

Circulating miR-125b but not miR-125a correlates with acute exacerbations of chronic obstructive pulmonary disease and the expressions of inflammatory cytokines

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Abstract

To investigate the correlation of miR-125a/b expression with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) patients and inflammatory cytokines.

Eighty-seven AECOPD patients, 93 stable chronic obstructive pulmonary disease (COPD) patients and 100 health volunteers (HCs) were recruited. Plasma samples were collected from AECOPD patients at the day 1, day 7, day 14, and day 28 of admission and from stable COPD patients as well as HCs. Total RNA was extracted from plasma, and miR-125a/b relative expressions were determined by quantitative real time-polymerase chain reaction.

MiR-125b had a great capacity for distinguishing AECOPD from stable COPD (AUC=0.926, 95% CI: 0.884–0.967) and HCs (AUC=0.923, 95% CI: 0.880–0.966), while miR-125a did not. There were associations between miR-125b expression with TNF- α , IL-8, and LTB-4 in AECOPD patients ($P=.012$, $P=.032$, and $P=.047$, respectively), while no correlation of miR-125a with inflammatory cytokines was found. MiR-125b expression gradually decreased at day 7, day 14, and day 28 compared with day 1 (all $P<.05$) on admission, while no difference in miR-125a was discovered between each visit compared to day 1. Besides, TNF- α , IL-1 β , IL-8, and LTB-4 were elevated in AECOPD patients compared with stable COPD patients (all $P<.01$).

MiR-125b, but not miR-125a, was positively associated with inflammatory cytokines and could be a novel biomarker for distinguishing AECOPD from stable COPD patients and HCs.

Abbreviations: AECOPD = acute exacerbations of chronic obstructive pulmonary disease, BMI = body mass index, CDX2 = caudal type homeobox 2, COPD = chronic obstructive pulmonary disease, ELISA = enzyme-linked immunosorbent assay, HC = health volunteer, ROC = receiver operating characteristic.

Keywords: AECOPD, chronic obstructive pulmonary disease, inflammatory cytokines, miR-125a, miR-125b

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive and partially reversible airflow limitation associated with inflammatory responses of normal.^[1–3] Stable COPD may lead to declines in lung functions, such as

airflow obstruction, airway function decline, and respiratory muscle fatigue, which influence patients' quality of life. However, acute exacerbations of COPD (AECOPD), defined as the worsening in respiratory symptoms may or may not warrant a change in underlying therapy and the symptoms will typically resolve over a period of days to weeks, is associated with high morbidity and WHO predicts that it will become the third leading cause of death by 2030.^[4]

MiRNAs are small endogenous RNAs that adjust gene expression and play a major role in the regulation of healthy development, disease status, and many other physiological processes.^[5,6] Besides, functional studies have identified the critical roles of many differentially expressed miRNAs in the regulation of airway inflammation, remodeling, and hyper-responsiveness.^[6,7] It has been suggested that miR-125a may inhibit innate macrophage responses by regulating macrophage differentiation and inflammation.^[8] Earlier studies have shown that miR-125a is related to the inflammatory chemokine pathway in systemic lupus erythematosus (SLE).^[9] Furthermore, miR-125b is found to increase type I IFN expression in airway epithelial cells, which potentially contributes to mucosal eosinophilia.^[10] In addition, recent data have shown that further elevation of miR-125b promotes greater activation and immune function in macrophages.^[11]

Previous studies have recognized numbers of microRNAs that may have remarkable regulatory functions in the progression of COPD, such as miR-223 and miR-15b in lung tissue.^[12–14] But

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the correlation of miR-125a or miR-125b in patients of AECOPD and stable COPD remains unclear. Hence, this study aimed to explore the associations of circulating miR-125a/b expressions with the risk of AECOPD and stable COPD and inflammatory cytokines.

