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RESEARCH ARTICLE

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Circulating JNK pathway-associated phosphatase: A novel biomarker correlates with Th17 cells, acute exacerbation risk, and severity in chronic obstructive pulmonary disease patients

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Abstract

Background: JNK pathway-associated phosphatase (JKAP) involves in the regulation of inflammation, immunity, and lung injury. The current study aimed to investigate correlation of JKAP with Th1, Th17 cells, acute exacerbation risk, and disease severity in chronic obstructive pulmonary disease (COPD) patients.

Methods: Totally, 45 stable COPD (SCOPD) patients, 45 acute exacerbation COPD (AECOPD) patients, and 45 controls were enrolled. Serum was collected for JKAP, interferon-gamma (IFN-γ) (Th1 cytokine), and interleukin 17 (IL-17) (Th17 cytokine) detection. Besides, peripheral blood mononuclear cell from COPD patients was collected for evaluating Th1 and Th17 cells.

Results: JKAP was highest in controls followed by SCOPD patients and lowest in AECOPD patients (median: 105.673 vs. 75.374 vs. 41.807 pg/ml, $p < 0.001$). Meanwhile, receiver operating characteristic (ROC) curves revealed that JKAP differentiated the AECOPD patients from the controls (area under curve (AUC): 0.910 (95% confidence interval (CI): 0.849–0.970)) and AECOPD patients from SCOPD patients (AUC: 0.726 (95% CI: 0.622–0.830)). Moreover, JKAP positively correlated with FEV_1 (%predicted) in AECOPD patients ($r = 0.347$ $p = 0.019$). Additionally, JKAP was negatively correlated with the GOLD stage in AECOPD patients ($r = -0.344$, $p = 0.021$) and SCOPD patients ($r = -0.357$, $p = 0.016$). Whereas, JKAP was not associated with other clinical features (all $p > 0.05$). Besides, JKAP was negatively linked with Th17 cells ($r = -0.378$, $p = 0.010$), IFN-γ ($r = -0.358$, $p = 0.016$), IL-17 ($r = -0.414$, $p = 0.005$) in AECOPD patients and Th17 cells ($r = -0.342$, $p = 0.022$), IL-17 ($r = -0.299$, $p = 0.046$) in SCOPD patients.

Conclusion: Downregulated JKAP correlates with Th17 cells, higher acute exacerbation risk, and severity in COPD patients, indicating its underlying potency as a biomarker for COPD.

KEYWORDS
acute exacerbation, chronic obstructive pulmonary disease, JNK pathway-associated phosphatase, T helper 1 cells, T helper 17 cells

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD), featured by persistent respiratory symptoms and progressive airflow obstruction, not only ranks as the third leading cause of death worldwide but also incurs intensive expenditure of healthcare resources globally.[1-3] More importantly, acute exacerbation of COPD (AECOPD) is an aggravation in the COPD symptoms featured by a heavier disease burden and deteriorate mortality.[4,5] Consequently, early diagnosis and persistently monitoring disease progression are crucial for timely intervention in order to reduce the COPD acute exacerbation.[6,7] Thus, exploring more valuable biomarkers for illuminating acute exacerbation risk in COPD patients is of great importance.

JNK pathway-associated phosphatase (JKAP), a member of dual-specificity phosphatases (DUSPs) family, is widely expressed in various types of mammalian cells such as T cells, B cells, and NK cells, indicating that JKAP may be involved in some inflammation and immunity-related biological processes.[8-10] Aforementioned evidences illustrate that JKAP might have an essential effect on mediating inflammation and immune responses via repressing the differentiation of $CD4^+$ T cells.[11,12] In detail, JKAP represses the $CD4^+$ T cells activation and its differentiation into T helper (Th) 1 and Th17 cells in a series of inflammation-related disease such as sepsis, lupus erythematosus nephritis, and inflammatory bowel disease.[11,13,14] Moreover, JKAP is supposed to dysregulate the lung disease via modulating PUMA and PI3K/AKT/mTOR pathway.[15] Interestingly, COPD is supposed to be an inflammation-related disease, which is linked with a series of Th-cell-mediated biological process.[16,17] Based on the evidences above, we supposed that JKAP might serve as a biomarker for monitoring disease progression in COPD patients.

