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Original Article

NLR and PLR can be used as diagnostic indicators of acute suppurative appendicitis in children and are related to the level of oxidative stress

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Abstract: This study aimed to investigate the diagnostic value of neutrophil to lymphocyte ratio (NLR) and platelets to lymphocyte ratio (PLR) in acute suppurative appendicitis (ASA) in children and the effect of transumbilical single-site laparoscopic appendectomy (LA) on oxidative stress. A total of 120 children with ASA in The Second People's Hospital of Liaocheng city were enrolled in the ASA group, all of whom were treated with LA. Another 60 children with non-suppurative appendicitis (NSA) who were admitted to Second People's Hospital of Liaocheng city during the same period were enrolled in the NSA group. Both NLR and PLR of the ASA group and NSA group, and superoxide dismutase (SOD) and malondialdehyde (MDA) of ASA group before and after surgery were measured. It was found that the AUC of children with ASA diagnosed by NLR combined with PLR was 0.949. NLR and PLR were positively correlated with SOD and negatively correlated with MDA. Age, operative time, perforation, NLR, PLR, SOD and MDA were independent risk factors for incision infection in ASA children. In conclusion, NLR and PLR can be used as markers of incision infection in children with AS and were correlated with oxidative stress.

Keywords: Acute suppurative appendicitis, transumbilical unilateral laparoscopic appendectomy, NLR, PLR, SOD, MDA

Introduction

Acute appendicitis (AA) is the most common cause of acute abdominal pain worldwide, with a higher risk in men than women, and an age range of 10-30 years old [1]. The histological classification of AA includes the following characteristics; simplicity, purulent, perforation and gangrene, etc., and specific diagnosis of histological classification of AA is conducive to the prediction of infectious complications [2, 3]. Acute suppurative appendicitis (ASA) is a middle-grade AA, typically characterized by acute suppurative infection, which progresses faster in children than in adults, and may trigger a generalized inflammatory state. Delayed diagnosis of ASA may lead to perforation or sepsis [4, 5]. Transumbilical single-site laparoscopic appendectomy (LA) is a surgical treatment for children with ASA, and non-surgical treatment for children with ASA shows low success rate [6, 7]. It is difficult to diagnose ASA in children, and clinical screening of imaging and biomarkers is still not ideal [8]. Therefore, exploring new diagnostic markers of ASA is of great significance for the clinical diagnosis and treatment of ASA in patients.

Currently, hematological indicators of neutrophils to lymphocytes ratio (NLR) and platelets to lymphocytes ratio (PLR) have extensive diagnostic value in human diseases. They not only serve as a prognostic indicator of solid tumors, but also help to improve the accuracy of AA diagnosis in pregnant women [9-11]. Neutrophils are the most abundant white blood cells circulating in the body, which can improve the immune defense of human cells. Congenital deficiency may lead to fatal infections [12]. Studies have revealed that ASA patients often have severe neutrophil infiltration, suggesting that neutrophils may have the potential to indicate the onset of ASA [13]. Lymphocytes are known as the immune regulators of human disease, and they participate in the regulation of human inflammation and infection [14]. As an inflammatory marker NLR is abnormally upregulated in patients with AA and has been found to play a role in distinguishing familial mediterranean fever from AA [15]. Platelets are active mediators of inflammatory responses and organizational stress after acute infection [16]. Some scholars have analyzed the diagnostic value of PLR and NLR in distinguishing the complexity and non-complexity of children with AA, and the results show that children with high level NLR and PLR are more likely to have complications, while the sensitivity and specificity of each single indicator to identify AA are not ideal [17].

Up to now, there have been few studies on the combination of NLR and PLR in the diagnosis of ASA in children and the postoperative effect on oxidative stress. Hence, we decided to carry out this study in the hope of providing clinical reference and value for the diagnosis and treatment of ASA in children.