2. Materials and methods

2.1. Participants

Eighty-seven AECOPD patients, 93 stable COPD patients, as well as 100 health volunteers (HCs) in the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology were consecutively included from December 1, 2014 to March 31, 2016. The eligibility of each group was presented as follows:

Stable COPD patients: Inclusion criteria were diagnosed with COPD by 2014 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria; age no <40 years; and no acute exacerbation for at least 3 months. The exclusive criteria were similar with AECOPD.

HCs were selected with age, gender, and body mass index (BMI) matched to total COPD patients. HCs with infection, lung diseases, renal or hepatic dysfunction and history of severe infection, solid tumor, hematological diseases, and autoimmune diseases were excluded.

AECOPD patients and stable COPD patients were recruited only once in our study, thus no overlap of patients between the 2 groups existed. All the participants signed the informed consents. This study was approved by the Ethics Committee of the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, and conducted according to Declaration of Helsinki.

The sample size was calculated as follows in this study: our primary endpoint was miR-125b expression between AECOPD patient and stable COPD patients or HCs, we firstly detected the miR-125b expression in 10 patients of each group, then based on the levels of miR-125b in each 2 groups (AECOPD vs. stable COPD, AECOPD vs. HCs) we calculated the smallest sample size as α set as 2-side 0.05, and β set as 2-side 0.1, and 2 smallest sample size were obtained as 43 and 59. However, we considered that more numbers of participants would be even better, thus we planned to enrolled participants in each group with number 100. And in the end, 87 patients in AECOPD group, 93 patients in stable COPD group, and 100 participants in HCs groups were included.

2.2. Plasma sample collection and miRNA determination by real time-polymerase chain reaction

A peripheral blood sample was collected from AECOPD patients at the day 1, day 7, day 14, and day 28 on admission, and from stable COPD patients as well as HCs. Subsequently, plasma was extracted from blood and stored at -80°C for further study.

Total RNA from plasma sample was extracted using TRIzol Reagent (Invitrogen, Waltham, MA), and then reverse transcription was performed by the PrimerScript Real-time reagent kit (Takara, Kusatsu, Japan). SYBR Premix Ex Taq II (Takara) was used to determine the expression of miR-125a and miR-125b by quantitative analysis, and calculated by utilizing the $2^{-\Delta\Delta t}$ method. U6 was used as an internal reference in the determination.

2.3. ELISA of the inflammatory cytokines

The measurement of TNF- α , IL-1 β , IL-8, and LTB-4 expressions in plasma samples from AECOPD patients at day 1 on admission and stable COPD patients were carried out by commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer instructions (all from eBioscience, Waltham, MA). ELISA assay for each sample was performed in triplicate, and the average value of triplicate data of each sample was used for the concentration analysis in this study. We used spearman test to check the correlation between each test of the triplicate result for each protein, the correlation coefficients were all above 0.80.

2.4. Statistics

Quantitative data were presented as mean value \pm standard deviation, median value (25–75% value), and qualitative data were presented as counts. Comparison among 3 groups was detected by 1-way analysis of variance test or chi-squared test, while the comparison between 2 individual groups was determined by Wilcoxon rank-sum test. And the comparison between paired groups (miR-125a/b expression at follow-ups compared with baseline) was determined by Wilcoxon signed-rank sum test. Receiver operating characteristic (ROC) was performed to distinguish AECOPD patients from stable COPD patients and HCs. And Spearman test was used to analyze the correlation of miR-125a/b expressions with inflammatory cytokines. Statistical analysis was performed by SPSS 22.0 software (IBM, Armonk, New York). P value $<.05$ was considered significant.

