European Review for Medical and Pharmacological Sciences 2021; 25: 7097-7107

# Neutrophil-to-lymphocyte ratio for the diagnosis of pediatric acute appendicitis: a systematic review and meta-analysis

S. EUN[1], I.G. HO[2], G.E. BAE[3], H. KIM[1], C.M. KOO[1], M.K. KIM[1], S.H. YOON[1]

[1]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Pediatric Surgery, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Department of Emergency Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

**Abstract. – OBJECTIVE: Acute appendicitis (AA) is one of the most common surgical emergencies and causes of acute abdominal pain in the pediatric population. However, it can be difficult to diagnose in children. We aimed to provide updated evidence on the diagnostic utility of the neutrophil-to-lymphocyte ratio (NLR) for AA, along with other conventional biomarkers, in pediatric patients.**

**MATERIALS AND METHODS: We searched the PubMed, Embase, Cochrane Library, and Web of Science databases for eligible articles published up to May 16, 2021.**

**RESULTS: We included 19 studies comprising a total of 5,974 pediatric cases. The overall sensitivity and specificity of the NLR were 0.82 (95% confidence interval [CI]: 0.79-0.85) and 0.76 (95% CI: 0.69-0.81), respectively. The overall diagnostic odds ratio was 14.34 (95% CI: 9.05-22.73). The area under the summary receiver operating characteristic curve was 0.86 (95% CI: 0.83-0.89). The pooled sensitivity and specificity of other biomarkers were as follows: 0.79 (95% CI: 0.71-0.86) and 0.66 (95% CI: 0.54-0.77) for the white blood cell count, 0.73 (95% CI: 0.69-0.77) and 0.68 (95% CI: 0.55-0.79) for the C-reactive protein level, 0.75 (95% CI: 0.65-0.82) and 0.78 (95% CI: 0.72-0.83) for the absolute neutrophil count, and 0.83 (95% CI: 0.79-0.87) and 0.68 (95% CI: 0.53-0.80) for the neutrophil percentage, respectively.**

**CONCLUSIONS: The NLR has moderate predictive power for AA and can be used as a simple, auxiliary tool for diagnosis. NLR can also help clinicians decide whether to perform imaging testing when the clinical symptoms or physical examination findings are vague.**

*Key Words:*
Adolescent, Appendicitis, Biomarkers, Child, diagnosis, Meta-analysis.

## Introduction

Acute appendicitis (AA) is an acute, suppurative, and inflammatory process of the appendix[1,2]. AA is one of the most common surgical emergencies and causes of acute abdominal pain in the pediatric population[3-5]. In the United States of America, 250,000 cases occur annually[6], and the most affected age group is 10-19 years[6,7]. Early and rapid diagnosis is needed for AA because the rate of appendix rupture increases with time[7]. However, diagnosis is difficult at the initial assessment, particularly in children[8], since up to 50% of pediatric AA cases present with nonspecific symptoms[8]. Moreover, young children are unable to fully describe the pain, rendering accurate history taking and physical examination more difficult than in adults[8,9]. In addition, there are many other differential diagnoses, depending on age[9].

In this respect, several diagnostic tools have been developed to support the clinical diagnosis of AA. Abdominal and pelvic computed tomography (CT) is the imaging modality of choice for diagnosis, but the risks associated with radiation exposure from CT is a concern in pediatric patients[7,10]. Therefore, the use of ultrasound (US) is increasing in children[7]. However, the accuracy of US is operator dependent[8]. Due to the varied sensitivities and high specificities of US, clinicians can diagnose AA from positive US findings, but negative US findings cannot rule out AA (sensitivity, 71-94% and specificity, 81-98%)[8,11]. Moreover, some pediatric patients need to be sedated for imaging studies, and the reported sedation failure rate is up to 20%[12,13].

*Corresponding Author:* Seo Hee Yoon, MD, Ph.D; e-mail: yoonsh@yuhs.ac

In contrast, laboratory tests are relatively simple and useful auxiliary modalities for the diagnosis of AA, particularly in resource-limited settings. To date, the utility of conventional inflammatory biomarkers (such as the white blood cell count [WBC], absolute neutrophil count [ANC], and C-reactive protein [CRP]) with secondary parameters from routine complete blood count (CBC) tests (such as the neutrophil-to-lymphocyte ratio [NLR], mean platelet volume [MPV], and platelet-to-lymphocyte ratio [PLR]) in diagnosing AA has been studied[14-16]. In a recent systematic review, Hajibandeh et al[17] reported that the NLR demonstrated high performance in the diagnosis of AA. However, their study missed a number of pediatric studies, even though AA is more common in the pediatric age group than in adults[6,7]. Additionally, a pooled analysis has not been undertaken to evaluate the diagnostic performance of the NLR for pediatric AA. Therefore, we aimed to provide updated evidence on the diagnostic accuracy of the NLR, along with other conventional biomarkers, in pediatric AA.

## Materials and Methods

The methods and results of this review are presented according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[18].

### Data Search

We searched the PubMed, EMBASE, Cochrane Library, and Web of Science electronic databases on May 16, 2021, using the following terms: ("acute appendicitis") AND ("neutrophil-to-lymphocyte ratio" OR "neutrophil to lymphocyte ratio") AND ("infant" OR "child" OR "adolescent" OR "pediatric"). We limited the articles to those published in English, without any date restrictions. Furthermore, we hand searched Google Scholar to identify additional suitable studies.

### Eligibility Criteria, Study Selection, and Data Extraction

Two authors (SE and SHY) independently assessed the retrieved studies for eligibility. Studies eligible for inclusion in the current analysis were as follows: studies assessing the diagnostic performance of NLR for AA in pediatric patients (≤19 years of age), studies using histopathologic findings as reference standards for AA, and studies with sufficient data to construct two-by-two contingency tables. Adult studies, reviews, editorials, letters, expert opinions, and *in vitro* and *in vivo* experiments were excluded. Studies that did not report pediatric patient results separately from those of adult patients were also excluded. Any disagreement between the reviewers' assessments was arbitrated through discussion.

