Diagnostic value of laboratory parameters for complicated appendicitis: A two-center study

QIAN ZHANG[1*], HONGWEI ZHAO[1*], FANGLI WANG[2], WENQIANG LI[2] and PENG ZHANG[1]

[1]Department of Gastrointestinal Surgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218; [2]Department of General Surgery, Aerospace Center Hospital, School of Clinical Medicine, Peking University, Beijing 100039, P.R. China

Received October 22, 2023; Accepted February 6, 2024

DOI: 10.3892/br.2024.1765

Abstract. There are two types of treatment for acute appendicitis (AA): surgery and antibiotic therapy. Some patients with complex appendicitis are treated with surgery; however, for uncomplex appendicitis, most could be treated effectively with antibiotics instead. How to distinguish complex appendicitis from uncomplex appendicitis before surgery is currently unknown. The present study aimed to assess the efficacy of the laboratory parameters to diagnose complicated appendicitis. Data from 1,514 cases with acute appendicitis who were admitted to Beijing Tsinghua Changgung Hospital and Beijing Aerospace General Hospital (both Beijing, China) from January 2016 to September 2021 were retrospectively analyzed. All cases were divided into uncomplicated and complicated appendicitis. Independent variables were analyzed by uni- and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curve analysis was used to identify significant parameters in the multivariate logistic regression analysis. Cut-off values, sensitivity, specificity and accuracy with area under the curve (AUC)>0.600 were considered significant parameters. Significant differences were found in age (P<0.001), body temperature (P<0.001), white blood cell (WBC) count (P<0.001), C-reactive protein (CRP; P<0.001), neutrophil count (P<0.001), neutrophil-to-lymphocyte ratio (NLR, P=0.019), platelet-to-lymphocyte ratio (PLR, P<0.001), platelet count (P<0.001), coefficient of variation (CV) and standard deviation (SD) of red blood cell distribution width (RDW); both P<0.001), mean platelet volume (MPV, P<0.001) and total (P<0.001) and direct bilirubin (P<0.001) between the two groups. CRP, neutrophil count, NLR, PLR, platelet count, RDW-CV, RDW-SD, MPV and direct bilirubin levels were found as the independent variables to diagnose complicated appendicitis. In patients with acute appendicitis, CRP >22.95 mg/l, NLR >5.7, serum direct bilirubin >6.1 mmol/l and RDW-SD>17.7 fl were significantly associated with complicated appendicitis.

Correspondence to: Dr Wenqiang Li, Department of General Surgery, Beijing Aerospace General Hospital, School of Clinical Medicine, Peking University, 15 Yuquan Road, Haidian, Beijing 100039, P.R. China
E-mail: 13911025919@139.com

*Contributed equally

Key words: complicated appendicitis, bilirubin, mean platelet volume, neutrophil-to-lymphocyte ratio, platelet count

Introduction

Acute appendicitis is a frequently encountered acute abdominal condition, with a morbidity rate of 1.5-1.9 per 10 million (1,2). Its incidence is 1.4 times higher in men compared with that in women (1). Lifetime risk of experiencing acute appendicitis is 7-8% (1). Elderly patients have higher incidence of complicated appendicitis, reported rates of perforation and morbidity were as high as 70 and 48%, respectively (3). Notably, 17-30% of patients with acute appendicitis may exhibit appendiceal perforation; this occurrence is notably more prevalent in the elderly (1,2). Appendicitis is divided into uncomplicated and complicated appendicitis according to its pathology (4). Uncomplicated appendicitis has a mild infection and fewer complications and can be treated with antibiotics (5). On the other hand, surgery is the primary treatment for complicated appendicitis (5). Early diagnosis and management are crucial to decrease incidence of complications and the length of hospitalization (4,5).

Several diagnostic modalities are available for appendicitis, such as laboratory inflammatory markers, scoring systems and imaging methods (6,7). Only 60% of patients present with typical symptoms, including shifting right lower abdominal pain, fever, nausea, and vomiting (1,2,8). The frequently measured laboratory parameters are C-reactive protein (CRP), white blood cell (WBC) count and neutrophil percentage. However, these tests can only evaluate the presence of abdominal infection and severity (1,7,9,10). Abdominal ultrasound and computed tomography (CT) scan are used in the diagnosis of appendicitis. Sensitivity and specificity of ultrasound are 86 and 81%, respectively, due to the influence of the intestinal gas (4,11). Although non-contrast-enhanced CT has better sensitivity and specificity (92.3%) than ultrasound (81%) (1,12,13), the high cost and the risk of radiation

may limit its broad application. Therefore, evaluation of acute appendicitis based on laboratory tests is essential.

