表 1

術式	手術件数 (n)	手術時間（分）		時間差 (分)	P値
		BMI<30	30≦BMI		
食道切除再建術	10,850	478	505	27	P=0.079
幽門側胃切除術	63,878	247	285	38	P<0.001
胃全摘術	37,913	277	326	49	P<0.001
結腸右半切除術	37,903	196	232	36	P<0.001
低位前方切除術	33,334	261	308	47	P<0.001
肝切除術(外側区域を除く1区域以上)	14,945	384	424	40	P<0.001
膵頭十二指腸切除術	17,544	467	519	52	P<0.001
急性汎発性腹膜炎手術	16,706	126	147	21	P<0.001
大動脈弁置換手術	14,835	303	321	18	P=0.005
大動脈弓部全置換手術	10,595	425	481	56	P<0.001
下行大動脈置換手術（左開胸）	5,606	273	328	55	P<0.001
冠動脈バイパス手術（on pump）	9,224	358	378	20	P<0.001
冠動脈バイパス手術（off pump）	15,979	302	327	25	P<0.001

5. おわりに

すべての術式においてBMIの上昇と共に手術時間は延長する傾向を示し，「高度肥満」では食道切除再建術を除くすべての術式において手術時間の有意な延長を認めた．さらに，「高度肥満」では30日死亡・手術死亡が増加する傾向も認めた．一方で，「痩せ」において輸血率や30日死亡・手術死亡の上昇を認め，「肥満」，「痩せ」のいずれも手術成績に影響を及ぼす因子と考えられた．

今後，この結果を，NCD本来の目的でもある医療水準改善への支援ならびに外科医労働環境改善を目指した政策提言に活用していきたいと考えている．

利益相反：なし

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RESEARCH ARTICLE

Impact of Body Mass Index on In-Hospital Complications in Patients Undergoing Percutaneous Coronary Intervention in a Japanese Real-World Multicenter Registry

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OPEN ACCESS

Citation: Numasawa Y, Kohsaka S, Miyata H, Kawamura A, Noma S, Suzuki M, et al. (2015) Impact of Body Mass Index on In-Hospital Complications in Patients Undergoing Percutaneous Coronary Intervention in a Japanese Real-World Multicenter Registry. PLoS ONE 10(4): e0124399. doi:10.1371/journal.pone.0124399

Academic Editor: Heye Zhang, Shenzhen institutes of advanced technology, CHINA

Received: November 9, 2014

Accepted: March 1, 2015

Published: April 14, 2015

Data Availability Statement: All relevant data are within the paper.

Funding: This research was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KAKENHI No. 21790751). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

Obesity is associated with advanced cardiovascular disease. However, some studies have reported the "obesity paradox" after percutaneous coronary intervention (PCI). The relationship between body mass index (BMI) and clinical outcomes after PCI has not been thoroughly investigated, especially in Asian populations.

Methods

We studied 10,142 patients who underwent PCI at 15 Japanese hospitals participating in the JCD-KICS registry from September 2008 to April 2013. Patients were divided into four groups according to BMI: underweight, BMI <18.5 (n=462); normal, BMI ≥18.5 and <25.0 (n=5,945); overweight, BMI ≥25.0 and <30.0 (n=3,100); and obese, BMI ≥30.0 (n=635).

Results

Patients with a high BMI were significantly younger (p<0.001) and had a higher incidence of coronary risk factors such as hypertension (p<0.001), hyperlipidemia (p<0.001), diabetes mellitus (p<0.001), and current smoking (p<0.001), than those with a low BMI. Importantly, patients in the underweight group had the worst in-hospital outcomes, including overall complications (underweight, normal, overweight, and obese groups: 20.4%, 11.5%, 8.4%, and 10.2%, p<0.001), in-hospital mortality (5.8%, 2.1%, 1.2%, and 2.7%, p<0.001), cardiogenic shock (3.5%, 2.0%, 1.5%, and 1.6%, p=0.018), bleeding complications (10.0%, 4.5%, 2.6%, and 2.8%, p<0.001), and receiving blood transfusion (7.6%, 2.7%, 1.6%, and 1.7%, p<0.001).

BMI was inversely associated with bleeding complications after adjustment by multivariate logistic regression analysis (odds ratio, 0.95; 95% confidence interval, 0.92–0.98; p=0.002). In subgroup multivariate analysis of patients without cardiogenic shock, BMI was inversely associated with overall complications (OR, 0.98; 95% CI, 0.95–0.99; p=0.033) and bleeding complications (OR, 0.95; 95% CI, 0.91–0.98; p=0.006). Furthermore, there was a trend that BMI was moderately associated with in-hospital mortality (OR, 0.94; 95% CI, 0.88–1.01; p=0.091).

Conclusions

Lean patients, rather than obese patients are at greater risk for in-hospital complications during and after PCI, particularly for bleeding complications.

Introduction

Obesity is an independent risk factor of advanced cardiovascular disease and mortality [1–3]. Some previous studies have reported that obesity is associated with adverse cardiovascular events after percutaneous coronary intervention (PCI) [4–6]. However, various studies performed in Western countries have reported that obese patients have better short- and long-term outcomes after PCI than non-obese patients [7–15]. This phenomenon is well known as an "obesity paradox", not only among patients with coronary artery disease (CAD), but also in those with heart failure [16,17]. However, the precise mechanisms of this phenomenon are still unclear [18–20]. Additionally, there are few data regarding the obesity paradox especially in Asian populations, because few studies have been conducted in Asia.

Patients with CAD in Asian countries have different characteristics compared with those in Western countries (e.g., older age, lower body mass index (BMI), frequently smoke, and have less traditional risk factors, except for diabetes mellitus) [21,22]. In addition, relationships between cardiovascular risk factors and cardiovascular disease may differ in Asian populations and Western populations [23]. In particular, one of the biggest differences between populations is physique. The average BMI in patients with CAD is remarkably lower in Asian countries compared with Western countries [21,22]. Moreover, the impact of BMI on the incidence of cardiovascular disease may differ in Asian populations and Western populations. Lu et al. reported higher hazard ratios per 5 kg/m^2 BMI increase for coronary heart disease and stroke in Asian cohorts than in Western cohorts [3]. Previous studies have suggested that lower cut-off points for BMI should be adopted in Asian than in Western countries [23]. Furthermore, Japanese patients with CAD tend to have more bleeding complications during and after PCI compared with Western populations [21,22], and undergo complex procedures because surgical revascularization is less preferred by patients.

Because the risk profiles and procedural preference of Japanese patients with CAD differ from those in Western populations, investigation of the obesity paradox in Japan is important. This study aimed to investigate the impact of BMI on in-hospital complications in patients undergoing PCI in a Japanese multicenter PCI registry.

Material and Methods

Study design

The Japan Cardiovascular Database (JCD) is a large, ongoing, prospective, multicenter cohort study that was designed to record clinical background and outcome data for PCI patients in

Japan [24–28]. Data for approximately 200 variables are continuously being collected in this study. Participating hospitals are instructed to record data from consecutive hospital visits for PCI and to register these data into an internet-based database system.

Entered data were checked for completeness and internal consistency. Quality assurance of the data was achieved through automatic system validation and reporting of data completeness, education, and training for dedicated clinical research coordinators specifically trained for the present PCI registry. The senior study coordinator (I.U.) and exclusive on-site auditing by investigators (S.K. and H.M.) ensured proper registration of each patient.

PCI with any commercially available coronary device was included. The decision to perform PCI was made according to the investigators' clinical assessment of the patients. This study did not mandate specific interventional or surgical techniques, such as vascular access, use of specific stents, or closure devices.