The following information was extracted: author names; publication year; country of origin; study period; age of study participants; inclusion and exclusion criteria; sample size; cutoff value of the NLR and other biomarkers, if available; reference standard; and the true positive, false positive, true negative, and false negative values. If the articles provided insufficient data, we attempted to contact the corresponding authors *via* email to obtain more information. If the studies presented results from multiple groups with sufficient data to construct two-by-two contingency tables, each group was treated as an individual study.

### Assessment of Methodological Quality

The methodological quality of the selected studies was independently assessed using the Quality Assessment of Diagnostic Accuracy Studies-2[19] by two reviewers (SE and SHY). Any discrepancies were arbitrated by discussion.

### Statistical Analysis

The pooled sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), diagnostic odds ratio (DOR), and corresponding 95% confidence intervals (CIs) of the NLR and other conventional biomarkers were calculated from the extracted data. We also calculated the area under the summary receiver operating characteristic (SROC) curve to obtain the overall test accuracy. Heterogeneity was assessed from the forest plots of the studies' estimates using Cochran's Q test ($p<0.05$, significant) and the $I^2$ statistic ($I^2$ >50%, significant) with 95% CIs. We performed a subgroup analysis and univariate meta-regression analysis in the presence of significant heterogeneity, using the following as covariates: publication year (≤2016 *vs.* >2016), country (Turkey *vs.* other country), sample size (≤250 *vs.* >250), and cutoff value (≤3.7 *vs.* >3.7).

Deeks' funnel plot was used to detect publication bias, with $p<0.1$ indicating the presence of publication bias. Statistical analyses were con-

ducted using STATA version 17.0 (StataCorp, College Station, TX, USA) with the MIDAS and Metandi module. *p*-values of <0.05 were considered statistically significant.

## Results

### Study Selection and Characteristics of the Included Studies

The search yielded 216 results. After removing the duplicates, the remaining 179 abstracts were screened, and 42 articles were included in the full-text review. Of these, 28 studies were excluded for the following reasons: 9 had insufficient data to construct a two-by-two contingency table, 3 were unrelated to NLR or AA, 2 did not demonstrate a clear reference standard for AA, and 14 included adult patients. Therefore, 14 studies were included in our qualitative assessment. Because two studies presented seven sets of results from different cutoff values or different patients with controls, each set of results was treated as a separate study. Finally, 19 articles[9,14-16,20-29] comprising 5,974 cases were included in the quantitative analyses (Figure 1).

The included studies were published between 2010 and 2021 and conducted in seven countries: Australia (n=1)[25], Bosnia and Herzegovina (n=1)[24], Greece (n=1)[22], Indonesia (n=1)[26], Mongolia (n=1)[27], Serbia (n=2)[23], and Turkey[9,14-16,20,21,28,29] (n=12). Participants ranged in age from 0 to 19 years. All studies used histopathologic findings as the reference standard for AA. However, the definition of control groups (non-appendicitis [non-AA] groups) was heterogeneous: they were defined by histopathology in 6 studies (31.6%)[21,23,27-29], and by clinical follow-up or healthy controls in 13 studies (68.4%)[9,14-16,20,22,24-26]. The NLR cutoff value for AA detection ranged from 2.5 to 6.14. The detailed characteristics of the included studies are listed in Table I.

### Methodological Quality

Figure 2 illustrates the quality assessment of the included studies. Regarding the patient selection domain, 68.4% of the studies were scored as having a "high" risk of bias because the authors did not state the methods used for patient enrollment (whether consecutive or random) or did not exclude patients with hematologic abnormalities (which can affect the CBC results). Regarding the index test domain, all studies had a low risk of bias because the NLR can be automatically determined when the CBC results are obtained. In the reference standard domain, all studies had an "unclear" risk of bias because they did not state whether the pathologists were blinded to the results of the NLR. In the flow and timing domain, most studies (78.9%) had a "high" risk of bias because the disease status of their control groups was not defined by the same reference standards as that of the patient groups. Regarding applicability, all studies had a low risk of bias in all three domains.

### Diagnostic Performance of the NLR for AA

The sensitivities and specificities of the included studies ranged from 0.63 to 0.91 and 0.57 to 0.95, respectively (Figure 3). The overall sensitivity and specificity were 0.82 (95% CI: 0.79-0.85) and 0.76 (95% CI: 0.69-0.81), respectively. The summary +LR and -LR were 3.37 (95% CI: 2.56-4.43) and 0.24 (95% CI: 0.19-0.29), respectively. The DOR was 14.34 (95% CI: 9.05-22.73). The area under the SROC curve was 0.86 (95% CI: 0.83-0.89) (Figure 4). Substantial heteroge-

