

Evaluation of the Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients Bleeding Score for Predicting the Long-term Out-of-hospital Bleeding Risk in Chinese Patients after Percutaneous Coronary Intervention

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Abstract

Background: The Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients (PARIS) bleeding score is a novel score for predicting the out-of-hospital bleeding risk after percutaneous coronary intervention (PCI). However, whether this score has the same value in non-European and American populations is unclear. This study aimed to assess the PARIS bleeding score's predictive value of bleeding in patients after PCI in the Chinese population.

Methods: We performed a prospective, observational study of 10,724 patients who underwent PCI from January to December 2013, in Fuwai Hospital, China. We defined the primary end point as major bleeding (MB) according to Bleeding Academic Research Consortium definition criteria including Type 2, 3, or 5. The predictive value of the PARIS bleeding score was assessed with the area under the receiver operating characteristic (AUROC) curve.

Results: Of 9782 patients, 245 (2.50%) MB events occurred during the 2 years of follow-up. The PARIS bleeding score was significantly higher in the MB group than that of non-MB group (4.00 [3.00, 5.00] vs. 3.00 [2.00, 5.00], $Z = 3.71$, $P < 0.001$). According to risk stratification of the PARIS bleeding score, the bleeding risk in the intermediate- and high-risk groups was 1.50 times (hazard ratio [HR]: 1.50; 95% confidence interval [CI]: 1.160–1.950; $P = 0.002$) and 2.27 times higher (HR: 2.27; 95% CI: 1.320–3.900; $P = 0.003$) than that in the low-risk group. The PARIS bleeding score showed a moderate predictive value for MB in the overall population (AUROC: 0.568, 95% CI: 0.532–0.605; $P < 0.001$) and acute coronary syndrome (ACS) subgroup (AUROC: 0.578, 95% CI: 0.530–0.626; $P = 0.001$) and tended to be predictive in the non-ACS subgroup (AUROC: 0.556, 95% CI: 0.501–0.611; $P = 0.054$).

Conclusion: The PARIS bleeding score shows good clinical value for risk stratification and has a significant, but relatively limited, prognostic value for out-of-hospital bleeding in the Chinese population after PCI.

Key words: Bleeding; Percutaneous Coronary Intervention; Prognosis

INTRODUCTION

Using dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor in patients undergoing percutaneous coronary intervention (PCI) could reduce the risk for ischemic cardiovascular events. However, this might occur at the expense of increasing the risk for bleeding.^[1] Bleeding not only prolongs the time of hospitalization and increases the cost of treatment, but also significantly

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increases the risk for adverse cardiovascular and even death events.^[2] Therefore, identifying patients at a high risk of bleeding is important in clinical work.

The novel Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) bleeding score was derived from European and American people to predict the out-of-hospital risk for stent thrombosis and the risk of bleeding^[3] after PCI. However, whether this score has the same predictive value in the Asian population is unclear. Validation of the risk score in different geographical and ethnic populations is important. An example of this importance is that a previous study showed that Framingham functions overestimated the risk of coronary heart disease in the Chinese population.^[4] Therefore, this study aimed to assess the PARIS bleeding score after PCI in a large sample of the Chinese population in patients with drug-eluting stents.

METHODS

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was by the hospital's Research Ethics Committee (No. 2013-449). The Institutional Review Board approved the study protocol and all of the patients provided written informed consent.

Study design

Data from all consecutive patients from a single center (Fuwai Hospital, China) who underwent PCI were prospectively collected. Between January and December 2013, a total of 10,724 consecutive patients were enrolled. We excluded patients who were not prescribed DAPT on discharge and those who did not successfully receive drug-eluting stents in at least one native coronary artery and those with in-hospital events including major bleeding (MB), stent thrombosis, myocardial infarction, and death. Finally, a total of 9782 patients were included in the final analysis. Aspirin was prescribed at a dose of 100 mg daily indefinitely. Clopidogrel 75 mg daily or ticagrelor 90 mg twice daily was advised for at least 1 year after PCI.

