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The Role of Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) in Appendicitis

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ABSTRACT

Aim: Predictive values of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with poor outcomes in several diseases. Furthermore, there has been limited publication of those parameters in appendicitis patients in Indonesia. This study aims to evaluate the role of NLR and PLR in differentiating complicated appendicitis and uncomplicated appendicitis. **Methods:** The design of this study is a retrospective using medical records of appendicitis patients from January 1, 2016, to December 31, 2020, conducted at PKU Muhammadiyah Bantul Hospital. There are 408 data on appendicitis patients that can be analyzed. **Results:** The WBC, neutrophils, NLR, and PLR was significantly higher in the complicated appendicitis group than in the uncomplicated group [11,5 (3.79-35.2) vs. 8.42 (3.32-39.30), p≤0.0001; 8.63 (2.359-2.647) vs. 5.446 (1.691-35.960), p≤0.0001; 5.65 (0.95-23.86) vs.3.82 (0.81-23.86), p≤0.0001; 168.57 (37.27-974.03) vs.139.40 (56.84-1274.31), p≤0.0001, respectively] followed by a significantly lower lymphocyte count [1.709 (0.154-5.71) vs. 2.094 (0.401-5.812), p≤0.0001, respectively]. The area under the receiver operating characteristic (ROC) curve, cutoff point, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio of NLR for diagnosis of complicated appendicitis were 0.76, >2.84, 75.21%, 62.65%, 74.6%, 63.4%, 2.01, 0.40, respectively. In contrast, an area under ROC curve, cutoff point, sensitivity, specificity, PPV, NPV, and likelihood ratio of PLR for differentiating complicated and uncomplicated appendicitis were 0.605, >140.6, 65.70%, 51.81%, 66.5%, 50.9%, 1.36, and 0.66 respectively. **Conclusion:** The cutoff values of NLR (>2.84) and PLR (>140.6) were significant diagnostic parameters for complicated appendicitis (p = 0.0001). Hence, NLR and PLR can assist in diagnosing complicated appendicitis**.**

Keywords: appendicitis, NLR, PLR.

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INTRODUCTION

Acute appendicitis is the most common cause of acute abdominal pain. The incidence of acute appendicitis in Indonesia is estimated at 95 cases per 1000 population and ten million cases annually. Appendicitis cases in infants are relatively low. It increases in childhood, reaching a peak at 10-30 years old. Appendicitis occurs 1.3-1.6 times more frequently in men.[1] Acute appendicitis requires immediate action to prevent complications that can increase morbidity and mortality. The complications include perforation, abscess, intestinal obstruction, peritonitis, and sepsis. Diagnosing acute appendicitis remains challenging because its signs and symptoms often mimic other abdominal diseases.[2] Thus, it is often missed.

As many as 30% of patients with proven appendicitis reported receiving other diagnoses previously and were discharged instead of being treated accordingly. Errors in diagnosing appendicitis are the fifth leading cause of successful litigation against physicians in the emergency department. They account for 15% of fines paid in malpractice claims in the emergency department.[3]

Several decades ago, under certain conditions, negative appendectomy (NA) was acceptable to prevent morbidity and mortality due to perforation.[4] However, currently, NA is no longer acceptable. Researchers developed several clinical scoring systems for acute appendicitis to prevent NA and improve the accuracy of preoperative diagnoses, such as Alvarado, Eskelinen, Ohmann, AIR, RIPASA, Tzanakis, Lintula, Fenyo-Lindberg, and Karaman.[5,6]

Several studies report a high rate of perforation in appendicitis, which is 15-45%, while the NA rate is 7-25%. This rate shows that with the development of technology and clinical experience, the perfect method of diagnosing appendicitis has not yet been found.[4] Imaging modalities, such as ultrasonography (USG) and computer tomography (CT-scan), are considered insufficient to diagnose properly despite their high cost and more sophisticated imaging capabilities.[6] Other examinations, several hematological parameters, can diagnose acute appendicitis. This examination is available throughout the hospital, affordable, and relatively fast.

