

RESEARCH ARTICLE

Expression and diagnostic value of circulating miRNA-190 and miRNA-197 in patients with pulmonary thromboembolism

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Abstract

Background: Diagnosing pulmonary thromboembolism (PTE) remains challenging due to the lack of specific clinical symptoms and biomarkers. Circulating microRNAs (miRNAs) have proved to be potential biomarkers for numerous cardiovascular diseases. The aims of this study were to quantitatively analyze the expression of plasma miRNA-190 and miRNA-197 in patients with PTE and to evaluate the diagnostic value for PTE.

Methods: Thirty patients diagnosed with PTE by computed tomographic pulmonary angiography at the emergency department were enrolled in this study, and plasma was collected immediately. For comparison, myocardial infarction (MI, $n = 45$) and healthy participants (NC, $n = 45$) were recruited as the control groups. Quantitative reverse transcription PCR (qRT-PCR) was conducted to reveal the relative expression levels of miRNA-190 and miRNA-197 in each group. The plasma concentrations of D-dimer were measured by immunoturbidimetric assay. The diagnostic value was evaluated by analyzing the area under the receiver operating characteristic curve (AUC).

Results: The relative expression levels of miRNA-190 and miRNA-197 in the PTE group were both significantly higher than in the MI group ($t = 3.602$, $t = 4.791$, $P < .05$, respectively) and the healthy control group ($t = 5.814$, $t = 5.886$, $P < .05$, respectively). As diagnostic indicator, the sensitivity and specificity of miRNA-190 were 75.56% and 80%, respectively, with an AUC of 0.7844 (95%CI: 0.6858-0.8831, $P < .001$). The sensitivity and specificity of miRNA-197 were 73.33% and 86.67%, respectively, with an AUC value of 0.7931 (95%CI: 0.6870-0.8991, $P < .001$). Combining miRNA-190 and miRNA-197 with D-dimer levels significantly increased the diagnostic power, improving the AUC to 0.9536 (95% CI: 0.9083-0.9989, $P < .001$).

Conclusions: The relative expression levels of miRNA-190 and miRNA-197 in PTE patients were significantly higher than in the MI and healthy control groups, indicating that (a) both may be involved in the pathophysiological process of PTE and (b) both may serve as potential noninvasive diagnostic markers for PTE. The combination of

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miRNA-190, miRNA-197, and D-dimer levels showed better sensitivity and specificity, which is more conducive to the diagnosis of PTE.

KEYWORDS

combined diagnosis, miRNA-190, miRNA-197, pulmonary thromboembolism

1 | INTRODUCTION

Pulmonary thromboembolism (PTE) is an emergent and common cardiovascular disease. It is caused by thrombi from the venous system or the right heart and shows high morbidity and mortality. Together with deep vein thrombosis, PTE is the third most common cause of cardiovascular death, after heart attack and stroke.¹ The clinical presentation of PTE is variable and non-specific, including symptoms such as asymptomatic thrombosis, chest pain, shortness of breath, and sudden death,² which are similar to those of myocardial infarction (MI) or aortic dissection, making the diagnosis of PTE difficult and frequently causing misdiagnosis.³ Computed tomographic (CT) pulmonary angiography or noninvasive ventilation-perfusion scintigraphy have become the preferred imaging methods for the diagnosis of PTE in patients with a high clinical probability,^{4,5} but there are some limiting situations, such as allergies, unstable vital signs and renal failure.⁶ The noninvasive examinations for diagnosing PTE include D-dimer level measurements, electrocardiography, and echocardiography, among which D-dimer tests are widely used in patients with suspected PTE⁷; however, although D-dimer tests exhibit high sensitivity, they are nonspecific.⁸ Therefore, the exploration of novel biomarkers with higher accuracy and sensitivity is very important and could greatly facilitate the diagnosis and treatment of PTE.