Over the past decade, studies have reported that neutrophil count and percentage, neutrophil-to-lymphocyte ratio (NLR), platelet (PLT) count, mean platelet volume (MPV) and direct bilirubin are key parameters in the diagnosis of appendicitis and predicting the complications (1,14-19). A recent study demonstrated an association between plasma sodium concentration ≤135 mmol/l and perforated appendicitis (5). The present study aimed to evaluate the diagnostic value of CRP, WBC count, NLR, PLT, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), red blood cell distribution width (RDW), MPV and serum bilirubin levels for acute appendicitis. The present study aimed to propose a standard was for the management of acute appendicitis.

Materials and methods

Study design and participant selection. The present study was approved by the Institutional Review Board of Beijing Tsinghua Changgung Hospital (Beijing, China; approval no. 22029-1-01). Because of the retrospective nature of the study, the requirement for patient consent for inclusion was waived. Data from 1,514 cases with acute appendicitis who were admitted to the Gastrointestinal Department of Beijing Tsinghua Changgung Hospital (n=978; 64.6%) and Surgery Department of Beijing Aerospace General Hospital (Beijing, China; n=536; 35.4%) from January 2016 to September 2021 were retrospectively analyzed. The inclusion criteria were as follows: i) Age ≥14 years and ii) pathological confirmation of acute appendicitis. The exclusion criteria were as follows: i) Postoperative pathology indicating a normal appendix; ii) concurrent autoimmune or infectious diseases of non-appendiceal origin; iii) concurrent severe liver, cardiovascular or kidney diseases; iv) concurrent cancer or other blood related diseases and v) antibiotic treatment <12 h before the surgery and blood test.

Blood test was performed <12 h before the surgery. Flow cytometry was used to detect blood cell composition and hydraulic focusing method (Automated Hematology Systems XN, Automated Hematology Analyzer XN series XN master, flow cell count + DNA/RNA fluorescence staining) was used for the complete blood count and blood chemistry tests. Additionally, liver function test was conducted using diazonium salt method (BECKMAN COULTER CHEMISTRY ANALYZER AU5800 Serie, Beckman Coulter AU5800 software, B000017AA, Beckman Coulter). All the cases underwent laparoscopic appendectomy.

Appendix pathology was evaluated by an experienced pathologist from each hospital. The pathological results were classified as follows: Simple/phlegmonous (intraoperative signs of congestion, an increased diameter, red) color change, exudate or pus; or histopathologic signs of transmural inflammation, ulceration, or thrombosis, with or without extramural pus), gangrenous and perforated (perioperative signs of a friable appendix with purple, green or black color changes, a visible perforation, and/or abscess formation, or histopathologic signs of transmural inflammation with signs of necrosis or perforation) appendicitis (20). Subsequently, all cases were categorized into two groups: Uncomplicated, comprising simple and phlegmonous appendicitis, and complicated appendicitis, encompassing gangrenous and perforated appendicitis and periappendicular abscess.

Data collection. The information of age, sex and body temperature was retrieved from the medical records. Routine blood tests provided data on WCC, CRP, MPV, neutrophil count and percentage, platelet (PLT), lymphocyte count and coefficient of variation (CV) and standard deviation (SD) of RDW. Liver function test yielded values for total and direct bilirubin and CRP. NLR was calculated as the ratio of neutrophil count to lymphocyte count, LMR as the ratio of lymphocyte count to monocyte count and PLR as the ratio of platelet count to lymphocyte count.

The primary outcomes of the study included the values of WCC, CRP, MPV, neutrophil count and percentage, lymphocyte count, RDW-CV and RDW-SD. The secondary outcomes were values of total and direct bilirubin, CRP, NLR, LMR and PLR.

