Role of immature granulocytes and total bilirubin values in the diagnosis of perforated appendicitis in patients over 65 years

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the effectiveness of immature granulocyte count, immature granulocyte percentage, and total bilirubin value in predicting complicated and perforated appendicitis in patients aged 65 years and older with a diagnosis of appendicitis.
METHODS: In this study, 84 patients, aged 65 years and older, who had appendectomy demographic information, preoperative white blood cell count, neutrophil/lymphocyte ratio, immature granulocyte count and immature granulocyte percentage, operation findings, and pathology results were collected retrospectively. They were grouped into 4 categories: complicated, non-complicated, perforated, and non-perforated, according to the data and surgical findings.
RESULTS: Total bilirubin and immature granulocyte count were found to be statistically significant in predicting complicated and perforated appendicitis in patients aged 65 years and older with a diagnosis of appendicitis. The total bilirubin was found to have the following values in differentiating complicated appendicitis: area under the curve=0.883, sensitivity=78.3%, and specificity=88.5%. Total bilirubin had the highest discrimination power with area under the curve=0.804 in differentiating perforation.
CONCLUSION: The immature granulocyte percentage and total bilirubin count are the fast, inexpensive, and reliable parameters that can be used to predict complicated and perforated appendicitis in patients aged 65 years and older.
KEYWORDS: Appendicitis. Aged. Bilirubin.

INTRODUCTION

Acute appendicitis (AA) is the most common cause of acute abdominal pain that requires surgical intervention[1]. It is often seen in the second and third decades of life. The incidence of AA after adolescence decreases with age[2]. While the mortality rate due to AA in elderly patients is 8%, it varies between 0 and 1% in young patients[3]. In addition to applying with an insignificant history and physical examination, they generally progress with a reduced inflammatory response accompanied by less leukocytosis. Therefore, elderly patients may go unnoticed at the time of diagnosis, and they have the possibility of complicated and perforated appendicitis. According to the multivariate analyses in a large observational study, being diagnosed with AA over the age of 65 years is one of the reasons that increase mortality. In addition, the rate of having perforated, abscess, or complicated appendicitis is higher in patients over 65 years of age with a diagnosis of AA[4].

Studies have demonstrated that in cases such as sepsis and infection, the number of immature granulocytes increases significantly compared to healthy individuals, and this value can be used as an inflammatory marker[5].

Although hyperbilirubinemia is usually increased in liver dysfunctions and biliary tract obstructions, increased bilirubin can also be observed in patients due to general peritonitis, AA, and sepsis. *Escherichia coli* and *Bacteroides fragilis* are the most common bacterial causes of appendicitis[6]. Complicated appendicitis causes intestinal edema and slowing of motility. These mechanisms result in increased bilirubin[7].

In this study, we examined the laboratory parameters that can be used to predict appendicitis perforation in patients aged 65 years and older.

METHODS

Our study was approved by the ethics committee (decision no.: E-21-758). Between January 8, 2017, and January 9, 2021, 84 adult patients over 65 years of age who underwent appendectomy with the preliminary diagnosis of AA in the

clinic were evaluated retrospectively by examining the hospital records. By examining the pathology reports of the patients, they were grouped as simple (edematous and phlegmon) appendicitis and complicated (perforated and gangrene) appendicitis according to the complication status and as non-perforated appendicitis and perforated appendicitis according to the perforation status.

Statistical analysis

For the statistical analyses of the study data, Statistical Package for Social Sciences (SPSS), version 23.0 for Windows (SPSS Inc. Chicago, IL, USA) software was used. In the descriptive statistics section, categorical variables have been presented as number and percentage, while continuous variables are presented with mean±standard deviation and the median (smallest-largest value). The compliance of continuous variables with normal distribution was evaluated using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. The Mann-Whitney U test was used for the comparison analysis. To determine the probability of using white blood cell (WBC) count, neutrophil/lymphocyte ratio (NLR), immature granulocyte count (IGC), immature granulocyte percentage (IG%), total bilirubin, direct bilirubin, and indirect bilirubin values in determining complicated appendicitis and perforated appendicitis, a receiver operating characteristic (ROC) curve analysis was performed. Within the scope of this analysis, the area under the curve (AUC) and its statistical significance were evaluated, and it was decided whether to calculate a threshold point for the relevant parameters. The threshold point was determined using the Youden

Index for the appropriate parameters. A $p < 0.05$ was considered statistically significant.

