

Validation of the Domestic High Bleeding Risk Criteria for Japanese Patients with Acute Myocardial Infarction

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Aims: The Academic Research Consortium (ARC) has proposed international criteria to standardize the definition of high bleeding risk (HBR) in patients undergoing percutaneous coronary intervention (PCI). In this context, Japan has also established its own guidelines, that is, the Japanese version of HBR (J-HBR) criteria. However, the J-HBR criteria have not been fully validated, especially in patients with acute myocardial infarction (MI).

Methods: This bi-center registry included 1079 patients with acute MI undergoing primary PCI in a contemporary setting. Patient bleeding risks were evaluated using the ARC-HBR and J-HBR criteria. The primary endpoint was rates of major bleeding events (Bleeding Academic Research Consortium type 3 or 5) at 1 year.

Results: Of the 1079 patients, 505 (46.8%) and 563 (52.2%) met the ARC-HBR and J-HBR criteria, respectively. Patients who met the J-HBR criteria were found to have a higher rate of major bleeding events at 1 year than those who did not (12.8% vs. 3.3%, $p < 0.001$). When patients were scored and stratified using the J-HBR major and minor criteria, risks of major bleedings were progressively increased with the increase in the number of J-HBR criteria. In the receiver operating characteristic curve analysis, the ARC-HBR and J-HBR significantly predicted subsequent major bleedings after PCI, with ARC-HBR having greater predictive ability than J-HBR.

Conclusions: More than half of the patients with acute MI undergoing primary PCI in Japan met the J-HBR criteria. Although the J-HBR criteria successfully identified patients who were likely to develop major bleeding events after primary PCI, the superiority of J-HBR to ARC-HBR in predicting bleeding outcomes warrants further investigation.

Key words: High bleeding risk, Acute myocardial infarction, Percutaneous coronary intervention

Introduction

Owing to advances in medical therapy and early reperfusion strategies, especially with primary percutaneous coronary intervention (PCI), the prognosis of acute myocardial infarction (MI) has significantly improved during the past decades¹. While rates of ischemic events including recurrent MI and stent thrombosis have declined, a risk of major

bleeding has been increased in patients with acute MI undergoing PCI^{2, 3}. The international criteria by the Academic Research Consortium for high bleeding risk (ARC-HBR) have been proposed to define HBR patients undergoing PCI⁴. However, East Asian patients including Japanese reportedly have different risk profiles for bleeding events as compared with those in Western countries⁵, which probably prevents the direct application of ARC-HBR to Japanese

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populations. In this context, the recent guidelines by the Japanese Circulation Society proposed the Japanese version of the HBR (J-HBR) criteria, in which Japanese-specific factors associated with HBR such as low body weight, frailty, heart failure, and peripheral artery disease were added to the original ARC-HBR criteria⁶. The ARC-HBR has been well validated in several previous studies⁷⁻¹⁰, but the applicability of J-HBR has been tested in only one large-scale all-comers PCI registry in Japan¹¹. In addition, a recent report indicated that the performance of ARC-HBR to discriminate bleeding risks was lower in patients with acute coronary syndrome than those with chronic coronary syndrome¹². In this present study, we aimed to examine the validity of the J-HBR, the domestically modified ARC-HBR, in Japanese patients with acute MI undergoing primary PCI.

Methods

Study Design and Population

This was a retrospective, bi-center, observational study at two tertiary referral hospitals, namely, Chiba University Hospital and Eastern Chiba Medical Center. Between January 2012 and March 2020, 1128 patients with acute MI underwent primary PCI. Study details were described in previous reports¹³⁻¹⁶. Briefly, acute MI, including both ST-segment elevation and non-ST-segment elevation MI, was defined based on the fourth universal definition of MI¹⁷. All PCI procedures were done according to local standard practice and guideline recommendations, including dual antiplatelet therapy, intracoronary imaging, and contemporary drug-eluting stents^{1, 6, 18-21}. Duplicated patients ($n=26$) and those with missing information for calculating the ARC-HBR and J-HBR ($n=23$) were excluded. Thus, in total, 1079 patients with acute MI undergoing primary PCI were included in this present study. Informed consent was obtained in the form of opt-out. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of Chiba University Hospital and Eastern Chiba Medical Center.

