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ORIGINAL ARTICLE
Ischemic Heart Disease

Validation of Japanese Bleeding Risk Criteria in Patients After Percutaneous Coronary Intervention and Comparison With Contemporary Bleeding Risk Criteria

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Background: The utility of the Japanese version of high bleeding risk (J-HBR) criteria compared with contemporary bleeding risk criteria, including Academic Research Consortium for High Bleeding Risk criteria, has not been fully investigated.

Methods and Results: This study included patients who underwent percutaneous coronary intervention between 2010 and 2019. The J-HBR score was calculated by assigning 1 point for each major criterion and 0.5 points for each minor criterion in the J-HBR criteria. Among 1,643 patients, 1,143 (69.6%) met the J-HBR criteria. Accumulated major bleeding event rates at 1 year were higher among those who met the J-HBR criteria (4.8% vs. 0.6%; P<0.001). J-HBR criteria had higher sensitivity (94.8%) and lower specificity (31.4%) than contemporary bleeding risk criteria in predicting major bleeding. Bleeding events increased with increasing J-HBR score. The C statistic for the J-HBR score for predicting major bleeding at 1 year was 0.75 (95% confidence interval 0.69–0.81), and is comparable to that of other risk scores. In multivariate analysis, of the factors included in J-HBR criteria, chronic kidney disease, heart failure, and active malignancy were associated with major bleeding.

Conclusions: J-HBR criteria identified patients at high bleeding risk with high sensitivity and low specificity. Bleeding risk was closely related to J-HBR score and its individual components. The discriminative ability of the J-HBR score was comparable to that of contemporary bleeding risk scores.

Key Words: Bleeding; Coronary artery disease; Risk stratification

Major bleeding events during antiplatelet therapy in patients with coronary artery disease who have undergone percutaneous coronary intervention (PCI) contribute to adverse outcomes, including mortality.[1] Several scoring systems have been developed to predict bleeding events, including the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score,[2] the Patterns of Non-adherence to Anti-platelet Regimen in Stented Patients (PARIS) bleeding risk score,[3] and the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) bleeding risk score,[4] to enable judgments to be made regarding the duration of dual antiplatelet therapy (DAPT). Recently, Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria were proposed to standardize the definition of high bleeding risk.[5] The ARC-HBR criteria were validated in several large cohorts of patients undergoing percutaneous coronary intervention (PCI), in which the ARC-HBR definition successfully identified patients at increased risk of a bleeding event.[6–9] Conversely, several particular patient characteristics have been reported to be predictors of bleeding events in East Asian, but not Western, populations,[10] such as low body weight,[11] end-stage renal failure undergoing dialysis,[12] heart failure,[13] and peripheral vascular disease.[4] In this regard, the Japanese Circulation Society's Working Group of Guidelines created the Japanese version of HBR (J-HBR) criteria by modifying, by consensus, the ARC-HBR criteria.[14] The J-HBR criteria include low body weight, renal failure involving dialysis, heart failure, and peripheral vascular disease in addition to the ARC-HBR criteria. The J-HBR criteria were validated in a large Japanese cohort, revealing the appropriateness of the criteria for identifying patients at high risk of a bleeding event.[15] However, the utility of the J-HBR criteria compared with contemporary bleeding risk criteria, includ-

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ing the ARC-HBR criteria, has not been fully investigated.

Therefore, in this study we validated the J-HBR criteria in a cohort of patients with coronary artery disease who were undergoing PCI, and compared the J-HBR criteria with contemporary bleeding risk criteria, including the ARC-HBR criteria, the PRECISE-DAPT score, the PARIS bleeding risk score, and the CREDO-Kyoto bleeding risk score. Furthermore, we examined the potential risk of each criterion in the J-HBR criteria for a major bleeding event.

Methods

Patient Population and Study Protocol

In all, 1,643 consecutive patients with coronary artery disease who underwent PCI at Fukushima Medical University Hospital between January 2010 and December 2019 were included in this study. Patients were divided into 2 groups, a J-HBR group and a non-HBR group, according to the definition of the J-HBR criteria.[14] Patients were followed up until March 2021. The status and/or dates of death of patients were obtained from patients' medical records, the attending physicians at the patients' referring hospitals, or by contacting patients by telephone.

All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Fukushima Medical University, and the study was performed in accordance with the principles outlined in the Declaration of Helsinki.

J-HBR Criteria

The J-HBR criteria included specific major criteria, such as low body weight (<55 kg for men, <50 kg for women), renal failure involving dialysis, heart failure, and peripheral vascular disease, in addition to the major and minor ARC-HBR criteria. Patients were considered to be at high bleeding risk if at least 1 major criterion or 2 minor criteria in the J-HBR criteria were met. Data for several major and minor J-HBR criteria, including history of non-traumatic bleeding event, chronic bleeding diathesis, liver cirrhosis with portal hypertension, non-deferrable major surgery on DAPT, and major surgery/trauma within 30 days prior to PCI, were not available in this study, and these criteria were regarded as absent. Therefore in the present study, patients with at least 1 major criterion, such as low body weight or frailty, severe chronic kidney disease (CKD) including dialysis (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), moderate to severe anemia (hemoglobin <11 g/dL), heart failure, anticoagulation, peripheral vessel disease, previous intracerebral hemorrhagic or severe stroke, thrombocytopenia, and active malignancy, or those with ≥2 minor criteria, such as age ≥75 years, moderate CKD (eGFR 30–59 mL/min/1.73 m^2), mild anemia (hemoglobin 11–12.9 g/dL for men, 11–11.9 g/dL for women), long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids, and prior ischemic stroke not meeting the major criterion, were defined as being at high bleeding risk (i.e., J-HBR group).

