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Correlation between preoperative and postoperative miR-29c-3p level changes and immune response in paediatric acute septic appendicitis and its predictive significance for complications: a retrospective study

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Abstract

Background Postoperative complications in children with acute suppurative appendicitis (ASA) can lead to very serious consequences. In this study, we investigated the pre- and postoperative expression of miR-29c-3p in ASA and its value in predicting postoperative complications.

Methods Retrospectively, 128 children with ASA and 93 healthy children were included. The qRT-PCR technique was used to detect miR-29c-3p expression in children with ASA preoperatively and 24 h postoperatively. The levels of immune cells (WBC, NEU, LYM) were detected by routine blood test, and the levels of immune proteins CRP and inflammatory factors (TNF-α and IL-6) were detected by ELISA.

Results Before surgery, children with ASA had higher levels of miR-29c-3p than healthy controls. But after surgery, miR-29ac-3p levels dropped a lot in children with ASA. The serum levels of immune cells (WBC, NEU, LYM), immune protein CRP and inflammatory factors (TNF-α and IL-6) were significantly decreased in children with ASA. Postoperative miR-29c-3p levels were positively correlated with the levels of immune indicators. The patients with higher miR-29c-3p expression levels showed a greater incidence of postoperative complications.

Conclusions The expression of miR-29c-3p was positively correlated to immune cells, immune proteins, and inflammatory factors. The expression levels of miR-29c-3p were related to the occurrence of postoperative complications and could, therefore, be utilized to predict the occurrence of postoperative complications in children with ASA.

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Keywords Acute septic appendicitis, miR-29c-3p, Immunological indicators, Post-operative complications

Background

Acute abdominal infections in children occur mainly due to acute appendicitis, with an incidence of 1–8% and a morbidity and mortality rate of up to 0.24–4% [1]. Acute suppurative appendicitis (ASA) is the main pathological feature of acute appendicitis [2]. Children with acute suppurative appendicitis (ASA) are young and have atypical clinical manifestations, which can lead to appendiceal perforation and even various serious complications if left untreated. A recent study showed a significant decreases in perforations depending on age, as follow: 100% 0–2 years; 83.3% 2–3 years; 71.4% 3–4 years; 78.6% 4–5 years and 47.3% 5 years [3]. With the continuous development of technology, laparoscopic appendectomy is gradually being commonly applied as a surgical procedure for the treatment of pediatric cases of ASA. This technique has low invasiveness, leading to reduced recovery time during postoperative recovery. However, surgery usually leads to an imbalance in the immune system, which might affect the child's condition or elicit an inflammatory response in the child [4].

As RNAs that do not encode proteins, miRNAs can influence the course of various diseases by regulating protein expression and thus cellular metabolism [5]. For example, miR-320a-3p levels are elevated in patients with paroxysmal atrial fibrillation [6]; and miR-127-3p levels are downregulated in patients with frontotemporal dementia [7]. Avni et al., on the other hand, investigated the miRNAs associated with acute appendicitis and reported that the expression of miR-29c-3p was increased 2-fold compared to that of the other miRNAs within 4–6 h of the initial stage of acute appendicitis (AA) [8].

It has been reported that miRNAs are considered to be potent regulators of numerous genes and pathways involved in the development of inflammatory and immune diseases [9]. miRNAs may demonstrate their potential in their therapeutic application in inflammatory and related diseases by regulating macrophage polarization [10]. It has been recognised that miR-29c-3p is aberrantly expressed in immune and inflammatory diseases [11]. Children with ASA are prone to immune responses and inflammatory complications after surgery, etc. The expression level of miR-29c-3p in the postoperative immune response of children with ASA is unknown. miR-29c-3p levels and their correlation with immune markers are also unknown. Therefore, we chose miR-29c-3p as a research subject to investigate the expression of miR-29c-3p in children with ASA after surgery and its correlation with the expression of immune indicators.

Methods

Inclusion of patients

We retrospectively included 128 children with ASA who attended Xingtai People's Hospital between January 2022 and December 2023 were included in the present study. In addition, 93 healthy children from the same periodwere included. The specific clinical information of all study participants is provided in Table 1. The inclusion criteria were as follows: (a) age ≤ 14 years; (b) those who fulfilled the diagnostic criteria for acute suppurative appendicitis [12]; (c) those who fulfilled the indications for surgery; (d) the children who were conscious and for whom the family members had signed the informed consent form. The exclusion criteria were as follows: (a) a history of abdominal surgery; (b) presence of other gastrointestinal or abdominal diseases; (c) presence of coagulation disorders; (d) presence of preoperative infection; (e) presence of contraindications to surgery.

