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# Post-discharge major bleeding/all-cause death in acute coronary syndrome: academic research consortium criteria versus Japan-specific criteria

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## Abstract

**Background** The differentiation of the Academic Research Consortium high bleeding risk (HBR) (ARC-HBR) criteria and those modified for Japanese patients (J-HBR) for predicting events following discharge in patients with acute coronary syndrome (ACS) has yet to be clarified. In this study**,** we compared the ARC-HBR and J-HBR criteria for predicting post-discharge bleeding and associated events in patients with ACS.

**Methods** We retrospectively analyzed data from 889 patients with ACS discharged alive at two tertiary hospitals in Japan between August 2009 and July 2018. We identified patients with HBR using both sets of criteria. We compared the incidence of major bleeding/all-cause death within 2 years following discharge and performance metrics between each set of criteria, and explored the efficacy of combining both sets of criteria to stratify risk levels for the prediction of clinical events.

**Results** Eighty patients experienced major bleeding/all-cause death. In the ARC-HBR and J-HBR criteria, 51% and 65% of patients were categorized as HBR, respectively. Both sets of criteria effectively identified patients at a high risk of major bleeding/all-cause death. The ARC-HBR demonstrated a significantly higher area under the curve (AUC) for major bleeding and all-cause death combined (AUC [95% confidence interval]: 0.67 [0.64–0.69]) than that of the J-HBR (0.63 [0.60–0.66], $P=0.015$). In each component, while the AUC for major bleeding was comparable between the two sets of criteria (0.61 [0.57–0.64] vs. 0.61 [0.57–0.63], $P=0.95$), the ARC-HBR criteria showed a significantly higher AUC for all-cause death than the J-HBR criteria (0.67 [0.64–0.70] vs. 0.61 [0.59–0.64], $P<0.001$).

The combined use of both sets of criteria effectively stratified the risk for major bleeding/all-cause death (hazard ratio [95% confident interval]: 5.81 [2.79–12.07] in those positive for both sets of criteria, compared to those negative in both sets of criteria).

**Conclusions** The ARC-HBR criteria demonstrated a greater discriminative capability for predicting major bleeding/all-cause mortality than the J-HBR criteria. For major bleeding alone, the discriminative ability of both sets of criteria was comparable.

**Keywords** ARC-HBR, High bleeding risk, Acute myocardial infarction

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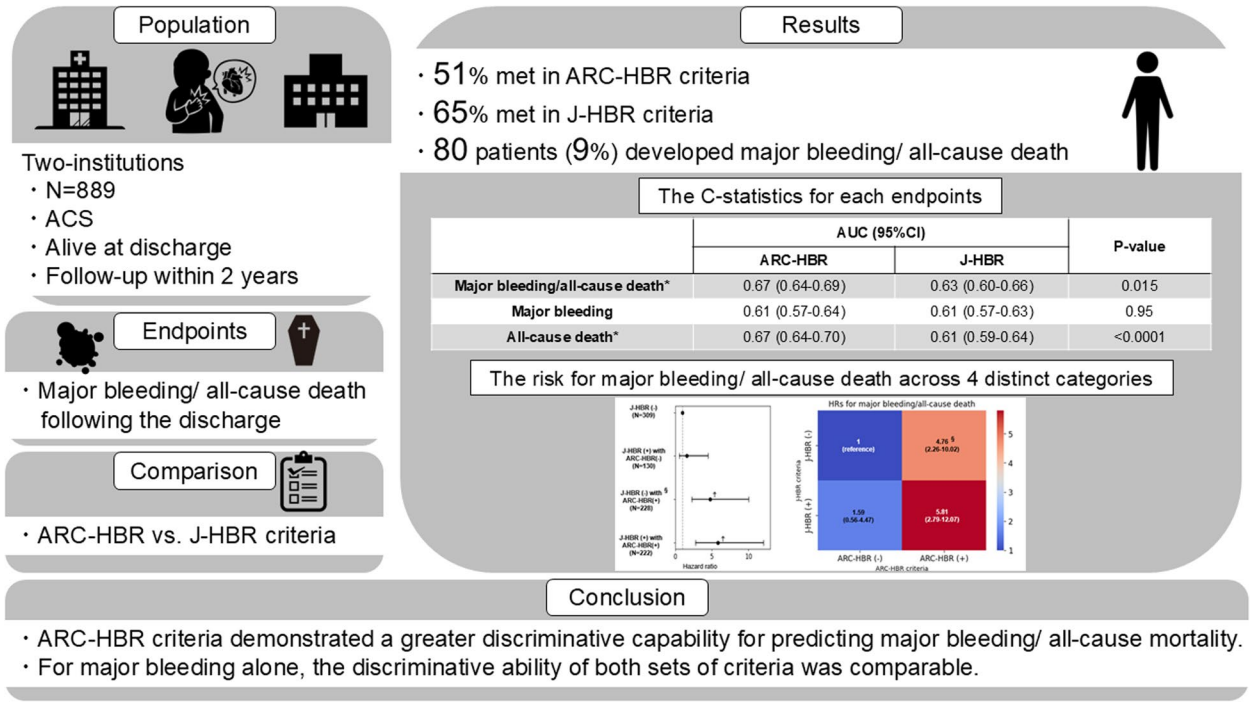
**Graphical Abstract**

ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium-High Bleeding Risk; AUC, area under the curve; CI, confidence interval; HR, hazard ratio; J-HBR, Japanese-High Bleeding Risk.

*: statistical significance.

§: patients with the ARC-HBR criteria but without the J-HBR unique components.




| | AUC (95%CI) | | P-value |
|---|---|---|---|
| | ARC-HBR | J-HBR | |
| Major bleeding/all-cause death* | 0.67 (0.64-0.69) | 0.63 (0.60-0.66) | 0.015 |
| Major bleeding | 0.61 (0.57-0.64) | 0.61 (0.57-0.63) | 0.95 |
| All-cause death* | 0.67 (0.64-0.70) | 0.61 (0.59-0.64) | <0.0001 |

## Introduction

Bleeding complications represent a significant clinical challenge among patients who have undergone percutaneous coronary intervention (PCI) [1–3]. The incidence of ischemic events and cardiovascular mortality in individuals with acute myocardial infarction (AMI) has diminished progressively in recent decades, attributable to the evolution of therapeutic apparatus and antithrombotic treatment [4]. Nevertheless, the incidence of bleeding events has been steadily escalating [4].