Hence, the present study measured JKAP level in AECOPD patients, SCOPD patients, and health subjects aiming to explore the correlation of JKAP with acute exacerbation risk, Th1 cells and Th17 cells as well as clinical features in COPD patients.

2 | METHODS

2.1 | Subjects

The study was approved by the Ethics Committee of China Rehabilitation Research Center, Beijing Bo'ai Hospital, and all informed consents were signed by the subjects. This study serially recruited 45 stable COPD (SCOPD) patients and 45 acute exacerbation COPD (AECOPD) patients who came to respiratory clinic of our hospital from January 2020 to October 2020. All study subjects aged more than 18 years. The diagnosis of COPD patients and the COPD exacerbations were defined according to the Global Strategy for Chronic Obstructive Lung Disease (GOLD) standard guideline.[18] The assignment of AECOPD group or stable COPD group was based on the status of patients at the enrollment, and the group was not changed with the disease status (that was to say, the patients in both groups were not overlapped). If patients were pregnant or nursing mother or were currently complicated with other pulmonary diseases, inflammatory diseases, autoimmune diseases, hematologic malignancies, or malignant tumors, they were excluded from the study. At the same period, 45 healthy subjects who came to our hospital for physical examination were enrolled as controls. All controls were confirmed that they had no history of chronic respiratory disease, other lung diseases, malignant blood disease, tumor, and heart, kidney, liver, or other important organ diseases.

2.2 | Collection of clinical data

Demographic data and accompanying diseases of patients were recorded after enrollment. Forced expiratory volume in 1 s (FEV_1) and forced volume vital capacity (FVC) were recorded by respiratory function examination. Based on the FEV_1 and FVC, the FEV_1 (% predicted) and FEV_1/FVC ratio were calculated. The airflow obstruction severity of patients (GOLD grade) was classified by the GOLD criteria based on the FEV_1 (% predicted).[18]

2.3 | Collection of blood samples

Peripheral blood (PB) samples were collected from COPD patients and controls. After collection, half of PB was centrifuged by centrifuge at 3500 revolutions per minute for 10 minutes to separate serum samples then stored at −80℃ for JKAP and cytokines quantification, and another half of PB was processed with to detect Th1 cells and Th17 cells in the $CD4^+$ T cells within 24 h.

2.4 | Assays

The level of JKAP, interferon-gamma (IFN-γ), and interleukin 17 (IL-17) in serum was detected by using enzyme-linked immunosorbent assay (ELISA) with the application of commercial ELISA kits (Shanghai Enzyme-linked Biotechnology Co., Ltd, China). The CD4 positive ($CD4^+$) T cells were isolated by human $CD4^+$ T Cell Isolation Kit (Miltenyi Biotec Inc., Auburn, California, United States). Then, Th1 cells and Th17 cells in the $CD4^+$ T cells were determined by flow cytometric analysis using Human Th1/Th17 Phenotyping Kit (BD Pharmingen™, Franklin Lake, USA). ALL procedures were carried out based on the guidance of instructions.

2.5 | Statistical analysis

Mann-Whitney U test and Kruskal-Wallis test were applied to evaluate the differences in JKAP concentration between different subjects, and the significance values of pairwise comparisons had been adjusted by the Bonferroni correction for multiple tests. Receiver operating characteristic (ROC) curve analysis was used to show the

efficiency of JKAP level in distinguishing different subjects. The association between JKAP concentration and the level of inflammatory cytokines or disease features was evaluated using the Chi-squared test, Spearman's rank correlation test, Mann-Whitney U test, and Kruskal-Wallis test. Logistic regressions were conducted for analysis of risk factors. SPSS 26.0 software (IBM Corp., Armonk, New York, USA) and GraphPad Prism 7.02 software (GraphPad Software Inc., San Diego, California, USA) were used to perform statistical analysis and plot figures. A p value less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of controls, SCOPD patients and AECOPD patients

