	2007-2012 (2.6 years)	685	57.0	67.0
Cai et al. [12] (China)	Single center study (100%)	1999-2013 (2.5 years)	247	59.2	67.2
Wang et al. [13] (China)	Multi-center study (NA)	2008-2011 (1 year)	806	68.4	43.4

ATTEND = the Acute Decompensated Heart Failure Syndromes registry; BMI = body mass index; CHART = the Chronic Heart Failure Analysis and Registry in the Tohoku District; GREAT = Global Research on Acute Conditions Team; JCARE-CARD, the Japanese Cardiac Registry of Heart Failure in Cardiology; NA = not available.

2 analyses, compared with the normal weight, the underweight had higher risk of all-cause mortality and cardiovascular mortality (HR 1.89 and 2.48, respectively), and the obesity had lower risk of noncardiovascular mortality (HR 0.41). If BMI was treated as a continuous variable, each 5-kg/m^2 increase in BMI was associated with all-cause mortality and noncardiovascular mortality in the model 2 analyses (HR 0.75 and 0.66, respectively). In advance, the stratified analyses within age show that BMI was associated with all-cause mortality in patients aged ≥65 years (HR 0.77) but on the contrary with noncardiovascular mortality in patients aged <65 years (HR 0.53; Table 3). The other independent predictors of higher risk of all-cause mortality among the model 2 covariates were diabetes mellitus and greater New York Heart Association functional class, and predictors associated with lower risk of all-cause mortality were the use of angiotensin II receptor blockers and spironolactone (Supplementary Table 1).

Table 4 lists the search results from MEDLINE regarding the association between BMI and all-cause mortality in East Asian patients with HF. There were overall 8 eligible studies (3 for the Chinese[11–13] and 5 for the Japanese[7–9,14,15]). Most studies showed an inverse association between BMI levels and all-cause mortality after controlling for multiple baseline covariates except the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study which revealed a U-shaped relation.[7] In addition, the CHART study lacked the data for the association of BMI treated as a continuous variable with mortality.

In Figure 3, the meta-analysis of TSOC-HFrEF and previous studies shows an inverse association of each 5-kg/m^2 increase in BMI with all-cause mortality (HR 0.65, I^2 = 37%). Figure 3 shows that the risk of all-cause mortality decreased with increasing BMI categories when the CHART study was excluded. However, there shows high heterogeneity in the mortality risk of the obesity group if the CHART study was included in the meta-analysis (Supplementary Figure 1).