To identify patients with high bleeding risk (HBR), the Academic Research Consortium (ARC-HBR) developed standardized criteria, which were later adapted into the Japanese-specific J-HBR definition [1, 5]. While both sets of criteria have been validated in the general PCI population, evidence specifically addressing their prognostic utility in acute coronary syndrome (ACS) cohorts, particularly with respect to post-discharge bleeding, is limited [6–8]. Notably, most prior studies have concentrated on in-hospital bleeding, which typically results from procedural complications and the initiation of dual antiplatelet therapy (DAPT) [2, 8, 9]. However, bleeding events occurring after discharge remain clinically relevant, as they may adversely impact long-term outcomes [10].

In this study, we aimed to directly compare the ARC-HBR and J-HBR criteria in predicting post-discharge bleeding events and related clinical outcomes in a contemporary ACS cohort.

## Methods

### Study population

This two-institutional historical cohort study utilized a database derived from our previous investigations [11, 12]. The database was originally established to examine the population-based incidence of ACS within Izumo

City, located in Shimane Prefecture, a mid-sized rural city in southwestern Japan, from 2009 to 2018.

The criteria for inclusion in the original cohort were: 1) patients diagnosed with ACS based on the universal definition [13] at either of the two institutions (Shimane Prefectural Central Hospital or Shimane University Hospital), encompassing all facilities within the area capable of performing PCI, and 2) residency within Izumo City. Despite the rising trend in the proportion of the elderly population within this city over the study period, the incidence rates of ACS remained stable [11].

This manuscript followed the tenets of the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. The Institutional Review Boards of Shimane Prefectural Central Hospital (Churin R20-63) and Shimane University Hospital (20,240,121–1) approved this study.

### Study design

The aim of our study was to compare both sets of HBR criteria (ARC-HBR and J-HBR) for predicting post-discharge bleeding and associated clinical events in patients with ACS. Our primary endpoint was the incidence of major bleeding or all-cause death within 2 years post-discharge. We selected this composite endpoint because all-cause death represents a competing risk for bleeding events, and identifying patients at high risk for either outcome has significant clinical utility in guiding treatment decisions. The inclusion criteria were patients in the database who: 1) were diagnosed from August 2009 to July 2018, 2) had information necessary for determining the primary endpoint, and 3) had data required for calculating HBR scores.

As the secondary endpoint, we explored the potential effectiveness of combining both sets of HBR criteria to stratify risk levels for the prediction of clinical events.

### Clinical practice and clinical events

As previously outlined [12], patients receiving bare metal stent implantation underwent DAPT, combining acetylsalicylic acid with a P2Y12 inhibitor (typically clopidogrel or prasugrel) for a minimum of 1 month. Those with drug-eluting stents were prescribed DAPT for at least 1 year, with the duration adjusted at the attending cardiologist's discretion. Upon completing DAPT, patients typically transitioned to lifelong acetylsalicylic acid monotherapy.

Bleeding events were classified as major if they met a severity level of ≥ 3, according to the Bleeding Academic Research Consortium criteria [14], as previously reported [12]. Each event was identified through a review of medical records or by inquiring with the primary physicians.

### HBR criteria

Patients were classified as ARC-HBR positive if they fulfilled at least one major criterion or two minor criteria of the ARC-HBR criteria (Supplementary Table 1) [1]. The major criteria included: 1) use of oral anticoagulants; 2) severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$); 3) severe anemia (hemoglobin < 11 g/dL); 4) low platelet count (< 100,000 /μL); 5) history of major bleeding (spontaneous bleeding necessitating hospitalization or transfusion within the past 6 months or recurrent episodes); 6) liver cirrhosis with portal hypertension; 7) active cancer within the past 1 year; 8) history of intracranial hemorrhage, recent stroke, or arteriovenous malformation; 9) planned major surgery under the DAPT; and 10) recent major trauma or surgery. The minor criteria comprised: 1) age ≥ 75 years, 2) moderate chronic kidney disease (30–60 mL/min/1.73 $m^2$), 3) moderate anemia (hemoglobin < 13 g/dL for males and < 12 g/dL for females), 4) history of minor bleeding (spontaneous bleeding necessitating hospitalization or transfusion within the past 6–12 months), 5) use of nonsteroidal anti-inflammatory drugs or steroids, and 6) minor stroke history. Although chronic bleeding diathesis is listed among the major criteria, it was not included in our analysis due to the challenges in objectively assessing it through a review of medical records.

Patients were classified as J-HBR positive if they met at least one of the following specific major criteria unique to the J-HBR criteria [5] in addition to those of the ARC-HBR criteria: 1) frailty, defined as a body weight < 55 kg for males and < 50 kg for females; 2) heart failure; or 3) peripheral vascular disease, or if they met two of the shared minor criteria with the ARC-HBR criteria.

In the present study, iatrogenic bleeding events, such as puncture site bleedings that occurred during the index hospitalization, were excluded from the major bleeding history since they were not spontaneous and generally exhibited reversibility.

### Statistical analysis

Variables adhering to a normal distribution were depicted as the mean ± standard deviation, whereas those deviating from normality were represented by medians and interquartile ranges (first to third quartiles). Given the long duration of the study period (2009–2018), we assessed the temporal trend in the proportion of patients with HBR using the Cochran–Armitage test prior to endpoint analysis. The incidences of endpoints were described as the cumulative incidence of freedom from the first event, expressed in percentages with 95% confidence intervals (CIs). Endpoint differences were evaluated using the log-rank test.

The performance metrics encompassed within each HBR score, including sensitivity, specificity, positive predictive value, negative predictive value, and C-statistics (as depicted by the area under the curve [AUC]), were analyzed. The comparison of C-statistics was conducted using the DeLong test. To stratify risk levels for predicting clinical events, we conducted a comparative analysis using the Cox proportional hazards model across four distinct categories: ARC-HBR positive/negative and J-HBR positive/ negative. We designated the group identified as ARC-HBR negative/J-HBR negative as the reference category. The comparative assessment was expressed in terms of hazard ratios (HRs) and 95% CIs for each group relative to the reference. Although J-HBR incorporates all components of ARC-HBR, in this study, we defined ARC-HBR positive with J-HBR negative as patients who met ARC-HBR criteria, but did not have any of the three unique components of J-HBR. This definition was used because the aim of this study was to evaluate the differences between ARC-HBR and J-HBR, specifically assessing the impact of the unique factors of J-HBR. Additionally, to account for competing risks in the evaluation of major bleeding events, we performed a supplementary analysis using the Fine and Gray model, with all-cause death treated as a competing event.

