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# Serum LncRNA PSMB8-AS1 as a novel biomarker for predicting acute coronary syndrome

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**Recent basic research has shown that Long non-coding RNA PSMB8-AS1 can promote the progression of atherosclerosis. The primary aim of this study was to investigate whether serum PSMB8-AS1 levels can predict acute coronary syndrome (ACS) in patients with chest pain. A total of 109 chest pain patients excluded from coronary artery disease (CAD), and 172 ACS patients, were enrolled from our center. Logistic regression analysis was performed to construct predictive models using traditional cardiovascular risk factors and then combined with PSMB8-AS1. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive ability of these models. Additionally, an external validation cohort, including 15 non-CAD chest pain patients and 26 ACS patients, was used for validation. Serum PSMB8-AS1 levels were significantly higher in ACS patients compared to non-CAD patients. After adjusting for traditional risk factors, PSMB8-AS1 was independently associated with ACS (Adjusted OR = 3.826, 95% CI 2.321–6.305, P < 0.001). ROC analysis indicated that the model incorporating PSMB8-AS1 significantly improved the predictive ability for ACS compared to the traditional risk factor-based model (AUC: 0.785 *vs* 0.705, DeLong test P = 0.0036). Importantly, these findings were validated in the external cohort. PSMB8-AS1 could serve as a novel biomarker for predicting acute coronary syndrome.**

**Keywords** Acute coronary syndrome, PSMB8-AS1, Chest pain, Predictive model

Acute coronary syndrome (ACS) refers to a set of clinical conditions resulting from the rupture or erosion of coronary atherosclerotic plaques[1–3]. Coronary angiography (CAG) is a widely adopted and effective diagnostic method for identifying ACS patients[4]. As an invasive procedure, it is generally considered safe and reliable, earning its reputation as the"gold standard"for diagnosing coronary artery disease[4] (CAD). However, certain patients, including those allergic to iodine or contrast agents[5,6], those with severe heart failure, uncontrolled severe arrhythmias[7], or severe liver and kidney impairment[8], are not suitable candidates for this procedure. Additionally, risks such as coronary artery perforation or dissection[9], and hematomas in the cervical or mediastinal areas[10] restrict its broader use. As a result, the identification of novel and effective early diagnostic markers for acute coronary syndrome has become increasingly critical[11].

LncRNA refers to a category of RNA molecules characterized by sequences that do not possess an open reading frame and play important biological functions[12–14]. some studies have shown that lncRNAs are closely related to various cardiovascular diseases, such as coronary heart disease[15–19] and heart failure[20–23]. LncRNA PSMB8-AS1 first gained attention due to its significant upregulation in the brains of individuals with HIV-associated neurocognitive disorders[24]. Subsequent research has linked PSMB8-AS1 to various cancers[25–27], including glioma, pancreatic cancer, and bladder cancer, as well as autoimmune diseases[28] like systemic lupus erythematosus. Interestingly, a recent study[29] found that human atherosclerotic plaques show significantly increased expression of PSMB8-AS1, and that its knock-in promoted atherosclerosis development in Apoe$^{-/-}$ mice by inducing monocyte/macrophage adhesion to endothelial cells and increasing VCAM1 and ICAM1 levels. Moreover, PSMB8-AS1 expression in the serum of patients with coronary heart disease was also significantly higher than in healthy individuals. Given the ability of PSMB8-AS1 to recruit monocytes/macrophages, as well as the critical role of monocytes/macrophages and their secreted inflammatory cytokines (IL-1β and IL-6) in the progression of atherosclerosis[30], we hypothesize that measuring serum PSMB8-AS1 levels could aid in identifying ACS patients among individuals presenting with chest pain.

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Thus, this study aims to investigate the clinical significance of PSMB8-AS1 in predicting ACS, and to explore its correlation with plaque burden, and concentrations of adhesion molecules (VCAM1 and ICAM1) and inflammatory cytokines (IL-1β and IL-6).

## Materials and methods

### Human subjects and sample collection

In this study, we recruited 172 ACS patients from July 2020 to October 2023 in the department of cardiology at The Seventh People's Hospital of Zhengzhou. This was in line with the following inclusion criteria: patients meeting the diagnostic criteria of ACS for the first time and confirmed through CAG. The exclusion criteria included: (1) those with severe liver and kidney impairment; (2) individuals with severe heart failure; (3) those with uncontrolled severe arrhythmias; (4) those with cancer; and (5) those with severe infections. We also recruited 109 patients who were admitted or visited the outpatient department due to chest pain from July 2020 to October 2023, but were excluded from a diagnosis of CAD based on CAG or coronary computed tomography angiography (CTA). The 109 non-CAD patients with chest pain demonstrated the following etiological distribution: intercostal neuralgia (n = 8), reflux esophagitis (n = 25), cervical spondylopathy (n = 9), cardiac neurosis (n = 29), myocardial bridging (n = 21), and unexplained chest pain (n = 17). To establish a stable biological reference baseline for PSMB8-AS1 expression, we additionally recruited 41 healthy individuals with no cardiovascular diseases undergoing routine health check-ups.