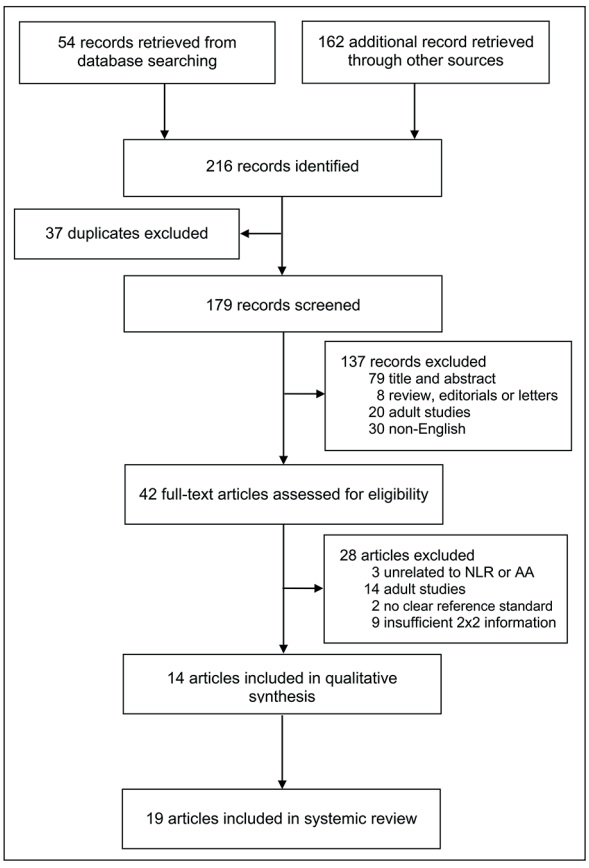


**Figure 1.** Flow diagram of the study selection process.

**Table I.** Characteristics of the included studies.

| Study id | Country | Study period | Age (range) | Patients | Controls | NLR cutoff | Reference standard | Sample size (n) |
|---|---|---|---|---|---|---|---|---|
| 2010 Yazici - a[14] | Turkey | 1994-2007 | 3-16 years | AA | NAP | 3.00 | Histopathology | 240 |
| 2010 Yazici - b[14] | Turkey | 1994-2007 | 3-16 years | AA | NAP | 3.50 | Histopathology | 240 |
| 2010 Yazici - c14 | Turkey | 1994-2007 | 3-16 years | AA | NAP | 4.00 | Histopathology | 240 |
| 2010 Yazici - d14 | Turkey | 1994-2007 | 3-16 years | AA | NAP | 4.50 | Histopathology | 240 |
| 2010 Yazici - e[14] | Turkey | 1994-2007 | 3-16 years | AA | NAP | 5.00 | Histopathology | 240 |
| 2015 Ertürk[15] | Turkey | Jan 2010-Dec 2010 | 1-17 years | AA | Other group* | 2.96 | Histopathology | 562 |
| 2017 Bekdas[20] | Turkey | 2008-2014 | 7 months-17 years | AA | NAP | 5.00 | Histopathology | 498 |
| 2017 Yilmaz[21] | Turkey | Jan 1, 2012-Dec 31, 2013 | < 18 years | AA | NAG | 3.50 | Histopathology | 658 |
| 2018 Kostakis[22] | Greece | Over a period of 94 months | 6-13 years | AA | Healthy children | 2.50 | Histopathology | 224 |
| 2018 Stanković - a[23] | Serbia | May-Nov 2015 | 3-16 years | UAA | NEAA | 5.06 | Histopathology | 72 |
| 2018 Stanković - b[23] | Serbia | May-Nov 2015 | 3-16 years | IAA | NEAA | 6.14 | Histopathology | 129 |
| 2019 Greer[25] | Australia | In the year 2017 | 2-15 years | AA | NAP | 3.66 | Histopathology | 546 |
| 2019 Prasetya[26] | Indonesia | Jan 2013-Dec 2017 | < 18 years | AA | Intussusception | 2.87 | Histopathology | 170 |
| 2019 Tuncer[16] | Turkey | Jan 1, 2014-Dec 31, 2016 | NA† | AA | FMF + ML | 3.50 | Histopathology | 301 |
| 2020 Chuluun[27] | Mongolia | May 2019-Dec 2019 | < 18 years | AA | NAG | 4.97 | Histopathology | 480 |
| 2020 Sengul[28] | Turkey | Jan 2016-Dec 2018 | 10-19 years | AA | NAG | 4.10 | Histopathology | 235 |
| 2020 Tartar[29] | Turkey | Jan 2017-Nov 2018 | 0-16 years | AA | NAG | 5.98 | Histopathology | 196 |
| 2021 Begic-Kapetanovic[24] | Bosnia and Herzegovina | Oct 1, 2016-Mar 30, 2017 | < 15 years | AA | Non-operated patients with suspected AA | 3.48 | Histopathology | 170 |
| 2021 Duman[9] | Turkey | 2011-2019 | < 16 years | AA | NAP + healthy controls | 4.40 | Histopathology | 533 |

AA, acute appendicitis; FMF, familial Mediterranean fever; IAA, patients with acute inflamed appendix (patients with phlegmonous or uncomplicated appendicitis + patients with gangrenous and/or perforated appendicitis noticed as complicated appendicitis); ML, mesenteric lymphadenitis; NAG, normal appendectomy group; NAP, nonspecific abdominal pain; NEAA, patients with normal appendix and/or early stage of appendicitis; NLR, neutrophil-to-lymphocyte ratio; UAA, patients with phlegmonous or uncomplicated appendicitis. *Other group consists of patients with negative exploration or those who were hospitalized with follow-up and discharged without surgical exploration. †Mean age: 11.5±4.33 years.

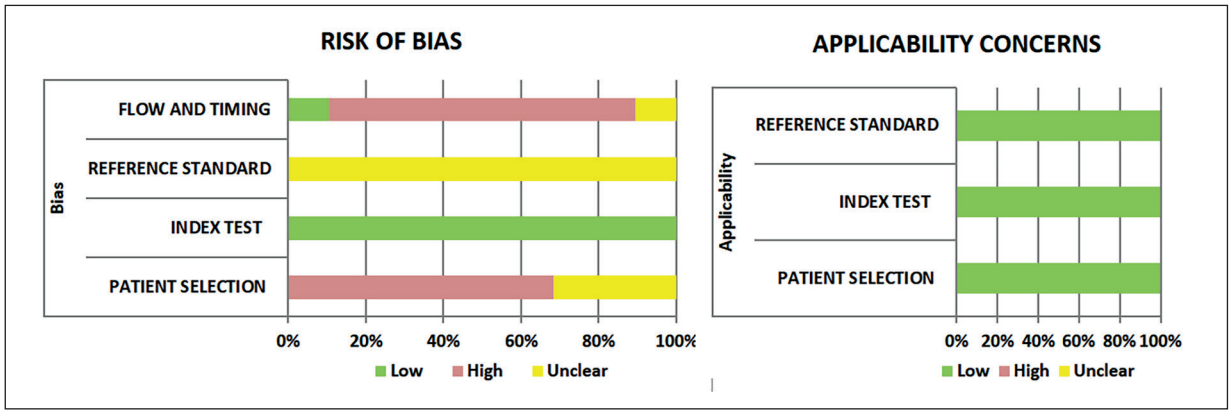


**Figure 2.** Quality assessment using the Quality Assessment of Diagnostic Accuracy Studies-2.

neity was present in both sensitivity ($I^2$ = 87%) and specificity ($I^2$ = 84%). Deeks' funnel plot ($p$=0.58) revealed no publication bias (Figure 5).