The Xingtai People's Hospital Ethics Committee approved the study. The trials were conducted in accordance with the tenets of the Declaration of Helsinki. The guardians of the children signed an informed consent form.

Quantitative reverse transcription PCR (qRT-PCR)

Before and after surgery, the children had 3 mL of fasting venous blood drawn, and the serum was centrifuged, and 1 mL of Trizol reagent was added to extract RNA from the tissues and reverse transcribed into cDNA using a reverse transcription kit (Takara, Dalian, China). A qRT-PCR kit (Takara, Dalian, China) was used to identify miR-29c-3p in the serum of the subjects. The expression level and the experimental steps were in accordance with the kit instructions, with GAPDH as an endogenous reference. Ct values were normalized using the $2^{-\Delta\Delta Ct}$ method.

Inflammatory and immune indicators

Before and 24 h after surgery, 3 mL fasting venous blood sample was collected from each subject and centrifuged at 2000 rpm for 10 min for serum sample collection. Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit (Beyotime, Shanghai China). White blood cells (WBC), neutrophils (NEU), and lymphocytes (LYM) were determined through a blood smear.

Postoperative complication

According to the miR-29c-3p expression level, they were divided into low expression group (< 1.43) and high

Table 1 Clinical data of the study subjects

Indicators	Control Group ($n=93$)	ASA Group ($n=128$)	*P*
Gender			0.822
Male	53	71	
Female	40	57	
Age (years)	8.05 ± 2.04	8.16 ± 2.44	0.735
Temperature (℃)	36.71 ± 0.29	37.83 ± 0.44	0.000
Systolic pressure (mmHg)	122.04 ± 6.58	120.91 ± 6.57	0.206
Diastolic pressure (mmHg)	68.20 ± 4.59	68.27 ± 4.91	0.915
WBC ($\times10^9$/L)	7.85 ± 1.18	15.68 ± 2.79	< 0.0001
NEU ($\times10^9$/L)	5.94 ± 0.94	10.08 ± 2.27	< 0.0001
LYM ($\times10^9$/L)	2.51 ± 0.99	5.54 ± 1.07	< 0.0001
CRP (mg/L)	/	27.02 ± 4.58	/
TNF-α (ng/L)	/	23.40 ± 4.29	/
IL-6 (ng/L)	/	40.69 ± 5.95	/

WBC, white blood cell; NEU, neutrophils; LYM, lymphocytes; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, Interleukin-6

expression group (≥ 1.43) according to the average value of miR-29c-3p [13]. The incidence of incision infection, mesenteric adhesion and bowel obstruction complications 30 days after surgery was recorded in both groups. Postoperative children with abdominal pain, abdominal distension, nausea, vomiting and other symptoms can be combined with ultrasound and other means of investigation, diagnosed as mesenteric adhesion. Postoperative intestinal obstruction can be diagnosed if intestinal peristalsis is not restored for more than 3 days after laparoscopic surgery.

The incision infection should be cleaned and disinfected with povidone-iodine, and debridement should be carried out if necessary, and the dressing should be changed regularly after the operation. If the child develops mesenteric adhesions, abdominal massage, respiratory contact or infrared electrotherapy may be used as appropriate. Children with concomitant intestinal obstruction should be strictly dehydrated and fasted.

Statistical analysis

Data analysis and graphing were performed using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9. Continuous variables quantified by Q-Q plots were analysed and all conformed to a normal distribution. Therefore, data were expressed as mean ± standard deviation. The significance of gender in the control and ASA groups was analysed using the chi-square test, and t-tests were used for the remaining continuous variables. The correlation between miR-29c-3p and immune levels was analyzed using Pearson's analysis. A significant difference was considered when the bilateral P value was less than 0.05.

Results

Differences in subjects' clinical baseline and miR-29c-3p expression levels

Table 1 demonstrates some of the preoperative indices of control children and children with ASA, there was no statistically meaningful difference in age, gender, systolic and diastolic blood pressure of the heart between the two groups of subjects ($P>0.05$). There were considerable differences in body temperature, white blood cells (WBC), neutrophils (NEU), and lymphocytes (LYM) ($P<0.001$). C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and Interleukin-6 (IL-6) in children with ASA were 27.02 ± 4.58 mg/L, 23.40 ± 4.29 ng/L, 40.69 ± 5.95 ng/L, respectively. miR-29c-3p levels were notably higher in children with ASA compared with healthy children ($P<0.001$, Fig. 1A).