Data and methods

General data

A total of 120 children with ASA admitted to Second People's Hospital of Liaocheng City from December 2017 to December 2018 were enrolled in the ASA group, all of who received treatment of LA. Another 60 children with NSA (acute simple appendicitis) were enrolled in the NSA group. Inclusion criteria were as follows: Patients who were histologically or pathologically confirmed with ASA or NSA [18]. Patients under the age of 14. Patients who had not taken any drugs that affect the indicators of the study in the past six months. Exclusion criteria were as follows: Patients complicated with other inflammatory or infectious diseases. Patients who took antibiotics four weeks before surgery. Patients with preoperative history of infection, and children with chronic appendicitis. The study was approved by the ethics committee of The Second People's Hospital of Liaocheng City, all the subjects and their families have been informed and signed an informed consent.

Operation methods

Children were given continuous epidural anesthesia. The observation hole was placed at the position of about 2 o'clock in the umbilical ring, which was relative to the mcburney point. The operation holes were placed at the positions of about 11 o'clock and 5 o'clock on both sides of the umbilical ring. Pneumoperitoneum was established based on CO_2, maintaining the pressure at about 11 mmHG. The children were put into the Trendelenburg position and tilted 20-30°C to the left. The mesoappendix was cut off by electrocoagulation to the root of appendix, and then it was ligated at 0.3 cm and 1.0 cm away from the appendix root. The appendix between the two sets of ligatures was cut. The electrocoagulation hook was used to burn the mucous membrane of the appendiceal stump, and the pus was absorbed. Then the abdomen and pelvic cavity were cleaned, and the specimen was taken out for incision and suture. The surgeries in this study were performed by one attending physician.

Detection methods

Routine blood analyzer (Wuhan Shengshida Medical Equipment Co., Ltd., China, 2600) was used to determine the number of neutrophils, lymphocytes and platelets in children with ASA and NSA, and calculate NLR and PLR. Three mL of venous blood from the elbow was taken from the patient before and 24 h after surgery, and then placed in blood vessel collection without anticoagulants in a EDTA-K2 blood collection tube. Venous blood collected without anticoagulants was centrifuged at 4°C 1500 g for 10 min in a centrifuge, and the upper serum was separated and stored in a freezer at -20°C for later use. Concentration of serum superoxide dismutase (SOD) and malondialdehyde (MDA) were detected by enzyme linked immunosorbent assay (ELISA) [19], with reference to the instructions of the SOD and MDA detection kit (Shanghai Qiaoyu Biotechnology Co., Ltd., China, QN-PS0387, QN-PS0433).

Outcome measures

The postoperative incision infection was observed in both groups. Incision infection diagnostic criteria [20]: Purulent drainage in deep incision. Wound dehiscence in incision. Pain or tenderness at the incision. Appearance of local swelling, heat and other phenomena. Other infection symptoms.

Statistical analysis

SPSS 20.0 (IBM Corp, Armonk, NY, USA) statistical Software was used for statistical analysis,

Table 1. Baseline data of the two groups [n (%)]/(mean ± SD)

Class	NSA group (n=60)	ASA group (n=120)	χ^2/t	P
Gender			1.646	0.200
Male	31 (51.67)	74 (61.67)		
Female	29 (48.33)	46 (38.33)		
Age (years old)			3.318	0.069
≤6	24 (40.00)	32 (26.67)		
>6	36 (60.00)	88 (73.33)		
BMI (kg/m^2)	15.57 (kg/m)	15.48 (kg/m)	0.251	0.803
Place of residence			0.102	0.750
Countryside	27 (45.00)	51 (42.50)		
Cities	33 (55.00)	69 (57.50)		
Mean course of disease (h)	4.78 cour	5.56 cour	3.445	<0.001
SBP (mmHg)	110.22 (mmHg)	109.54 (mmHg)	0.864	0.389
DBP (mmHg)	75.00 (mmHg)	74.83 (mmHg)	0.219	0.827

