Expression level of miR-146a is associated with the coronary lesion severity and clinical prognosis in patients with unstable angina pectoris

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ABSTRACT

Objective: To investigate the association between plasma miR-146a expression levels, severity of coronary lesions, and clinical prognosis in patients with unstable angina pectoris (UAP).

Methods: A total of 100 patients with UAP and 100 controls were selected for assessment of plasma miRNA-146a expression levels. We assessed the severity of coronary lesions in patients with UAP using the Gensini score. Additionally, we analyzed the correlation between miR-146a expression and the degree of coronary artery stenosis in patients with UAP. The incidence of major adverse cardiovascular events (MACEs) was followed-up for 48 months after hospitalization and discharge. The median grouping method was employed to categorize patients into high- and low-expression groups based on their miR-146a levels. Thereafter, the incidence of MACEs in these groups was analyzed using the Kaplan–Meier method.

Results: The plasma expression level of miR-146a in the UAP group was 1.8-fold greater than that in the control group ($Z = 6.970$, $P < 0.001$) and correlated with the severity of coronary lesions; a high expression level was associated with a higher Gensini score ($P < 0.05$). Patients with high miR-146a expression levels showed a significantly higher incidence of MACEs than those with low miR-146a expression levels (log-rank test: $P = 0.004$).

Conclusion: Plasma miR-146a expression levels in patients with UAP correlated with the severity of coronary lesions, and patients with high miR-146a expression levels had poorer clinical prognoses than those with lower expression levels.

1. Introduction

Unstable angina pectoris (UAP) is a type of acute coronary syndrome (ACS). It is primarily caused by the rupture of coronary atherosclerotic plaques and thrombosis, which leads to partial or complete occlusion of the coronary artery, myocardial ischemia, and in severe cases, myocardial infarction. Compared to stable angina pectoris, UAP is associated with more severe and prolonged chest pain, which can be induced by lower levels of physical activity, may occur at rest, and is susceptible to progressive aggravation [1–3]. Compared to patients with stable angina pectoris, those with UAP have complex coronary artery lesions and a poor clinical prognosis. Exploring the mechanisms of UAP

development and identifying sensitive markers have become popular research topics [4].

MicroRNAs (miRNAs) are small non-coding RNAs that regulate approximately 30 % of genes in eukaryotes at the post-transcriptional level [5]. MicroRNAs primarily exert their regulatory effects by binding to the 3′ untranslated region (3′UTR) of target mRNAs, leading to either degradation or translational repression of target genes. Thus, microRNAs are involved in numerous physiological and pathological processes [6,7]. Several miRNAs are associated with the occurrence of coronary artery disease (CAD). For instance, miR-133, miR-208a, and miR-499 are linked to acute myocardial infarction (AMI); miR-21, miR-221, and miR-375 are associated with heart failure (HF); and

miR-34a, miR-126, and miR-217 are related to atherosclerosis (AS) [8–11]. Inflammation is a crucial factor in the development of ACS [12–14], and miRNAs may serve as biomarkers for the diagnosis, treatment, and prognosis of ACS [15–17]. MiR-146 was the first miRNA to be associated with inflammatory factors. miR-146 has two isoforms: miR-146a and miR-146b. Most studies on miR-146a have focused primarily on polymorphisms and tumors, and limited studies have investigated the correlation between miR-146a expression levels and the clinical prognosis of patients with UAP [18–23]. Therefore, the present study aimed to explore the relationship between miR-146a expression levels, coronary lesion severity, and clinical prognosis in patients with UAP.

