

The Role of Inflammatory Ratios: Neutrophils to Lymphocytes Ratio, Platelet to Lymphocyte Ratio, and C-reactive Protein to Platelets Ratio in Diagnosis of Acute Appendicitis and Its Severity

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ABSTRACT

Background: Acute appendicitis is one of the most common surgical emergencies encountered in clinical practice. New inflammatory markers, named neutrophils/lymphocytes ratio (NLR), platelet/ lymphocyte ratio (PLR), and C-reactive protein /platelets ratio (CRP/PLT), have been implemented recently in clinical practice for the diagnosis and assessment prognosis of many conditions like malignancies, cardiovascular diseases, and end-stage renal disease. However, none of those markers have been well studied in acute appendicitis. In this article, the role of NLR, PLR, and CRP/PLT in diagnosing acute appendicitis and the correlation of their values to the severity of the disease has been studied. **Methods:** A retrospective study was conducted on 346 patients of all ages and genders who were admitted to Al-Makassed Islamic Charitable Hospital in Palestine for three years, from 2018 to 2021, with the diagnosis of acute appendicitis. Complete blood count and CRP were reviewed. NLR, PLR, and CRP/PLT ratios were calculated and compared between divided groups according to the age and severity of the disease. A T-test was used for the analysis of the results. **Results:** Neither NLR nor PLR showed a statistically significant association with the diagnosis of acute appendicitis or prediction of its severity. Regarding CRP/PLT ratio, it was 0.202 ± 0.431 in the pediatric group who were diagnosed with acute appendicitis and 0.039 ± 0.061 in the pediatric group who had normal appendix (P value of 0.029), while it was 0.194 ± 0.316 in adult appendicitis group and 0.107 ± 0.132 in an adult group with normal appendix (P value of 0.567). The CRP/PLT ratio in the pediatric group who had uncomplicated acute appendicitis was 0.186 ± 0.452 compared to 0.305 ± 0.323 in complicated appendicitis (P value of 0.001), while the ratio in the adult simple appendicitis group was 0.154 ± 0.293 compared to complicated cases that were 0.426 ± 0.345 (P value of <0.001). **Conclusion:** Based on a complete analysis of the novel inflammatory markers in the two age groups, pediatrics, and adults, in both simple and complicated acute appendicitis, only the CRP/PLT ratio showed high accuracy for diagnosis of acute appendicitis in pediatrics and distinguishing complicated cases from simple ones in both pediatric and adult age groups.

Keywords: Appendicitis, Neutrophils to lymphocytes ratio, Platelet to lymphocytes ratio, C-reactive protein to platelets ratio, severity.

INTRODUCTION

Acute appendicitis is one of the most common abdominal surgical emergencies affecting 6-7 % of the population, with a lifetime incidence of 8.6% in men and 6.7% in women [1, 2]. There is a slight male predominance of 3:2 in teenagers. In adults, the incidence of the disease is approximately 1.4 times greater in men [3, 1]. Despite the common practice of diagnosing acute appendicitis, some cases remain challenging as pa-

tients may present with non-specific symptoms and do not exhibit typical clinical examination. For this reason, ongoing research has been implemented to find suitable laboratory markers to help diagnose acute appendicitis and predict the disease's severity at the presentation time [4, 5].

The diagnosis of acute appendicitis and decision for operation can result in appendectomy with a normal appendix; a study of 441 patients conducted in Saudi Arabia proved

that a normal appendix could be encountered in about 9% of appendectomies done for presumably acute appendicitis, and it reached up to 15% of the cases elsewhere [6, 4]. Other studies reported acceptable rates of about 10% in males and 20% in females [2]. This makes the need to reach an accurate diagnosis before undergoing the operation crucial to decrease the morbidity of the patients and avoid unnecessary surgical intervention.

Although acute appendicitis is still considered mainly a clinical diagnosis, some cases remain challenging for physicians as symptoms may vary depending on the anatomical variations of the appendix and severity of the inflammatory process, thus increasing the percentage of negative and complicated appendectomies. In order to get an early diagnosis of appendicitis, researchers began searching for novel lab parameters that change with the inflammatory process of the appendix to anticipate the severity of the disease, which in turn allowed for quick intervention [7].

