ORIGINAL ARTICLE

Association between complete blood count parameters and histologically proven acute appendicitis

Asociación entre los parámetros del hemograma y la apendicitis aguda histológicamente probada

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Abstract

Objectives: *The objective of the study was to assess the role of complete blood count (CBC) parameters in the detection of acute appendicitis (AA) severity in children and adults.* **Method:** *This is a retrospective analytic cross-sectional study on cases operated for AA between June 1, 2020, and February 28, 2021, in Salmaniya Medical Complex, Bahrain. Patients of all ages and genders were included in the study. Exclusion criteria included other appendiceal pathologies, the presence of another intraoperative pathology that is the likely cause of abdominal pain, normal appendix, and missing parameters. Data included patient demographics, CBC parameters, and histopathology. Patients were divided into groups based on age and severity of AA.* **Results:** *A total of 569 patients were included in the study. Ages ranged from 4 to 75 years. Majority of the patients were males (74.87%) and adults (89.81%). A quarter of the patients were diagnosed with complicated AA, while the rest had simple AA. A statistically significant difference was observed between adults with complicated and simple AA in white blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). None of the parameters was statistically significant in children.* **Conclusion:** *WBC, ANC, ALC, NLR, and PLR can be useful parameters in the discrimination between complicated and simple AA in adults. PLR was found to be the least predictive.*

Keywords: *Platelet-to-lymphocyte ratio. Neutrophil-to-lymphocyte ratio. Lymphocyte. Neutrophil. Leukocyte. Appendicitis.*

Resumen

Objetivos: *Evaluar la función de los parámetros del conteo sanguíneo completo (CSC) en la detección de la gravedad de la apendicitis aguda (AA) en niños y adultos.* **Método:** *Se trata de un estudio transversal analítico retrospectivo de casos operados por AA en nuestro hospital. Se incluyeron pacientes de todas las edades y sexos. Los criterios de exclusión incluyeron otras patologías apendiculares, presencia de otra patología intraoperatoria que es la causa probable de dolor abdominal, apéndice normal y ausencia de parámetros. Los datos incluyeron datos demográficos de los pacientes, parámetros de CSC e histopatología. Los pacientes se dividieron en grupos según la edad y la gravedad de la AA.* **Resultados:** *Se incluyeron un total de 569 pacientes. Las edades oscilaron entre los 4 y los 75 años. La mayoría de los pacientes eran hombres (74.87%) y adultos (89.81%). Una cuarta parte de los pacientes fueron diagnosticados con AA complicada. Se observó una diferencia estadísticamente significativa entre adultos con AA complicada y simple en GB, RAN, RAL, INL e IPL. Ninguno de los parámetros fue estadísticamente significativo en niños.* **Conclusión:** *GB, RAN, RAL, INL e IPL pueden ser útiles en la discriminación entre AA complicada y simple en adultos. IPL fue el menos predictivo.*

Palabras clave: *Índice plaqueta-linfocito. Índice neutrófilo-linfocito. Linfocito. Neutrófilo. Leucocito. Apendicitis.*

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Introduction

Acute appendicitis (AA) is a common surgical problem. There were an estimated 17.7 million cases worldwide in 2019[1]. The diagnosis is guided by clinical assessment, laboratory investigations, radiological studies, and clinical scores and can often be challenging[2]. Hence, there is always a need to explore additional tools to aid in the diagnosis of this common disease.

White blood cell (WBC) count is a marker that is well-studied and known to be associated with AA. It forms part of the Alvarado score that is used to aid in diagnosing AA[3-6]. Absolute neutrophil count (ANC) has been found to be associated with AA[6]. Several recent studies have investigated the use of other complete blood count (CBC) parameters as new biomarkers in the diagnosis of AA with varying results. Absolute lymphocyte count (ALC), particularly lymphocytopenia, has been reported to be associated with gangrenous AA[7]. Platelets play a role in inflammation. Accordingly, platelet indices including platelet (PLT) count, platelet size distribution or platelet distribution width (PDW), and mean platelet volume (MPV) have been studied and found to be associated with various inflammatory conditions. For example, MPV was found to be altered in several inflammatory conditions, including AA. A systematic review reported high MPV values in complicated AA and low values in non-complicated cases[8,9]. Red blood cell distribution width (RDW) is another marker that has been found to be associated with inflammatory pathologies in addition to AA[10,11]. Ratios including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are recognized as novel inflammatory markers in several conditions[12]. Their role in the diagnosis of AA and assessing its severity has been studied with promising results[13,14].