Definitions of ARC-HBR and J-HBR

Supplementary Table 1 lists the definitions of ARC-HBR and J-HBR criteria. The ARC-HBR and J-HBR have major and minor criteria, and a patient is defined as having HBR when one major criterion or two minor criteria were met^{4, 6}. Patients with HBR were estimated to have a risk of major bleeding defined as Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding of $\geq 4\%$ or intracranial

hemorrhage of $\geq 1\%$ at 1 year after PCI^{4, 22}. The J-HBR included low body weight, frailty, heart failure, and peripheral artery disease as major criteria, in addition to the original ARC-HBR. In this present study, some ARC-HBR and J-HBR criteria were modified, as shown in **Supplementary Table 1**^{11, 23}. Scores were calculated by allocating one point for each major criterion and 0.5 points for each minor criterion (i.e., HBR was defined as ≥ 1 point)²³. Patients were divided into two groups according to the presence or absence of J-HBR.

Endpoint and Statistical Analysis

Follow-up data were obtained from medical records at Chiba University Hospital and Eastern Chiba Medical Center. The primary endpoint of this present study was the rates of major bleeding (BARC type 3 or 5) events at 1 year²². Major bleedings were further divided into gastrointestinal, intracranial, access site-related, and other bleeding events. The prevalence of J-HBR, impact of J-HBR and each component on bleeding outcomes, and diagnostic ability of J-HBR as compared with ARC-HBR were evaluated.

Statistical analysis was performed using JMP Pro 15.0.0 (SAS Institute, Cary, USA). All data are expressed as mean \pm standard deviation or frequency (%). Continuous variables were compared with Student's *t*-test, while categorical variables were assessed using Fisher's exact test. The Kaplan–Meier analysis was used to calculate the time to major bleeding events and to estimate major bleeding event rates at 1 year, and the log-rank test was applied for between-group comparisons. The receiver operating characteristics (ROC) curve analysis was performed based on bleeding events. The area under the curve (AUC) of the ROC curve was compared using the Delong method. A *p*-value <0.05 was considered statistically significant.

Results

Of the 1079 patients with acute MI undergoing primary PCI, 505 (46.8%) and 563 (52.2%) met the ARC-HBR and J-HBR, respectively. **Table 1** lists the baseline characteristics. Patients who met the J-HBR were older and were likely to have more cardiovascular risk factors and comorbidities; however, they were less likely to receive medications for secondary prevention such as angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β -blocker, and statin (**Table 1**). In terms of proton pump inhibitor, the prescription rate was not significantly different between the two groups in patients who recovered and

