

RESEARCH ARTICLE

JNK pathway-associated phosphatase illustrates low expression and negative correlations with inflammation, disease activity, and T-helper 17 cells in inflammatory bowel disease children

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Abstract

Background: C-Jun N-terminal kinase pathway-associated phosphatase (JKAP) modulates the T cell receptor and mitogen-activated protein kinase pathway-mediated autoimmunity, thus participating in the pathogenesis of autoimmune diseases. This study aimed to explore the clinical implication of JKAP in inflammatory bowel disease (IBD) children.

Methods: C-Jun N-terminal kinase pathway-associated phosphatase, tumor necrosis factor- α (TNF- α), interleukin-23, interferon- γ (T-helper 1 secreted cytokine), and interleukin-17A (T-helper 17 secreted cytokine) in serum samples from 140 IBD children (including 60 Crohn's disease (CD) children and 80 ulcerative colitis (UC) children) were detected by ELISA. Meanwhile, JKAP from serum samples of 10 healthy controls (HCs) was also detected by ELISA.

Results: C-Jun N-terminal kinase pathway-associated phosphatase was reduced in CD children (median (interquartile range (IQR)): 51.6 (36.8–69.5) pg/ml) and UC children (median (IQR): 57.5 (43.4–78.5) pg/ml) compared with HCs (median (IQR): 101.8 (70.0–143.2) pg/ml) (both $p < 0.05$). In CD children, JKAP was negatively correlated with C-reactive protein (CRP) ($p = 0.016$) and erythrocyte sedimentation rate (ESR) ($p = 0.029$); while in UC children, JKAP was also negatively correlated with CRP ($p = 0.006$) and ESR ($p = 0.022$). Regarding the correlation of JKAP with disease activity, it presented negative correlations with PCDAI ($p = 0.001$) and PUCAI ($p = 0.002$). Besides, JKAP was negatively related to TNF- α (both $p < 0.05$) but not interleukin-23 (both $p > 0.05$) in CD and UC children. Additionally, JKAP was not correlated with interferon- γ in CD or UC children (both $p > 0.05$), while negatively correlated with interleukin-17A in CD and UC children (both $p < 0.05$).

Conclusion: C-Jun N-terminal kinase pathway-associated phosphatase shows low expression and negative correlations with inflammation, disease activity, and T-helper 17 cells in IBD children.

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KEYWORDS

C-Jun N-terminal kinase pathway-associated phosphatase, disease activity, inflammation, inflammatory bowel disease children, T-helper 17

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is an autoimmune disease that mainly includes Crohn's disease (CD) and ulcerative colitis (UC), which impacts the gastrointestinal tract in both adults and children.^{1,2} In children, IBD may also affect their growth and even lead to reduced quality of life and psychological health.^{3,4} In recent decades, the incidence of IBD in children is steadily increasing in Europe, North American, and Asia, which renders IBD in children a critical health issue internationally.^{5,6} Although nutritional management, 5-aminosalicylic acid (5-ASA), glucocorticoids, immunosuppressive agents, and biologics may be useful in the treatment of IBD in children, there still lacks biomarkers to reflect the risk and characteristics of IBD in children, which could hinder the in-time management of IBD in children.^{4,7-10}

C-Jun N-terminal kinase (JNK) pathway-associated phosphatase (JKAP) is a dual-specificity phosphatase to activate the JNK pathway and thus participates in various cellular functions, including malignant behavior of cancer cells, cell motility, and notably, T cell receptor (TRC) signaling-mediated autoimmunity.¹¹⁻¹³ Clinically, a bunch of studies has reported the potential of JKAP as a biomarker in autoimmune diseases. For instance, it is suggested that JKAP is associated with inflammation and disease activity in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis.¹⁴⁻¹⁶ Another interesting study discloses that JKAP is insufficiently expressed and negatively correlates with disease activity in IBD patients¹⁷; however, this study only enrolled adult IBD patients, and it is restricted by the limited sample size ($N = 81$). Therefore, the role of JKAP as a biomarker in IBD should be verified in a larger cohort, and whether JKAP could also act as a biomarker in IBD in children remained unclear.

The current study enrolled 140 IBD children (including 60 CD children and 80 UC children) and detected JKAP level in their serum, which aimed to explore the correlation of JKAP with T-helper (Th) 1, Th17 cells inflammation, and disease activity in children with IBD.