The aim of this study is to evaluate the utilization of the aforementioned CBC parameters in the detection of simple and complicated AA in children and adults.

Method

Study design

This is a retrospective, analytic, cross-sectional study on cases operated for AA between June 1, 2020, and February 28, 2021, in Salmaniya Medical Complex, Kingdom of Bahrain. Data included patient demographics (age and gender), laboratory parameters, and histopathological evaluation. CBC parameters included are as follows (with laboratory reference range): WBC count (normal: 3.6-9.6 × 10^9/L), RDW (11.6-13.7 fL), PLT count (150-400 × 10^9/L), MPV (8-11.5 fL), PDW (46-50%), ANC (2.3-8.1 × 10^9/L), and ALC (not defined). Investigations were obtained preoperatively at the time of presentation to the emergency department. NLR and PLR were calculated. Data were collected from the National Health Information System (I-SEHA) using current procedural terminology (CPT®) codes from operating theater logs and pathology department records.

Table 1. Excluded cases

Exclusion criteria	n	%
Presence of another significant intraoperative pathology that is the likely cause of abdominal pain (in which the appendix was included with another specimen)	8	1.36
Other pathologies within the appendix (polyp, mucocele, neuroendocrine tumor)	6	1.02
Incomplete laboratory parameters	4	0.68
Normal appendix	0	0.00
Total number of patients	18	3.07

Participants

Patients of all ages, both males and females, were included in the study. Exclusion criteria included other pathologies within the appendix, the presence of another significant intraoperative pathology that is the likely cause of abdominal pain, normal appendix, and incomplete laboratory parameters (Table 1).

Patients were initially divided into two groups according to age: adults and pediatrics. They were further divided into subgroups according to histopathological diagnosis and operation records: complicated (including perforated, gangrenous by histopathology, early mass-forming or mass-forming appendicitis, and presence of abscess or pus) and simple (any case that does not satisfy the above criteria, also including fibrous obliteration of the lumen and reactive lymphoid hyperplasia) AA.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS®)

Table 2. Descriptive statistics of the study groups

Parameter	Group I: adults			Group II: pediatrics		
Cases (%)	511 (89.81%)			58 (10.19%)		
Histopathological diagnosis	**Complicated AA (%)**	**Simple AA (%)**	**p**	**Complicated AA (%)**	**Simple AA (%)**	**p**
	124 (86.11%)	387 (91.06%)		20 (13.89%)	38 (8.94%)	
Age (years)†	35.63 ± 10.97 (15-62)‡	31.30 ± 9.66 (14-75)‡	0.000	8.85 ± 3.18 (4-13)‡	9.82 ± 2.41 (4-13)‡	0.303
Male (%)	101 (81.45%)	288 (74.42%)	0.110	14 (70.00%)	23 (60.53%)	0.479
Female (%)	23 (18.55%)	99 (25.58%)		6 (30.00%)	15 (39.47%)	
WBC (× 10^9/L)	13.44§	11.48§	0.000	13.38 ± 3.01†	11.85 ± 4.57†	0.183
RDW (fL)	13.65§	13.80§	0.218	13.55§	13.95§	0.226
PLT (× 10^9/L)	227.50§	238§	0.090	259.50§	266.50§	0.851
MPV (fL)	9.20§	8.90§	0.095	8.56 ± 1.93†	8.75 ± 1.59†	0.685
PDW (%)	42.30§	42.70§	0.814	36.42 ± 10.33†	37.10 ± 9.44†	0.800
ANC (× 10^9/L)	11.00§	9.00§	0.000	10.80 ± 2.90†	9.68 ± 4.62†	0.330
ALC (× 10^9/L)	1.36§	1.74§	0.000	1.27§	1.29§	0.819
NLR	7.77§	4.76§	0.000	9.02§	7.26§	0.659
PLR	158.78§	140.65§	0.028	214.20§	202.37§	0.545