Statistical analyses were conducted using R (version 4.0.4; R Core Foundation, Vienna, Austria) and Python (version 3.10.12; Python Software Foundation, Wilmington, DE, USA). *P*-values < 0.05 were considered statistically significant.

## Results

### Patient population

The study's flow diagram is depicted in Fig. 1. From a total of 987 patients with ACS on the database, 889 were included in the current analysis. Patient demographics are detailed in Table 1. The predominant presentation was ST-elevation myocardial infarction, accounting for 63% of cases, with 89% undergoing PCI and 59% receiving drug-eluting stents.

### HBR

Table 2 displays the proportion of patients classified according to each set of HBR criteria. Over half of the patients were classified as high-risk in both criteria (51% for ARC-HBR and 65% for J-HBR). No significant time trends were observed in either criterion over the study period (ARC-HBR: $P=0.461$; J-HBR: $P=0.722$).

### Incidence of clinical events

A total of 80 patients (9%) experienced 89 events, including 36 major bleeding and 53 all-cause deaths. In bleeding events, the majority of the bleeding sites was gastrointestinal (22 patients; 61%), followed by intracranial (8 patients; 22%). The major causes of death were cardiovascular-related (including heart failure, recurrent ACS, and stroke) accounting for 28%, followed by cancer

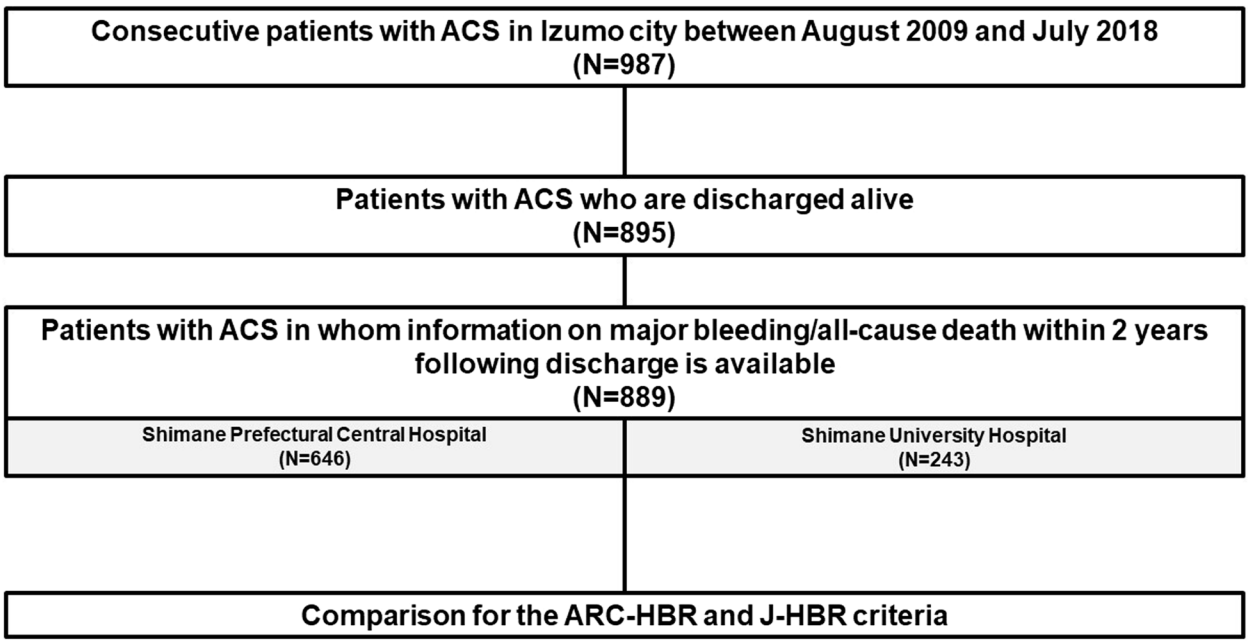



**Fig. 1** Flow Diagram. ACS, acute coronary syndrome; ARC-HBR, Academic Research Consortium-High Bleeding Risk; J-HBR, Japanese-High Bleeding Risk

**Table 1** Patient demographics

| | ACS ($n=889$) |
|---|---|
| Age (years), mean ± SD | 70 ± 12 |
| Male, n (%) | 655 (74) |
| STEMI, n (%) | 558 (63) |
| NSTE-ACS, n (%) | 331 (37) |
| Time from symptom onset to arrival (h), median (IQR) | 3 (1, 10) |
| PCI, n (%) | 795 (89) |
| CABG, n (%) | 44 (5) |
| Conservative therapy, n (%) | 56 (6) |
| Use of BMS, n (%) | 226 (25) |
| Use of the DES, n (%) | 519 (59) |
| Peak CK (IU/L), median (IQR) | 1066 (229,2467) |
| Hospital stay (days), median (IQR) | 13 (8, 19) |
| BMI, (kg/m$^2$), mean ± SD | 24 ± 4 |
| LVEF (%), mean ± SD | 51 ± 11 |
| Cre (mg/dl), median (IQR) | 0.81 (0.66, 1.01) |
| LDL (mg/dl), mean ± SD | 98 ± 34 |
| HDL (mg/dl), mean ± SD * | 46 ± 14 |
| CRP (mg/dl), median (IQR) | 0.2 (0.07, 0.83) |
| Medical history/comorbidities | |
| Current/Ex-smoker, n (%) | 532 (59) |
| History of PCI/CABG, n (%) | 119 (13) |
| Hypertension, n (%) | 617 (69) |
| Dyslipidemia, n (%) | 528 (59) |
| Diabetes mellitus, n (%) | 334 (38) |
| Atrial fibrillation, n (%) | 105 (12) |
| Therapeutic agents | |
| ASA, n (%) | 841 (95) |
| Ticlopidine/Clopidogrel, n (%) | 631 (71) |
| Prasugrel, n (%) | 142 (16) |
| Other antiplatelet agents, n (%) | 12 (0.1) |
| ACEI/ARB, n (%) | 645 (72) |
| Beta-blocker, n (%) | 627 (70) |
| Statin, n (%) | 798 (90) |
| Diuretics, n (%) | 258 (29) |
| OHA/insulin, n (%) | 217 (24) |
| SGLT2 inhibitor, n (%) | 8 (1) |
| Warfarin, n (%) | 85 (10) |
| DOACs, n (%) | 35 (4) |