Table 1. Baseline characteristics

Variable	J-HBR (n=563)	No J-HBR (n=516)	p value
Age (years)	72.9 ± 10.8	61.3 ± 10.5	<0.001
Men	376 (66.8%)	451 (87.4%)	<0.001
Body mass index (kg/m ²)	22.9 ± 3.6	25.6 ± 3.3	<0.001
Hypertension	404 (71.8%)	328 (63.7%)	0.005
Diabetes	208 (36.9%)	198 (38.4%)	0.63
Dyslipidemia	310 (55.1%)	359 (69.7%)	<0.001
Current smoker	104 (18.5%)	255 (49.5%)	<0.001
Prior myocardial infarction	45 (8.0%)	27 (5.2%)	0.07
Prior heart failure	29 (5.2%)	0 (0%)	<0.001
Atrial fibrillation	67 (11.9%)	4 (0.8%)	<0.001
Peripheral artery disease	29 (5.2%)	0 (0%)	<0.001
Hemodialysis	39 (6.9%)	0 (0%)	<0.001
eGFR (ml/min/1.73 m ²)	53.4 ± 24.3	74.2 ± 19.4	<0.001
Hemoglobin (g/dl)	12.6 ± 2.2	14.9 ± 1.5	<0.001
Platelet (10 ⁴ /μl)	21.4 ± 8.5	23.2 ± 6.4	<0.001
LVEF (%)	45.5 ± 13.8	49.0 ± 12.5	<0.001
Active malignancy	59 (10.5%)	0 (0%)	<0.001
Prior intracranial hemorrhage	14 (2.5%)	0 (0%)	<0.001
Prior ischemic stroke	70 (12.4%)	10 (1.9%)	<0.001
Prior GI bleeding	19 (3.4%)	5 (1.0%)	0.007
Liver cirrhosis	9 (1.6%)	0 (0%)	0.004
Clinical presentation			0.76
STEMI	378 (67.1%)	351 (68.0%)	
NSTEMI	185 (32.9%)	165 (32.0%)	
Killip class on admission			<0.001
I	337 (59.9%)	404 (78.3%)	
II	64 (11.4%)	29 (5.6%)	
III	47 (8.3%)	15 (2.9%)	
IV	115 (20.4%)	68 (13.2%)	
Mechanical circulatory support	83 (14.7%)	45 (8.7%)	0.003
IABP	69 (12.3%)	41 (7.9%)	0.02
ECMO	31 (5.5%)	24 (4.7%)	0.58
Impella	3 (0.5%)	0 (0%)	0.25
Arterial access site			<0.001
Radial	458 (81.3%)	471 (91.3%)	
Brachial	18 (3.2%)	7 (1.4%)	
Femoral	87 (15.5%)	38 (7.4%)	
Medication at discharge			
Antiplatelet therapy			
Aspirin	489 (86.9%)	513 (99.4%)	<0.001
Clopidogrel	287 (51.0%)	197 (38.2%)	<0.001
Prasugrel	221 (39.3%)	307 (59.5%)	<0.001
Oral anticoagulation	124 (22.0%)	0 (0%)	<0.001
ACE-I/ARB	405 (71.9%)	441 (85.5%)	<0.001
β-blocker	356 (63.2%)	400 (77.5%)	<0.001
Statin	462 (82.1%)	475 (92.1%)	<0.001
NSAIDs/steroids	53 (9.4%)	15 (2.9%)	<0.001
PPI	511 (90.8%)	490 (95.0%)	0.009
H2-blocker	17 (3.0%)	7 (1.4%)	0.10

Mechanical circulatory support includes intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and percutaneous transvalvular microaxial flow pump (Impella; Abiomed, Danvers, USA).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; J-HBR, the Japanese version of the high bleeding risk; LVEF, left ventricular ejection fraction; NSAIDs, non-steroidal anti-inflammatory drugs; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; PPI, proton pump inhibitor.

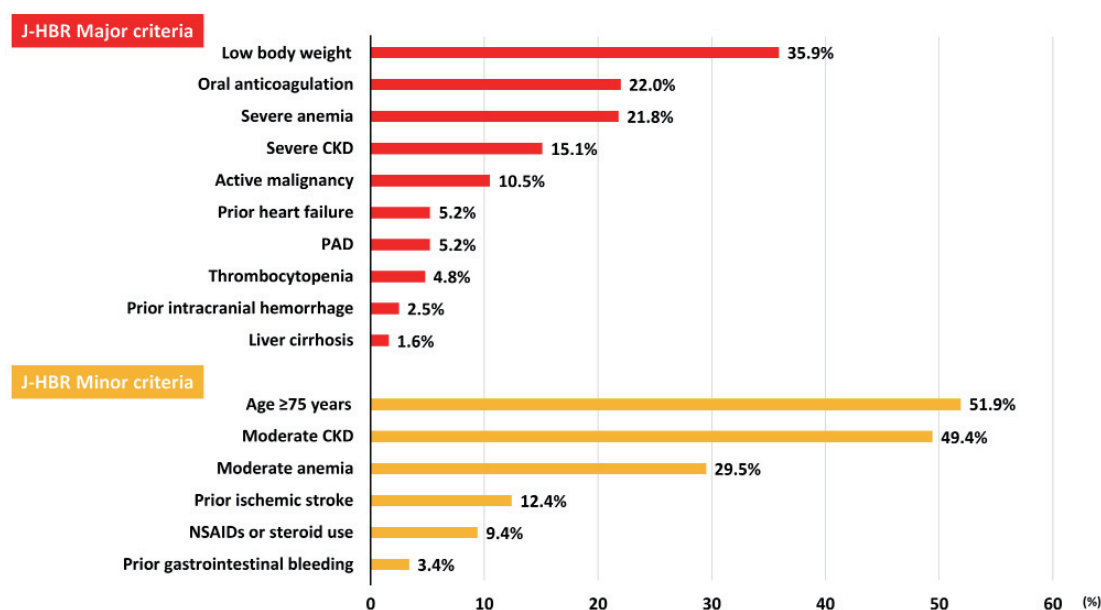


Fig. 1. Prevalence of major and minor criteria in the J-HBR

CKD, chronic kidney disease; J-HBR, the Japanese version of the high bleeding risk; PAD, peripheral artery disease.

