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Original Article General Surgery

Evaluation of the predictive power of laboratory markers in the diagnosis of acute appendicitis in the elderly

Savas Bayrak,[1] Cihad Tatar,[1] Ekrem Cakar,[1] Sukru Colak,[1] Mehmet Emin Gunes,[2] Kemal Tekesin,[3] Bunyamin Gurbulak,[1] Erdem Kinaci,[1] Mert Mahsuni Sevinc[1]

[1]Department of General Surgery, Istanbul Training and Research Hospital, Istanbul, Turkey
[2]Department of General Surgery, Bakirkoy Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[3]Department of General Surgery, Umraniye Training and Research Hospital, Istanbul, Turkey

ABSTRACT

OBJECTIVE: The aim of this study was to analyze the predictive value of preoperative laboratory findings in acute appendicitis in geriatric patients aged >65 years.

METHODS: We enrolled a total of 4121 patients. A retrospective evaluation of the demographic features was made using preoperative laboratory values such as the white blood cell (WBC), neutrophil, and lymphocyte counts; platelet counts; the mean platelet volume and bilirubin values; and postoperative pathological data of the patients from the electronic file system. The neutrophil-to-WBC and neutrophil-to-lymphocyte ratios were calculated. Patients were divided into two groups, as geriatric (≥65 years old, n=140) and non-geriatric (<65 years old, n=3981).

RESULTS: The white blood cell and lymphocyte counts, and the neutrophil-to-WBC ratio, were significantly higher in the non-geriatric group (p<0.001, p=0.013, and p=0.021, respectively). The neutrophil and platelet counts were higher in the non-geriatric group, but this difference was not statistically significant (p=0.073 and p=0.072, respectively). A higher neutrophil-to-lymphocyte ratio was determined in the geriatric group, but the difference was not significant (p=0.176). According to the optimumal cutoff value of 12.11×10^3/μL for WBC, specificity and sensitivity values of 65.4% and 57.9% were calculated, respectively; the AUC value was 0.632±0.024 (p<0.001). A receiver operating characteristic (ROC) analysis was used to calculate the optimum cutoff values of neutrophil-to-WBC ratio, lymphocyte, and the mean platelet volume, but the diagnostic accuracy of these tests was inadequate with an AUC of <0.6.

CONCLUSION: WBC values >12.11×10^3/μL were predictive of acute appendicitis in geriatric patients. The other parameters were not predictive, and further studies are required.

Keywords: Acute appendicitis; geriatric patients; laboratory parameters.

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Acute appendicitis resulting from inflammation of the appendix is one of the most common clinical situations necessitating an abdominal surgical intervention [1–3]. The incidence of appendicitis is 233:100,000, and its lifetime incidence is approximately 7%–10% [4]. Appendicitis is often seen in young adults in the second and third decades of life, and its incidence is highest in those aged 10–19 years. The main management goal is early diagnosis with appropriate and timely surgical procedures. In cases where patients have not sought medical care, the

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Correspondence: Dr. Savas BAYRAK. Istanbul Egitim ve Arastirma Hastanesi, Genel Cerrahi Klinigi, Istanbul, Turkey.
Tel: +90 533 248 0409 e-mail: savasbayrak74@gmail.com

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diagnosis may be delayed and difficult [5]. Negative appendectomies have previously been acceptable at a rate of approximately 15%. However, as imaging methods have become increasingly common, this rate has decreased to <10% [6]. Clinical approaches to the management of acute appendicitis may be complicated in some patient groups, particularly children, women of reproductive age, and geriatric patients [7].

Acute appendicitis is not rare in geriatric patients; 0.05% of the geriatric population develops acute appendicitis each year. In developed countries, appendicitis in the geriatric population is even rarer, although it is now becoming more common [8]. Appendicitis has become a significant cause of abdominal pain in older patients. Due to a blunted inflammatory response (such as leukocytosis and cytokine pool), elderly patients generally have a less remarkable history and physical findings [9]. This clinical situation may lead to a delayed diagnosis and increased complication rates, such as perforation on presentation [10, 11]. Perforation particularly significantly increases morbidity and mortality [12]. Geriatric patients also have a higher tendency for comorbidities, which increases morbidity and mortality rates. They often have other conditions such as diverticulitis or neoplasms that can mimic acute appendicitis. Thus, a broad list should be considered during the differential diagnosis of a geriatric population [13]. Computed tomography can increase the rate of accurate diagnosis [14], and laparoscopic appendectomies offer a shorter hospitalization time and fewer complications in geriatric patients [15–17].