### *Heterogeneity Exploration*

Sources of heterogeneity were investigated using univariate meta-regression (Table II). Among the covariates analyzed, the publication year and sample size were the only factors significantly affecting heterogeneity in the joint model. When comparing the sensitivity and specificity estimates with the covariates, the pooled sensitivities were significantly higher in the following studies: studies published before 2016, studies conducted

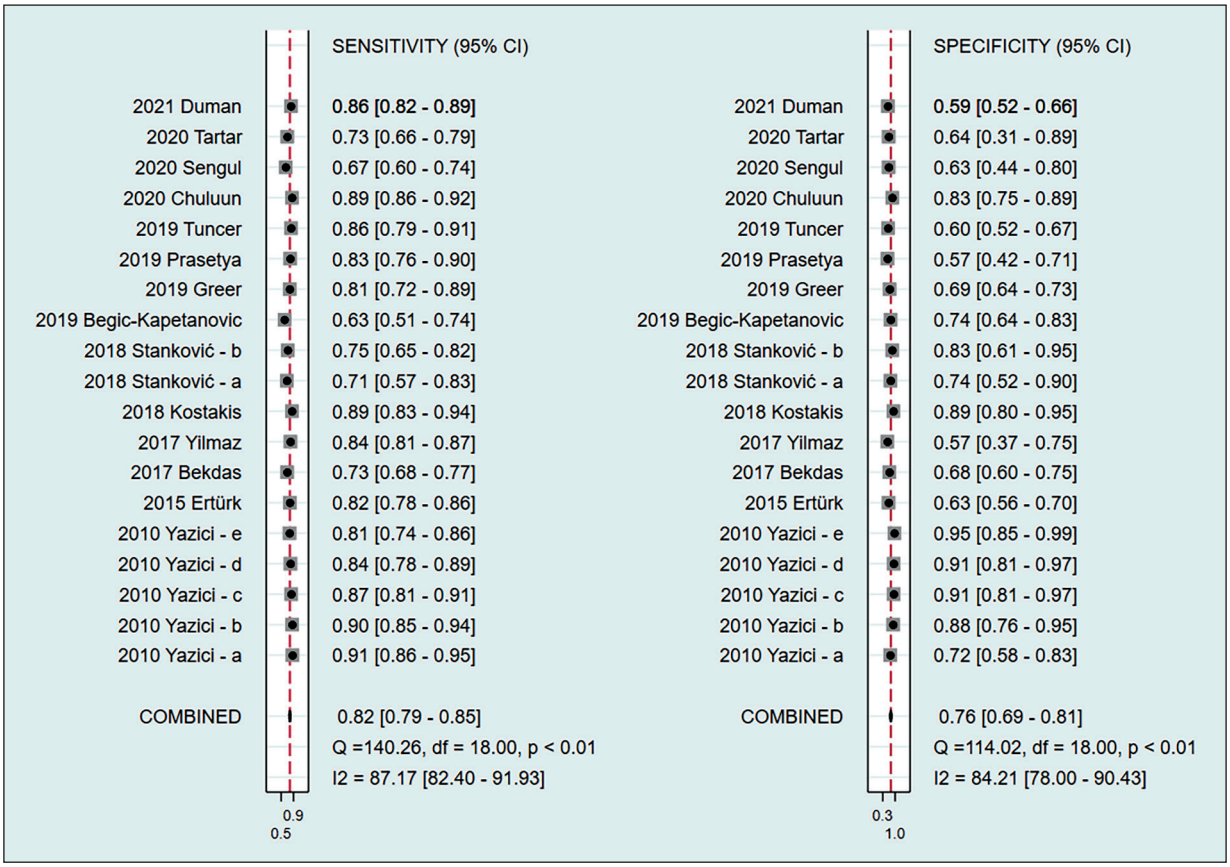


**Figure 3.** Coupled forest plots of summary sensitivity and specificity. Numbers are pooled estimates with 95% confidence intervals (CIs) in parentheses. Heterogeneity statistics are provided at the bottom-right corners. Horizontal lines indicate 95% CIs.

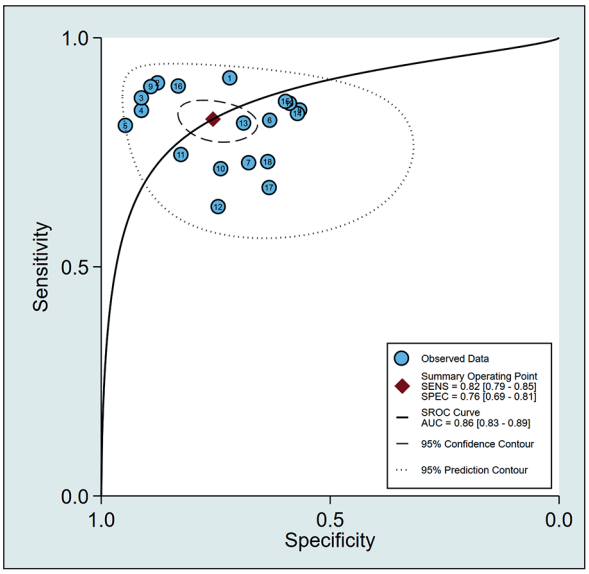


**Figure 4.** Summary receiver operating characteristic curve of the diagnostic utility of the neutrophil-to-lymphocyte ratio for acute appendicitis in pediatric patients. The area under the summary receiver operating characteristic curve was 0.86.

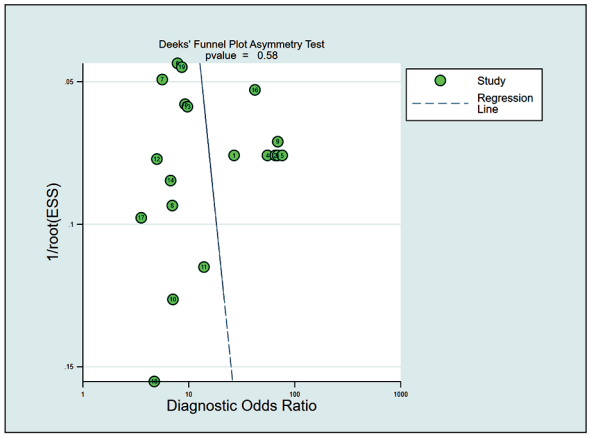


**Figure 5.** Deeks' funnel plot asymmetry test. The likelihood of publication bias was low with a *p* value of 0.58 for the slope coefficient. ESS = effective sample size.

in Turkey, studies with a cutoff value of ≤3.7, and studies with a sample size of >250. The pooled specificities were significantly higher in the following studies: studies published before 2016, studies conducted in countries other than Turkey, and studies with a sample size of ≤250 (Table II).