Ages were 66.0 ± 6.1 years, 67.1 ± 7.4 years, and 66.4 ± 7.2 years in controls, SCOPD patients, and AECOPD patients, separately (Table 1). In regards to gender, there were 19 (42.2%) females and 26 (57.8%) males in controls, 15 (33.3%) females and 30 (66.7%) males in SCOPD patients, and 12 (26.7%) females and 33 (73.3%) males in AECOPD patients. Additionally, there was no difference among controls, SCOPD patients, and AECOPD patients regarding BMI, family history of COPD, hypertension, hyperlipidemia, diabetes mellitus, GOLD stage (all $p > 0.05$). Additionally, Th1 cells, Th17 cells, IFN-γ, and IL-17 were higher in AECOPD patients compared with SCOPD patients (all $p < 0.05$). More detailed information about the clinical characteristics of three groups is listed in Table 1.

3.2 | Comparison of JKAP expression among controls, SCOPD patients, and AECOPD patients

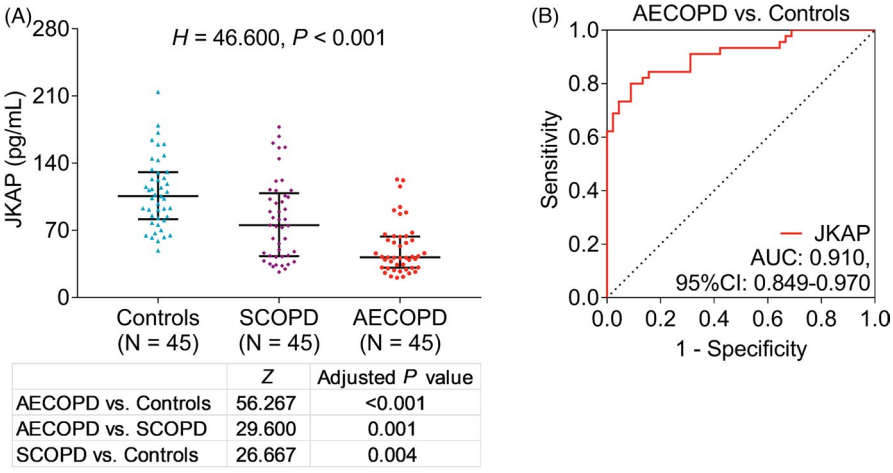
JKAP expression was varied among controls, SCOPD patients, and AECOPD patients ($p < 0.001$, Figure 1A). In detail, JKAP was highest in controls followed by SCOPD patients and lowest in AECOPD patients. Post hoc multiple comparison showed that JKAP in AECOPD patients was lower than that in controls (adjusted $p < 0.001$) than that in SCOPD patients (adjusted $p = 0.001$). Moreover, JKAP in SCOPD was lower than that in controls (adjusted $p = 0.004$).

Meanwhile, ROC curve revealed that JKAP differentiated AECOPD patients from SCOPD patients with AUC of 0.726 (95%