MicroRNA (miRNA) is a type of endogenous, noncoding, single-stranded RNA with a length of 21 to 25 nucleotides. MiRNAs possess tissue or organ specificity and can participate in the pathological processes of diseases by regulating gene expression via translational repression or mRNA degradation.⁹ Also, miRNA has been detected *in vitro* as a stable form in the blood circulation. Therefore, it has the potential to become a diagnostic biomarker for numerous diseases, such as lung cancer,¹⁰ heart failure,¹¹ and acute MI.¹²

Recent studies have reported that overexpression of miRNA-190 enhances the hypoxia response, which is mediated by hypoxia-inducible factors (HIFs),¹³ thereby participating in the regulation of hypoxia-induced pulmonary hypertension.¹⁴ MiRNA-197 has been linked with platelet activation and intravascular inflammation,¹⁵ and it can be used as a diagnostic biomarker for nonsmall cell lung cancer.¹⁶ However, the plasma levels of miRNA-190 and miRNA-197 in PTE patients have not been investigated. The purpose of the present study was to explore the sensitivity and specificity of miRNA-190 and miRNA-197 as PTE diagnostic markers to evaluate their potential clinical significance.

2 | METHODS

2.1 | Patients of the study group

Thirty patients with PTE who were admitted to the Suzhou Ninth People's Hospital between July 2017 and June 2019 were enrolled in this study. PTE was diagnosed by CT pulmonary angiography in line with the "2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism".¹⁷ Whole blood samples were taken at the emergency department on the day of admission. Participation in the study was voluntary and all patients gave their written informed consent before they entered the study. The study was approved by the ethics committee of the Suzhou Ninth People's Hospital.

2.2 | Patients of the control groups

Forty-five patients with MI at the emergency department and forty-five healthy individuals in the same time period were included for comparison. Also, whole blood samples were taken on the day of admission.

2.3 | Blood sampling and RNA isolation

Blood samples from individuals were obtained with EDTA-anticoagulant vacuum tubes. The samples were centrifuged at 1800 *g* for 20 minutes at 4°C within 2 hours after collection. After centrifugation, the supernatant was transferred to an RNase/DNase-free tube and stored at -80°C until further analysis. Total RNA was isolated from plasma using TRIzol LS (Invitrogen) according to the manufacturer's instructions. One volume of plasma was mixed with three volumes of TRIzol LS, and samples were incubated for 5 minutes at room temperature for dissociation of nucleoprotein complexes. Chloroform was added to the homogenate and after 5 minutes incubation at room temperature; samples were centrifuged at 12 000 *g* for 15 minutes at 4°C. The upper aqueous phase was transferred to a fresh reagent tube and washed in 75% ethanol by vortexing. Finally, purified RNA was dissolved with 10 μ L of RNase-free water, and samples were stored at -80°C until qRT-PCR analysis.

2.4 | Quantitative reverse transcription PCR

Total RNA (normalized to 5ng/ μ L by nuclease-free water) was reverse-transcribed using PrimeScript RT reagent Kit with gDNA

Eraser according to the manufacturer's protocol. The resulting cDNA was stored at -20°C for the following qRT-PCR. qRT-PCR was carried out according to the standard protocol on a PCR system (ABI7500) using a FastStart Universal SYBR Green Master Mix kit (Roche, Basel, Switzerland). Each reaction was performed in a final volume of $20\ \mu\text{L}$, containing $10\ \mu\text{L}$ SYBR Green I mix, $4\ \mu\text{L}$ cDNA, $1\ \mu\text{L}$ forward primer, $1\ \mu\text{L}$ reverse primer, and $4\ \mu\text{L}$ RNase-free H_2O . The mix was incubated at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds, 62°C for 45 seconds, and 72°C for 45 seconds. Each sample was tested in triplicate and melting curve analysis (collected at $60\text{--}95^{\circ}\text{C}$) was performed to validate the specificity of the PCR products. The sequences of primers were as follows: miRNA-190, forward 5'-GGGTGATATGTTTATATATTAGG-3' and reverse 5'-CAGTGCCTGTCGTGGAGT-3'; miRNA-197, forward 5'-GGTTCACCACCTTCTC-3' and reverse 5'-CAGTGCCTGTCGTGGAG-3'; GAPDH, forward 5'-GGTGAAGTCCGAGTCAACG-3' and reverse 5'-CAAAGTTGCATGGATGACC-3'. The relative expression of miRNA-197 and miRNA-190 was calculated by the $2^{-\Delta\Delta\text{Ct}}$ method¹⁸ and normalized to the level of GAPDH.