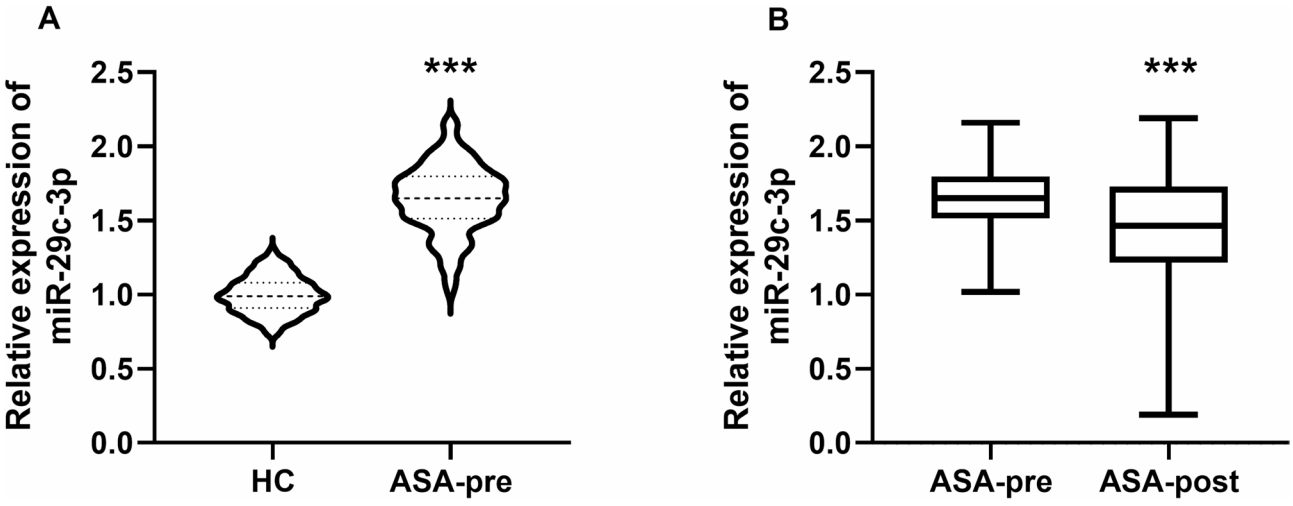

Fig. 1 **A** Children with ASA had significantly higher levels of miR-29c-3p compared to healthy children (*** $P<0.001$). **B** Postoperative miR-29c-3p levels were reduced in children with ASA (*** $P<0.001$)

Preoperative and postoperative changes in immune markers and miR-29c-3p

The miR-29c-3p levels in children with ASA were notably lower postoperatively compared to preoperatively ($P < 0.001$, Fig. 1B). The value of WBC, NEU, and LYM in children with ASA were remarkably lower after the laparoscopic surgery (ASA-post) compared to the corresponding levels determined during the pre-operative period (ASA-pre) ($P < 0.001$, Fig. 2A and C).

Preoperative and postoperative changes in inflammatory markers

The serum levels of CRP, TNF-α, and IL-6 were also markedly reduced in the children with ASA after surgery ($P < 0.001$, Fig. 2D and F).

Correlation of miR-29c-3p expression with inflammation and immunity

Pearson's correlation coefficients revealed a positive correlation between the miR-29c-3p levels and the counts of leukocytes ($r = 0.8498$), neutrophils ($r = 0.7805$), and lymphocytes ($r = 0.7258$), which are immune markers, during the postoperative period ($P < 0.001$, Fig. 3A and C). An increase in the levels of immune markers was accompanied by a corresponding increase in miR-29c-3p expression. The same trend was noted for the levels of CRP ($r = 0.6898$), TNF-α ($r = 0.6610$), and IL-6 ($r = 0.6846$), the three inflammatory factors that exhibited levels correlated positively to the miR-29c-3p levels ($P < 0.001$, Fig. 3D and F).

Post-operative complications

Children with ASA were divided into high and low-expression groups based on miR-29c-3p. The occurrence of postoperative complications in both groups is illustrated in Table 2. 16 cases of postoperative complications were found in the two groups of children with ASA. In the miR-29c-3p high-expression group, there were 5 cases of incisional infection, 4 cases of mesenteric adhesion and 4 cases of intestinal obstruction, totalling 13 cases. miR-29c-3p low-expression group had 2 cases of incisional infection, 1 case of mesenteric adhesion and no intestinal obstruction, totalling 3 cases. This suggests that the probability of postoperative complications was greater in the miR-29c-3p high-expression group than in the low-expression group.