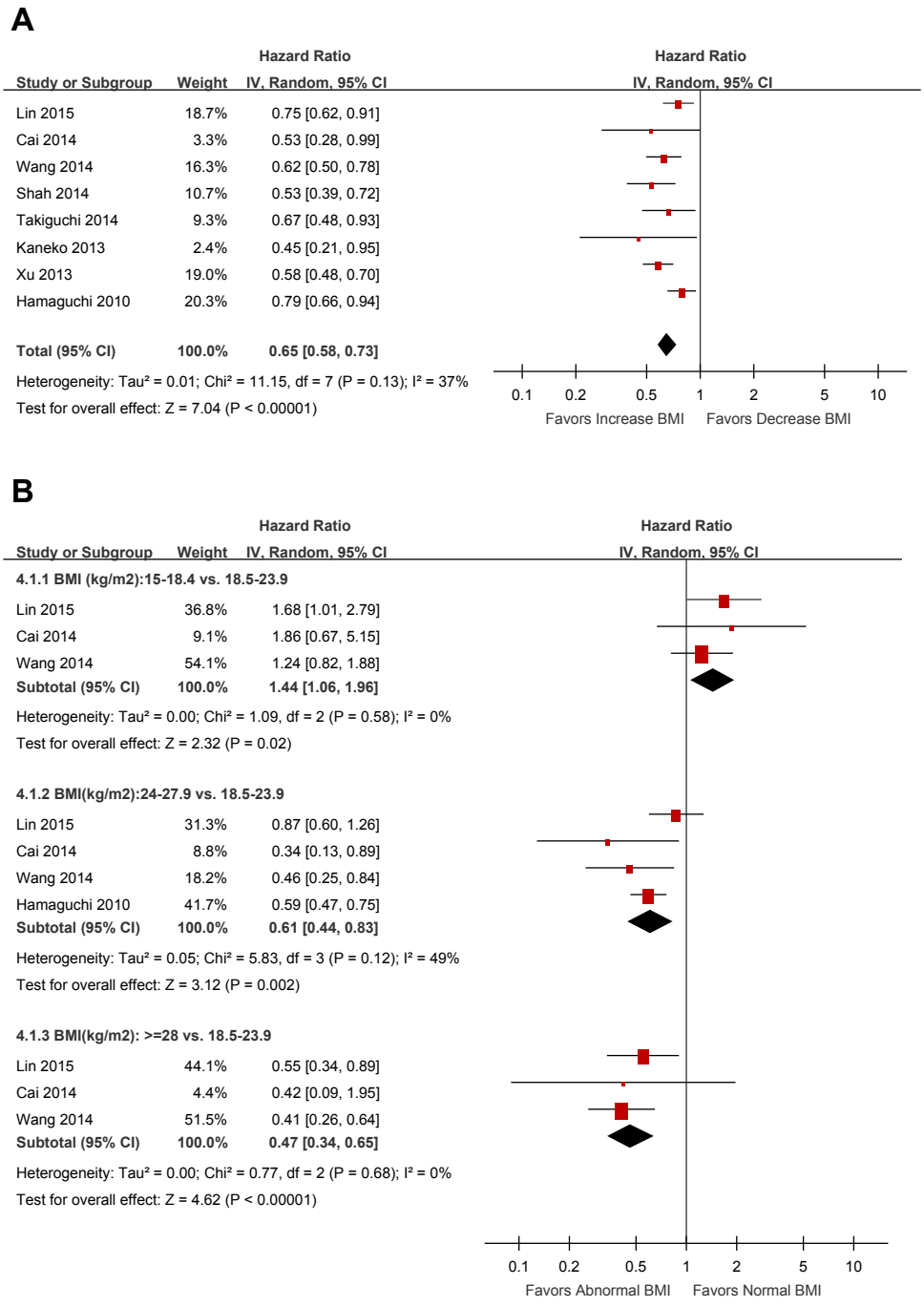

Figure 3. A meta-analysis of the adjusted association between BMI (each 5-kg/m^2 increase) and all-cause mortality among East Asian patients with HF *(A)*; and the association of BMI categories with all-cause mortality (the BMI: 18.5 to 23.9 kg/m^2 was referred to the reference). In comparison with previous studies, the BMI categories were modified to: <18.5, 18.5 to 23.9, 24 to 27.5, and >27.5 kg/m^2 in the present study (TSOC-HFrEF) by Lin et al *(B)*.

Discussion

Our principal finding in TSOC-HFrEF was that BMI was inversely associated with all-cause mortality in patients with systolic HF during an average 1-year follow-up period in Taiwan. Underweight patients had higher cardiovascular mortality risk than normal-weight patients. On the contrary, obese patients had lower noncardiovascular mortality risk than normal-weight patients where the association may be moderated by age. In addition, the meta-analysis confirmed a strong inverse BMI association (HR 0.65 for each 5-kg/m^2 increase in BMI) with all-cause mortality in East Asian patients with HF within an average 3-year follow-up. Notably, the inverse association in East Asian patients remains stronger than that in the systolic HF subcohort (HR 0.85) in the global HF registry.[9]

Some mechanisms have been proposed to explain the obesity paradox including malnutrition-inflammation complex syndrome, endotoxin-lipoprotein hypothesis, survival

bias, reverse causation, and discrepancies among competitive factors.[16−18] Several vascular risk factors such as hypertension, inflammation, and cigarette smoking have been reported with lower risk of mortality in obese patients with established CVD or the equivalent than lean patients.[19−23] East Asian adult populations have smaller body size and less prevalent morbid obesity but higher amounts of body fat at lower BMI than the Western ones.[24] Whether the racial differences in the composition of adiposity and BMI distribution between the East Asian and the Western populations may affect the obesity paradox in HF was unclear. Some studies highlighted a metabolically obese normal weight population who conferred a high risk of mortality.[25,26] Sarcopenic obesity with high body fat and reduced lean body mass is associated with a reduction in cardiorespiratory fitness and physical function leading to disability and premature death.[27] It is important that the metabolically obese normal weight phenotype has an accelerating epidemic in Asian populations.[28]

To our best knowledge, some moderators for the obesity paradox in HF have been identified. As was described previously, Shah et al[9] found the obesity paradox merely present in patients with advanced age, nondiabetes, systolic HF, or recent onset HF. We also showed that the obesity paradox was only present in the elderly patients. Since there was an inverse BMI association with noncardiovascular mortality in the younger patients, further studies should have enough power to clarify the association with specific noncardiovascular cause of death in the future. In addition, the obesity paradox was also time dependent. In ET-CHD and a meta-analysis for patients with coronary heart disease,[4,29] an inverse BMI-mortality association existed within 5 years follow-up, whereas a U-shaped relation was noted after 5 years. This finding was consistent with the result of CHART study, which had the longest mean follow-up time and showed a U-shaped relation.

The strengths of our study included that the TSOC-HFrEF registry was conducted strictly in a nationwide spectrum and prospectively followed up the mortality events by which the selection bias could be largely avoided. In addition, the participants who were collected from large medical centers may receive standard treatment for HF.[30] Moreover, there were 7,224 East Asian patients with HF included in the meta-analysis, which had enough power to accurately estimate the BMI-mortality association. The limitation of our study included that first some confounders such as physical fitness, natriuretic peptides levels, troponin levels, body fat, and lean mass were not available at discharge in the TSOC-HFrEF study, possibly overestimating the BMI association. Second, some East Asian countries' data were lacking, and the result of meta-analysis may not be directly applied to these countries.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.06.056.

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