2 | METHODS

2.1 | Participants

Between July 2019 and January 2022, this study serially enrolled a total of 140 IBD children (including 60 CD children and 80 UC children) who were admitted to the hospital. The inclusion criteria were: (i) confirmed as IBD (CD or UC) according to conventional radiological, endoscopic, and histological examinations; (ii) less than 16 years old; (iii) willing to provide peripheral blood (PB) samples. The exclusion criteria were: (i) complicated with other immune system

diseases; (ii) had a prior history of hematologic malignancies or solid tumors. In addition, during the same period, a total of 10 healthy children who underwent health examinations in the hospital were also recruited in the study as health controls (HCs). The HCs who had a history of IBD or met the exclusion criteria for IBD children were ineligible for the study. The study was permitted by Ethics Committee of The Affiliated Hospital of Qingdao University. The statutory guardians of all participants signed the informed consents.

2.2 | Data document

Clinical characteristics were collected from CD children and UC children at admission, as well as from HCs after enrollment, which included age, gender, height, weight, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Additionally, pediatric Crohn's disease activity index (PCDAI) was assessed among CD children, based on which the disease activity was evaluated, then classified as quiescent, mild, moderate, and severe.¹⁸ Besides, pediatric ulcerative colitis activity index (PUCAI) was assessed among UC children, then the disease severity was evaluated and classified as remission, mild, moderate, and severe.¹⁹ Treatments for all patients were also recorded, including 5-ASA, glucocorticoid treatment, immunosuppressant treatment, biologics treatment.

2.3 | Sample collection and assessment

Peripheral blood samples were obtained from IBD children at admission and HCs after enrollment, then serum samples were separated to assess the levels of JKAP, proinflammatory cytokines TNF- α and interleukin-23 (IL-23)), Th1 cell-secreted cytokine (interferon-gamma (IFN- γ)), and Th17 cell-secreted cytokine (interleukin-17A (IL-17A)) by enzyme-linked immunosorbent assay (ELISA) using commercial Human ELISA Kits. All kits used in the study analysis were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd, and the experimentations were performed in strict accordance with the protocols from manufacturers.

2.4 | Statistics

Statistical analysis and graphs construction were carried out using SPSS V.24.0 (IBM Corp.) and GraphPad Prism V.6.01 (GraphPad Software Inc.), respectively. Differences of clinical characteristics among three groups were analyzed using one-way analysis of variance (ANOVA) test, Chi-square test, and Kruskal-Wallis H rank-sum test. Comparison of JKAP level among three groups was determined using

Kruskal–Wallis H rank-sum test, and comparison between groups was adjusted using Bonferroni test. The ability of JKAP level in differentiating participants was assessed using receiver-operating characteristic (ROC) analysis and area under the curve (AUC). The association of two variables was evaluated using Spearman's rank correlation test. The association between treatment and JKAP level was assessed by Wilcoxon rank-sum test. A p value < 0.05 indicated statistical significance.

3 | RESULTS

3.1 | Clinical characteristics

The UC children had a mean age of 8.5 ± 2.6 years with 34 (42.5%) males and 46 (57.5%) females; meanwhile, the CD children showed a mean age of 8.6 ± 2.8 years with 29 (48.3%) males and 31 (51.7%) females; besides, the HCs presented a mean age of 8.8 ± 2.3 years, consisting of 4 (40.0%) males and 6 (60.0%) females. The comparison analysis revealed that no difference was found in age, gender, height, or weight among UC children, CD children, and HCs (all $p > 0.05$), whereas CRP (median (interquartile range (IQR)): 31.1 (18.0–45.5) versus 25.2 (16.9–43.2) versus 2.6 (1.4–3.3) mg/L) and ESR (median (IQR): 29.9 (19.2–40.9) versus 30.5 (20.6–45.1) versus 10.1 (8.8–13.7) mm/h) were different among the three groups (both $p < 0.001$). Moreover, TNF- α , IL-23, and IL-17A were similar between UC children and CD children (all $p > 0.05$), but IFN- γ showed an increase in CD children compared with UC children ($p < 0.001$). Regarding disease activity of UC children, the median (IQR) value of PUCAI score was 25.0 (15.0–40.0); meanwhile, there were 12 (15.0%) children with remission disease, 39 (48.8%) children with mild UC, and 29 (36.2%) children with moderate or severe UC. In terms of disease activity in CD children, the median (IQR) value of PCDAI score was 25.0 (17.5–40.0); besides, the numbers of children with quiescent, mild, and moderate/severe CD were 9 (15.0%), 28 (46.7%), and 23 (38.3%), respectively (Table 1).