Major teaching hospitals within the metropolitan Tokyo area were selected for this study. Patients were enrolled based on the individual PCI event, and all consecutive PCI procedures during the study period were registered, including cases of failure. Patients aged <18 years were excluded from the study.

The majority of clinical variables in the JCD are defined according to the National Cardiovascular Data Registry. This registry is sponsored by the American College of Cardiology for conducting comparative research to determine factors that can lead to disparities in PCI management. The National Cardiovascular Data Registry is a large PCI registry system with over 1,000,000 entries for ischemic heart disease and over 500,000 entries for PCI that were collected from more than 500 institutions in the United States [29].

Information disclosure

The study protocol was approved by the institutional review board committee at Keio University, School of Medicine in Japan. All of the participants provided written informed consent for the present study. Before the launch of the JCD registry, information on the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network. This Network is recognized by the International Committee of Medical Journal Editors as an "acceptable registry," according to a statement issued in September 2004 (UMIN R000005598).

Study population

We analyzed data from 10,788 consecutive patients who underwent PCI at 15 Japanese hospitals participating in the JCD-KICS registry from September 2008 to April 2013. For the present analysis, 646 patients were excluded because of missing data on basic information, including sex, height, and/or body weight. We divided the remaining 10,142 patients into four groups according to BMI. BMI was defined as weight in kilograms divided by the square of the height in meters. The National Heart, Lung, and Blood Institute and the World Health Organization have introduced a weight classification for BMI. According to this classification, patients with a BMI of 18.5–24.9 kg/m^2 are considered normal, those with a BMI of 25–30 kg/m^2 are considered overweight, and those with a BMI >30 kg/m^2 are considered obese [4]. Patients were divided into four groups according to BMI in the present study: underweight, BMI <18.5; normal, BMI ≥18.5 and <25.0; overweight, BMI ≥25.0 and <30.0; and obese, BMI ≥30.0.

Clinical, angiographic, and procedural complications were prospectively entered into the JCD-KICS registry database. The choice of access site was based on the preference of the interventional cardiologist. Although the sizes of the sheath and guiding catheter were not protocol mandated in this cohort, the commonly used size was 6–8 Fr in transfemoral intervention, and

6 Fr in transradial intervention (TRI). All of the patients underwent periprocedural anticoagulation via heparin based on institutional dosing instructions during PCI. A bolus dose of 5000–10000 IU was usually administered and additional doses were provided based on an activated clotting time of > 300 seconds during PCI. We did not have a mandated protocol for hemostasis after the PCI procedures. Details of post-procedural management were left to the primary operators' discretion. The recommended antiplatelet therapy was long-term 81 mg aspirin daily and a thienopyridine (75 mg clopidogrel or 200 mg ticlopidine daily). The loading dose of clopidogrel was 300 mg, and dual antiplatelet therapy was continued for at least 12 months after drug-eluting stent implantation, and 1 month after bare-metal stent implantation.

The endpoints were defined as in-hospital mortality and other complications. Complications were defined as all complications as follows: severe coronary artery dissection or coronary perforation; myocardial infarction after PCI; cardiac shock or heart failure; cerebral bleeding or stroke; and bleeding complications. Severe coronary artery dissection was defined as an intimal tear of the coronary artery, leading to impaired blood flow (final thrombolysis in myocardial infarction flow grade <3) on an angiogram. Myocardial infarction was defined as the new occurrence of a biomarker-positive myocardial infarction after PCI. Bleeding complications in this registry were further defined as those requiring blood transfusion, prolonging hospital stay, or causing a decrease in hemoglobin of >3.0 g/dL. Furthermore, bleeding complications were divided into puncture-site bleeding, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other bleeding. Hematomas >10 cm for femoral access or >2 cm for radial access also qualified as access site bleeding.

Data analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as a percentage. Continuous variables were compared using the Student's t-test, and the differences between categorical variables were examined using the chi-squared test. Univariate logistic regression analysis was performed to specify the odds ratio (OR) for overall complications, in-hospital mortality, and bleeding complications within 72 hours. Multivariate logistic regression analysis was then performed to investigate independent predictors for overall complications, in-hospital mortality, and bleeding complications. Variables in these models were selected based on univariate p values <0.05 and overall clinical significance. Variables that were entered in these models included age, sex, BMI, hyperlipidemia, diabetes mellitus, current smoking, previous PCI, previous myocardial infarction, previous heart failure, cerebrovascular disease, peripheral artery disease, chronic obstructive pulmonary disease, hemodialysis, ST elevation myocardial infarction (STEMI), non-STEMI, unstable angina, stable angina, cardiogenic shock, use of intra-aortic balloon pumping (IABP), TRI, transfemoral intervention, three-vessel disease, left main trunk lesion, type C lesion, chronic total occlusion, and use of a rotablator. All statistical calculations and analyses were performed using JMP version 10.0 (SAS Institute, Cary, NC, USA). A p value of <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

The distribution of BMI for the 10,142 study patients is shown in Fig 1. The average BMI in the total cohort was 24.2. The baseline clinical characteristics of the study patients according to BMI are shown in Table 1. Of 10,142 patients, 4.5% (n = 462) were underweight, 58.6% (n = 5,945) were normal weight, 30.6% (n = 3,100) were overweight, and 6.3% (n = 635) were obese. Patients with a high BMI were significantly younger (p<0.001), had a higher incidence of coronary risk factors such as hypertension (p<0.001), hyperlipidemia (p<0.001), and