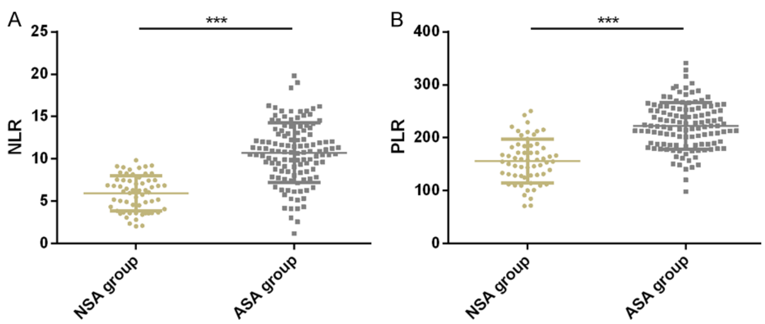

Figure 1. NLR and PLR levels of ASA patients. A. NLR of ASA patients was significantly higher than that of the NSA group. B. The PLR of ASA patients was significantly higher than that of the NSA group. Note: ***P<0.001.

and GraphPad Prism 6 (GraphPad Software, San Diego, USA) was used to illustrate the data. Measurement data in line with normal distribution were expressed as mean ± standard deviation (mean ± SD). Intergroup measurement data were compared using independent sample t-test, multi-group measurement data were compared using one-way ANOVA, F-test, and paired t-test were used before and after treatment. Enumeration data was expressed by the number of cases/percentage [n (%)], and chi-square test was used for comparison of enumeration data between groups. The diagnostic value of serum NLR and PLR in ASA was evaluated by receiver operating characteristic curve (ROC). Pearson correlation coefficient was used to analyze the correlation of NLR and PLR with SOD and MDA. Multivariate Logistic regression analysis was used to analyze the risk factors affecting incision infection in children with ASA. P<0.05 was considered statistically significant.

Results

Baseline data

There were no significant differences in gender, age, body mass index (BMI), place of residence, mean course of disease, systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the NSA group and ASA group (P>0.05). More details were shown in **Table 1**.

NLR and PLR levels in patients with ASA

The NLR and PLR levels in the ASA group were significantly higher than those of the NSA group (P<0.001). As shown in **Figure 1**.

The diagnostic value of NLR and PLR in children with ASA

The ROC curve of children with ASA diagnosed by NLR and PLR was drawn. The AUC of children with ASA diagnosed by NLR was 0.880 (95% CI: 0.832-0.928), and the optimal cut-off value was 9.30. The sensitivity and specificity were 70.83% and 98.33%, respectively. The AUC of children with ASA diagnosed by PLR was 0.866 (95% CI: 0.812-0.921), the optimal cut-off value was 173.40, and the sensitivity and specificity were 90.00% and 71.67%, respectively. The AUC of children with ASA diagnosed by NLR combined with PLR was 0.949 (95% CI: 0.920-0.977), the optimal cut-off value was 0.74, and

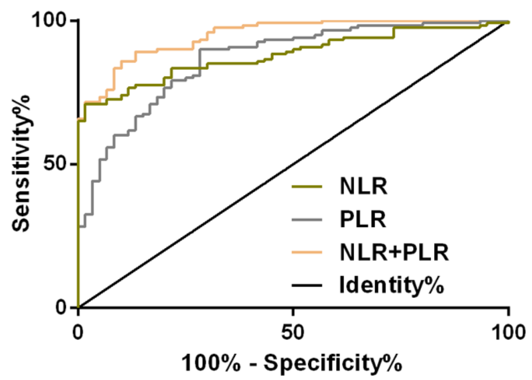

Figure 2. ROC curve of children with ASA diagnosed by NLR and PLR.

the sensitivity and specificity were 85.83% and 90.00%, respectively. Data shown in **Figure 2**; **Table 2**.

The levels of SOD and MDA in children with ASA

The levels of SOD and MDA in children with ASA were not significantly different before treatment (P>0.05). After surgery, SOD in children was significantly decreased, while MDA in children was significantly increased, with statistically significant differences (P<0.05). As shown in **Figure 3**.

The correlation of NLR and PLR with oxidative stress

The correlation of NLR and PLR with oxidative stress indicators was analyzed by Pearson correlation coefficient, and it was found that NLR of children with ASA was significantly positively correlated with SOD level before treatment and significantly negatively correlated with MDA level before treatment (r=0.637, P<0.001; r=-0.601, P<0.001). There was a significant positive correlation between PLR and SOD level before treatment and a significant negative correlation between PLR and MDA level before treatment (r=0.611, P<0.001; r=-0.606, P<0.001). As shown in **Figure 4**.