Several studies have evaluated the value of parameters such as preoperative complete blood count (CBC), white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), neutrophil percentage (neutrophil/WBC ratio, NWR), the mean platelet volume (MPV), and bilirubin levels in acute appendicitis [18–23]. However, studies investigating the predictive value of laboratory parameters in acute appendicitis in the geriatric population are limited. The aim of this study was to analyze the predictive value of preoperative laboratory findings in acute appendicitis in geriatric patients aged >65 years.

MATERIALS AND METHODS

This study, which was approved by the ethical board of the Istanbul Training and Research Hospital (09/22/2017-1090), included 4144 patients who applied with open or laparoscopic appendectomy in our clinic between March 2005 and December 2016. Informed consent was obtained from all individual participants included in the study. The data of 23 patients could not be retrieved. Thus, the demographic features and preoperative laboratory values such as WBC, neutrophil, lymphocyte and platelet counts, MPV and bilirubin values, and postoperative histopathological results of 4121 patients were collected from the electronic file system. CBC and bilirubin were measured with an automated hematology analyzer and chemiluminescence, respectively. The NWR and NLR ratios were calculated. The study included patients aged 15–95 years who were then grouped as <65 years or ≥65 years. Patients aged <15 years, pregnant patients, and those with chronic liver disease or malignancy were excluded.

Statistical Analysis

Data analysis used the SPSS 22.0 (IBM Corporation, Armonk, New York, USA) and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs. The conformity of the univariate data to normal distribution was evaluated using the Shapiro– Wilk test. When comparing two independent groups according to quantitative data, the Mann–Whitney U test was used with the Monte Carlo results. When comparing categorical variables, the Pearson chi-squared exact test was applied. The association between the classification separated by cutoff values calculated according to variables, and real classification was analyzed with a receiver operating characteristic (ROC) curve. Quantitative and categorical variables were shown in the tables as the median range (maximum–minimum) and number (n) and percentage (%), respectively. Variables were examined at the 95% confidence interval, and a p-value <0.05 was accepted as statistically significant.

RESULTS

The patients included 1574 (37.98%) females and 2547 (62.02%) males, with a mean age of 34.55±12.14 years (median age, 32 years; age range, 15–95 years). The patients were classified as geriatric (≥65 years old) and non-geriatric (<65 years old) groups according to their age. The geriatric group comprised 140 (3.4%) of the total patient group with statistically significantly more females in the geriatric group than the non-geriatric groups (p=0.001) (Fig. 1).

Perforation was detected in 24 (17.14%) and 598 (15.02%) patients in the geriatric and non-geriatric group, respectively. There is no statistically significant difference between groups in terms of perforation rates.

The WBC mean of 24 patients with perforated ap-

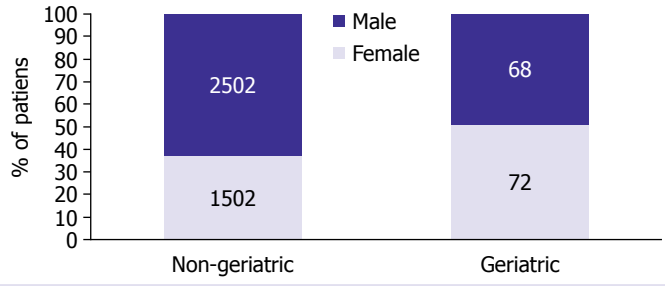

FIGURE 1. Gender differences between the geriatric and non-geriatric groups.