Clinical Endpoint and Definitions

The primary endpoint was a bleeding event defined as Bleeding Academic Research Consortium (BARC) Type 3 or 5.[16] The secondary endpoint was major adverse cardiovascular events (MACE), including cardiac death, nonfatal myocardial infarction, and stent thrombosis. Cardiac death was defined as any death caused by cardiac disease, procedure-related death, and sudden death of unknown cause. Myocardial infarction and stent thrombosis were defined according to the Academic Research Consortium criteria.[17]

Comorbidities were assessed by several attending physicians using definitions reported previously.[18] Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure ≥140 mmHg, and/or diastolic pressure ≥90 mmHg. Diabetes was defined as the recent use of antidiabetic drugs, fasting blood glucose ≥126 mg/dL, and/or HbA1c ≥6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, triglyceride ≥150 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, and/or high-density lipoprotein cholesterol <40 mg/dL. Heart failure was defined based on the Framingham criteria.[19] Peripheral vascular disease was regarded as present when patients were being treated for carotid, aortic, or other peripheral vascular diseases or were scheduled for surgical or endovascular interventions. Stroke was defined as the rapid development of clinical signs of the disturbance of cerebral function lasting >24 h with imaging evidence of an acute and clinically relevant ischemic brain lesion. Severe stroke was defined as a National Institutes of Health Stroke Scale score ≥5. Intracerebral hemorrhage was defined as the rapid development of clinical signs of the disturbance of cerebral function lasting with imaging evidence of clinically relevant intracerebral bleeding. Patients were considered to have active malignancy if surgery for cancer was being planned or they were currently undergoing oncological systemic therapy and/or radiation therapy. The duration of DAPT left to the discretion of individual physicians. Unless there serious bleeding events occurred, the standard duration of DAPT was at least 1 month after bare metal stent implantation and 12 months after implantation of a drug-eluting stent, regardless of anticoagulation therapy.

Statistical Analysis

Normally distributed continuous variables are presented as the mean±SD, and were compared using Student's t test or the Mann-Whitney U test. Categorical variables are presented as numbers and percentages, and were compared using Chi-squared tests. Kaplan-Meier cumulative event curves were constructed for bleeding events and MACE, with curves compared using the log-rank test and generalized Wilcoxon test (Gehan-Breslow). To distinguish bleeding events during the duration of DAPT, landmark analysis at 1-year was conducted. To assess the influence of the number of criteria for bleeding events and MACE, J-HBR and ARC-HBR scores were calculated by assigning 1 point for each major criterion and 0.5 points for each minor criterion in the J-HBR and ARC-HBR criteria. Cox regression models and receiver operating characteristics (ROC) curve analysis were used as measures of discrimination of the J-HBR, ARC-HBR, PRECISE-DAPT, PARIS bleeding risk, and CREDO-Kyoto bleeding risk scores to predict bleeding events at 1 year. The C statistic of the J-HBR score was compared against that of each of the other risk scores using the DeLong test, treating ROC curves as paired.[20] Univariate and multivariate Cox proportional hazard analyses were conducted for variables in the J-HBR criteria.

Two-sided $P<0.05$ was considered statistically significant for all comparisons. Statistical analyses were performed using SPSS ver. 25.0 (IBM, Armonk, NY, USA).

Table 1. Clinical Characteristics of Patients Who Met the Japanese Version of High Bleeding Risk (J-HBR) Criteria and Those Who Did Not (Non-HBR)