2. Materials and methods

2.1. Study population

Two hundred participants (100 patients with UAP and 100 controls) who visited the Department of Cardiology of Xuzhou Medical University Affiliated Hospital between August 2018 and December 2018 were recruited for this study. The diagnosis of UAP conforms to the 2023 ESC guidelines [1]. All patients with UAP underwent coronary angiography to assess the severity of coronary lesions. The inclusion criterion for the UAP group required coronary artery stenosis of $\geq$50 % in at least one major coronary artery or its primary branches, accompanied by aggravation of angina pectoris or onset of angina at rest, without ST-segment elevation on an electrocardiogram or elevated myocardial markers. One hundred individuals meeting the criteria of coronary artery stenosis of $\leq$30 %, as determined through computed tomography angiography or coronary angiography, were simultaneously included as controls. Patients with congenital heart disease, rheumatic heart disease, history of viral myocarditis, chronic obstructive pulmonary disease, respiratory failure, severe liver and/or renal insufficiency, peripheral vascular disease, hematologic disease, tumors, or history of recent infection or trauma were excluded. The follow-up period was measured from the date of diagnosis to the occurrence of a major adverse cardiac event (MACE) or until December 15, 2022 (whichever came first). Cases lost to follow-up were classified as censored data. Plasma miR-146a levels were classified into high- and low-expression groups based on the median miR-146a expression levels. The study was conducted in accordance with the relevant guidelines and regulations of the Declaration of Helsinki. Informed consent was obtained from all participants and/or their legal guardians, and the study protocol was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (No: XYFYLW2017-002).

2.2. Clinical and laboratory data collection

The clinical and laboratory data of the patients were recorded upon admission and discharge. Those who meet the inclusion criteria will receive relevant examinations including biochemical routine, coagulation function, stool routine, and other index on an empty stomach in the early morning on the second day after admission, and send blood samples to detect the expression level of miR-146a. Venous blood (4 mL) was collected from each patient and placed in an anticoagulation tube containing ethylenediaminetetraacetic acid (EDTA). Plasma (1 mL) was collected from the blood sample and transferred to a DNAse/RNAse-free tube. It was thoroughly mixed with 1 mL of red blood cell lysate for 5 min and then centrifuged at 12 000 rpm for 60 s. The supernatant was discarded, and 1 mL of TRIzol was added to resuspend the precipitate. The samples were then stored in a refrigerator at −80 °C for cryopreservation to detect the expression level of miRNA-146a.

Polymerase chain reaction (PCR) amplification was conducted using a real-time fluorescence quantitative instrument (denaturation at 95 °C for 4 min, denaturation at 94 °C for 30 s, annealing at 55 °C for 50 s, elongation at 72 °C for 40 s, and elongation at 72 °C for 5 min after 40

cycles). The reaction system was as follows: 1 μL of downstream primer (10 μmol/L), 2 μL of DNA template, and water were added to replenish the solution to 50 μL. Total RNA was extracted using TRIzol LS Reagent, and 1 μg of total RNA was reverse transcribed into cDNA (KR118, Tiangen Biochemical). Quantitative reverse transcription (qRT)−PCR was performed to determine the expression of hsa-miRNA-146a-5p (miRbase accession number: MIMAT0000449). The relative expression of miRNA-146a was calculated using the $2^{-\Delta\Delta CT}$ method.

2.3. Calculation of the Gensini score

The severity of coronary stenosis was estimated via the Gensini score [24], where the degree of vascular stenosis was scored as follows: stenosis of $\leq$25 %, 1 point; 26–50 %, 2 points; 51–75 %, 4 points; 76–90 %, 8 points; 91–99 %, 16 points; and 100 % (occlusion), 32 points. The scoring coefficients of the different segmental coronary arteries were as follows: left main artery × 5.0; proximal segment of the left anterior descending × 2.5, middle segment × 1.5, and distal segment × 1.0; proximal segment of the left circumflex × 2.5; and both middle and distal segments × 1.0; proximal, middle, and distal segments of the right coronary artery × 1.0; and small branch × 0.5. The Gensini score for each patient with UAP was the sum of the product of the vascular stenosis score and the corresponding coefficient. Patients with UAP were classified into four groups according to the Gensini score quartile, and the relationship between the expression level of miR-146a and Gensini score was determined.

2.4. Clinical follow-up

MACEs in patients with UAP were followed-up for up to 48 months after discharge through outpatient review or telephone. The MACEs identified in this study were recurrent angina, HF, AMI, malignant arrhythmia, target vessel revascularization, and cardiac death.