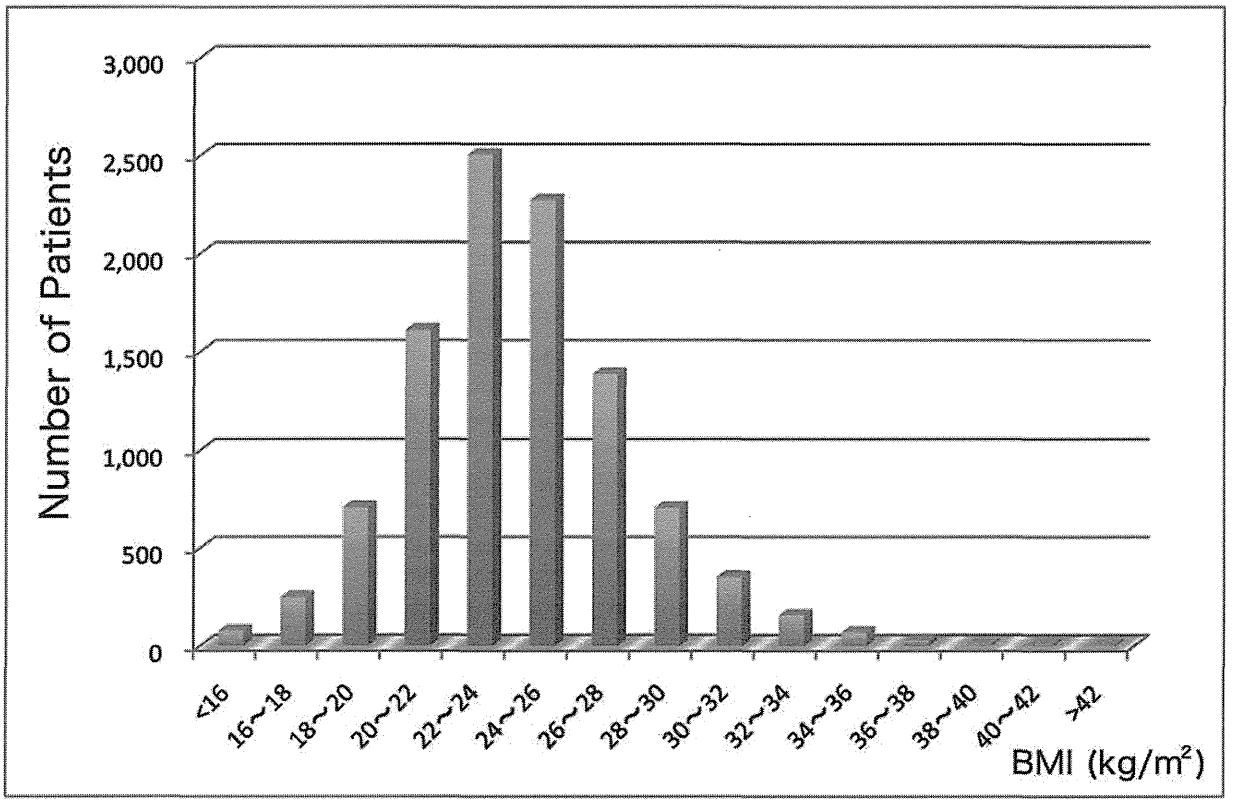

Fig 1. Distribution of BMI values. The distribution of BMI for 10,142 patients is shown.

doi:10.1371/journal.pone.0124399.g001

diabetes mellitus ($p<0.001$), and had a higher rate of previous PCI ($p<0.001$) and current smoking habit ($p<0.001$) than those with a low BMI. On the other hand, patients with a low BMI were older ($p<0.001$), more often female ($p<0.001$), and more likely to have previous heart failure ($p<0.001$), peripheral artery disease ($p<0.001$), higher baseline serum creatinine level ($p<0.001$), and end-stage renal disease ($p<0.001$) than those with a high BMI. Furthermore, patients with a low BMI were more likely to present with acute coronary syndrome, especially with STEMI ($p<0.001$), unstable angina ($p = 0.031$) and cardiogenic shock ($p<0.001$) compared with those with a high BMI. The rate of administration of antiplatelet agents was not significantly different among the BMI groups.

Angiographic and Procedural Data

Angiographic and procedural data are shown in Table 2. TRI was performed more frequently in patients with a high BMI ($p = 0.002$). However, transfemoral intervention was performed more frequently in patients with a low BMI ($p = 0.005$). There was no difference in the frequency of use of a closure device in each group. The rotablator and IABP were used more frequently in patients with a low BMI than in those with a high BMI ($p = 0.003$).

Complications

In-hospital complications are shown in Fig 2 and Table 3. Importantly, patients in the underweight group had the worst in-hospital outcomes, including overall complications ($p<0.001$),

Table 1. Baseline Clinical Characteristics.

	Underweight (BMI<18.5, n = 462)	Normal (18.5≦BMI<25.0, n = 5945)	Overweight (25.0≦BMI<30.0, n = 3100)	Obese (30.0≦BMI, n = 635)	P-value
Age, years	74.7±10.0	69.4±10.1	65.4±10.6	59.2±11.8	<0.001
Female gender	200(43.3%)	1233(20.7%)	512(16.5%)	135(21.3%)	<0.001
Height (cm)	157.9±9.8	161.7±8.7	163.1±8.6	164.1±9.5	<0.001
Weight (kg)	42.9±6.1	59.0±8.0	71.7±8.2	88.0±13.5	<0.001
Hypertension	317(68.6%)	4213(70.9%)	2481(80.0%)	539(84.9%)	<0.001
Hyperlipidemia	219(47.4%)	3801(63.9%)	2261(72.9%)	498(78.4%)	<0.001
Diabetes mellitus	156(33.8%)	2375(40.0%)	1438(46.4%)	372(58.6%)	<0.001
Insulin use	39(8.4%)	469(7.9%)	295(9.5%)	102(16.1%)	<0.001
Current smoking	121(26.2%)	1982(33.3%)	1201(38.7%)	284(44.7%)	<0.001
Family History	40(8.7%)	748(12.6%)	439(14.2%)	109(17.2%)	<0.001
Previous PCI	146(31.6%)	2316(39.0%)	1280(41.3%)	280(44.1%)	<0.001
Previous CABG	36(7.8%)	325(5.5%)	147(4.7%)	35(5.5%)	0.048
Previous HF	72(15.6%)	552(9.3%)	212(6.8%)	58(9.1%)	<0.001
Previous MI	121(26.2%)	1610(27.1%)	866(27.9%)	184(29.0%)	0.598
CVD	61(13.2%)	559(9.4%)	250(8.1%)	45(7.1%)	<0.001
PAD	77(16.7%)	518(8.7%)	193(6.2%)	33(5.2%)	<0.001
COPD	25(5.4%)	204(3.4%)	72(2.3%)	6(0.9%)	<0.001
STEMI	150(32.5%)	1423(23.9%)	628(20.3%)	132(20.8%)	<0.001
non-STEMI	42(9.1%)	482(8.1%)	220(7.1%)	52(8.2%)	0.255
Unstable angina	101(21.9%)	1098(18.5%)	551(17.8%)	96(15.1%)	0.031
Stable angina	76(16.5%)	1573(26.5%)	938(30.3%)	189(29.8%)	<0.001
Cardiogenic shock	39(8.4%)	239(4.0%)	83(2.7%)	26(4.1%)	<0.001
Serum creatinine (mg/dl)	1.8±2.3	1.3±1.9	1.2±1.7	1.3±1.9	<0.001
Hemodialysis	61(13.2%)	272(4.6%)	84(2.7%)	28(4.4%)	<0.001
Aspirin	442(95.7%)	5735(96.5%)	3022(97.5%)	615(96.9%)	0.113
Clopidogrel	325(70.4%)	4523(76.1%)	2378(76.7%)	492(77.5%)	0.084
Ticlopidine	15(3.3%)	183(3.1%)	110(3.6%)	29(4.6%)	0.311

Values are presented as n (%) or mean ± SD, as indicated.

BMI = body mass index; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; HF = heart failure; MI = myocardial infarction; CVD = cerebrovascular disease; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction.

doi:10.1371/journal.pone.0124399.t001

in-hospital mortality (p<0.001), heart failure after PCI (p = 0.048), cardiogenic shock (p = 0.018), bleeding complications within 72 hours (p<0.001), and a higher incidence of receiving blood transfusion (p<0.001).

The results of multivariate logistic regression analysis on overall complications, in-hospital mortality, and bleeding complications within 72 hours in the total cohort are shown in Tables 4, 5 and 6. When BMI was entered as a continuous variable, it was not an independent predictor of overall complications (OR, 0.99; 95% CI, 0.97–1.01; p = 0.247) and in-hospital mortality (OR, 0.98; 95% CI, 0.94–1.03; p = 0.411), but was inversely associated with bleeding complications after adjustment for confounding variables (OR, 0.95; 95% CI, 0.92–0.98; p = 0.002). Because cardiogenic shock is known to be such a strong predictor of mortality and complications after PCI, we performed subgroup multivariate analysis in patients without cardiogenic shock (n = 9755, Tables 7, 8 and 9). In subgroup multivariate analysis, BMI was inversely associated with overall complications (OR, 0.98; 95% CI, 0.95–0.99; p = 0.033) and bleeding complications

Table 2. Angiographical and Procedural Data.