To validate the predictive capacity of PSMB8-AS1 for ACS, we included a validation cohort comprising 26 ACS patients from Nanyang Central Hospital and 15 patients with chest pain who were excluded from a diagnosis of CAD based on CAG or coronary CTA.

Serum samples were collected from all participants at the time of their hospitalization or outpatient visit. Blood samples were collected into serum separation tubes containing clot activator. Tubes were gently inverted 5–8 times and allowed to clot at room temperature for 30–45 min. Clotted samples were centrifuged at 1,500 × g for 10 min to separate serum. The supernatant serum was aliquoted into cryovials and stored at −80 °C until analysis. All procedures were completed within 2 h of blood collection.

The ethical committee of The Seventh People's Hospital of Zhengzhou and Nanyang Central Hospital approved the protocol for this study. All procedures were conducted in strict accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all patients or their first-degree relatives prior to the study.

### Coronary angiography and optical coherence tomography analysis

The severity and extent of coronary stenosis in all 172 ACS patients were assessed using the Gensini scoring system. Among these patients, optical coherence tomography (OCT) examinations were performed on the culprit plaques of 40 individuals. The underlying plaques were analyzed from the distal reference to the proximal reference. The reference was defined as the cross-section with the largest lumen area within 10 mm distal and proximal to the target lesion. Plaques were classified as fibrous plaques (n = 4) or lipid plaques (n = 36). For each lipid plaque, the lipid arc was measured at 1 mm intervals throughout the entire lesion to calculate the mean lipid arc, while the fibrous cap thickness (FCT) was measured at its thinnest point three times, and the average value was computed. Additionally, the lipid core length was recorded based on the longitudinal OCT view. Minimal lumen area (MLA) was defined as the smallest lumen area within the length of the plaque.

### Enzyme-linked immunosorbent assay (ELISA) of inflammatory cytokines

According to the manufacturer's protocol (ELISA array kit, Boster, Wuhan, China), we measured the concentrations of adhesion molecules (VCAM1 and ICAM1) and inflammatory cytokines (IL-1β and IL-6) in serum isolated from coronary blood samples in 18 ACS patients undergoing thrombus aspiration.

### RNA isolation and real-time PCR

In this study, real-time PCR was performed to assess the expression levels of PSMB8-AS1 in serum samples. Initially, total RNA from serum was extracted using Trizol® reagent (Invitrogen, Carlsbad, CA), following the supplier's standard protocol. RNA quality was assessed by measuring A260/A280 ratios using a Nanodrop ND-3000 (Thermo Fisher Scientific). Samples with ratios outside 1.8–2.1 were excluded. RNA integrity was verified by 1.5% agarose gel electrophoresis, confirming intact 28S and 18S ribosomal RNA bands (28S:18S ≈ 2:1). The concentration of qualified RNA was determined at 260 nm absorbance.

Subsequently, 300 ng of total RNA from each qualified sample was reverse transcribed using the SuperScript™ IV First-Strand Synthesis System (Thermo Fisher Scientific; Cat. No. 18091050) according to the manufacturer's protocol. Real-time qPCR was performed using TaqMan™ Fast Advanced Master Mix (Thermo Fisher Scientific; Cat. No. 4444557) with Taqman probe assay Hs04232148_m1 for PSMB8-AS1 (Thermo Fisher Scientific) and Hs99999905_m1 for GAPDH (Thermo Fisher Scientific) on a StepOnePlus system (Applied Biosystems).

The expression levels of PSMB8-AS1 were normalized to the expression of GAPDH. For each sample, the relative expression of PSMB8-AS1 was calculated using the ΔCt method. Specifically, the difference in Ct values between PSMB8-AS1 and GAPDH was calculated (ΔCt = Ct[PSMB8-AS1]—Ct[GAPDH]). The relative expression level of PSMB8-AS1 was then determined using the formula 2^(-ΔCt). Then, the individual relative expression values of ACS and non-CAD patients were normalized to the average PSMB8-AS1 expression level in the 41 healthy individuals, enabling calculation of fold changes relative to this unified baseline.

### Statistical analysis

Continuous variables were reported as mean ± standard deviation for normally distributed data or as median (25 th–75 th percentiles) for non-normally distributed data. The normality of data distribution was assessed

using the Kolmogorov–Smirnov test. Independent sample t-test or Mann–Whitney U test was performed for comparison of continuous variables between groups. Categorical data were shown as counts (proportions) and were compared with the chi-squared test or Fisher exact test as appropriate.