2.5. Statistical analysis

All collected data were processed using the SPSS software (version 25.0; Chicago, USA). Count data are expressed as cases/percentages (n, %), and comparisons between groups were performed using the χ^2 test. All measurement data were assessed for normality using the Kolmogorov–Smirnov test. The normally distributed measurement data are expressed as the mean ± standard deviation (m ± SD) or presented as the median and interquartile range. Independent sample t-tests were used to compare data between the two groups. The Mann−Whitney *U* test was employed for pairwise comparisons if homogeneity of variance was not met. Univariate and multivariate Cox regression analyses were performed to identify prognostic factors, and factors with P < 0.2 in the univariate Cox analysis were included in the multivariate Cox model. Kaplan−Meier survival analysis (with the log-rank test) was used to evaluate the relationship between different expression levels of miR-146a and MACEs. Statistical significance was set at P < 0.05.

3. Results

3.1. Baseline characteristics

Compared with that in the control group, the number of male participants, smokers, and patients with hypertension or diabetes were significantly higher in the UAP group (P < 0.05). Age and body mass index (BMI) were significantly greater in the UAP group than in the control group (P < 0.05), whereas high-density lipoprotein cholesterol (HDL-C) and ApoA levels were significantly lower in the UAP group than in the control group (P < 0.05). No significant differences in WBC count, low-density lipoprotein (LDL-C), TC, TG, ApoB, LP(a), hsCRP levels, and Time (which was defined as the time interval between chest pain onset and the first blood samples collection) were observed between the two

Table 1
Baseline characteristics of the study participants.

	UAP group (n = 100)	Control group (n = 100)	F/χ²/t	P
Male sex (%)	74 (74 %)	48 (48 %)	14.208	<0.001
Hypertension (%)	58 (58.0 %)	34 (34.0 %)	11.594	0.001
Diabetes (%)	29 (29.0 %)	9 (9.0 %)	12.995	<0.001
Smoking (%)	31 (31.0 %)	11 (11.0 %)	12.055	0.001
Age (years)	65.15 ± 10.36	53.65 ± 12.91	3.124	<0.001
WBC (× 10^9/L)	6.00 (5.10, 7.18)	5.6 (4.9, 6.8)	1.343	0.179
HDL-C (mmol/L)	1.06 (0.90, 1.25)	1.22 (1.06, 1.38)	3.647	<0.001
LDL-C (mmol/L)	2.70 ± 1.00	2.81 ± 0.78	6.456	0.402
TC (mmol/L)	4.32 ± 1.23	4.59 ± 0.95	6.316	0.094
TG (mmol/L)	1.31 (0.93, 1.93)	1.12 (0.83, 1.77)	1.658	0.097
apoA (g/L)	1.00 (0.89, 1.13)	1.10 (0.99, 1.23)	2.808	0.005
apoB (g/L)	0.88 ± 0.26	0.87 ± 0.20	6.771	0.765
LP(a) (mg/L)	204 (119, 385)	165 (112, 268)	1.440	0.150
BMI (kg/m²)	25.18 ± 3.15	23.31 ± 4.64	2.747	<0.01
hs-cTnT(ng/L)	7.80 (4.10, 15.84)	5.26 (4.06, 12.92)	1.630	0.103
hsCRP (mg/L)	1.6 (1.1, 6.7)	1.3 (0.5, 4.75)	1.630	0.103
Time (h)	5.52 ± 2.02	5.18 ± 2.47	0.395	0.594

Abbreviations: WBC, white blood cell; TC, total cholesterol; TG, triglycerides; BMI, body mass index; Time, the time interval between chest pain onset and the first blood samples collection.

groups (P > 0.05) (Table 1).

3.2. Differences in the plasma miR-146a expression levels between the two groups

The expression levels of miR-146a differed between the two groups (Fig. 1). The expression level in the UAP group was significantly higher than that in the control group (P < 0.001).

3.3. Relationships between plasma miR-146a expression levels and the severity of coronary artery stenosis in patients with UAP

The Gensini scores of patients with UAP were grouped using the quartile method, and the relationship between the expression level of miR-146a and the Gensini score was determined. As the expression level of miR-146a increased, the Gensini score also gradually increased; this trend was statistically significant (P < 0.05). The results revealed that the expression level of miR-146a was related to the severity of coronary stenosis in patients with UAP (Table 2).