2.5 | D-dimer testing

Plasma D-dimer levels were measured by an immunoturbidimetric assay (ACL TOP 750 LAS; Instrumentation Laboratory, Fullerton, CA, USA) according to the manufacturer's protocol.

2.6 | Statistical analysis

Data were analyzed with SPSS version 20.0 (SPSS, Inc, Chicago, IL), and values are expressed as mean \pm SEM. For continuous variables, the independent samples Student t test was used. The receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were utilized to assess the diagnostic value of the identified miRNAs for PTE. Data were considered statistically significant at $P \leq .05$. Each experiment consisted of at least three replicates per condition.

3 | RESULTS

3.1 | Baseline characteristics of individuals

Thirty patients (age, 46.15 ± 8.25 years; 57% male) who presented with acute symptom onset at the emergency department and were diagnosed with PTE were enrolled. Characteristics of individuals enrolled in the study are listed in Table 1. No significant difference in the distribution of age, gender, and D-dimer was found between PTE patients, MI patients, and healthy individuals (Table 2).

TABLE 1 Characteristics of PTE patients

Characteristics	
PTE patients	30
Age	46.15 ± 8.25
Male	17
CTA confirmed central PTE	100%
Risk stratification	
High (>15%)	3/30
Intermediate (3-15%)	18/30
Low (<1%)	9/30
Symptoms	
Dyspnea	22/30
Chest pain	14/30
Cough	5/30
Hemoptysis	4/30
Syncope	2/30
Idiopathic DVT	12/30
Risk factors	
Malignancy	3/30
Surgery within 1 mo	4/30
Immobilization	5/30
COPD	2/30
Previous deep vein thrombosis	6/30

TABLE 2 No significant differences in the distribution of age, gender, and D-dimer levels were found between PTE patients, MI patients, and healthy individuals

	PTE patients n = 30	MI patients n = 45	P-value
Age	46.15 ± 8.25	49.20 ± 5.35	.21
Male (%)	57	52	.13
BMI (kg/m ²)	28.6 ± 6.8	30.9 ± 5.3	.26
LV-EF (%)	62 ± 3	57 ± 6	.04
Hypertension (%)	67	83	.14
Smoking (%)	13	44	.01
Diabetes mellitus (%)	23	26	.54
Positive family history (%)	7	40	.001
D-dimer (mg/L)	10.7 ± 8.65	7.24 ± 5.32	.10

3.2 | The expression levels of miRNA-190 and miRNA-197 in PTE patients and control groups

The expression levels of miRNA-190 in the PTE, MI, and healthy control groups were 3.01 ± 2.01 , 1.80 ± 1.02 , and 1.18 ± 0.67 , respectively, indicating a significant upregulation in PTE patients compared to the other two groups ($t = 3.602$, $t = 5.814$, $P < .05$) (Figure 1A).

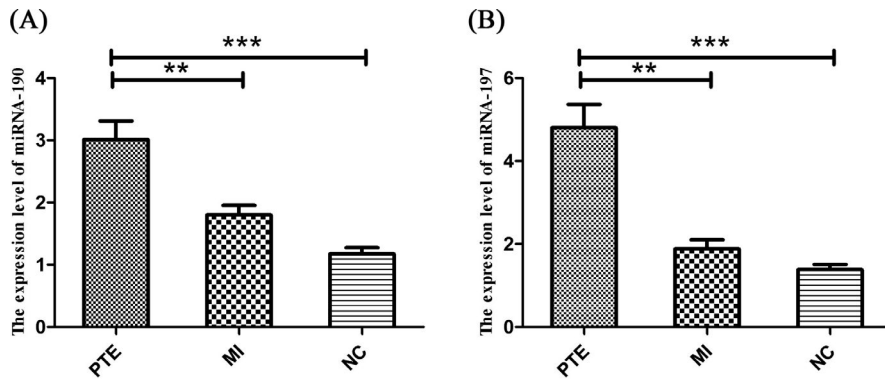


FIGURE 1 Plasma levels of miRNA-190 and miRNA-197 in PTE patients and matched control groups. PTE: pulmonary thromboembolism; MI: myocardial infarction; NC: normal controls. * $P < .05$

