Low Body Mass Index, Serum Creatinine, and Cause of Death in Patients Undergoing Percutaneous Coronary Intervention

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Background—Low body mass index (BMI) and serum creatinine are surrogate markers of frailty and sarcopenia. Their relationship with cause-specific mortality in elderly patients undergoing percutaneous coronary intervention is not well studied.

Methods and Results—We determined long-term cardiovascular and noncardiovascular mortality in 9394 consecutive patients aged ≥65 years who underwent percutaneous coronary intervention from 2000 to 2011. BMI and serum creatinine were divided into 4 categories. During a median follow-up of 4.2 years (interquartile range 1.8–7.3 years), 3243 patients (33.4%) died. In the multivariable model, compared with patients with normal BMI, patients with low BMI had significantly increased all-cause mortality (hazard ratio [HR] 1.4, 95% CI 1.1–1.7), which was related to both cardiovascular causes (HR 1.4, 95% CI 1.0–1.8) and noncardiovascular causes (HR 1.4, 95% CI 1.06–1.9). Compared with normal BMI, significant reduction was noted in patients who were overweight and obese in terms of cardiovascular mortality (overweight: HR 0.77, 95% CI 0.67–0.88; obese: HR 0.80, 95% CI 0.70–0.93) and noncardiovascular mortality (overweight: HR 0.85, 95% CI 0.74–0.97; obese: HR 0.82, 95% CI 0.72–0.95). In a multivariable model, in patients with normal BMI, low creatinine (≤0.70 mg/dL) was significantly associated with increased all-cause mortality (HR 1.8, 95% CI 1.3–2.5) and cardiovascular mortality (HR 2.3, 95% CI 1.4–3.8) compared with patients with normal creatinine (0.71–1.0 mg/dL); however, this was not observed in other BMI categories.

Conclusions—We identified a new subgroup of patients with low serum creatinine and normal BMI that was associated with increased all-cause mortality and cardiovascular mortality in elderly patients undergoing percutaneous coronary intervention. Low BMI was associated with increased cardiovascular and noncardiovascular mortality. Nutritional support, resistance training, and weight-gain strategies may have potential roles for these patients undergoing percutaneous coronary intervention. (*J Am Heart Assoc.* 2016;5:e003633 doi: 10.1161/JAHA.116.003633)

Key Words: body mass index • cause of death • creatinine • frailty • percutaneous coronary intervention

More than 250 000 adults aged >65 years underwent percutaneous coronary intervention (PCI) in the United States in 2010.[1] Because this number is expected to increase with the changing demographics, it is important to ascertain the factors related to cause of death in patients undergoing high-risk procedures. Sarcopenia, which is age-related decline in skeletal muscle mass,[2] and frailty, which is a biological syndrome of decreased reserve and resistance to stressors,[3] are associated with adverse outcomes in older adults.[4]

Both low body mass index (BMI; in kg/m^2) and low serum creatinine are surrogate markers of frailty and sarcopenia in older adults.[4–7] No study, to our knowledge, has explored their combined association with cause-specific mortality in elderly patients with coronary artery disease (CAD). The inverse association of BMI and all-cause mortality in patients with CAD[8] and those undergoing PCI[9,10] has been recognized as the "obesity paradox." Low serum creatinine has been noted to be associated with higher all-cause mortality in critically ill patients[11]; however, prior studies in these patients have either excluded or included few patients with low BMI (<20 kg/m^2) and with low creatinine (<0.7 mg/dL).[9,10]

A possible explanation for the nonlinear relationship of BMI and serum creatinine to mortality is higher prevalence of sarcopenia, frailty, and other comorbidities in elderly patients. Consequently, we explored the association of low serum creatinine and BMI with cause-specific mortality

and cardiovascular outcomes in elderly patients undergoing PCI.

Methods

Patient Population

The Mayo Clinic PCI registry contains prospectively collected data since 1979 on all patients undergoing PCI at the Mayo Clinic in Rochester, Minnesota.[12] For the present study, we included consecutive patients aged ≥65 years who underwent PCI at the Mayo Clinic in Rochester from January 1, 2000, to December 31, 2011, and had serum creatinine level available within 1 month prior to PCI. If patients had >1 PCI during the study period at our institution, only the first PCI was used. All participants gave consent to use their medical records for research purposes. Of the 10 399 patients aged ≥65 years that had PCI during the study time frame, 1005 patients were excluded because of unavailable serum creatinine levels, leaving 9394 for the current study. Demographic, clinical, angiographic, procedural, and medication data available in the data registry were assessed for all patients, as described previously.[12] The study was approved by the Mayo Clinic institutional review board.

Definitions

The patient population was divided into 4 groups according to serum creatinine levels: low (≤0.7 mg/dL), normal (0.71–1.0 mg/dL), high (1.01–1.4 mg/dL), and very high (>1.4 mg/dL). BMI categories were defined as low (<20 kg/m^2), normal (20–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2).

Outcomes

The primary outcome was all-cause mortality classified into cardiovascular and noncardiovascular deaths. Cardiovascular deaths included causes that were cardiac (myocardial infarction [MI], sudden cardiac death, congestive heart failure or structural heart disease, interventional or surgical procedure related, and other cardiac) and vascular (hemorrhagic stroke, ischemic or undefined stroke, abdominal aortic aneurysm rupture, and other vascular). Noncardiovascular deaths were from cancer (solid organ, hematologic), infection, chronic diseases (neurological, pulmonary, renal failure, liver or multiorgan failure, natural causes), hemorrhage (gastrointestinal, other), pulmonary embolus, iatrogenic causes (noncardiac procedure or surgery related), trauma (accident or trauma, suicide), acute surgical noncardiac causes, and other noncardiac causes. The details of the classification of mortality and ascertainment of deaths were described previously.[13] Secondary outcomes included in the study were MI and target vessel revascularization (TVR), as defined previously.[14] The composite end point for long-term outcomes was all-cause mortality or MI or TVR. Postdischarge follow-up was obtained by a centralized telephone interview conducted by an experienced data technician 6 and 12 months after the index procedure and annually thereafter. The details of the follow-up have been mentioned previously.[14]