TABLE 1 Characteristics of COPD patients and controls

Items	Controls (N = 45)	SCOPD (N = 45)	AECOPD (N = 45)	Statistic ($F/\chi^2/H/Z$)	p value
Age (years), mean ± SD	66.0 ± 6.1	67.1 ± 7.4	66.4 ± 7.2	0.308	0.735
Gender, No. (%)				2.440	0.295
Female	19 (42.2)	15 (33.3)	12 (26.7)		
Male	26 (57.8)	30 (66.7)	33 (73.3)		
BMI (kg/m^2), mean ± SD	22.8 ± 2.5	22.3 ± 2.7	22.4 ± 2.7	0.526	0.592
Family history of COPD, No. (%)	7 (15.6)	12 (26.7)	11 (24.4)	1.800	0.407
Smoke, No. (%)	12 (26.7)	26 (57.8)	20 (44.4)	8.948	0.011
Hypertension, No. (%)	19 (42.2)	24 (53.3)	28 (62.2)	3.625	0.163
Hyperlipidemia, No. (%)	10 (22.2)	12 (26.7)	12 (26.7)	0.315	0.854
Diabetes mellitus, No. (%)	6 (13.3)	9 (20.0)	11 (24.4)	1.810	0.405
FEV1/FVC (%), median (IQR)	82.1 (79.9–84.0)	61.1 (57.3–63.6)	60.7 (55.9–65.7)	89.370	<0.001
FEV1 (% predicted), median (IQR)	98.5 (95.6–100.4)	66.6 (52.6–82.9)	57.8 (45.6–82.0)	90.396	<0.001
GOLD stage, No. (%)				−1.136	0.256
Stage I	—	19 (42.2)	12 (26.7)		
Stage II	—	15 (33.3)	21 (46.6)		
Stage III	—	11 (24.5)	12 (26.7)		
Th1 cells (% of CD4$^+$ T cells), median (IQR)	—	12.9 (10.8–14.2)	14.5 (12.3–17.7)	−2.909	0.004
Th17 cells (% of CD4$^+$ T cells), median (IQR)	—	3.6 (3.1–5.4)	6.1 (4.5–7.6)	−4.432	<0.001
IFN-γ (pg/ml), median (IQR)	—	67.3 (54.2–78.7)	99.3 (70.2–151.7)	−4.846	<0.001
IL–17 (pg/ml), median (IQR)	—	51.7 (41.9–67.6)	82.2 (63.1–132.3)	−3.700	<0.001

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced volume vital capacity; GOLD, Global Initiative for Chronic Obstructive lung Disease; IFN-γ, interferon-gamma; IL-17, interleukin 17; IQR, interquartile range; SCOPD, stable chronic obstructive pulmonary disease; SD, standard deviation; Th, T helper.



	Z	Adjusted P value
AECOPD vs. Controls	56.267	<0.001
AECOPD vs. SCOPD	29.600	0.001
SCOPD vs. Controls	26.667	0.004

FIGURE 1 JKAP expression was varied among controls, SCOPD patients, and AECOPD patients. Comparison of JKAP expression among controls, SCOPD patients, and AECOPD patients (A); ROC curve of JKAP in differentiating AECOPD patients from controls (B); AECOPD patients from SCOPD patients (C); SCOPD patients from controls (D). AECOPD, acute exacerbation chronic obstructive pulmonary disease; AUC, area under curve; CI, confidence interval; JKAP, JNK pathway-associated phosphatase; ROC, receiver operating characteristic; SCOPD, stable chronic obstructive pulmonary disease

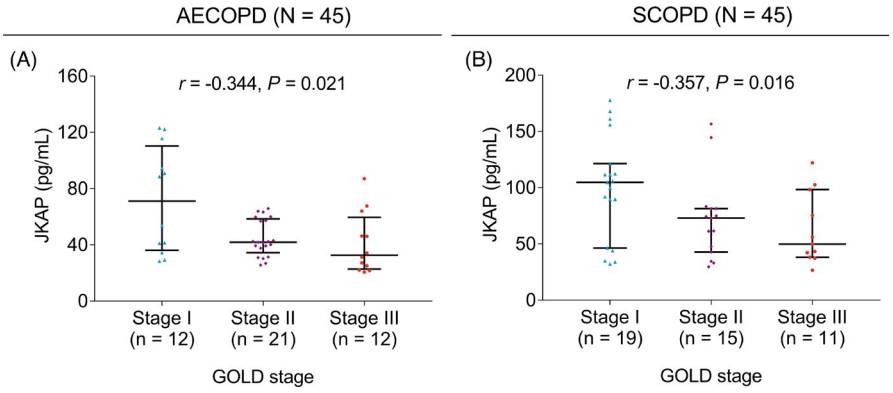


FIGURE 2 Association of JKAP with GOLD stage in COPD patients. Association of JKAP with GOLD stage in AECOPD patients (A) and SCOPD patients (B). AECOPD, acute exacerbation chronic obstructive pulmonary disease; GOLD, Global Initiative for chronic obstructive lung disease; JKAP, JNK pathway-associated phosphatase; SCOPD, stable chronic obstructive pulmonary disease

confidence interval (CI): 0.622–0.830), besides, JKAP also distinguished AECOPD patients from controls with AUC of 0.910 (95% CI: 0.849–0.970) and distinguished SCOPD patients from controls with AUC of 0.705 (95% CI: 0.596–0.813) (Figure 1B–D).