	Underweight (BMI<18.5, n = 462)	Normal (18.5≦BMI<25.0, n = 5945)	Overweight (25.0≦BMI<30.0, n = 3100)	Obese (30.0≦BMI, n = 635)	P-value
Two-vessel disease	142(30.7%)	1933(32.5%)	1007(32.5%)	233(36.7%)	0.135
Three-vessel disease	124(26.8%)	1432(24.1%)	751(24.2%)	169(26.6%)	0.315
Bifurcation lesion	127(27.5%)	1702(28.6%)	839(27.1%)	196(30.9%)	0.183
LMT lesion	20(4.3%)	258(4.3%)	87(2.8%)	22(3.5%)	0.003
CTO lesion	33(7.1%)	349(5.9%)	209(6.7%)	48(7.6%)	0.161
Type C lesion	163(35.3%)	1761(29.6%)	918(29.6%)	219(34.5%)	0.006
Transradial Intervention	116(25.1%)	1862(31.3%)	1026(33.1%)	218(34.3%)	0.002
Transfemoral Intervention	336(72.7%)	3939(66.3%)	2011(64.9%)	403(63.5%)	0.005
Drug-eluting stent	304(65.8%)	4183(70.4%)	2237(72.2%)	436(68.7%)	0.018
Sirolimus-eluting stent	22(4.8%)	349(5.9%)	173(5.6%)	31(4.9%)	0.584
Paclitaxel-eluting stent	24(5.2%)	208(3.5%)	117(3.8%)	24(3.8%)	0.303
Zotarolimus-eluting stent	47(10.2%)	487(8.2%)	272(8.8%)	47(7.4%)	0.307
Everolimus-eluting stent	176(38.1%)	2648(44.5%)	1393(44.9%)	275(43.3%)	0.044
Biolimus-eluting stent	37(8.0%)	445(7.5%)	231(7.4%)	49(7.7%)	0.973
Bare-metal stent	105(22.7%)	1363(22.9%)	670(21.6%)	158(24.9%)	0.265
Rotablator	32(6.9%)	251(4.2%)	108(3.5%)	21(3.3%)	0.003
Thrombus aspiration	104(22.5)	1195(20.1)	600(19.4)	139(21.9)	0.260
IVUS use	367(79.4%)	4803(80.8%)	2539(81.9%)	511(80.5%)	0.449
IABP use	46(10.0%)	465(7.8%)	191(6.2%)	40(6.3%)	0.003
Closure device	68(14.7%)	831(14.0%)	453(14.6%)	89(14.0%)	0.851

Values are presented as n (%) or mean ± SD, as indicated.

LMT = left main trunk; CTO = chronic total occlusion; IVUS = intravascular ultrasound; IABP = intra-aortic balloon pumping.

doi:10.1371/journal.pone.0124399.t002

(OR, 0.95; 95% CI, 0.91–0.98; p = 0.006) after adjustment for confounding variables. Furthermore, there was a trend that BMI was moderately associated with in-hospital mortality (OR, 0.94; 95% CI, 0.88–1.01; p = 0.091).

Notably, variables that were independent predictors for overall complications, in-hospital mortality, and bleeding complications in the total cohort included age, previous heart failure, hemodialysis, STEMI, non-STEMI, cardiogenic shock, and use of IABP. TRI was an independent predictor of preventing overall complications (OR, 0.61; 95% CI, 0.39–0.98; p = 0.040). Use of a closure device was not a predictor of reducing bleeding complications by univariate analysis (OR, 0.91; 95% CI, 0.67–1.21; p = 0.522).

Discussion

The major findings of this study were that lean patients, rather than obese patients, were at greater risk for in-hospital complications during and after PCI in one of the largest, contemporary, multicenter registries in Japan. Our dataset included more than 10,000 patients. This allowed us to analyze the various in-hospital outcomes in each BMI group.

One of the biggest differences between Japanese patients with CAD and those in Western countries is physique. The average BMI is remarkably lower in Japanese CAD patients compared with those in Western countries. Wang et al. reported a comparative study of Asian versus non-Asian White Americans with non-STEMI. In their study, BMI was significantly lower in Asian patients than in non-Asian White Americans (24.9 vs 27.8 kg/m^2, p<0.001) [21]. Consistent with their study, the average BMI was 24.2 in our cohort. In addition, previous

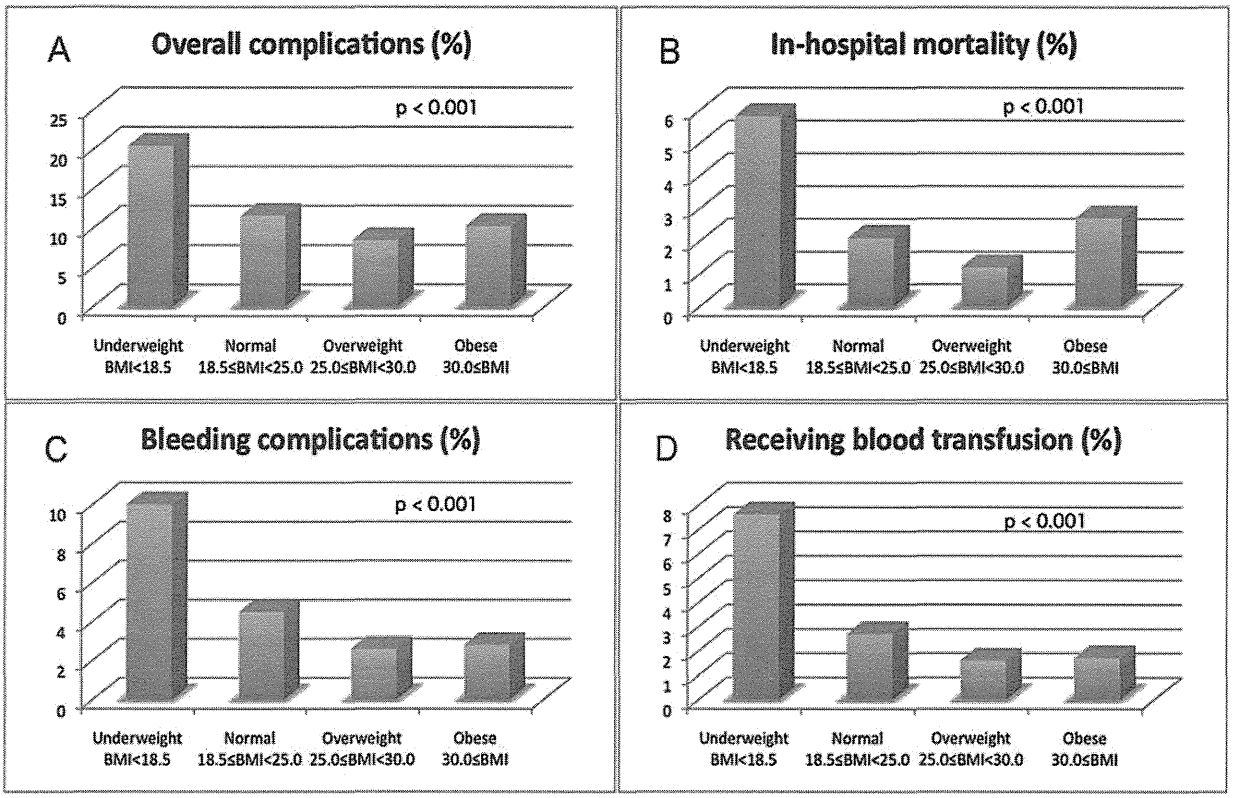

Fig 2. Relationship between BMI and in-hospital complications. In-hospital complication rates by BMI groups in 10,142 patients are shown. A: Overall complications; B: in-hospital mortality; C: bleeding complications within 72 hours; and D: rates of receiving blood transfusion.

doi:10.1371/journal.pone.0124399.g002

studies have reported that more than 70% of patients were overweight or obese in Western PCI registries [4,8,12]. However, only 36.8% of the patients (3,735/10,142) were overweight or obese in our study. Our data regarding BMI in Japanese CAD patients are consistent with previous studies in Japan [30,31]. Some previous studies have reported that patients with a BMI >40 kg/m^2 are considered extremely obese [32–34]. However, because the present Japanese study group included only 18 patients (0.2%) with a BMI >40 kg/m^2, they were included in the highest BMI subgroup [10]. Previous studies in Western countries have reported that lean patients and extremely obese patients are at greater risk for adverse outcomes after PCI [7,10,14,20,35,36]. In our study, complication rates showed a reverse J-shape relation with a peak in risk in the lowest BMI group (Fig 2), but not a bi-modal (U-shaped) relation with a peak in risk in the lowest and highest BMI groups, as observed in Western registries [20,35,36]. The small number of extremely obese patients in Japan is one of the major reasons for the unique obesity paradox that is observed in this country.