Statistical Analysis

Continuous variables were summarized as mean (standard deviation), and categorical variables were summarized as frequencies (percentages). Differences in clinical and angiographic characteristics between the 4 creatinine and BMI groups were compared using 1-way ANOVA for continuous variables, the Kruskal–Wallis test for ordinal variables, and the Pearson chi-square test for categorical variables. The Spearman correlation coefficient was used to assess the relationship between serum creatinine and BMI. Long-term follow-up started after discharge for participants who survived to discharge. Only 2.6% of these participants had <30 days of follow-up and were treated as censored on the last day that vital status was available. Unadjusted competing risk plots were made for cardiovascular and noncardiovascular mortality by serum creatinine and BMI groups. Cox proportional hazards models were used to estimate the association of BMI and creatinine groups with all-cause mortality, cardiovascular mortality, noncardiovascular mortality, recurrent MI, TVR, and the composite end point. These models were adjusted for age; sex; BMI group; diabetes mellitus; hypertension; smoking; history of MI; peripheral vascular disease; cerebrovascular accident; chronic obstructive pulmonary disease; congestive heart failure; hypercholesterolemia; Canadian heart class; unstable angina; history of tumor, lymphoma, or leukemia; metastatic cancer; prior PCI; prior coronary artery bypass grafting; ejection fraction; pre-PCI shock; use of intra-aortic balloon pump; presence of thrombus; type C lesions; use of drug-eluting stents; and number of diseased vessels. Sensitivity analysis after including the procedure date in our Cox model changed the parameter estimates by <0.025, so time variable was not included in the final models. Missing values were imputed using the median values for continuous variables and the most common value for binary variables. Because all imputed variables had <4% missing values except for number of diseased vessels (7%), thrombus in any lesion (6%), congestive heart failure (6%), history of cholesterol (5%), and type C lesion (5%), simple imputation was used instead of multiple imputation.[15] All models were fit with and without an interaction term between creatinine group and BMI group. All tests were 2-sided, and *P*<0.05 was considered statistically significant. SAS version 9.3 or higher (SAS Institute) was used for all analyses.

Table 1. Clinical and Angiographic Characteristics Stratified by Serum Creatinine

Variable	Serum Creatinine, mg/dL				P Value
	≤0.7 (n=498)	0.71–1.0 (n=2923)	1.01–1.4 (n=4302)	>1.4 (n=1669)	
Demographics and risk factors					
Age, y, mean (SD)	75.3 (6.6)	74.9 (6.3)	75.8 (6.6)	77.2 (6.7)	<0.001
Male, n (%)	116 (23)	1575 (54)	3230 (75)	1295 (78)	<0.001
BMI, mean (SD)	28.7 (6.1)	29.0 (5.5)	29.4 (5.2)	29.9 (5.7)	<0.001
MI <24 hours, n (%)	108 (22)	508 (18)	654 (15)	243 (15)	<0.001
Preprocedural shock, n (%)	14 (3)	63 (2)	159 (4)	102 (6)	<0.001
Canadian Heart Class (III, IV, V), n (%)	259 (52)	1649 (56)	2365 (55)	877 (53)	0.044
Current CHF status, n (%)	68 (14)	316 (11)	698 (17)	566 (36)	<0.001
Diabetes mellitus, n (%)	145 (29)	740 (25)	1235 (29)	703 (42)	<0.001
Hypertension, n (%)	412 (85)	2323 (82)	3472 (83)	1485 (91)	<0.001
History of cholesterol ≥240 mg/dL, n (%)	379 (81)	2413 (87)	3524 (87)	1368 (87)	0.002
Current smokers, n (%)	53 (11)	226 (8)	224 (5)	80 (5)	<0.001
Prior PTCA, n (%)	155 (31)	1027 (35)	1723 (40)	700 (42)	<0.001
Prior CABG, n (%)	67 (13)	699 (24)	1321 (31)	647 (39)	<0.001
Peripheral vascular disease, n (%)	54 (11)	315 (11)	610 (15)	462 (28)	<0.001
CVA/TIA, n (%)	56 (11)	414 (14)	669 (16)	377 (23)	<0.001
Moderate or severe renal disease, n (%)	1 (0)	12 (0)	65 (2)	321 (20)	<0.001
COPD, n (%)	82 (16)	357 (12)	584 (14)	339 (21)	<0.001
Peptic ulcer disease, n (%)	42 (8)	213 (7)	306 (7)	144 (9)	0.19
Tumor, lymphoma, or leukemia, n (%)	90 (18)	504 (17)	772 (18)	312 (19)	0.66
Metastatic cancer, n (%)	8 (2)	24 (1)	65 (2)	27 (2)	0.041
Cardiac arrest before procedure, n (%)	1 (0)	5 (0)	5 (0)	2 (0)	0.91
LVEF ≤40%, n (%)	37 (7)	298 (10)	556 (13)	326 (20)	<0.001
Procedural characteristics					
Multivessel disease, n (%)	291 (62)	1859 (67)	2884 (71)	1167 (74)	<0.001
Type C lesion, n (%)	241 (51)	1420 (51)	2096 (51)	912 (58)	<0.001
Thrombus, n (%)	138 (29)	671 (24)	925 (23)	339 (22)	0.009
Bifurcation in any lesion, n (%)	98 (21)	521 (19)	672 (17)	246 (16)	0.006
TIMI flow 0–1 before procedure, n (%)	90 (21)	435 (18)	606 (18)	216 (17)	0.30
PCI, n (%)					0.023
Elective	166 (33)	1035 (35)	1563 (36)	548 (33)	
Urgent	236 (47)	1431 (49)	2093 (49)	844 (51)	
Emergency	96 (19)	457 (16)	645 (15)	275 (16)	
Use of drug-eluting stents, n (%)	318 (64)	1693 (58)	2053 (48)	739 (44)	<0.001
TIMI 3 after procedure in all lesions, n (%)	457 (94)	2679 (96)	3877 (94)	1495 (94)	0.07
Prophylactic intra-aortic balloon pump, n (%)	11 (2)	49 (2)	80 (2)	37 (2)	0.58
GP IIb/IIIa use, n (%)	306 (61)	1662 (57)	2335 (54)	795 (48)	<0.001
Discharge medications					
Aspirin, n (%)	476 (97)	2822 (97)	4076 (95)	1542 (94)	0.001
Beta blocker, n (%)	426 (86)	2481 (85)	3555 (83)	1352 (83)	0.14
Calcium channel blocker, n (%)	101 (20)	542 (19)	769 (18)	438 (27)	<0.001