Table 2. Major bleeding events

Variable	All (n=1079)	J-HBR (n=563)	No J-HBR (n=516)	p value
Major bleeding events	91 (8.4%)	71 (12.6%)	20 (3.9%)	<0.001
BARC 3	83 (7.7%)	64 (11.4%)	19 (3.7%)	<0.001
BARC 5	8 (0.7%)	7 (1.2%)	1 (0.2%)	0.07
Gastrointestinal bleeding	30 (2.8%)	26 (4.6%)	4 (0.8%)	<0.001
Access site-related bleeding	27 (2.5%)	19 (3.4%)	8 (1.6%)	0.08
Intracranial bleeding	11 (1.0%)	10 (1.8%)	1 (0.2%)	0.01
Others	23 (2.1%)	16 (2.8%)	7 (1.4%)	0.14

BARC, Bleeding Academic Research Consortium; J-HBR, Japanese version of the high bleeding risk.

were discharged (**Supplementary Table 2**). **Fig. 1** displays the prevalence of criteria included in the J-HBR. The common major criteria were low body weight, oral anticoagulation, and severe anemia (**Fig. 1**). In-hospital mortality was noted to be significantly higher in patients with J-HBR than those without (11.6% vs. 4.7%, $p < 0.001$). During the median follow-up period of 418 days, 91 (8.4%) patients experienced major bleeding events, in which gastrointestinal bleedings were most frequently observed (**Table 2**). **Fig. 2** shows that patients with J-HBR had a significantly increased risk of major bleedings than those without. The cumulative incidence of major bleeding events at 1 year was stratified by the J-HBR criteria in **Fig. 3**, in which oral anticoagulation, severe anemia, moderate and severe chronic kidney disease (CKD), active malignancy,

thrombocytopenia, and prior ischemic stroke were identified as significant factors associated with major bleedings. When patients were scored and stratified by J-HBR major and minor criteria, risks of major bleeding events were progressively increased with the increase in the number of J-HBR criteria (**Fig. 4**). In the ROC curve analysis, the ARC-HBR (AUC 0.73, $p < 0.001$) and J-HBR (AUC 0.71, $p < 0.001$) were able to significantly predict subsequent major bleedings after PCI, with ARC-HBR having greater diagnostic ability than J-HBR ($p = 0.004$). **Supplementary Table 3** shows sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ARC-HBR and J-HBR for predicting major bleeding events.

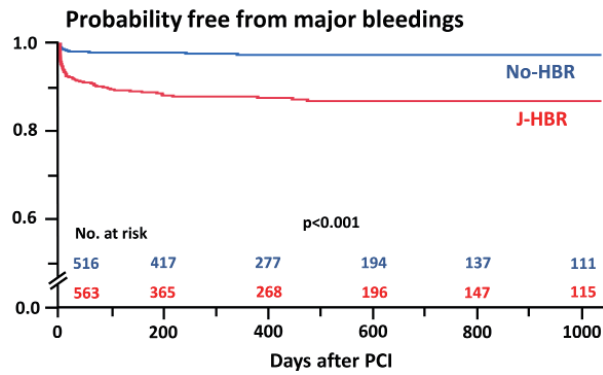


Fig. 2. Probability free from major bleeding events in patients with and without J-HBR
J-HBR, the Japanese version of the high bleeding risk; PCI, percutaneous coronary intervention.