End points and definitions

The PARIS bleeding score in this study was based on the bleeding risk score of PARIS.^[3] The PARIS bleeding score consisted of six factors including age, body mass index, current smoking, anemia, creatinine clearance (CrCl) <60 ml/min, and triple therapy on discharge. Bleeding was quantified according to Bleeding Academic Research Consortium (BARC) definition criteria. MB was defined as Type 2, 3, or 5 from the BARC criteria.^[5] According to the PARIS study definitions,^[3] anemia was classified as hemoglobin levels <120 g/L in men and <110 g/L in women. CrCl was calculated using the Cockcroft-Gault formula.

Follow-up

All of the patients were evaluated by a clinical visit or by phone at 30 days and at 6, 12, and 24 months. Patients were advised to return for coronary angiography if clinically indicated by symptoms or documentation of myocardial

ischemia. All adverse events were observed and adjudicated centrally by two independent cardiologists, and disagreement was resolved by consensus.

Statistical analysis

Categorical variables are expressed as frequency (percentage) and continuous variables are expressed as mean \pm standard deviation (SD) or median (P25, P75). Mean values of continuous variables with normal distribution were compared by the Student's *t*-test, median values of continuous variables with nonnormal distribution were compared using nonparametric test (Wilcoxon), and the Pearson's Chi-square test or Fisher's exact test was used to compare categorical variables. Risk stratification was performed according to the original PARIS bleeding score as three risk strata (low risk, 0–3; moderate risk, 4–7; and high risk, ≥ 8).^[3] The predictive value of the PARIS bleeding score was assessed with the area under the receiver operating characteristic (AUROC) curve. All tests were two-sided, and a value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SAS 9.2 software (SAS Institute, Cary, NC, USA).

RESULTS

Patients' characteristics

Among 10,724 patients undergoing PCI, we excluded those who failed to satisfy the enrollment requirements according to the original PARIS study [Figure 1].^[3] A total of 9782 patients were involved in the final analysis, with a mean age of 58.2 ± 10.2 years, 22.90% of patients were women, and 60.00% had acute coronary syndrome (ACS). Only 13 (0.13%) patients received ticagrelor and the rest of the patients took clopidogrel (99.87%). Only 17 (0.17%) patients received triple therapy with aspirin, a P2Y12 receptor inhibitor, and an oral anticoagulant drug. No patients received bivalirudin or prasugrel. A high proportion (91.20%) of patients with the transradial approach (TRA) of PCI was observed in this study.

After the 2-year follow-up, 245 (2.50%) patients had MB events. Baseline characteristics are shown in Table 1.

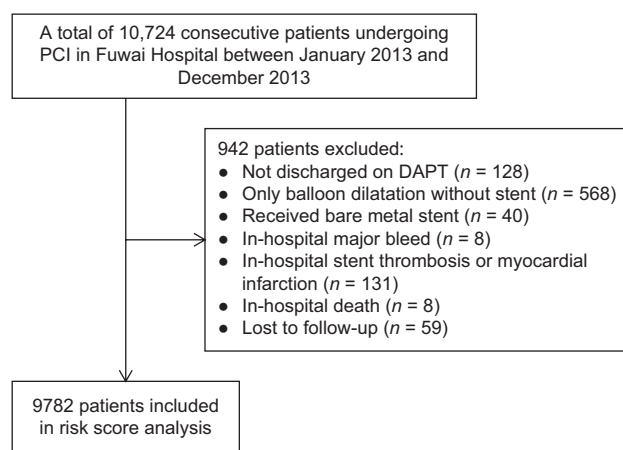


Figure 1: Patient flow chart for the study cohort. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy.