3.2 | JKAP level

C-Jun N-terminal kinase pathway-associated phosphatase presented a distinctive expression among CD children (median (IQR): 51.6 (36.8–69.5) pg/ml), UC children (median (IQR): 57.5 (43.4–78.5) pg/ml), and HCs (median (IQR): 101.8 (70.0–143.2) pg/ml) ($p < 0.001$); meanwhile, it was reduced in CD children ($p < 0.001$) and UC children ($p = 0.005$) compared with HCs; in addition, JKAP was similar between CD children and UC children ($p = 0.281$) (Figure 1A). Further ROC curve analysis showed that JKAP illustrated good potential in discriminating CD children (AUC: 0.868, 95% confidence interval (CI): 0.759–0.978) and UC children (AUC: 0.824, 95% CI: 0.687–0.961) from HCs; JKAP at the best cut-off point was 73.25 pg/ml for discriminating CD children versus HCs and 83.65 pg/ml for discriminating UC children versus HCs, accordingly (Figure 1B).

3.3 | Correlation of JKAP with inflammation markers

In CD children, JKAP showed a negative correlation with CRP ($r_s = -0.310$, $p = 0.016$) (Figure 2A) and ESR ($r_s = -0.281$, $p = 0.029$) (Figure 2B). In UC children, JKAP also displayed negative correlations with both CRP ($r_s = -0.307$, $p = 0.006$) (Figure 2C) and ESR ($r_s = -0.257$, $p = 0.022$) (Figure 2D).

3.4 | Correlation of JKAP with disease activity

C-Jun N-terminal kinase pathway-associated phosphatase was negatively correlated with PCDAI score in CD children ($r_s = -0.421$, $p = 0.001$) (Figure 3A); after categorizing CD children into children with quiescent, mild, and moderate/severe CD, it was revealed that JKAP was negatively correlated with disease severity in CD children ($r_s = -0.392$, $p = 0.002$) (Figure 3B). Simultaneously, JKAP showed a reverse correlation with PUCAI score in UC children ($r_s = -0.342$, $p = 0.002$) (Figure 3C); UC children were also divided into children with remission, mild, or moderate/severe UC; correlation analysis presented that JKAP was also negatively correlated with disease severity in UC children ($r_s = -0.241$, $p = 0.031$) (Figure 3D).

3.5 | Correlation of JKAP with proinflammatory cytokines

C-Jun N-terminal kinase pathway-associated phosphatase was negatively correlated with TNF- α in both CD children ($r_s = -0.437$, $p < 0.001$) and UC children ($r_s = -0.238$, $p = 0.033$). However, it presented no correlation with IL-23 in neither CD children ($r_s = -0.240$, $p = 0.065$) nor UC children ($r_s = -0.205$, $p = 0.068$) (Figure 4A–D).

3.6 | Correlation of JKAP with Th1- and Th17-secreted cytokines

C-Jun N-terminal kinase pathway-associated phosphatase was not correlated with IFN- γ ($r_s = -0.186$, $p = 0.156$) (Figure 5A), while it illustrated a negative correlation with IL-17A ($r_s = -0.342$, $p = 0.008$) (Figure 5B); however, it was not correlated with IFN- γ /IL-17A ratio ($r_s = -0.149$, $p = 0.256$) (Figure 5C) in CD children. Meanwhile in UC children, JKAP showed no correlation with IFN- γ ($r_s = -0.101$, $p = 0.373$) (Figure 5D), but it was negatively correlated with IL-17A ($r_s = -0.255$, $p = 0.022$) (Figure 5E); besides, it was not correlated with IFN- γ /IL-17A ratio ($r_s = -0.035$, $p = 0.756$) (Figure 5F) in UC children. In addition, JKAP did not vary in IBD children with or without 5-ASA, glucocorticoid, immunosuppressant, or biologics treatment (all $p > 0.05$) (Figure 6A–H).