### *Comparison of the Diagnostic Performances of Other Biomarkers*

We performed a subgroup analysis for other available biomarkers among the included studies. Descriptive statistics of the diagnostic accuracy of the WBC, ANC, neutrophil percentage (N%), and CRP for the diagnosis of pediatric AA are summarized in Table III. Among them, the N% had the highest pooled sensitivity (0.83, 95% CI: 0.79-0.87) and pooled DOR (10.53, 95% CI: 4.49-24.69). The ANC had the highest pooled specificity (0.78, 95% CI: 0.72-0.83) (Table III). When comparing with NLR, the highest pooled estimates of sensitivities and specificities of other biomarkers were similar to those of the NLR. However, their pooled estimates of LR+ and DOR were lower than those of the NLR (Table III).

## Discussion

This systematic review and meta-analysis demonstrated that the NLR had moderate sensitivity (0.82) and specificity (0.76) with an area

**Table II.** Stratified meta-regression analyses.

| Parameter | Category | No. of Studies | Sensitivity | | Specificity | | LRT Chi-Square | *p* (Joint Model) |
|---|---|---|---|---|---|---|---|---|
| | | | Pooled value [95% CI] | *p* | Pooled value [95% CI] | *p* | | |
| Publication year | ≤ 2016 [14,15] | 6 | 0.86 [0.82-0.91] | < 0.01 | 0.85 [0.78-0.92] | < 0.01 | 8.35 | 0.02 |
| | > 2016 [9,16,20-29] | 13 | 0.80 [0.76-0.84] | | 0.70 [0.63-0.78] | | | |
| Cut off value | ≤ 3.7 [22,26 14-16,21,24,25] | 9 | 0.85 [0.81-0.89] | < 0.01 | 0.72 [0.62-0.81] | 0.17 | 5.41 | 0.07 |
| | > 3.7 [9,14,20,23,27-29] | 10 | 0.80 [0.75-0.85] | | 0.79 [0.71-0.87] | | | |
| Size (n) | ≤ 250 [14,22-24,26,28,29] | 12 | 0.81 [0.77-0.86] | < 0.01 | 0.81 [0.75-0.87] | < 0.01 | 8.24 | 0.02 |
| | > 250 [9,15,16,20,21,25,27] | 7 | 0.84 [0.79-0.89] | | 0.66 [0.57-0.76] | | | |
| Country | Turkey [9,14-16,20,21,28,29] | 12 | 0.83 [0.79-0.87] | < 0.01 | 0.75 [0.67-0.83] | 0.03 | 0.50 | 0.78 |
| | Other countries [22-27] | 7 | 0.81 [0.75-0.87] | | 0.77 [0.67-0.87] | | | |

CI = confidence interval; LRT = likelihood-ratio test.

**Table III.** Summary estimates of diagnostic accuracy of the other biomarkers.

| Biomarkers | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR– (95% CI) | DOR (95% CI) |
|---|---|---|---|---|---|---|
| WBC | 8[9,14-16,22,25,27,28] | 0.79 (0.71-0.86) | 0.66 (0.54-0.77) | 2.36 (1.71-3.26) | 0.31 (0.22-0.44) | 7.60 (4.32-13.37) |
| ANC | 5[15,22,25,27,28] | 0.75 (0.65-0.82) | 0.78 (0.72-0.83) | 3.35 (2.44-4.59) | 0.33 (0.22-0.48) | 10.25 (5.23-20.12) |
| N% | 4[9,15,22,26] | 0.83 (0.79-0.87) | 0.68 (0.53-0.80) | 2.59 (1.62-4.15) | 0.25 (0.17-0.37) | 10.53 (4.49-24.69) |
| CRP | 4[9,15,25,29] | 0.73 (0.69-0.77) | 0.68 (0.55-0.79) | 2.28 (1.61-3.24) | 0.40 (0.34-0.46) | 5.77 (3.60-9.26) |

ANC, absolute neutrophil count; CI, confidence interval; CRP, C-reactive protein; DOR, diagnostic odds ratio; LR+, positive likelihood ratio; LR–, negative likelihood ratio; N%, neutrophil percentage; WBC, white blood cell count.

under the curve of 0.86 for diagnosing AA in pediatric patients. Owing to its moderate diagnostic performance, the NLR can be a useful auxiliary tool for the diagnosis of AA. Moreover, it can help clinicians to decide whether to perform imaging testing in pediatric patients when their clinical symptoms or physical examination findings are vague.

The NLR has been studied as an inflammation marker that reflects the systemic inflammatory response in various diseases, such as atherosclerosis, cancers, and severe coronavirus disease 2019[30-33]. The NLR can be easily measured, is inexpensive, and available in most laboratories. Basically, the NLR is defined as the ANC divided by the absolute lymphocyte count. Neutrophils are involved in inflammation, macrophage recruitment, angiogenesis, and immune system activation[34]; thus, increased neutrophil counts are considered a marker of acute inflammation[32,35]. Lymphocytes play a major role in the adaptive immune response[36]. Reduced lymphocyte count ("lymphopenia") has been reported as a marker of stress[37] and is associated with viral infection or septic shock[38]. In addition, lymphopenia has been reported to be associated with appendicitis[25,39,40]. Either neutrophilia or lymphopenia can increase the NLR, which allows us to explicate the potential mechanism of the increasing NLR in the systemic inflammatory status.

Recently, Hajibandeh et al[17] reported a meta-analysis on the diagnostic accuracy of the NLR for detecting AA. The authors[17] included 11 studies in the comparison of the AA *vs.* no-AA groups, enrolling 7,214 adult and pediatric patients. The authors demonstrated that an NLR cutoff of 4.7 showed high sensitivity (0.89) and specificity (0.91) with an area under the curve of 0.96 for diagnosing AA. Their result showed a superior diagnostic performance than our results. However, their study[17] included mainly adult or mixed age (adult and children) patients; and only one pediatric study was included in the analysis, whereas our result was obtained from 19 studies comprising 5,914 pediatric patients. Although Hajibandeh et al[17] did not conduct subgroup analyses according to the age groups, the superior diagnostic performance of the NLR was observed in their study that comprised mainly adult patients[17]. Thus, it can be inferred that the utility of the NLR for diagnosing AA may be higher in adult populations than in pediatric populations.