3.4. Relationship between the plasma miR-146a expression level and prognosis of patients with UAP

One hundred patients in the UAP group were followed-up for MACE during hospitalization and 48 months after discharge. Among these patients, 35 (35 %) were readmitted due to UAP, two (2 %)had malignant arrhythmia, two (2 %)exhibited HF; one (1 %)showed AMI, three (3 %)had revascularization of the target vessels, and three (3 %), died from cardiac causes. The UAP group was further divided into high- and low-expression groups based on their miR-146a expression levels using the median grouping method. Except for LP(a), no significant differences existed in the clinical characteristics between the two groups (Table 3). Kaplan–Meier analysis (Fig. 2) indicated that the incidence of MACEs in the high-expression group was significantly higher than that in the low-expression group (log-rank test, P = 0.004).
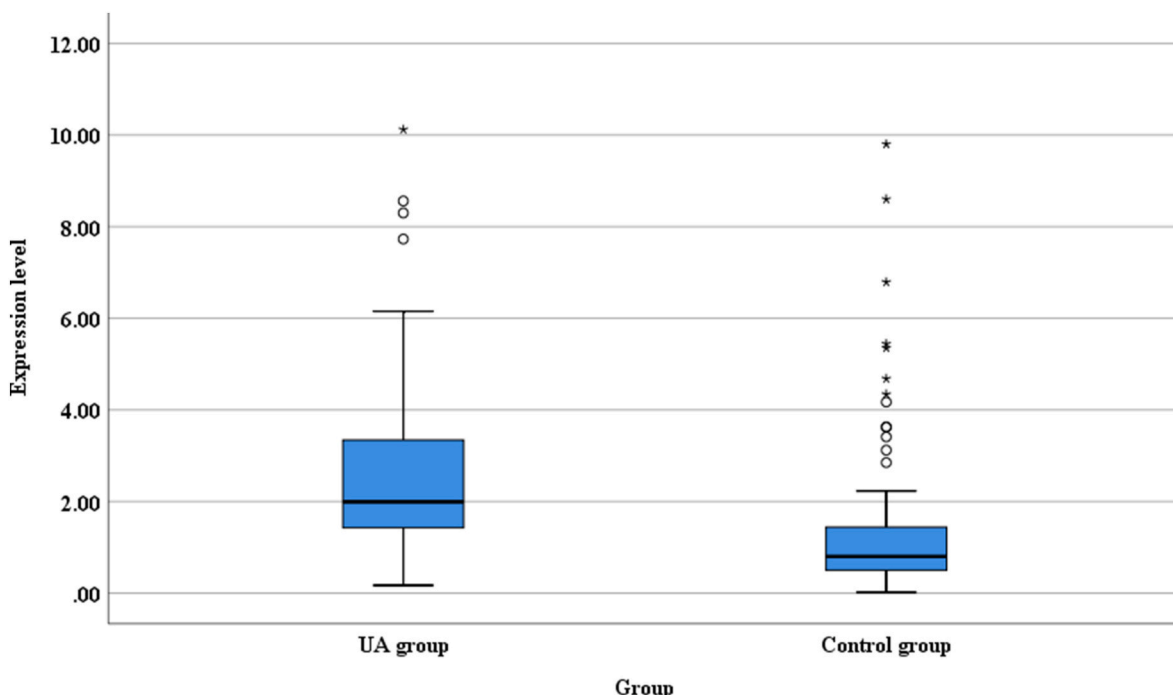

Fig. 1. Differences in the plasma miR-146a expression levels between the two groups.

Table 2

Relationship between the miR-146a expression level and coronary artery lesion stenosis severity in patients with UAP (Q1, 0–20; Q2, 21–30; Q3, 31–48; and Q4, >48).

Gensini Score	Q1	Q2	Q3	Q4	F	P
Expression level	2.12 ± 1.35	2.40 ± 1.72	2.42 ± 1.40	3.45 ± 2.46	2.702	<0.05

Table 3

Clinical characteristics of the UAP group.