Table 1: Baseline clinical characteristics in patients undergoing coronary interventions with versus without 2-year MB

Parameters	MB group (n = 245)	Non-MB group (n = 9537)	Statistics	P
Age (years)	61.2 ± 10.2	58.2 ± 10.2	-4.67*	<0.001
Female	70 (28.57)	2166 (22.71)	4.65 [†]	0.031
BMI (kg/m ²)	25.62 ± 3.12	25.95 ± 3.18	1.60*	0.110
PARIS bleeding score	4.00 (3.00, 5.00)	3.00 (2.00, 5.00)	3.71 [‡]	<0.001
Clinical presentation				
Stable CHD	101 (41.22)	3814 (39.99)	0.68 [†]	0.713
Tropin-negative ACS	106 (43.27)	4052 (42.49)		
Troponin-positive ACS	38 (15.51)	1671 (17.52)		
Hypertension	171 (69.80)	6103 (63.99)	3.50 [†]	0.061
Diabetes mellitus				
Noninsulin-treated	46 (18.78)	1866 (19.57)	1.50 [†]	0.473
Insulin-treated	20 (8.16)	988 (10.36)		
Current smoking	143 (58.37)	5448 (57.12)	0.15 [†]	0.698
Dyslipidemia	170 (69.39)	6409 (67.20)	0.52 [†]	0.471
Previous MI	39 (15.92)	1801 (18.88)	1.38 [†]	0.241
Previous PCI	50 (20.41)	2264 (23.74)	1.47 [†]	0.226
Previous CABG	11 (4.49)	377 (3.95)	0.18 [†]	0.671
Previous stroke	42 (17.14)	1000 (10.49)	11.12 [†]	0.001
Previous vascular disease	46 (18.78)	1176 (12.33)	9.08 [†]	0.003
Anemia	10 (4.08)	325 (3.41)	0.33 [†]	0.567
Ccr <60 ml/min	31 (12.86)	1052 (11.47)	0.45 [†]	0.502
Heart rate >100 beats/min	1 (0.41)	93 (0.98)	0.81 [†]	0.369
Systolic BP <90 mmHg	2 (0.82)	20 (0.21)	3.92 [†]	0.048
ST deviation	48 (19.59)	2058 (21.58)	0.56 [†]	0.455
Heart failure history	6 (2.49)	179 (1.92)	0.41 [†]	0.524
Abnormal myocardial enzyme	48 (19.59)	2053 (21.53)	0.53 [†]	0.467
Creatinine (mg/L)	8.60 ± 1.90	8.50 ± 1.80	-0.28*	0.783
Baseline syntax score	10.00 (5.00, 17.00)	10.00 (6.00, 17.00)	-0.61 [‡]	0.543
IABP use	4 (1.63)	99 (1.04)	0.34 [†]	0.560
Number of stents per patient	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	-0.78 [‡]	0.438
Triple therapy	1 (0.41)	16 (0.17)	0.01 [†]	0.908

Values are presented as mean ± SD, n (%), or median (P25, P75). **t* values; [†] χ^2 values; [‡]*Z* values. 1 mmHg = 0.133 kPa. MB: Major bleeding; BMI: Body mass index; PARIS: Patterns of Non-Adherence to Anti-Platelet Regimens in Stented patients; CHD: Coronary heart disease; ACS: Acute coronary syndrome; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; Ccr: Creatinine clearance rate; IABP: Intra-aortic balloon pump; BP: Blood pressure; SD: Standard deviation.

Patients with MB had significantly older age ($t = -4.67$, $P < 0.001$), the higher rate of female ($\chi^2 = 4.65$, $P = 0.031$), the higher prevalence of previous cerebral stroke ($\chi^2 = 11.12$, $P = 0.001$) and previous vascular disease ($\chi^2 = 9.08$, $P = 0.003$), and more frequent of systolic blood pressure at admission <90 mmHg (1 mmHg = 0.133 kPa), compared with patients without MB ($\chi^2 = 3.92$, $P = 0.048$).

Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients score in the major bleeding and non-major bleeding groups

The bleeding risk score of PARIS was significantly higher in the MB group than that in the non-MB group (4.00 [3.00, 5.00] vs. 3.00 [2.00, 5.00], $Z = 3.71$, $P < 0.001$; Table 1).