	All patients (n=1,643)	J-HBR (n=1,158)	Non-HBR (n=485)	P value
Age (years)	69.3±11.5	71.8±11.3	63.3±9.6	<0.001
Male sex	1,291 (78.6)	850 (73.4)	441 (90.9)	<0.001
Weight (kg)	63.0±12.9	60.5±13.0	69.1±10.3	<0.001
Body mass index (kg/m²)	24.2±3.7	23.7±3.8	25.4±3.2	<0.001
Smoker	1,056 (64.3)	705 (60.9)	351 (72.4)	<0.001
Family history	442 (26.9)	286 (24.7)	156 (32.2)	0.002
Acute coronary syndrome	833 (50.7)	599 (51.7)	234 (48.2)	0.198
Multivessel disease	805 (49.0)	592 (51.1)	213 (43.9)	0.008
Transfemoral intervention	1,231 (74.9)	867 (74.9)	364 (75.1)	0.996
Comorbidities				
Hypertension	1,334 (81.2)	939 (81.1)	395 (81.4)	0.919
Diabetes	827 (50.3)	595 (51.4)	232 (47.8)	0.164
Dyslipidemia	1,323 (80.5)	910 (78.6)	413 (85.2)	<0.001
Chronic kidney disease	736 (44.8)	632 (54.6)	104 (21.4)	<0.001
Dialysis	97 (5.9)	97 (8.4)	0 (0)	<0.001
Anemia	760 (46.3)	669 (57.8)	91 (18.8)	<0.001
Atrial fibrillation	249 (15.6)	223 (19.3)	26 (5.4)	<0.001
Peripheral vessel disease	201 (12.2)	201 (17.4)	0 (0)	<0.001
Heart failure	322 (19.6)	322 (27.8)	0 (0)	<0.001
Previous ICH	14 (0.9)	14 (1.2)	0 (0)	0.085
Previous ischemic stroke	278 (16.9)	224 (19.3)	54 (11.1)	<0.001
Active malignancy	75 (4.6)	75 (6.5)	0 (0)	<0.01
Medications (at discharge)				
Dual antiplatelet therapy	1,299 (79.1)	850 (73.4)	449 (92.6)	<0.001
Anticoagulation	196 (11.9)	196 (16.9)	0 (0)	<0.001
NSAIDs	38 (2.3)	28 (2.4)	10 (2.0)	0.376
Steroid	33 (2.0)	27 (2.3)	6 (1.2)	0.594
Laboratory data				
eGFR (mL/min/1.73 m²)	58.8±22.7	53.7±23.7	70.9±14.2	<0.001
30≤eGFR<60 mL/min/1.73 m²	604 (36.8)	506 (43.7)	98 (20.2)	<0.001
eGFR <30 mL/min/1.73 m²	167 (10.2)	167 (14.4)	0 (0)	<0.001
Hb (g/dL)	13.2±2.1	12.7±2.1	14.4±1.3	<0.001
11.0≤Hb<12.9 g/dL (males); 11.0≤Hb<11.9 g/dL (females)	447 (27.2)	385 (33.2)	62 (12.8)	<0.001
Hb <11.0 g/dL	210 (12.8)	210 (18.1)	0 (0)	<0.001
Thrombocytes (×10⁹/L)	207.0±66.7	202.9±69.2	216.5±59.7	0.010
Thrombocytes <100×10⁹/L	29 (1.8)	29 (2.5)	0 (0)	<0.001

Unless indicated otherwise, data are given as the mean±SD or n (%). eGFR, estimated glomerular filtration rate; Hb, hemoglobin; ICH, intracerebral hemorrhage; NSAIDs, non-steroidal anti-inflammatory drugs.

Results

Clinical Characteristics

Comparisons of clinical characteristics between the J-HBR and non-HBR groups are presented in **Table 1**. Of the 1,643 patients in this study, 1,158 (70.5%) patients met the J-HBR criteria and 827 (50.3%) patients met the ARC-HBR criteria. Patients in the J-HBR group were older, were more likely to be female, had a higher prevalence of multivessel coronary artery disease, CKD, anemia, and atrial fibrillation, had a lower body mass index, were less likely to be smokers, had a lower prevalence of dyslipidemia, and lower eGFR, hemoglobin, and thrombocyte levels. The prevalence of each J-HBR criterion is shown in **Figure 1**. Low body weight (21.4%) and heart failure (19.6%) were the most prevalent major criteria. Moderate CKD and age >75 years were the most prevalent minor criteria.

Clinical Outcomes

During the follow-up period (mean 1,445 days), there were 97 major bleeding events and 181 MACEs. Kaplan-Meier analysis revealed that the cumulative incidence of bleeding events and MACEs was significantly higher in the J-HBR than non-HBR group (bleeding events, 4.8% vs. 0.6% at 1 year, respectively [P<0.001, log-rank test]; MACEs, 14.8% vs. 3.8% at 1 year, respectively [P<0.001, log-rank test]; **Figure 2**). The Gehan-Breslow Wilcoxon test revealed that the cumulative incidence of bleeding events and MACE was significantly higher in the J-HBR than non-HBR group (P<0.001 for both).