Statistical analysis. The statistical analysis was performed using SPSS 25.0 software (IBM Corp.). Normally distributed continuous variables are expressed as mean ± SD and compared using unpaired t test. Abnormally distributed continuous variables are presented as median and compared using the Kruskal-Wallis H test. Numerical data were expressed as number and percentage and compared using χ^2 test. Multivariate logistic regression analysis was conducted on parameters exhibiting significant differences in the univariate analysis. Diagnostic accuracy was evaluated by receiver operating characteristic (ROC) curve analysis. The appropriate cut-off values were identified and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated for parameters with an area under the curve (AUC)>0.600. All tests were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

The cohort comprised 780 (51.5%) men and 734 (48.5%) women with a mean age of 36.000±15.135 (range, 14-88) years. A total of 1,172 (77.4%) cases were allocated to the uncomplicated appendicitis group, while 342 (22.6%) cases were in the complicated appendicitis group. Age, body temperature, WCC, CRP, neutrophil percentage and count, NLR, PLR, PLT, RDW-CV, RDW-SD, MPV, total bilirubin and direct bilirubin exhibited significant differences (all P<0.001) between the two groups as evidenced by univariate analysis (Table I).

Multivariate logistic regression analysis revealed that CRP (P<0.001), neutrophil count (P<0.001), NLR (P=0.019), PLR (P<0.001), PLT (P<0.001), RDW-CV (P=0.045), RDW-SD (P<0.001), MPV (P=0.007) and direct bilirubin (P<0.001) were the independent risk factors associated with complicated appendicitis (Table II). According to ROC curve analysis, factors with AUC>0.600 were CRP, NLR, RDW-SD and direct bilirubin (all P<0.001; Table II). The cut-off values of CRP, NLR, RDW-SD and direct bilirubin are presented in Table III.

Table I. Univariate analysis.

Variable	Uncomplicated appendicitis	Complicated appendicitis	P-value
N	1,172	342	
Median age (range), years	35 (14-81)	41 (16-88)	<0.001
Sex (%)			0.868
Male	606 (51.70)	174 (50.90)	
Female	566 (48.30)	168 (49.10)	
Mean body temperature, ˚C	37.0±0.70	37.50±0.93	<0.001
Mean WBC count, x10^9/l	13.0±3.92	14.24±3.98	<0.001
Mean CRP, mg/l	10.18±50.8	43.29±74.41	<0.001
Mean neutrophil, %	84.40±9.40	86.20±7.73	<0.001
Mean neutrophil count, x10^9/l	10.79±3.93	12.17±3.67	<0.001
Mean NLR	8.21±8.36	9.95±11.88	<0.001
Mean LMR	2.43±3.12	1.87±3.43	0.919
Mean PLR‡	167.53±200.27	191.43±374.31	<0.001
Mean PLT, x10^9/l	222.50±57.46	225.50±58.21	<0.001
Mean RDW-CV, %	11.90±1.55	12.10±1.36	<0.0001
Mean RDW-SD, fl	37.40±12.6	38.50±10.56	<0.001
MPV, fl	10.30±14.28	10.10±11.80	<0.001
Mean bilirubin, mmol/l	14.60±8.78	17.95±10.78	<0.001
Mean direct bilirubin, mmol/l	4.24±2.6	5.80±3.80	<0.001

WBC, white blood cell; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; RDW, red blood cell distribution width; MPV, mean platelet volume; CV, coefficient of variation.

Table II. Logistic regression and ROC curve in factors associated with complicated appendicitis.

	Multivariate analysis			ROC curve analysis		
Variable	OR	95% CI	P-value	AUC	95% CI	P-value
CRP	1.008	1.005-1.010	<0.001	0.679	0.642-0.714	<0.001
Neutrophil count	1.120	1.055-1.189	<0.001	0.589	0.556-0.621	<0.001
NLR	0.944	0.900-0.991	0.019	0.603	0.556-0.621	<0.001
PLR	1.005	1.003-1.008	<0.001	0.573	0.537-0.607	<0.001
PLT	0.996	0.993-1.000	0.039	0.502	0.466-0.535	<0.001
RDW-CV	0.809	0.657-0.996	0.045	0.579	0.544-0.610	<0.001
RDW-SD	1.147	1.079-1.219	<0.001	0.605	0.571-0.637	<0.001
MPV	1.067	1.018-1.118	0.007	0.567	0.535-0.601	<0.001
Direct bilirubin	1.128	1.075-1.184	<0.001	0.657	0.622-0.690	<0.001

OR, odds ratio; AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; CV, coefficient of variation.