Numerical data are expressed as the mean ± SD or as the median (IQR; first quartile, third quartile). Categorical data are expressed as the percentage (%) and number

*ACEI* angiotensin-converting enzyme inhibitors, *ACS* acute coronary syndrome, *ARB* angiotensin II receptor blockers, *ASA* acetylsalicylic acid, *BMI* body mass index, *BMS* bare metal stent, *CABG* coronary artery bypass graft, *CK* creatine kinase, *CRP* C-reactive protein, *DES* drug eluting stent, *DOACs* direct oral anticoagulants, *HDL* high density lipoprotein cholesterol, *HT* hypertension, *Hx* history, *IQR* interquartile range, *LDL* low density lipoprotein cholesterol, *LVEF* left ventricular ejection fraction, *NSTE-ACS* non-ST-segment elevation-acute coronary syndrome, *OHA* oral hypoglycemic agents, *PCI* percutaneous coronary intervention, *SD* standard deviation, *SGLT2* sodium-glucose cotransporter-2, *STEMI* ST-segment elevation myocardial infarction

**Table 2** Prevalence of each component of high bleeding risk criteria

| | |
|---|---|
| Patients positive for ARC-HBR/J-HBR criteria | |
| ARC-HBR criteria, n (%) | 450 (51) |
| J-HBR criteria, n (%) | 580 (65) |
| Major criteria (common in both the ARC-HBR and J-HBR) | |
| OAC use, n (%) | 120 (13) |
| Severe CKD, n (%) | 66 (7) |
| Severe anemia, n (%) | 111 (12) |
| Low platelet counts, n (%) | 20 (2) |
| Major bleeding history, n (%) | 20 (2) |
| Liver cirrhosis with portal hypertension, n (%) | 5 (0.6) |
| Active cancer, n (%) | 37 (4) |
| History of ICH/recent stroke/AVM, n (%) | 26 (3) |
| Major surgery under DAPT, n (%) | 37 (4) |
| Recent major trauma/surgery, n (%) | 5 (0.6) |
| Major criteria (specific in the J-HBR) | |
| Frailty, n (%) | 115 (13) |
| Heart failure, n (%) | 203 (23) |
| Peripheral vascular disease, n (%) | 97 (11) |
| Minor criteria (common in both the ARC-HBR and J-HBR) | |
| ≥ 75 years, n (%) | 342 (38) |
| Moderate CKD, n (%) | 278 (31) |
| Moderate anemia, n (%) | 155 (18) |
| Minor bleeding history, n (%) | 4 (0.4) |
| NSAIDS/steroids, n (%) | 49 (5) |
| Minor stroke, n (%) | 75 (8) |

Categorical data are expressed as the percentage (%) and number

*ARC-HBR* Academic Research Consortium-High Bleeding Risk, *AVM* arteriovenous malformation, *CKD* chronic kidney disease, *DAPT* dual antiplatelet therapy, *ICH* intracranial hemorrhage, *J-HBR* Japanese-High Bleeding Risk, *NSAIDs* Non-steroidal anti-inflammatory drugs, *OAC* oral anticoagulants

at 21%, while both bleeding-related deaths and infection each represented 13% of mortality cases. The cumulative incidence of major bleeding or all-cause death was compared between patients with positive HBR and those with negative HBR, as depicted in Fig. 2 and detailed in Table 3 (A: based on ARC-HBR; B: based on J-HBR). In analyses using both sets of criteria, patients identified as HBR demonstrated higher event incidences than that of either set of criteria alone. In each component of the endpoint, this trend was consistent (Fig. 3).

### Metrics of HBR criteria

The performance metrics for each set of criteria are detailed in Table 4. Notably, the negative predictive value for any type of event was consistently higher across both sets of criteria (Table 4). Although the J-HBR criteria demonstrated higher sensitivity compared to that of the ARC-HBR criteria, its specificity was lower.

The comparison of C-statistics for major bleeding/all-cause death showed higher AUC for ARC-HBR than