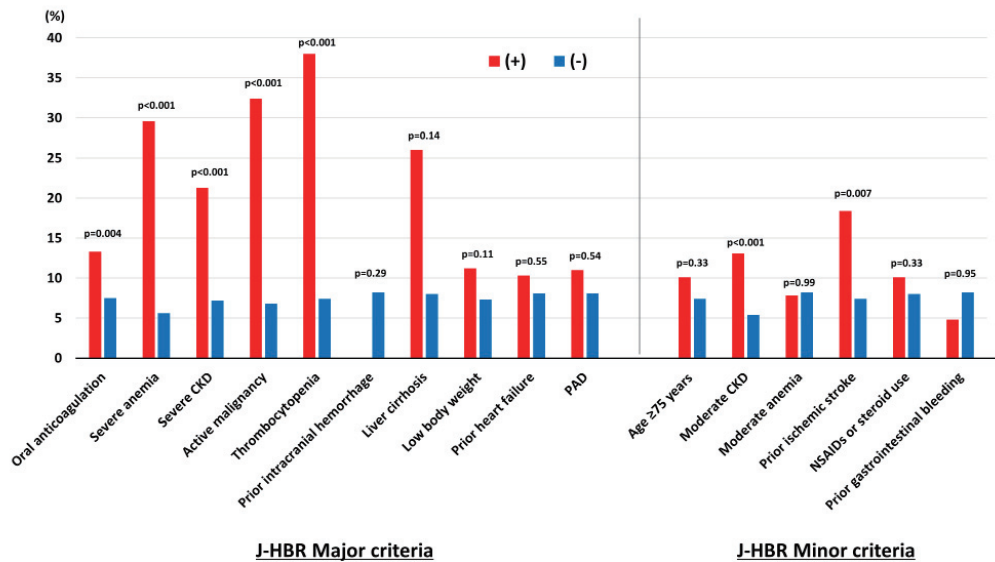


Fig. 3. Cumulative incidence of major bleedings at 1 year by each J-HBR criterion
CKD, chronic kidney disease; J-HBR, the Japanese version of the high bleeding risk; PAD, peripheral artery disease.

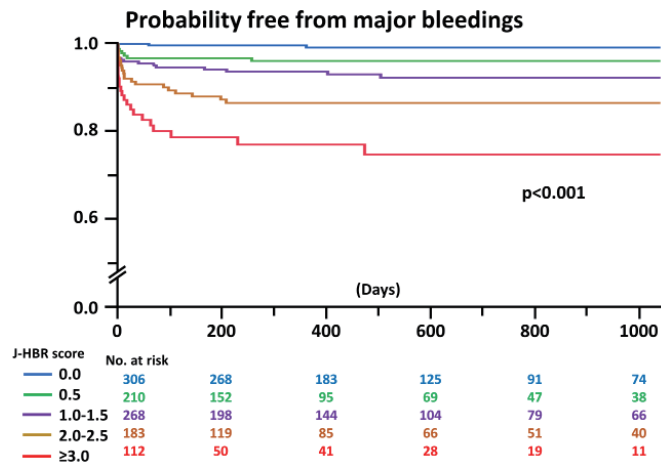


Fig. 4. Probability free from major bleeding events by J-HBR score categories
J-HBR, the Japanese version of the high bleeding risk; PCI, percutaneous coronary intervention.

Discussion

This present study demonstrated the applicability of J-HBR, the domestically modified ARC-HBR, in patients with acute MI undergoing primary PCI in Japan. More than half of patients with acute MI were defined as having J-HBR, and those with J-HBR had a higher rate of major bleeding events at 1 year than those without. Although the J-HBR criteria were useful to identify patients at HBR after PCI for acute MI, whether the J-HBR criteria were clinically superior to the ARC-HBR criteria remains unclear.

ARC-HBR and J-HBR

Both ischemic and bleeding events have a similar prognostic impact on subsequent mortality after PCI⁴. However, the definitions of bleeding outcomes in previous clinical studies have varied widely⁷, and in 2019, the ARC proposed a set of HBR criteria to globally standardize the definitions⁴. In 2020, the J-HBR criteria were domestically proposed in the Japanese guidelines to better discriminate patient bleeding risks, because of different bleeding risk profiles between patients in Western countries and East Asia^{5, 11}. While the ARC-HBR has been well investigated inside and outside of Japan⁷, the J-HBR was not fully validated.