Discussion

Acute appendicitis is the prevailing cause of acute abdominal conditions, with morbidity rates up to 2% (1,21). The diagnosis of appendicitis depends on symptoms, signs, laboratory tests and imaging results (1,7,8). Surgery is the primary therapy for acute appendicitis, especially for complicated appendicitis (22-25). Complicated appendicitis accounts for 18-34% of acute appendicitis cases (1). Conservative treatment is the first option for uncomplicated appendicitis (1,7,8,26). Therefore, it is necessary to choose an effective and simple method to distinguish complicated and uncomplicated appendicitis. Parameters such as temperature, CRP, WBC, NLR, PLR, MPV, RDW-CV, RDW-SD and total bilirubin may improve the diagnostic accuracy for complicated appendicitis, however, the efficacy varies (10,16-19,21,27-29). The present study analyzed 1,514 cases who underwent laparoscopic appendectomy at two surgical centers. The results suggested that CRP, neutrophil,

Table III. Proposed cut-off values for significant parameters in prediction of acute complicated appendicitis.

Variable	Cut-off value	Sensitivity, %	Specificity, %	PPV	NPV	pLLR	nLLR	AUC
CRP	22.95	64.24	66.09	38.10	85.00	1.89	0.54	0.679
NLR	5.7	82.46	32.51	26.30	86.40	1.22	0.54	0.603
RDW-SD	17.7	82.16	33.45	26.50	86.50	1.23	0.53	0.605
Direct bilirubin	6.1	47.66	78.16	38.90	83.70	2.18	0.67	0.657

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; pLLR, positive likelihood ratio; nLLR, negative likelihood ratio; AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; RDW, red blood cell distribution width.

NLR, PLR, PLT, RDW-CV, RDW-SD, MPV and direct bilirubin could be the independent risk factors of complicated appendicitis.

CRP is a serum inflammatory marker and a critical factor associated with complicated appendicitis (16,19,30). Its concentration increases rapidly by several-fold in the early stage of inflammation (6-12 h) (31). Notably, WBC count is a sensitive indicator during the first 24 h of acute appendicitis, while CRP is sensitive after the first 24 h (31). Ahmed (32) reported that the probability of appendix perforation significantly increases when CRP >48 mg/dl. A study including 42 acute appendicitis cases found that the sensitivity and specificity of perforated appendicitis are 71 and 100%, respectively, when CRP is >40.1 mg/dl (33). Choudhary *et al* (34) demonstrated that the sensitivity and specificity of perforated appendicitis are 100 and 54%, respectively, when CRP is >6.15 mg/l. Hence, the appropriate cut-off of CRP is key for distinguishing complicated appendicitis. The present study found that the sensitivity and specificity of complicated appendicitis were 64.24 and 66.09%, respectively, when CRP was >22.95 mg/l. This cut-off value was lower than that reported in previous studies (32,33).

NLR is obtained from complete blood count. It is a routine and cost-effective blood test during diagnosis of appendicitis. NLR can effectively elucidate the severity of acute appendicitis (18,27,28,35,36), while the cut-off value remains controversial (27,28,35,36). Ishizuka *et al* (14) reported that NLR of 8.0 is significantly associated with gangrenous appendicitis based on the analysis of 314 cases who underwent appendectomy. Kahramanca *et al* (15) analyzed 897 cases and concluded that NLR of 5.74 is associated with complicated appendicitis; sensitivity and specificity of clinical features were 70.8 and 48.5%, respectively. The present study reported an NLR of 5.7 associated with complicated appendicitis and the sensitivity and specificity were 82.46 and 32.51%, respectively. This finding was similar to that of Kahramanca *et al* (15) and lower than that reported by Ishizuka *et al* (14). Prior research (14) suggests that the lower the cut-off value of NLR, the higher the sensitivity of NLR. Cut-off value of 3.5 results in the highest sensitivity (35) and the specificity increases when NLR >5.0 (21). Further investigation with a larger sample size is essential to find an optimal cut-off value of NLR.