The precise mechanism of the obesity paradox remains unclear. However, there are some possible explanations for this phenomenon. Previous studies have shown that obese patients tend to have more aggressive and invasive therapy for CAD at a younger age [10,20,32,37]. Our data are consistent with those previous studies, and patients with a high BMI were younger than those with a low BMI in our study. Younger age at the time of PCI in patients with a high BMI may be one of the reasons for the obesity paradox [5,31]. However, Gruberg et al. reported that the relationship between BMI and mortality rate after PCI, and analysis by age groups showed that 1-year mortality rate was higher in patients with a normal BMI for all age groups,

Table 3. Complications.

	Underweight (BMI<18.5, n = 462)	Normal (18.5≦BMI<25.0, n = 5945)	Overweight (25.0≦BMI<30.0, n = 3100)	Obese (30.0≦BMI, n = 635)	P-value
Overall complications	94(20.4%)	681(11.5%)	261(8.4%)	65(10.2%)	<0.001
In-hospital mortality	27(5.8%)	127(2.1%)	38(1.2%)	17(2.7%)	<0.001
Severe dissection	10(2.1%)	66(1.1%)	26(0.8%)	15(2.4%)	0.002
Coronary perforation	8(1.7%)	54(0.9%)	29(0.9%)	8(1.3%)	0.309
Myocardial infarction after PCI	10(2.2%)	135(2.3%)	61(2.0%)	13(2.1%)	0.819
Heart failure after PCI	10(2.2%)	121(2.0%)	40(1.3%)	8(1.3%)	0.048
Cardiogenic shock	16(3.5%)	117(2.0%)	45(1.5%)	10(1.6%)	0.018
Cardiac tamponade	3(0.7%)	22(0.4%)	6(0.2%)	1(0.2%)	0.244
Cerebral bleeding	3(0.7%)	2(0.1%)	1(0.1%)	0(0%)	<0.001
Cerebral infarction	5(1.1%)	23(0.4%)	11(0.4%)	1(0.2%)	0.086
Bleeding complications(<72h)	46(10.0%)	266(4.5%)	81(2.6%)	18(2.8%)	<0.001
Puncture site bleeding	13(2.8%)	66(1.1%)	25(0.8%)	5(0.8%)	0.001
Puncture site hematoma	7(1.5%)	60(1.0%)	25(0.8%)	2(0.3%)	0.154
Retroperitoneal bleeding	1(0.2%)	11(0.2%)	1(0.1%)	0(0%)	0.185
Gastrointestinal bleeding	2(0.4%)	24(0.4%)	8(0.3%)	3(0.5%)	0.687
Genitourinary bleeding	2(0.4%)	8(0.1%)	3(0.1%)	2(0.3%)	0.225
Other bleeding	12(2.6%)	64(1.1%)	20(0.7%)	4(0.6%)	0.001
New hemodialysis	5(1.1%)	53(0.9%)	26(0.8%)	5(0.8%)	0.951
Transfusion	35(7.6%)	163(2.7%)	49(1.6%)	11(1.7%)	<0.001

Values are presented as n (%).

PCI = percutaneous coronary intervention.

doi:10.1371/journal.pone.0124399.t003

Table 4. Multivariate Logistic Regression Analysis on Overall Complications in the Total Cohort.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.03	1.02–1.03	<0.001	1.02	1.01–1.03	<0.001
Female gender	1.62	1.41–1.87	<0.001	1.45	1.23–1.71	<0.001
BMI	0.94	0.92–0.95	<0.001	0.99	0.97–1.01	0.247
Previous HF	1.84	1.52–2.21	<0.001	1.52	1.22–1.89	<0.001
PAD	1.38	1.11–1.69	0.004	1.30	1.02–1.64	0.036
COPD	1.67	1.21–2.25	0.002	1.53	1.07–2.14	0.020
Hemodialysis	1.74	1.34–2.24	<0.001	1.48	1.09–1.97	0.011
STEMI	2.64	2.32–3.01	<0.001	2.08	1.66–2.61	<0.001
non-STEMI	1.42	1.14–1.74	0.002	1.45	1.09–1.92	0.010
Cardiogenic Shock	9.04	7.32–11.17	<0.001	2.39	1.84–3.09	<0.001
IABP use	9.73	8.27–11.45	<0.001	4.90	4.02–5.96	<0.001
Transradial Intervention	0.39	0.33–0.46	<0.001	0.61	0.39–0.98	0.040
Three-vessel disease	1.57	1.37–1.80	<0.001	1.19	1.02–1.39	0.024
Type C lesion	1.74	1.53–1.98	<0.001	1.41	1.21–1.64	<0.001
CTO	1.46	1.15–1.82	0.002	1.42	1.08–1.85	0.013
Rotablator	1.95	1.50–2.51	<0.001	1.68	1.25–2.24	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; HF = heart failure; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping; CTO = chronic total occlusion.

doi:10.1371/journal.pone.0124399.t004

Table 5. Multivariate Logistic Regression Analysis on In-hospital Mortality in the Total Cohort.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.07	1.05–1.09	<0.001	1.07	1.05–1.09	<0.001
BMI	0.90	0.87–0.94	<0.001	0.98	0.94–1.03	0.411
Hyperlipidemia	0.35	0.27–0.46	<0.001	0.60	0.43–0.83	0.002
Previous HF	3.02	2.14–4.19	<0.001	2.42	1.53–3.76	<0.001
Hemodialysis	4.00	2.65–5.85	<0.001	7.31	4.14–12.66	<0.001
STEMI	5.65	4.27–7.53	<0.001	3.90	2.16–7.45	<0.001
non-STEMI	2.25	1.52–3.25	<0.001	2.96	1.51–6.01	0.002
Cardiogenic Shock	30.8	22.9–41.5	<0.001	5.74	3.89–8.50	<0.001
IABP use	24.5	18.4–32.9	<0.001	6.91	4.71–10.15	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; HF = heart failure; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping.

doi:10.1371/journal.pone.0124399.t005

except for those younger than 50 years old [12]. Furthermore, obese patients tend to have a high rate of guideline-based optimal medical therapy, including statins, angiotensin-converting enzyme inhibitors, and beta-blockers [7,8,32]. Cessation of smoking, cardiac rehabilitation, and dietary counseling are more frequently enforced in overweight and obese patients than in lean patients [8,38]. Furthermore, patients with a low BMI tend to have more disease-induced cachexia induced by carcinoma, smoking, chronic obstructive pulmonary disease, chronic