Multivariable logistic regression analysis was used to assess the association between PSMB8-AS1 and ACS. Adjustments were made for traditional cardiovascular risk factors (age, sex, hypertension, current smoking, diabetes, and dyslipidemia). The results are presented as odds ratios (OR) with 95% confidence intervals (CI).

*Correlation analysis was conducted using Spearman correlation*

Receiver operating characteristic curves (ROC) were plotted to examine the sensitivity, specificity, and area under the curves (AUC) of PSMB8-AS1 to predict ACS. The cut-off values were determined using Youden index. The AUC of PSMB8-AS1 for predicting ACS was compared using nonparametric method with pROC package in R 4.2.0.

Statistical significance was assumed at p less than 0.05, and all reported p values are 2-sided. Statistical analysis was performed with SPSS (Version 22.0) and R (Version 4.2.0).

## Results

### Baseline characteristics

Table 1 presents the baseline characteristics of the 109 non-CAD patients and 172 ACS patients included in this study. As shown, ACS patients were significantly older, had a higher proportion of males, more current smokers, and a greater prevalence of hypertension. Additionally, they exhibited higher white blood cell counts, neutrophil percentages, and levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), HbA1c, creatinine, and hs-CRP compared to non-CAD patients. The incidence of other cardiovascular risk factors, including diabetes and hyperlipidemia, were not significantly different between the two groups.

We also show the baseline characteristics of 41 healthy individuals (Table S1).

### Upregulated expression levels of PSMB8-AS1 in ACS patients

Figure 1A shows that the relative expression levels of PSMB8-AS1 in ACS patients (n = 172) were significantly higher than those in non-CAD patients (n = 109) [Mann–Whitney U test, 1.61 (1.25–2.21) vs 1.05 (0.81–1.46), $P < 0.0001$]. Additionally, thrombus aspiration was performed on the culprit vessels of 18 ACS patients, allowing us to compare the expression levels of PSMB8-AS1 in serum obtained from coronary blood and peripheral blood in these patients. The results indicated that PSMB8-AS1 expression was higher in coronary blood [Fig. 1B, Wilcoxon signed-rank test, 2.85 (2.34–3.60) vs 1.72 (1.29–2.10), $P < 0.0001$].

### Correlation between expression levels of PSMB8-AS1 and plaque burden

Animal studies have shown that the overexpression of PSMB8-AS1 accelerates atherosclerosis development. Therefore, we analyzed the correlation between PSMB8-AS1 expression levels and the severity of coronary lesions. Spearman correlation analysis indicated a positive correlation between the relative expression levels of PSMB8-AS1 and Gensini scores ($R = 0.504$, $P < 0.0001$, Fig. 2A). Additionally, among 40 ACS patients undergoing OCT examinations of the culprit lesion, 36 lipid plaques were identified. We investigated the relationship between the relative expression levels of PSMB8-AS1 and the quantitative OCT parameters of lipid plaque (Fig. 2B-E),

| Variable | non-CAD patient (n = 109) | ACS patient (n = 172) | P-value |
|---|---|---|---|
| Age, years | 57.5 ± 11.5 | 62.6 ± 11.2 | < 0.001 |
| Female, n(%) | 48 (44.0) | 54 (31.4) | 0.032 |
| Smoking, n(%) | 46 (42.2) | 96 (55.8) | 0.026 |
| Hypertension, n(%) | 33 (30.3) | 74 (43.0) | 0.032 |
| Diabetes, n(%) | 18 (16.5) | 45 (26.2) | 0.059 |
| Dyslipidemia, n(%) | 56 (51.4) | 104 (60.5) | 0.134 |
| Platelet count, $10^3$/ul | 212 ± 78 | 220 ± 64 | 0.341 |
| Hemoglobin, g/l | 143 ± 18 | 145 ± 16 | 0.393 |
| White blood count, $10^3$/ul | 6.6 ± 2.5 | 7.7 ± 3.2 | 0.002 |
| Neutrophil percentage, % | 62.8 ± 6.7 | 71.8 ± 11.1 | < 0.001 |
| TC, mmol/l | 3.83 ± 1.32 | 4.47 ± 1.19 | < 0.001 |
| TG, mmol/l | 1.18 (0.87–1.69) | 1.43 (1.06–2.02) | 0.003 |
| LDL-C, mmol/l | 2.32 ± 1.11 | 2.74 ± 0.94 | 0.001 |
| HDL-C, mmol/l | 1.26 ± 0.29 | 1.12 ± 0.27 | < 0.001 |
| HbA1c, % | 5.6 (5.5–6.0) | 5.9 (5.6–6.5) | < 0.001 |
| NTpro-BNP, pg/ml | 187 (60–438) | 200 (68–688) | 0.148 |
| Creatinine, μmol/l | 82 (64–91) | 84 (74–97) | 0.029 |
| hs-CRP, mg/L | 3.78 (1.90–4.71) | 5.76 (2.55–13.64) | < 0.001 |