Findings

Of the patients included in our study, 41 (48.8%) were male and 43 (51.2%) were female. The mean age was determined as 70±5.9 years. According to the pathology results, the patients were divided into four groups according to their complication status and perforation status; 61 (72.6%) patients were grouped under the simple appendicitis group, 23 (27.4%) patients were grouped under the complicated appendicitis group, 73 (86.9%) patients were grouped under the non-perforated appendicitis group, and 11 (13.1%) patients were grouped under the perforated appendicitis groups. It was investigated whether WBC count, NLR, IGC, and IG%, total bilirubin, direct bilirubin, and indirect bilirubin values are the parameters that can be used to determine the complication status and perforation status in patients over 65 years of age with a preliminary diagnosis of AA.

Between simple appendicitis and complicated appendicitis groups, a statistically significant difference was found in terms of WBC count, NLR, IGC, and IG%, total bilirubin, direct bilirubin, and indirect bilirubin values ($p < 0.05$).

Between non-perforated appendicitis and perforated appendicitis groups, a statistically significant difference was found in terms of IGC and IG%, total bilirubin, direct bilirubin, and indirect bilirubin values ($p < 0.05$). Between non-perforated appendicitis and perforated appendicitis groups, no statistically significant difference was found in WBC count and NLR ($p < 0.05$) (Table 1).

Table 1. Comparison of laboratory findings between appendicitis groups, 2021.

	Simple appendicitis Median (min–max)	Complicated appendicitis Median (min–max)	p*	Non-perforated appendicitis Median (min–max)	Perforated appendicitis Median (min–max)	p*
IGC	0.04 (0.01–0.30)	0.10 (0.04–0.70)	<0.001	0.05 (0.01–0.31)	0.10 (0.04–1.80)	0.012
IG%	0.40 (0.10–0.70)	0.60 (0.30–1.80)	<0.001	0.40 (0.10–1.80)	0.60 (0.30–1.00)	0.048
Total bilirubin	0.48 (0.21–1.28)	1.10 (0.34–1.86)	<0.001	0.55 (0.21–1.86)	0.96 (0.34–1.53)	0.001
Direct bilirubin	0.19 (0.04–0.54)	0.36 (0.04–0.80)	<0.001	0.20 (0.04–0.80)	0.36 (0.04–0.66)	0.005
Indirect bilirubin	0.30 (0.09–0.84)	0.65 (0.25–1.33)	<0.001	0.34 (0.09–1.07)	0.55 (0.25–1.33)	0.015
WBC	11800 (4190–28250)	14590 (5330–25810)	0.001	12210 (4190–28250)	14590 (5330–25810)	0.072
NLR	5.41 (0.56–25.08)	8.02 (1.71–30.64)	0.026	6.20 (0.56–30.64)	6.97 (2.20–27.12)	0.343

*Mann-Whitney U test. IGC: immature granulocyte count; IG%: immature granulocyte percentage; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio.

Accordingly, the highest differential power was found in the total bilirubin parameter. The AUC value was determined as 0.883. Limit values were determined for all parameters according to the ROC curves. It was observed that the parameter with the highest sensitivity was total bilirubin, while the parameters with the highest specificity were IG% and IGC (Table 2).

Accordingly, the highest differential power was found in the total bilirubin parameter. The AUC value was determined as 0.804. Limit values were determined for all parameters according to the ROC curves. It was observed that the parameter with the highest sensitivity was total bilirubin, and the parameter with the highest specificity was the percentage of immature granulocytes (Table 3).

The use of IG%, WBC count, and NLR values in differentiating the perforated AA group from the non-perforated AA group was not found to be statistically significant (p<0.05).

DISCUSSION

Acute appendicitis is the most common surgical emergency, which is seen more rarely in elderly patients, and most frequently in the second and third decades, and its incidence decreases over the years after puberty[2]. Since cardiac, renal, and pulmonary diseases are also more common in this age group, they are more mortal in this age group.

The diagnosis of appendicitis is made by the clinician's physical examination, laboratory tests, and the combined use of visualization methods. It has been reported that the use of ultrasonography and computed tomography makes the diagnosis of AA more accurate in some cases and reduces false negativity by 10%[8,9]. In addition to this, opaque substances to be given are not preferred in this age group since they are nephrotoxic. Although the use of ultrasound helps to avoid these risks, it is dependent on the person performing it, and the appendix cannot be seen at a rate of 55%, which does not help with diagnosis in some cases[10].

Table 2. Receiver operating characteristic analysis of laboratory parameters in differentiating simple appendicitis and complicated appendicitis, 2021.

