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RESEARCH ARTICLE

The Role of Basic Laboratory Parameters in Diagnosing Acute Appendicitis and Determining Disease Severity in the Elderly

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ABSTRACT

Aim: Acute appendicitis (AA) is the most common cause of acute abdomen in elderly patients. The aim was to investigate the role of basic laboratory parameters in diagnosing AA and determining disease severity.

Method: Elderly patients aged over 65 years who underwent appendectomy were included. The patients were divided into groups according to the severity of AA: group 1 (negative appendectomy) and group 2 (AA). Group 2 was sub-divided into group 2a: uncomplicated appendicitis and group 2b: complicated appendicitis. Differences in basic laboratory parameters between the groups were evaluated statistically.

Results: One hundred and forty three elderly patients were examined. Sixty (41.95%) were male and the mean age of the whole cohort was 69.69±6.34 years (range: 65-104 years). Patient numbers in the groups were: group 1 (n=15) (10.5%); group 2a (n=79) (55.2%) and group 2b n=49 (34.3%). As the time of admission to the hospital increases, the severity of the disease increases (p<0.001). Group 2b had higher length of stay (p=0.007) and complication rates (p=0.042). When comparing group 1 with group 2, the most sensitive test (88%) was mean platelet volume, while the most specific test was bilirubin (85%). For distinguishing group 2a and group 2b, the most sensitive test (72%) was C-reactive protein (CRP) while the most specific test (82%) was platelet to lymphocyte ratio (PLR).

Conclusion: Preoperative laboratory parameters can be used as biomarkers to aid AA diagnosis in the elderly. Neutrophil to lymphocyte ration, PLR, red cell distribution width, CRP, and direct and total bilirubin levels may help identify complications in appendicitis.

Keywords: Geriatric patients, acute appendicitis, morbidity, laboratory parameters

Introduction

One of the most common causes of acute abdomen, acute appendicitis (AA), is caused by inflammation of the appendix. It is the most common condition that requires emergency surgery and has an incidence of about 7-10% throughout life.[1,2] While generally thought of as a condition affecting young people, the incidence of AA has been increasing in the elderly with increased life expectancy.[3] Abdominal pain constitutes the most common complaint for geriatric patients who present to the emergency department, with nearly 20% suffering from AA. In geriatric patients, emergency appendectomy is the third most common reason for abdominal surgery.[4,5]

The diagnosis of AA includes the use of anamnesis, physical examination, laboratory tests, and radiologic methods.[6] Classical appendicitis findings, such as right lower abdominal pain and tenderness, leukocytosis, and fever, are seen in only 26% of elderly patients.[2,7] Thus, it is difficult to diagnose AA in the elderly population. Geriatric patients undergo a number of physiological changes and in this patient group, clinical symptoms and signs are also weaker and atypical. Patients tend to present late to the emergency department, leading to delayed diagnosis and treatment. Elderly patients have a worse prognosis and higher complication rates compared to young patients.[2,3,8]

Moreover, elderly patients are likely to have more comorbid diseases, so that morbidity and mortality rates are also

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increased. Hence, early diagnosis and appropriate surgical intervention are vital for elderly patients.[8,9] Due to the greater unreliability of classical symptoms and findings, a hesitation in using advanced imaging methods for initial diagnosis, and the potential difficulty in accessing more informative imaging techniques particularly in rural regions, basic laboratory tests gain greater importance. These tests are simple, inexpensive, and easily accessible in almost all health institutions, providing information on biomarkers with an acceptable diagnostic value.[10] Although studies about this topic have increased recently, there is limited research on the diagnostic efficiency of laboratory parameters in geriatric AA.[1,9]

The aim of this study was to analyze elderly patients operated with the diagnosis of AA and to investigate the predictive value of basic preoperative laboratory parameters in diagnosing AA and determining disease severity.

Materials and Methods

Approval was obtained from the Ethics Committee of Erzurum Regional Training and Research Hospital (approval number: 2020/13-146). Between January 2015 and August 2020 a total of 3,856 adult patients aged over 18 years were operated for the diagnosis of AA. The clinical, demographic and laboratory data of patients aged over 65 years were extracted and retrospectively analyzed. Exclusion criteria were patients in whom blood parameters were affected by causes other than AA, including blood results not available, malignancy, multiple comorbid diseases and other surgical pathology.

Data items included patient sex, age, time from symptom onset to admission, comorbidities, preoperative blood results, preoperative images, type of anesthesia, type of surgery, length of hospital stay, complication status, and histopathological results for appendectomy materials which were obtained from the electronic hospital records. The patients were divided into two main groups (group 1 and group 2) based on the results of their appendix histopathology. Then group 2 was further divided into two subgroups (group 2a, b).