**Table 1**. Baseline characteristics of non-CAD patients and ACS patients.

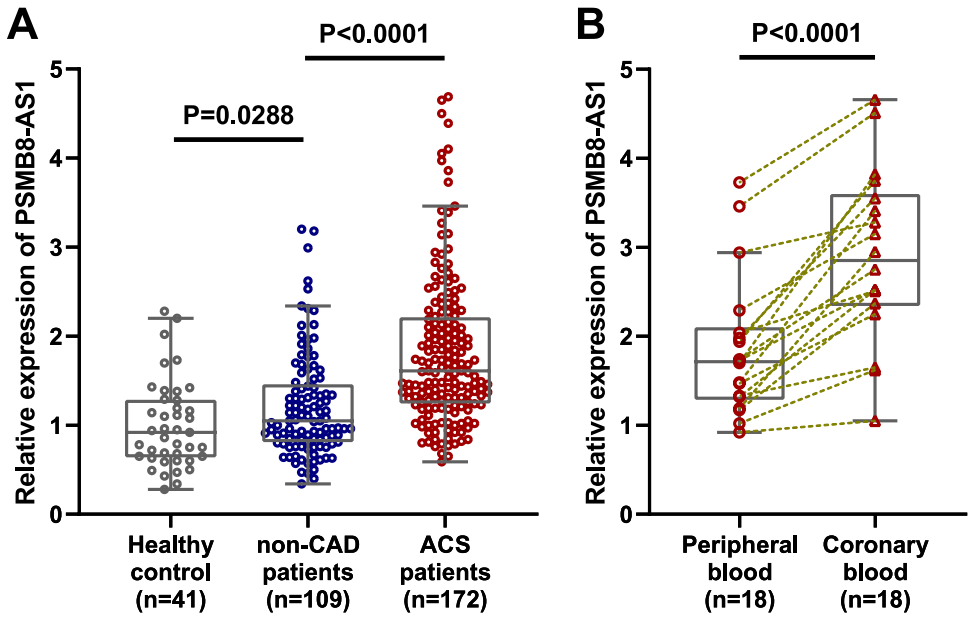



**Fig. 1**. Expression levels of lncRNA PSMB8-AS1. (**A**): Relative expression levels of PSMB8-AS1 in peripheral blood between healthy individuals (n = 41), non-CAD patients (n = 109), and ACS patients (n = 172). (**B**) Relative expression levels of PSMB8-AS1 between peripheral blood and coronary blood in ACS patients (n = 18). P-values are for Mann–Whitney U test (**A**) or Wilcoxon signed-rank test (**B**). Boxplots represented the median, interquartile (box) and 1.5 interquartile range (whiskers).