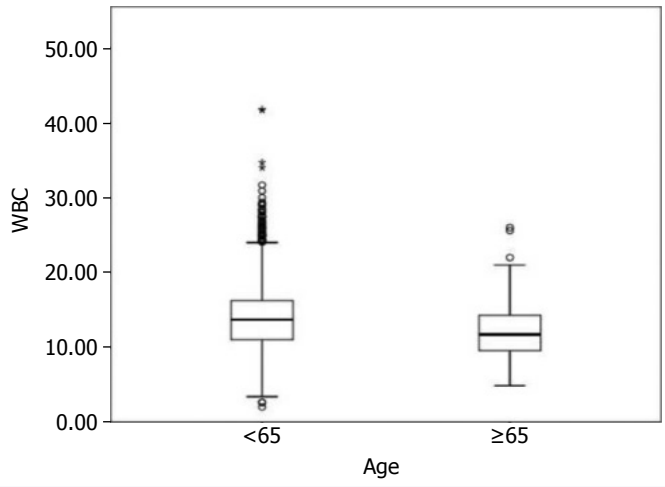

FIGURE 2. The comparison of WBC counts between the age groups.

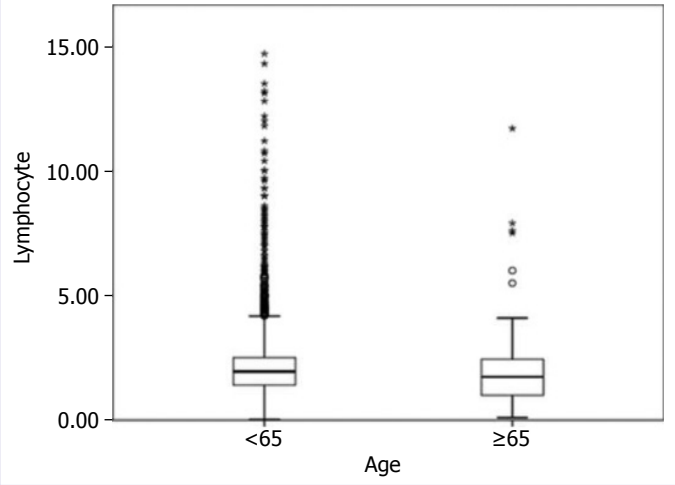

FIGURE 3. The comparison of lymphocyte counts between the age groups.

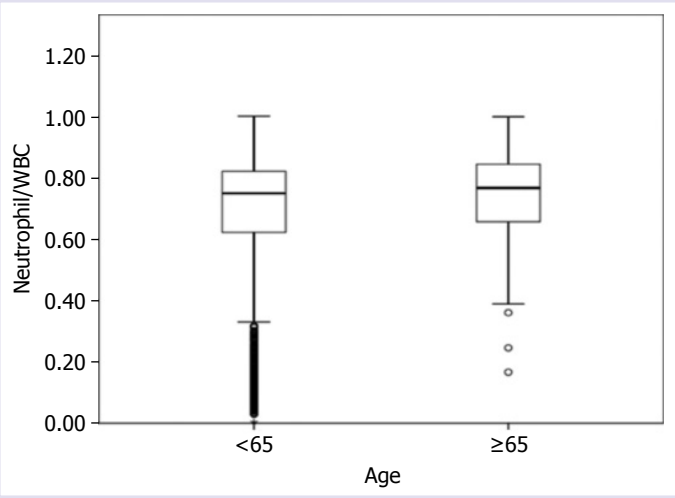

FIGURE 4. The distribution of NWR between the age groups.

pendicitis in the geriatric group was 13.39×10³/μL, and the WBC mean of the 598 patients with perforated appendicitis was 16.4×10³/μL. This analysis shows that there is no statistically significant difference between the geriatric and non-geriatric patients (p=0.094).

The WBC, lymphocyte counts, and NWR were significantly higher in the non-geriatric group (p<0.001, p=0.013, and p=0.021, respectively). These distributions are shown in Figures 2, 3, and 4. Neutrophil and platelet counts were higher in the non-geriatric group, but this difference was not statistically significant (p=0.073 and p=0.072, respectively). A higher NLR was determined in the geriatric group, but the difference was not significant (p=0.176). The MPV values were increased in geriatric patients (p=0.036). Bilirubin levels of the patients were similar between the age groups (p=0.797). Acute perforated gangrenous appendicitis was determined in 87.47% of the non-geriatric cases and in 77.14% of the geriatric patients, according to pathological results, with a significant difference between the age groups (p=0.001) (Fig. 5). The demographic and clinical features of the patients are shown in Table 1.