Table 6. Multivariate Logistic Regression Analysis on Bleeding Complications within 72 Hours in the Total Cohort.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.04	1.03–1.05	<0.001	1.01	1.00–1.03	0.011
Female gender	2.35	1.91–2.88	<0.001	2.13	1.68–2.69	<0.001
BMI	0.89	0.87–0.92	<0.001	0.95	0.92–0.98	0.002
Previous PCI	0.54	0.43–0.68	<0.001	0.70	0.52–0.94	0.016
Previous HF	2.14	1.62–2.78	<0.001	1.55	1.13–2.10	0.007
PAD	1.69	1.24–2.26	0.001	1.45	1.03–2.03	0.035
COPD	1.97	1.24–2.99	0.005	1.88	1.14–2.97	0.015
Hemodialysis	2.79	1.98–3.83	<0.001	2.14	1.45–3.11	<0.001
STEMI	2.27	1.85–2.77	<0.001	1.59	1.19–2.14	0.002
non-STEMI	2.09	1.56–2.75	<0.001	1.92	1.35–2.70	<0.001
Cardiogenic Shock	7.99	6.10–10.38	<0.001	2.45	1.74–3.42	<0.001
IABP use	7.64	6.11–9.51	<0.001	3.50	2.63–4.63	<0.001
Transradial Intervention	0.33	0.25–0.44	<0.001	0.55	0.29–1.12	0.551
Closure device	0.91	0.67–1.21	0.522			
CTO	1.64	1.16–2.27	0.006	1.78	1.20–2.61	0.005
Rotablator	2.63	1.84–3.67	<0.001	2.25	1.50–3.31	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; PCI = percutaneous coronary intervention; HF = heart failure; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping; CTO = chronic total occlusion.

doi:10.1371/journal.pone.0124399.t006

Table 7. Multivariate Logistic Regression Analysis on Overall Complications in Patients without Cardiogenic Shock.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.03	1.02–1.04	<0.001	1.02	1.01–1.03	<0.001
Female gender	1.73	1.49–2.02	<0.001	1.49	1.26–1.76	<0.001
BMI	0.93	0.91–0.95	<0.001	0.98	0.95–0.99	0.033
Previous HF	1.80	1.46–2.20	<0.001	1.41	1.12–1.75	0.003
PAD	1.41	1.12–1.76	0.003	1.31	1.02–1.66	0.034
COPD	1.51	1.05–2.10	0.026	1.36	0.92–1.95	0.114
Hemodialysis	1.78	1.35–2.33	<0.001	1.43	1.05–1.92	0.025
STEMI	2.07	1.79–2.40	<0.001	2.02	1.69–2.40	<0.001
non-STEMI	1.32	1.03–1.65	0.025	1.38	1.06–1.77	0.017
IABP use	7.87	6.47–9.55	<0.001	5.57	4.52–6.86	<0.001
Transradial Intervention	0.43	0.36–0.51	<0.001	0.61	0.50–0.73	<0.001
Three-vessel disease	1.53	1.32–1.78	<0.001	1.15	0.98–1.35	0.087
Type C lesion	1.74	1.51–2.00	<0.001	1.44	1.22–1.69	<0.001
CTO	1.51	1.18–1.92	0.001	1.40	1.05–1.84	0.020
Rotablator	2.25	1.73–2.92	<0.001	1.66	1.23–2.21	0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; HF = heart failure; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping; CTO = chronic total occlusion.

doi:10.1371/journal.pone.0124399.t007

heart failure, and insulin-dependent diabetes mellitus. These comorbidities have been suggested as a possible explanation for the obesity paradox [10,12,16,17].

Potential overdosing of antiplatelets or anticoagulants, and differences in platelet biology have been reported as reasons for the high risk of bleeding with a low BMI [9,39]. Notably, in our study, almost all of the Japanese patients underwent PCI with a unified regimen of aspirin and clopidogrel during and after the procedure. This was because other agents, such as prasugrel and ticagrelor were not available at the time of this study in Japan. A unified regimen of antiplatelets for all CAD patients with various BMIs may affect the obesity paradox in bleeding complications after PCI [13]. Wang et al. reported that Asian patients with non-STEMI had a significantly higher risk of bleeding compared with non-Asian white patients [21]. They also

Table 8. Multivariate Logistic Regression Analysis on In-hospital Mortality in Patients without Cardiogenic Shock.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.10	1.08–1.13	<0.001	1.09	1.07–1.12	<0.001
BMI	0.82	0.77–0.87	<0.001	0.94	0.88–1.01	0.091
Hyperlipidemia	0.40	0.27–0.58	<0.001	0.70	0.46–1.05	0.087
Previous HF	3.69	2.35–5.63	<0.001	2.47	1.46–4.06	0.001
Hemodialysis	5.40	3.24–8.61	<0.001	7.82	4.25–13.96	<0.001
STEMI	4.74	3.24–6.96	<0.001	6.12	3.78–10.11	<0.001
non-STEMI	1.93	1.07–3.25	0.030	2.74	1.38–5.21	0.005
IABP use	15.35	10.34–22.64	<0.001	9.01	5.81–13.91	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; HF = heart failure; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping.

doi:10.1371/journal.pone.0124399.t008

Table 9. Multivariate Logistic Regression Analysis on Bleeding Complications within 72 Hours in Patients without Cardiogenic Shock.

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	1.04	1.03–1.05	<0.001	1.02	1.01–1.04	<0.001
Female gender	2.29	1.77–2.96	<0.001	1.82	1.38–2.38	<0.001
BMI	0.89	0.86–0.93	<0.001	0.95	0.91–0.98	0.006
Previous PCI	0.60	0.45–0.78	<0.001	0.69	0.51–0.92	0.012
Previous HF	2.12	1.50–2.93	<0.001	1.55	1.07–2.20	0.021
PAD	1.27	0.82–1.88	0.273			
COPD	1.59	0.83–2.74	0.151			
Hemodialysis	2.97	1.97–4.34	<0.001	2.20	1.40–3.34	<0.001
STEMI	1.61	1.22–2.11	<0.001	1.65	1.19–2.29	0.003
non-STEMI	1.98	1.36–2.80	<0.001	1.97	1.31–2.89	0.001
IABP use	4.52	3.22–6.21	<0.001	3.07	2.15–4.32	<0.001
Transradial Intervention	0.37	0.26–0.51	<0.001	0.55	0.38–0.78	<0.001
Closure device	1.01	0.70–1.42	0.944			
CTO	2.06	1.38–2.99	<0.001	2.39	1.57–3.54	<0.001
Rotablator	3.42	2.29–4.95	<0.001	2.67	1.73–4.01	<0.001

OR = odds ratio; CI = confidence interval; BMI = body mass index; PCI = percutaneous coronary intervention; HF = heart failure; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; STEMI = ST elevation myocardial infarction; IABP = intra-aortic balloon pumping; CTO = chronic total occlusion.

doi:10.1371/journal.pone.0124399.t009

reported that Asian patients were more likely to receive excess doses of antithrombotic agents compared with non-Asians. Appropriate doses of antiplatelets or anticoagulants may reduce bleeding complications. Furthermore, patients with a low BMI were older ($p<0.001$), more likely to have end-stage renal disease ($p<0.001$) and systemic atherosclerotic disease including cerebrovascular disease ($p<0.001$) and peripheral artery disease ($p<0.001$), than those with a high BMI in our cohort. These results are consistent with previous studies [9,13,14,40], and indicate that patients with a low BMI in our present study tended to have progressive atherosclerosis in the arterial system of the whole body. Arterial stiffness due to progressive atherosclerosis might be associated with a higher risk of bleeding in patients with a low BMI [9,14], although we performed multivariate analysis to adjust for possible confounding variables.