The optimal NLR cutoffs for detecting pediatric AA varied, ranging from 2.5 to 6.14. A possible explanation for this diversity is that the cutoff value of biomarkers can vary depending on patient and control characteristics, clinical settings, laboratory assays, and the reference standard[41]. In our study, all the included studies used histopathologic findings as a reference standard for diagnosing AA, but the definition of control groups varied (i.e., healthy children or negative appendectomy patients). Further, the included studies were conducted in various clinical settings and countries. Thus, all these factors can result in variation in the cut off value. To date, the optimal NLR cutoff value for detecting pediatric AA has been not established; however, we found similar pooled sensitivities and specificities in studies using a cutoff value of ≤3.7 (range, 2.5-3.66) compared to studies using a cutoff of >3.7 (range, 4.0-6.14). Therefore, if an NLR of ≥2.5 was found in pediatric patients with AA, it can be assumed that the NLR would show a similar moderate sensitivity and specificity for diagnosing pediatric AA. Nevertheless, clinicians should apply these results with caution in practice, because of the heterogeneous characteristics of the included studies.

There are several clinical scores for diagnosing pediatric AA; the most popular ones are the Alvarado score[42] and Pediatric Appendicitis Score (PAS). Kulik et al[43] reported in a systematic review that the sensitivity of the PAS varied be-

tween 0.82 and 1 and the sensitivity of the Alvarado score varied between 0.72 and 0.93 in validation studies. However, the authors assumed that both clinical scores would have over diagnosed AA (the PAS by 35% and the Alvarado score by 32% on average)[43]. To establish evidence-based guidelines on the diagnosis and management of AA, the first consensus conference of the World Society of Emergency Surgery (WSES) was held in Jerusalem in July 2015[44]. The 2020 update of the WSES Jerusalem guidelines[45] states that the Alvarado score and PAS are useful for excluding pediatric AA. However, the guideline has recommended against diagnosing AA solely based on clinical scores[45]. Compared with clinical scores, the NLR has the advantages of simplicity and a low risk of inter-observer variation.

Regarding biomarkers, the updated 2020 WSES guidelines also suggests the adoption of both parameters, biomarkers and clinical scores, for predicting inflammation severity and the need for imaging tests in pediatric patients highly suggestive of having AA[45]. Specifically, inflammatory biomarkers, such as WBC, ANC, and CRP, have been widely used and recommended as routine workup for possible AA patients[45]. Zouari et al[46] studied 102 consecutive children (aged <6 years) who underwent appendectomy and compared the AA group with the non-AA group. The authors reported that a CRP level of ≥10 mg/L on admission ($p < 0.001$, odds ratio = 7.44) and leukocytosis of ≥16,100/mL ($p = 0.046$, odds ratio = 2.803) were predictive factors for pediatric AA. The 2020 WSES guidelines has adopted these results and included them in the statement for pediatric AA[45].

Further, Yu et al[47] compared the diagnostic performance of biomarkers for AA through a meta-analysis, including seven studies comprising both adult and pediatric patients. The pooled sensitivity and specificity were 0.62 (95% CI: 0.47-0.74) and 0.75 (95% CI: 0.55-0.89) for WBC, 0.57 (95% CI: 0.39-0.73) and 0.87 (95% CI: 0.58-0.97) for CRP, and 0.33 (95% CI: 0.21-0.47) and 0.89 (95% CI: 0.78-0.95) for procalcitonin (PCT), respectively. Particularly, PCT was found to have greater specificity for diagnosing complicated appendicitis, with a pooled sensitivity of 0.62 (95% CI: 0.33-0.84) and specificity of 0.94 (95% CI: 0.90-0.96)[4]; this result was also confirmed in another meta-analysis[48]. When compared with our results, the NLR showed the highest pooled sensitivity, but showed lower pooled specificity than PCT. Additionally, the pooled estimates of WBC and CRP showed higher sensitivity, but lower specificity in the pediatric population than in the mixed population (adults and children) for the diagnosis of AA. From the point of view of sensitivity, availability, and price, the NLR can be a more useful screening tool than PCT for diagnosing pediatric AA.

In our study, among the several biomarkers that we analyzed, the N% showed the highest pooled sensitivity, which was similar to that of the NLR (0.83 *vs.* 0.82). The ANC showed the highest pooled specificity, but it was also similar to that of the NLR (0.79 *vs.* 0.76). For comparing the test's discriminatory performance, the DOR can be used as a single indicator[49-52]. The DOR is the ratio of the odds of positivity in patients to the odds of positivity in a person without the disease[49]. The DOR reflects the discriminatory power of the test[50] and can be used when comparing diagnostic accuracy for more than two diagnostic tests[51,52]. The N% and ANC showed similar pooled estimates of DOR (10.53 *vs.* 10.25), but the NLR achieved the highest pooled DOR (14.34). Therefore, the NLR is a valuable diagnostic marker compared to other conventional biomarkers in diagnosing pediatric AA. Unfortunately, the NLR was not mentioned or adopted in the updated 2020 WSES guidelines[45]. However, owing to its moderate diagnostic performance and its simplicity, with good availability in various clinical settings, the NLR has the potential to be a good supplementary marker for diagnosing pediatric AA.

One of the strengths of our study is that it is the first systematic review and meta-analysis on the diagnostic performance of the NLR for pediatric AA, along with other blood biomarkers. However, our study also has several limitations. First, the majority of the included studies were retrospective and carried a high risk of patient selection bias. Second, due to the heterogeneous characteristics of the included studies, physicians should be careful when applying these results in clinical practice. Third, almost 50% of the included studies were conducted in Turkey. Fourth, assessing the performance of the NLR relative to clinical scores (i.e., the PAS or Alvarado score), other known biomarkers (i.e., PCT, pentraxin-3), or secondary blood parameters (i.e., MPV, PLR) was not possible due to the limited number of clinical studies that provided these corresponding data. Finally, comorbidity in the included patients, interval between symptom onset and testing, or blinding of testing were rarely reported;

thus, we could not evaluate their effect through a meta-analysis. Future well-designed prospective studies in various countries are needed to determine and validate the optimal NLR cutoff value for diagnosing pediatric AA.