The predictive values of the preoperative laboratory results of the patients were examined using a ROC analysis. At a cutoff value of 12.11×10³/μL for WBC, the specificity and sensitivity were 65.4% and 57.9%, respectively, and the AUC was 0.632±0.024 (p<0.001). A ROC analysis with optimum cutoff values of NWR, lymphocyte, and MPV gave inadequate diagnostic accuracy; the AUC values were <0.6. The ROC analysis results for these laboratory parameters are shown in Table 2 and Figures 6–9.

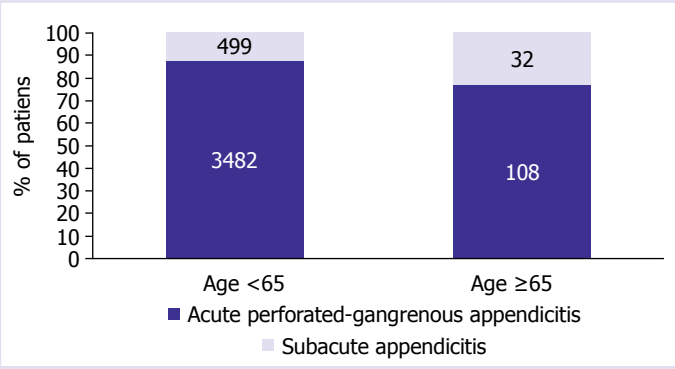

Figure 5. Pathological analysis according to the age groups.

DISCUSSION

Approximately half of the geriatric patients who present to the Emergency Depatment have abdominal pain complaints [24]. Intestinal obstruction and biliary diseases are the most common causes of acute abdomen in geriatric patients, followed by acute appendicitis [25]. The prognosis may be unfavorable, and geriatric patients may experience more complications compared to younger patients because their clinical signs of appendicitis may be atypical [26]. For example, this age group has increased perforation rates compared to younger patients, which may be associated with a diagnostic delay due to both late admission and a lack of classic signs and symptoms [27].

In our study, the geriatric group had a perforation ratio that was higher than in the non-geriatric group, but this difference was not statistically significant. An analysis of the subgroups of perforated patients showed no statistically significant difference in the WBC values between geriatric and non-geriatric patients.

Higher rates of misdiagnosis (up to 50%) are observed in the geriatric patient group, and some of those patients require more than a day to be diagnosed [27]. To improve the diagnostic accuracy in appendicitis, several scoring systems have been developed such as the Alvarado score that was first described in 1986 [28–34]. The Alvarado scoring system consists of several par–ameters including leukocytosis (WBC>$10\times10^3/\mu L$) and neutrophil-to-WBC ratio. Some other clinical features of the patients were also considered. Although there are several studies in the literature evaluating the accuracy of this scoring system in patients with appendicitis, there have been only a few studies that have only investigated the predictive role of preoperative laboratory parameters. Furthermore, studies of the predictive value of scoring systems and laboratory parameters are rare in older patients.

Inflammatory markers that emerge in acute appendicitis may change according to several factors, such as the bone marrow capacity, liver synthesis function, co-

Table 1. Demographic features and laboratory values of the patients

	Age <65 Median (Max.-Min.)	Age ≥65 Median (Max.-Min.)	Total Median (Max.-Min.)	p
WBC	13.70 (41.80–2)	11.70 (26–4.86)	13.60 (41.80–2)	<0.001
Neutrophil	9.71 (27.56–0.03)	8.70 (18.30–1)	9.70 (27.56–0.03)	0.073
NWR	0.740 (1-0)	0.751 (1–0)	0.740 (1-0)	0.021
Lymphocyte	1.95 (14.70–0.03)	1.73 (11.70–0.10)	1.94 (14.70–0.03)	0.013
NLR	5.07 (324–0.01)	5.48 (72–0.54)	5.08 (324–0.01)	0.176
Platelet	247 (789–20.90)	232.50 (533–38)	247 (789–20.90)	0.072
MPV	8.30 (18–0.10)	8.40 (11.50–5.90)	8.30 (18–0.10)	0.036
Bilirubin	0.60 (6.60–0.10)	0.60 (2.50–0.10)	0.60 (6.60–0.10)	0.797
Gender, n (%)				
Female	1502 (37.51)	72 (51.43)	1574 (37.98)	0.001
Male	2502 (62.49)	68 (48.57)	2570 (62.02)	
Pathological analysis, n (%)				
Sub-lymphoid hyperplasia	499 (12.53)	32 (22.86)	531 (12.89)	0.001
Acute-perforated-gangrenous appendicitis	3482 (87.47)	108 (77.14)	3590 (87.11)	