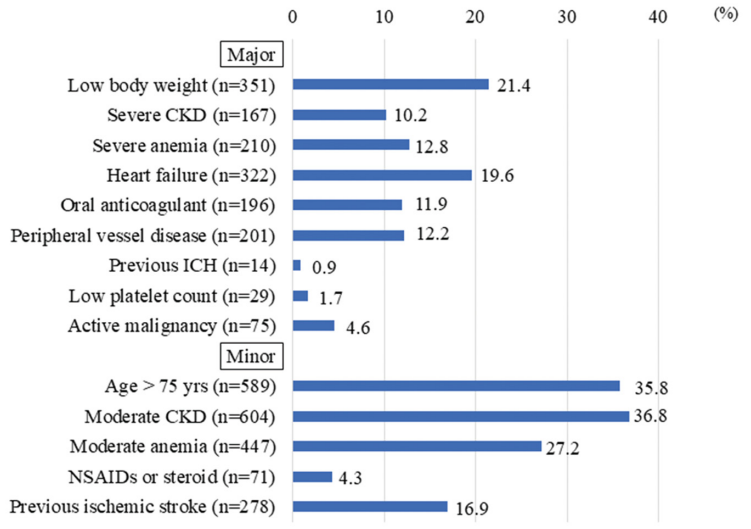
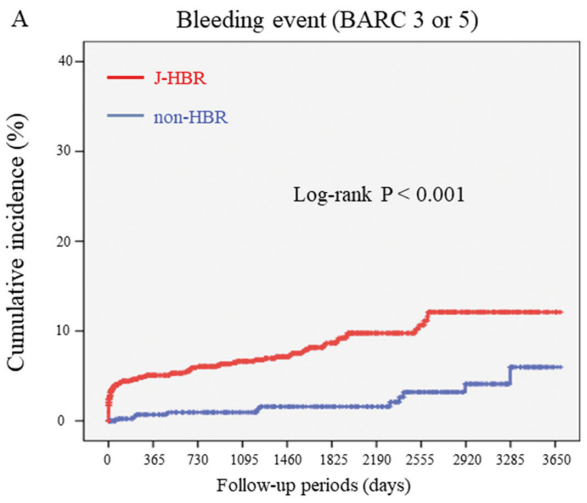
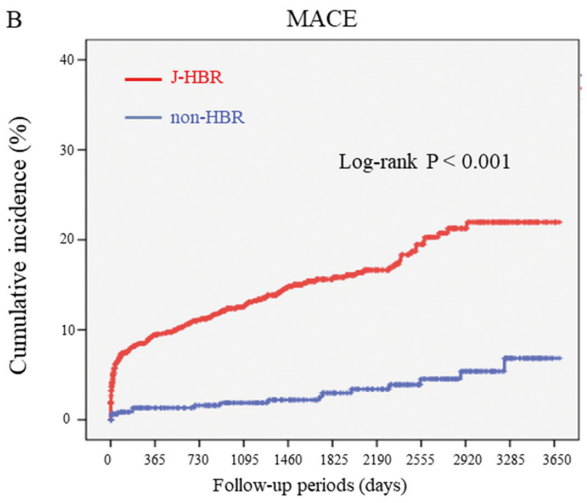


Figure 1. Distribution of major and minor Japanese version of high bleeding risk (J-HBR) criteria. CKD, chronic kidney disease; ICH, intracerebral hemorrhage; NSAIDs, non-steroidal anti-inflammatory drugs.



Interval	0	1 year	3 years	5 years	7 years
J-HBR					
No. at risk	1158	838	605	356	195
Cumulative incidence		5.1%	6.6%	8.7%	10.7%
Non-HBR					
No. at risk	485	402	325	242	151
Cumulative incidence		0.7%	0.9%	1.6%	3.2%

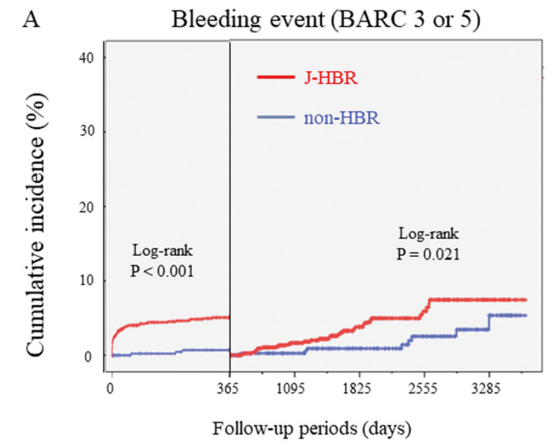


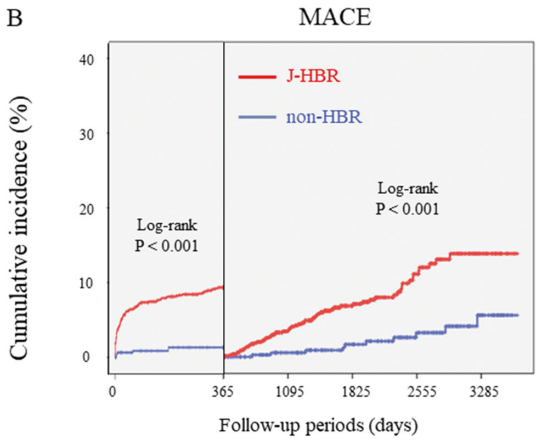
Interval	0	1 year	3 years	5 years	7 years
J-HBR					
No. at risk	1158	851	615	368	205
Cumulative incidence		9.4%	12.5%	15.6%	19.5%
Non-HBR					
No. at risk	485	399	321	241	150
Cumulative incidence		1.3%	1.9%	3.0%	4.5%

Figure 2. Kaplan-Meier cumulative event curves for (**A**) major bleeding events (Bleeding Academic Research Consortium [BARC] 3 or 5) and (**B**) major adverse cardiovascular events (MACE) in patients who met the Japanese version of high bleeding risk (J-HBR) criteria and those who did not (non-HBR).