Bleeding risk stratifications of Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients

According to the bleeding risk stratification of PARIS, low risk (0–3), intermediate risk (4–7), and high risk (≥ 8), the

bleeding risk in the intermediate-risk group was 1.50 times higher than that in the low-risk group (hazard ratio [HR]: 1.50; 95% confidence interval [CI]: 1.160–1.950; $P = 0.002$). The bleeding risk in the high-risk group was 2.27 times higher than that in the low-risk group (HR: 2.27; 95% CI: 1.320–3.900; $P = 0.003$). Therefore, the PARIS bleeding risk score of MB appeared to be significantly increased in a sequence of the low-, intermediate-, and high-risk groups [Table 2].

Predictive value of bleeding events using the Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients bleeding score

The PARIS bleeding score appeared to have predictive value for MB in the overall population (AUROC: 0.568; 95% CI: 0.532–0.605; $P < 0.001$). This score was further assessed in the ACS and non-ACS subgroups. The PARIS bleeding score appeared to have predictive value for MB in the ACS population, with

an AUROC of 0.578 (95% CI: 0.530–0.626; $P = 0.001$). In the non-ACS population, the AUROC from the PARIS bleeding score was 0.556 (95% CI: 0.501–0.611; $P = 0.054$), but this only tended to have predictive value [Figure 2].

DISCUSSION

At present, some bleeding scores are used clinically, and different bleeding scores are used for different patients. The Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED) score for bleeding risk assessment is used in patients with atrial fibrillation, and the CRUSADE and ACUITY bleeding scores for in-hospital bleeding risk assessment are used in patients with acute myocardial infarction. The PARIS bleeding score is a newly reported score system for assessing out-of-hospital bleeding and thrombosis in patients with DAPT after PCI.^[3] Due to possible ethnic variations, we assessed the PARIS bleeding score according to BARC Type 2, 3, or 5 as a clinical end point in a large-scale, single-center, Chinese population in the real world.

We found that the PARIS bleeding score showed the good clinical value of risk stratification in the Chinese population.

Table 2: Bleeding risk stratification of major bleeding by PARIS bleeding score

Parameters	Major bleeding, % (n/N)	HR	95% CI	P
All patients	2.50 (245/9782)			
PARIS bleeding score				
Low (≤ 3)	1.99 (103/5166)	Reference		
Intermediate (4–7)	2.97 (127/4271)	1.50	1.160–1.950	0.002
High (≥ 8)	4.37 (15/343)	2.27	1.320–3.900	0.003

PARIS: Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients; HR: Hazard ratio; CI: Confidence interval.

In patients who experienced out-of-hospital MB after PCI, the PARIS bleeding score was significantly raised. Based on the risk stratification of the PARIS bleeding score, the score in the high-risk group was 2.27 times higher than that in the low-risk group, and that in the intermediate-risk group was 1.50 times higher than that in the low-risk group. These findings indicated that risk stratification of the PARIS bleeding score had satisfactory discrimination for a low, intermediate, and high risk of bleeding in patients with DAPT after PCI. Clinicians may find that identifying patients at high risk of bleeding and adopting corresponding treatments for populations at different bleeding risks are useful strategies.^[6,7] For patients at a high risk of bleeding, to reduce the risk of bleeding, enhancing monitoring and preventing bleeding, selecting appropriate types of antiplatelet and antithrombotic therapy,^[8] deploying new-generation drug-eluting stents,^[9] and choosing a relatively short DAPT duration are important.^[10]

The present study is the first to evaluate the PARIS bleeding score according to BARC Type 2, 3, or 5 as end points in a large, real-world, Chinese population. The AUROC (0.568) in this study was relatively lower than the original PARIS bleeding score according to BARC Type 3 or 5 as a clinical end point (AUROC of 0.72 in the original PARIS study^[3] and 0.64 in a validation study^[3]). This difference among studies might be related to the following reasons: (1) there were different definitions for MB between this study and the PARIS study. MB under the definition of the PARIS study refers to BARC Type 3 or 5, whereas MB in the current study refers to BARC Type 2, 3, or 5. Different MB definitions might affect the results. (2) There was a relatively low incidence of bleeding events in the study. The bleeding incidence in this study was 2.50%, which is lower than that in the PARIS study (3.17%).