TABLE 1 Characteristics of IBD children and HCs

Items	HCs (N = 10)	UC children (N = 80)	CD children (N = 60)	Statistic ($F/\chi^2/H/Z$)	p Value
Age (years), mean \pm SD	8.8 \pm 2.3	8.5 \pm 2.6	8.6 \pm 2.8	0.058	0.944
Gender, No. (%)				0.566	0.753
Male	4 (40.0)	34 (42.5)	29 (48.3)		
Female	6 (60.0)	46 (57.5)	31 (51.7)		
Height (cm), mean \pm SD	134.8 \pm 13.1	128.7 \pm 18.0	133.1 \pm 20.2	1.206	0.302
Weight (kg), mean \pm SD	29.9 \pm 8.6	27.9 \pm 8.7	28.9 \pm 10.0	0.314	0.731
CRP (mg/L), median (IQR)	2.6 (1.4–3.3)	31.1 (18.0–45.5)	25.2 (16.9–43.2)	27.682	<0.001
ESR (mm/h), median (IQR)	10.1 (8.8–13.7)	29.9 (19.2–40.9)	30.5 (20.6–45.1)	22.440	<0.001
PUCAI, median (IQR)	-	25.0 (15.0–40.0)	-	-	-
Severity of UC, No. (%)				-	-
Remission	-	12 (15.0)	-		
Mild	-	39 (48.8)	-		
Moderate or severe	-	29 (36.2)	-		
PCDAI, median (IQR)	-	-	25.0 (17.5–40.0)	-	-
Severity of CD, No. (%)				-	-
Quiescent	-	-	9 (15.0)		
Mild	-	-	28 (46.7)		
Moderate or severe	-	-	23 (38.3)		
TNF- α (pg/ml), median (IQR)	-	67.4 (52.8–107.0)	83.2 (57.4–147.2)	-1.756	0.079
IL-23 (pg/ml), median (IQR)	-	107.0(85.2–160.0)	124.1 (91.2–172.9)	-1.392	0.164
IFN- γ (pg/ml), median (IQR)	-	9.8 (8.0–12.5)	12.9 (9.6–17.2)	-3.622	<0.001
IL-17A (pg/ml), median (IQR)	-	75.7 (59.2–90.8)	70.8 (55.7–101.4)	-0.101	0.920
5-ASA treatment, No. (%)	-	72 (90.0)	10 (16.7)	75.985	<0.001
Glucocorticoid treatment, No. (%)	-	26 (32.5)	23 (38.3)	0.513	0.474
Immunosuppressant treatment, No. (%)	-	11 (13.8)	32 (53.3)	25.244	<0.001
Biologics treatment, No. (%)	-	10 (12.5)	20 (33.3)	8.838	0.003

Abbreviations: 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HCs, health controls; IBD, inflammatory bowel disease; IFN- γ , interferon-gamma; IL-17A, interleukin 17A; IL-23, interleukin 23; IQR, interquartile range; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index; SD, standard deviation; TNF- α , tumor necrosis factor alpha; UC, ulcerative colitis.

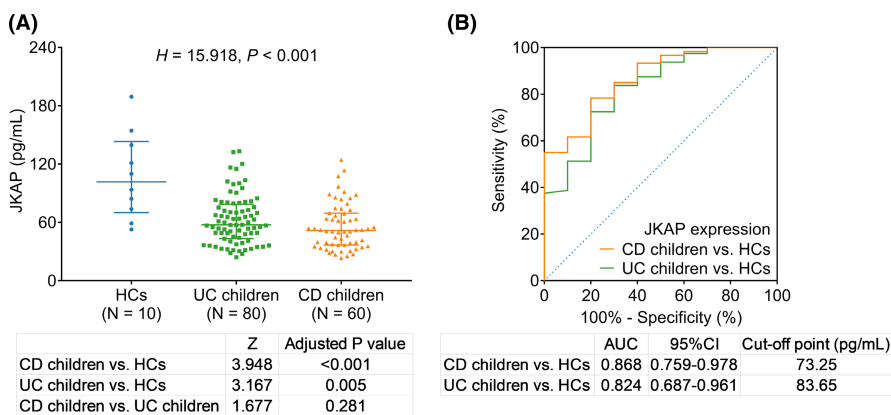


FIGURE 1 C-Jun N-terminal kinase pathway-associated phosphatase expression in IBD children and HCs. Comparison of JKAP expression among UC children, CD children, and HCs (A); Ability of JKAP in discriminating UC and CD children from HCs (B)

4 | DISCUSSION

C-Jun N-terminal kinase pathway-associated phosphatase is reported to suppress TCR signaling and autoimmunity through inactivating lymphocyte-specific protein-tyrosine kinase (Lck).¹³ Based

on this finding, several studies have inquired about the clinical role of JKAP in autoimmune diseases, which illustrate that JKAP is lower in patients with rheumatoid arthritis or IBD.^{14,17} However, whether JKAP also presented aberrant expression in IBD children remained unclear. In the current study, it was observed that JKAP was reduced

FIGURE 2 Correlation of JKAP with inflammatory markers in IBD children. Correlation of JKAP with CRP (A) and ESR (B) in CD children; correlation of JKAP with CRP (C) and ESR (D) in UC children