Table 1. Continued

Variable	Serum Creatinine, mg/dL				P Value
	≤0.7 (n=498)	0.71–1.0 (n=2923)	1.01–1.4 (n=4302)	>1.4 (n=1669)	
Lipid-lowering agent, n (%)	139 (28)	1314 (45)	2437 (57)	916 (56)	<0.001
Clopidogrel, n (%)	471 (95)	2795 (96)	4043 (94)	1527 (92)	<0.001
In-hospital outcomes					
In-hospital death, n (%)	9 (2)	28 (1)	69 (2)	61 (4)	<0.001
In-hospital any MI, n (%)	20 (4)	123 (4)	219 (5)	99 (6)	0.047

The following variables had <2% missing: moderate or severe renal disease; history of MI; MI <24 hours; tumor, lymphoma, or leukemia; cardiac arrest preprocedure; body mass index; use of drug-eluting stents; diabetes mellitus; GP IIb/IIIa use; metastatic cancer; multivessel disease; prior CABG; preprocedural shock; PCI (elective, urgent, or emergency); aspirin; beta blocker; calcium channel blocker; lipid-lowering agent; and clopidogrel. The following variables had other percentages missing: current CHF status, 5.4%; COPD, 2.1%; CVA/TIA, 2.1%; history of cholesterol ≥240 mg/dL, 5.5%; hypertension, 2.7%; peptic ulcer disease, 2.9%; peripheral vascular disease, 2.5%; current smokers, 2.7%; TIMI 3 after procedure, 4.5%. All other variables did not have any missing data. BMI indicates body mass index; CABG, coronary artery bypass surgery; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; GP, glycoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction.

Results

Descriptive Characteristics

The mean age of the study population was 75.7±6.6 years, and 66% were male (n=6217). Mean BMI was 29.3±5.4. Table 1 summarizes the clinical and angiographic characteristics stratified by the 4 groups of serum creatinine. Mean BMI in the patients with low serum creatinine was significantly lower than other groups (*P*<0.001); however, the correlation between BMI and creatinine was very weak (*r*=0.065; *P*<0.001). Patients with low serum creatinine were also younger, more frequently women, and current smokers and presented more frequently with MI compared with patients with very high serum creatinine. Traditional cardiovascular risk factors were less prevalent in patients with low serum creatinine compared with patients with high serum creatinine. History of tumor, lymphoma, or leukemia was similar in patients with low and higher creatinine levels. Angiographic characteristics such as presence of thrombus and bifurcation lesions were significantly more common in patients with low serum creatinine. Patients with low creatinine levels had a significantly higher frequency of emergency PCI (*P*=0.02), use of drug-eluting stents (*P*<0.001), and glycoprotein IIb/IIIa inhibitors (*P*<0.001) compared with other creatinine groups.

The number of patients in various BMI categories was as follows: <20 kg/m^2, n=193; 20 to 25 kg/m^2, n=1775; 25.1 to 30.0 kg/m^2, n=3644; >30 kg/m^2, n=3754. Patients with low BMI were significantly older; were more often female; had higher incidence of preprocedural shock, history of cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, or tumor, lymphoma, or leukemia; and had higher use of prophylactic intra-aortic balloon pump (Table 2).

In-Hospital Outcomes

The rate of in-hospital death was 4%, 3%, 2%, and 1% in patients with low, normal, overweight, and obese BMI, respectively (*P*<0.001). There was no difference in the rate of in-hospital MI between these groups (*P*=0.21) (Table 2).

The rate of in-hospital death was 2%, 1%, 2%, and 4% in patients with serum creatinine of ≤0.7, 0.7 to 1.0, 1.01 to 1.4, and >1.4 mg/dL, respectively (*P*<0.001). The rate of in-hospital MI was 4%, 4%, 5%, and 6%, respective to the 4 creatinine groups (*P*=0.047) (Table 1).

Long-Term Outcomes

During a median follow-up of 4.2 years (interquartile range 1.8–7.3 years), 3243 deaths (1510 cardiovascular deaths, 1631 noncardiovascular deaths), 1229 recurrent MIs, 1416 TVRs, and 4464 composite events of death, MI, or TVR occurred. In the multivariable adjusted model, low BMI was associated with a significantly increased risk of all-cause mortality (hazard ratio [HR] 1.37, 95% CI 1.12–1.68) compared with those with normal BMI (Figure 1), which was due to both increased cardiovascular mortality (HR 1.35, 95% CI 1.01–1.80) and noncardiovascular mortality (HR 1.42, 95% CI 1.06–1.89). The composite end point of death, MI, or TVR was also significantly increased in patients with low BMI (HR 1.28, 95% CI 1.06–1.55). Compared with normal BMI, overweight or obese BMI (>25) was associated with a ≈20% reduction in cardiovascular mortality, a 15% reduction in noncardiovascular mortality, and a 15% reduction in the composite end point (Table 3).

Low serum creatinine was not associated with increased risk of outcomes compared with normal serum creatinine (Figure 2). Groups with high and very high serum creatinine were associated with worse outcomes compared with normal serum creatinine (Table 3).