The study had a relatively low-risk bleeding rate compared with the PARIS study.^[3] Previous studies reported a large

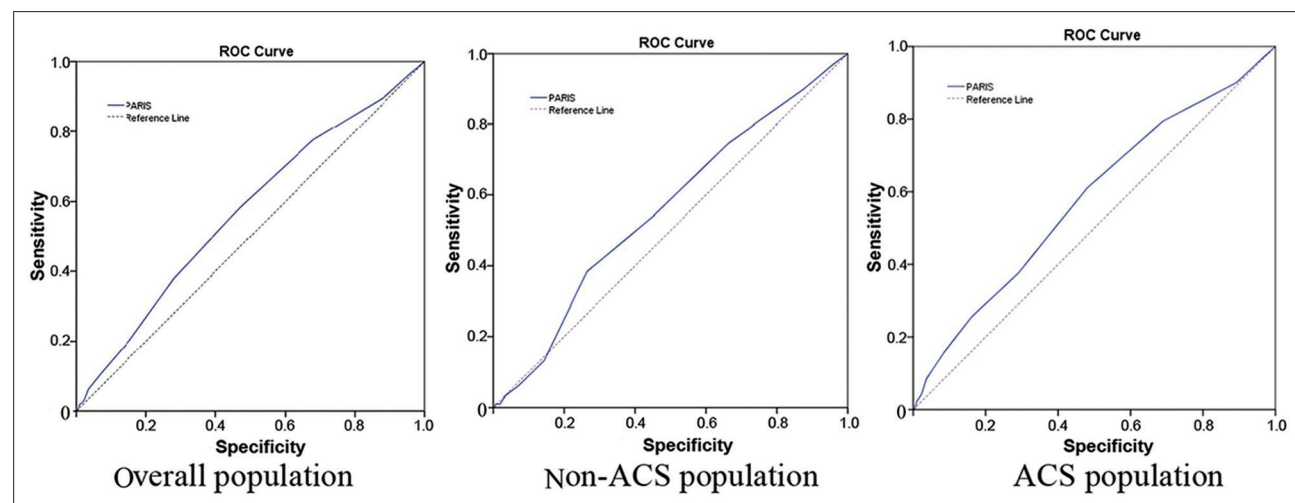


Figure 2: Predictive value of PARIS bleeding score for major bleeding. PARIS bleeding score showed predictive value on bleeding in overall population (AUROC: 0.568; $P < 0.001$), ACS subgroup (AUROC: 0.578; $P = 0.001$). In the non-ACS subgroup, presenting statistical tendency (AUROC: 0.556; $P = 0.054$). PARIS: Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients; ACS: Acute coronary syndrome; AUROC: Area under the receiver-operating characteristic curve.

difference in the incidence of bleeding after PCI, ranging from 0.20%^[11] to 8.80%^[12]. These differences were mainly associated with different definitions of bleeding, ethnic variations, various study populations, different frequencies of using anticoagulant drugs, and various follow-up durations among the studies. Ratib *et al.*^[11] showed that the incidence of bleeding in 30 days after PCI through TRA was only 0.20%. Mehran *et al.*^[13] showed that the out-of-hospital incidence of bleeding in a 2-year follow-up after PCI was 1.4%. In addition, in the CREDO study,^[12] the incidence of bleeding at 1 year was as high as 8.80%. This study had some characteristics that might have affected the bleeding rate as follows: (1) there was a high proportion of patients with TRA-PCI in the present study (91.20%); (2) a low percentage of the population received oral triple therapy comprising anticoagulants, aspirin, and a P2Y₁₂ receptor inhibitor ($n = 17$, 0.17%); (3) none of the maintenance doses of aspirin were higher than 100 mg; and (4) there was a low rate of using ticagrelor in 2013 in China (only 0.13% in this study). Previous studies showed that the use of the TRA^[11] and a low maintenance dose of aspirin may decrease the incidence of bleeding,^[14-16] triple therapy,^[17,18] and the use of strong P2Y₁₂ receptor inhibitors may increase the bleeding risk.^[19] All of the above factors might affect the PARIS bleeding score's predictive value in this study. Therefore, the present study suggested that the clinical value of the PARIS bleeding score was limited in the Chinese population according to BARC Type 2, 3, or 5 as the clinical end point.