## Conclusions

In conclusion, the NLR showed moderate sensitivity, specificity, and accuracy for diagnosing pediatric AA. Because of its simple measurement, low cost, and availability in most laboratories, the NLR can be useful as an auxiliary tool for the diagnosis of pediatric AA, particularly in resource-limited settings. However, physicians should be cautious when using only the NLR for diagnosis.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Declaration of Funding Interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Availability of Data and Materials

The data used in the present study are appropriately cited.

### Authors' Contribution

IGH and SHY conceptualized the study. SE and SHY performed the investigation, data curation, and manuscript drafting. SHY conducted the supervision, formal analysis, and visualization of the study. HK and GEB validated the study. CMK, IGH, and MKK reviewed and revised the manuscript. All authors have read and approved the final version of manuscript.

## References

1) Baxter KJ, Nguyen HTMH, Wulkan ML, Raval MV. Association of health care utilization with rates of perforated appendicitis in children 18 years or younger. JAMA Surg 2018; 153: 544-550.
2) Murphy CG, Glickman JN, Tomczak K, Wang YY, Beggs AH, Shannon MW, Horwitz BH. Acute appendicitis is characterized by a uniform and highly selective pattern of inflammatory gene expression. Mucosal Immunol 2008; 1: 297-308.
3) Cameron DB, Anandalwar SP, Graham DA, Melvin P, Serres SK, Dunlap JL, Kashtan M, Hall M, Saito JM, Barnhart DC, Kenney BD, Rangel SJ. Development and implications of an evidence-based and public health-relevant definition of complicated appendicitis in children. Ann Surg 2020; 271: 962-968.
4) Held JM, McEvoy CS, Auten JD, Foster SL, Ricca RL. The non-visualized appendix and secondary signs on ultrasound for pediatric appendicitis in the community hospital setting. Pediatr Surg Int 2018; 34: 1287-1292.
5) Almaramhy HH. Acute appendicitis in young children less than 5 years: review article. Ital J Pediatr 2017; 43: 15.
6) Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990; 132: 910-925.
7) Gadiparthi R, Waseem M. Pediatric Appendicitis. StatPearls Publishing, 2021.
8) Téoule P, Laffolie J, Rolle U, Reissfelder C. Acute appendicitis in childhood and adulthood. Dtsch Arztebl Int 2020; 117: 764-774.
9) Duman L, Karaibrahimoğlu A, Büyükyavuz BI, Savaş MÇ. Diagnostic value of monocyte-to-lymphocyte ratio against other biomarkers in children with appendicitis. Pediatr Emerg Care 2021. doi: 10.1097/PEC.0000000000002347. Epub ahead of print.
10) Al-Rammah TY. CT radiation dose awareness among paediatricians. Ital J Pediatr 2016; 42: 77.
11) Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, Antoniou SA, Arolfo S, Babic B, Boni L, Bruntink M, van Dam DA, Defoort B, Deijen CL, DeLacy FB, Go PM, Harmsen AM, van den Helder RS, Iordache F, Ket JC, Muysoms FE, Ozmen MM, Papoulas M, Rhodes M, Straatman J, Tenhagen M, Turrado V, Vereczkei A, Vilallonga R, Deelder JD, Bonjer J. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc 2016; 30: 4668-4690.
12) Arlachov Y, Ganatra RH. Sedation/anaesthesia in paediatric radiology. Br J Radiol 2012; 85: e1018-e1031.
13) Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by nonanesthesiologists. Anesth Analg 1997; 85: 1207-1213.
14) Yazici M, Özkisacik S, Öztan MO, Gürsoy H. Neutrophil/lymphocyte ratio in the diagnosis of childhood appendicitis. Turk J Pediatr 2010; 52: 400-403.
15) Ertürk A, Tuncer İS, Balci Ö, Karaman İ, Karaman A, Afşarlar ÇE, Yilmaz E, Özgüner IF, Çavuşoğlu YH, Erdoğan D. The value of pediatric appendicitis score and laboratory findings on the diagnosis of pediatric appendicitis. Turkish J Pediatr Dis 2015; 2: 79-84.
16) Tuncer AA, Cavus S, Balcioglu A, Silay S, Demiralp I, Calkan E, Altin MA, Eryilmaz E, Karaisaoglu AO, Bukulmez A, Dogan I, Embleton DB, Cetinkursun S. Can mean platelet volume, neu-

trophil-to-lymphocyte, lymphocyte-to-monocyte, platelet-to-lymphocyte ratios be favourable predictors for the differential diagnosis of appendicitis? J Pak Med Assoc 2019; 69: 647-654.

17) Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M. Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: a systematic review and meta-analysis. Am J Surg 2020; 219: 154-163.

18) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-1012.

19) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536.

20) Bekdas M, Ozturk H, Goksugur SB, Demircioglu F, Tahaoglu M. Neutrophil to lymphocyte ratio in diagnosis of complicated and non-complicated appendicitis. Sri Lanka J Child Health 2017; 46: 59-65.

21) Yilmaz BK, Acar YA. Investigation of the diagnostic value of neutrophil to lymphocyte ratio in pediatric appendicitis cases. Iran J Pediatr 2017; 27: e9593.

22) Kostakis ID, Angelidou M, Kambouri K, Gardikis S, Cholidou GK, Gioka T, Vaos G. Hematological diagnostic markers of acute appendicitis in children. Hellenic J Surg 2018; 90: 127-136.

23) Stanković N, Stanojević I, Đorđević D, Kostić Z, Udovičić I, Miličković M, Savić Đ, Grujić B, Đuričić S, Šurbatović M. Neutrophil-to-lymphocyte ratio in pediatric acute appendicitis. Vojnosanit Pregl 2018; 75: 46-55.

24) Begic-Kapetanovic S, Avdagic N, Zaciragic A, Hasic S, Babic N, Hadzimuratovic A. Could the neutrophil-to-lymphocyte ratio serve as a marker in the diagnosis and prediction of acute appendicitis complications in children? Arch Med Sci 2021; 17.