- **Group 1** (normal appendix, lymphoid hyperplasia, obliterative appendix) were evaluated as normal (negative appendectomy),
- **Group 2** (AA),
- **Group 2a** (phlegmonous appendicitis, catarrhal appendicitis, and suppurative appendicitis) were evaluated as non-complicated appendicitis.
- **Group 2b** (gangrenous appendicitis, perforated appendicitis, and plastron appendicitis) were evaluated as complicated appendicitis.

Statistical Analysis

Descriptive data were expressed as mean and standard deviation for the numerical variables and as number and percentages for the categorical variables. The distribution of the data was examined with histogram graphics. After examining the homogenity of the data, analysis was performed with One-Way ANOVA, Kruskal-Wallis tests. Tukey and Tamhane tests were used for post-hoc analysis. Chi-square test was used to compare two groups of categorical data. Receiver operating characteristic (ROC) curves were created to measure the ability of laboratory values to distinguish AA and complicated appendicitis status. The area under the curve (AUC) and cut-off value of each measurement were determined. Specificity, sensitivity and positive likely-hood ratio (LR+) cut-off values were calculated and evaluated together. A $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 23.0 (IBM Inc., Armonk, NY, USA).

Receiver Operating Characteristic Curve Analysis

ROC curves were created to examine the differentiation of laboratory parameters for pathology positivity. AUC and cut-off values of some parameters were determined and their sensitivity, specificity, and LR+ cut-off points were calculated. ROC analyses was carried out both for patients diagnosed with AA and those with normal appendix. Also, separate ROC analyses were performed for complicated and uncomplicated patients.

Results

Of the 160 elderly patients identified, 17 (10.65%) whose blood parameters were affected by causes other than AA were excluded: blood parameters not available (n=3); malignant pathology (n=3); patients with multiple comorbid diseases (n=5); and six with other surgical pathologies. Thus the final study included 143 (89.4%) of the patients aged over 65 years who had presented over a period of six years. Of the patients, 60 (41.95%) were male and 83 (58.05%) were female, with a mean age of 69.69±6.34 years (range: 65-104 years). More than two-thirds (69.9%) had a comorbid disease. The sample was divided into three groups. These were group 1 - negative appendectomy (n=15, 10.49%); group 2a - uncomplicated appendicitis (n=79, 55.24%); and group 2b - complicated appendicitis (n=49, 34.27%) (Table 1). There was no significant difference between the groups in terms of age, sex, or comorbid disease.

Time from the onset of abdominal pain to hospital admission was 1.67±1.04 days in group 1, 1.59±0.65 days in group 2a, and 3.33±1.28 days in group 2b, with a significant difference between the groups ($p<0.001$) (Table 1).

Table 1. Demographic and clinical features of the patients

Parameters	Group 1 (n=15)	Group 2a (n=79)	Group 2b (n=49)	p
Gender				0.110
- Male	8	27	25	-
- Female	7	52	24	-
Age (mean ± SD)	70.53±6.17	69.15±6.47	70.31±6.22	0.278
Comorbid disease				**0.518**
- Present	9	58	33	-
- Absent	6	21	16	-
Pre-hospital delay (day)	1.67±1.04	1.59±0.65	3.33±1.28	<0.001*
Length of stay (day)	3.13±2.56	3.34±2.01	6.59±5.93	0.007*
Postoperative complication				0.042
- Present	3	24	24	-
- Absent	12	55	25	-

*: Group 2b was significantly loner than other groups (group 1, group 2a) in post-hoc analysis. SD: Standard deviation

Table 2. The ROC analysis for group 1 and group 2

Parameters	Cut-off value	AUC (p)	Sensitivity (%)	Specificity (%)	LR+
CRP	1.23	0.668 (0.143)	77	57	1.81
WBC	8.97	0.722 (0.052)	85	57	1.98
Neutrophil	6.36	0.743 (0.033)	86	71	3.02
NLR	3.28	0.700 (0.080)	83	71	2.93
MPV	6.905	0.624 (0.277)	88	42	1.55
Total bilirubin	0.695	0.718 (0.057)	61	85	4.32
Direct bilirubin	0.235	0.716 (0.061)	65	85	4.58

AUC: Area under curve, CRP: C-reactive protein, WBC: White blood cell, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volüme, LR: Likelihood ratio, ROC: Receiver operating characteristic

Regarding advanced imaging methods, 77.6% of the patients were examined by ultrasonography (USG) and 69.9% by abdominal computed tomography (CT). CT was found to have a sensitivity of 77.7% and a specificity of 70%, while USG was found to have a sensitivity of 74.2% and a specificity of 18.2%.