†Mean ± SD.
‡: (min-max).
§Median.
AA: acute appendicitis; WBC: white blood cells; RDW: red blood cell distribution width; PLT: platelets; MPV: mean platelet volume; PDW: platelet size distribution or platelet distribution width; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

software for Windows, version 28.0, and Microsoft Excel for Mac, version 16.54. Categorical variables were reported as the absolute frequency and percentage (%). Shapiro–Wilk test and histograms with Bell curves were used to test for normality of data distribution. Normally distributed continuous variables were reported as the mean ± standard deviation (SD) and compared using the independent sample t-test while continuous variables with deviation from normality were reported as the median and compared using Mann–Whitney U test. Receiver operating characteristic (ROC) curves were created to measure the ability of CBC parameters to distinguish complicated cases. The area under the curve (AUC) and the optimal cutoff point for significant parameters were determined. AUC ranges were classified as: 0.9-1.0 (Excellent), 0.8-0.9 (Good), 0.7-0.8 (Fair), 0.6-0.7 (Poor), and 0.5-0.6 (Failure). Sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated. A significance level of probability (p) of less than 0.05 was considered statistically significant.

Ethical consideration

This study was approved by the Secondary Health Care Research Committee, Kingdom of Bahrain.

Results

A total of 569 patients were included in the study. The age range of the patient population was from 4 to 75 years. The majority of the patients were males; 426 (74.87%) and adults; 511 (89.81%). One hundred forty-four (25.31%) patients were diagnosed with complicated AA while 425 (74.69%) patients were diagnosed with simple AA. Descriptive data of all patients and a comparison of CBC parameters are presented in Table 2. A statistically significant difference was observed between adult patients with complicated and simple AA in WBC, ANC, ALC, NLR, and PLR values. None of the CBC parameters was found to be statistically significant in pediatric patients.

Table 3. Significant CBC parameters in adults

CBC parameter	Proposed optimal cutoff point	AUC	p	Sensitivity (%)	Specificity (%)	LR+	LR−
WBC (× 10^9/L)	12.46	0.632	0.000	58.9	58.9	1.43	0.70
ANC (× 10^9/L)	9.50	0.652	0.000	65.3	55.3	1.46	0.63
ALC (× 10^9/L)†	1.55	0.613	0.000	58.1	58.9	1.41	0.71
NLR	6.52	0.651	0.000	62.1	60.7	1.58	0.62
PLR	146.16	0.566	0.028	51.6	52.2	1.08	0.93

†For small values.
CBC: complete blood count; AUC: area under the curve; LR+: positive likelihood ratio; LR-: negative likelihood ratio; WBC: white blood cells; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