Discussion

ASA is an acute abdominal disease that presents as metastatic pain in the right lower abdomen accompanied by nausea, vomiting, and fever. ASA progresses rapidly and, in severe cases, may lead to appendiceal perforation,

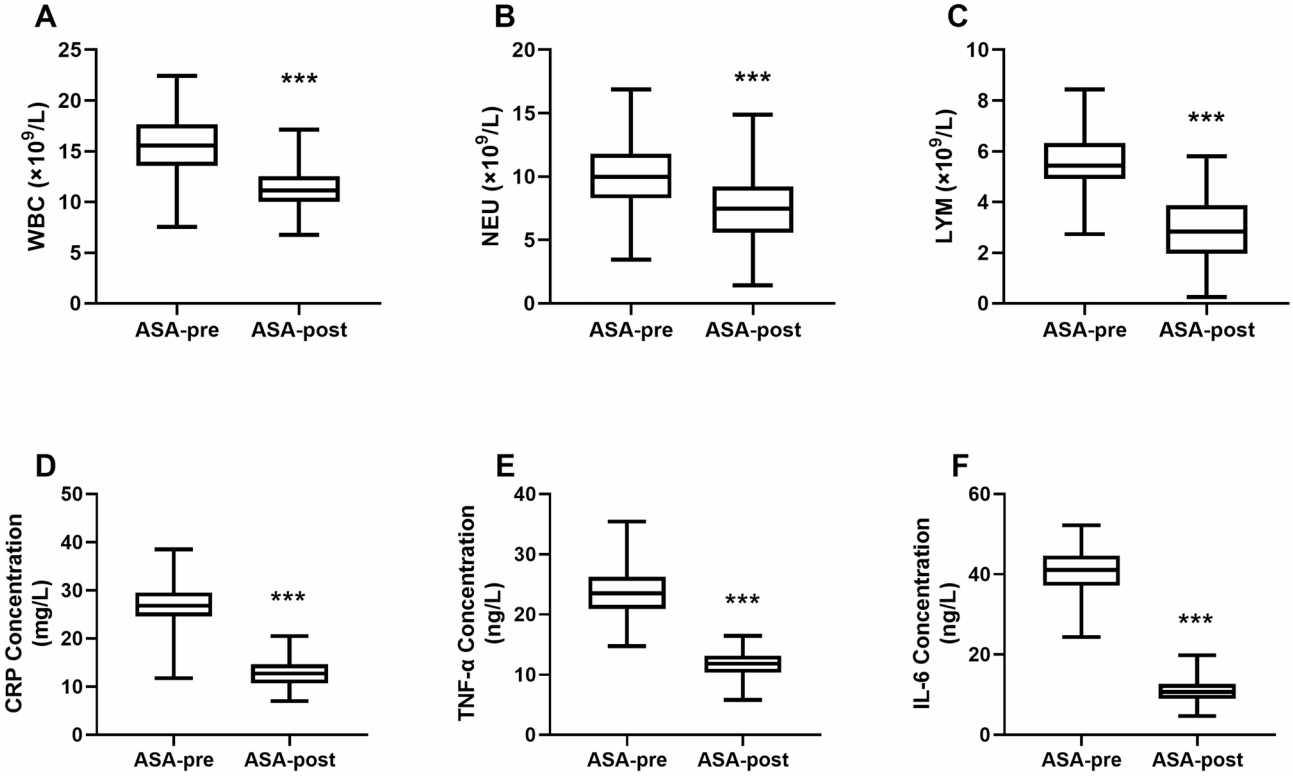

Fig. 2 Changes in preoperative and postoperative inflammatory markers in children with ASA. **A** Changes in preoperative and postoperative WBC counts; **B** Changes in preoperative and postoperative NEU counts; **C** Changes in preoperative and postoperative LYM counts. **D** Changes in preoperative and postoperative CRP levels; **E** Postoperative TNF-α levels were significantly reduced. **F** Postoperative IL-6 levels decreased markedly (*** $P < 0.001$)