One of the most helpful laboratory tests for diagnosing acute appendicitis is the elevation of white blood cells (WBC) with the left shift. It has been reported that leukocytosis is a sensitive marker for diagnosis, but it is not specific and has low value, especially in the presence of atypical symptoms in about 40% of people. In addition to WBCs, many parameters include C-reactive protein (CRP) and procalcitonin [8, 9].

The CBC and CRP are cheap, easy to use, interrupt, and widely available tests [8]. They are still the initial investigations used in the diagnosis alongside the imaging studies such as abdominal ultrasound and abdominal computed tomography (CT) scan with intravenous (IV) contrast which is the imaging modality of choice despite radiation exposure concerns in pediatrics and females groups [10, 5]. Many scoring systems were established and are still used to aid the diagnosis, such as Alvarado and Appendicitis inflammatory response scores [11, 12].

This study aims to apply the novel inflammatory markers, Neutrophils to lymphocytes ratio, Platelets to lymphocytes, and CRP/Platelet ratio in the diagnosis of acute

appendicitis and in predicting its severity in adults and children.

MATERIAL AND METHODS

Subjects

A retrospective study was conducted on 346 patients of all ages and genders diagnosed with acute appendicitis and admitted to Al-Makassed Hospital in Jerusalem for three years, from January 2018 to December 2021. Data were retrospectively collected from the patient's medical records, including age, gender, absolute neutrophils count, absolute lymphocytes count, platelet count, CRP value, pre-operative imaging findings, intra-operative findings, and post-operative histopathology reports. The inclusion criteria were all subjects diagnosed with acute appendicitis based on history, clinical examination, and who underwent the previously described laboratory and imaging investigations. On the other hand, the exclusion criteria were incomplete medical records of any studied data and appendectomies that were done incidentally during other procedures.

Measures

The diagnosis of acute appendicitis at Al-Makassed hospital was established according to clinical manifestations, physical examination, laboratory findings, and abdominal ultrasound or abdomen CT scan with IV contrast results. Histopathological findings determined the final diagnosis. All these investigations were done at the Al-Makassed hospital Laboratory and radiology Department. Nearly all samples were analyzed within 2 hours of specimen collection. The complete blood count (CBC) was tested at admission with an automated hematology analyzer (Sysmex, XP-300, Japan), while the CRP was tested by an automated device (Cobas, c-111, Switzerland).

The hospital policy for differentiation between adult and pediatric groups is according to age cut point, meaning that pediatric patients are those who are 14 years old or less. In comparison, patients are considered adults if they are above 14 years old, which was also used as a parameter for differentiation between the two groups in other studies, such as an African study on 2020[13]. The diagnosed appendicitis cases were subdivided

into uncomplicated appendicitis (including acute suppurative appendicitis) group and complicated appendicitis (including acute gangrenous appendicitis, perforated cases, abscess, and generalized peritonitis) group [14].

Laboratory data were collected, including neutrophil and lymphocyte counts. The neutrophil/lymphocyte ratio (NLR) was calculated by dividing the neutrophil by lymphocyte counts (Absolute neutrophils count /absolute lymphocytes count) [15]. The Platelet's/lymphocyte ratio (PLR) was calculated by dividing the platelets by lymphocyte counts (Platelet count /absolute lymphocytes count). We calculated the CRP /Platelets ratio (CRP/PLT) by dividing the CRP by platelet counts (CRP/ Platelet count).

Statistical analysis

All data were entered and analyzed using the Statistical Package for Social Sciences version 22 (SPSS-22). Descriptive statistical analysis was used to determine the Mean \pm SD for numerical variables and frequency and percentage for categorical variables. An Independent t-Test was used to analyze the differences between groups. The difference was considered to be statistically significant at $P < 0.05$. The Ethical Committee approved this study of our institution (IRB) at Al-Makassed Hospital, Jerusalem (Reference No.2022/112/3).

RESULTS

Patients' characteristics and pre-operative findings:

The mean age of the patient was 23.2 years. Almost one-third (33.2%) were children (≤ 14 years), and 66.8% were adults, with male predominance (57.2%). Regarding the pre-operative laboratory results, the mean neutrophils, lymphocytes, platelets, and CRP counts were 11.5 ± 5.1 , 5.5 ± 40.7 , 262.9 ± 75.6 , and 42.9 ± 66.4 , respectively.