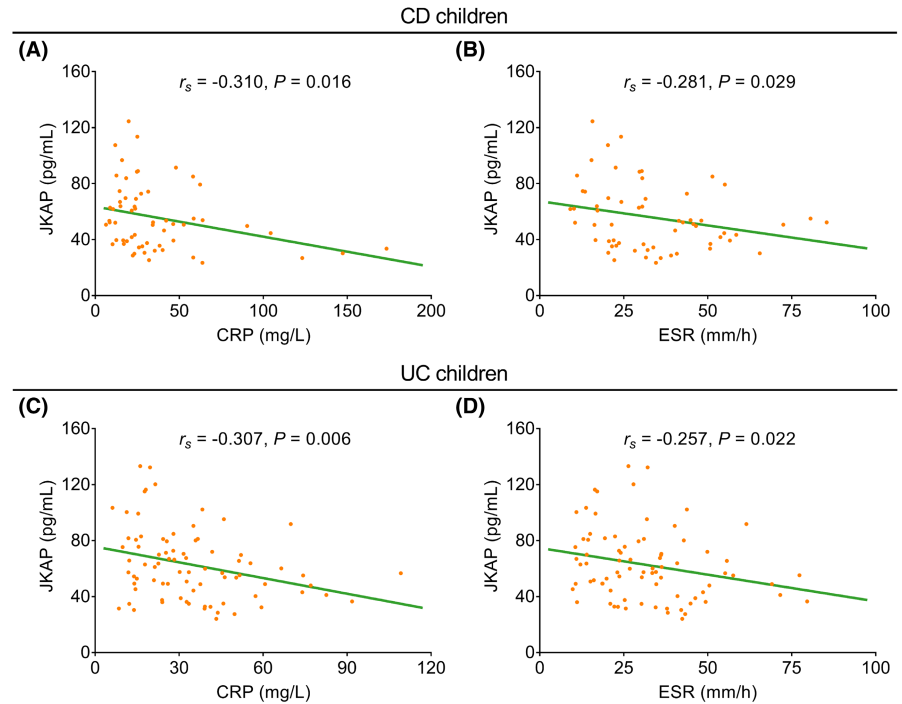
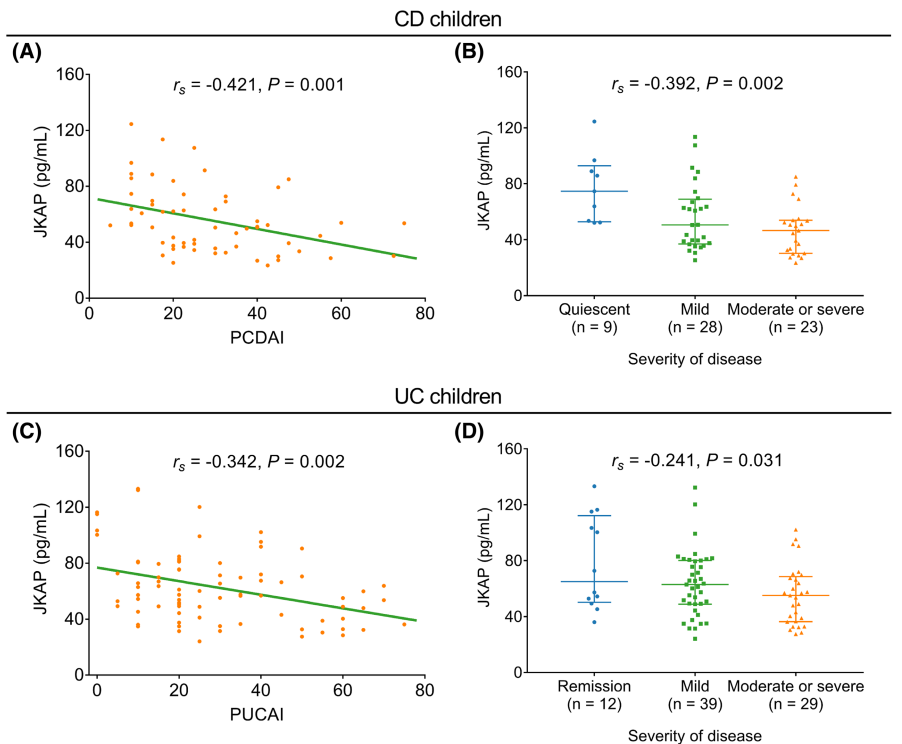