Table 2. Clinical and Angiographic Characteristics Stratified by BMI

Variable	BMI, kg/m²				P Value
	<20 (n=193)	20–25 (n=1775)	25–30 (n=3644)	>30 (n=3754)	
Demographics and risk factors					
Age, y, mean (SD)	79.5 (7.8)	77.7 (7.0)	75.9 (6.5)	74.4 (6.1)	<0.001
Male, n (%)	68 (35)	1001 (56)	2650 (73)	2483 (66)	<0.001
BMI, mean (SD)	18.7 (1.1)	23.2 (1.3)	27.5 (1.4)	34.5 (4.2)	<0.001
MI <24 hours, n (%)	45 (24)	376 (21)	574 (16)	505 (14)	<0.001
Preprocedural shock, n (%)	14 (7)	98 (6)	129 (4)	92 (2)	<0.001
Canadian Heart Class (III, IV, V), n (%)	95 (49)	894 (50)	1975 (54)	2178 (58)	<0.001
Diabetes mellitus, n (%)	26 (13)	321 (18)	866 (24)	1603 (43)	<0.001
Hypertension, n (%)	157 (83)	1338 (78)	2889 (81)	3287 (90)	<0.001
History of cholesterol ≥240, n (%)	131 (73)	1356 (82)	2963 (87)	3218 (90)	<0.001
Current smokers, n (%)	29 (15)	158 (9)	220 (6)	172 (5)	0.008
History of MI (>7 days), n (%)	69 (37)	575 (33)	1206 (34)	1333 (36)	0.034
Prior PTCA, n (%)	59 (31)	602 (34)	1387 (38)	1545 (41)	<0.001
Prior CABG, n (%)	33 (17)	455 (26)	1091 (30)	1148 (31)	<0.001
Peripheral vascular disease, n (%)	42 (22)	278 (16)	534 (15)	579 (16)	0.08
CVA/TIA, n (%)	52 (27)	291 (17)	602 (17)	570 (15)	<0.001
Moderate or severe renal disease, n (%)	14 (7)	81 (5)	145 (4)	158 (4)	0.15
COPD, n (%)	50 (26)	280 (16)	494 (14)	532 (15)	<0.001
Peptic ulcer disease, n (%)	23 (12)	129 (8)	273 (8)	278 (8)	0.17
Tumor, lymphoma, or leukemia, n (%)	39 (20)	342 (20)	672 (19)	620 (17)	0.028
Metastatic cancer, n (%)	3 (2)	26 (1)	49 (1)	44 (1)	0.80
Cardiac arrest before procedure, n (%)	0 (0)	5 (0)	5 (0)	3 (0)	0.28
LVEF ≤40%, n (%)	41 (21)	280 (16)	465 (13)	425 (11)	<0.001
Procedural characteristics					
Multivessel disease, n (%)	127 (71)	1189 (71)	2400 (69)	2467 (70)	0.83
Type C lesion, n (%)	100 (56)	893 (54)	1808 (52)	1852 (52)	0.41
Thrombus, n (%)	49 (28)	455 (27)	790 (23)	768 (22)	<0.001
TIMI 0–1 before procedure in any lesion, n (%)	35 (23)	297 (21)	504 (18)	500 (17)	0.002
PCI, n (%)					<0.001
Elective	50 (26)	553 (31)	1323 (36)	1378 (37)	
Urgent	96 (50)	849 (48)	1767 (49)	1890 (50)	
Emergency	47 (24)	373 (21)	552 (15)	485 (13)	
Use of drug-eluting stents, n (%)	88 (46)	837 (47)	1857 (51)	2009 (54)	<0.001
TIMI 3 after procedure in all lesions, n (%)	175 (96)	1604 (95)	3334 (95)	3376 (94)	0.07
Prophylactic intra-aortic balloon pump, n (%)	8 (4)	48 (3)	65 (2)	54 (1)	0.001
Discharge medications					
Aspirin at discharge, n (%)	179 (95)	1658 (95)	3456 (95)	3601 (97)	0.08
Beta blocker at discharge, n (%)	160 (85)	1422 (81)	3023 (83)	3186 (85)	0.006
Lipid lowering agent at discharge, n (%)	77 (41)	859 (49)	1931 (53)	1932 (52)	0.002
Clopidogrel at discharge n (%)	180 (93)	1649 (93)	3440 (94)	3545 (94)	0.30
In-hospital outcomes					
In-hospital death, n (%)	7 (4)	50 (3)	58 (2)	50 (1)	<0.001
In-hospital any MI, n (%)	13 (7)	101 (6)	169 (5)	177 (5)	0.21

BMI indicates body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction.
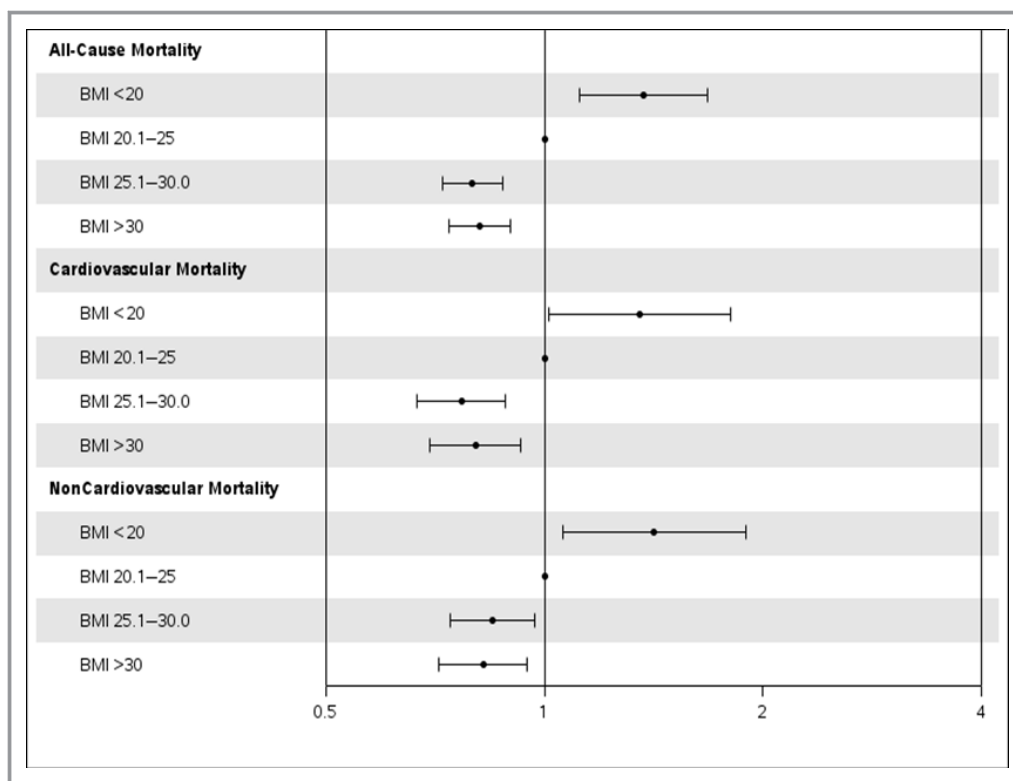
Figure 1. Adjusted association of BMI with cause-specific mortality in elderly patients undergoing PCI. The gray line corresponds to a hazard ratio of 1. Hazard ratios (circles) and 95% CIs (error bars) are shown after adjusting for age; sex; BMI; diabetes mellitus; hypertension; smoking; history of myocardial infarction; peripheral vascular disease; cerebrovascular accident; chronic obstructive pulmonary disease; congestive heart failure; hypercholesterolemia; Canadian heart class; unstable angina; history of tumor, lymphoma, or leukemia; metastatic cancer; prior PCI; prior coronary artery bypass grafting; ejection fraction; pre-PCI shock; use of intra-aortic balloon pump; presence of thrombus; type C lesions; use of drug-eluting stents; and number of diseased vessels. BMI indicates body mass index; PCI, percutaneous coronary intervention.