3. Results

3.1. Demographic and clinical characteristics of AECOPD, stable COPD patients, and HCs

Nine hundred seventy-four COPD patients were invited, and 648 cases were excluded since patients refused to participate in this study. The remaining 326 patients were screened, and 96 cases disagreed with the informed consents and 50 patients were excluded according to inclusion and exclusion criteria, the remaining 180 were included into the analysis which consisted of 87 patients in AECOPD group and 93 patients in stable COPD group. As to HCs group, 175 participants were invited, and 29 cases were excluded due to refusing of participating. The remaining 146 participants were screened, and 39 patients disagreed with the informed consents and 7 participants were excluded according to the exclusion criteria, thus 100 HCs were included finally.

As presented in Table 1, 87 patients in AECOPD group had a mean age 68.63 ± 7.54 years with 72 males and 15 females, no difference of age, gender, and BMI were found among 3 groups. After taking medicine of bronchodilator, the values of FEV₁/FVC (%) and FEV₁ (% predicted) in AECOPD were 46.30 ± 10.03 and 43.00 ± 7.02 , respectively, and in stable COPD patients were 46.82 ± 9.82 and 43.53 ± 7.56 , respectively, which were lower than HCs ($P < .001$). AECOPD and stable COPD patients also had a reduced FVC% predicted and DLCO% predicted value compared with HCs (both $P < .001$). As to smoke and family COPD history, AECOPD and stable COPD patients presented with an increased rate of smoke history (71% and 76%, respectively) compared with HCs (43%) ($P < .001$), while AECOPD and stable COPD patients had numerically higher rate of family COPD history (28% and 31%, respectively) compared with HCs (18%) but without statistical significant

Table 1
Demographic and clinical characteristics of AECOPD, stable COPD patients, and HCs.

Parameters	AECOPD patients (N=87)	Stable COPD patients (N=93)	HCs (N=100)	P
Age, y	68.63 ± 7.54	69.90 ± 6.61	68.66 ± 6.84	.368
Gender (male/female)	72/15	74/19	82/18	.254
BMI, kg/m ²	22.56 ± 2.57	22.58 ± 2.71	22.22 ± 2.15	.532
Smoke history, n/%	62 (71)	71 (76)	43 (43)	<.001
Family COPD history, n/%	24 (28)	29 (31)	18 (18)	.093
FEV ₁ /FVC, %	46.30 ± 10.03*	46.82 ± 9.82	78.83 ± 4.71	<.001
FEV ₁ , % predicted	43.00 ± 7.02*	43.53 ± 7.56	83.38 ± 3.22	<.001
FVC, % predicted	62.13 ± 12.89	62.93 ± 14.07	92.3 ± 5.93	<.001
DLCO, % predicted	50.36 ± 12.82	51.64 ± 13.60	81.5 ± 5.02	<.001
GOLD stage				.280 [†]
Stage 1, n/%	5 (6)	10 (11)	—	
Stage 2, n/%	34 (39)	44 (47)	—	
Stage 3, n/%	42 (48)	33 (35)	—	
Stage 4, n/%	6 (7)	6 (6)	—	
Bronchodilator, n/%	87 (100)	82 (88)	—	.001 [†]
Corticosteroid, n/%	76 (87)	53 (57)	—	<.001 [†]
Antibiotics, n/%	49 (56)	15 (16)	—	<.001 [†]

Data were presented by mean value ± standard deviation or counts (with or without percentage). Comparison among 3 groups was determined by 1-way analysis of variance test or chi-squared test. *P* < .05 was considered significant.

AECOPD = acute exacerbations of chronic obstructive pulmonary disease, BMI = body mass index, COPD = chronic obstructive pulmonary disease, DLCO = carbon monoxide diffusing capacity, FEV₁ = forced expiratory volume in 1 s, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, HCs = health controls.

* FEV₁/FVC and FEV₁ predicted were detected postbronchodilator.

[†] Comparison between AECOPD and stable COPD patients was detected by chi-squared test.

Bold emphasized values were values with *P* < .05.

(*P* = .093). When comparing the lung function indexes between AECOPD and stable COPD patients, no difference of FEV₁/FVC (%), FEV₁ (%predicted), FVC (% predicted), and DLCO (% predicted) were observed, while GOLD stage was numerically higher in AECOPD patients than stable COPD patients, but still with no statistical significance (*P* = .280).