FIGURE 3 Correlation of JKAP with disease activity in IBD children. Correlation of JKAP with PCDAI (A) and comparison of JKAP among patients with different severity (B) in CD children; correlation of JKAP with PUCAI (C) and comparison of JKAP among patients with different severity (D) in UC children



in CD children and UC children compared with HCs. A possible explanation was that: a low level of JKAP might activate the TCR signaling through activating Lck, while activated TCR signaling was a critical inducer of IBD.^{13,20} Therefore, JKAP was lower in IBD children compared with HCs. Currently, the diagnosis of IBD is mainly based on a complex combination of clinical symptoms, laboratory findings, endoscopy, histopathological examination, and imageology examination; meanwhile, there lacks a gold standard for the diagnosis of IBD, which may cause a delay in the treatment of IBD.²¹ Our

data revealed that JKAP showed good potential in discriminating IBD children from HCs, which implied that JKAP might be helpful for the diagnosis of IBD in children. However, since the main objective of this study was not to explore the effect of JKAP on diagnosing IBD in children, this hypothesis could be explored in further studies.

It is worth noting that JKAP is able to reflect the disease activity in patients with autoimmune diseases. For instance, JKAP is negatively correlated with psoriasis area severity index score in patients with psoriasis¹⁵; meanwhile, JKAP is associated with lower CD

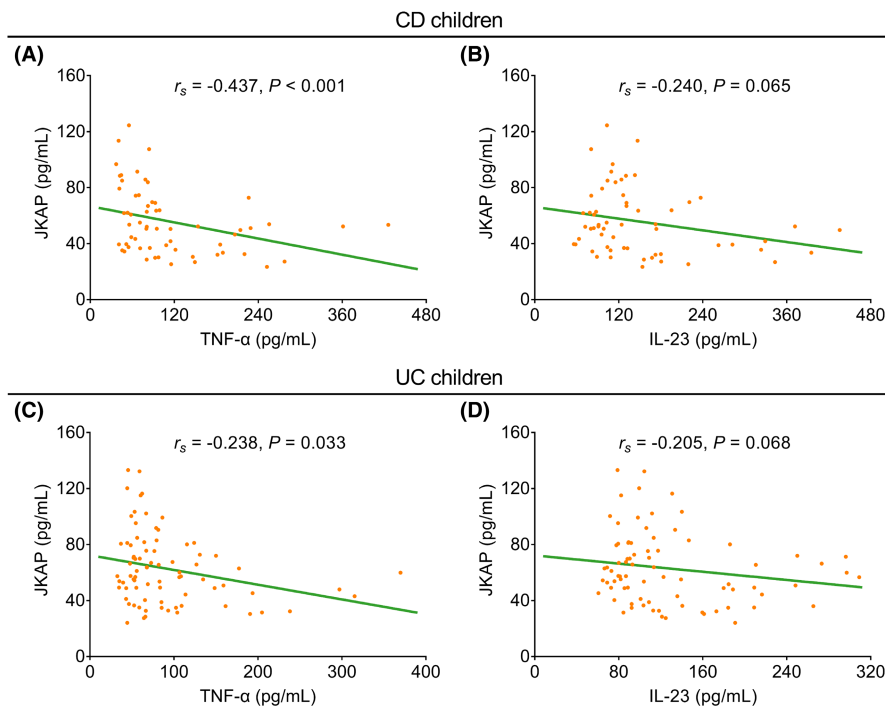


FIGURE 4 Correlation of JKAP with proinflammatory cytokines in IBD children. Correlation of JKAP with TNF- α (A) and IL-23 (B) in CD children; correlation of JKAP with TNF- α (C) and IL-23 (D) in UC children