More importantly, univariate logistic regression disclosed that higher JKAP ($p < 0.001$) was linked with decreased risk of COPD (Table S1). In addition, multivariate logistic regression uncovered that higher JKAP ($p < 0.001$) was independently associated with lower risk of COPD.

3.3 | Association of JKAP with clinical features in AECOPD patients and SCOPD patients

More importantly, JKAP was negatively correlated with the GOLD stage in AECOPD patients ($r = -0.344$, $p = 0.021$, Figure 2A) and SCOPD patients ($r = -0.357$, $p = 0.016$, Figure 2B). What is more, upregulated JKAP was correlated with the smoke in AECOPD patients ($p = 0.024$, Table 2). Additionally, JKAP was positively associated with FEV_1 (% predicted) both in AECOPD patients ($p = 0.019$)

TABLE 2 Correlation of JKAP with categorically clinical features in COPD patients and controls

	Controls (N = 45)			SCOPD (N = 45)			AECOPD (N = 45)		
Items	**JKAP (pg/ml), median (IQR)**	**Statistic (Z)**	***p* value**	**JKAP (pg/ml), median (IQR)**	**Statistic (Z)**	***p* value**	**JKAP (pg/ml), median (IQR)**	**Statistic (Z)**	***p* value**
Gender		−0.161	0.872		−1.035	0.301		−0.924	0.355
Female	103.0 (76.0–143.2)			47.7 (38.2–144.6)			43.8 (33.7–92.8)		
Male	108.8 (85.2–126.2)			82.3 (48.9–107.4)			41.8 (30.5–61.6)		
Family history of COPD		−1.190	0.234		−0.821	0.411		−1.241	0.214
No	108.0 (84.1–131.6)			81.3 (44.9–111.6)			44.5 (31.3–64.5)		
Yes	92.8 (62.8–113.0)			54.6 (36.9–97.7)			37.6 (29.2–42.4)		
Smoke		−0.873	0.383		−0.391	0.696		−2.261	**0.024**
No	105.7 (83.7–132.2)			74.9 (43.9–106.0)			37.6 (27.8–57.1)		
Yes	101.6 (62.4–124.1)			82.3 (41.2–111.8)			49.9 (39.6–82.5)		
Hypertension		−0.437	0.662		−1.274	0.203		−0.866	0.386
No	99.6 (77.4–130.9)			83.3 (47.0–116.8)			41.5 (30.8–56.7)		
Yes	110.3 (91.3–131.0)			67.3 (39.2–104.1)			42.1 (31.0–81.8)		
Hyperlipidemia		−1.611	0.107		−0.821	0.411		−0.744	0.457
No	107.3 (83.0–143.2)			81.3 (45.1–112.0)			41.5 (31.1–61.6)		
Yes	91.5 (76.5–112.2)			74.8 (36.8–91.4)			48.0 (30.4–88.2)		
Diabetes mellitus		−1.803	0.071		−0.057	0.955		−0.924	0.355
No	110.3 (85.4–131.0)			78.3 (43.5–105.7)			41.5 (31.0–59.8)		
Yes	80.2 (60.8–108.5)			74.9 (42.5–116.8)			46.0 (30.9–87.1)		

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; JKAP, JNK pathway-associated phosphatase; SCOPD, stable chronic obstructive pulmonary disease.

TABLE 3 Correlation of JKAP with continuously clinical features in COPD patients and controls

	Controls (N = 45)		SCOPD (N = 45)		AECOPD (N = 45)	
Items	**Statistic (*r*)**	***p* value**	**Statistic (*r*)**	***p* value**	**Statistic (*r*)**	***p* value**
Age	0.089	0.561	0.201	0.185	0.193	0.203
BMI	0.211	0.164	−0.151	0.323	−0.153	0.316
FEV1/FVC (%)	0.124	0.415	0.225	0.137	0.241	0.110
FEV1 (% predicted)	0.210	0.166	0.327	**0.029**	0.347	**0.019**

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced volume vital capacity; JKAP, JNK pathway-associated phosphatase; SCOPD, stable chronic obstructive pulmonary disease.

and SCOPD patients ($p = 0.029$) (Table 3). However, JKAP was not correlated with other clinical features in all subjects (all $p > 0.05$). More detailed information is listed in Tables 2 and 3.