Most of the patients (70.5%) were diagnosed with acute appendicitis by ultrasound (AA-US), while only 15% were diagnosed according to CT scan (AA-CT) findings. A minority (1.4% and 0.9%) were diagnosed with acute complicated appendicitis on ultrasound (ACA-US) and CT scan (ACA-CT), respectively. In about 12.1% of the cases, the imaging assessment for the presence of an inflamed appendix was not possible either due to patient-related causes such as obesity or due to operator-dependent issues in the evaluation of the performed images, so the decision for surgery was based on patient history, clinical findings, and laboratory results. Furthermore, most of the patients (87%) were found to have acute suppurative appendicitis (ASA) intraoperatively, while 13% had complicated appendicitis, including gangrenous ones (AGA) (3.5%) (**Table 1**).

Table (1): Socio-demographic features, pre- and intra-operative findings of the patients (n= 346).

Characteristics	Frequency (%)	Mean \pm SD
Age		23.2 \pm 14.6
Children (≤ 14)	115 (33.2%)	
Adults (>14 years)	231 (66.8%)	
Gender		
Male	198 (57.2%)	
Female	148 (42.8%)	
Laboratory Results		
Neutrophils		11.5 \pm 5.1
Lymphocytes		5.5 \pm 40.7
Platelets		262.9 \pm 75.6
CRP		42.9 \pm 66.4
Pre-operative Imaging		
AA_US	244 (70.5%)	
AA-CT	52 (15.0%)	

Characteristics	Frequency (%)	Mean \pm SD
ACA-US	5 (1.4%)	
ACA-CT	3 (0.9%)	
Not seen	42 (12.1%)	
Intra-operative findings		
ASA	301 (87.0%)	
AGA	12 (3.5%)	
ACSA	33 (9.5%)	

Pathological results

The pathological findings of the studied specimens were as follow; 94.5% of the patient had appendicitis, divided into 81.2%

with acute suppurative appendicitis, 2% were gangrenous, and 11.3% were complicated suppurative, while 5.5% showed normal appendix (**Figure 1**).

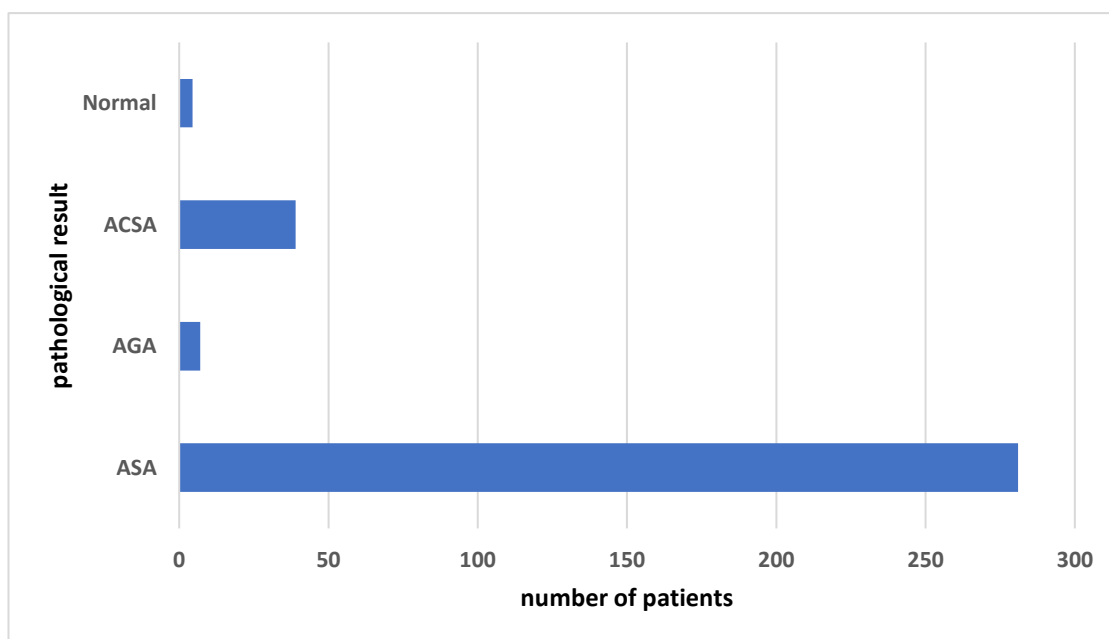


Figure (1): The histopathological results of excised appendix specimens (n= 346).