In addition, used drugs were recorded in AECOPD and stable COPD patients, and bronchodilators, corticosteroid, and antibiotics were used more frequent in AECOPD patients compared with stable COPD patients.

3.2. Expressions of plasma miR-125a/b in AECOPD patients, stable COPD patients, and HCs

Plasma miR-125a expression was decreased in AECOPD patients (3.452 [2.607–4.313]) compared with HCs (3.862 [2.805–5.017],

P < .001). However, there was no difference between stable COPD patients (3.782 [2.823–4.570]) and HCs, as well as between AECOPD patients and stable COPD patients (Fig. 1A). MiR-125b expression level was illuminated to be increased in AECOPD patients than stable COPD patients and HCs (5.287 [4.188–6.385]) versus (2.265 [1.490–3.199]) and 2.340 [1.528–2.912], both *P* < .001). But there was no difference between stable COPD patients and HCs as shown in Fig. 1B.

In addition, we made a comparison of miR-125a and miR-125b expressions between COPD patients and HCs using GEO database. According to GEO database in Fig. 2, there were no difference of miR-125a level in tissue specimen (A) or blood specimens (B) between COPD patients and HCs, which was in line with our research. MiR-125b expression in tissue (C) and blood (D) both had a rising trend in COPD patients, especially in the blood; the pattern was very similar to our study.

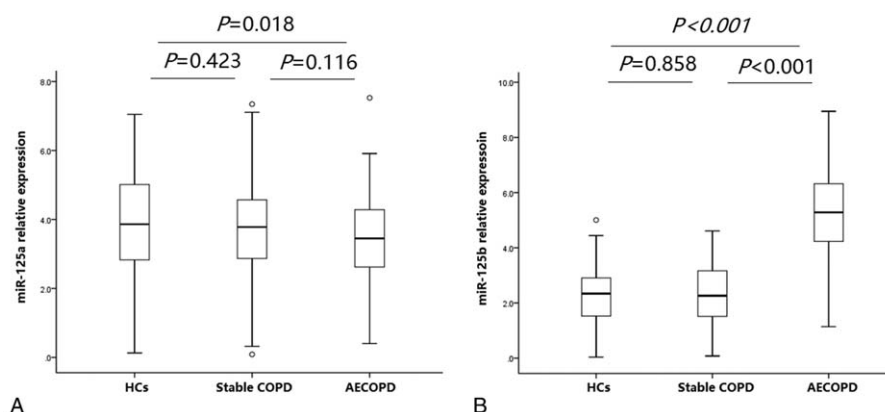


Figure 1. MiR-125a/b expressions in AECOPD patients, stable COPD patients, and HCs. (A) miR-125a; (B) miR-125b. AECOPD = acute exacerbations of chronic obstructive pulmonary disease, COPD = chronic obstructive pulmonary disease, HC = health volunteer.