According to previous reports in Japan, the rate of HBR by the ARC criteria ranged from 40% to 50%⁷, which is in line with our results (i.e., 46.8%). In the CREDO-Kyoto Registry Cohort-3, which is the only previous large-scale study to evaluate the J-HBR criteria, patients having J-HBR were found in 64.1%¹¹. Based on the definition that the J-HBR includes additional components to the ARC-HBR criteria (e.g., low body weight, frailty, heart failure, and peripheral artery disease), the number of patients with J-HBR is inevitably greater than those with ARC-HBR. While the J-HBR criteria were significantly associated with a risk of major bleeding events after PCI in the CREDO-Kyoto Registry Cohort-3, the prognostic impact of J-HBR in patients with acute MI remained unclear. In this present study, patients with J-HBR had a three- to four-fold higher risk of major bleedings at 1 year than those without (12.8% vs. 3.3%, $p < 0.001$). Given that the original ARC-HBR was arbitrarily defined as a risk of major bleeding of $\geq 4\%$ at 1 year after PCI⁴, it is deemed conceivable that the J-HBR criteria successfully identified patients at HBR. In addition, when the HBR criteria were considered as a scoring system with allocating one point for major criterion and 0.5 points for minor criterion, the J-HBR further stratified patient bleeding risks. Although the ROC curve

analyses indicated that the predictivity of ARC-HBR was slightly better than that of J-HBR, the AUCs (i.e., 0.71–0.73) in this present study were numerically better than that in previous reports (i.e., 0.68–0.69)⁷. Taking into account that the sensitivity of J-HBR criteria was numerically higher than that of ARC-HBR criteria (78.0% vs. 76.9%), the J-HBR might be a better screening tool to identify HBR patients. Further investigations are needed to evaluate the diagnostic ability of ARC-HBR and J-HBR and whether individualized therapeutic strategies under J-HBR guidance are superior to no risk score guidance.

Impact of Component of J-HBR on Bleedings

In the J-HBR criteria, oral anticoagulation, severe anemia, moderate and severe CKD, active malignancy, thrombocytopenia, and prior ischemic stroke were associated with an increased risk of major bleeding events, all of which were included in the original ARC-HBR major or minor criteria. Although 35.9% of patients were found to be of low body weight (i.e., < 55 kg for men and < 50 kg for women) in this present study, this major criterion in the J-HBR was not significantly related to major bleedings after primary PCI. The prevalence of low body weight in this present study was higher as compared with the previous CREDO-Kyoto Registry Cohort-3 (i.e., 22.8%)¹¹, suggesting that the prognostic impact of the HBR criteria may differ in different populations¹². Interestingly, the PARIS bleeding risk score, a risk stratifying system derived from a large PCI cohort from Western countries, includes low body mass index as a criterion to predict bleeding outcomes²⁴, while the Japanese CREDO-Kyoto bleeding risk score does not²⁵. The prevalence of other Japanese-specific factors associated with HBR including heart failure and peripheral artery disease was low in this present study. Thus, larger sample size studies may elucidate the prognostic impact of these factors.

Oral anticoagulation is a significant factor in determining antithrombotic regimens in the guidelines and was shown to have an impact on bleeding events in this present study. Beyond oral anticoagulation, severe anemia and CKD, active malignancy, thrombocytopenia, and prior ischemic stroke were identified as significant factors associated with major bleedings. Although gastrointestinal bleeds were the most common, accounting for more than 30%, prior gastrointestinal bleeding was not associated with an increased risk of major bleeding events. Given the high risks of having severe anemia and CKD, active malignancy, thrombocytopenia, and prior ischemic

stroke for major bleedings after PCI for acute MI, patients with those factors should be followed up with a caution on bleeding events. In addition, thrombotic risks must be balanced against bleeding complications as the guidelines recommend⁶⁾. Risk stratification using risk-predicting models such as the PARIS and CREDO-Kyoto scores may be deemed useful¹⁵⁾.

Study Limitations

This study has several limitations. For one, this was a retrospective study with a moderate sample size. Because some J-HBR criteria were modified in this present study (**Supplementary Table 1**), HBR was underestimated in the present study as well as many previous studies validating the ARC-HBR criteria^{7, 11)}. In particular, J-HBR has the frailty criterion in addition to low body weight, which was not included in the present analysis. Given that clinically assessed frailty was reportedly associated with an increased risk of bleeding outcomes in patients with acute MI^{26, 27)}, the additional information on frailty may improve the diagnostic ability of J-HBR. All medical therapies were left to treating physicians due to the retrospective nature. Thus, therapeutic strategies including antithrombotic regimens may have affected the results. Furthermore, data on medications including antithrombotic therapy during follow-up period were not available.

