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Ultrasound for Appendicitis: Performance and Integration with Clinical and Laboratory Parameters

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Objective: We aimed to assess the relationship between white blood cell count, pediatric appendicitis score and the measurement of the outer diameter of the appendix. **Methods:** The study was performed on 480 children admitted for suspected acute appendicitis and underwent an appendectomy at the National Center for Maternal and Child Health, Ulaanbaatar, Mongolia, between May 2019 and December 2019. Clinical diagnosis was performed using the pediatric appendicitis score based on the pre-operative blood test results, including white blood cell count, neutrophil count, lymphocytes count, and neutrophil-lymphocyte ratio. The diameter of the appendix was determined by ultrasound. **Results:** 516 pediatric patients (≤ 18 years old) were suspected of having acute appendicitis and subsequently underwent surgery. The pediatric appendicitis score and neutrophil-lymphocyte ratio were moderately correlated (r = 0.494), but the neutrophil-lymphocyte ratio and outer diameter of the appendix were poorly correlated (r = 0.169). In patients with an appendix outer diameter of ≤ 6 mm, 44% were inflamed, and 56% were not. **Conclusions:** Ultrasonic measurement of the outer diameter of the appendix had a 79.8% accuracy. This diagnostic accuracy can be enhanced with the combined usage of the pediatric appendicitis score and the neutrophil-lymphocyte ratio.

Keywords: Appendicitis, Neutrophil, Lymphocytes, Pediatrics, Ultrasound

Introduction

Acute appendicitis is the common cause of surgery for acute abdominal pain in children. The diagnosis of acute appendicitis in pediatric patients remains a challenge internationally. This disease is most common among patients between the age of 10 and 19 years old [1]. The primary curative treatment is the surgical removal of the appendix. Antibiotics can be used to treat uncomplicated cases [2-4]. The surgical removal of a healthy appendix occurs in 15% of male patients and 26% of female patients with suspected appendicitis [5]. The most common symptoms of appendicitis are pain in the right lower quadrant, nausea, vomiting and anorexia. In pediatric patients, about 30% of cases have an abnormal presentation [1, 6].

A possible postoperative complication is the formation of adhesions at the surgery site, which may lead to bowel obstruction and lead to a second operation [7]. Delaying the treatment not only increases the risks of complications but can also lead to death. Therefore, accurate diagnosis is essential to reduce the risk of unnecessary surgeries and perforation [8]. In recent years, there has been a significant increase in the use of imaging techniques in the diagnosis of acute appendicitis.

Studies have shown that CT scans have a sensitivity and specificity of up to 95% in diagnosing appendicitis [9, 10]. However, CT scans carry the risk of exposing children to notable dose radiation early in life [11, 12]. Several parameters have been used to diagnose appendicitis. The increase in the outer diameter of the appendix is important in the diagnosis of appendicitis [13]. Research continues to confirm the effectiveness of blood cell tests to detect appendicitis. Numerous studies have highlighted the importance of the white blood cell count, neutrophil to lymphocytes ratio (NLR), neutrophil cells, lymphocytes, C-reactive protein, mean platelet volume and platelet count [14-17]. Yazici et al. investigated NLR in childhood appendicitis of 240 patients with appendicitis. Their study indicated that NLR seems to be a more sensitive parameter, found in 90.2% of the appendicitis group and 12.3% of the non-specific abdominal pain group having NLR higher than 3.5 [17]. In the research by Virmani et al. the laboratory markers from 185 patients who underwent appendectomy due to the simple acute appendicitis showed that NLR > 4.8, total lymphocyte count > 13,500 cells/mm 3, percentage of lymphocytes < 14.8% and percentage of neutrophils > 75% were associated with complicated appendicitis. The highest sensitivity and specificity among these findings were found with the percentage of lymphocytes [18]. Moreover, Kim et al. demonstrated an appendix diameter of > 8 mm or periappendiceal fat inflammation strongly correlated with true appendicitis. At the same time, the absence of appendiceal wall thickening or mesenteric lymphadenopathy was associated with an absence of appendicitis [19]. According to Daldal et al. there was a significant correlation between appendix diameter and WBC, lymphocyte, neutrophil, NLR. The sensitivity of the NLR (cutoff = 2.6057) in the diagnosis of appendicitis was 86.1% [19]. The pediatric appendicitis score (PAS) is also a widely used tool to diagnose acute appendicitis. It is scored based on symptoms, signs, exam and lab findings characteristic of pediatric appendicitis [20].