The serum bilirubin levels increase due to liver dysfunction during infection, especially sepsis. Hence, serum bilirubin levels are included in the evaluation of patients with complicated appendicitis (37-39). The sensitivity and specificity of total and direct bilirubin in recognizing complicated appendicitis are 48 and 61%, respectively (40). Sand *et al* (41) reported that hyperbilirubinemia has a specificity of 86% for appendiceal perforation or gangrene, while CRP has a specificity of 35%. Estrada *et al* (42) found that bilirubin levels >1 mg/dl are associated with three-fold risk of perforated appendicitis. Pogorelić *et al* (43) demonstrated that hyperbilirubinemia is a reliable indicator for perforated acute appendicitis in children with sensitivity of 92% and specificity of 77.3%. By contrast, certain studies have reported no diagnostic value for bilirubin in the prediction of perforated appendicitis (44,45). Bilirubin alone is sufficient to identify patients with acute appendicitis and predict perforated appendicitis. The value of bilirubin as a marker increases when combined with clinical symptoms and other blood markers (44,46). In the present study, total and direct bilirubin levels were significantly elevated in the complicated appendicitis group. Direct bilirubin was an independent risk factor of complicated appendicitis with a sensitivity of 47.66% and specificity of 78.16% when the cut-off value was 6.1 mmol/l. Although total bilirubin levels can be measured, few studies have reported the efficiency of direct bilirubin (44-46). Therefore, these results need to be verified with further studies.

RDW reflects volumetric heterogeneity of red blood cells. At present, it is primarily used for the differential diagnosis of anemia (47,48). RDW is altered in certain types of inflammatory and infectious disease, such as inflammatory bowel disease, celiac disease, acute pancreatitis, rheumatoid arthritis, bacteremia, sepsis and septic shock (47-51). Previous studies have reported a strong correlation between RDW and inflammatory markers, such as CRP, erythrocyte sedimentation rate and interleukin-6 (48,49). The inflammatory mediators affect survival of red blood cells in the circulation by suppressing erythrocyte maturation. Thus, newer, larger reticulocytes enter peripheral circulation and increase the RDW (48). Narci *et al* (52) found that RDW significantly decreases in patients with acute appendicitis compared with healthy individuals. Conversely, Aktimur *et al* (53) and Tanrikulu *et al* (54) did not identify any diagnostic value of RDW in acute appendicitis. Jung *et al* (55) demonstrated that the RDW is significantly higher in complicated appendicitis compared with that in the uncomplicated appendicitis; by contrast, RDW does not significantly differ between patients with appendicitis

and healthy individuals. A recent meta-analysis, which included 5,222 cases, showed that RDW does not differentiate patients with acute appendicitis from healthy individuals (56) and highlighted the lack of evidence for the diagnosis of acute appendicitis using RDW. The results of the present study indicated that RDW-CV and RDW-SD were independent risk factors for complicated appendicitis. RDW-SD had a sensitivity of 82.16% and specificity of 33.45% for complicated appendicitis when the cut-off value was 17.7 fl. Therefore, RDW could serve as a parameter to identify complicated appendicitis.

Although the present multicenter study indicated CRP, NLR, direct bilirubin and RDW-SD as potential biomarkers for complicated appendicitis, the retrospective nature of the analysis may introduce the possibility of bias. Therefore, randomized controlled trials should be conducted. Moreover, the present study only assessed laboratory results. In the future, physical examination should also be included to improve sensitivity and specificity.

In conclusion, elevated levels of CRP (>22.95 mg/l), NLR (>5.7), RDW-SD (>17.7 fl) and direct bilirubin (>6.1 mmol/l) could serve as valuable indicators for diagnosing acute complicated appendicitis. For patients exhibiting these indicators, surgery is the primary recommended treatment.