Besides, generally, Elevated JKAP was correlated with increased age ($r = 0.216$, $p = 0.041$, Figure S1A) and smoke ($Z = -2.099$, $p = 0.036$, Figure S1B) in COPD patients.

3.4 | Correlation of JKAP with Th1 and Th17 cells in AECOPD patients and SCOPD patients

In AECOPD patients, JKAP was negatively correlated with Th17 cells (% of $CD4^+$ T cells) ($r = -0.378$, $p = 0.010$) and IL-17 ($r = -0.414$, $p = 0.005$); however, JKAP was negatively linked with IFN-γ ($r = -0.358$, $p = 0.016$) but not with Th1 cells (% of $CD4^+$ T cells) ($p = 0.053$) (Figure 3A–D). Meanwhile, in SCOPD patients, JKAP was negatively correlated with Th17 cells (% of $CD4^+$ T cells) ($r = -0.342$, $p = 0.022$) and IL-17 ($r = -0.299$, $p = 0.046$), whereas JKAP was not correlated with Th1 cells (% of $CD4^+$ T cells) ($p = 0.313$) or IFN-γ ($p = 0.125$) (Figure 3E-H).

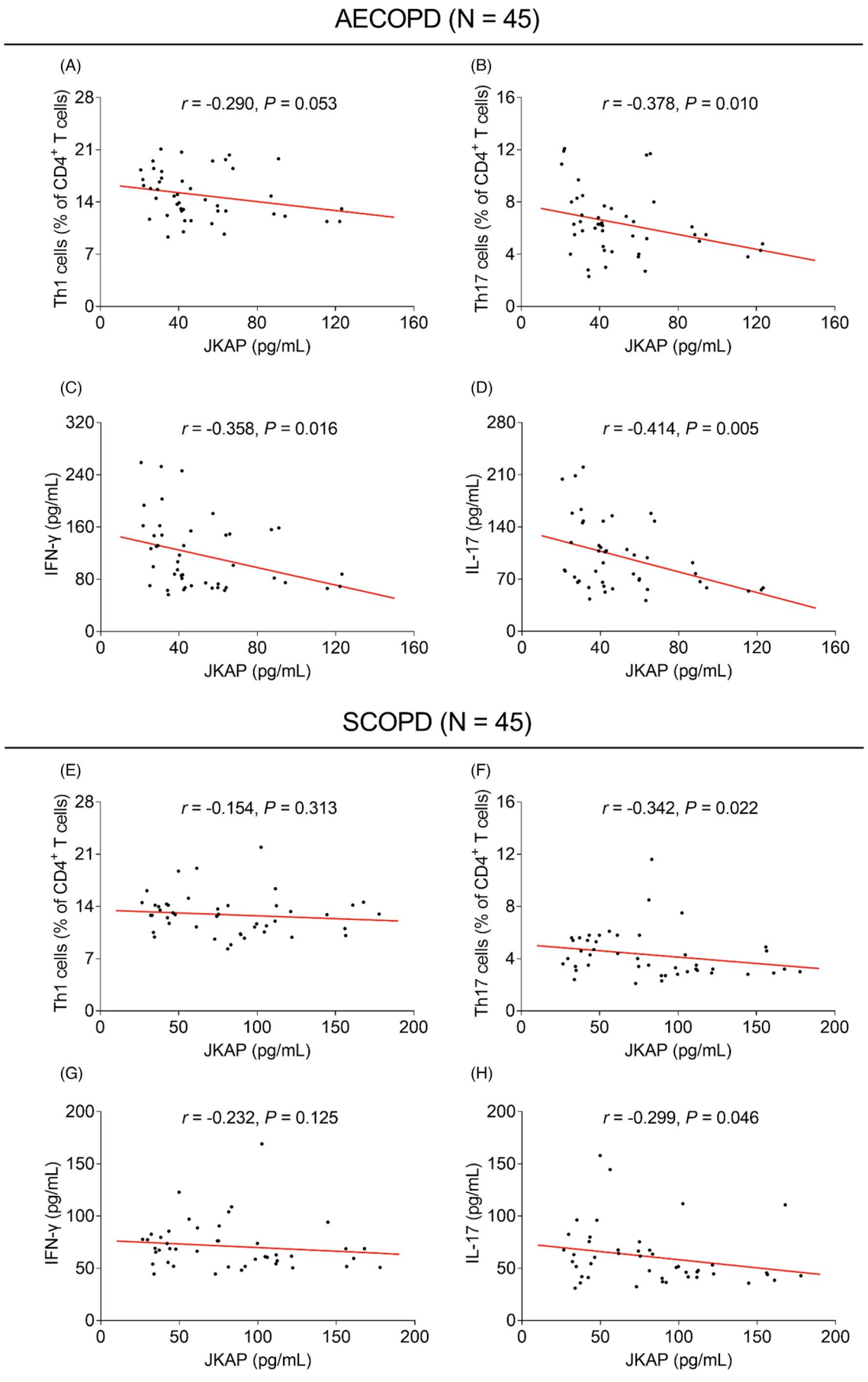
4 | DISCUSSION

JKAP, which is secreted by a series of immune cells including T cells, B cells, and NK cells, not only dephosphorylates the JNK kinase but also regulates several inflammation-and immunity-related biological processes.[8-10,19] To be specific, JKAP suppresses the activation of T-cell receptor signaling and further inhibits the $CD4^+$ T cells differentiating into Th1 cells and Th17 cells via facilitating mitogen-activated protein kinase kinase kinase kinase1 (MAP4K1) or mitogen-activated protein kinase kinase kinase kinase4 (MAP4K4) signaling.[20,21] What is more, JKAP inhibits T-cell proliferation and differentiation, as well as its cytokine production *in vitro* and suppresses T-cell-mediated immune responses *in vivo*.