	High-expression group (n = 50)	Low-expression group (n = 50)	$F/\chi^2/t$	P
Male sex (%)	37 (74.00 %)	37 (74.00 %)	0.000	1.000
Hypertension (%)	31 (62.00 %)	27 (54.00 %)	0.657	0.418
Diabetes (%)	14 (28.00 %)	15 (30.00 %)	0.049	0.826
Smoking (%)	16 (32.00 %)	15 (30.00 %)	0.047	0.829
Age (years)	63.96 ± 10.71	66.34 ± 9.96	0.251	0.253
WBC ($\times 10^9$/L)	6.38 ± 1.62	6.03 ± 1.58	0.000	0.271
HDL-C (mmol/L)	1.04 (0.90, 1.26)	1.06 (0.93, 1.24)	0.292	0.770
LDL-C (mmol/L)	2.77 ± 0.99	2.62 ± 0.88	0.110	0.410
TC (mmol/L)	4.46 ± 1.17	4.17 ± 1.17	0.076	0.229
TG (mmol/L)	1.19 (0.90, 1.76)	1.53 (1.02, 2.16)	1.678	0.093
apoA (g/L)	1.03 ± 0.19	1.03 ± 0.19	0.029	0.847
apoB (g/L)	0.92 ± 0.25	0.83 ± 0.23	0.285	0.069
LP(a) (mg/L)	147.5 (108.75, 290.25)	223 (131, 440.5)	1.979	0.048
BMI (kg/m^2)	25.26 ± 3.13	25.09 ± 2.97	0.007	0.776
hs-cTnT(ng/L)	7.82 (3.85, 11.97)	7.60 (5.17, 18.17)	1.106	0.269
hsCRP (mg/L)	2.4 (1.275, 17.325)	1.4 (0.7, 4.9)	0.993	0.321
Time (h)	5.61 ± 2.08	5.44 ± 1.97	0.231	0.754
Gensini score	32.00 (20.75, 50.00)	26.50 (19.00, 45.00)	1.104	0.270
Culprit lesion, n (%)				
Left main	4 (8.00 %)	2 (4.00 %)	/	0.678
Left anterior descending	41 (82.00 %)	42 (84.00 %)	0.071	0.790
Left circumflex	29 (58.00 %)	25 (50.00 %)	0.644	0.422
Right	30 (60.00 %)	32 (64.00 %)	0.170	0.680
Three-vessel disease	17 (34.00 %)	15 (30.00 %)	0.184	0.668
In-hospital PCI (%)	35 (70.00 %)	37 (74.00 %)	0.198	0.656
Medication at discharge				
DAPT (%)	46 (92.00 %)	47 (94.00 %)	0.154	1.000
Statins (%)	47 (94.00 %)	46 (92.00 %)	0.154	1.000
Beta-blockers (%)	34 (68.00 %)	27 (54.00 %)	2.060	0.151
ACEI/ARB (%)	14 (28.00 %)	11 (22.00 %)	0.480	0.488
CCB (%)	13 (26.00 %)	7 (14.00 %)	2.250	0.134

Abbreviations: DAPT, dual antiplatelet drug therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Time, the time interval between chest pain onset and the first blood samples collection.

3.5. Cox regression analysis of factors influencing the survival of patients with UAP

Univariate and multivariate Cox regression analyses were performed to identify prognostic factors, and factors with P < 0.2 in the univariate Cox analysis were included in the multivariate Cox model. The results showed that miR-146a expression was independently associated with the occurrence of MACEs in patients with UAP (Table 4).

4. Discussion

UAP is a key component of ischemic heart disease. Owing to its variable nature, it can either revert to stable angina or rapidly progress to AMI or lead to sudden death. Therefore, it is clinically significant to timely diagnose and treat UAP [1,2,25].