Stratified Analysis

A significant interaction was noted between creatinine and BMI for all-cause mortality and cardiovascular mortality (P=0.013); however, there was nonsignificant evidence of an interaction for noncardiovascular mortality (P=0.076). Table 3 summarizes the association of creatinine groups with outcomes stratified by low, normal, overweight, and obese BMI groups. In patients with normal BMI, low creatinine was significantly associated with increased all-cause mortality (HR 1.80, 95% CI 1.28–2.52) and cardiovascular mortality (HR 2.29, 95% CI 1.37–3.83) compared with normal creatinine (Figure 3). There was no significant association between low creatinine and noncardiovascular mortality (HR 1.35, 95% CI 0.84–2.19) in patients with normal BMI. High creatinine was significantly associated with worse outcomes in all BMI groups except those with BMI <20 kg/m^2. In patients with BMI <20 kg/m^2, no significant association was noted between serum creatinine and cause of death, possibly secondary to a small sample size and reduced power (Table 4).

Discussion

The major findings of this study were: 1), In elderly patients undergoing PCI, low BMI was associated with increased long-term cardiovascular and noncardiovascular mortality, whereas overweight and obesity BMIs were associated with reduced cardiovascular and noncardiovascular mortality, demonstrating a J-shaped curve. Second, in patients with normal BMI, low serum creatinine was associated with increased long-term cardiovascular mortality. Third, high creatinine was associated with increased mortality and cardiovascular events.

It is expected that by 2030, every fifth person in the United States will be aged >65 years and represents the fastest growing demographic group. We and others have demonstrated a shift in the burden of CAD toward older persons in the past 2 decades, and during the same period, novel therapeutic approaches have improved their survival. These 2 concomitant forces—displacement of the burden of disease toward older persons and improved survival—led to a fundamental change in the epidemiology of CAD, and

Table 3. Adjusted Multivariable Analysis for Long-Term Outcomes

Outcomes	BMI				P Value
	<20 (n=193)	20–25 (n=1775)	25–30 (n=3644)	>30 (n=3754)	
	Serum Creatinine				
	≤0.7	0.71–1.0	1.01–1.4	>1.4	
All-cause mortality	1.37 (1.12–1.68)	Reference	0.80 (0.72–0.87)	0.82 (0.74–0.90)	<0.001
Cardiovascular mortality	1.35 (1.01–1.80)	Reference	0.77 (0.67–0.88)	0.80 (0.70–0.93)	<0.001
Noncardiovascular mortality	1.42 (1.06–1.89)	Reference	0.85 (0.74–0.97)	0.82 (0.72–0.95)	<0.001
Recurrent MI	1.56 (1.06–2.30)	Reference	1.03 (0.87–1.22)	0.95 (0.80–1.13)	0.071
TVR	0.75 (0.44–1.26)	Reference	0.98 (0.84–1.14)	0.90 (0.77–1.06)	0.36
Composite end point (death/MI/TVR)	1.28 (1.06–1.55)	Reference	0.87 (0.80–0.94)	0.84 (0.77–0.91)	<0.001
All-cause mortality	1.09 (0.88–1.35)	Reference	1.19 (1.09–1.31)	1.78 (1.60–1.98)	<0.001
Cardiovascular mortality	1.17 (0.83–1.64)	Reference	1.44 (1.24–1.66)	1.97 (1.68–2.32)	<0.001
Noncardiovascular mortality	1.01 (0.76–1.35)	Reference	1.02 (0.90–1.16)	1.72 (1.49–1.99)	<0.001
Recurrent MI	0.97 (0.69–1.36)	Reference	1.18 (1.03–1.37)	1.33 (1.12–1.59)	0.010
TVR	1.26 (0.96–1.67)	Reference	1.19 (1.05–1.36)	1.03 (0.87–1.23)	0.018
Composite end point (death/MI/CABG/TVR)	1.15 (0.98–1.37)	Reference	1.19 (1.10–1.28)	1.54 (1.40–1.68)	<0.001

BMI was measured as kg/m^2, and serum creatinine was measured as mg/dL. Results are presented as hazard ratio (95% CI). BMI indicates body mass index; CABG, coronary artery bypass grafting; MI, myocardial infarction; TVR, target vessel revascularization.

survivors are now older persons with substantial comorbidity that presents enormous societal and economic challenges. Consequently, prognostic determination of surrogate variables linked to aging such as low BMI and serum creatinine becomes important.[3] Previous studies were limited by the number of elderly patients with low BMI and serum creatinine[10] and did not have details of cause of death.[16] The present study is one of the largest studies including elderly patients who underwent PCI with an adequate number of patients with low BMI and/or low serum creatinine.