Acknowledgements

Not appliable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

QZ, HWZ and WQL designed the study, analyzed data and wrote the manuscript. FW and PZ reviewed the manuscript and analyzed and interpreted data. QZ, HWZ, and WQL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Beijing Tsinghua Changgung Hospital (Beijing, China approval no. 22029-1-01). The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Baird DLH, Simillis C, Kontovounisios C, Rasheed S and Tekkis PP: Acute appendicitis. BMJ 357: j1703, 2017.
2. Pogorelić Z, Mihanović J, Ninčević S, Lukšić B, Elezović Baloević S and Polašek O: Validity of appendicitis inflammatory response score in distinguishing perforated from non-perforated appendicitis in children. Children (Basel) 8: 309, 2021.
3. Weinandt M, Godiris-Petit G, Menegaux F, Chereau N and Lupinacci RM: Appendicitis is a severe disease in elderly patients: A twenty-year audit. JSLS 24: e2020.00046, 2020.
4. Bhangu A, Søreide K, Di Saverio S, Assarsson JH and Drake FT: Acute appendicitis: Modern understanding of pathogenesis, diagnosis, and management. Lancet 386: 1278-1287, 2015.
5. Pogorelić Z, Lukšić B, Ninčević S, Lukšić B and Polašek O: Hyponatremia as a predictor of perforated acute appendicitis in pediatric population: A prospective study. J Pediatr Surg 56: 1816-1821, 2021.
6. Rafiq MS, Khan MM, Khan A and Ahmad B: Total leukocyte and neutrophil count as preventive tools in reducing negative appendectomies. Ulus Travma Acil Cerrahi Derg 21: 102-106, 2015.
7. Ünal Y: A new and early marker in the diagnosis of acute complicated appendicitis: Immature granulocytes. Ulus Travma Acil Cerrahi Derg 24: 434-439, 2018.
8. Andersson REB: Meta-analysis of the clinical and laboratory diagnosis of appendicitis. Br J Surg 91: 28-37, 2004.
9. Di Saverio S, Birindelli A, Kelly MD, Catena F, Weber DG, Sartelli M, Sugrue M, De Moya M, Gomes CA, Bhangu A, *et al*: WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. World J Emerg Surg 11: 34, 2016.
10. Farooqui W, Pommergaard HC, Burcharth J and Eriksen JR: Platelet-to-Lymphocyte ratios be favourable predictors for the differential diagnosis of appendicitis? J Pak Med Assoc 69: 647-654, 2019.
11. Peixoto Rde O, Nunes TA and Gomes CA: Indices of diagnostic abdominal ultrasonography in acute appendicitis: Influence of gender and physical constitution, time evolution of the disease and experience of radiologist. Rev Col Bras Cir 38: 105-111, 2011 (In English, Portuguese).
12. Ramalingam V, Bates DD, Buch K, Uyeda J, Zhao KM, Storer LA, Roberts MB, Lebedis CA, Soto JA and Anderson SW: Diagnosing acute appendicitis using a nonoral contrast CT protocol in patients with a BMI of less than 25. Emerg Radiol 23: 455-462, 2016.
13. Nielsen JW, Boomer L, Kurtovic K, Lee E, Kupzyk K, Mallory R, Adler B, Bates DG and Kenney B: Reducing computed tomography scans for appendicitis by introduction of a standardized and validated ultrasonography report template. J Pediatr Surg 50: 144-148, 2015.
14. Ishizuka M, Shimizu T and Kubota K: Neutrophil-to-lymphocyte ratio has a close association with gangrenous appendicitis in patients undergoing appendectomy. Int Surg 97: 299-304, 2012.
15. Kahramanca S, Ozgehan G, Seker D, Gökce EI, Seker G, Tunç G, Küçükpınar T and Kargıcı H: Neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis. Ulus Travma Acil Cerrahi Derg 20: 19-22, 2014.
16. Shimoda M, Maruyama T, Nishida K, Suzuki K, Tago T, Shimazaki J and Suzuki S: Preoperative high C-reactive protein level is associated with an increased likelihood for conversion from laparoscopic to open appendectomy in patients with acute appendicitis. Clin Exp Gastroenterol 12: 141-147, 2019.
17. Haghi AR, Pourmohammad P and Rabiee MAS: Accuracy of mean platelet volume (MPV) and red cell distribution width (RDW) for the diagnosis of acute appendicitis: Evaluation of possible new biomarkers. Adv J Emerg Med 4: e20, 2019.
18. Hajibandeh S, Hajibandeh S, Hobbs N and 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 219: 154-163, 2020.
19. Özozan ÖV and Vural V: High C-reactive protein level as a predictor for appendiceal perforation. Ulus Travma Acil Cerrahi Derg 26: 63-66, 2020.
20. Nijssen DJ, van Amstel P, van Schuppen J, Eeftinck Schattenkerk LD, Gorter RR and Bakx R: Accuracy of ultrasonography for differentiating between simple and complex appendicitis in children. Pediatr Surg Int 37: 843-849, 2021
21. Sevinç MM, Kınacı E, Çakar E, Bayrak S, Özakay A, Aren A and Sari S: Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: An analysis of 3392 cases. Ulus Travma Acil Cerrahi Derg 22: 155-162, 2016.