Multivariate Logistic regression analysis of factors affecting postoperative incision infections in children with ASA

There were 15 cases of children with postoperative incision infections and 105 cases of children without infection. The differences in clinical parameters and related indicators of postoperative incision infection and non-infection were compared. There was no significant difference in gender, BMI and length of incision between children with infection and non-infection (P>0.05), while there were statistical differences in age, operative time, perforation, NLR, PLR, SOD, and MDA (P<0.05). Multivariate Logistic regression analysis showed that age (P=0.001), operative time (P=0.005), perforation (P=0.020), NLR (P=0.003), PLR (P=0.004), SOD (P=0.006) and MDA (P=0.001) were all independent risk factors affecting postoperative incision infection in children with ASA. Children with ASA who were older than 6 years old, with surgery lasting more than one hour, along with perforation, high NLR, high PLR, high SOD and low MDA were at increased risk of incision infection. More details were shown in **Tables 3-5**.

Discussion

ASA is one of the most common causes of surgery in children, with a lifetime risk of 7.7% [21]. Suppurative infection of ASA can be caused by pathogens such as staphylococcus, streptococcus and escherichia coli. The impact of acute abdominal pain caused by the disease on children is self-evident, which can seriously affect children's health, learning and communication, etc. Therefore, early intervention for children with ASA is particularly important [22, 23].

In addition to acute abdominal pain and other clinical symptoms, the imbalance between inflammatory response and oxidative stress can occur in ASA [24]. NLR and PLR are biomarkers of systemic inflammatory responses and are relatively sensitive to the inflammatory response produced by the body [25]. In the study of Yazar et al. [26], perforated AA patients had higher levels of NLR and PLR, and NLR could be used as an auxiliary diagnostic tool to help surgeons avoid unnecessary appendectomy, so that patients could avoid the risk of surgical complications. In the study of Acar et al. [27] on the diagnostic value of NLR and PLR, the AUC of NLR and PLR in distinguishing renal colic from AA was up to 0.888 and 0.725, indicating that NLR and PLR might be helpful for doctors to assess the cause of the two types of abdominal pain. In this study, it was found that the NLR and PLR levels of children with ASA were significantly higher than those children with NSA, suggesting that NLR and PLR might indicate the severity of appendicitis. We further analyzed the diagnostic value

Table 2. ROC parameters of children with ASA diagnosed by NLR and PLR

Indicators	AUC	95% CI	S.E	Cut-offZ	Sensitivity (%)	Specificity (%)
NLR	0.880	0.832-0.928	0.025	9.30	70.83	98.33
PLR	0.866	0.812-0.921	0.028	173.40	90.00	71.67
NLR+PLR	0.949	0.920-0.977	0.015	0.74	85.83	90.00

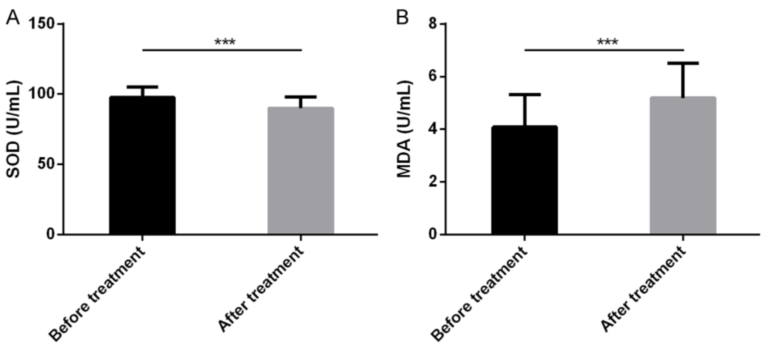

Figure 3. Levels of SOD and MDA of children in group A and B before and after treatment. A. SOD level in children with ASA decreased significantly after treatment. B. MDA level in children with ASA increased significantly after treatment. Note: ***P<0.001.