Inflammatory response is an important pathological mechanism that can affect CAD progression and prognosis. MiR-146a, which is located on human chromosome 5q33, was initially identified as an inflammation-associated miRNA. Expression levels of miR-146a are reportedly elevated in young patients with CAD, suggesting an association with this condition [7]. Notably, plasma miR-146a levels could serve as an indicator of the quality of coronary collateral circulation in patients with CAD [26]. The present study corroborated previous findings by revealing a positive correlation between miR-146a expression and the degree of coronary artery stenosis in patients with UAP. These findings indicate that miR-146a functions as an inflammation-associated miRNA involved in the initiation and progression of CAD.

Therapies targeting inflammation can effectively reduce the risk of cardiovascular events. Therefore, plasma inflammatory biomarkers hold promise for providing valuable prognostic information and potential targets for interventions in clinical practice [27,28]. To explore the relationship between plasma miR-146a expression levels and the prognosis of patients with UAP, MACEs in patients with UAP were monitored during hospitalization and up to 48 months after discharge. Our findings revealed that the incidence of MACEs in the high-expression group was significantly higher than that in the low-expression group. High miR-146a expression was associated with poorer clinical prognosis than low miR-146a expression in patients with UAP, indicating that miR-146a may be a reliable biomarker for evaluating the severity of coronary artery stenosis and predicting the prognosis of patients with UAP. Zhang et al. reported that miR-146a expression is elevated in patients with CHD and restenosis compared to that in patients with CHD but without restenosis [29]. Polymorphisms in miR-146a rs2910164 and rs2431697 are closely related to the risk of ACS, and patients with the miR-146a rs2910164 G allele may exhibit more serious lesions and worse prognoses after PCI [30,31]. Xiao et al. reported that patients with STEMI and high expression levels of miR-146a have a greater risk of MACEs than those with low expression levels of miR-146a over a 3-year follow-up period [32]. Scărlătescu et al. revealed an association between high levels of miR-146a-5p and MACE, and demonstrated that the expression level of miR-146a-5p is a predictor of MACE during 1 year of follow-up in STEMI patients [33]. Li et al. demonstrated that miR-4513 and miR-499 affect the probability of subsequent cardiovascular events following a diagnosis of CAD but observed no relationship between miRNA-146a and prognosis [21]. This contrasts with the findings of our study. Finally, considering that the present study was conducted in a single center with a small sample size, larger multicenter studies are required to confirm the correlation between miR-146a expression levels, coronary lesion severity, and clinical prognosis in patients with UAP. In addition, the follow-up time was too long, the intervals were lengthy, and recall bias may have been present.

In summary, our research indicates that the expression level of miRNA-146a is related to coronary lesion severity and prognosis. Detecting miRNA-146a levels may help evaluate disease severity and prognosis in patients with UAP. In addition, miR-146a can serve as a prognostic indicator and a potential novel target for UAP treatment.
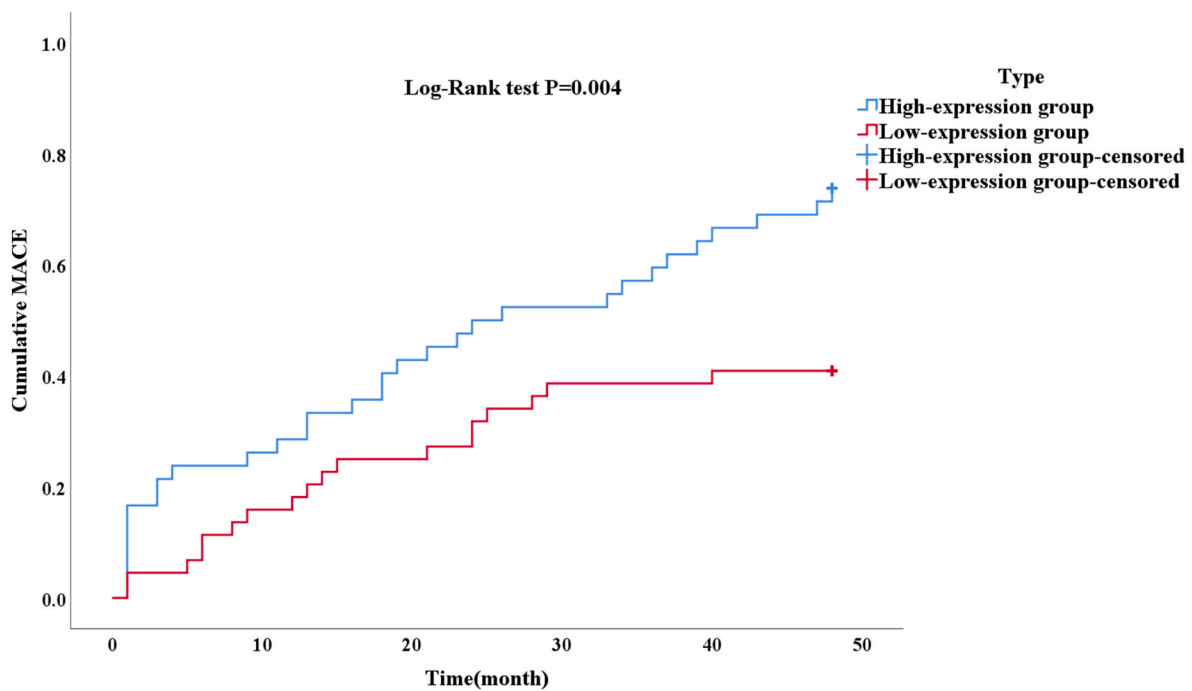
Fig. 2. Kaplan–Meier analysis of the cumulative incidence of MACEs.

