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# The predictors of complicated acute appendicitis: large unstained cells, gamma-glutamyl transferase, monocyte to platelet ratio, age and gender

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## ABSTRACT

**Aim**: In this study, we sought to investigate possible biomarkers markers that can preoperatively distinguish complicated and non-complicated acute appendicitis.

**Material and Method**: Patients who underwent appendectomy between February and December 2019 were screened retrospectively. Patients with pathology findings other than appendicitis were excluded. Patients with a confirmed diagnosis of acute appendicitis were categorized as complicated and non-complicated appendicitis for analysis of sociodemographic characteristics, comorbidities and preoperative laboratory parameters.

**Results**: A total of 575 patients were included in the study. Among these, 432 (75.1%) were diagnosed with non-complicated appendicitis and 143 (24.9%) were diagnosed with complicated appendicitis. The mean (SD) age was 34.2±14.2 years. Hypertension, diabetes mellitus and hypothyroidism were the most frequent comorbidities. Age (OR, 1.026; p=0.010), male gender (OR, 1.837; p=0.044), LUC (OR: 19.868; p=0.034) and GGT (OR: 1.013; p=0.013) were associated with a higher risk of complicated appendicitis. An increase in monocyte to platelet ratio (MPR) (OR: 0.920; p=0.047) was associated with a lower risk of complicated appendicitis.

**Conclusion**: In patients with acute appendicitis, parameters including age, gender, as well as LUC, GGT and MPR, which are easily available and relatively cheap biomarkers, can be useful to distinguish non-complicated and complicated cases preoperatively.

**Keywords**: Acute appendicitis, appendectomy, large unstained cells

## INTRODUCTION

Acute appendicitis is one of the most common abdominal emergencies worldwide. It occurs more often in males than females, with a lifetime incidence of 8.6% and 6.7%, respectively (1). Appendicitis is provoked by direct luminal obstruction. Although the certain etiology remains unknown, genetic, environmental and infectious factors could be the triggers (2). Appendectomy is one of the most commonly performed operations in emergency settings and is the gold standard treatment for acute appendicitis. Even the mortality rate is low (0.09-0.24%), postoperative adverse event rates of 8.2-31.4% have been reported (2,3). Since Bailey published the non-operative treatment algorithm in 1930, conservative treatment with antibiotics has been proposed, but this is not without controversies (4). A meta-analysis of five randomized trials including 980 patients with uncomplicated appendicitis showed that in patients treated conservatively, the relative odds of complications by 46%. Furthermore, the analgesic consumption decreased, and the duration of sick leave was shorter in the patients treated with antibiotics (5). Even if there are scoring systems such as the Alvarado score to determine the likelihood of acute appendicitis, there is no classifier to distinguish between complicated and non-complicated appendicitis (6).

In this study, we investigated the factors including demographic data, comorbidities, type of surgery and laboratory findings at admission, which could be effective to distinguish complicated and non-complicated appendicitis in patients with acute appendicitis.

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## MATERIAL AND METHOD

### Patient Selection

Patients who underwent surgery for acute appendicitis between February and December 2019 at Ankara City Hospital were screened for this study. Exclusion criteria were pathology findings other than acute appendicitis (e.g., normal appendix, malignancy) and missing data. Approval for the study was granted by the Ankara City Hospital No 1 Clinical Researches Ethics Committee (Date: 18.08.2020, Decision No: E1-20-977). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Comorbidities

Sex, age, type of surgery (open or laparoscopic), comorbidities including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, peripheral arterial disease, hyperlipidemia, cerebrovascular disease, rheumatological diseases, hypothyroidism, hyperthyroidism, osteoporosis, cancer, hyperprolactinemia, polycystic ovary syndrome, benign prostate hyperplasia and history of organ transplantation were recorded using electronic health records, physician and nursery reports.

### Laboratory Findings

Admission laboratory parameters [white blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophil, basophil, red blood cell (RBC), hemoglobin hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, mean platelet volume (MPV), procalcitonin (PCT), platelet distribution width (PDW), large unstained cells (LUC), urea, creatinine, C-reactive protein (CRP), lactate dehydrogenase (LDH), sodium, potassium, direct/indirect/total bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin] were recorded for each patient. Neutrophil-lymphocyte-platelet ratio (NLPR), mean platelet volume/platelet count ratio (MPR), lymphocyte-to-monocyte ratio (LMR), systemic immune inflammation index (SII), prognostic nutritional index (PNI) and monocyte to platelet ratio were calculated for each patient. The SII was calculated by the formula: neutrophil×platelet/lymphocyte and the PNI was calculated as 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (per $mm^3$).