BMI and Outcomes

A meta-analysis of 10 studies in patients undergoing PCI reported that low BMI (<20 kg/m^2) was associated with increased total and cardiac mortality compared with those with normal BMI.[17] Another study including 23 604 participants pooled from 11 PCI clinical studies reported that low BMI (<18.5) was associated with a significantly increased risk of all-cause mortality.[16] A recent study of elderly patients with acute MI also found that low BMI was associated with increased long-term mortality after adjusting for markers of cachexia, frailty, and nutritional status.[18] None of these studies, however, had detailed assessment of noncardiovascular mortality, and some of them assumed that mortality after PCI was from cardiovascular causes only.[16] Because of the availability of cause-specific mortality in our database, we found that increased all-cause mortality in patients with low BMI was not only secondary to cardiovascular causes but also for

noncardiovascular reasons. A higher prevalence of smoking, chronic lung disease, and leukemia or lymphoma and other unrecognized factors such as frailty, disability, poor nutritional intake, and sarcopenia[4,5,18] may account for the increased risk of noncardiovascular death in patients with low BMI. This finding is similar to the general population of the United States in the National Health and Nutrition Examination Survey (NHANES) database, for which low BMI was associated with increased noncardiovascular mortality primarily from noncancerous etiologies like chronic respiratory diseases, infectious diseases, or injuries.[19] Patients with low BMI had >50% higher relative risk of recurrent MI compared with those with normal BMI, translating into increased cardiovascular mortality. These patients had a higher frequency of pre-PCI shock, intra-aortic balloon pump use, low ejection fraction at presentation, and left anterior descending artery obstruction, placing them at a higher risk of recurrent cardiovascular events during follow-up. Furthermore, previous studies have reported that patients with low BMI are also less likely to receive guideline-based medical therapies.[18,20]

An obesity paradox has been reported among CAD patients wherein overweight and obese patients have reduced all-cause mortality compared with patients with normal BMI.[8,9,21,22] In a recent meta-analysis, Sharma et al reported that overweight BMI was associated with reduced cardiac mortality; however, obese BMI was not.[17] In the present study, overweight and obese patients had significantly reduced cardiovascular and noncardiovascular mortality compared with those with normal BMI. Reduced
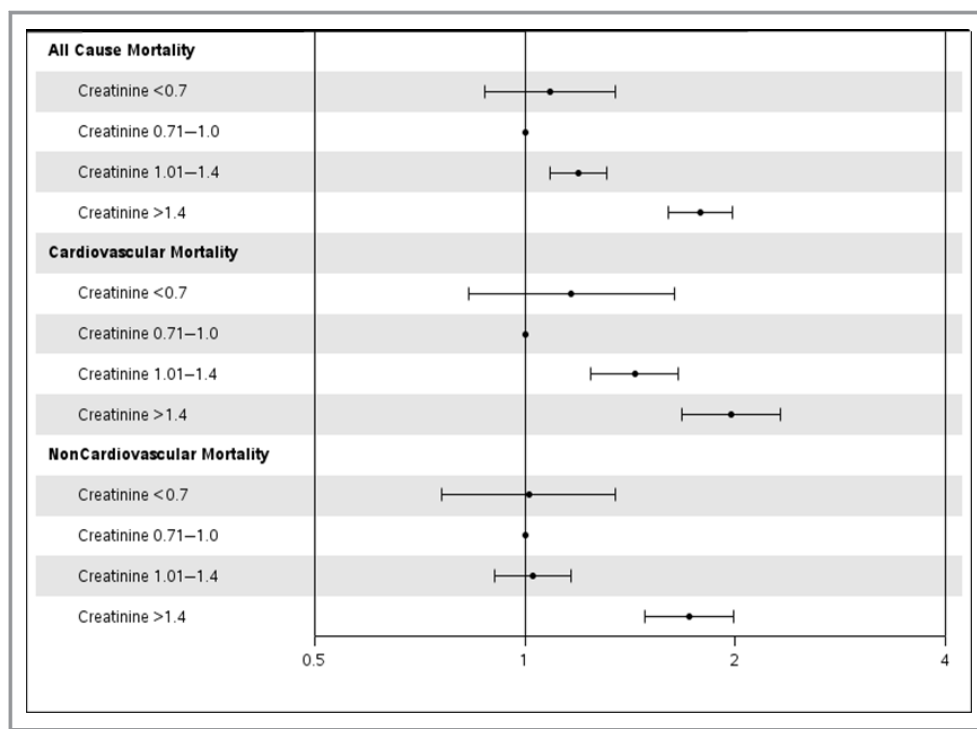
Figure 2. Adjusted association of serum creatinine with cause-specific mortality in elderly patients undergoing PCI. The gray line corresponds to a hazard ratio of 1. Hazard ratios (circles) and 95% CIs (error bars) are shown after adjusting for age; sex; body mass index; diabetes mellitus; hypertension; smoking; history of myocardial infarction; peripheral vascular disease; cerebrovascular accident; chronic obstructive pulmonary disease; congestive heart failure; hypercholesterolemia; Canadian heart class; unstable angina; history of tumor, lymphoma, or leukemia; metastatic cancer; prior PCI; prior coronary artery bypass grafting; ejection fraction; pre-PCI shock; use of intra-aortic balloon pump; presence of thrombus; type C lesions; use of drug-eluting stents; and number of diseased vessels. PCI indicates percutaneous coronary intervention.

cardiovascular mortality in these patients is likely explained by several factors including misclassification of lean and fat mass by BMI,[21] more aggressive risk factor management in obese patients,[23] increased production of soluble tumor necrosis factor α receptors in the adipose tissue neutralizing the deleterious effects of tumor necrosis factor α on the myocardium,[24] lower atrial natriuretic peptides, and improved endothelial function.[21,22] Overweight and obese patients also have higher metabolic reserve and less cachexia, which may benefit them in critically ill states.[25] Other factors that have been implicated include the presence of unadjusted confounding factors, selection and lead time bias, and genetic differences.[21,22] No significant differences were noted in the rate of recurrent MI or repeat revascularizations between patients with overweight/obese BMI and normal BMI.[21,26]