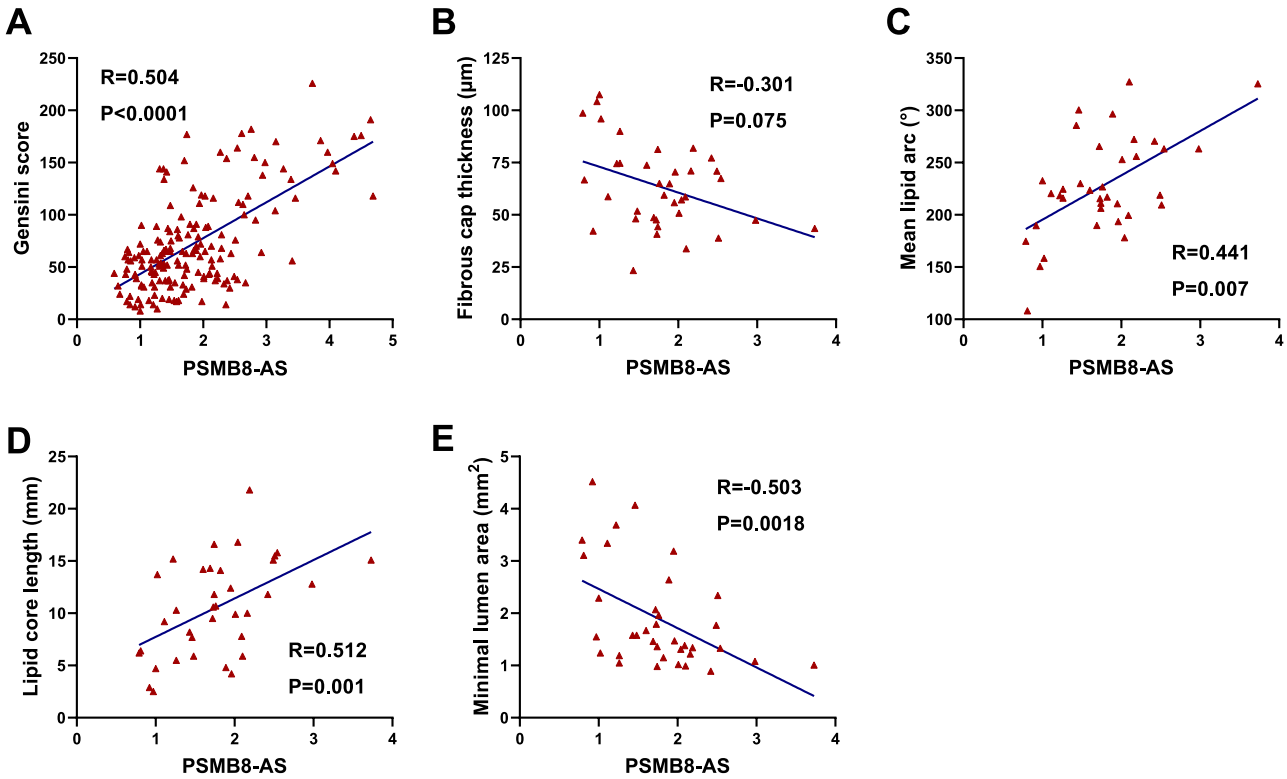



**Fig. 2**. Spearman correlation analysis of the expression of PSMB8-AS1 with plaque burden. Gensini scores (**A**, n = 172); Quantitative OCT parameters (n = 36): fibrous cap thickness (**B**), mean lipid arc (**C**), lipid core length (**D**), and minimal lumen area (**E**). P-values and R-values are for Spearman correlation analysis.

finding that higher expression levels were associated with larger mean lipid arc (R = 0.441, P = 0.007) and lipid core length (R = 0.512, P = 0.001), as well as smaller MLA (R = −0.503, P = 0.0018).

### Correlation between PSMB8-AS1 with adhesion molecules and inflammatory cytokines in coronary blood

The previous study showed that PSMB8-AS1 promotes monocyte/macrophage-endothelial cell adhesion and increases the expression of VCAM1 and ICAM1 in endothelial cells, suggesting that elevated levels of PSMB8-AS1 in the culprit plaques of ACS patients may be associated with higher concentrations of soluble adhesion molecules (VCAM1 and ICAM1) and inflammatory factors (IL-1B and IL-6). To investigate this further, we analyzed the correlation between PSMB8-AS1 levels and adhesion molecules and inflammatory factors in coronary serum from 18 ACS patients who underwent thrombectomy. Spearman correlation analysis revealed a strong correlation between PSMB8-AS1 levels and VCAM1 (R = 0.647, P = 0.0037), ICAM1 (R = 0.778, P = 0.0001), and IL-1B (R = 0.593, P = 0.01) in coronary serum (Fig. 3).

### PSMB8-AS1 could serve as an independent predictor of ACS

To investigate whether PSMB8-AS1 can independently predict ACS in patients presenting with chest pain, we conducted a multivariate logistic regression analysis, adjusting for age, gender, and cardiovascular risk factors. Our analysis revealed that higher levels of PSMB8-AS1 were independently associated with the occurrence of ACS (Unadjusted: OR = 3.973, 95% CI 2.467–6.398, P < 0.001; Adjusted: OR = 3.826, 95% CI 2.321–6.305, P < 0.001; Fig. 4). Additionally, we performed subgroup analyses, which showed no significant interaction effects, except for the gender subgroup (Fig. 4).

### Diagnostic value of PSMB8-AS1

ROC analysis demonstrated that PSMB8-AS1 alone exhibits good predictive ability (AUC = 0.746, 95% CI 0.686–0.805, P < 0.0001; Fig. 5A). The optimal cutoff level of PSMB8-AS1 for predicting acute coronary syndrome (ACS) was 1.345, with a sensitivity of 68.6% and a specificity of 70.6% (Fig. 5C). To evaluate the additional predictive value of PSMB8-AS1, we incorporated its levels into a model containing established risk factors for ACS, including age, sex, hypertension, current smoking, diabetes, and dyslipidemia. Notably, the