In the 1-year landmark analysis, the cumulative incidence of bleeding events was significantly higher in the J-HBR than non-HBR group both within 1 year (P<0.001) and beyond 1 year (P=0.021). The cumulative incidence of MACE was also significantly higher in the J-HBR than non-HBR group both within 1 year (P<0.001) and beyond 1 year (P<0.001; **Figure 3**).

With increasing J-HBR scores, there were gradual increases in the risk of bleeding events (0.6%, 2.5%, 4.6%, and 8.4% at 1 year for J-HBR scores of 0–0.5, 1–1.5, 2–2.5, and >3, respectively; P<0.001) and MACE (3.8%, 8.8%, 11.6%, and 27.1% at 1 year for J-HBR scores of 0–0.5, 1–1.5, 2–2.5, and >3, respectively; P<0.001; **Figure 4A**,**B**). The frequency of bleeding events was 2.5% for a J-HBR

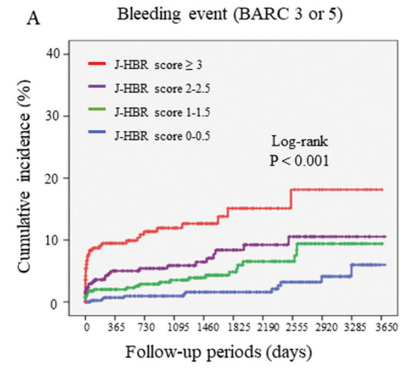


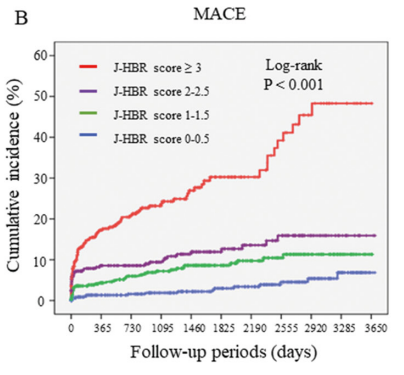


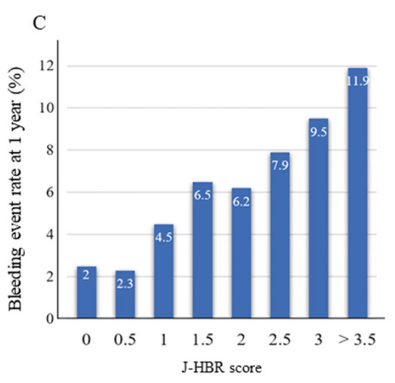
Interval	0	1 year	3 years	5 years	7 years
J-HBR					
No. at risk	1158	838	605	356	195
Cumulative incidence		5.1%	1.6%	3.8%	5.9%
Non-HBR					
No. at risk	485	402	325	242	151
Cumulative incidence		0.7%	0.3%	0.9%	2.5%

Interval	0	1 year	3 years	5 years	7 years
J-HBR					
No. at risk	1158	851	615	368	205
Cumulative incidence		9.4%	3.4%	6.8%	11.1%
Non-HBR					
No. at risk	485	399	321	241	150
Cumulative incidence		1.3%	0.6%	1.7%	2.6%

Figure 3. Landmark analysis within and beyond 1 year. Kaplan-Meier cumulative event curves for (**A**) major bleeding events (Bleeding Academic Research Consortium [BARC] 3 or 5) and (**B**) major adverse cardiovascular events (MACE) in patients who met the Japanese version of high bleeding risk (J-HBR) criteria and those who did not (non-HBR).