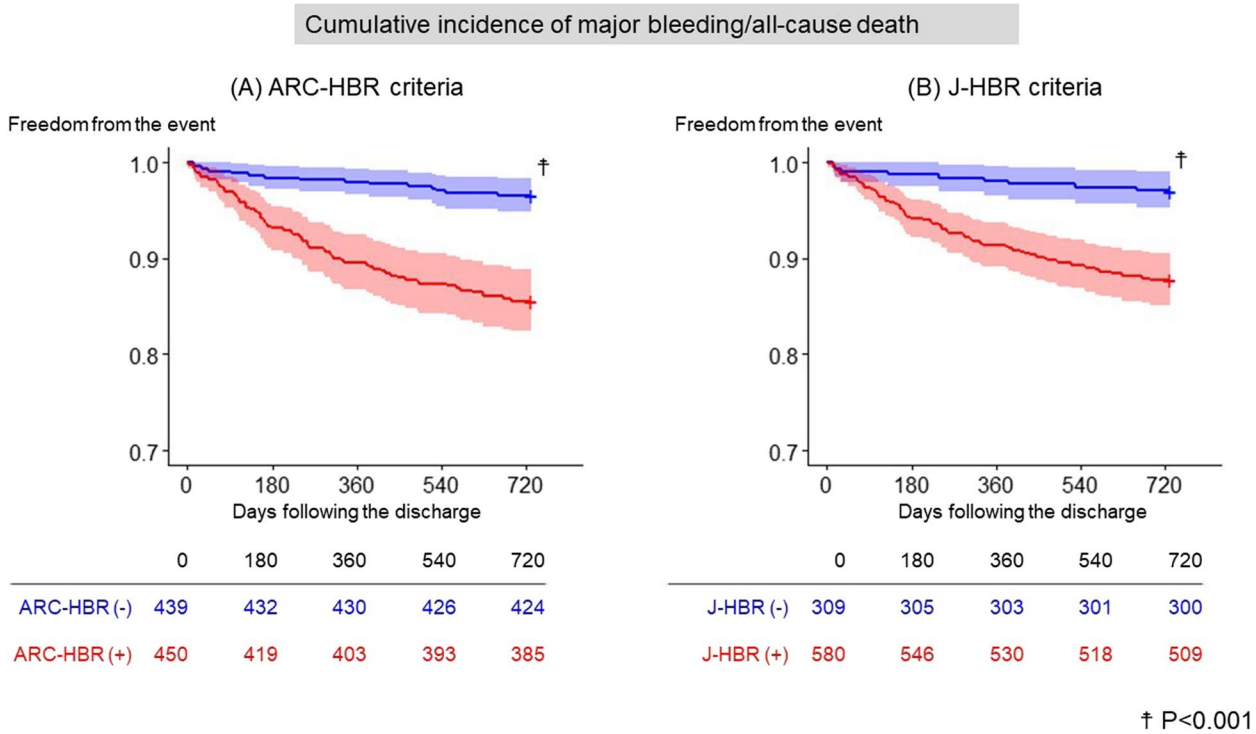



**Fig. 2** Cumulative Incidence of Major Bleeding/All-Cause Death. **A** Based on the ARC-HBR criteria. **B** Based on the J-HBR criteria. ARC-HBR, Academic Research Consortium-High Bleeding Risk; J-HBR, Japanese-High Bleeding Risk. ‡: statistical significance ($P < 0.001$)

**Table 3** The cumulative incidence of each endpoint. Comparison of C-statistics in each set of high bleeding risk criteria

| | Cumulative incidence freedom from the event, % (95% CI) | | | | *P*-value (ARC-HBR) | *P*-value (J-HBR) |
|---|---|---|---|---|---|---|
| | ARC-HBR | | J-HBR | | | |
| | Negative | Positive | Negative | Positive | | |
| Major bleeding/all-cause death | 96.6 (94.9–98.3) | 85.5 (82.3–88.9) | 97.1 (95.2–99.0) | 87.7 (85.1–90.4) | < 0.001 | < 0.001 |
| Major bleeding | 97.7 (96.3–99.1) | 94.2 (92.0–96.4) | 98.4 (97.0–99.8) | 94.6 (92.8–96.5) | < 0.001 | < 0.001 |
| All-cause death | 97.9 (96.6–99.3) | 90.2 (87.5–93.0) | 97.7 (96.1–99.4) | 92.1 (89.9–94.2) | < 0.001 | < 0.001 |

*ARC-HBR* Academic Research Consortium-High Bleeding Risk, *CI* confidence interval, *J-HBR* Japanese-High Bleeding Risk

J-HBR (Table 5; 0.67 [95% CI: 0.64–0.69] vs. 0.63 [0.60–0.66], $P = 0.015$). In each component, while the AUC for major bleeding was comparable between the two sets of criteria, the ARC-HBR criteria showed higher AUC for all-cause death than the J-HBR criteria (0.67 [0.64–0.70] vs. 0.61 [0.59–0.64], $P < 0.001$).

### Risk stratification using both criteria

Figures 4 and 5 illustrate the risks associated with events across four distinct categories, as defined by the ARC-HBR and J-HBR criteria. For major bleeding/all-cause death, the highest risk was observed in patients positive for both sets of criteria (HR [95% CI]: 5.81 [2.79–12.07], $P < 0.001$), compared to that in those who were negative in both sets of criteria. This was followed by patients positive for the ARC-HBR criteria but negative for the unique components of the J-HBR criteria (HR: 4.76 [2.26–10.02], $P < 0.001$); patients negative for the ARC-HBR criteria but positive for the unique components of J-HBR criteria (HR: 1.59 [0.56–4.47], $P = 0.370$); and finally, those negative in both sets of criteria.

In contrast, for major bleeding alone, the highest risk was observed in patients positive for the ARC-HBR criteria but negative for the unique components of the J-HBR criteria (HR: 3.98 [1.43–11.07], $P = 0.007$). This was followed by those positive for both sets of criteria