Max.: Maximum; Min.: Minimum. Mann Whitney U Test (Monte Carlo) - Pearson Chi-Square Test (Exact).

TABLE 2. Analysis for optimal cutoff values of predictive laboratory parameters

	Age <65		Age ≥65		AUC±SE.	p
	n	%	n	%		
WBC						
>12.11	2616	65.4**	59	42.1	0.632±0.024	<0.001
≤12.11	1387	34.6	81	57.9*		
NWR						
≤0.5449	708	17.7**	8	5.7	0.552±0.023	0.028
>0.5449	3293	82.3	132	94.3*		
Lymphocyte						
>1.3	3097	77.4**	85	60.7	0.562±0.028	0.026
≤1.3	903	22.6	55	39.3*		
MPV						
≤9.25	3269	84.4**	102	73.9	0.552±0.026	0.043
>9.25	602	15.6	36	26.1*		

AUC: Area under the ROC; WBC: White blood cell; MPV: Mean platelet volume. (Roc (Receiver Operating Curve) Analysis (Honley&McNell - Youdenindex J).

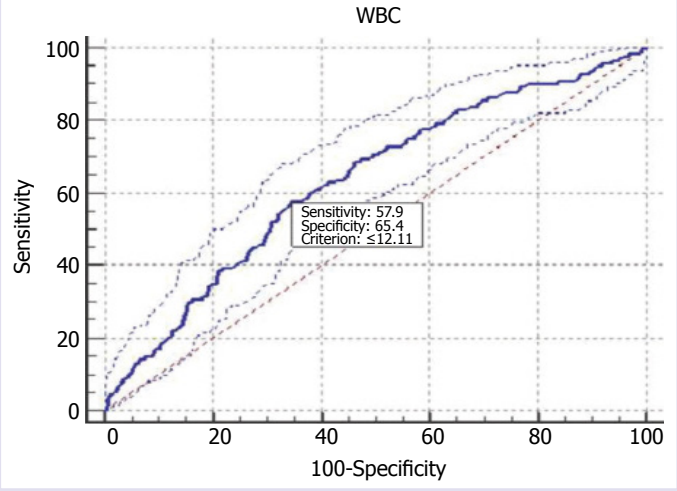

FIGURE 6. Receiver operating characteristics (ROC) curve showing the predictive value for the white blood cell count (WBC).

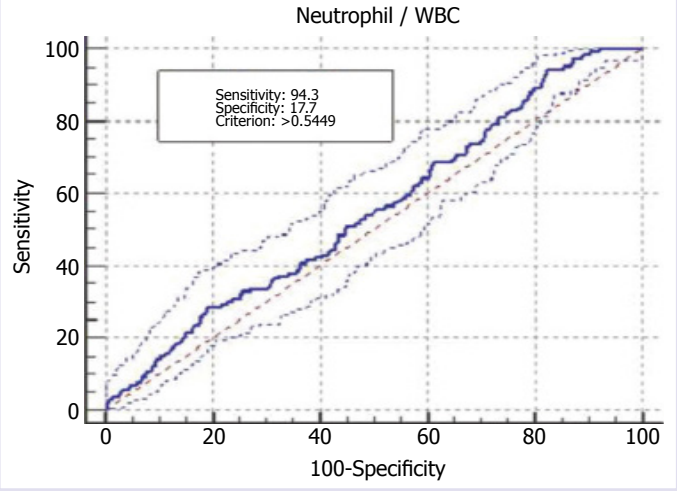

FIGURE 7. Receiver operating characteristics (ROC) curve showing the predictive value for NWR.

morbidities, and drugs. The age of the patient is one of the most important factors affecting the degree of elevation in inflammatory markers. The WBC count is one of these inflammatory markers. Although there are many studies that have evaluated the benefits of using WBC, consensus has yet been reached [35].