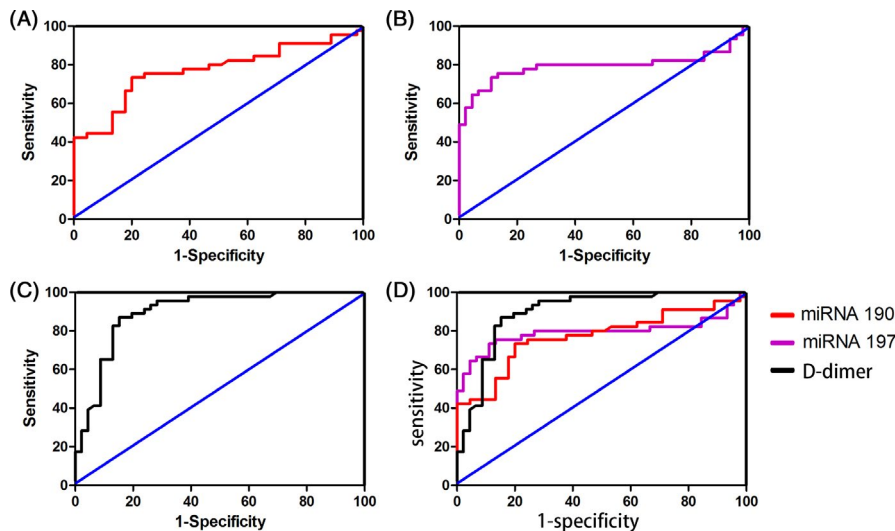


FIGURE 2 Receiver operating characteristic (ROC) curve analysis of miRNA-190 and miRNA-197 to discriminate PTE patients from healthy controls

TABLE 3 ROC statistics

	AUC	95% CI	P	Sensitivity (%)	Specificity (%)
miRNA190	0.7844	0.6858~0.8831	<.001	75.56%	80%
miRNA197	0.7931	0.6870~0.899	<.001	73.33%	86.67%
D-dimer	0.8970	0.8301~0.9639	<.001	95.96%	71.74%
miRNA190 + D-dimer	0.9294	0.8757~0.9830	<.001	93.33%	82.22%
miRNA197 + D-dimer	0.9190	0.8587~0.9793	<.001	84.44%	86.67%
miRNA190 + miRNA197	0.9136	0.8516~0.9756	<.001	80.00%	93.33%
miRNA190 + miRNA197+ D-dimer	0.9536	0.9083~0.9989	<.001	86.87%	95.56%

Likewise, the levels of miRNA-197 were higher in the PTE group than in the other two groups ($t = 4.791$, $t = 5.886$, $P < .05$) (Figure 1B).

3.3 | The diagnostic power of miRNA-190 and miRNA-197 for PTE

ROC curve analysis was performed to evaluate the diagnostic capability of miRNA-190 and miRNA-197. For miRNA-190, the AUC was 0.7844 (95% CI: 0.6858-0.8831, $P < .001$), with a sensitivity of 75.56% and a specificity of 80% at the optimal cutoff value of 1.598 (Figure 2A). For miRNA-197, the AUC was 0.7931 (95% CI: 0.6870-0.8991, $P < .001$),

with a sensitivity of 73.33% and a specificity of 86.67% at the optimal cutoff value of 2.40 (Figure 2B). ROC curve analysis revealed that the AUC of D-dimer was 0.8970 (95% CI: 0.8301-0.9639), with a sensitivity of 95.96% and a specificity of 71.74% (Figure 2C).