As noted above, accurate diagnosis of acute appendicitis in children preoperatively can be challenging. Moreover, laboratory markers mentioned are significantly different in patients with an appendix diameter of > 6 mm. Some studies showed that the percentage of neutrophils is a better indicator of the type of appendicitis, while other studies placed greater value on NLR in diagnosing childhood appendicitis. Differing from the above studies that primarily focus on the relations between NLR and PAS, we utilized the relationship between NLR and the outer diameter of the appendix measured ultrasonically to better understand the PAS and these tests' diagnostic value in childhood appendicitis.

Materials and Methods

Subjects

Our study includes 480 pediatric patients who underwent surgery for suspected acute appendicitis at the General Surgery Department of the National Center for Maternal and Child Health hospital between May 2019 and December 2019.

Inclusion criteria

Patients were included if they were less than < 18 years of age**,** underwent appendectomy, had the necessary lab results and US, and they and their families agreed and provided signed informed consent.

Exclusion criteria

Patients with incomplete medical records, who did not undergo US imaging, did not present signs of appendicitis upon US evaluation, had incomplete blood tests, had a history of mental illness or chronic disease or previously underwent abdominal surgery were excluded from this study.

Clinical assessment

The clinical diagnosis was made using the PAS based on the symptoms, exam, and pre-operative blood test results, including white blood cell count, neutrophil count, lymphocytes count, and neutrophil-lymphocytes ratio (NLR). The width of the appendix was determined by ultrasound (US). A postoperative histological evaluation of the appendix divided the participants into two groups based on the presence or absence of inflammation: those with a positive diagnosis (appendicitis) and those with a

negative diagnosis (non-appendicitis).

Statistical analysis

Descriptive statistics, including frequency, percentages, mean and standard deviation (SD), were calculated to evaluate data characteristics. For categorical variables, the chi-square test, and for continuous variables between groups, un-paired t-test was conducted to determine statistical significant differences. The (ROC receiver operating characteristic) curve analysis calculated the cut-off point and diagnostic accuracy of each parameter. For categorical variables, the chi-square test was used. The statistical significance was set at $p < 0.05$. All the statistical analysis were conducted using SPSS (Version 20.0 SPSS Inc.,Chicago, IL, USA).

Ethical statement

The study was approved by the Research Ethics Committee of Mongolian National University of Medical Sciences on June 12, 2019 (No. 2019/3-07).

Results

A total of 516 children (≤ 18 years old) underwent surgical removal of the appendix based on the clinical diagnosis of acute appendicitis. Thirty-six children were excluded from this study as they didn't meet the selection criteria. Thus, the results were calculated from 480 children, 269 (56%) male and 211 (44%) female. The male-to-female ratio was 1.3:1. The mean age was 10.57 ± 3.53 years. The comparison of pathological confirmation of appendicitis between those whose appendix had an outside diameter of ≤ 6 mm and those whose appendix was > 6 mm are presented in Table 1.

The white blood cell count, neutrophil count and PAS were significantly different in cases with an outer appendix diameter > 6 mm (Table 2, 3). The PAS and NLR were moderately correlated (r = 0.494), as were the PAS and outer diameter of the appendix (r = 0.437). But there was a minimal correlation between the NLR and the outer diameter of the appendix (r = 0.169). Among patients with an outer appendix diameter > 6 mm, 94.6% were inflammatory (positive diagnosis), and 5.4% had no inflammation present (negative diagnosis).

In cases with an outer appendix diameter ≤ 6 mm, 44% were inflamed, and 56% were not. The diagnostic potential of each parameter and the area under the ROC are presented in Tables 4.

Table 1. Comparison of the pathology results and outer diameter of the appendix measured using ultrasound. The pathology was considered positive for appendicitis if inflammation was present on the histological sections and negative if inflammation was absent.

	Histological results			
Diameter (mm)	**Positive (n=361)**	**Negative (n=109)**	**Total (n=470)**	**p-value**
	N (%)	N (%)	N (%)	
≤ 6	81 (22.4)	103 (84.5)	184 (37.8)	0.001
> 6	280 (77.6)	16 (15.5)	296 (62.2)	

Table 2. Laboratory parameters and Pediatric Appendicitis Score in children stratified by the outer diameter of their appendix.