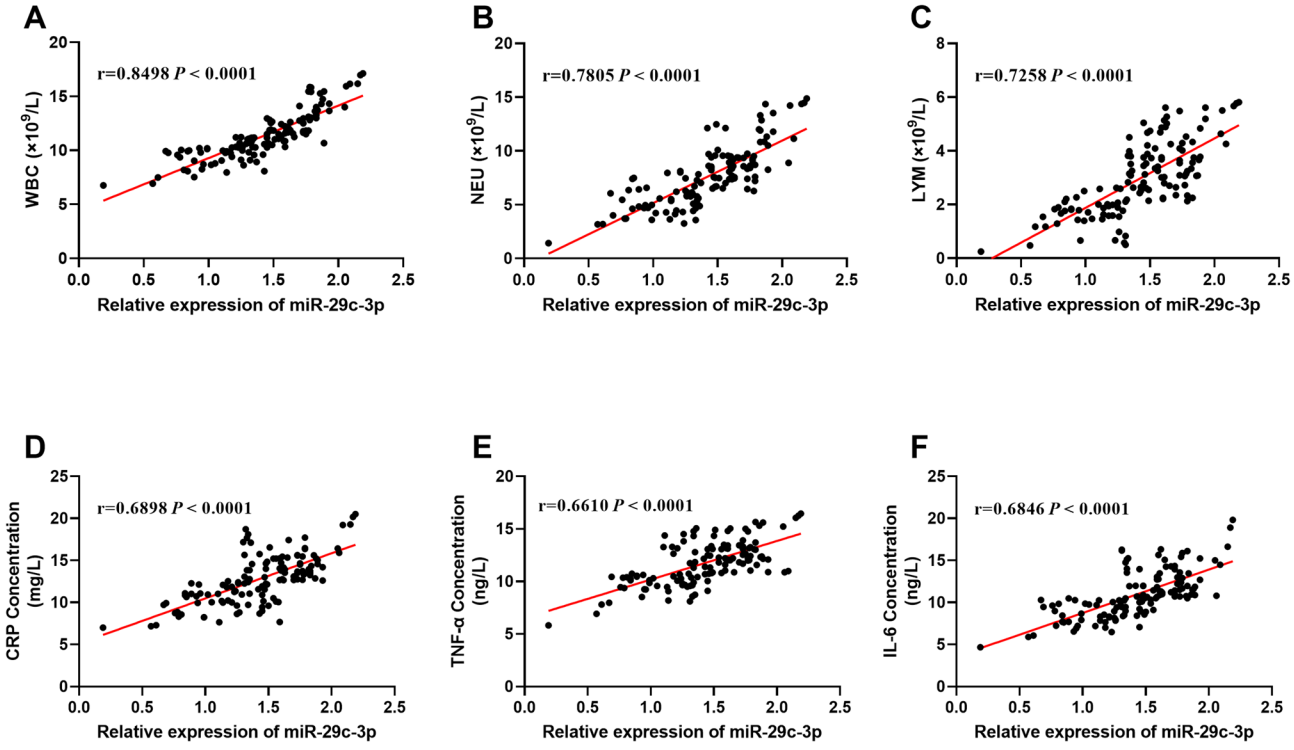

Fig. 3 Correlation between miR-29c-3p expression and inflammation and immunity. **A** The number of WBC in postoperative serum was positively correlated with the level of miR-29c-3p ($r=0.8498$, $P<0.001$); **B** The number of NEU in postoperative serum was positively correlated with miR-29c-3p level ($r=0.7805$, $P<0.001$); **C** LYM in postoperative serum was correlated adversely with miR-29c-3p level ($r=0.7258$, $P<0.001$); **D** The level of postoperative CRP was positively correlated with miR-29c-3p expression ($r=0.6898$, $P<0.001$); **E** The level of postoperative TNF-α was positively correlated with miR-29c-3p expression ($r=0.6610$, $P<0.001$); **F** The level of postoperative CRP was directly correlated with the expression of miR-29c-3p ($r=0.6846$, $P<0.001$)

Table 2 Complications occur after resection in pediatric patients with acute suppurative appendicitis

Indicators	High miR expression group ($n=71$)	Low miR expression group ($n=57$)	*P*
Incision infection	5	2	0.382
Mesenteric adhesions	4	1	0.260
Bowel obstruction	4	0	0.069
Total	13	3	0.027

peritonitis, etc [14]. Children require early surgical treatment because of their incomplete physical development and low resistance. Laparoscopy offers the advantages of minimal invasiveness and rapid recovery after surgery [15]. Laparoscopic appendectomy is another available surgical procedure. However, surgical procedures often lead to impaired immune function, rendering the body more susceptible to microbes and eliciting an inflammatory response that affects organ systems and tissue cells throughout the body, thereby increasing the likelihood of post-operative complications [16, 17].