A leukogram, including leukocyte count and type count, helps diagnose appendicitis. Leukocytosis above 20,000 cells/mm3 may indicate a perforation and requires immediate action.[7] An increase in the percentage of polymorphonuclear >85% is associated with the severity of diseases such as necrosis and perforation.[8] The lymphocyte count in patients with severe appendicitis is significantly lower than in the early stages.[9] Recently, studies reported the predictive value of neutrophil to lymphocyte ratio (NLR) in inflammation, which can be used as a diagnostic parameter in the perioperative diagnosis of acute appendicitis. Apart from NLR, platelet-to-lymphocyte ratio (PLR) is also associated with poor outcomes in several diseases.[10] Furthermore, publications on NLR and PLR in appendicitis patients in Indonesia are still limited. This study examines the role of NLR and PLR to distinguish complicated appendicitis and uncomplicated appendicitis.

METHODS

Patient Population

This diagnostic test study was a retrospective design using medical records of acute appendicitis patients. The subjects of this study included acute appendicitis patients at PKU Muhammadiyah Bantul Hospital who were diagnosed with acute appendicitis both clinically and anatomically from January 2016 – December 2020. The exclusion criteria were acute appendicitis patients with other inflammatory diseases or incomplete data on their medical records. The variables studied included data on the characteristics of subjects: clinical, laboratory, and imaging examination results. This research has obtained permission from the Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada (FK-KMK UGM) ethics committee with ethical eligibility Number: KE/0067/01/2021.

NLR and PLR measurement

Neutrophil and lymphocyte counts were examined using a hematology analyzer. The NLR and the PLR were calculated as the ratio of neutrophil count to lymphocyte count and platelet count to lymphocyte count, respectively.

Statistical analysis

We checked the collected data for completeness, then coded, tabulated, and entered it into the computer. Subject characteristic data are presented descriptively in mean ± standard deviation if the data distribution is normal, or median (min-max) if the data distribution is not normal, and categorical data are present in frequency and proportion.

RESULTS

We acquired 429 patients data with acute appendicitis. There were 21 data excluded due to other inflammatory diseases or incomplete data. The variables studied included clinical and laboratory data on the characteristics of subjects. Hematological parameters in the medical record were hemoglobin, leukocyte count, type count, and platelet count. Clinical parameters recorded were operative diagnosis: complicated appendicitis and uncomplicated appendicitis. We analyzed 408 subjects in this study, as shown in **Table 1.**

Parameters tested by Receiver Operating Characteristic (ROC) were the number of leukocytes, neutrophils, Neutrophil Lymphocyte Ratio (NLR), and Platelet Lymphocyte Ratio (PLR). The ROC test results are shown in **Figure 1**, **Table 2**, and **Table 3**.

Table 1. Comparison of sex, age, and hematological parameters in complicated and uncomplicated appendicitis group.

Variable	Complicated appendicitis n=242	Uncomplicated appendicitis n=166	p
Sex n= (%)			
Male	158 (65.3%)	55 (33.1%)	0.0001[a]
Female	84 (34.7%)	111 (66.9%)	
Age (years old)	33 (1-80)	25 (2-95)	0.025[b]
Hemoglobin (g/dL) Mean (SD)	13.62 (1.82)	13.32 (1.48)	0.08[c]
Platelets count (x10^3/µL)	278,5 (150-802)	289 (165-758)	0.136[b]
White blood cell count (x10^3/µL)	11,5 (3.79-35.2)	8.42 (3.32-39.30)	0.0001[b]
Neutrophil (x10^3/µL)	8.63 (2.359-2.647)	5.446 (1.691-35.960)	0.0001[b]
Lymphocyte (x10^3/µL)	1.709 (0.154-5.71)	2.094 (0.401-5.812)	0.0001[b]
Neutrophil-to-Lymphocyte Ratio (NLR)	5.65 (0.95-23.86)	3.82 (0.81-23.86)	0.0001[b]
Platelet-to-Lymphocyte Ratio (PLR)	168.57 (37.27-974.03)	139.40 (56.84-1274.31)	0.0001[b]

Note: Result showed in Median (Min-Max); a.Chi-square; b.Mann Whitney; c.Independent t-test, significant if $p \leq 0.05$.

Table 2. The AUC value of Hematology parameters for diagnosing complicated appendicitis.