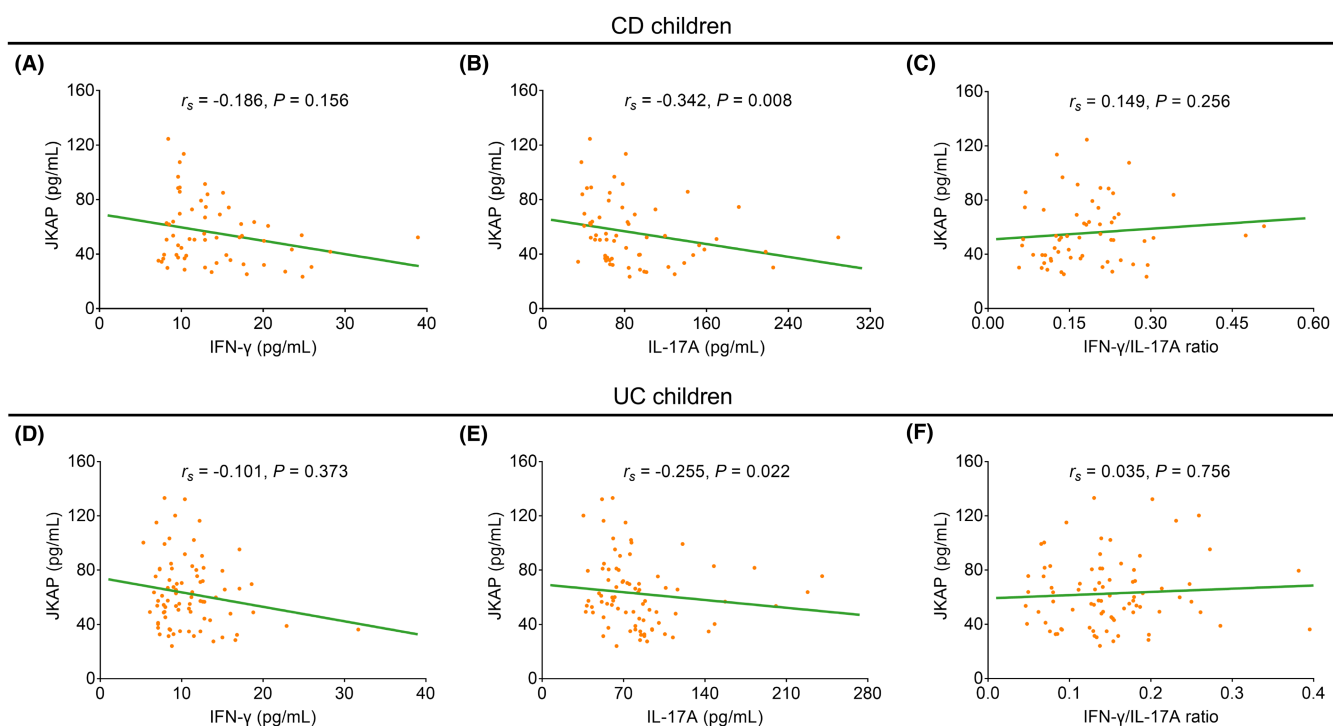
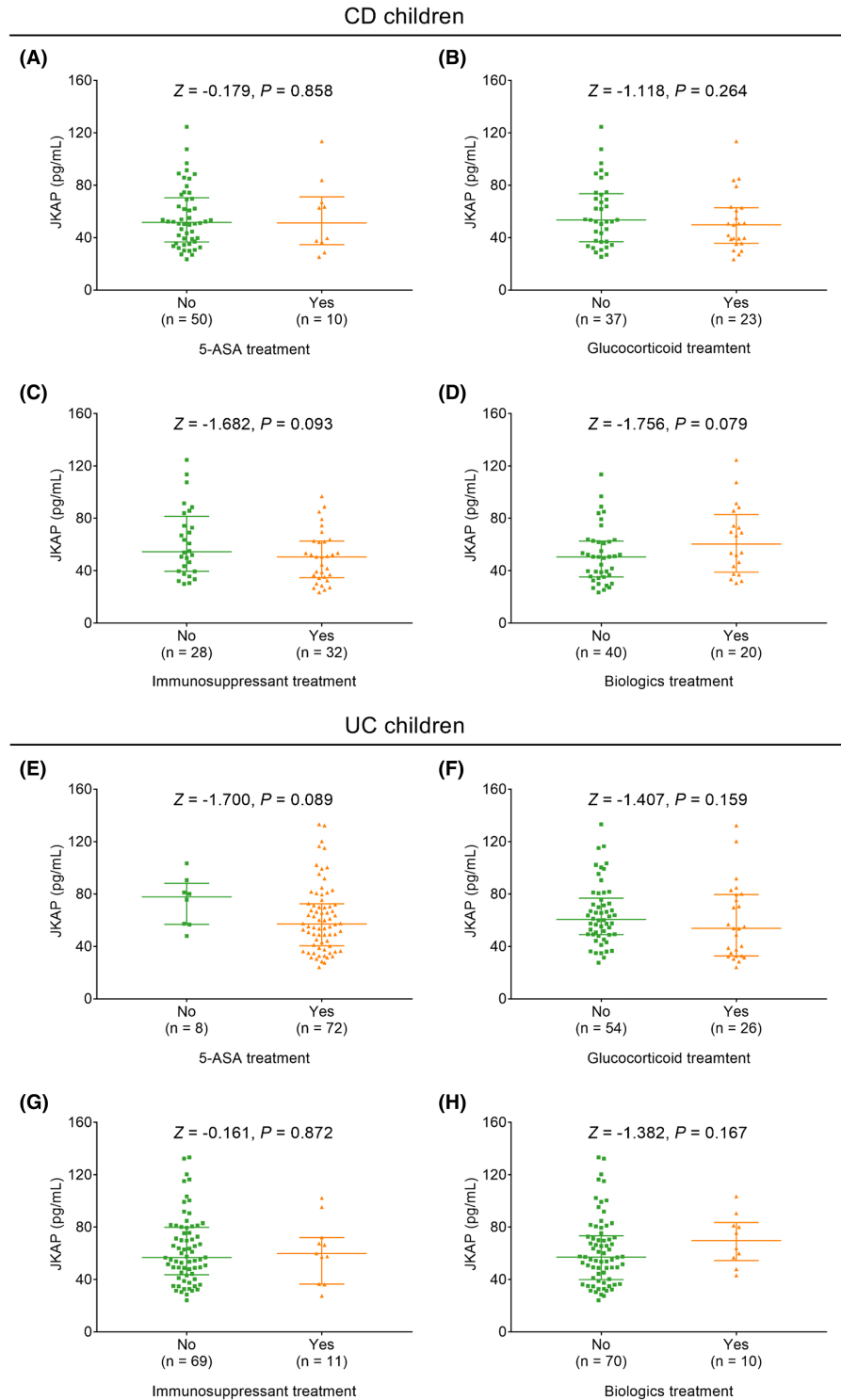