The patients were evaluated for total bilirubin (TB), direct bilirubin (DB), C-reactive protein (CRP) and 11 hemogram subparameters. Only hemogram subparameters with a high diagnostic value were further analyzed. There were significant differences between the groups in terms of neutrophil, neutrophil to lymphocyte ratio (NLR), CRP, TB, and DB levels. White blood cell count (WBC), neutrophil count, NLR, mean platelet volume (MPV), TB, DB, and CRP levels were found to be markers with high diagnostic value for AA (Table 2, Figure 1).

NLR, Platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW), CRP, TB, and DB levels were found to be markers with high diagnostic value for differentiating between complicated and uncomplicated appendicitis (Table 3, Figure 2).

Of the patients, 2.8% were operated under spinal anesthesia and 97.2% under general anesthesia. One hundred and two of the operations (71.3%) were open (48.3% Mc Burney, 17.5% paramedian, 5.6% midline) and 42 (28.7%) were laparoscopic.

Mean length of hospital stay was 3.13±2.56 days in group 1, 3.34±2.01 days in group 2a, and 6.59±5.93 days in group 2b, with a significant difference between the groups ($p<0.05$) (Table 1). Postoperative complication rate was 35.7%. Complication rates in the groups were 20% in group 1, 30.4% in group 2a, and 48.9% in group 2b, with significant differences ($p<0.05$) (Table 1). No mortality was observed.

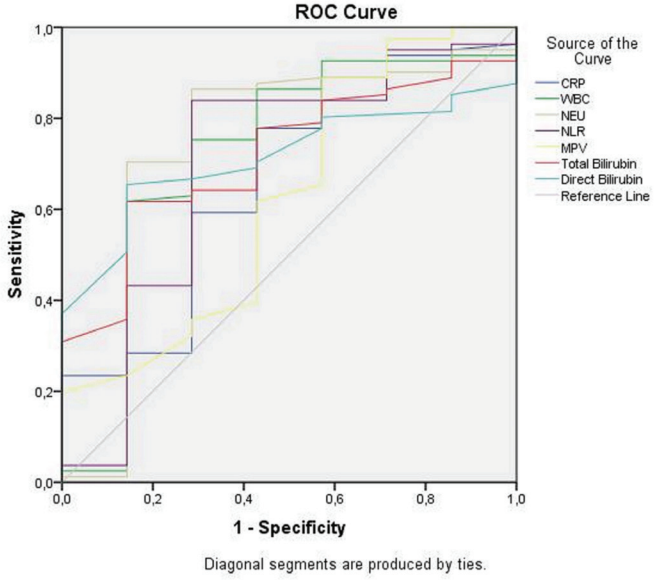

Figure 1. ROC analysis for normal appendix (group 1) and acute appendicitis (group 2)
ROC: Receiver operating characteristic, CRP: C-reactive protein, WBC: White blood cell count, NEU: Neutrophil, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume

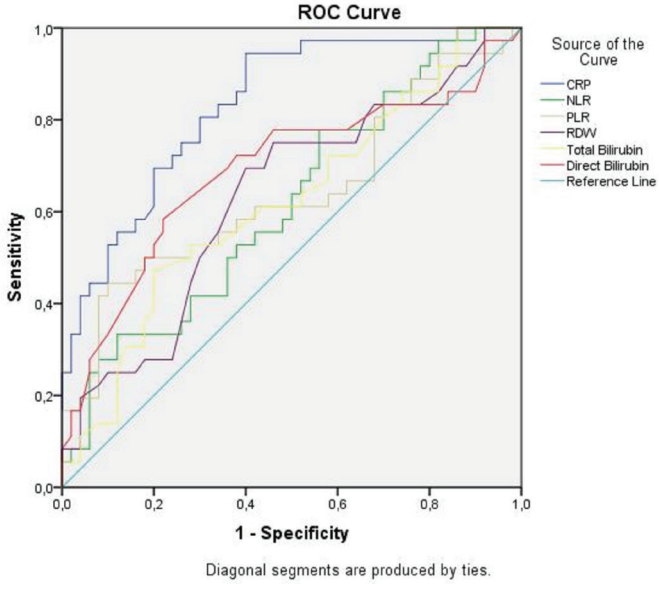

Figure 2. ROC analysis for uncomplicated and complicated appendicitis
ROC: Receiver operating characteristic, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width

Discussion

In elderly individuals, rebound sensitivity decreases due to atrophy of the abdominal muscles, along with increased pain threshold, due to conduction differences in the nervous system and certain changes in the detection and limitation of pain. Hence, the clinical picture tends to be atypical and less clear in the elderly.[11] The time from the onset of symptoms to hospital admission and surgery has also been reported to be higher in the elderly.[12,13] Delayed admission increases the risk of perforation of the appendix.