Because bleeding complications are associated with short- and long-term adverse outcomes after PCI [39,41], efforts for reducing bleeding complications are important. Bivalirudin, TRI, and use of a closure device are considered as bleeding avoidance strategies [42]. Bivalirudin is not available in Japan. Therefore, appropriate use of a closure device and TRI may be useful for reducing bleeding complications after PCI. In our study, there was no difference in the frequency of using a closure device in each BMI group, and use of a closure device was not a predictor of reducing bleeding complications by univariate analysis. TRI has been reported as a useful method for reducing bleeding complications compared with conventional transfemoral intervention [24,43]. In our study, TRI was an independent predictor of preventing overall complications in the total cohort. TRI was also associated with a small risk of bleeding in a subgroup analysis of patients without cardiogenic shock in multivariate logistic regression analysis. Approximately one-third of all of the PCIs in our dataset were performed with the transradial approach. Furthermore, TRI is performed more frequently in patients with a high BMI than in those with a low BMI [36]. Although TRI is more commonly performed in Japan than in Western countries [24], more frequent use of radial access in patients with a low BMI for reducing

bleeding complications should be considered. Because patients with a low BMI have small vessels compared with patients with a high BMI, an unfavorable arterial sheath size has been reported as a possible explanation for increased access site bleeding complications in those with a low BMI [7,40,44]. Kang et al. reported that a high BMI was associated with a large diameter of the coronary arteries, and was associated with a large stent area after intravascular ultrasound-guided stent implantation [45]. They concluded that a high BMI is not associated with worse outcomes after drug-eluting stent implantation, despite more comorbidities, greater plaque burden, and more plaque rupture. A large vessel diameter in patients with a high BMI is one of the potential causes of the obesity paradox after PCI. Endovascular techniques and devices have evolved over the years, and smaller sheaths, guiding catheters, stents, and balloons have become available in recent years. However, physicians should be aware that lean patients are at greater risk for complications during and after PCI.

Obesity is an independent risk factor of advanced cardiovascular disease and mortality [1–3]. Although the obesity paradox may be a real phenomenon, physicians should be aware that patients with an increased body mass remain at high risk for development of CAD and poor outcomes over the long term [2,3,32]. Current guidelines recommend weight reduction to a BMI <25 as a second prevention for patients with CAD [46,47]. However, there is no clear evidence that a reduction in weight improves the prognosis of patients after PCI. Further long-term studies are needed in the future regarding this important issue.

Study limitations

The first limitation of our study is that it was an observational clinical trial. The study population was heterogenous, including patients with different severities of coronary artery disease, ranging from acute coronary syndrome with cardiogenic shock to stable angina. Although we performed multivariate logistic regression analysis to adjust for possible confounding variables, some selection bias might not have been completely adjusted for in our statistical model, and the heterogeneity of the patients may have affected the incidence of complications in each of the BMI groups. Furthermore, we excluded 646 patients with missing data of basic information, including sex, height and/or body weight, which might have affected selection bias. Another limitation is that the duration of antiplatelet therapy and the size of the sheaths and guiding catheters were not recorded, and patients with cancer or other serious comorbidities were not excluded in our registry. These factors might have been associated with the rate of bleeding complications. Finally, the impact of BMI and in-hospital bleeding complications on long-term clinical outcomes in patients who undergo PCI should be investigated in our registry in the future.

Conclusions

Lean patients, rather than obese patients are at greater risk for in-hospital complications during and after PCI, particularly for bleeding complications.

Acknowledgments

We thank all of the investigators, clinical coordinators and institutions involved in the JCD-KICS study.

Investigators: Toshiki Kuno, Hiroyuki Motoda, Masaki Kodaira (Ashikaga Red Cross Hospital), Yutaka Okada (Eiju General Hospital), Soushin Inoue, Iwao Nakamura (Hino Municipal Hospital), Shunsuke Takagi, Takashi Matsubara (Hiratsuka City Hospital), Masashi Takahashi, Keishu Li, Koichiro Sueyoshi (Kawasaki City Municipal Hospital), Taku Inohara, Fumiaki Yashima, Atsushi Anzai, Ryota Tabei, Kentaro Hayashida, Takashi Kawakami, Hideaki

Kanazawa, Shunsuke Yuasa, Yuichiro Maekawa, Akio Kawamura (Keio University School of Medicine), Masahiro Suzuki, Keisuke Matsumura (National Hospital Organization Saitama National Hospital) Yukinori Ikegami, Jun Fuse, Munehisa Sakamoto, Yukihiko Momiyama (National Hospital Organization Tokyo Medical Center), Ayaka Endo, Tasuku Hasegawa, Toshiyuki Takahashi, Susumu Nakagawa (Saiseikai Central Hospital), Takashi Yagi, Kenichiro Shimoji, Shigetaka Noma (Saiseikai Utsunomiya Hospital), Masahito Munakata, Shiro Ishikawa, Takashi Koyama (Saitama City Hospital), Atsushi Mizuno, Yutaro Nishi (St Luke's International Hospital Heart Center), Daisuke Shinmura, Kazunori Moritani, Masaru Shibata (Tachikawa Kyosai Hospital), Kimi Koide, Yoshinori Mano, Takahiro Oki (Tokyo Dental College Ichikawa General Hospital), Koji Negishi, Yusuke Jo, and Takahiro Koura (Yokohama Municipal Hospital)

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ORIGINAL ARTICLE

Nomogram Prediction of Metachronous Colorectal Neoplasms in Patients With Colorectal Cancer

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Objective: To construct a predictive model of postoperative colorectal neoplasm development using a nomogram.

Background: Although patients with colorectal cancer (CRC) are known to be at high risk of developing metachronous adenoma or CRC, no statistical model for predicting the incidence of postoperative colorectal lesions has been reported.

Methods: A total of 309 CRC patients who underwent surgical resection received regular endoscopic follow-up to detect the development of metachronous adenoma or adenocarcinoma. The patients were divided into the derivation set (n = 209) and the validation set (n = 100). The nomogram to predict the 3- and 5-year adenoma-free survival rates was constructed using the derivation set, and a calibration plot and concordance index (c-index) were calculated. The predictive utility of the nomogram was validated in the validation set.

Results: Sex, age, and number of synchronous lesions at the time of surgery for primary CRC were adopted as variables for the nomogram. The nomogram showed moderate calibration, with a c-index of 0.709 in the derivation set and 0.712 in the validation set.

Conclusions: A nomogram based on sex, age, and number of synchronous lesions at the time of surgery has the ability to predict postoperative adenoma-free survival.

Keywords: colonoscopy, colorectal adenoma, colorectal cancer, nomogram, postoperative surveillance

(*Ann Surg* 2015;261:926–932)

Colorectal cancer (CRC) is one of the most common malignancies in Japan and in Western countries.[1] Furthermore, those with a history of CRC are at a higher risk for developing second metachronous adenomas or CRC recurrence during the follow-up period.[2–5] Chen et al[6] reported that 0.7% of patients develop metachronous CRC during the 3 years after surgical resection for the initial CRC.

It is generally accepted that most CRCs develop through a continuous process, transforming from normal mucosa to adenoma to carcinoma,[7–9] a process known as the adenoma-carcinoma sequence. Therefore, the early detection and endoscopic resection of newly developed adenomas constitute an important preventive strategy, especially in patients who have undergone surgical resection for primary CRC. However, there are no definite guidelines for adenoma surveillance after the surgical resection of primary CRC. The 2006 guidelines issued by the American Cancer Society indicate that a postoperative colonoscopy should be performed 1, 4, and 9 years after the initial surgical procedure,[10] but these guidelines also state that the currently available evidence does not fully address any clinical, genetic, or biologic markers that may predict the development of metachronous CRC. Therefore, the development of a prediction model of metachronous colorectal lesions after resection of initial CRC is very important.