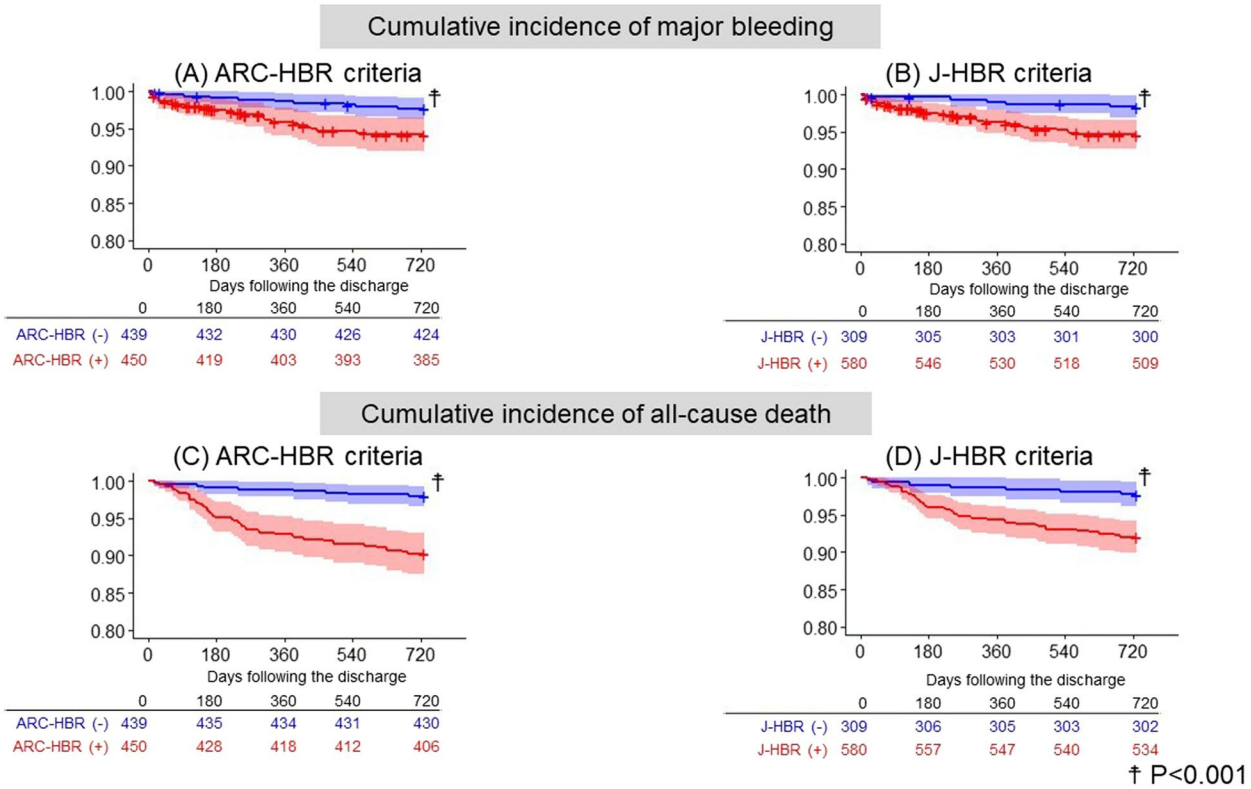



**Fig. 3** Cumulative Incidence of Each Event. **A** The cumulative incidence of major bleeding based on the ARC-HBR criteria. **B** The cumulative incidence of major bleeding based on the J-HBR criteria. **C** The cumulative incidence of all-cause death based on the ARC-HBR criteria. **D** The cumulative incidence of all-cause death based on the J-HBR criteria. ARC-HBR, Academic Research Consortium-High Bleeding Risk; J-HBR, Japanese-High Bleeding Risk. ‡: statistical significance ($P < 0.001$)

**Table 4** The Performance metrics in each set of high bleeding risk criteria

| | Major bleeding/all-cause death | | Major bleeding | | All-cause death | |
|---|---|---|---|---|---|---|
| | ARC-HBR | J-HBR | ARC-HBR | J-HBR | ARC-HBR | J-HBR |
| Sensitivity | 0.81 | 0.88 | 0.71 | 0.86 | 0.83 | 0.87 |
| Specificity | 0.52 | 0.37 | 0.50 | 0.36 | 0.51 | 0.36 |
| Positive predictive value | 0.14 | 0.12 | 0.05 | 0.05 | 0.09 | 0.08 |
| Negative predictive value | 0.97 | 0.97 | 0.98 | 0.98 | 0.98 | 0.98 |

*ARC-HBR* Academic Research Consortium-High Bleeding Risk, *J-HBR* Japanese-High Bleeding Risk

**Table 5** Comparison of C-statistics in each set of high bleeding risk criteria

| | AUC (95% CI) | | *P*-value |
|---|---|---|---|
| | ARC-HBR | J-HBR | |
| Major bleeding/all-cause death* | 0.67 (0.64–0.69) | 0.63 (0.60–0.66) | 0.015 |
| Major bleeding | 0.61 (0.57–0.64) | 0.61 (0.57–0.63) | 0.950 |
| All-cause death[a] | 0.67 (0.64–0.70) | 0.61 (0.59–0.64) | < 0.001 |

*ARC-HBR* Academic Research Consortium-High Bleeding Risk, *AUC* area under the curve, *CI* confidence interval, *J-HBR* Japanese-High Bleeding Risk

[a] statistical significance

(HR: 3.28 [1.14–9.45], $P = 0.027$), negative for the ARC-HBR criteria but positive for the unique components of J-HBR criteria, and those negative in both sets of criteria. When accounting for the competing risk of all-cause death using the Fine and Gray model, the results remained consistent with our original analysis: patients with only J-HBR unique components showed subdistribution HR 2.40 (0.69–8.28, $P = 0.160$), those with only ARC-HBR criteria showed subdistribution HR 3.88 (1.40–10.74, $P = 0.009$), and those positive for both

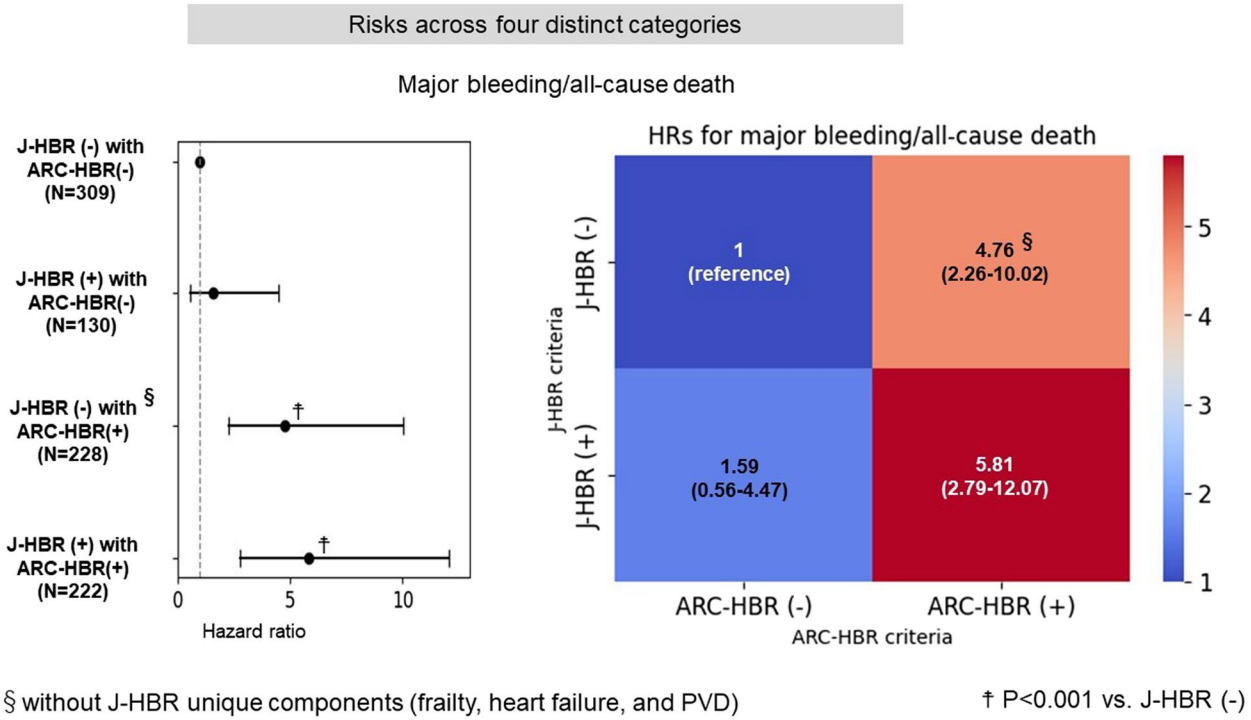



**Fig. 4** Risks across four distinct categories. **A** The comparison of hazard ratios with 95% confidence intervals for developing major bleeding/all-cause death, compared to patients negative for both the ARC-HBR and J-HBR criteria. **B** Heat map across four categories. ARC-HBR, Academic Research Consortium-High Bleeding Risk; HR, hazard ratio; J-HBR, Japanese-High Bleeding Risk; PVD, peripheral vascular disease. ‡: statistical significance ($P < 0.001$). §: patients with the ARC-HBR criteria but without the J-HBR criteria unique components

criteria sets showed subdistribution HR 3.13 (1.09–9.01, $P = 0.034$).