3.4 | Diagnostic value of the combination of miRNA-190, miRNA-197, and D-dimer levels for PTE

To evaluate the diagnostic value of miRNA-190 and miRNA-197 as new diagnostic biomarkers of PTE, ROC analysis was performed on the combination of the two markers. Detailed ROC statistics

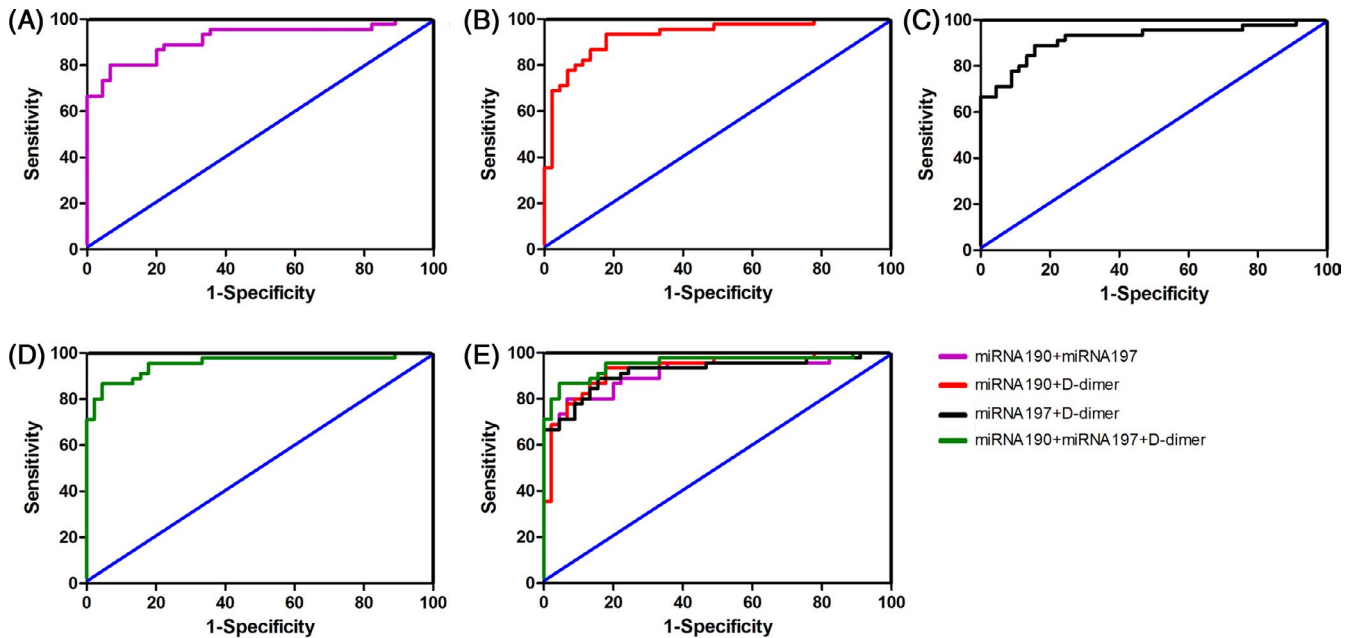


FIGURE 3 ROC analysis of combinations of miRNAs and D-dimer for PTE diagnosis

are shown in Table 3. Combining miRNA-190 with miRNA-197 significantly increased the diagnostic power, improving the AUC to 0.9136 (95% CI: 0.8516-0.9756, $P < .001$) (Figure 3A). We then tested the combination of miRNA-190, miRNA-197, and D-dimer. The diagnostic sensitivity and specificity for differentiating PTE from healthy individuals was further improved, with an AUC of 0.9536 (95% CI: 0.9083-0.9989, $P < .001$) (Figure 3E).

4 | DISCUSSION

PTE is one of the most common types of pulmonary embolism and is a leading cause of death due to cardiovascular disease, second only to acute coronary syndrome and stroke.² Owing to the acuteness and nonspecific clinical symptoms, PTE is difficult to diagnose, with a misdiagnosis rate of 30% in the emergency department.¹⁹ Nowadays, diagnosis of PTE mainly depends on the comprehensive evaluation of blood tests and imaging examinations, including D-dimer levels, B-ultrasound, electrocardiography, and echocardiography.²⁰ D-dimer is an important biomarker for PTE which can also be positive in patients with MI, infections, cancer, etc. As a result, it is better for exclusion than for diagnosis of PTE.⁷ CT pulmonary angiography is widely used for the diagnosis of PTE, with a sensitivity of 83%;⁶ however, there are some limiting situations, such as allergies, renal failure, and excessive exposure to radiation.²¹ Therefore, the exploration of a simple and reliable biomarker for PTE remains important.