FIGURE 5 Correlation of JKAP with cytokines secreted by Th1 and Th17 in IBD children. Correlation of JKAP with IFN- γ (A), IL-17A (B), and IFN- γ /IL-17A ratio (C) in CD children; correlation of JKAP with IFN- γ (D), IL-17A (E), and IFN- γ /IL-17A ratio (F) in UC children

activity index in adult patients with CD²²; besides, JKAP presents a negative correlation with 28-joints disease activity score based on ESR in rheumatoid arthritis patients.²³ These studies suggest that JKAP could serve as a potential biomarker to timely monitor disease activity in autoimmune diseases. However, whether this correlation also existed in IBD children should be investigated. In the present

study, it was observed that JKAP was negatively correlated with inflammation markers, proinflammatory cytokine, and disease activity scores in IBD children. Possible explanations might be that: (1) as a phosphatase, JKAP might downregulate inflammation through several pathways, such as the JNK pathway and the TCR pathway.^{12,13} Therefore, JKAP was negatively correlated with inflammation in IBD

FIGURE 6 Correlation of JKAP with treatment in IBD children. Comparison of JKAP in CD children with or without 5-ASA (A), glucocorticoid (B), immunosuppressant (C), or biologics (D) treatment. Comparison of JKAP in UC children with or without 5-ASA (E), glucocorticoid (F), immunosuppressant (G), or biologics (H) treatment



children; (2) through downregulating inflammation, JKAP connected to reduced disease activity in IBD patients.

$CD4^+$ T cells are critically involved in the pathophysiology of IBD. For instance, it is reported that Th1 and Th17 are dysregulated in patients with IBD.²⁴ Meanwhile, Th1 and Th17 also modulate the progression of IBD.²⁵ Apart from these, previous studies also present that JKAP not only correlates with Th1 and Th17 in several comprehensive diseases such as chronic obstructive pulmonary disease,

Alzheimer's disease, and Parkinson's disease, but also modulates the differentiation of Th1 and Th17 in IBD.^{17,26-28} Therefore, it was reasonable to deduce that JKAP was also correlated with Th1 and Th17 in IBD children. In the current study, it was observed that JKAP presented a negative correlation with Th17 in IBD children, which could be a result from that JKAP might suppress the differentiation of Th17 in IBD children.¹⁷ Meanwhile, since Th17 critically regulates the pathogenesis and progression of IBD, these above-mentioned

data could also explain the correlation of JKAP with IBD risk and activity.

Although several interesting results were found, there existed some limitations in this study. Firstly, this study had a relatively low sample size, which might cause low statistical power. Secondly, the clinical role of JKAP in unclassified IBD children could be further explored. Thirdly, the molecular mechanism of JKAP in regulating the differentiation of CD4⁺ T cells into Th17 cells in IBD could be investigated in the future. Fourthly, the monitoring of longitudinal change of JKAP in IBD children should be conducted in the future. Fifthly, the correlation of JKAP with treatment response to biologics in IBD children could be investigated in further studies. Sixthly, the comparison of JKAP as a biomarker between pediatric and adult IBD children could be explored in the future.

Conclusively, JKAP is insufficiently expressed and negatively correlates with inflammation, disease activity, and Th17 cells in IBD children.

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None.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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