Perforation associated with AA is observed in 18-34% of the general population.[6] However, this rate increases up to 41-56.3% in geriatric patients.[2,3,9] Male sex, anorexia, fever ≥38 °C, and duration of pain before admission are risk factors for perforated appendicitis. The most important factor remains delayed admission to hospital.[3,6] Male patients are observed to be more reluctant for admission to hospital and therefore present later.[14] In the current study, the rate of complicated appendicitis was 34.27%, somewhat below the reported rates. Time to hospital admission remains the most important factor for perforation, with a mean of 3.3 days in the complicated appendicitis group. Gender played no role as a factor in the occurrence of complicated appendicitis.

Comorbid diseases tend to increase morbidity and mortality, although they have not been identified as a significant factor for perforation.[3] For elderly patients, the rate of comorbid disease is 43-60.7%.[3,6] The rate of comorbid disease in our sample was higher than the reports in the literature (69.9%), with no significant difference between the groups, suggesting that it was not a risk factor for complicated appendicitis.

There is single definitive clinical symptom, finding, laboratory test, or radiological method to diagnose AA. This proves even more complicated in geriatric patients.[15] Thus, studies have focused on easily accessible and cost-efficient markers with a high diagnostic value.[1,9] Surgeons have been interested in simple laboratory markers that can help diagnose AA and determine perforation status.[16]

Complete blood count (CBC) is an ideal marker for these properties.[10] WBC count is the most commonly used laboratory parameter for diagnosing AA.[16] One study reported that WBC had a cut-off value of 10.6, AUC: 0.66, a sensitivity of 71.2%, and a specificity of 68.2% for determining perforation in the elderly.[9] Here, WBC count

Table 3. The ROC analysis for group 2a and group 2b

Parameters	Cut-off value	AUC (p)	Sensitivity (%)	Specificity (%)	LR+
CRP	5.11	0.833 (<0.001)	72	76	3.00
NLR	5.10	0.617 (0.065)	72	44	1.28
PLR	190.62	0.641 (0.027)	50	82	2.77
RDW	13.15	0.634 (0.035)	69	60	1.73
Total bilirubin	0.87	0.621 (0.056)	52	72	1.88
Direct bilirubin	0.30	0.690 (0.003)	58	78	2.65

AUC: Area under curve, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width, LR: Likelihood ratio, ROC: Receiver operating characteristic

was found to be a marker with high sensitivity and low specificity for diagnosing AA (cut-off value: 8.97, AUC: 0.72, sensitivity 85%, specificity 57%). However, it was not found to be a biomarker with high diagnostic value for determining complicated appendicitis.

NLR has been used as a biomarker for morbidity, mortality, and survival in many disorders, including inflammatory and neoplastic diseases.[16-18] NLR has been demonstrated to be superior to other traditional infection markers, including WBC, neutrophil counts, and CRP, for determining AA severity.[9,19] Here, neutrophil count and NLR were determined to be biomarkers for diagnosing AA with similar diagnostic values, while only NLR was a significant biomarker for determining complicated appendicitis.

MPV is one of the routine CBC tests.[20] However, there are conflicting findings in the literature, some showing increased MPV in AA patients,[21] while others showing decreased MPV.[20,22] Similar to the literature, we obtained conflicting results on MPV. MPV was highest in the complicated appendicitis group. While MPV was expected to be the lowest in the negative appendectomy group, it was the lowest in the uncomplicated appendicitis group. Despite the conflicting findings, MPV was determined as a marker with the highest diagnostic value for appendicitis.

PLR is another inflammatory marker that can easily be obtained during simple hemogram tests. PLR levels can be used for diagnosing appendicitis.[23] Yıldırım et al.[24] found PLR to be a useful marker for differentiating between complicated and uncomplicated appendicitis. Our findings showed that PLR was an important marker for differentiating between complicated and uncomplicated appendicitis. Although it was found to have the lowest sensitivity, it had the highest specificity (cut-off value: 190.6, AUC: 0.64, sensitivity 50%, specificity 82%).