Table 4
Univariate and multivariate Cox regression analyses.

Variable	Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P
Male sex	1.164 (0.607–2.234)	0.647		
Age	1.012 (0.982–1.043)	0.434		
Hypertension	0.714 (0.407–1.252)	0.239		
Diabetes	0.996 (0.543–1.830)	0.991		
Smoking	0.518 (0.258–1.040)	0.064	0.58 (0.26–1.32)	0.197
HDL-C	0.815 (0.271–2.451)	0.716		
LDL-C	1.087 (0.799–1.479)	0.596		
TC	1.068 (0.846–1.350)	0.579		
TG	1.207 (0.863–1.688)	0.271		
WBC	1.055 (0.889–1.252)	0.538		
N	1.055 (0.873–1.275)	0.582		
L	1.344 (0.831–2.175)	0.228		
M	4.876 (0.681–34.902)	0.115	10.88 (0.54–219.41)	0.119
PLT	1.000 (0.995–1.005)	0.976		
SII	1.000 (0.999–1.001)	0.517		
SIRI	1.274 (0.920–1.765)	0.145	0.96 (0.55–1.66)	0.884
apoA	0.277 (0.054–1.428)	0.125	0.32 (0.06–1.88)	0.208
apoB	1.813 (0.551–5.966)	0.327		
LP	1.000 (0.999–1.001)	0.859		
BMI	1.018 (0.940–1.103)	0.660		
Expression level	1.284 (1.099–1.500)	0.002	1.28 (1.06–1.53)	0.008
Gensini score	1.002 (0.992–1.013)	0.696		
hs-cTnT	0.999 (0.988–1.011)	0.919		
hsCRP	1.010 (0.975–1.048)	0.572		
In-hospital PCI	1.235 (0.644–2.371)	0.525		

Abbreviations: N, Neutrophil; L, Lymphocyte; M, Monocyte; PLT, Platelet; SII, systemic immune-inflammation index; SIRI, system inflammation response index.

5. Conclusion

The findings of our study demonstrated that the plasma miR-146a expression level in patients with UAP was correlated with the severity of coronary lesions. In addition, patients with higher miR-146a expression levels had poorer clinical prognoses than those with lower expression levels.

CRediT authorship contribution statement

Binbing Shi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Xiaotong Wang:** Writing – original draft, Methodology, Data curation, Conceptualization. **Tongneng Xue:** Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Jie Liu:** Methodology, Investigation, Data curation, Conceptualization. **Wanling Wu:** Methodology, Data curation, Conceptualization. **Yuanyuan Luo:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Hong Zhu:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Defeng Pan:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Data curation, Conceptualization.

Data Availability Statement

The datasets used in this research are available on aupon reasonable request from the corresponding author (Defeng Pan, MD.).

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Conflict of interest

The authors declare that they have no competing interests.

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Not applicable.

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