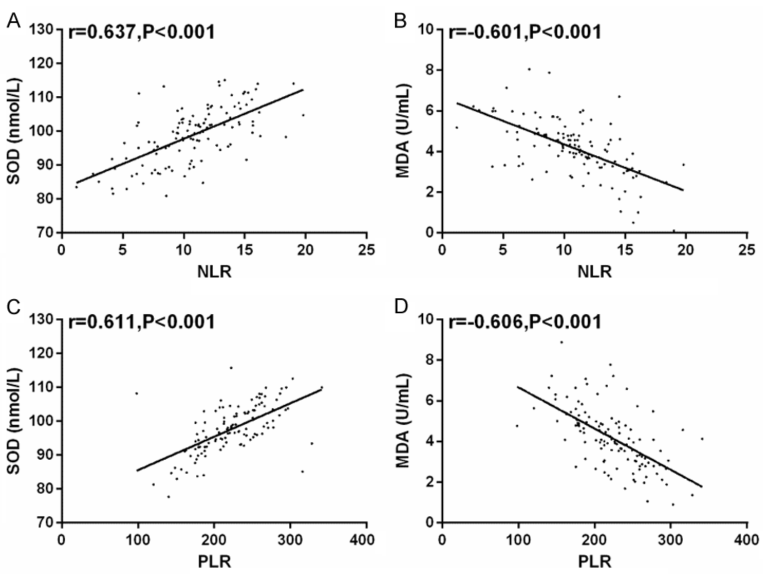

Figure 4. Correlation of NLR and PLR and oxidative stress indicators (SOD, MDA). A, B. NLR was positively correlated with SOD and negatively correlated with MDA (r=0.637, P<0.001; r=-0.601, P<0.001). C, D. PLR was positively correlated with SOD and negatively correlated with MDA (r=0.611, P<0.001; r=-0.606, P<0.001).

of NLR and PLR for children with ASA, and the results showed that the AUC of NLR combined with PLR for children with ASA was up to 0.949, indicating that NLR combined with PLR had satisfactory diagnostic value for children with ASA, and could be an effective diagnostic marker. SOD is an endogenous cellular defense system, and its function of degrading peroxides and inducing neutrophil apoptosis might be used to treat inflammatory diseases [28]. High levels of MDA are often associated with the increase of free radicals and are often used as a marker of oxidative stress and antioxidant status in patients with disease [29]. Koltuksuz et al. [30] revealed in their study that plasma oxidative stress indicators SOD and MDA in ASA patients showed abnormal levels. In our study, SOD and MDA were significantly decreased after surgery, while MDA was significantly increased after surgery, suggesting that SOD and MDA might be involved in the pathological process of children with ASA. In order to understand whether NLR and PLR were correlated with oxidative stress, we also conducted correlation analysis, and the results showed that NLR and PLR were negatively correlated with SOD and positively correlated with MDA, indicating that NLR and PLR might reflect the oxidative stress of children.

Since its appearance, LA has been widely applied due to its advantages of a small incision, visualization and rapid postoperative recovery. Patients treated with LA not only have less pain and shorter hospital stay, but also have a significantly lower incidence of surgical incision infections [31]. Our results showed that the incidence of incision infection in children treated with LA was only 12.50%. In the study of Buicko et al. [32] on infection in

Table 3. Relationship between clinical parameters and indicators of ASA and incision infection in children [n (%)]/(mean ± SD)

Class	n	Infection (n=15)	Non-infection (n=105)	χ^2/t	P
Gender				0.987	0.321
Male	74	11 (73.33)	63 (60.00)		
Female	46	4 (26.67)	42 (40.00)		
Age (years old)				6.234	0.013
≤6	32	8 (53.33)	24 (22.86)		
>6	88	7 (46.67)	81 (77.14)		
BMI (kg/m^2)	120	16.10±2.13	15.23±1.98	1.577	0.117
Length of incision				1.558	0.212
≤3	88	6 (40.00)	82 (78.10)		
>3	32	9 (60.00)	23 (21.90)		
Perforation				7.619	0.006
No	96	8 (53.33)	88 (83.81)		
Yes	24	7 (46.67)	17 (16.19)		
Operative time (h)				4.736	0.030
≤1	91	8 (53.33)	83 (79.05)		
>1	29	7 (46.67)	22 (20.95)		
NLR	120	10.840.95)	6.3840.95	4.881	<0.001
PLR	120	225.46.95)	176.82.95)	4.316	<0.001
SOD (nmol/L)	120	92.53 (nmol/L)	84.27 (nmol/L)	4.145	<0.001
MDA (U/mL)	120	4.85 (U/mL)	6.41 (U/mL)	4.150	<0.001