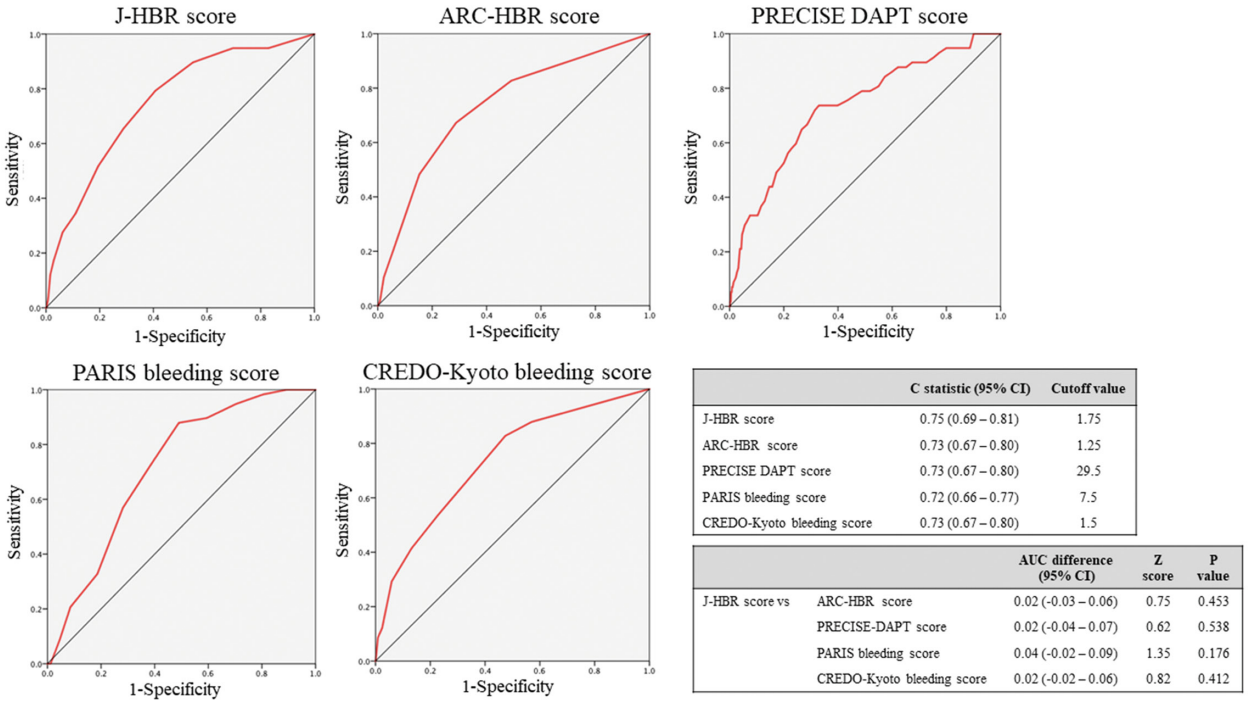




Interval	0	1 year	3 years	5 years	7 years
J-HBR score ≥ 3					
No. at risk	338	218	135	61	27
Cumulative incidence		9.5%	11.9%	15.1%	17.1%
J-HBR score 2-2.5					
No. at risk	354	256	189	119	66
Cumulative incidence		5.0%	5.9%	8.4%	10.5%
J-HBR score 1-1.5					
No. at risk	466	364	281	176	102
Cumulative incidence		2.0%	3.5%	4.8%	6.5%
J-HBR score 0-0.5					
No. at risk	485	402	325	242	151
Cumulative incidence		0.7%	0.9%	1.6%	3.2%

Interval	0	1 year	3 years	5 years	7 years
J-HBR score ≥ 3					
No. at risk	338	226	140	68	33
Cumulative incidence		17.3%	23.2%	30.3%	39.2%
J-HBR score 2-2.5					
No. at risk	354	260	191	119	67
Cumulative incidence		8.6%	9.4%	11.9%	15.9%
J-HBR score 1-1.5					
No. at risk	466	365	284	181	105
Cumulative incidence		4.3%	7.2%	8.6%	10.4%
J-HBR score 0-0.5					
No. at risk	485	399	321	241	150
Cumulative incidence		1.3%	1.9%	3.0%	4.5%

Figure 4. Kaplan-Meier cumulative event curves for (**A**) major bleeding events (Bleeding Academic Research Consortium [BARC] 3 or 5) and (**B**) major adverse cardiovascular events (MACE) stratified by the Japanese version of high bleeding risk (J-HBR). (**C**) Major bleeding event rate at 1 year according to J-HBR scores.



	C statistic (95% CI)	Cutoff value
J-HBR score	0.75 (0.69 – 0.81)	1.75
ARC-HBR score	0.73 (0.67 – 0.80)	1.25
PRECISE DAPT score	0.73 (0.67 – 0.80)	29.5
PARIS bleeding score	0.72 (0.66 – 0.77)	7.5
CREDO-Kyoto bleeding score	0.73 (0.67 – 0.80)	1.5

		AUC difference (95% CI)	Z score	P value
J-HBR score vs	ARC-HBR score	0.02 (-0.03 – 0.06)	0.75	0.453
	PRECISE-DAPT score	0.02 (-0.04 – 0.07)	0.62	0.538
	PARIS bleeding score	0.04 (-0.02 – 0.09)	1.35	0.176
	CREDO-Kyoto bleeding score	0.02 (-0.02 – 0.06)	0.82	0.412

Figure 5. Receiver operating characteristic curve analysis for predicting Bleeding Academic Research Consortium (BARC) 3 or 5 major bleeding events at 1 year for the different bleeding risk scores. ARC-HBR, Academic Research Consortium for High Bleeding Risk; CREDO-Kyoto, Coronary Revascularization Demonstrating Outcome Study in Kyoto; J-HBR, Japanese version of high bleeding risk; PARIS, Patterns of Non-adherence to Anti-platelet Regimen in Stented Patients; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.