22. Phillips AW, Jones AE and Sargen K: Should the macroscopically normal appendix be removed during laparoscopy for acute right iliac fossa pain when no other explanatory pathology is found? Surg Laparosc Endosc Percutan Tech 19: 392-394, 2009.
23. Gaitán HG, Reveiz L, Farquhar C and Elias VM: Laparoscopy for the management of acute lower abdominal pain in women of childbearing age. Cochrane Database Syst Rev 2014: CD007683, 2014.
24. Lee M, Paavana T, Mazari F and Wilson TR: The morbidity of negative appendicectomy. Ann R Coll Surg Engl 96: 517-520, 2014.
25. Slotboom T, Hamminga JT, Hofker HS, Heineman E and Haveman JW; Apple Study Group Appendicitis and Laparoscopic Evaluation: Intraoperative motive for performing a laparoscopic appendectomy on a postoperative histological proven normal appendix. Scand J Surg 103: 245-248, 2014.
26. Xu H, Yang S, Xing J, Wang Y, Sun W, Rong L and Liu H: Comparison of the efficacy and safety of antibiotic treatment and appendectomy for acute uncomplicated appendicitis: A systematic review and meta-analysis. BMC Surg 23: 208, 2023.
27. Pehlivanli F and Aydin O: Role of platelet to lymphocyte ratio as a biomedical marker for the pre-operative diagnosis of acute appendicitis. Surg Infect (Larchmt) 20: 631-636, 2019.
28. Ahmad KA, Ideris N and Aziz SHSA: A cross-sectional study of neutrophil-to-lymphocyte ratio in diagnosing acute appendicitis in Hospital Melaka. Malays J Med Sci 26: 55-66, 2019.
29. Boshnak N, Boshnaq M and Elgohary H: Evaluation of platelet indices and red cell distribution width as new biomarkers for the diagnosis of acute appendicitis. J Invest Surg 31: 121-129, 2018.
30. Bayrak S, Tatar C, Cakar E, Colak S, Gunes ME, Tekesin K, Gurbulak B, Kinaci E and Sevinc MM: Evaluation of the predictive power of laboratory markers in the diagnosis of acute appendicitis in the elderly. North Clin Istanb 6: 293-301, 2019.
31. Çetinkaya E, Erdoğan A, Akgül Ö, Çelik C and Tez M: High serum cancer antigen 125 level indicates perforation in acute appendicitis. Am J Emerg Med 33: 1465-1467, 2015.
32. Ahmed N: C-reactive protein: An aid for diagnosis of acute appendicitis. J Ayub Med Coll Abbottabad 29: 250-253, 2017.
33. Lai CY, Leung YK and Graham CA: Could C-reactive protein be a potential biomarker of complicated acute appendicitis? Hong Kong J Emerg Med 21: 354-360, 2014.
34. Choudhary SK, Yadav BL, Gupta S, Kumar N, Bansal S and Verma PK: Diagnostic value of C-reactive protein as a predictor of complicated appendicitis like perforated/gangrenous appendicitis. Int Surg J 6: 1761, 2019.
35. Yazar FM, Urfalioglu A, Bakacak M, Boran OF and Bülbüloğlu E: Efficacy of the evaluation of inflammatory markers for the reduction of negative appendectomy rates. Indian J Surg 80: 61-67, 2018.
36. Celik B, Nalcacioglu H, Ozcatal M and Altuner Torun Y: Role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in identifying complicated appendicitis in the pediatric emergency department. Ulus Travma Acil Cerrahi Derg 25: 222-228, 2019.
37. Brienza N, Dalfino L, Cinnella G, Diele C, Bruno F and Fiore T: Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Med 32: 267-274, 2006.
38. Emmanuel A, Murchan P, Wilson I and Balfe P: The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl 93: 213-217, 2011.
39. Hong YR, Chung CW, Kim JW, Kwon CI, Ahn DH, Kwon SW and Kim SK: Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soc Coloproctol 28: 247-252, 2012.