RDW is a subparameter that relates to the distribution of the volume of circulating erythrocytes.[22] RDW has been shown to increase significantly in complicated appendicitis, but its diagnostic values have not been specified.[25] Comparing those with appendicitis and those without, no significant difference has been found.[22,25] Similarly, in the current study, RDW was found to be a marker for differentiating between complicated and uncomplicated appendicitis with a high diagnostic value, but not a significant marker for diagnosing AA (cut-off value: 13.15, AUC: 0.63, sensitivity 69%, specificity 60%).

It is well known that bilirubin levels increase in AA.[26] Direct and TB levels increase in acute and complex appendicitis and are used as a diagnostic marker.[27] Despite few studies, research has shown hyperbilirubinemia to be a biomarker for predicting perforation in geriatric patients.[9] Here, both DB and TB levels were found to be important biomarkers for diagnosing AA and predicting complications. Also, they were the markers with the highest specificity for predicting AA status.

The most frequently used serological indicators for diagnosing AA are leukocyte counts and CRP levels. CRP is an acute-phase reactant that is synthesized in the liver in response to infection or inflammation[28]. Jung et al.[9] found CRP as a marker for determining perforation in geriatric patients with a high diagnostic value and a cut-off value of 2.09/mg/dL. Another study highlighted the high diagnostic value of CRP for determining perforation in elderly patients (AUC: 0.811 with a cut-off value of 10.19 mg/dL).[29] The most recent SIFIPAC/WSES/SICG/SIMEU guidelines recommend

the use of CRP and leukocyte levels together for diagnosing AA in the elderly.[30]

In determining perforation, CRP and TB are noted to be significant markers with high diagnostic value when used together.[31] In the present study, CRP was found to be an important marker for diagnosing AA and determining complication status. Again, similar to the findings in the literature, TB and CRP were found to increase in parallel to each other. To the best of our knowledge, this is the first study in the literature to demonstrate the diagnostic utility of MPV, PLR, and RDW for determining the severity of AA in the elderly. We suggest that these biomarkers may be useful as new diagnostic markers of AA for geriatric age patients.

USG and CT are some of the basic imaging modalities that are most commonly used for diagnosing AA and determining complications. CT has been reported to have a low sensitivity for detecting perforated appendicitis without abscess or phlegm.[32] In the current study, we found CT to have a sensitivity of 77.7% and a specificity of 70%, while USG had a sensitivity of 74.2% and a particularly low specificity of 18.2%.

Omari et al.[3] found a mean length of hospital stay of 4.2 days for uncomplicated appendicitis patients and 7.4 days for complicated appendicitis patients. In our patients, as expected, the longest length of stay was observed in the complicated appendicitis group, while the shortest length of stay was observed in the negative appendectomy group. With a descending order, length of hospital stay was 6.59, 3.34, and 3.13 days in our groups.

Prognosis for uncomplicated appendicitis is similar between young and elderly patients. However, in the case of perforation, morbidity and mortality increase dramatically in the elderly.[8,29] Elderly appendicitis patients have a postoperative complication rate of 21-60% and a mortality rate of 0.97-3%.[3,6,7] In our study, the rate of postoperative complications was 35.7%, with no mortality. The rate of complications was found to be higher in the perforated patient group. The low mortality and morbidity rates in our findings can be explained by the low number of perforated appendicitis cases.

Study Limitations

The major limitation of our study is that it was a retrospective study. Another limitation was a lack of analysis of symptoms and physical examination findings, which are crucial for diagnosing AA. Still, our research had certain strengths, including the high number of patients compared to most earlier studies, the analyses of many common biomarkers and obtaining new data, and providing more information by dividing the patients into three groups.

Conclusion

Elderly patients with abdominal pain present to hospitals later due to the lack of clinical clarity of their symptoms and signs. The high rates of comorbidities in the elderly also lead to more complicated appendicitis. This results in an increased rate of postoperative complications and longer hospital stay. The USG and CT modalities used for diagnosis have almost the same, or sometimes even lower sensitivity and specificity values compared to the laboratory parameters examined here. Preoperative WBC, neutrophil count, NLR, MPV, CRP, and direct and TB levels appear to have utility in the diagnosis of AA in elderly patients. Again, NLR, PLR, RDW, CRP, and direct and TB levels can be used to identify elderly patients with complications when AA has been diagnosed.

Ethics

Ethics Committee Approval: Ethics committee approval was received from the Erzurum Regional Training and Research Hospital Ethics Committee (approval number: 2020/13-146).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., R.P., Concept: M.Y., R.P., Design: M.Y., R.P., Data Collection or Processing: M.Y., R.P., Analysis or Interpretation: M.Y., R.P., Literature Search: M.Y., R.P., Writing: M.Y., R.P.

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