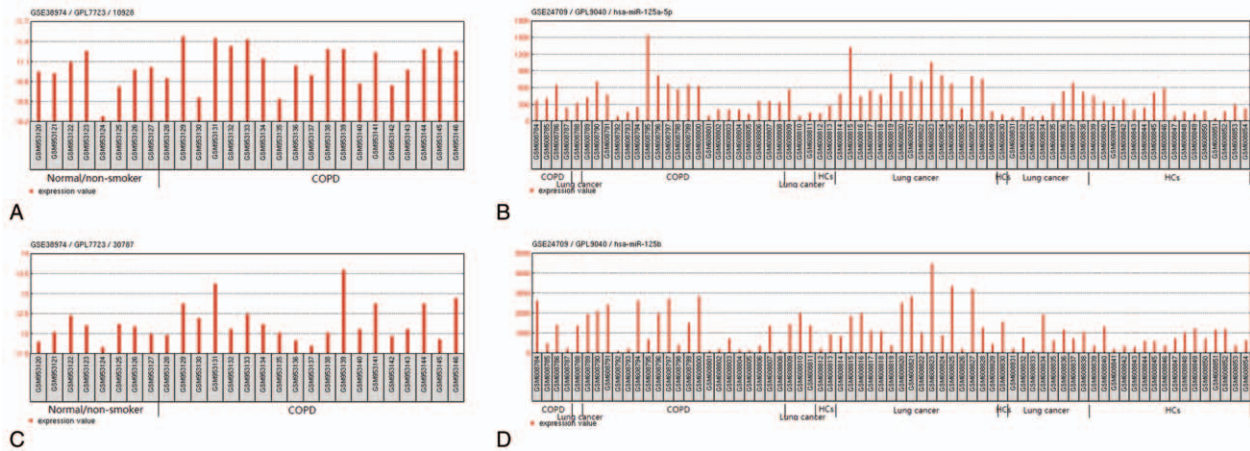


Figure 2. GEO database analysis of miR-125a/b expression in COPD patients and HCs. (A) Tissue sample, miR-125a; (B) blood sample, miR-125a; (C) tissue sample, miR-125b; (D) blood sample, miR-125b. COPD=chronic obstructive pulmonary disease, HC=health volunteer.

3.3. Values of plasma miR-125a/b in distinguishing among AECOPD, stable COPD, and HCs

To further explore the identified ability of candidate miR-125a and miR-125b among 3 groups, ROC curves were performed as shown in Fig. 3. To our surprise, there were great diagnostic values for miR-125b to distinguish AECOPD from stable COPD (AUC=0.926, 95% CI: 0.884–0.967) (Fig. 3C) and HCs (AUC=0.923, 95% CI: 0.880–0.966) (Fig. 3B). However, miR-125a lacked predictive value for AECOPD from stable COPD (AUC=0.568, 95% CI: 0.484–0.652) (Fig. 3C) and HCs (AUC=0.600, 95% CI: 0.519–0.682) (Fig. 3B). Besides, both miR-125a and miR-125b could not distinguish stable COPD from HCs (AUC=0.533, 95% CI: 0.452–0.615; AUC=0.507, 95% CI: 0.425–0.590, respectively) (Fig. 3A).

3.4. The correlation of miR-125a/b expression and inflammatory cytokines in AECOPD and stable COPD patients

As shown in Fig. 4, inflammatory cytokines such as TNF- α , IL-1 β , IL-8, and LTB-4 levels are extremely increased in AECOPD

patients compared with stable COPD patients (all $P < .001$). Furthermore, we found that miR-125b expression with inflammatory cytokines TNF- α , IL-8, and LTB-4 have a correlation in AECOPD patients ($P = .012$, $P = .032$, and $P = .047$, respectively) except for inflammatory cytokine IL-1 β ($P = .170$) in Table 2. However, there was no association between miR-125a expression level and inflammatory cytokines in AECOPD patients. As for stable COPD patients, no other correlation of miR-125a and miR-125b with inflammatory cytokines above was observed in Table 3.

Interestingly, miR-125b gradually decreased after admission on day 7, day 14, and day 28 compared with day 1 in AECOPD patients in Fig. 5B (all $P < .05$), while no difference in miR-125a were discovered between each visit compared with day 1 as presented in Fig. 5A (all $P > .05$).