Conclusions

More than half of the patients with acute MI undergoing PCI met the J-HBR. The J-HBR criteria have successfully identified patients at HBR after primary PCI.

Disclosures

None

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Supplementary Table 1. High bleeding risk definitions

J-HBR criteria	Criteria in the present study	Category	Comments
Age ≥ 75 years	Age ≥ 75 years	Minor	Identical
Anticipated use of long-term OAC	OAC use at discharge	Major	Modified
Severe CKD (eGFR < 30 ml/min)	eGFR < 30 ml/min	Major	Identical
Moderate CKD (eGFR 30-59 ml/min)	eGFR 30- < 60 ml/min	Minor	Identical
Hemoglobin < 11 g/dl	Hemoglobin < 11 g/dl	Major	Identical
Hemoglobin 11-12.9 g/dl for men	Hemoglobin 11-12.9 g/dl for men	Minor	Identical
Hemoglobin 11-11.9 g/dl for women	Hemoglobin 11-11.9 g/dl for women		
Bleedings requiring hospitalization or transfusion in the past 6 months	N/A	Major	N/A
Bleedings requiring hospitalization or transfusion in the past 6 months not meeting the major criterion	Prior gastrointestinal bleeding at any time	Minor	Modified
Thrombocytopenia (Plt < 100 × 10 ⁹ /l)	Thrombocytopenia (Plt < 100 × 10 ⁹ /l)	Major	Identical
Chronic bleeding diathesis	N/A	Major	N/A
LC with portal hypertension	LC	Major	Modified
Long-term use of NSAIDs or steroids	NSAIDs or steroids use at discharge	Minor	Modified
Active malignancy (excluding non-melanoma skin cancer) within the past 12 months	Active malignancy at baseline	Major	Modified
Previous spontaneous intracranial hemorrhage (at any time); Traumatic intracranial hemorrhage within the past 12 months; Brain arteriovenous malformation; Moderate or severe ischemic stroke within the past 6 months	History of intracranial hemorrhage at any time	Major	Modified
Any ischemic stroke at any time not meeting the major criterion	History of ischemic stroke without intracranial hemorrhage at any time	Minor	Identical
Non-deferrable major surgery on DAPT	N/A	Major	N/A
Recent major surgery or trauma within 30 days before PCI	N/A	Major	N/A
Low body weight (< 55 kg for men and < 50 kg for women) or frailty	Low body weight (< 55 kg for men and < 50 kg for women)	Major	Modified
Peripheral vascular disease	Peripheral artery disease	Major	Modified
Heart failure	Heart failure	Major	Identical

CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; J-HBR, Japanese version of the high bleeding risk; LC, liver cirrhosis; NSAIDs, non-steroidal anti-inflammatory drugs; N/A, not applicable; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; Plt, platelet count.

Supplementary Table 2. Medication at discharge in patients who survived to discharge

Variable	J-HBR (<i>n</i> =498)	No J-HBR (<i>n</i> =492)	<i>p</i> value
Antiplatelet therapy			
Aspirin	441 (88.6%)	491 (99.8%)	<0.001
Clopidogrel	260 (52.2%)	187 (38.0%)	<0.001
Prasugrel	199 (40.0%)	295 (60.0%)	<0.001
Oral anticoagulation	112 (22.5%)	0 (0%)	<0.001
ACE-I/ARB	391 (78.5%)	434 (88.2%)	<0.001
β -blocker	336 (67.5%)	389 (79.1%)	<0.001
Statin	435 (87.4%)	464 (94.3%)	<0.001
NSAIDs/steroids	49 (9.8%)	15 (3.1%)	<0.001
PPI	468 (94.0%)	473 (96.1%)	0.14
H2-blocker	14 (2.8%)	7 (1.4%)	0.18

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; J-HBR, the Japanese version of the high bleeding risk; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplementary Table 3. Diagnostic ability of ARC-HBR and J-HBR for major bleeding events

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
ARC-HBR	76.9%	56.0%	13.9%	96.3%	57.7%
J-HBR	78.0%	50.2%	12.6%	96.1%	52.5%

ARC-HBR, Academic Research Consortium for high bleeding risk; J-HBR, Japanese version of the high bleeding risk; NPV, negative predictive value; PPV, positive predictive value.