Serum Creatinine and Outcomes

The association of very high serum creatinine with increased mortality and worse cardiovascular outcomes is known.[27] Low

serum creatinine is a surrogate marker for reduced muscle mass and sarcopenia.[4,5] Previous studies in critically ill patients have demonstrated that low serum creatinine was associated with increased mortality[11,28]; however, limited studies have investigated this association in CAD patients, and there are no data on the association with cause-specific mortality.[4–7] We identified a unique subgroup of patients with normal BMI and low serum creatinine, which was associated with increased cardiovascular mortality after PCI compared with patients with normal BMI and normal serum creatinine. Competing risk plots also suggested that the noncardiovascular mortality rate was higher in the first 2 years after PCI in patients with low serum creatinine and normal BMI compared with those with normal creatinine and normal BMI (Figure 4). The number of patients in this subgroup was small (n=128), so this finding is only hypothesis generating. Reduced muscle mass or sarcopenia is associated with frailty, metabolic derangements, and poor long-term outcomes.[4,5,29,30] Previous studies have also shown that participants with normal BMI and central obesity may have reduced lean mass.[31,32] A combination of sarcopenia and obesity, termed "sarcopenic
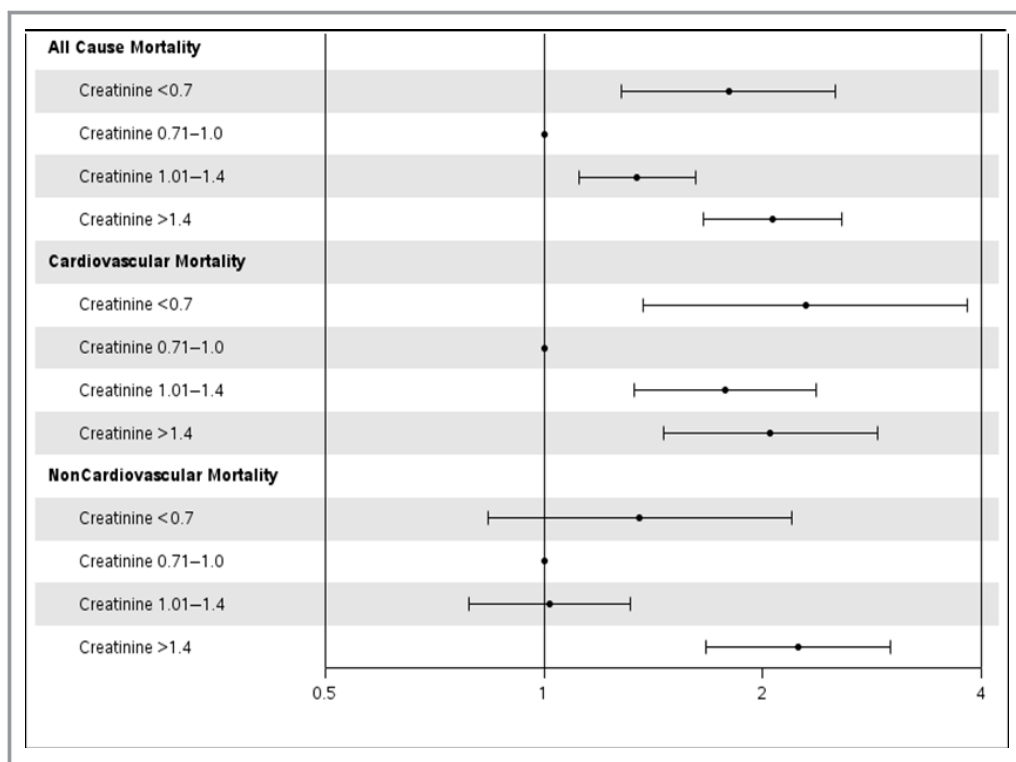
Figure 3. Adjusted association of serum creatinine with cause-specific mortality in patients with normal BMI. The gray line corresponds to a hazard ratio of 1. Hazard ratios (circles) and 95% CIs (error bars) are shown after adjusting for age; sex; BMI; diabetes mellitus; hypertension; smoking; history of myocardial infarction; peripheral vascular disease; cerebrovascular accident; chronic obstructive pulmonary disease; congestive heart failure; hypercholesterolemia; Canadian heart class; unstable angina; history of tumor, lymphoma, or leukemia; metastatic cancer; prior PCI; prior coronary artery bypass grafting; ejection fraction; pre-PCI shock; use of intra-aortic balloon pump; presence of thrombus; type C lesions; use of drug-eluting stents; and number of diseased vessels. BMI indicates body mass index; PCI, percutaneous coronary intervention.

obesity," may explain this association in patients with normal BMI because sarcopenic obesity is common in elderly persons[33] and is associated with increased morbidity and mortality.[34–36] Patients with low serum creatinine in our study had worse angiographic features like intracoronary thrombus and bifurcation lesions at presentation compared with patients with normal creatinine, and this could partly explain the increased long-term cardiovascular mortality. This finding would need prospective measurement of muscle mass or body composition, stratification of this subset based on lifestyle and physical activity, and performance of serial measurements to account for changes over time of weight and BMI.

We did not find a significant association between low serum creatinine and mortality in patients with low BMI, possibly secondary to a very small sample size (n=18) and insufficient power. The association of low creatinine with outcomes in the overweight and obese groups is complex and is most likely modified by the obesity paradox. Other possible reasons include a poor correlation between BMI and serum creatinine and nonavailability of cardiorespiratory fitness. Prospective studies with data on cardiorespiratory fitness and

central adiposity or national registry studies with more patients with low BMI and low serum creatinine may help elucidate this finding.

Clinical Implications

Unique prognostic markers need to be identified with aging of the population with CAD. In our study, low serum creatinine is associated with higher overall and cardiovascular mortality in patients with normal BMI undergoing PCI. Recognition of this simple laboratory variable can help refine the prognosis of patients with normal BMI. Future studies are needed to further characterize the patients with low serum creatinine and low BMI, especially as it relates to comorbidity, deficit accumulation, physical functioning, and frailty.