	Pathological diagnoses					
	Diameter of the appendix ≤ 6 mm			Diameter of the appendix > 6 mm		
Variables	**Inflammation (n = 81)**	**No inflammation (n = 103)**	**p-value**	**Inflammation (n = 280)**	**No inflammation (n = 16)**	**p-value**
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
WBC	14.5 ± 6.1	11.2 ± 4.9	0.001	16.1 ± 5.9	10 ± 3.9	0.001
NC	10.4 ± 5.7	7.9 ± 4.6	0.002	12.6 ± 6.2	6.6 ± 2.6	0.001
NLR	6.8 ± 4.7	5.1 ± 6.5	0.062	8.0 ± 6.1	5.08 ± 2.9	0.052
PAS	6.5 ± 1.2	4.2 ± 1.8	0.001	7.1 ± 1.34	4.3 ± 1.45	0.001

WBC = White Blood Cell; NC = Neutrophil Count; NLR = Neutrophil to Lymphocyte Ratio; PAS = Pediatric Appendicitis Score

Table 3. Area under the ROC curve for laboratory parameters and Pediatric Appendicitis Score used to detect pediatric appendicitis.

Variable	AUC	SE	95% CI
WBC	0.614	0.030	0.55-0.67
NC	0.716	0.026	0.67-0.77
NLR	0.934	0.013	0.91-0.96
PAS	0.889	0.017	0.85-0.93

WBC = White Blood Cell; NC = Neutrophil Count; NLR = Neutrophil to Lymphocyte Ratio; PAS = Pediatric Appendicitis Score; AUC = Area of Under Curve; SE = Standard Error; CI = Confidence Interval

Table 4. Diagnostic accuracy of laboratory parameters and Pediatric Appendicitis Score cutoff points for detecting pediatric appendicitis.

Variable	Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
WBC	12.7	57.7%	62.5%	82.2%	33.0%	58.9%
NC	9.6	62.5%	75.8%	88.5%	40.2%	65.8%
NLR	4.97	89.4%	83.3%	94.1%	72.4%	87.9%
PAS	6	90.8%	81.6%	93.6%	74.8%	88.5%

PPV = Positive predictive value; NPV = Negative predictive value; WBC = White Blood Cell; NC = Neutrophil Count; NLR = Neutrophil to Lymphocyte Ratio; PAS = Pediatric Appendicitis Score

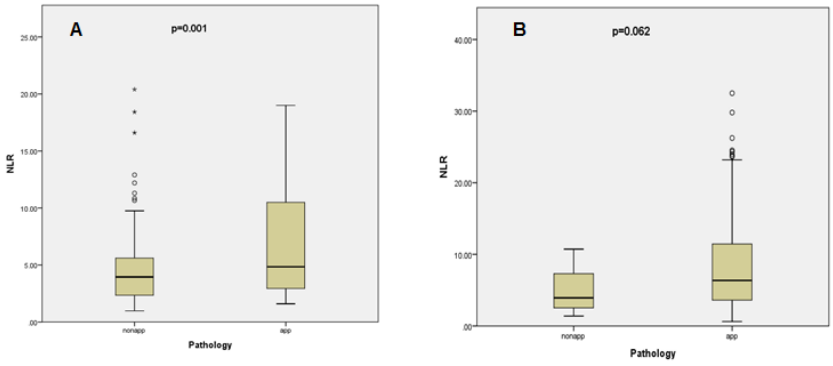

Figure 1. Neutrophil-lymphocyte ratio (NLR) stratified by pathological diagnosis of non-appendicitis (nonapp) or not appendicitis (app). A. Pediatric Appendicitis Score ≤ 6 and B. Pediatric Appendicitis Score > 6.

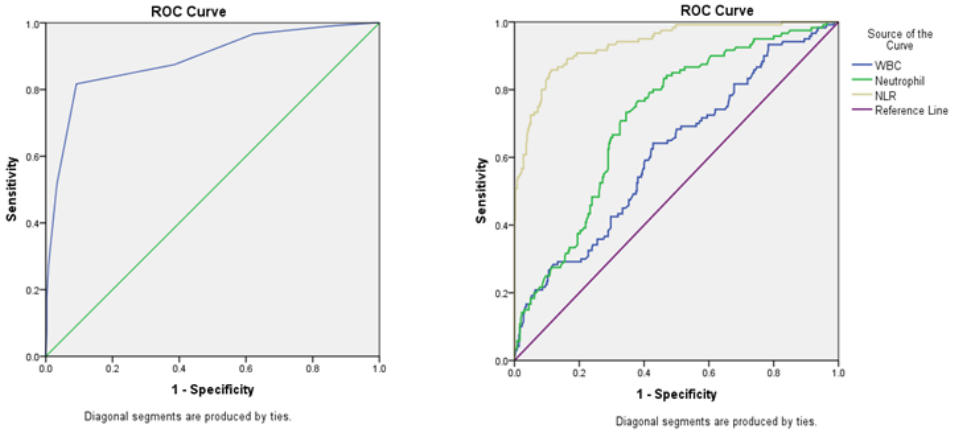

Figure 2. Recessive Operating Curves of laboratory parameters and Pediatric Appendicitis Score to detect pediatric appendicitis.