4. Discussion

In the present study, we found that plasma miR-125b had a great capacity for distinguishing AECOPD patients from stable COPD patients and HCs, while miR-125a did not; there was an

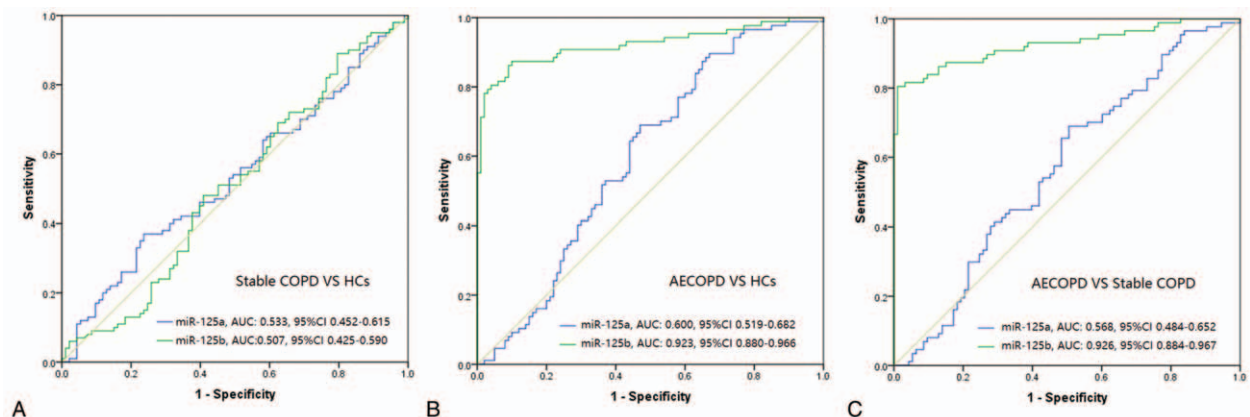


Figure 3. ROC curve analysis for plasma miR-125a/b in distinguish AECOPD, stable COPD, and HCs. (A) ROC curve analysis of miR-125a/b expressions for predicting stable COPD risk from HCs; (B) ROC curve analysis of miR-125a/b expressions for predicting AECOPD risk from HCs; (C) ROC curve analysis of miR-125a/b expressions for predicting AECOPD risk from stable COPD status. AECOPD=acute exacerbations of chronic obstructive pulmonary disease, COPD=chronic obstructive pulmonary disease, HC=health volunteer, ROC=receiver operating characteristic.