Several studies have previously attempted to identify risk factors for the development of metachronous adenomas after resection of initial CRC. The location of CRC in the proximal colon and previous or synchronous adenoma presence were reported to be risk factors for the early development of metachronous lesions.[5,11] However, there have been no previous studies investigating the time course of adenoma formation after surgery using the log-rank test or Cox proportional hazard model. Recently, we demonstrated that age, presence of a synchronous lesion, and diabetes mellitus were independent predictive variables affecting the development of postoperative colorectal neoplasms.[11] By extending the previously reported regression results, we have designed the present study to construct a predictive model of postoperative colorectal neoplasm development using a nomogram, a tool widely used among clinicians because of its utility as a prediction model and its user-friendly interface.[12,13]

MATERIALS AND METHODS

Patient Selection

We retrospectively evaluated the medical records of 552 consecutive patients with colorectal adenocarcinoma, diagnosed between January 2004 and December 2007, who underwent surgical resection at the Department of Surgical Oncology, the University of Tokyo Hospital. Patients with adenomatous polyposis (>30 lesions at the time of surgery or familial adenomatous polyposis), those with hereditary non-polyposis colon cancer, and those with inflammatory bowel disease were excluded from the study. After surgical resection, all specimens were histopathologically reviewed, and the pathological TNM class and stage were determined according to the classification established by the American Joint Committee on Cancer.[14] In cases of multifocal disease, the histopathological variables were determined by assessing the dominant lesion (the most extensive lesion based on tumor invasion or size). Primary colon cancer located proximal to the splenic flexure was defined as right-sided, and the distally located one was defined as left-sided; all variables were assessed at the time of surgery. This study was approved by the institutional review board, and all patients gave written informed consent.

The first colonoscopy was scheduled at 1 year after surgery, and adenomas detected during the first colonoscopy were treated as synchronous lesions. Polyps larger than 5 mm were removed by endoscopic mucosal resection and were histopathologically analyzed. Hyperplastic polyps and other nonneoplastic colorectal lesions were recorded but not included in the analysis. After confirming the absence of colonic lesions (clean colon) by perioperative colonoscopy, endoscopic surveillance was conducted every 1 to 2 years. Patients who failed to undergo the second colonoscopy, which was usually scheduled 2 years after surgery, were excluded from the study; the final number of patients enrolled in this surveillance program was

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 0003-4932/14/26105-0926
DOI: 10.1097/SLA.0000000000000881

309. The patients were divided into 2 groups: the derivation and validation groups. The derivation group consisted of 209 patients who underwent surgery from January 2004 to June 2006, and the validation group consisted of 100 patients who underwent surgery from July 2006 to December 2007. The nomogram was constructed on the basis of derivation group data, and its predictive utility was validated in the validation group.

Statistical Analysis

The Kaplan-Meier method was used to estimate overall survival and recurrence-free survival, and the log-rank test was used to analyze differences in survival between groups. For the derivation group, the following potential prognostic variables were assessed: sex, age, and sex (general characteristics); tumor location, depth of invasion, regional lymph node metastasis, distant metastasis, lymphatic invasion, venous invasion, histologic differentiation, and the presence of concomitant CRCs and/or adenomas at the time of surgery (cancer-related variables); and smoking, body mass index greater than 25 kg/m^2, history of previous malignancies (CRC or extracolic malignancy), first-degree family history of CRC, hypertension, hyperlipidemia, and diabetes mellitus (patient background variables). A multivariate Cox proportional hazards analysis was performed using variables whose P value was less than 0.2 in univariate analysis. By following the method of Wang et al,[15] we built nomograms for predicting the probability of 3- and 5-year adenoma-free survival rates after surgery. The nomogram was subjected to 100 bootstrap resamples for calculating the estimated Harrell concordance index (c-index) as an index of model performance.[16] The c-index estimates the probability of concordance between predicted and observed outcomes in rank order and is equivalent to the area under the receiver operating characteristic curve, if there are no censored cases.[16] It represents the ability of the model to discriminate between patients who survived without adenoma development and those who did not. Higher values indicate better discrimination: a value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates perfect separation of patients with different outcomes.

We also performed calibration using a calibration curve, a graphic representation of the relationship between the observed outcome frequencies and the predicted probabilities, with both the derivation and validation groups. Using the constructed nomogram, the score of predicting the 5-year adenoma-free survival rate was calculated for both groups. All statistical analyses were performed using the statistical software program R 3.0.1 with rms and Hmisc packages (http://www.r-project.org/).

RESULTS

Of the 552 patients enrolled in the study, 243 were excluded for the following reasons: 227 patients did not undergo colonoscopic surveillance (CRC progression in 108 patients, other disease progression in 64 patients, and a move or change of hospital in 55 patients), 4 patients had colitic cancers, 3 patients had polyposis, and 3 patients died during the perioperative period. The differences between the included and excluded patients are presented in Table 1. Because a large proportion of the patients excluded from the analysis had residual cancer or recurrence, and most of the remaining excluded patients failed to receive surveillance because of the development of diseases other than CRC, the age and stage of initial CRC were higher in the excluded group than in the included group. General characteristics related to adenoma formation are also presented in Table 2. The characteristics of patients in the derivation and validation groups were comparable. The incidence of CRC formation per year was 0.0064 in both groups, and that of adenoma formation was approximately 0.084 in both groups. Although the 5-year adenoma-free rate was a little lower in the validation group, this difference was not statistically significant ($P = 0.077$).

TABLE 1. Differences Between Included and Excluded Patients

	Included	Excluded	P
Total, n	309	243	
Sex, n			
Male	199	149	
Female	110	94	0.4564
Age, mean ± SD, yr	63.2 ± 10.3	68.0 ± 11.7	<0.001
Location, n (%)			
Right hemicolon	68 (22.0)	78 (32.1)	
Left hemicolon	112 (36.2)	76 (31.3)	
Rectum	129 (41.7)	89 (36.6)	0.0288
Stage, n (%)			
0/I	99 (32.0)	45 (18.5)	
II	105 (34.0)	69 (28.4)	
III	84 (27.2)	70 (28.8)	
IV	21 (6.8)	59 (24.3)	<0.001

TABLE 2. Patient Characteristics

	Derivation Data Set	Validation Data Set
No. patients	209	100
Sex, n (%)		
Male	134 (64.1)	64 (64)
Female	75 (35.9)	36 (36)
Median follow-up time, yr	5.57	5.04
Total follow-up time, yr	1097.0	466.5
Total colorectal cancer cases developed during follow-up time, n	7	3
Incidence per year	0.00638	0.00643
Total colorectal adenoma cases developed during follow-up time, n	93	39
Incidence per year	0.08470	0.08359
Cumulative 5-yr adenoma-free rate	75.35%	71.71%
95% CI	68.31–81.25	61.30–80.22

CI indicates confidence interval.

Development of the Nomogram

The results of the univariate and multivariate analyses of the association between variables and the 5-year adenoma-free survival rate are shown in Table 3. In the univariate analysis, male patients and older patients had a significantly shorter adenoma-free survival time. The variables associated with progression of the primary cancer, such as T stage and presence of lymph node or distant metastasis, showed no correlation with postoperative adenoma development, consistent with our previous report. Although the presence of second or additional primary CRC showed no correlation, if both synchronous CRC and adenomas were included in the category sublesions, the presence of sublesions was strongly associated with postoperative adenoma development. We previously reported that the presence of diabetes mellitus correlated with postoperative development[11]; however, in this study, no variables concerning patient background, including diabetes mellitus, correlated with adenoma development.

Therefore, we performed multivariate analysis using the variables of sex, age, and the presence of concomitant colorectal