Parameter	AUC	IK 95%	p
WBC count	0.697	0.646 – 0.748	0.0001
Neutrophil count	0.721	0.671 – 0.771	0.0001
Neutrophil-to-Lymphocyte Ratio (NLR)	0.726	0.677 – 0.775	0.0001
Platelet-to-Lymphocyte Ratio (PLR)	0.605	0.550 – 0.659	0.0001

Note: AUC: Area Under the ROC Curve.

Table 3. Diagnostic ability of Hematology parameters for diagnosing complicated appendicitis.

Parameter	COV	Sn	Sp	+PV	-PV	LR (+)	LR (-)	YI
WBC count	>8700	73,55	56,02	70,9	59,2	1,67	0,47	0,33
Neutrophil count	>6127	72,31	64,46	74,8	61,5	2,03	0,43	0,38
NLR	>2,84	75,21	62,65	74,6	63,4	2,01	0,40	0,39
PLR	>140,6	65,70	51,81	66,5	50,9	1,36	0,66	0,21

Note: COV cut-off value; Sn sensitivity; Sp specificities; LR (+) likelihood ratio positive; LR (-) likelihood ratio negative; +PV positive predictive value; -PV negative predictive value; YI Youden Index.

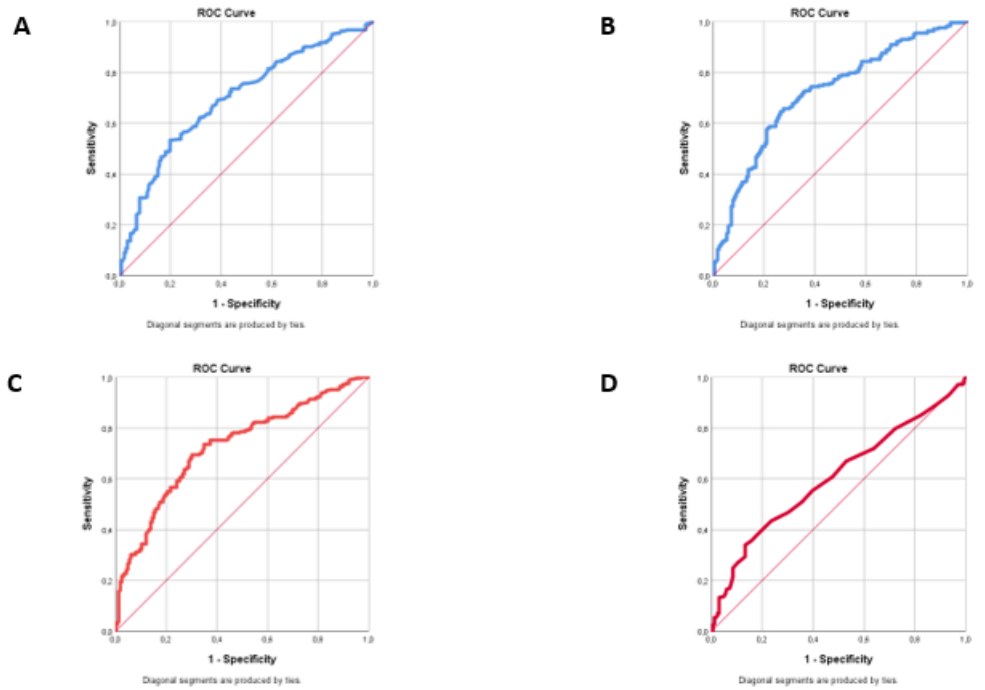

Figure 1. The ROC curve of Hematology parameters for diagnosing complicated appendicitis. A: WBC count, B: neutrophil count, C: Neutrophil-to-Lymphocyte Ratio (NLR), and D: Platelet-to-Lymphocyte Ratio (PLR).