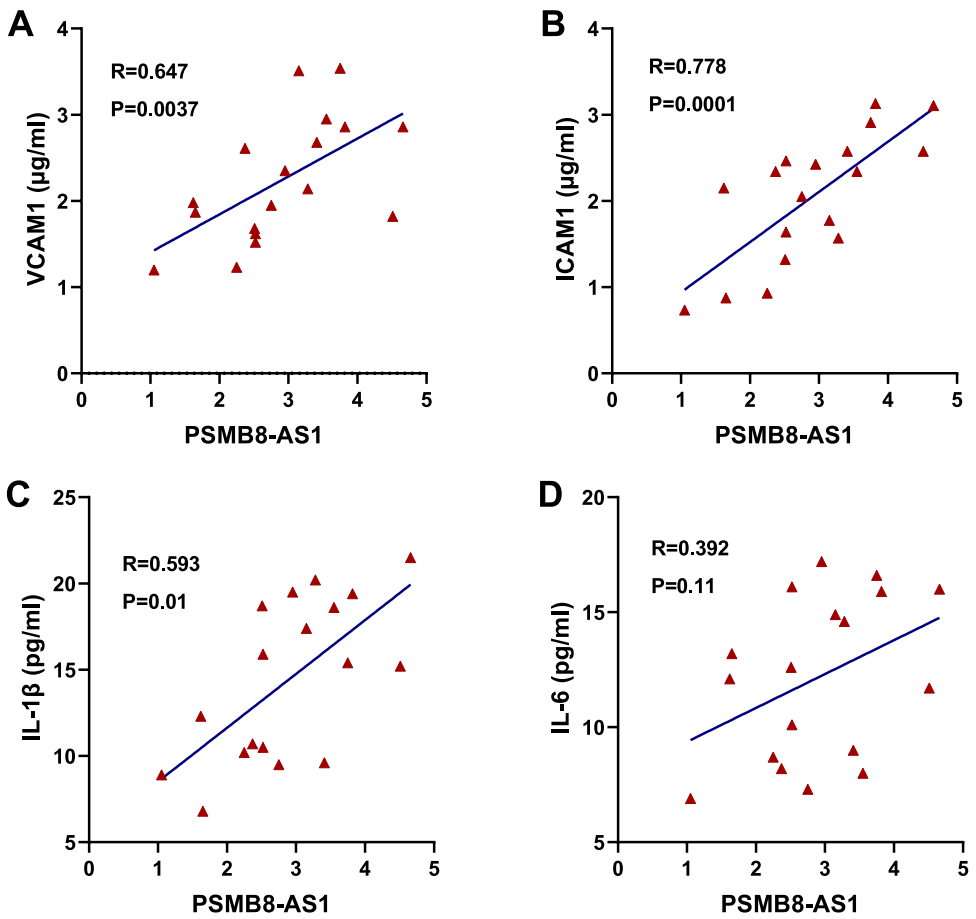



**Fig. 3**. Spearman correlation analysis of the expression of PSMB8-AS1 with adhesion molecules and inflammatory cytokines in coronary serum. Adhesion molecules (n = 18): VCAM1 (**A**) and ICAM1 (**B**); Inflammatory cytokines: IL-1B (**C**) and IL-6 (**D**). P-values and R-values are for Spearman correlation analysis.