Appendicitis diagnosis and pathological severity to pre-operative laboratory results:

In the pediatric population, the mean NLR of patients diagnosed with appendicitis was 7.96 ± 5.67 compared to 7.42 ± 4.60 with a normal appendix. The mean PLR was 176.5 ± 102.3 in patients with appendicitis and 165.1 ± 63.4 in those with normal appendixes. Finally, the mean of CRP/PLT was 0.201 ± 0.431 in a patient with appendicitis compared to 0.039 ± 0.061 in a normal appendix. A statistically significant difference was found only in the CRP/PLT ratio between the patients with and without appendicitis in the pediatric group ($P = 0.029$).

In the adult group, the mean NLR, PLR, and CRP/PLT ratios of the patient with ap-

pendicitis were 7.61 ± 7.34 , 159.6 ± 113.2 , and 0.194 ± 0.316 , respectively, while in the patient with a normal appendix, were 5.85 ± 4.35 , 137.2 ± 100.5 and 0.107 ± 0.132 , respectively. After statistical analysis, none of the ratios showed a significant difference between the two groups ($P = 0.467$, $P = 0.279$, and $P = 0.567$).

The pediatric group with confirmed appendicitis divided these ratios into simple and complicated groups and compared them. The mean of NLR in simple vs. complicated appendicitis was 7.49 ± 5.73 vs. 8.08 ± 5.48 , PLR was 176.3 ± 103.2 vs. 178.0 ± 99.3 , and CRP/PLT ratio was 0.186 ± 0.452 vs. 0.305 ± 0.323 . Only CRP/PLT ratio showed a statistically significant difference in the diag-

nosis of severity of appendicitis in pediatrics ($P= 0.001$).

These ratios were also compared in adults with confirmed appendicitis. The mean of NLR in simple vs. complicated appendicitis was 7.08 ± 6.07 vs. 10.72 ± 12.11 , PLR was $154.6\pm 99.6.2$ vs. 188.4 ± 171.5 , and CRP/PLT

ratio was 0.154 ± 0.293 vs. 0.426 ± 0.345 . Moreover, as in the pediatric group, only CRP/PLT ratio has a great statistically significant difference in the diagnosis of severity of appendicitis in adults ($P= 0.000$) (Table 2).

Table (2): Diagnosis of appendicitis and pathological severity with pre-operative laboratory results.

Lab. ratio	Pediatrics			Adults		
Presence of appendicitis	Yes (mean±SD)	No (mean±SD)	P value*	Yes (mean±SD)	No (mean±SD)	P value*
NLR	7.96 ± 5.7	7.425 ± 4.602	0.953	7.61 ± 7.345	5.85 ± 4.3	0.467
PLR	176.5 ± 102.3	165.1 ± 63.4	0.888	159.6 ± 113.2	137.2 ± 100.5	0.279
CRP/PLT	0.20 ± 0.43	0.03 ± 0.06	0.029	0.194 ± 0.316	0.107 ± 0.132	0.567
Severity of appendicitis	Simple (mean±SD)	Complicated (mean±SD)	P value*	Simple (mean±SD)	Complicated (mean±SD)	P value*
NLR	7.492 ± 5.728	8.084 ± 5.482	0.848	7.081 ± 6.069	10.72 ± 12.11	0.238
PLR	176.3 ± 103.2	178.0 ± 99.32	0.993	154.6 ± 99.6	188.4 ± 171.5	0.731
CRP/PLT	0.186 ± 0.45	0.305 ± 0.32	0.001	0.154 ± 0.293	0.426 ± 0.345	0.000

*Independent t-test.

DISCUSSION

Diagnosis of acute appendicitis is not always easy. The decision between undergoing early surgery and watchful expectancy represents a severe dilemma for surgeons due to the disadvantages associated with each option. The conservative option is associated with a risk of higher complications rate if failed and requires more hospitalization days, while surgery could be associated with negative appendectomy rates and the possible consequences of the post-recovery period. For this reason, an accurate diagnosis of acute appendicitis and evaluation of its severity is vital.