Paajanen et al. investigated the preoperative WBC and C-reactive protein (CRP) levels of 6,000 patients consisting of all age groups including infants, children, adolescents, adults, and geriatric patients [36]. A ROC analysis showed that WBC counts were better than CRP in suggesting the correct diagnosis in all age groups, except for those aged 0–5 years. However, systemic infections may generally result in less leukocytosis in geriatric patients, and some studies investigating infective endocarditis have shown a blunted leukocytosis response in older patients [37]. Acute appendicitis might also produce a very high degree of inflammation. Moreover, in

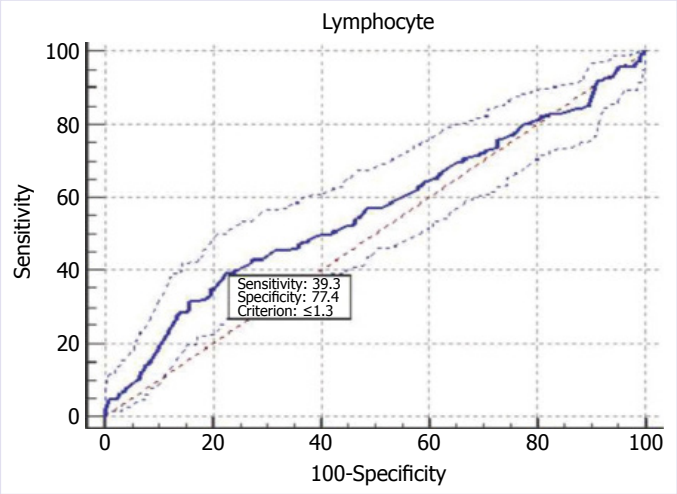

Figure 8. Receiver operating characteristics (ROC) curve showing the predictive value for lymphocytes.

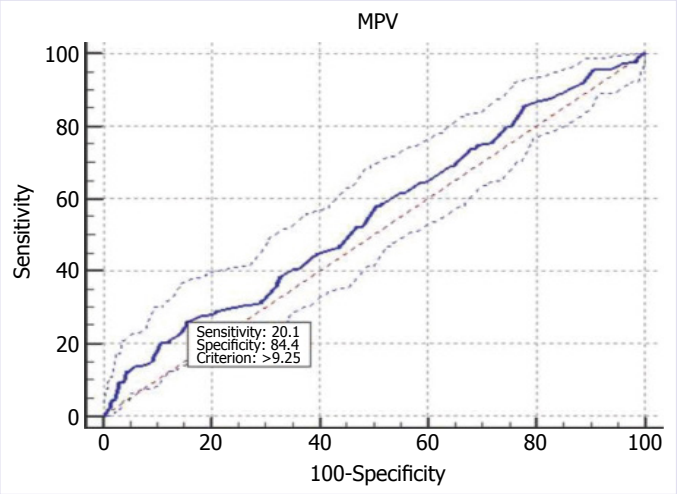

Figure 9. Receiver operating characteristics (ROC) curve showing the predictive value for the mean platelet volume (MPV).

geriatric patients, decreased production of WBC and CRP due to diminished capacity can hinder the prompt diagnosis of appendicitis [36]. Thus, geriatric patients have generally less remarkable inflammatory factors [38].

In this study, geriatric patients with appendicitis had lower WBC counts than the non-geriatric group. Increased WBC counts were also determined to be predictive in the geriatric group. Sevinc et al. analyzed 3392 patients undergoing appendectomy and classified the patients according to pathological examination: those with a normal appendix (n=531) or with appendicitis (n=2861) [38]. The optimum cutoff value for WBC was 11.9x10^3/μL, and a ROC analysis showed an AUC value >0.6. Therefore, elevated WBC levels (>11.9x10^3/μL) were predictive of appendicitis with a positive predictive value of 0.92. This study included all patients over the age of 15 years who underwent appendectomy. Styrud et al. investigated 47 patients aged >80 years who underwent appendectomy with a pre-diagnosis of appendicitis. They found higher complication rates in the older age group [39]. In contrast, they showed that the inflammatory parameters did not differ in the older group compared to the younger group. Therefore, elevated inflammatory markers were not associated with complications in the geriatric population.