The trend for all-cause death alone generally followed the result in major bleeding/all-cause death.

## Discussion

### General findings

The key findings of this study were as follows (graphical abstract). First, more than half of the patients with ACS were classified as HBR according to the ARC-HBR criteria (51%), a proportion that increased to 65% when using the J-HBR criteria. Second, both sets of criteria effectively identified patients at high risk of major bleeding and all-cause death within 2 years following discharge, with the ARC-HBR criteria demonstrating higher AUC for the composite of major bleeding/all-cause death and for all-cause death alone than the J-HBR criteria. The AUC for major bleeding alone was comparable in both sets of criteria. Third, the combined use of both sets of criteria effectively stratified the risk for major bleeding/all-cause death, indicating the highest risk among patients who were positive for HBR according to both sets of criteria, and the lowest risk among those negative for both sets of criteria.

### Bleeding risk profile in patients with ACS

As patients with ACS require a more extended duration of DAPT compared to those with chronic coronary syndrome, managing bleeding risk is of greater importance in the ACS population. Although current guidelines offer antithrombotic regimens that vary depending on the presence of HBR [1, 15], detailed information on the bleeding risk profile in patients with ACS remains scarce as many previous studies have utilized populations comprised of both ACS and chronic coronary syndrome cases combined. Our observation that 51% of patients were classified as HBR using the ARC-HBR criteria exceeds the prevalence rates reported in previous studies for patients with AMI, which ranged from approximately 32% to 46% [16–19]. The prevalence using the J-HBR criteria also showed a slightly higher prevalence rate than that in other studies (65% in our study, versus 52% and 61% in two other studies, respectively) [16, 17]. Given that our study population was not limited to patients who underwent PCI, the inclusion of a higher number of elderly and severe cases, severe enough to give pause

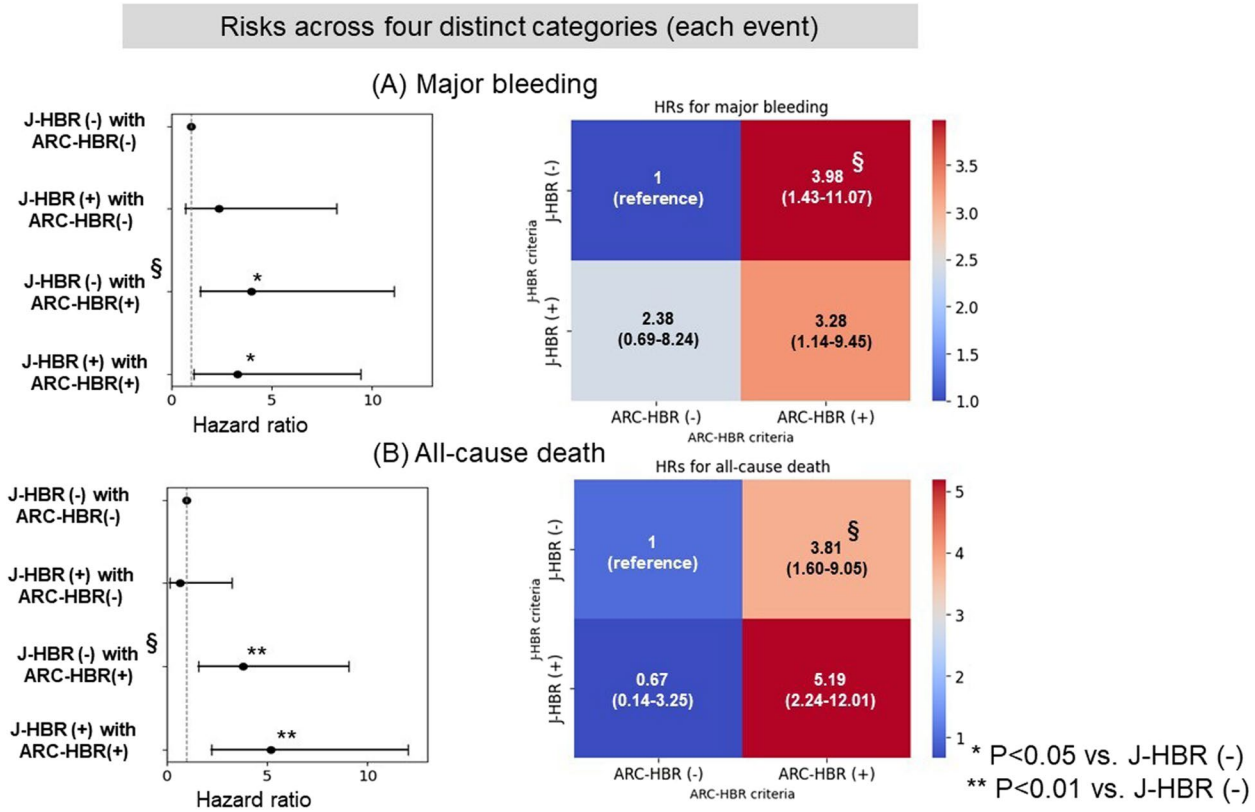



**Fig. 5** Risks across four distinct categories in each event. **A** The comparison of hazard ratios with 95% confidence intervals for developing major bleeding, compared to patients negative for both the ARC-HBR and J-HBR criteria (left panel). Heat map across four categories (right panel). **B** The comparison of hazard ratios with 95% confidence intervals for developing all-cause death, compared to patients negative for both the ARC-HBR and J-HBR criteria (left panel). Heat map across four categories (right panel). ARC-HBR, Academic Research Consortium-High Bleeding Risk; HR, hazard ratio; J-HBR, Japanese-High Bleeding Risk. *$P < 0.05$, **$P < 0.01$. §: patients with the ARC-HBR criteria but without the J-HBR unique components

to the decision for PCI, might explain the observed disparity. In addition, previous studies have been conducted with three to four major criteria of the ARC-HBR criteria unassessed [6, 8, 16, 17]. In our data, only one criterion (chronic bleeding diathesis) was not assessed, suggesting that we may have been able to identify HBR cases that were missed out in previous studies.

