Neutrophil/lymphocyte ratio in the diagnosis of childhood appendicitis

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Total leukocyte count (TLC) and neutrophil count are not reliable parameters in the diagnosis of appendicitis in children, necessitating a search for more sensitive criteria. This study's goal was to investigate the diagnostic value of neutrophil/lymphocyte (N/L) ratio in childhood appendicitis.

The patients admitted for acute abdominal symptoms were reviewed retrospectively. Data collected included initial preoperative TLC, together with neutrophil and lymphocyte values. N/L ratio was calculated by dividing the values obtained.

One hundred eighty-three of 240 patients were treated operatively and were proven as appendicitis histopathologically. The other observed 57 cases were accepted as non-specific abdominal pain (NAP). 90.2% of the appendicitis group and 12.3% of the NAP group had N/L ratio higher than 3.5. The results indicate that N/L ratio seems to be a more sensitive parameter than TLC when evaluated retrospectively. N/L ratio of 3.5 can be used in the prediction of appendicitis in children.

Key words: appendicitis, acute abdomen, diagnosis, neutrophil/lymphocyte (N/L) ratio.

Appendicitis is the most common and misdiagnosed surgical cause of acute abdomen in childhood[1]. From the beginning of abdominal complaints to admission to the hospital, delays of a few hours to a few days may occur. Furthermore, in infants with an atypical clinical progression, establishing a diagnosis is much more difficult, leading to perforation and unnecessarily high negative appendectomy rates[2].

Accurate and prompt diagnosis reduces the risk of perforation and negative appendectomy rate. In general, total leukocyte count (TLC) and neutrophil count are used as diagnostic tools in appendicitis. Recently Goodman et al.[3] advocated the use of neutrophil/lymphocyte (N/L) ratio as a diagnostic tool in adults, and a ratio above 3.5 was stated as optimally diagnostic for appendicitis. However, immunological mechanisms and anatomical characteristics are quite different in children compared to adults, leaving unanswered the question of how the rise in N/L ratio correlates with the probability of appendicitis. We aimed to investigate whether the N/L ratio might provide a more sensitive parameter in children and to find the optimal N/L ratio for the diagnosis of appendicitis in this age group.

Material and Methods

Two hundred forty patients (240) with acute abdominal pain admitted to our clinic between 1994 and 2007 were included in the retrospective chart review. The age range for selection of patients was 3 to 16 years. The patients were divided into two groups as the acute appendicitis group and non-specific abdominal pain (NAP) group. The patients with NAP were observed 24-48 hours and discharged. Patients with pathological conditions established such as urinary tract infection, Henoch-Schönlein purpura and gastroenteritis, which cause symptoms similar to appendicitis, were excluded from the study.

Total leukocyte count (TLC), the number of neutrophils and lymphocytes as well as the percentages of neutrophils and lymphocytes in peripheral blood samples at the time of the first evaluation were recorded in the chart review. The peripheral blood samples were analyzed for differential white blood cell counts by automated cell counters (Coulter STKS^{R}). N/L ratio was calculated by dividing the percentage values of neutrophils and lymphocytes obtained. Leukocytosis was accepted for TLC levels higher than 10,000 per cubic millimeter, and 3.5 was accepted as the cut-off value. Specificity, sensitivity, positive predictive value of N/L ratio, and negative operative risk were calculated. The patients who were in the appendicitis group were operated after correction of their fluid and electrolyte imbalance.

Data are expressed as mean ± 1 SD. Student's t-test, chi-square test and likelihood ratios were used in the statistical analysis. Significance level was set at 0.05.

Results

Of the 240 patients, a total of 183 were treated operatively. All of the patients treated operatively had histopathologically proven appendicitis. Fifty-seven cases were accepted as having NAP.

The TLCs of the groups are summarized in Table I. The average TLC of the appendicitis group was 16.198±5.3/mm^3 and 162 of them had higher than normal TLC (88.5%). The average TLC of the NAP group was 12.401±4.1/mm^3, and 39 of them had higher than normal TLC (68.8%). The difference in average TLC was statistically significant between groups ($t=4.90$, $p<0.001$).

The N/L ratios of the groups are summarized in Table I. The appendicitis group had an average N/L ratio of 9.335±6.6 and the NAP group had an average N/L ratio of 2.2943±2.7. The difference between average N/L ratios in the two groups was statistically significant ($t=7.04$, $p<0.001$). Of 183 patients, 90 (49.2%) were perforated. The patients with perforation were admitted late. Perforation was not observed in our primarily followed patients. The perforated and non-perforated groups had similar average N/L ratios, with no statistically significant difference between them ($p>0.05$).

The sensitivity, specificity, positive predictive value, negative operation risk, and likelihood ratios depicted by TLC and several N/L ratios are shown in Table II.

Discussion

Diagnosis of appendicitis, especially in children, is difficult. Several diagnostic methods are used for appendicitis. Serious morbidity and even death may occur when the diagnosis is late. Thus, the first aim of surgeons must be true and earlier diagnosis. Unfortunately, there is no laboratory value for true and certain diagnosis of appendicitis. In medical practice, leukocyte and neutrophil count are the most widely used laboratory parameters in the diagnosis of appendicitis, but their specificity and sensitivity values are low. Thus, a stronger parameter of confidence in doubtful cases is needed.