MiRNA is a type of endogenous, noncoding, single-stranded RNA. MiRNAs can be stably expressed in plasma and play important roles in the regulation of gene expression in eukaryotic cells.¹⁰ MiRNA, which can serve as noninvasive biomarkers, has been widely studied in recent years due to their potential use in diseases such

as pulmonary inflammation and lung cancer.^{10,11,22} Studies have reported that miRNA-190 may participate in the regulation of hypoxia-induced pulmonary hypertension and miRNA-197 has been linked with platelet activation and intravascular inflammation.¹⁵ In the present research, we evaluated the expression levels of miRNA-190 and miRNA-197 in PTE patients, MI patients, and healthy participants by RT-PCR, to explore the potential clinical significance of miRNA-190 and miRNA-197 as novel biomarkers for PTE.

MiRNA-190 is an endogenous noncoding RNA derived from human *Kcnq5* mRNA, and it is believed to be significantly associated with hypoxic diseases, breast cancer, lung cancer, and pulmonary hypertension.^{13,23} A previous study has shown that miRNA-190 can be upregulated under hypoxic conditions,²⁴ reducing the activity of prolyl-4-hydroxylase, increasing the expression of HIFs and target genes of HIFs, and ultimately leading to the organism's response to hypoxia tolerance.¹³ According to a recent bioinformatics analysis, miR-190 plays an important role in vasoconstriction under hypoxic conditions.²⁵ The expression of miRNA-190 in pulmonary arterial smooth muscle cells was significantly increased under hypoxic conditions, which enhanced L-type Ca^{2+} channel-dependent Ca^{2+} entry in smooth muscles cells, resulting in the contraction of pulmonary arterial smooth muscle cells, which ultimately caused an imbalance in ventilation-perfusion and aggravated tissue hypoxia.²⁶ In this study, we found that miR-190 was upregulated in PTE patients compared to the other two groups. We speculate that in PTE patients, the thrombus elevates pulmonary circulation resistance and increases the pulmonary arterial pressure, thereby causing pulmonary hypoxia and enhancing the expression of miR-190. In MI patients, cardiac output is decreased and the degree of hypoxia in the pulmonary arteries is significantly lower than in the PTE group, so the expression of miRNA-190 is significantly lower than in the PTE group.

The expression of miRNA-197 in endothelial cells was proved to be significantly increased during platelet activation, suggesting that selected platelet miRNAs may have potential as biomarkers for vascular thrombosis.^{27,28} Studies have shown that platelet activation can cause changes in the expression of miRNAs, of which miRNA-197 is a marker of hypercoagulability and is significantly associated with venous thromboembolism; it is also a predictor of poor prognosis.²⁹ In the present study, the expression of miRNA-197 was significantly increased in PTE patients, suggesting that platelet activation is involved in the pathological process of PTE. It also explains the large amount of platelet consumption in PTE patients, especially in high-risk patients. To evaluate the diagnostic value of miRNA-190, miRNA-197, and D-dimer as biomarkers in PTE, ROC analysis was performed on the combination of the three. The results showed that the diagnostic power was significantly increased when the three markers were combined, indicating that this combination can improve the detection rate of PTE.

However, there are some limitations in our study. First, the number of individuals enrolled in this study is relatively small. Second, expression levels of miRNA-190 and miRNA-197 were not detected over a long period of time and the control group employed in this study was limited. Therefore, our findings need to be replicated in a larger cohort of patients.

5 | CONCLUSIONS

Our study shows that miRNA-190 and miRNA-197 are promising noninvasive and stable biomarkers to distinguish PTE from MI in the emergency department. Joint detection of miRNA-190 and miRNA-197 can improve the sensitivity and specificity of PTE diagnosis. Furthermore, combination with the traditional D-dimer marker can significantly increase the diagnostic power further and reduce the missed diagnosis and misdiagnosis rates.

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