40. Motie MR, Nik MM and Gharaee M: Evaluation of the diagnostic value of serum level of total bilirubin in patients with suspected acute appendicitis. Electron Physician 9: 4048-4054, 2017.
41. Sand M, Bechara FG, Holland-Letz T, Sand D, Mehnert G and Mann B. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis. Am J Surg 198: 193-198, 2009.
42. Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S and Mason RJ: Hyperbilirubinemia in appendicitis: A new predictor of perforation. J Gastrointest Surg 11: 714-718, 2007.
43. Pogorelić Z, Lukšić AM, Mihanović J, Đikić D and Balta V: Hyperbilirubinemia as an indicator of perforated acute appendicitis in pediatric population: A prospective study. Surg Infect (Larchmt) 22: 1064-1071, 2021.
44. Panagiotopoulou IG, Parashar D, Lin R, Antonowicz S, Wells AD, Bajwa FM and Krijgsman B: The diagnostic value of white cell count, C-reactive protein and bilirubin in acute appendicitis and its complications. Ann R Coll Surg Engl 95: 215-221, 2013.
45. Beltran MA, Mendez PE, Barrera RE, Contreras MA, Wilson CS, Cortes VJ and Cruces KS: Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein?-a prospective study. Indian J Surg 71: 265-272, 2009.
46. Giordano S, Pääkkönen M, Salminen P and Grönroos JM: Elevated serum bilirubin in assessing the likelihood of perforation in acute appendicitis: A diagnostic meta-analysis. Int J Surg 11: 795-800, 2013.
47. Ku NS, Kim HW, Oh HJ, Kim YC, Kim MH, Song JE, Oh DH, Ahn JY, Kim SB, Jeong SJ, *et al*: Red blood cell distribution width is an independent predictor of mortality in patients with gram-negative bacteremia. Shock 38: 123-127, 2012.
48. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G and Guidi GC: Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 133: 628-632, 2009.
49. Şenol K, Saylam B, Kocaay F and Tez M: Red cell distribution width as a predictor of mortality in acute pancreatitis. Am J Emerg Med 31: 687-689, 2013.
50. Sadaka F, O'Brien J and Prakash S: Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 28: 307-313, 2013.
51. Harmanci O, Kav T and Sivri B: Red cell distribution width can predict intestinal atrophy in selected patients with celiac disease. J Clin Lab Anal 26: 497-502, 2012.
52. Narci H, Turk E, Karagulle E, Togan T and Karabulut K: The role of red cell distribution width in the diagnosis of acute appendicitis: A retrospective case-controlled study. World J Emerg Surg 8: 46, 2013.
53. Aktimur R, Cetinkunar S, Yildirim K, Ozdas S, Aktimur SH and Gokakin AK: Mean Platelet Volume is a Significant Biomarker in the Differential Diagnosis of Acute Appendicitis. Eur J Prev Cardiol 19: 484-489, 2015.
54. Tanrikulu CS, Tanrikulu Y, Sabuncuoglu MZ, Karamercan MA, Akkapulu N and Coskun F: Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. Iran Red Crescent Med J 16: e10211, 2014.
55. Jung SK, Rhee DY, Lee WJ, Woo SH, Seol SH, Kim DH and Choi SP: Neutrophil-to-lymphocyte count ratio is associated with perforated appendicitis in elderly patients of emergency department. Aging Clin Exp Res 29: 529-536, 2017.
56. Anand S, Krishnan N, Jukić M, Križanac Z, Llorente Muñoz CM and Pogorelić Z: Utility of red cell distribution width (RDW) as a noninvasive biomarker for the diagnosis of acute appendicitis: A systematic review and meta-analysis of 5222 cases. Diagnostics (Basel) 12: 1011, 2022.