#### Efficacy of both sets of HBR criteria

Considering the unique bleeding risk profile of East Asian patients and their higher incidence of bleeding compared to their non-Asian counterparts, the J-HBR criteria were developed [1, 2]. These criteria further integrate three more factors (frailty, heart failure, and peripheral artery disease) into the major criteria of the ARC-HBR [2, 9]. While the J-HBR criteria are anticipated to improve sensitivity in identifying the HBR population, studies comparing the discriminative capabilities and applicability of both sets of criteria within an ACS cohort are limited. Sotomi et al. [17] demonstrated that the J-HBR criteria were more effective than the ARC-HBR criteria in identifying fatal bleeding events within an AMI cohort. Conversely, Matsumoto et al. [16] found that the ARC-HBR criteria exhibited superior diagnostic performance in predicting bleeding events following PCI compared to that of the J-HBR criteria within an AMI cohort. Our study revealed that the ARC-HBR criteria significantly outperformed the J-HBR criteria in predicting the incidence of major bleeding events combined with all-cause mortality, although the performance of both sets of criteria was comparable when evaluating major bleeding events alone. Regarding isolated bleeding events, we observed the greatest risk in the ARC-HBR–positive/J-HBR–negative subgroup rather than in the double-positive subgroup. This seemingly paradoxical finding may reflect imprecise ascertainment of heart failure—the most common J-HBR-specific component (23%)—as its presence was determined retrospectively from attending physicians' records. Such documentation introduces potential misclassification risk, especially

during the acute reperfusion phase of ACS, where transient hemodynamic deterioration can mimic congestive heart failure. Consequently, our data do not permit definitive conclusions about the bleeding-predictive value of the J-HBR-specific components. In contrast, for all-cause death and for the composite endpoint, the double-positive category exhibited the highest risk. This indicates that our approach to identifying J-HBR positivity still captures patients with the broadest adverse-event profile in this population. Therefore, although ARC-HBR alone appears adequate for identifying individuals at imminent hemorrhagic risk, the incremental contribution of J-HBR-specific components—particularly heart failure—requires confirmation in larger, prospectively adjudicated cohorts that minimize misclassification and ensure balanced subgroup sizes.

### Clinical implications

By examining the differences in risk elevation between the two sets of criteria, we observed varying risk profiles depending on which criteria patients met. Given that all-cause death has been recognized as a competing risk for bleeding events [20], the inclusion of both events in this study's composite endpoint can be considered to provide a more practical and comprehensive indicator. Although we found a statistically significant difference in discriminative performance between ARC-HBR and J-HBR criteria, the modest difference in AUC (0.67 vs. 0.63) may not translate to substantial clinical differences in real-world practice. For many clinical scenarios, either set of criteria could provide acceptable risk stratification. Our findings indicated that individuals meeting both the ARC-HBR and J-HBR criteria may present the highest risk, surpassing those identified by the ARC-HBR criteria alone. The J-HBR criteria, developed not only for the Japanese population but also for the broader East Asian demographic, suggests that its application, when combined with other criteria, could be expanded beyond Japanese individuals to encompass the entire East Asian population. However, in the context of assessing the risk of major bleeding alone, our data do not support the efficacy of utilizing a combination of the two sets of criteria. In this scenario, we argue that using either the ARC-HBR or J-HBR criteria alone is beneficial for risk stratification.

### Limitations

Our study was subject to several limitations. Firstly, our cohort was assembled prior to the evidence supporting shortened durations of DAPT, leading to a standard prescription of DAPT for at least 1 year for patients undergoing PCI [21]. This likely resulted in higher bleeding rates than would be observed with contemporary shortened DAPT regimens, which may inhibit the applicability of our findings in current clinical practice that increasingly customizes antiplatelet therapy duration based on individual bleeding risks. Second, the retrospective design of our study, combined with data collection from only two institutions in the same medical region, may limit the generalizability of our results across different healthcare settings. Our data from rural Japan may not fully represent outcomes in urban centers or non-Japanese East Asian populations. The potential for unaccounted variables further exacerbates this limitation. Notably, we did not include data on chronic bleeding diathesis, despite its very low prevalence (~0.03%) in other studies [6, 16, 17]. Third, while our male predominance (74%) reflects typical ACS demographics, this limited our ability to perform sex-stratified analyses that might reveal different performance of HBR criteria between males and females. Fourth, by including only patients who were discharged alive, our study may have overlooked cases at very high risk, such as those who died from in-hospital fatal bleeding complications..

## Conclusions

Our results indicated that the ARC-HBR criteria demonstrated a greater discriminative capability for predicting major bleeding/all-cause mortality within 2 years post-discharge in patients with ACS than the J-HBR criteria. For major bleeding alone, the discriminative ability of both sets of criteria was comparable. While the ARC-HBR criteria showed relatively stronger discriminative performance, our findings reinforce that both ARC-HBR and J-HBR offer clinically acceptable frameworks for mid-term bleeding risk stratification in patients with ACS.

### Abbreviations

| | |
|---|---|
| ACS | Acute coronary syndrome |
| ARC-HBR | Academic Research Consortium high bleeding risk |
| AMI | Acute myocardial infarction |
| AUC | Area under the curve |
| CI | Confidence interval |
| DAPT | Dual antiplatelet therapy |
| HBR | High bleeding risk |
| HR | Hazard ratio |
| J-HBR | High bleeding risk modified for Japanese patients |
| PCI | Percutaneous coronary intervention |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04834-1.

Supplementary Material 1.

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**Authors' contributions**
HI, TO, and SK contributed to conceptualization. YY, HM, and MY contributed to data curation. HI, YY, and TO contributed formal analysis. HI and YY contributed to the investigation. HI, TO, AE, SK, KT, and MS contributed methodology. HI and TO contributed to project administration. HI, and YY contributed visualization. HI, YY, KM, and KI contributed validation. HI wrote an original draft. YY, TO, AE, SK, KT, and MS contributed to the review & editing of the draft. SK, TK, MS, and TO contributed supervision. NK, TK, MY, KS, and KI provided resources. All authors reviewed the manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
This study is a historical cohort study, and the data were collected retrospectively. This manuscript was followed the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation. The Institutional Review Boards of Shimane Prefectural Central Hospital (Churin R20-63) and Shimane University Hospital (20240121–1) approved this study. The informed consent was waived due to the decision of the review boards from both institutions.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note