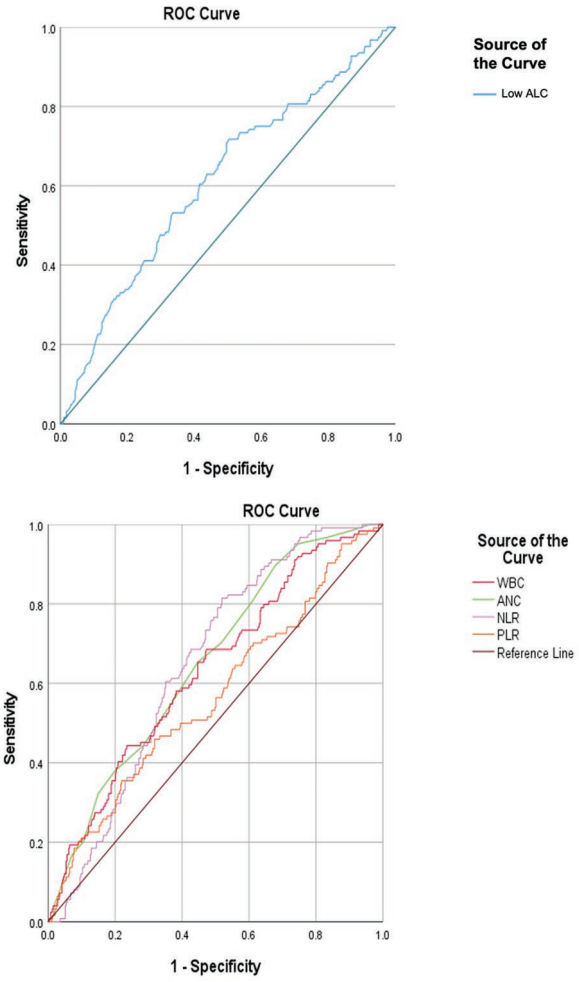

Figure 1. *ROC curves for significant CBC parameters in adults. ROC: receiver operating characteristic; ALC: absolute lymphocyte count; WBC: white blood cells; ANC: absolute neutrophil count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.*

The ability of CBC parameters to distinguish the two groups was evaluated by generating ROC curves for the significant parameters in adults. AUC ranges were considered poor for WBC, ANC, NLR and low ALC or lymphocytopenia and a failure for PLR. AUC was found to be statistically significant for all parameters (Table 3 and Fig. 1).

Discussion

The diagnosis of AA can often be challenging and hence, there is a need to explore biomarkers to aid in the diagnosis of this common disease and detect complicated cases early. CBC is a widely available and routinely requested test for patients presenting with abdominal pain and suspected AA.

Leukocytosis refers to elevated WBC count and is associated with acute and chronic inflammatory stressors. The specific value of elevation varies between laboratories depending on their defined reference ranges[15]. In this study, the means and medians of WBC count were found to be high among all patient groups. Higher values were observed in patients in the complicated AA group. At a cutoff point of 12.46, it has a sensitivity and specificity of 58.9%, LR+ of 1.43, and LR- of 0.70 (AUC = 0.632) in distinguishing cases of complicated and simple AA in adult patients. In a study by Yang et al., it was reported that elevated WBC count was found to be associated with a higher risk of perforation in children[4]. However, in the present study, a statistically significant difference was found among adult patients of the two groups with regard to elevated WBC counts but not in pediatrics. Similarly, Peksöz et al. reported WBC count as an important factor in predicting complicated AA[16]. On the other hand, Sevinç et al. have found that WBC count is not associated with perforated cases in adults[3].

RDW is a part of the CBC panel and is a measure of variation in the size of red blood cells or anisocytosis[17]. There is a recent increased interest in RDW as an inflammatory biomarker. It has been found to be

elevated in several conditions including post-operative complications in surgical patients, active systemic lupus erythematosus, viral infections, cardiovascular, and cerebrovascular diseases, among many others[10,18-20]. The medians of RDW were found to be high in all groups except for pediatrics with complicated AA (upper limit of normal). No statistically significant difference was found among the groups for the detection of complicated AA. A study conducted on children found that RDW has no diagnostic value in predicting the severity of AA[21]. Maghsoudi et al. as well did not favor the use of RDW when studied on patients with negative and positive appendectomies[22]. However, two other studies have found that RDW was significantly higher in complicated AA cases[11,23]. Moreover, a systematic review and meta-analysis of 5,222 cases revealed no statistical significance in RDW among cases with AA and others[24].

Platelets play a role in inflammation, including recognizing microorganisms and facilitating immune responses[8]. Platelet indices were found to be altered in several medical and surgical conditions, including diabetes mellitus, active Crohn's disease, acute cholecystitis, and AA, among others[9]. Platelet indices were investigated in the present study in relation to AA, namely, PLT count, MPV, and PDW. The means and medians of PLT count and MPV were found to be within normal ranges among all patients, while PDW was found to be lower than normal. No statistically significant difference was observed among the groups. In a meta-analysis including nine studies on the role of platelet indices in the diagnosis of AA and prediction of its complications, it was concluded that low MPV was useful in the diagnosis of AA but could not predict its complications[25].