Table 2. Sensitivity and Specificity of Each High Bleeding Risk Score for Predicting Bleeding Academic Research Consortium 3 or 5 Bleeding Events at 1 Year

	Sensitivity (%)	Specificity (%)
J-HBR	94.8	31.4
ARC-HBR	82.8	50.9
PRECISE-DAPT score ≥25[A]	75.9	54.1
PARIS bleeding risk score ≥8[A]	87.9	51.0
CREDO-Kyoto bleeding risk score ≥4[A]	41.4	86.1

[A]These cut-off values were considered as high bleeding risk in the original reports.[2–4] ARC-HBR, Academic Research Consortium for high bleeding risk; CREDO-Kyoto, coronary revascularization demonstrating outcome study in Kyoto; J-HBR, Japanese version of high bleeding risk criteria; PARIS, patterns of non-adherence to anti-platelet regimen in stented patients; PRECISE-DAPT, the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy.

score of 0, 2.3% for a score of 0.5, 4.5% for a score of 1, 6.5% for a score of 1.5, 6.2% for a score of 2, 7.9% for a score of 2.5, 9.5% for a score of 3, and 11.9% for a score >3.5 (**Figure 4C**).

Comparison With Contemporary Bleeding Risk Criteria

ROC curve analysis revealed C statistics (95% confidence intervals [CI]) for bleeding events at 1 year of 0.75 (0.69–0.81), 0.73 (0.67–0.80), 0.73 (0.67–0.80), 0.72 (0.66–0.77), and 0.73 (0.67–0.80) for the J-HBR, ARC-HBR, PRECISE-DAPT, PARIS bleeding risk, and CREDO-Kyoto bleeding risk scores, respectively (**Figure 5**). The cut-off values for the J-HBR, ARC-HBR, PRECISE-DAPT, PARIS bleeding risk, and CREDO-Kyoto bleeding risk scores for predicting bleeding events at 1 year were 1.75, 1.25, 29.5, 7.5, and 1.5, respectively (**Figure 5**). The discriminative ability of the J-HBR score was similar to that of the ARC-HBR, PRECISE-DAPT, PARIS bleeding risk, and CREDO-Kyoto bleeding risk scores (**Figure 5**). The sensitivity and specificity of the J-HBR, ARC-HBR, PRECISE-DAPT score ≥25, PARIS bleeding score ≥8, and CREDO-Kyoto bleeding score ≥4, which are considered as high bleeding risk in original reports,[2–4] for predicting bleeding events at 1 year were 94.8% and 31.4%, 81.0% and 52.6%, 75.9% and 54.1%, 87.9% and 51.0%, and 41.1% and 86.2%, respectively (**Table 2**).

Table 3. Cox Proportional Hazard Model of Bleeding Academic Research Consortium 3 or 5 Bleeding Events

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥75 years	1.53 (1.03–2.29)	0.037	1.30 (0.76–2.23)	0.337
Weight <55 kg (males), <50 kg (females)	1.45 (0.92–2.28)	0.114	1.25 (0.71–2.21)	0.448
Moderate CKD (30≤eGFR<60 mL/min/1.73 m^2)	1.77 (0.49–2.19)	0.247	1.76 (0.87–3.53)	0.114
Severe CKD (eGFR <30 mL/min/1.73 m^2)	6.41 (4.15–9.90)	<0.001	5.58 (2.56–12.14)	<0.001
Moderate anemia (11.0≤Hb<12.9 g/dL (males), 11.0≤Hb<11.9 g/dL (females))	1.24 (0.81–1.90)	0.291	1.65 (0.86–3.18)	0.132
Severe anemia (Hb <11.0 g/dL)	3.42 (2.17–5.39)	<0.001	1.56 (0.75–3.25)	0.235
Heart failure	2.99 (1.98–4.51)	<0.001	2.95(1.57–5.55)	0.001
Anticoagulation	1.21 (0.67–2.16)	0.527	1.04 (0.50–2.18)	0.912
Peripheral vessel disease	1.45 (0.83–2.45)	0.178	1.15 (0.57–2.32)	0.697
History of ICH	20.37 (0.05–50.67)	0.560	125.5 (0.02–451.52)	0.977
Thrombocytes <100×10^9/L	0.63 (0.08–4.57)	0.660	0.14 (0.01–163.2)	0.973
Active malignancy	3.64 (1.98–6.67)	<0.001	2.90 (1.35–6.26)	0.007
Previous ischemic stroke	1.38 (0.85–2.23)	0.195	1.40 (0.70–2.80)	0.338
NSAIDs or steroid	2.87 (0.71–11.63)	0.140	2.49 (0.60–10.31)	0.208

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, hazard ratio; ICH, intracerebral hemorrhage; NSAIDs, non-steroidal anti-inflammatory drugs.

Effects of Individual Criteria on Bleeding Events

Univariate and multivariate Cox proportional hazard analyses were conducted for variables in the J-HBR criteria (**Table 3**). Among the criteria, severe CKD (hazard ratio [HR] 5.58; 95% CI 2.56–12.14; P<0.001), heart failure (HR 2.95; 95% CI 1.57–5.55; P=0.001), and active malignancy (HR 2.90; 95% CI 1.35–6.26; P=0.007) were significant variables for predicting bleeding events.