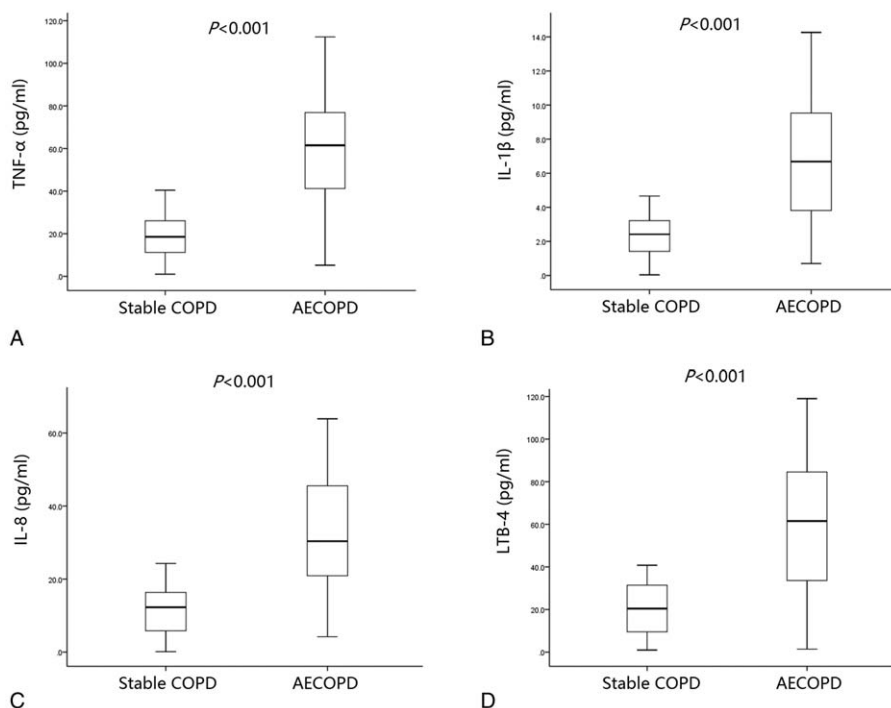


Figure 4. Expressions of TNF- α , IL-1 β , IL-8, and LTB-4 in AECOPD and stable COPD patients. (A) TNF- α ; (B) IL-1 β ; (C) IL-8; and (D) LTB-4. AECOPD=acute exacerbations of chronic obstructive pulmonary disease, COPD=chronic obstructive pulmonary disease.

association between miR-125b expression with inflammatory cytokines including TNF- α , IL-8, and LTB-4 in AECOPD patients, while no correlation of miR-125a with inflammatory cytokines was found; and miR-125b expression gradually decreased at day 7, day 14, and day 28 compared with day 1 on admission, while no difference in miR-125a was discovered between each visit compared with day 1.

Over the last decades, considerable improvement has been built on the understanding of the pathophysiology, epidemiology, diagnosis, and treatment of AECOPD,^[15,16] but lots of issues remain to be resolved, especially for the mechanism of inflammation and the effective biomarkers for early recognition.^[17] MiR-125, a small noncoding RNA molecular, is currently being investigated as a novel biomarker for diagnosis and therapeutic target in various diseases. For example, miR-125a level is

remarkably reduced in patients with SLE.^[9] Recently, Halvorsen finds that miR-125b might be a biomarker for detection of early stage lung cancer from those with COPD and HCs.^[13] Unlike miR-125 in lung carcinoma and SLE,^[18,19] our knowledge about the role of miR-125a/b in AECOPD is limited.^[20]

MiR-125b, a highly conserved gene among mammals, exists 2 paralogs coding for the same mature sequence.^[21] Besides, miR-125b expression is induced by caudal type homeobox 2 (CDX2) and modulated by nuclear factor kappa beta signaling, which could exert positive effects to secrete inflammatory factors, including TNF- α .^[16,22] Besides, miR-125b potentiates macrophage activation and takes part in innate immune regulation.^[11] Research conducted in Tetsuya illuminates that miR-125b, but not miR-125a, is significantly associated with human osteoarthritis attributing to regulation of IL-1 β and TNF- α .^[7,23] Also,

Table 2
Correlation of miR-125a/b expression with inflammatory cytokines in AECOPD patients.

	TNF- α	IL-1 β	IL-8	LTB-4
miR-125a				
Coefficient <i>R</i>	-0.125	-0.210	0.034	0.138
<i>P</i>	.249	.051	.757	.201
N	87	87	87	87
miR-125b				
Coefficient <i>R</i>	0.269*	0.148	0.231*	0.214*
<i>P</i>	.012	.170	.032	.047
N	87	87	87	87

Data were presented by coefficient *R* and *P* value. Coefficient analysis was performed by Spearman test. $P < .05$ was considered significant.

AECOPD=acute exacerbations of chronic obstructive pulmonary disease.

* $P < .05$.

Bold emphasized values were values with $P < .05$.

Table 3
Correlation of miR-125a/b expression with inflammatory cytokines in stable COPD patients.

	TNF- α	IL-1 β	IL-8	LTB-4
miR-125a				
Coefficient <i>R</i>	-0.069	-0.178	-0.060	-0.192
<i>P</i>	.508	.088	.570	.065
N	93	93	93	93
miR-125b				
Coefficient <i>R</i>	0.078	0.190	0.066	0.012
<i>P</i>	.455	.067	.529	.912
N	93	93	93	93

Data were presented by Coefficient *R* and *P* value. Coefficient analysis was performed by Spearman test. $P < .05$ was considered significant.

COPD=chronic obstructive pulmonary disease.