Grönroos et al. [40] evaluated 83 patients who underwent abdominal surgery with a clinical diagnosis of acute appendicitis. Histopathological analysis of the surgical specimens revealed that 10 patients had a non-inflamed appendix, and the others had acute appendicitis. These two groups were compared in terms of preoperative WBC and CRP values, and analysis showed that all patients with acute appendicitis had histopathologically confirmed elevated preoperative WBC and/or CRP levels. In that study, normal leukocyte counts and CRP excluded acute appendicitis with a predictive value of 100%. Similar to our study, they showed that elevated leukocyte counts were an important finding for the prediction of acute appendicitis, but there was no examination of ROC curves or analysis of any cutoff values for the leukocyte counts.

The NWR is another important parameter to diagnose or predict complications in acute appendicitis. However, studies evaluating these patients generally consider the absolute neutrophil count rather than the NWR. Here higher NWR values were seen in geriatric patients compared to the non-geriatric group, but the diagnostic accuracy of NWR was inadequate (AUC<0.6). Jung et al. evaluated 103 geriatric patients with acute appendicitis [41], 56.3% of whom developed perforation; a ROC analysis was performed to identify the optimal cutoff values. The cutoff value for WBC was 10.6×10^3/μL. The odds ratio was 5.29, and the AUC was 0.664. The neutrophil count was predictive for perforation with a cutoff value of 8.1×10^3/μL (odds ratio of 4.776; AUC of 0.699).

The NWR is considered when calculating the "appendicitis inflammatory response" score, but the NWR was not analyzed with ROC analysis. Ayrık et al. compared 254 patients with appendicitis, 66 of whom had a normal appendix according to the postoperative pathological examination [42]. That study was not restricted to geriatric patients. The positive (PPV) and negative

predictive values (NPV) of WBC were 88% and 33.3%, respectively, in predicting the diagnosis of acute appendicitis (AUC=0.660). The cutoff value for NWR was >73, and the PPV and NPV were 88.2% and 42.9% (AUC=0.701) for diagnosis of acute appendicitis. When differentiating complicated and uncomplicated appendicitis, a cutoff value of 78.51 for NWR was not statistically significant. A multiple logistic regression analysis showed that an increased NWR could increase the risk of uncomplicated and complicated appendicitis (OR 1.082 and 1.066, respectively). These results suggest that surgical treatment of acute appendicitis can be selected by considering NWR [42].

Yang et al. [43] showed that the NWR was higher in patients with acute appendicitis than in patients with a normal appendix in the geriatric population. In another study, NWR was shown to be higher in complicated appendicitis than in uncomplicated cases [44]. However, another study showed no significant differences for WBC or NWR between patients with perforated and non-perforated acute appendicitis [45]. Elangoven et al. [46] showed a very high predictive value and an increased percentage of band forms (>6%) in predicting acute appendicitis in patients aged ≥60 years. Leukocytosis also increased the specificity in that study.

In recent years, some hematological parameters such as NLR have gained importance in addition to classical blood counts. The NLR is a pro-inflammatory marker in some studies [47–49]. NLR is a simple, cheap, and effective biomarker. It has been widely investigated for predicting morbidity and mortality in inflammatory disorders, neoplastic diseases, and solid tumors [50–54]. Recent studies have suggested that the NLR can predict cardiovascular diseases and cancer [47–49]. The predictive value of NLR in acute appendicitis was first studied by Goodman et al. [55]. The NLR is more sensitive than the WBC count in predicting acute appendicitis.