The pathophysiology of acute appendicitis is mainly an inflammation. Inflammation is the response of living tissue to damage. The inflammatory response consists of changes in blood flow, increase in permeability of blood vessels and migration of cells from the blood stream into the tissue. In this inflammatory response, neutrophils first accumulate in the blood stream via marginal pool, then from the bone marrow according to the amount of inflammation. This early response increases neutrophil count in the blood stream[4-6].

Table I. Total Leukocyte Counts and Neutrophil/Lymphocyte Ratios of the Groups*

Total Leukocyte Count	Appendicitis group (%)	Non-specific abdominal pain group (%)	Total
> 10000 / mm^3	162	39	201
< 10000 / mm^3	21	18	39
N/L ratio			
>3.5	165 (90.2)	7 (12.3)	172
<3.5	18 (9.9)	50 (87.7)	68
Total	183	57	240

* $p>0.05$ Pearson's chi-square test

Table II. The Sensitivity, Specificity, Positive Predictive Value, Risks of Negative Operation and Likelihood Ratios Depicted by TLC and Several N/L Ratios

	Sensitivity %	Specificity %	Positive predictive value %	Negative operation risk %	Likelihood ratios for a positive test	Likelihood ratios for a negative test
TLC	89	32	81	19	1.3	0.34
N/L > 3.0	91	72	91	9	3.2	0.12
N/L > 3.5	90	88	96	4	7.5	0.11
N/L > 4.0	87	91	97	3	9.7	0.14
N/L > 4.5	84	91	97	3	9.3	0.17
N/L > 5.0	81	95	97	3	16.2	0.20

TLC: Total leukocyte count. **N/L:** Neutrophil/Lymphocyte.

Although in recent years progress in diagnostic techniques has resulted in a decrease in the number of perforations and negative appendectomies, it is still inevitable to face difficulty in the diagnosis of atypical cases[1]. The challenge is whether to observe or to operate in children with atypical signs.

Other than radiological diagnostic techniques, two hematological variables are used on a widespread basis in the differential diagnosis of abdominal pain in children: the TLC and neutrophil count[7-12]. Both of these variables are mainly affected by inflammation; non-specific increases in TLC and neutrophils are observed in appendicitis. The tests are easy and quick to perform but they do not reveal significant results regarding the existence and severity of appendicitis[13].

Our study revealed similar results for TLC in both groups; it did not seem to be a reliable indicator for the diagnosis of appendicitis. Although its sensitivity was above 80%, its positive predictive value was only 81%, meaning that 19% of patients would have been needlessly operated, and 11% would have been left undiagnosed and at risk of perforation.

Since TLC and neutrophil count do not seem reliable for diagnosis, a search for other diagnostic parameters is necessary. It is well known that the concentration of several of the leukocyte types may change at the same time and in the same or in opposite directions[14]. For this reason and because it is now evident that each cell system has its own unique functions and control mechanisms, it is best to determine the absolute blood concentration of each cell type. Such information can provide significant clues to alert the physician.

Goodman et al.[3] have searched for a diagnostic criterion using the N/L ratio; they compared the relationship of neutrophil and lymphocyte counts and stated that a N/L ratio higher than 3.5 was a sensitive indicator for the diagnosis of appendicitis in adults. They also suggested that marked lymphopenia may be the other major factor changing this ratio in the existence of gangrenous appendicitis, which was reported in another study[9]. The pathophysiological mechanism of lymphopenia was not known completely, but the direct effect of toxins or glucocorticoids, cytokines and other mediators or sequestration in inflammatory phlegmon were suggested as the reasons. Zahorec[15] suggested the use of the N/L ratio as a rapid and simple parameter for systemic inflammation and stress in critically ill patients, when he observed a correlation between the severity of their clinical course and the grade of neutrophilia and lymphopenia in his preliminary study.

In our study, we found that acceptance of higher ratios of N/L resulted in decreased negative operation risk but increased risk of being undiagnosed and of perforation. Considered together with the likelihood ratios for positive and negative tests as seen in Table II, the N/L ratio of 3.5 seems to be the most useful cut-off value in the diagnosis of appendicitis in children.

Significant rise in N/L ratio over 3 in cases with appendicitis may be explained by neutrophilia together with lymphopenia in cases with gangrenous type appendicitis[9]. The significant increase in the N/L ratio in cases without gangrenous pathology may also have a valid pathophysiological explanation. In the beginning of the acute phase of inflammation,

when lymphocyte count is normal, the increase in the number of neutrophils may elevate the N/L ratio. Even in cases with both neutrophilia and lymphocytosis, the N/L ratio may still be elevated since neutrophilia is noticeably more marked in the beginning of inflammation.

In conclusion, the N/L ratio seems to be a more sensitive parameter than TLC. We suggest that a N/L ratio of 3.5 may be considered as a diagnostic cut-off value in children with appendicitis and that negative operations for suspected appendicitis in children can be effectively reduced; we thus recommend the N/L ratio as a useful diagnostic test for appendicitis in children.

We believe that the N/L ratio will be helpful as a diagnostic parameter for childhood appendicitis, which is difficult to diagnose. Since the high ratio of perforation (49%) among our patients revealed that referral to our clinic is delayed, another diagnostic parameter that is very easily applied anywhere and at anytime is needed. We suggest that the N/L ratio may serve well in this regard.

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