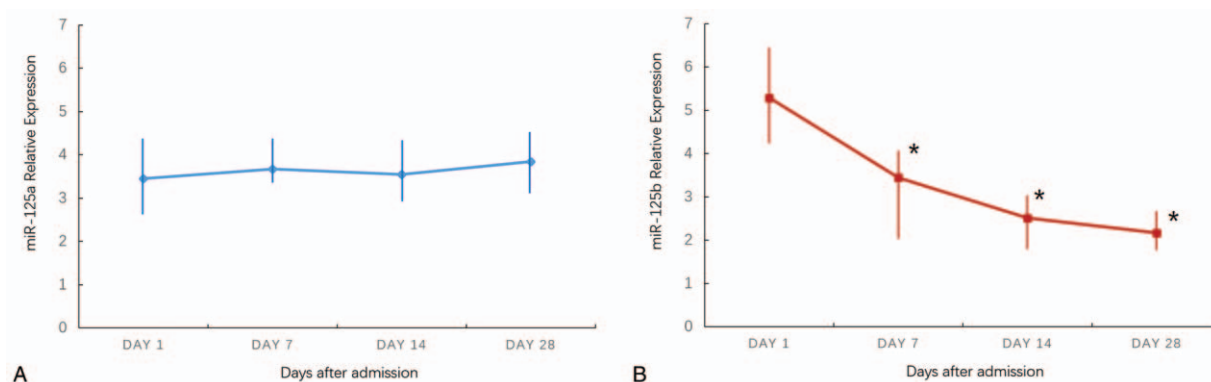


Figure 5. MiR-125a/b expression after admission in AECOPD patients. (A) MiR-125a expression numerically increased after admission on day 7, day 14, and day 28 but without statistical significance; (B) miR-125b dramatically decreased on day 7, day 14, and day 28. AECOPD = acute exacerbations of chronic obstructive pulmonary disease.

Van Pottelberge et al^[24] report that miR-125b expression in patients who smoke currently compared with nonsmokers is different. Furthermore, Blick et al^[25] identifies that miR-125b is hypoxia-regulated miRNA in bladder cancer. These studies are consistent with our results that miR-125b was increased in AECOPD patients and had a great power to distinguish AECOPD patients from stable COPD patients and HCs. These might result from miR-125b promotes inflammatory response by increasing inflammatory cytokines TNF- α , IL-8, and LTB-4 in AECOPD patients as demonstrated in our study, which acts as a critical role in the initiation and progression of AECOPD. And previous studies also report that these miR-125b-related inflammatory cytokines are increased in the serum of patients with bronchial asthma and relate to the inhibition of muscle shrinkage,^[26,27] which further confirms the proinflammatory effect of miR-125b in AECOPD pathogenesis. MiR-125b induces the injury of lung tissue by regulating apoptosis of airway epithelial cells as a hypoxia-regulated miRNA, which contributes to the acute exacerbation of COPD.

As to miR-125a, it is located on chromosome 19 and in a same cluster with miR-99b and miR-7e.^[28] Recently, a study shows that miR-125a could suppress classical activation of macrophages to resist inflammation while promotes alternative activation of macrophages to help inflammation.^[18] But we found there was no correlation between miR-125a and inflammatory factors in AECOPD patients, and it could not distinguish AECOPD patients from stable COPD patients and HCs. This might because that there is a dual effect of both proinflammation and anti-inflammation for miR-125a.

According to the best of our knowledge, this is the first study to investigate the association of circulating miR-125a/b expressions with acute exacerbations of COPD. However, this study also had some limitations. First, the sample size was relatively small, and a large sample size study is needed in the future. Second, we only obtained the blood specimen of AECOPD patients, not the sample of lung tissue which probably limited the veracity of study.

Overall, our study suggested that circulating miR-125b might be a proinflammatory factor and could be regarded as a novel and promising biomarker for diagnosis of AECOPD patients. This information is crucial for effective prevention, early diagnosis, and treatment of AECOPD.

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