[22] More importantly, in inflammatory bowel disease and lupus erythematosus patients, decreased JKAP levels in peripheral blood T cell may contribute to T-cell hyperactivation and corresponding inflammatory cytokines overproduction.[11,14] Whereas clinical involvement of JKAP in COPD patients is seldom reported. Therefore, efforts were made to validate this issue in the current study.

JKAP is downregulated in several immune or inflammation-related diseases such as inflammatory bowel disease, lupus erythematosus patients, idiopathic arthritis, and sepsis.[11,13,14,23] In the current study, JKAP in AECOPD patients was lower than that in SCOPD patients, meanwhile JKAP distinguished AECOPD from SCOPD patients. Likewise, JKAP in AECOPD and SCOPD patients was lower than that in healthy subjects, meanwhile JKAP might distinguish AECOPD and SCOPD patients from health subjects. Possible explanations could be that (1) declined JKAP is associated with elevated Th1 and Th17 cells, as well as their secreted inflammatory cytokines.[11,13,14] Besides, COPD is supposed to be linked with a series of Th-cell-mediated biological process such as the recruitment of inflammation.[16,17] Consequently, downregulated JKAP is correlated with COPD risk. (2) Former studies exhibit that JKAP is correlated with the differentiation of $CD4^+$ T cells, which is supposed to be linked with acute exacerbation risk in COPD patients.[11,13,14,21,23] Subsequently, JKAP is correlated with acute exacerbation risk in COPD patients.