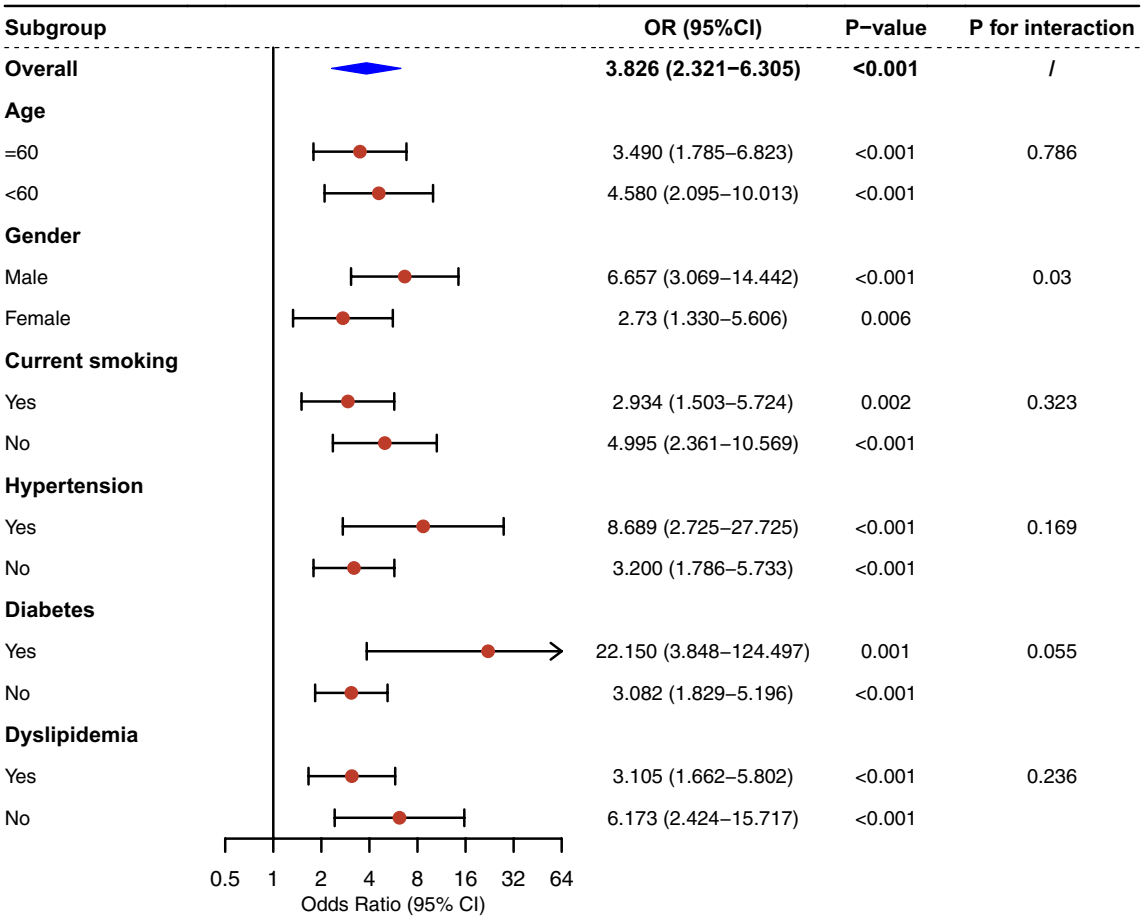



**Fig. 4**. Subgroup analysis for expression of PSMB8-AS1 and ACS across traditional cardiovascular risk factors. For the forest plot, red circle represents the point estimate of odds ratio, horizontal lines are the 95% confidence interval, vertical line signifies odds ratio of 1, and the diamond showed the odds ratio in the overall cohorts.

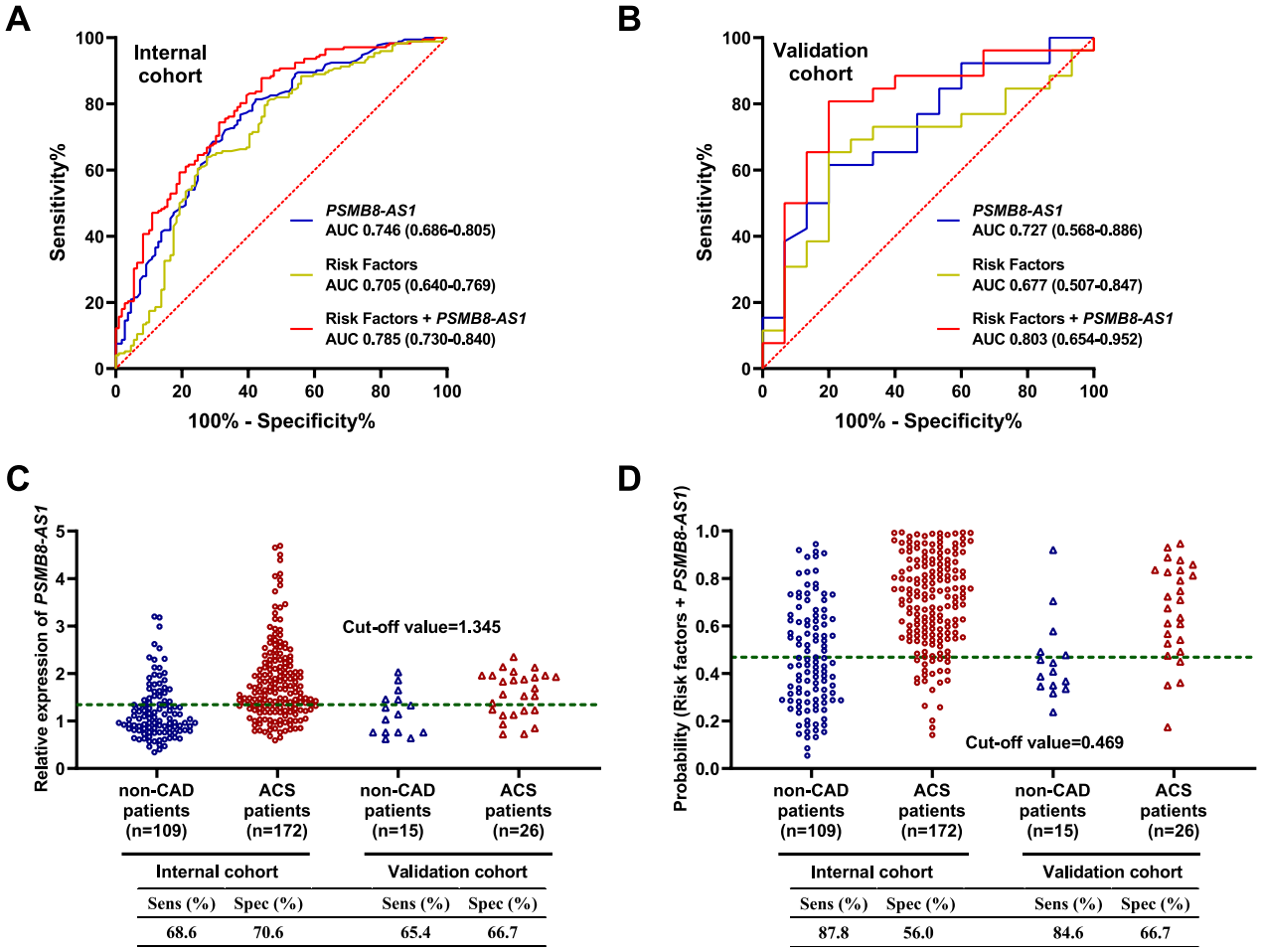
AUC significantly increased with the inclusion of PSMB8-AS1 (AUC: 0.705 vs 0.785, DeLong test P = 0.0036, Fig. 5A). The optimal cutoff probability threshold for this model was 0.469, achieving a sensitivity of 87.8% and a specificity of 56.0% (Fig. 5D).