DISCUSSION

In this study, the results showed that the Neutrophil-to-Lymphocyte Ratio (NLR) had the largest diagnostic ability among other hematological parameters for diagnosing complicated appendicitis (AUC 0.726; IK 0.677-0.775; p<0.0001). These results aligned with several studies with the same purpose. A study involved 1,597 patients undergoing appendectomy and compared the NLR values between the perforated appendicitis group and the acute appendicitis group (the cutoff point was 6.17, AUC 0.7 (0.63–0.77), p-value ≤0.001, sensitivity 76.32%, specificity 58.72%).[11,12]

Shashirekha et al. revealed that NLR could be one of the supporting parameters to diagnose perforated appendicitis, one aspect of complicated appendicitis. The systemic inflammatory response results in neutrophilia and lymphocytopenia, thus increasing NLR, which can be a marker for various abnormalities.[13,14]

The neutrophil count showed a fairly good ability, followed by leukocytes and PLR. The leukocyte count can be a significant parameter for diagnosing acute appendicitis.[11] One study stated that the leukocyte count could help differentiate complicated and uncomplicated appendicitis. The study involved 425 patients with appendicitis. The cutoff values for leukocytes were 11.47, with a sensitivity of 71.9% and a specificity of 51.5%.[15] These results have a sensitivity and specificity similar to ours, 73.55% and 56.02%, respectively.

To discriminate between uncomplicated and complicated appendicitis at the second diagnostic stage, excluding it is more critical than its inclusion. The clinician or surgeon should exclude complicated appendicitis if antibiotic treatment is considered. Therefore, the sensitivity and NPV values for detecting complicated appendicitis should be high.[16]

Several studies reported a significant increase in NLR in cases of acute appendicitis. The rise in NLR was also higher compared to

patients with complicated and uncomplicated appendicitis.[16,17] NLR 4.68 can be a reasonably reliable parameter in diagnosing appendicitis, and NLR 5.74 can help differentiate between complex and uncomplicated appendicitis.[17] Another study revealed that the cutoff value of 8.96 in the NLR can predict the occurrence of perforation in acute appendicitis. The results of the two studies differ from ours, with a cutoff value of NLR $\geq$2.84.

Laboratory tests greatly assist clinical decision-making when combined with signs and symptoms or radiological studies. A study of 845 people (mean age=11; the prevalence of acute appendicitis = 46.5%) found that even when the white blood cell count (WBC) was less than 10,000 per L (10.0 × 109 per L), 20% of patients still had acute appendicitis. However, in patients with equivocal ultrasound findings, a WBC count of less than 9,000 per L (9.0 × 109 per L) and less than 65% polymorphonucleocytes increased, and the negative predictive value increased from 41.9% to 95.8% (only 4,2% suffering from acute appendicitis).[18]

This study found that the characteristics of the male subjects are more than that of female subjects (52.2% vs. 47.8%). This result is similar to a study involving 67 complicated appendicitis patients and 106 uncomplicated patients, with 64.16% male subjects and 35.84% female subjects.[19] Many studies also revealed more male appendicitis patients than women, and epidemiological data showed a ratio of 3:2.[19,20] The median age of patients with appendicitis was 16 years (15 – 19) in this study, in line with several studies which revealed that acute appendicitis was most common in the young adult age group (60.3%).[21]

Our study found that the operative diagnosis of complicated appendicitis is higher than uncomplicated appendicitis (59.31% vs. 40.69%). These results align with other studies, which showed a 59.67% result for the diagnosis of complicated appendicitis.[22] The development from uncomplicated appendicitis to complicated appendicitis can be caused by various factors, such as limited access to health facilities, delays in examinations and logistical problems when referring patients. In addition, the behavior of delaying appendicitis patients decision to check their condition made it difficult for clinicians to determine the following treatment. Delay in diagnosing appendicitis can cause appendix complications into perforation, abscess formation, intra-abdominal adhesions, and sepsis.[23] This study still has several limitations, such as unused medical record data because it lost some documents or was not stored correctly, causing us not to analyze the data obtained. In the future, similar research can be carried out with more detailed inclusion and exclusion criteria, increasing the number of subjects, or using different research methods. Thus, the outcome would have better and statistically meaningful data.

CONCLUSION

Hematological parameters: an increased number of leukocytes, neutrophils, monocytes, NLR, PLR, and a decreased number of lymphocytes can assist clinicians in diagnosing acute appendicitis, especially in establishing the operative diagnosis of complicated appendicitis. These parameters can also help clinicians or surgeons predict the severity of acute appendicitis, preventing delays in treating appendicitis patients. A hematological examination is a relatively easy test available in almost all hospitals, including the lowest type, in this case, type-C hospitals in Indonesia. Besides, this method is cost-effective without budgeting for new modalities in hospitals/health services.

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DISCLOSURE

None.

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