Table 4. Assignment of Logistic multivariate regression analysis

Factors	Variables	Assignment
Age	X1	≤1 eignmenold =0, >6 years old =1
Operative time	X2	≤2 era, >1 h =1
Perforation	X3	No =0, yes =1
NLR	X4	Continuous variable
PLR	X5	Continuous variable
SOD	X6	Continuous variable
MDA	X7	Continuous variable

Table 5. Multivariate Logistic regression analysis of postoperative incision infection in children with ASA

Variables	B	S.E	Wals	P	OR	95% CI
Age	0.394	0.196	10.674	0.001	1.486	1.170-1.892
Operative time	1.124	0.025	9.062	0.005	1.389	1.122-1.749
Perforation	1.022	0.452	5.113	0.020	2.676	1.141-6.738
NLR	1.898	0.573	9.836	0.003	6.701	2.113-13.814
PLR	1.354	0.473	8.617	0.004	4.029	1.608-10.248
SOD	0.501	0.182	7.698	0.006	1.640	1.155-2.336
MDA	-0.198	0.061	11.295	0.001	1.224	1.087-1.367

children with AA, the main reason for readmission after LA treatment was postoperative infection, followed by abdominal abscess. Although LA is the standard strategy for the treatment of children with ASA, postoperative complications such as incision infection, abdominal infection and intestinal obstruction are still difficult to avoid [33]. We thereby made multivariate Logistic regression analysis on the factors influencing the ASA incision infection in children with ASA, and the study showed that age, operative time, perforation, NLR, PLR, SOD, MDA are independent risk factors for incision infection in children with ASA. This suggested that children who were less than 6 years old, with operative times of less than one hour, without perforation, along with low levels of NLR, PLR and SOD, and high level of MDA are at reduced risk of ASA incision infection, and NLR, PLR were incision infection markers after LA. We further explored the potential causes of incision infection caused by these risk factors. For example, according to the report of Mallick et al. [34], pre-school children under the age of six are at a high risk for ASA. At this time, children are in the growth and development stage, and their immune function is not perfect. It is easy to cause diseases such as ASA due to dietary problems. ASA accompanied by perforation belongs to complex ASA, which presents atypical symptoms, requiring longer recognition period, which increases the risk of postoperative complications. Another study by Gomila et al. [35] pointed out that longer surgery time may cause patients to bleed more, along with the misuse of antibiotics. Studies have shown that SOD and MDA are involved in the process of tissue damage repair after infection. When the body shows symptoms of infection, it will cause an increase in reactive oxygen metabolites. The consumption of SOD can neutralize this product, and MDA mediated lipid peroxidation can play a key role in the process of tissue damage [36]. The protagonists NLR and PLR which are helpful for the early prediction of postoperative infection have been reported in this study to have higher levels in patients infected after cesarean section, and are related to the operation time, the use of hemostatic agents and the control of skin closure technology [37].

The diagnostic value of NLR and PLR in children with ASA, as well as the effect of LA on oxidative stress in children with ASA were confirmed in this study. However, there is still room for improvement in the study. First, the recurrence rate of children with ASA can be increased. Second, the specific infection type and regulation mechanism of ASA can be supplemented. Furthermore, we can also expand the sample range, studying the diagnostic value of NLR and PLR in complex AA and non-complex AA. All of these improvements need to be further supplemented in future research.

In conclusion, serum NLR and PLR may be effective diagnostic markers for children with ASA and incisions infection markers after treatment of LA, and may also reflect the state of oxidative stress in children.

Disclosure of conflict of interest

None.

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