Some studies were conducted to evaluate the accuracy of diagnosis and the severity of the disease. However, most of these studies were done on the pediatric population only. The advantage of our study is that it included all ages and divided the patients into pediatric and adult groups. Few studies had used the same age group and division, including one in Ankara (Turkey) in the period between 2005 & 2013 [8]. In our article, as described in previous studies, acute appendicitis had been associated with male predominance [2, 8, 16, 17].

After pathological analysis of the specimens for definitive diagnosis, 5.5% were normal, which is within the range of the global percentage (<10%) of accepted negative appendectomies, and this percentage is globally accepted to prevent the more severe complications of missing acute appendicitis [2]. In this article, the analysis showed that NLR is not a good predictor for diagnosing acute appendicitis in pediatrics and adults.

Depending on the post-operative pathologic evaluation of the appendix, the sample was divided into simple and complicated appendicitis. The NLR was insignificant in predicting appendicitis severity in both age groups. This result corresponds with a study conducted in a Korean systemic review and meta-analysis on 2021, which concluded that NLR can be used only in source-limited settings and should be used cautiously when used alone to diagnose acute appendicitis [10]. However, some other studies showed that NLR can be considered as an inflammatory marker equivalent to white cell counts and can help to guide towards the diagnosis of acute appendicitis, one of these studies was the Turkish study which was conducted between 2013 and 2015 that studied NLR in

acute appendicitis cases compared to normal appendix (P value <0.0001) [18]. Another Turkish study showed similar results with a p-value of 0.001 [19]. On 2022, a British study also stated that NLR could be used as a predictor in the diagnosis of acute appendicitis (P value of <0.001) [16].

It has also been reported that changes in platelet counts are involved in the inflammatory process. It is a simple, non-invasive, and cost-effective inflammatory marker easily obtained from the complete blood count. For this reason, PLR was studied in our article. However, it showed no significance in diagnosing acute appendicitis in adults and pediatrics groups or predicting its severity. The results of our study match with a Turkish study that was conducted on 2020 and revealed that PLR value alone is insufficient in the diagnosis of acute appendicitis, and normal PLR values alone cannot exclude acute appendicitis (P value of 0.382) [17]. Despite that, some other studies in the US and Turkey showed that PLR had significant value in the diagnosis of appendicitis, and it was a strong predictor of severity [7, 20, and 21].

Regarding CRP/PLT ratio, the available information is insufficient to make statements about its role in predicting the presence and severity of acute appendicitis; the data studied recently only proved the role of CRP in differentiation between simple and complex appendicitis but does not use its relation to platelet count in the diagnosis and assessment of severity [22]. In this article, the analysis of the collected data showed a strong correlation between the presence of acute appendicitis and the CRP/PLT ratio in the pediatric age group (P value 0.029) but not in adults (P value 0.567). Moreover, the ratio was valuable in predicting the severity of acute appendicitis in both pediatrics and adults (P values 0.001 and 0.000, respectively). Therefore, the CRP/PLT ratio is recommended in the emergency department for diagnosing acute appendicitis in pediatrics and assessing its severity in adults and pediatrics as it is easily applicable.

CONCLUSION

This study demonstrated that CRP/PLT ratio is significant in diagnosing acute appendicitis in a pediatric age group but not

adults. This ratio is recommended in the emergency department for diagnosing acute appendicitis in pediatrics and assessing its severity in adults and pediatrics as it is easily applicable. On the contrary, NLR and PLR showed no significant association with the diagnosis and assessment of the severity of acute appendicitis in both age groups, so their role is limited in such settings.

Author's contribution

Motaz S Sulaiman: conceptualization, writing-original draft, investigation, project administration, resources, software, supervision, validation, visualization, and writing review & editing. **Abbas W Abbas, Raed Al-Zyoud, Khaled Al-Shawa, Ahmad K Hodali:** Data collection, investigation. **Mohammad M Maree, Bashar T Jaber, Haitham K Alhasan:** validation, visualization. **Zaher Nazzal, Haneen H Nuairat:** conceptualization, data curation, investigation, methodology, project administration, and writing review & editing. **Omar Abu Zaydeh:** project administration, supervision, validation, visualization.

Competing interests

The authors declare that there is no conflict of interest.

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Conflict of interest

The authors declare that they have no conflict of interest.

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