Discussion

The main findings of this study are as follows. First, almost 70% of Japanese coronary artery disease patients undergoing PCI met J-HBR criteria, and these patients were at higher risk of major bleeding events as well as MACE than patients who did not meet the J-HBR criteria. Second, an increase in the number of J-HBR criteria met was associated with an incrementally higher incidence of major bleeding events. Third, the discriminative ability of the J-HBR score for predicting 1-year major bleeding events was comparable to that of contemporary bleeding risk scores, namely the ARC-HBR, PRECISE-DAPT, PARIS bleeding risk, and CREDO-Kyoto bleeding risk scores, whereas the J-HBR score had higher sensitivity and lower specificity than the other 4 bleeding risk scores. Finally, Cox proportional hazard analysis revealed that, among the J-HBR criteria, severe CKD, heart failure, and active malignancy were significant predictors of major bleeding events. This is the first study to show the utility of the scoring approach with the J-HBR criteria for predicting major bleeding events, and to examine the discriminative ability of J-HBR relative to that of other contemporary bleeding risk scores.

The proportion of patients at high bleeding risk has been reported to be higher in the Japanese population than in Western populations. Ueki et al[7] and Cao et al[8] reported that 39.4% and 44.4% of patients met ARC-HBR criteria in Western populations, respectively, whereas Nakamura et al[21] and Natsuaki et al[15] reported that 50.8% and 48.3% of patients met the ARC-HBR criteria in Japanese populations, respectively. Natsuaki et al also reported that 64% of patients from the CREDO-Kyoto Registry Cohort met the J-HBR criteria.[15] In the present study, 50.3% of patients met the ARC-HBR criteria and 70.5% met the J-HBR criteria. The higher proportion of HBR criteria induced higher sensitivity and lower specificity of J-HBR for predicting bleeding events than other HBR criteria. In contrast, the high bleeding risk defined by the CREDO-Kyoto bleeding risk score (≥4) showed low sensitivity and high specificity for predicting bleeding events. This is because of the low cut-off value of the CREDO-Kyoto bleeding risk score in this cohort. A previous study reported that an increasing number of ARC-HBR criteria met was associated with a higher incidence of bleeding events.[7] In the present study, an increasing number of J-HBR criteria met was associated with a higher cumulative incidence of major bleeding events and the J-HBR score was found to have appropriate discriminative ability. Because the J-HBR criteria include more variables than contemporary risk scores, a scoring approach based on the J-HBR criteria may stratify patients with an extremely higher risk of bleeding from those with a high bleeding risk.

In the present study, severe CKD, heart failure, and active malignancy were independent risk factors for predicting major bleeding events with high hazard risks, with severe CKD having the highest HR for major bleeding events. Ueki et al reported that anticoagulation, moderate and severe CKD, moderate and severe anemia, a history of spontaneous non-intracerebral hemorrhage, thrombocytopenia, and active malignancy were the independent predictors of major bleeding among the ARC-HBR criteria in a Western population.[7] Nakamura et al reported that low body weight, heart failure, acute coronary syndrome, severe anemia, severe CKD, and anticoagulation were independent predictors of major bleeding in a Japanese population.[21] In that study, severe CKD, anticoagulation, heart failure, and severe anemia had the strongest relationship with the incidence of major bleeding. Although there is some difference in the hazard risk for individual criteria in the different cohorts, it is certain that the importance of

each component in the prediction of bleeding is differs. Further investigation is required into the management of J-HBR criteria taking into consideration the hazard risk of each component for the accurate estimate of bleeding risk in patients.

Recently, several randomized trials testing shorter DAPT durations have suggested comparable antithrombotic efficacy and benefit to reduce major bleeding incidence.[22] The GLOBSAL LEADERS trial revealed the effectiveness of 1-month DAPT with ticagrelor after PCI with a biolimus A9-eluting stent in a Western population.[23] Among the Japanese population, the STOPDAPT-2 trial showed the safety of 1-month DAPT with clopidogrel in patients with a relatively low bleeding risk after PCI with a cobalt–chromium everolimus-eluting stent.[24] However, the efficacy and safety of short DAPT for patients at high bleeding risk is still controversial, because almost all patients at high bleeding risk are also at high thrombotic risk, including acute coronary syndrome.[25] The present study revealed that patients who met the J-HBR criteria had a higher risk for MACE, as well as major bleeding. The stratification of high bleeding risk may have an important role in decisions regarding the duration of DAPT for patients with high bleeding risk.

Study Limitations

This study has several limitations. First, some J-HBR criteria were not applicable, which may hinder precise estimation of bleeding risk. Second, the study was performed in a single center with a relatively small number of patients. Third, clinical practices, especially DAPT duration and PCI approach site, in the study differ to current practice. Moreover, because the information about DAPT duration was missing, the prognostic impact of DAPT duration is unclear.

Conclusions

The J-HBR criteria successfully identified patients at high bleeding risk, with high sensitivity and low specificity. The bleeding risk was closely related to J-HBR score and its individual components. The discriminative ability of the J-HBR score was comparable to that of contemporary bleeding risk scores.

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IRB Information

The study protocol was approved by the Ethics Committee of Fukushima Medical University (Reference no. 823).

Data Availability

The deidentified participant data will not be shared.

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