JKAP is negatively associated with disease severity in multiple immune- or inflammation-related disease such as sepsis, lupus erythematosus nephritis, and inflammatory bowel disease.[11,13,14] Interestingly, it was revealed that downregulated JKAP was linked with poor clinical features such as declined FEV1 (% predicted) and elevated GOLD stage in AECOPD or SCOPD patients in the present study. Possible explanation is as follows: In COPD patients, downregulated JKAP is linked with elevated inflammation recruitment

FIGURE 3 Association of JKAP with Th1 and Th17 cells. Correlation of JKAP with Th1 cells (% of $CD4^+$ T cells) (A), Th17 cells (% of $CD4^+$ T cells) (B), IFN-γ (C) and IL-17 (D) in AECOPD patients; correlation of JKAP with Th1 cells (% of $CD4^+$ T cells) (E), Th17 cells (% of $CD4^+$ T cells) (F), IFN-γ (G) and IL-17 (H) in SCOPD patients. AECOPD, acute exacerbation chronic obstructive pulmonary disease; IFN-γ, interferon-gamma; IL-17, interleukin 17; JKAP, JNK pathway-associated phosphatase; SCOPD, stable chronic obstructive pulmonary disease; Th, T helper


AECOPD (N = 45)
(A)
r = -0.290, P = 0.053
Th1 cells (% of CD4+ T cells)
JKAP (pg/mL)
(B)
r = -0.378, P = 0.010
Th17 cells (% of CD4+ T cells)
JKAP (pg/mL)
(C)
r = -0.358, P = 0.016
IFN-γ (pg/mL)
JKAP (pg/mL)
(D)
r = -0.414, P = 0.005
IL-17 (pg/mL)
JKAP (pg/mL)
SCOPD (N = 45)
(E)
r = -0.154, P = 0.313
Th1 cells (% of CD4+ T cells)
JKAP (pg/mL)
(F)
r = -0.342, P = 0.022
Th17 cells (% of CD4+ T cells)
JKAP (pg/mL)
(G)
r = -0.232, P = 0.125
IFN-γ (pg/mL)
JKAP (pg/mL)
(H)
r = -0.299, P = 0.046
IL-17 (pg/mL)
JKAP (pg/mL)

via facilitating differentiation of Th17 cells. Given that inflammation recruitment would induce the lung injury and subsequently links with reduced FEV1 (% predicted) and elevated GOLD stage.[4] Thus, downregulated JKAP is linked with declined FEV1 (% predicted) and advanced GOLD stage.

Preceding studies illustrate that JKAP is negatively correlated with Th1 or Th 17 cells in various disease.[11,13,14] To be specific, a study discloses that JKAP suppresses the differentiation of $CD4^+$ T cells into Th17 cells in lupus erythematosus nephritis.[14] What is more, another study illustrates that inhibiting JKAP facilitates $CD4^+$ T cells activation, proliferation, and Th1 and Th17 cells differentiation in inflammatory bowel disease[11]; besides, it is revealed that increased blood JKAP level is linked with decreased Th1 and Th17 cells in sepsis.[13] In line with previous studies, we also found that in AECOPD patients, JKAP expression was negatively correlated with Th17 cells and IL-17, whereas JKAP was slightly negatively linked with Th1 cells and IFN-γ, which could be explained by that (1) increased JKAP might inhibit the proliferation, activation, and differentiation of $CD4^+$ T cells into Th17 cells via various signal pathways.[20,22] Therefore, JKAP level is negatively correlated with Th17 cells as well as its secreted inflammatory cytokine. (2) JKAP probably mainly suppresses the differentiation of T cells into Th17 cells but not Th1 cells. Hence, JKAP is only slightly correlated with Th1 cells.

Some limitations existed in the present study. (1) The sample size was relatively small, which might lead to a lower statistical power and a lower reliability of the findings. (2) As a single-center study, a selection bias might exist. (3) Whether JKAP causing the occurrence of COPD or the occurrence of COPD causing the JKAP decrement needed further exploration. (4) JKAP level in the sputum or bronchoalveolar fluid should be measured in our forthcoming study. (5) In the further study, JKAP level should be measured at multiple time points to monitor disease progression or reflect the treatment response of COPD patients. (6) Another validation cohort should be recruited to explore the value of JKAP in discriminating individuals with high risk of COPD.

In conclusion, downregulated JKAP correlates with elevated Th17 cells, higher acute exacerbation risk, and severity in COPD patients, indicating its underlying potency as a biomarker for COPD.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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