25) Greer D, Bennett P, Wagstaff B, Croaker D. Lymphopaenia in the diagnosis of paediatric appendicitis: a false sense of security? ANZ J Surg 2019; 89: 1122-1125.

26) Prasetya D, Rochadi, Gunadi. Accuracy of neutrophil lymphocyte ratio for diagnosis of acute appendicitis in children: a diagnostic study. Ann Med Surg (Lond) 2019; 48: 35-38.

27) Chuluun E, Ankhbayar B, Ganzorig G, Luuzan G, Dambadarjaa D, Dungerdorj Z, Chimedtseye P. Usefulness of the pediatric appendicitis score and neutrophil to lymphocyte ratio for assessing the complicated appendicitis in children. Open J. Clin. Diagn 2020; 10: 93-103.

28) Sengul S, Guler Y, Calis H, Karabulut Z. The role of serum laboratory biomarkers for complicated and uncomplicated appendicitis in adolescents. J Coll Physicians Surg Pak 2020; 30: 420-424.

29) Tartar T, Bakal Ü, Saraç M, Aydin S, Kazez A. Diagnostic value of laboratory results in children with acute appendicitis. TJB 2020; 45: 553-558.

30) McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009; 12: 223-226.

31) Faria SS, Fernandes PC JR, Silva MJ, Lima VC, Fontes W, Freitas-Junior R, Eterovic AK, Forget P. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience 2016; 10: 702.

32) Meng LB, Yu ZM, Guo P, Wang QQ, Qi RM, Shan MJ, Lv J, Gong T. Neutrophils and neutrophil-lymphocyte ratio: inflammatory markers associated with intimal-media thickness of atherosclerosis. Thromb Res 2018; 170: 45-52.

33) Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. J Med Virol 2020; 92: 1733-1734.

34) Selders GS, Fetz AE, Radic MZ, Bowlin GL. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regen Biomater 2017; 4: 55-68.

35) Dale DC, Boxer L, Liles WC. The phagocytes: neutrophils and monocytes. Blood 2008; 112: 935-945.

36) Bezuidenhout J, Schneider JW. Tuberculosis. Saunders, 2009.

37) Ramaekers LH, Theunissen PM, Went K. Acute lymphopenia, stress, and plasma cortisol. Arch Dis Child 1975; 50: 555-558.

38) Mohan SS, McDermott BP, Cunha BA. The diagnostic and prognostic significance of relative lymphopenia in adult patients with influenza A. Am J Med 2005; 118: 1307-1309.

39) Jahangiri M, Wyllie JH. Peripheral blood lymphopenia in gangrenous appendicitis. BMJ 1990; 301: 215.

40) Devuyst O, Maldague P, Francois P, Dekeuleneer R, Michaux JL. Time-course of lymphopenia in gangrenous appendicitis. Lancet 1991; 338: 1074.

41) Raghavan R, Ashour FS, Bailey R. A review of cutoffs for nutritional biomarkers. Adv Nutr 2016; 7: 112-120.

42) Badebarin D, Parsay S, Aslanabadi S. Alvarado vs. Pediatric Appendicitis Score (PAS) in acute appendicitis of children. IRJPS 2020; 6: 1-9.

43) Kulik DM, Uleryk EM, Maguire JL. Does this child have appendicitis? A systematic review of clinical prediction rules for children with acute abdominal pain. J Clin Epidemiol 2013; 66: 95-104.

44) Di Saverio S, Birindelli A, Kelly MD, Catena F, Weber DG, Sartelli M, Sugrue M, De Moya M, Gomes CA, Bhangu A, Agresta F, Moore EE, Soreide K, Griffiths E, De Castro S, Kashuk J, Kluger Y, Leppaniemi A, Ansaloni L, Andersson M, Coccolini F, Coimbra R, Gurusamy KS, Campanile FC, Biffl W, Chiara O, Moore F, Peitzman AB, Fraga GP, Costa D, Maier RV, Rizoli S, Balogh ZJ, Bendinelli C, Cirocchi R, Tonini V, Piccinini A, Tugnoli G, Jovine E, Persiani R, Biondi

A, Scalea T, Stahel P, Ivatury R, Velmahos G, Andersson R. WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. World J Emerg Surg 2016; 11: 34.

45) Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, Boermeester M, Sartelli M, Coccolini F, Tarasconi A, De' Angelis N, Weber DG, Tolonen M, Birindelli A, Biffl W, Moore EE, Kelly M, Soreide K, Kashuk J, Ten Broek R, Gomes CA, Sugrue M, Davies RJ, Damaskos D, Leppäniemi A, Kirkpatrick A, Peitzman AB, Fraga GP, Maier RV, Coimbra R, Chiarugi M, Sganga G, Pisanu A, De' Angelis GL, Tan E, Van Goor H, Pata F, Di Carlo I, Chiara O, Litvin A, Campanile FC, Sakakushev B, Tomadze G, Demetrashvili Z, Latifi R, Abu-Zidan F, Romeo O, Segovia-Lohse H, Baiocchi G, Costa D, Rizoli S, Balogh ZJ, Bendinelli C, Scalea T, Ivatury R, Velmahos G, Andersson R, Kluger Y, Ansaloni L, Catena F. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg 2020; 15: 27.

46) Zouari M, Louati H, Abid I, Ben Abdallah AK, Ben Dhaou M, Jallouli M, Mhiri R. C-reactive protein value is a strong predictor of acute appendicitis in young children. Am J Emerg Med 2018; 36: 1319-1320.

47) Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg 2013; 100: 322-329.

48) Cui W, Liu H, Ni H, Qin X, Zhu L. Diagnostic accuracy of procalcitonin for overall and complicated acute appendicitis in children: a meta-analysis. Ital J Pediatr 2019; 45: 78.

49) Šimundić AM. Measures of diagnostic accuracy: basic definitions. EJIFCC 2009; 19: 203-211.

50) Bossuyt P, Davenport C, Deeks J, Hyde C, Leeflang M, Scholten R. Cochrane handbook for systematic reviews of diagnostic test accuracy. The Cochrane Collaboration, 2013.

51) Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003; 56: 1129-1135.

52) Eusebi P. Diagnostic accuracy measures. Cerebrovasc Dis 2013; 36: 267-272.