Here, the NLR was higher in the non-geriatric group, but the difference was not significant. Cigsar et al. [56] investigated 755 patients who underwent surgery with a pre-diagnosis of appendicitis and grouped the patients as geriatric and non-geriatric. The patients were also grouped as positive or negative appendectomy according to postoperative pathological analysis. The NLR was higher in both the geriatric and non-geriatric patients with a positive appendectomy. The cutoff value of NLR was determined to be 4.90 with a sensitivity of 73.3% and specificity of 73.3%. When the age, gender, and NLR were analyzed together in the negative and positive appendectomy groups, the NLR could independently predict positive appendectomy ($p<0.001$).

Sevinc et al. also found NLR to be predictive for appendicitis with a positive predictive value of 0.89 in patients aged >15 years [38]. Jung et al. studied patients with acute appendicitis and found that the highest AUC value among inflammatory markers for predicting perforation was with NLR [41]. The NLR marker points to subclinical inflammation. It has been investigated in several studies including in patients with acute appendicitis [57]. Aydin et al. [58] investigated 195 patients with acute complicated or noncomplicated appendicitis. The cutoff values for WBC and NLR were $>13.8\times10^3/\mu L$ (AUC=0.614) and >4.87 (AUC=0.641), respectively. The OR of WBC and NLR were calculated for complicated appendicitis (3.103 and 3.025, respectively). Other studies have compared the NLR in patients with acute appendicitis to those in patients with other acute abdominal pain. For example, increased WBC and NWR were found to be predictive for appendicitis in a study of renal colic and acute appendicitis [59].

MPV is another marker of inflammation. It has been broadly investigated in clinical studies. MPV reflects the platelet size and is part of a CBC analysis; however, practitioners often overlook its importance [60]. It can indicate inflammation and disease activity in several conditions including acute coronary syndromes, inflammatory bowel diseases, and pancreatitis [61]. It has been postulated that MPV is an inflammatory marker in severe inflammatory conditions—primarily acute appendicitis. Here, the MPV value was higher in geriatric patients with acute appendicitis than the non-geriatric group. However, this parameter had an inadequate value in predicting acute appendicitis—at an optimum cutoff value of 9.25, the AUC level was <0.6.

Previously, MPV levels in patients with acute appendicitis (n=226) were found to be lower than normal [62]. However, contrasting results were also detected in other studies. Narci et al. [63] compared patients with acute appendicitis (n=503) to a control group (n=121). The MPV levels were statistically significantly higher in patients with acute appendicitis (median MPV=7.92 fL) than the control group (median MPV=7.43 fL) ($p<0.001$). The optimum cutoff value was 7.87 fL according to the ROC analysis (AUC=0.62). Studies on the predictive value of MPV in geriatric patients with acute appendicitis are limited.

Bilirubin levels have been proposed to an appendicitis prediction tool. Although the value of hyperbilirubinemia for predicting severe appendicitis is well known [64], this parameter has not been used in routine clinical management. Some authors have suggested that bilirubin levels predict complicated appendicitis. However, in our study, there was no significant difference between the geriatric and non-geriatric groups according to bilirubin levels. In a study evaluating 103 geriatric patients with acute appendicitis, bilirubin was found to be predictive for perforation [41]. In that study, the cutoff value, odds ratio, and AUC values for total bilirubin were 0.7 mg/dL, 4.41, and 0.646, respectively. Further studies are needed in geriatric patients to evaluate the predictive value of bilirubin in appendicitis.

There is no single symptom or clinical sign, laboratory test, or radiological finding to make a precise diagnosis of acute appendicitis. It is absolutely necessary to consider all clinical and laboratory findings, as well as the radiological methods for diagnosing acute appendicitis. Further studies are required to clearly define the predictive values of inflammatory markers in geriatric patients with acute appendicitis.

In conclusion, the results showed that WBC and lymphocyte counts as well as the NLR were higher in the non-geriatric group. The NWR and MPV were higher in the geriatric group. The WBC counts $>12.11\times10^3/\mu L$ were predictive for acute appendicitis in the geriatric group.

Ethics Committee Approval: This study, which was approved by the ethical board of the Istanbul Training and Research Hospital (09/22/2017-1090).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – CT, SB; Design – SB, EC; Supervision – EK, MMS; Materials – EC, MMS; Data collection and/or processing – SC, MMS, EC; Analysis and/or interpretation – BG, CT; Writing – CT, SB; Critical review – KT, MEG.

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