Neutrophils are considered the first line of defense by the innate immune system as they destroy microorganisms and also act as mediators of inflammation[26]. Together with the WBC count, they are the earliest indicators of inflammation in AA but are not specific to it[27]. In this study, the values of ANC were found to be higher than normal in all groups and to be statistically significant among adult patients but not in pediatrics. Higher values were detected in patients in the complicated AA group. At a cutoff point of 9.50, it has a sensitivity of 65.3%, specificity of 55.3%, LR+ of 1.46, and LR- of 0.63 (AUC = 0.652) in distinguishing cases of complicated and simple AA in adults. It is well known that elevated neutrophil counts or neutrophilia is correlated with AA and forms part of the Alvarado score that is used to aid in diagnosing AA, along with high WBC count[5,6]. In addition to that, neutrophilia was found in some studies to be useful in determining the severity of AA in adolescents and adults[16]. Moreover, in pediatrics, neutrophil percentage was reported to be useful in detecting perforated AA by Yang et al.[4]

Lymphocytopenia associated with gangrenous AA has been reported in the literature[7]. In the present study, reduced ALC values were used in the comparison between complicated and simple AA groups with a statistically significant difference. When the cutoff point was set at 1.55, low ALC was found to have a sensitivity of 58.1%, specificity of 58.9%, LR+ of 1.41, and LR- of 0.71 (AUC = 0.613) in adults. In a study by Platon et al., leukocytosis, together with lymphocytopenia, was associated with significant pathology on computed tomography (CT) scan of the abdomen, including one case of AA out of 71 cases with other pathologies[28].

There is a growing interest in novel CBC-based inflammatory indices or ratios including NLR and PLR as markers and prognostic factors in a number of disease conditions[12]. Their role in AA and the detection of complicated cases was explored in the present study. The values of NLR were found to be higher than normal with a statistically significant difference between the two age groups. At a cutoff point of 6.52, it has a sensitivity of 62.1%, specificity of 60.7%, LR+ of 1.58, and LR- of 0.62 (AUC = 0.651) in distinguishing cases of complicated and simple AA in adults. This is in line with other studies that reported NLR as a useful biomarker in predicting complicated AA. NLR was useful in diagnosing AA and predicting its severity by Peksöz et al. Furthermore, Sevinç et al. observed that NLR >3.0 was significantly associated with a definite diagnosis of AA in suspected cases while in confirmed cases, NLR >4.8 was significantly associated with perforated AA[3].

Finally, the levels of PLR were found to be higher than normal with a statistically significant difference between the two age groups. At a cutoff point of 146.16, it has a sensitivity of 51.6%, specificity of 52.2%, LR+ of 1.08, and LR- of 0.93 (AUC = 0.566) in distinguishing cases of complicated and simple AA in adults. PLR has been reported in the literature to be a useful marker in the diagnosis of AA and its complications. Celik et al. evaluated the role of both NLR and PLR in 334 pediatric patients who underwent surgery for AA. Subjects with higher NLR and PLR values were more likely to

develop complicated AA[29]. Comparably, Pehlivanlı et al. found that patients with normal appendix on pathological assessment had lower values of NLR and PLR compared to those with AA and perforated AA[30]. In a systematic review and meta-analysis, significant increase in PLR values was detected in patients with AA[13]. Additional studies are required to confirm and support the above reported findings and to establish the appropriate cutoff values in relation to AA.

There are several limitations to this study. The retrospective design of the study meant that some data could not be retrieved due to documentation factors. Patients who were diagnosed with AA but were not operated on for any reason were not included in the study. Timing of symptom onset to presentation and blood sample extraction could influence the results.

Conclusion

There is no specific biomarker for the diagnosis of AA and its complications. CBC is a comprehensive and widely available test. WBC, ANC, ALC, NLR, and PLR can be useful parameters in the discrimination between complicated and simple AA in adults. PLR, however, was found to be the least predictive among these parameters.

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Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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