The clinical value of the PARIS bleeding score for predicting bleeding in the ACS and non-ACS subgroups after drug-eluting stents has not been previously reported. Therefore, we further assessed the PARIS bleeding score in the ACS and non-ACS subgroups. We found that the PARIS bleeding score showed a significant predictive value of bleeding in the ACS population. However, in the non-ACS population, this score only showed a tendency to predict bleeding. Therefore, we concluded that the predictive value of the PARIS bleeding score was better in patients with ACS than that in those with non-ACS. Further studies and validation are required for determining the clinical predictive value of the PARIS bleeding score in the non-ACS population.

In this study, the PARIS bleeding score showed a significant, but relatively limited, prognostic value for out-of-hospital bleeding after stent implantation in the Chinese population. Therefore, further evaluation is required to determine whether adding more plasma markers and platelet function testing could improve the prognostic value. In addition, a new bleeding risk score that is more suitable for the Chinese population might need to be established. The present study provided the reliable clinical data on the PARIS bleeding score in a Chinese population and provided an important reference for clinical practice.

There are some limitations to this study. First, this study was a single-center, observational study, which might have affected the generalizability. Second, most patients in this study received clopidogrel, and the number of patients who

received ticagrelor or triple therapy was relatively small. Therefore, the clinical value of using new types of oral antiplatelet drugs, including ticagrelor and prasugrel, and triple therapy requires further assessment using a large-scale clinical study. Finally, more studies should be conducted to evaluate the prognostic value of PARIS according to BARC Type 3 or 5 as end point.

This large-population, real-world study shows that the PARIS bleeding score has good clinical value for risk stratification. In addition, the PARIS bleeding score shows a significant, but relatively limited, prognostic value of out-of-hospital bleeding according to BARC Type 2, 3, or 5 in the Chinese PCI population. The PARIS bleeding score also has predictive value for bleeding in the ACS subgroup.

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Conflicts of interest

There are no conflicts of interest.

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评估PARIS出血评分对中国经皮冠状动脉介入患者长期院外出血风险的预测价值

摘要

背景: 支架术后抗血小板药物停药模式 (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients, PARIS) 的出血评分为评估经皮冠状动脉介入 (percutaneous coronary intervention, PCI) 患者院外出血风险的新型评分。但该评分是否对非欧美人群具有同样价值尚不清楚。本研究目的为评估PARIS评分对中国PCI人群出血的预测价值。

方法: 本研究为前瞻、观察性研究, 纳入10724例从2013年1月到12月在阜外医院行PCI治疗的患者。主要出血事件的定义为出血学术研究协会定义 (Bleeding Academic Research Consortium Definition, BARC) 的2, 3或5型的出血。使用受试者操作特征的曲线下面积 (Area under the receiver operating characteristics curve, AUROC) 评估PARIS出血评分的预测价值。

结果: 9872例患者经2年随访, 共发生245 (2.5%) 例主要出血事件。PARIS出血评分在出血事件组明显高于非出血事件组 (4.00 [3.00, 5.00] vs. 3.00 [2.00, 5.00], $Z=3.71$, $P<0.001$)。按照PARIS评分的危险分层, 中危组的出血风险是低危组的1.5倍 (风险比[HR]:1.50; 95%可信区间[CI]:1.160-1.950; $P=0.002$); 高危组的出血风险是低危组的2.27倍 (HR: 2.27; 95%CI: 1.320-3.900; $P=0.003$)。PARIS出血评分对总人群(AUROC: 0.568, 95%CI:0.532-0.605; $P<0.001$)和急性冠脉综合征 (Acute coronary syndrome, ACS) 亚组患者有预测价值 (AUROC:0.578, 95% CI:0.530-0.626; $P=0.001$); 对非ACS亚组的患者显示有统计学趋势 (AUROC:0.556, 95% CI:0.501-0.611; $P=0.054$)。

结论: 对于行PCI的中国人群, PARIS出血评分显示对院外出血有较好的危险分层的临床价值, 并且显示出有统计学意义, 但出血预测价值相对有限。