Limitations

Our study has several limitations. The patient population includes mainly white participants, and the results of our study may not be generalizable to other races and ethnic

Table 4. Association Between Serum Creatinine and Long-Term Outcomes Within BMI Strata

Outcomes	Serum Creatinine			
	≤0.7	0.71–1.0	1.01–1.4	≥1.4
BMI <20	n=18	n=76	n=64	n=35
All-cause mortality	1.05 (0.52–2.13)	Reference	0.75 (0.47–1.19)	1.32 (0.80–2.16)
Cardiovascular mortality	0.90 (0.26–3.13)	Reference	0.98 (0.51–1.89)	1.14 (0.54–2.39)
Noncardiovascular mortality	1.15 (0.50–2.73)	Reference	0.52 (0.25–1.05)	1.46 (0.74–2.88)
BMI 20–25	n=128	n=631	n=755	n=261
All-cause mortality	1.80 (1.28–2.52)	Reference	1.34 (1.12–1.62)	2.07 (1.66–2.57)
Cardiovascular mortality	2.29 (1.37–3.83)	Reference	1.77 (1.33–2.37)	2.05 (1.46–2.88)
Noncardiovascular mortality	1.35 (0.84–2.19)	Reference	1.02 (0.79–1.31)	2.24 (1.67–3.00)
BMI 25.1–30	n=165	n=1094	n=1721	n=664
All-cause mortality	0.84 (0.57–1.25)	Reference	1.06 (0.91–1.23)	1.43 (1.21–1.69)
Cardiovascular mortality	0.76 (0.39–1.45)	Reference	1.18 (0.94–1.49)	1.54 (1.20–1.98)
Noncardiovascular mortality	0.91 (0.55–1.49)	Reference	0.98 (0.80–1.20)	1.42 (1.13–1.79)
BMI ≥30	n=181	n=1114	n=1752	n=706
All-cause mortality	0.70 (0.43–1.15)	Reference	1.29 (1.10–1.50)	2.07 (1.75–2.45)
Cardiovascular mortality	0.76 (0.35–1.65)	Reference	1.57 (1.23–2.01)	2.50 (1.93–3.24)
Noncardiovascular mortality	0.70 (0.37–1.33)	Reference	1.11 (0.90–1.37)	1.86 (1.47–2.35)

Serum creatinine was measured as mg/dL. Results are presented as hazard ratio (95% CI). BMI indicates body mass index.
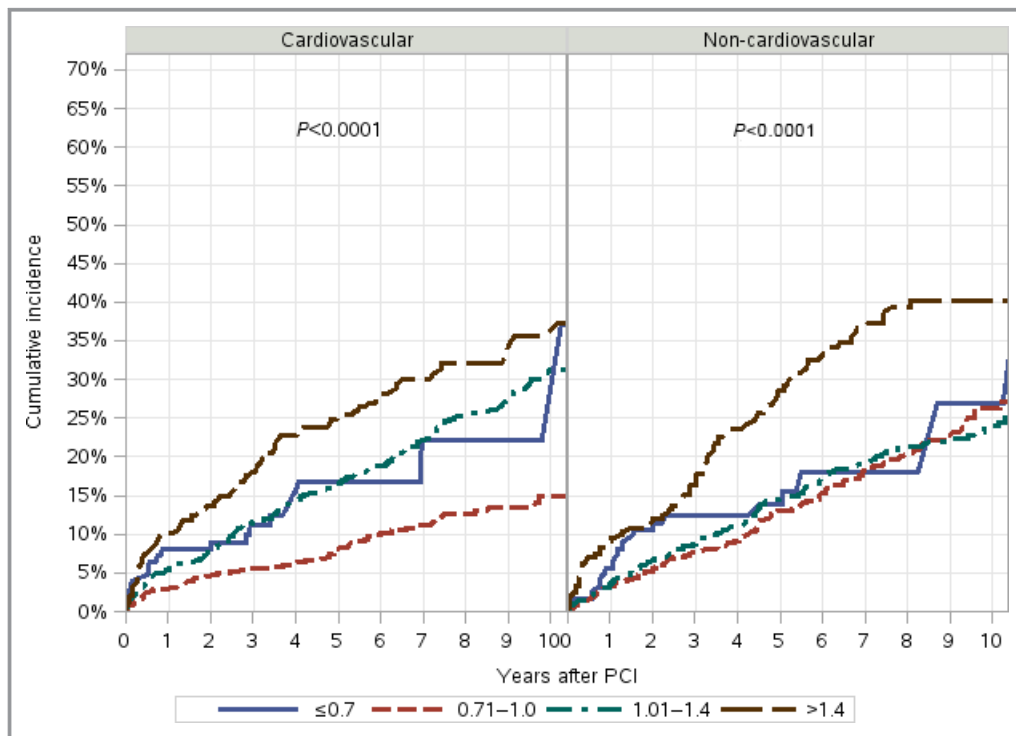

Figure 4. Unadjusted competing risk plots for cardiovascular and noncardiovascular mortality by serum creatinine in patients with normal body mass index. Creatinine levels are shown: Solid blue line: ≤0.7 mg/dL; dashed red line: 0.71 to 1.0 mg/dL; dash-dot line: 1.01 to 1.4 mg/dL; long-dash line: ≥1.4 mg/dL. Increased cardiovascular mortality was noted in the first year after PCI, and increased noncardiovascular mortality was noted in the first 2 years after PCI. PCI indicates percutaneous coronary intervention.

groups. In addition, the medical therapy and technologies evolved over the course of the study period, and factors such as these and other unknown factors might have confounded the results of the present study. The number of patients in the low BMI and low serum creatinine group were small, and a larger sample size is needed to confirm our findings. This study was retrospective, so the possibility of selection bias cannot be excluded, and no definitive causal relationships can be inferred. We did not have complete data on bleeding outcomes after PCI because patients with low BMI may have increased risk of procedure-related bleeding.[37] Serum creatinine levels in elderly persons may be misleading because the levels relate not only to skeletal mass but also to the hydration status of the patient and reflect factors relating to formation and clearance. Correlation and analyses of such data with creatinine clearance may be needed.

Conclusions

In elderly patients undergoing PCI, we identified a new subgroup with low serum creatinine and normal BMI that is associated with increased cardiovascular mortality. Low BMI was associated with both cardiovascular and noncardiovascular mortality. Nutritional support, resistance training, and weight-gain strategies should be tested in these patients undergoing PCI.

Disclosures

None.

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