Studies have reported the association of miRNAs with inflammatory responses and immune responses [18–20]. Certain miRNAs activated during inflammation reportedly limit excessive immune responses [21]. Síbia et al. reported that the level of inflammatory factors may influence the level of miRNA expression [22]. Similarly, Liu et al. reported that the expression of miR-223 in the gingival sulcus fluid of the periodontal group was positively correlated to TNF-α [23]. The expression levels of miR-29c-3p were significantly upregulated in patients with acute appendicitis [8]. We also found that miR-29c-3p expression was significantly increased in children with ASA. However, when the appendix was removed by laparoscopic surgery, the level of miR-29c-3p decreased significantly. This may be due to the fact that miR-29c-3p expression is relatively high at the site of the lesion and its level decreases significantly after the lesion is removed [24, 25]. After surgical removal of the appendix, the counts of leukocytes, lymphocytes and neutrophils decreased significantly, as did the levels of inflammatory factors such as CRP, TNF-α and IL-6. The associations between miR-29c-3p and different immune markers and inflammatory factors during the postoperative period were analyzed next. A significant positive correlation was noted between miR-29c-3p and all immune-related indices in the children with ASA. As the levels of immune cells, immune proteins, and inflammatory factors decreased, the expression levels of miR-29c-3p also decreased significantly.

The level of immunity usually has a significant impact on the occurrence of prognostic postoperative complications [26, 27]. Perioperative neutrophil, lymphocyte and IL-6 [28, 29] counts are important factors in the assessment of postoperative complications. The higher the inflammation-related factors, the higher the likelihood of postoperative complications in patients [30, 31]. In the present study, the high miR-29c-3p expression group also had a relatively high rate of postoperative complications. This may be due to the positive correlation between miR-29c-3p and immune-related markers. The high miR-29c-3p expression group also presented high expression levels of leukocytes, lymphocytes, CRP, etc., as well as relatively high levels of the inflammatory mediators TNF-α and IL-6, resulting in a higher complication rate compared to that noted in the low-expression group. This result also suggests that high miR-29c-3p expression could be utilized to predict poor prognosis in children with ASA.

However, this study has some limitations: first, we need to increase the sample size and obtain more homologous samples to further confirm our current findings. Second, we need more experimental models, such as in vitro cellular models, mouse models, and in vivo models, to investigate the association between miR-29c-3p and post-operative complications of ASA. The potential mechanisms involved in the regulation of ASA by miR-29c-3p can also be explored by Gene Ontology (GO) and Kyoto Encyclopedia of the Genome (KEGG) databases. Finally, the use of Pearson's correlation coefficient to analyse the correlation between various immune indicators and miR-29c-3p also has some limitations because Pearson's correlation coefficient can only capture linear relationships, and it may not accurately reflect the true correlation if the two variables have a non-linear relationship. Subsequently, we will improve the correlation analysis method. In addition, we will improve the data of CRP, TNF-α and IL-6 in the control group as well as the expression of the target genes in the excised lesion tissues in the subsequent experiments.

Conclusions

The expression of miR-29c-3p is high at the lesion site, and lesion resection leads to a decrease in the miR-29c-3p levels. In addition, miR-29c-3p is correlated positively to immune-related indicators, and elevated levels of immune-related indicators are connected to elevated miR-29c-3p levels. The association of the levels of immune-related factors with postoperative complications suggests miR-29c-3p is an important factor involved in the development of postoperative complications in children with ASA.

Abbreviations

ASA	Acute suppurative appendicitis
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
GO	Gene ontology
IL-6	Interleukin-6
KEGG	Kyoto encyclopedia of the genome
LYM	Lymphocytes
NEU	Neutrophils
qRT-PCR	Quantitative reverse transcription PCR
TNF-α	Tumor necrosis factor-α
WBC	White blood cells

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: L H, BH Y; data collection: CS D, LX Z; analysis and interpretation of results: YX H, LX Z; draft manuscript preparation: L H, BH Y. All authors reviewed the results and approved the final version of the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The Xingtai People's Hospital Ethics Committee approved the study. The trials were conducted in accordance with the tenets of the Declaration of Helsinki. The guardians of the children signed an informed consent form.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflicts of interest.

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