Test result variable(s)	AUROC	p	Asymptotic 95% confidence interval		Cutoff value	Sensitivity (%)	Specificity (%)
			Lower bound	Upper bound			
IGC	0.831	<0.001	0.725	0.936	>0.075	73.9	83.6
IG%	0.778	<0.001	0.662	0.894	>0.65	47.8	95.1
Total bilirubin	0.883	<0.001	0.801	0.966	>0.85	78.3	88.5
Indirect bilirubin	0.841	<0.001	0.749	0.934	>0.49	73.9	85.2
WBC	0.735	0.001	0.614	0.856	>13,615	69.6	73.8
Direct bilirubin	0.838	<0.001	0.725	0.951	>0.32	73.9	88.5
NLR	0.658	0.026	0.517	0.799	>6.65	60.9	63.9

IGC: immature granulocyte count; IG%: immature granulocyte percentage; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio; ROC: receiver operating characteristic curve; AUROC: area under the receiver operating characteristics.

Table 3. Receiver operating characteristic analysis of laboratory parameters in the differentiation of non-perforated appendicitis and perforated appendicitis, 2021.

Test result variable (s)	AUROC	p	Asymptotic 95% confidence interval		Cutoff value	Sensitivity (%)	Specificity (%)
			Lower bound	Upper bound			
IGC	0.732	0.013	0.582	0.883	>0.075	72.7	74
IG%	0.682	0.053	0.504	0.860	>0.650	45.5	87.7
Total bilirubin	0.804	0.001	0.671	0.937	>0.875	81.8	80.8
Indirect bilirubin	0.729	0.015	0.573	0.884	>0.515	63.6	76.7
WBC	0.669	0.072	0.490	0.848	>13.785	63.6	79.9
Direct bilirubin	0.762	0.005	0.591	0.934	>0.345	72.7	80.8
NLR	0.589	0.343	0.391	0.787	>14.200	36.4	94.5

IGC: immature granulocyte count; IG%: immature granulocyte percentage; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio; ROC: receiver operating characteristic curve; AUROC: area under the receiver operating characteristics.

Prolonging the time between symptom onset and the surgery increases the risk of appendix perforation. Therefore, early diagnosis is of great importance in the success of treatment[11]. Studies have demonstrated that older patients are diagnosed with appendicitis less accurately before surgery than younger patients[4,12]. Considering the relationship of delay in the diagnosis and treatment of severe appendicitis with postoperative mortality, morbidity, and length of hospital stay, new biomarkers are needed to predict the severity of this type of appendicitis[13].

In our study, the rate of complicated appendicitis is 27.4%, which is compatible with the studies in the literature[5,6]. It has been demonstrated that total bilirubin value is an important marker in the differentiation of perforated, non-perforated, complicated, and simple appendicitis in patients aged 65 years and older. Due to the increased bacterial load, it invades the portal system directly or by translocation. This causes bacteria both to interact with the liver parenchyma and to increase bilirubin by causing acholia[14]. Sevinc et al., after evaluating 3,392 cases of hyperbilirubinemia (>1.0 mg/dL), stated that it has an important place in determining appendicitis perforation, especially in elderly patients[15]. Eren et al. also found a significant relationship between perforated or gangrenous appendicitis and total bilirubin[16]. In addition to these studies, the results we found are compatible with other studies in the literature[6,17,18,19].

The new-generation hemogram devices used in recent years can calculate the number and percentage of immature granulocytes, thus enabling them to be used as an easily and quickly accessible marker without requiring additional costs. There are many studies indicating the prognostic importance of immature granulocyte in patients with sepsis and bacteremia in the literature[5,20-23]. Soh et al. conducted a study on patients who applied to the emergency department with abdominal pain complaint and stated that immature granulocyte value should be considered in terms of making an emergency abdominal surgery decision or in terms of peritonitis[24]. Durak et al. stated that immature granulocytes can be used for evaluating intestinal necrosis in mesenteric ischemia[25].

Preoperative diagnostic steps gain more importance in geriatric patients aged 65 years and older, both because they are diagnosed late and because of more complications in the postoperative period. New inflammatory markers are needed that can be used due to the inadequacy of the values such as WBC and NLR that we used routinely in these patients, the limitation in the use of radiological examinations due to the frequency of nephrotoxicity in this patient population, and the inability of these patients to express themselves. In our study, on the contrary, it was concluded that immature granulocyte is a distinguishing parameter in both the differentiation of complicated and simple appendicitis and the differentiation of perforated and non-perforated appendicitis in the geriatric-sensitive population aged 65 years and older. Many studies in the literature support our results.

CONCLUSION

Early prediction of complicated and perforated appendicitis in geriatric patients aged 65 years and older is extremely important in terms of reducing high mortality rates and hospital costs. Total bilirubin and immature granulocyte are reliable parameters that can be used to determine the severity of AA in patients aged 65 years and older.

AUTHORS' CONTRIBUTIONS

SA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **EC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **BBS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **MC:** Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. **IE:** Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. **AS:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **YU:** Formal Analysis, Visualization, Writing – original draft. **MRP:** Formal Analysis, Visualization, Writing – original draft.

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