To validate the predictive ability of PSMB8-AS1 levels and the model that included PSMB8-AS1 with optimal cutoff values derived from the internal cohort, we tested it in an external validation cohort consisting of 15 non-CAD patients and 26 ACS patients. ROC analysis showed that the inclusion of PSMB8-AS1 improved predictive ability (AUC: 0.677 vs 0.803, DeLong test P = 0.0514, Fig. 5B), and the sensitivity and specificity in the validation cohort were similar to those observed in the internal cohort (Figs. 5C and D).

## Discussion

Many studies have shown that lncRNAs are key regulators in the development of atherosclerosis and vascular injury[15–19]. While PSMB8-AS1 has previously been linked to other diseases, a recent study[29] found that PSMB8-AS1 enhances the adhesion of monocytes/macrophages to endothelial cells, promoting the progression of atherosclerosis in animal models. In line with these findings[29], our current research demonstrates that the PSMB8-AS1 level in the peripheral blood of ACS patients is significantly higher compared to non-CAD patients and healthy individuals. Furthermore, by analyzing the Gensini score and quantitative indicators from OCT measurements, we observed positive correlations between PSMB8-AS1 expression and the severity of coronary lesions or plaque burden. Additionally, we confirmed that, in blood from the local culprit lesions, PSMB8-AS1 levels positively correlate with VCAM1 and ICAM1 concentrations, further supporting findings[29] from the animal study suggesting that PSMB8-AS1 increases VCAM1 and ICAM1 levels.

Previous studies[31,32] have shown that the expression levels of various lncRNAs differ significantly between ACS patients and healthy controls, suggesting that certain lncRNAs could serve as novel biomarkers for predicting ACS. In our study, we found higher serum levels of PSMB8-AS1 in ACS, and further logistic regression analysis, adjusted for traditional cardiovascular risk factors, revealed that PSMB8-AS1 is independently associated with ACS. Furthermore, when we incorporated PSMB8-AS1 into the predictive model based on traditional cardiovascular risk factors, we found that this lncRNA significantly enhanced the model's ability to predict ACS.




| | Internal cohort | | Validation cohort | |
|---|---|---|---|---|
| | Sens (%) | Spec (%) | Sens (%) | Spec (%) |
| C | 68.6 | 70.6 | 65.4 | 66.7 |
| D | 87.8 | 56.0 | 84.6 | 66.7 |

**Fig. 5**. Diagnostic Value of PSMB8-AS1 in the internal and external validation cohorts. Roc analysis of PSMB8-AS1 alone, risk factors (age, sex, hypertension, current smoking, diabetes, and dyslipidemia), and risk factors combined with PSMB8-AS1 in the internal (**A**) and external validation (**B**) cohorts. The predictive ability by the relative expression of PSMB8-AS1 (**C**) and probability (**D**) derived from logistic regression model (risk factors combined with PSMB8-AS1) in the internal and external validation cohorts were compared between non-CAD patients and ACS patients.

Importantly, when we validated the model using an external cohort including additional non-CAD and ACS patients from other center, the model also demonstrated good predictive power.

While the animal study and our clinical data provide novel evidence of the association between PSMB8-AS1 and ACS, more researches are necessary to further establish its potential clinical applications. First, the sample size of our external validation cohort was relatively small, so larger cohorts are needed to confirm the ability of PSMB8-AS1 to distinguish ACS in patients with chest pain. Second, whether peripheral blood levels of PSMB8-AS1 in ACS patients can independently predict major adverse cardiovascular events is an area for future investigation. Finally, exploring whether combining PSMB8-AS1 with other ACS-related lncRNAs could further enhance diagnostic accuracy is a promising direction for future research.

## Conclusion

In summary, the expression level of PSMB8-AS1 in the peripheral blood of ACS patients is significantly higher than that in healthy individuals and non-CAD patients, correlating with the severity of coronary lesions. Locally at the site of the culprit lesion, PSMB8-AS1 expression positively correlates with VCAM1 and ICAM1 concentrations. More importantly, PSMB8-AS1 serves as an independent predictor for ACS, aiding in the differentiation of ACS patients from those presenting with chest pain.

## Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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## Author contributions

Conceptualization HW,; Investigation, HW, ZQZ, FZ, WHX; Writing, HW; Review, LY.

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## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

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