Figure 1 presents the differences in NRL based on the pathological diagnosis stratified by outer appendix diameter ≤ 6 mm and > 6 mm. The area under the ROC curve for white blood cell count, neutrophil count, lymphocyte count, NLR and PAS criteria are presented in Figure 2. The white blood cell count and PAS were significantly different between the pathological diagnosis groups (inflammatory and non-inflammatory) for an outer appendix diameter ≤ 6 mm. The relationship between PAS, NLR and the outer diameter of the appendix is shown in Figure 3.

Discussion

Acute appendicitis is an infection of the appendix, usually resulting from an obstruction of the appendiceal lumen. It is the most common surgical emergency worldwide, with an overall incidence of approximately 52 cases per 100.000 population. As reported in the 2015 Health Statistics, Mongolia, 13% of hospitalized patients with non-infectious gastrointestinal conditions were hospitalized due to acute appendicitis [18, 19].

Acute appendicitis is usually diagnosed based on clinical presentation. The accurate diagnosis of the disease leads to prompt initiation of treatment and avoids unnecessary surgery. Researchers continue to highlight the importance of assessing the size of the appendix to diagnose appendicitis. However, 5.4% of the appendixes removed with an outer diameter greater than 6 mm are, in fact, uninflamed and healthy. Acute appendicitis is the most common surgical illness in children. However, the diagnosis can be difficult in children due to the absence of the classic symptoms. Laboratory parameters often used for diagnosis are white blood count and NLR derived directly from the white blood count. The parameter with the highest sensitivity is the PAS, but it has low specificity.

The NLR has the highest specificity. Several studies have reported that NLR is more important than the white blood count cell in the diagnosis of appendicitis. In our previous study of 480 pediatric patients, we showed that the outer diameter of the appendix was poorly correlated with NLR, and the diagnosis could be improved by the combination of PAS and neutrophil-lymphocyte ratio [19]. A prospective investigation of NLR values in 129 consecutive patients admitted to the Mother and Child Healthcare Institute of Serbia revealed a strong positive correlation between NLR and C-reactive protein postoperatively and between NLR and PAS preoperatively. The optimal cutoff NLR value between negative and positive appendectomies in their study was 6.14 [20, 21]. Praja et al. on the other hand, demonstrated that there was a statistically significant relationship between the appendix diameter and the PAS. As PAS increased, there was a proportional increase in the size of the appendix [22-25]. Further, a cohort study over 2.5 years in a tertiary care referral pediatric surgery department in Saudi Arabia showed that a total leucocyte count was not significant across categories of complicated, uncomplicated as well as negative appendicitis groups. However, there was a significant difference in the neutrophil count across these groups (82% and 77% accuracy in complicated and uncomplicated appendix group, respectively). On the other hand, the ultrasound detection rate of acute appendicitis was 71.43% [26].

In this study, we observed that the white blood cell neutrophil counts could be used for the diagnosis. The mean of the correlation between white blood count and the outer diameter of the appendix less than 6 mm was equal to 14.5 ± 6.06, while the neutrophil count mean correlation was 10.4 ± 5.7. For appendixes greater than 6 mm diameter, these correlations were significantly increased (Table 3). Moreover, NLR and PAS values were higher in acute appendicitis cases than in non-appendicitis cases. The diagnostic accuracy of ultrasound imaging using the 6 mm cutoff value was 88.4%. In the retrospective study conducted by Daldal et al. there was a significant correlation between appendix diameter and NLR. In this study, the authors revealed that the sensitivity of the NLR in the diagnosis of appendicitis was 86.1% [19]. However, in our study, NLR and the outer diameter of the appendix were poorly correlated ($r = 0.169$). It should be noted that the increase in white blood cells and neutrophils during the initial examination can also occur in other inflammatory diseases. However, our study shows that blood test results and PAS are important when measuring the diameter of the appendix to diagnose appendicitis. Moreover, it is more accurate to use a combination of the less expensive and accessible diagnostic tests.

The limitation of our study is a single-center observational study. It included measurements of patients admitted to the General Surgery Department of the National Center for Maternal and Child Health hospital in Ulaanbaatar. Therefore, the next step

of our research is to investigate acute appendicitis patients who are admitted to district hospitals and hospitals in Mongolia's provinces.

Conclusion

The ultrasonic measurement of the outer diameter of the appendix had a diagnostic accuracy of 79.8% using a threshold of ≤ 6 mm. This accuracy can be enhanced with the combined usage of the PAS and the assessment of the neutrophil-lymphocyte ratio.

Conflict of Interest

The authors state no conflict of interest.

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