### Outcomes

Patients were classified into two groups as complicated and non-complicated appendicitis. Those with perforation, peritonitis and/or gangrenous/necrotizing changes on pathology were classified as complicated appendicitis or simple appendicitis without complication were classified as non-complicated appendicitis as described previously in details (2,7).

### Statistical Method

All statistical evaluations were done using Stata MP 16. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. Mean values (with standard deviation) were used for numerical variables with normal distribution. Categorical variables were specified as numbers and percentages. Student T test was used to compare numerical variables with normal distribution between the two groups, and Mann-Whitney U test was used to compare numerical variables without normal distribution. A stepwise backward regression model was used to identify independent predictors of acute complicated appendicitis. The diagnostic performance of the regression model was evaluated by receiver operating characteristic (ROC) analysis. Cases where type-1 error level was below 5% ($p < 0.05$) were considered as statistically significant.

## RESULTS

### Patient Characteristics

Totally 615 patients underwent appendectomy, of which 32 (5.2%) who had normal appendix, and 8 (1.3%) who had malignant tumors in appendix were excluded. Finally, 575 patients [432 (75.1%) with non-complicated appendicitis and 143 (24.9%) with complicated appendicitis] were included in the study.

Laparoscopic surgery was performed in 49 patients. (13 complicated and 36 non complicated cases) (**Figure 1**).

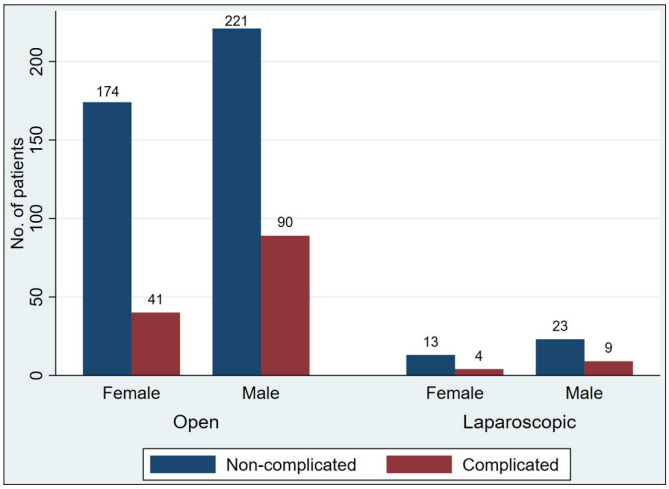


**Figure 1.** Number of patients according to sex and type of surgery in complicated vs. non-complicated groups

The mean (SD) age of the enrolled 575 patients was 34.2±14.2. Of these patients, 343 (59.7%) were male and 232 (40.3%) were female. Hypertension (7.5%, n=43), diabetes mellitus (4.7%, n=27) and hypothyroidism (3.8%, n=22) were the most frequent comorbidities in the study population. Male gender was significantly higher in complicated group [n=99 (68.5%) in complicated vs. n=244 (56.4%) in non-complicated group (p=0.011)]. Among the comorbidities, cerebrovascular disease was significantly higher in complicated group [n=2 (1.4%) in complicated vs. n=0 (0%) in non-complicated group (p=0.014)]. Demographic characteristics of the enrolled patients are summarized in **Table 1**.

### Laboratory Findings

The mean (SD) levels of monocyte count [0.7 (0.3) in complicated vs. 0.6 (0.3) in non-complicated group (p=0.031)], CRP [105.8 (86.6) in complicated vs. 61.6 (76.5) in non-complicated group (p<0.001)], ALT [27.4 (19.6) in complicated vs. 23.1 (17.5) in non-complicated group (p=0.016)], GGT [30.3 (28.4) in complicated vs. 22.5 (19.0) in non-complicated groups (p<0.001)] were significantly higher in the complicated appendicitis compared to non-complicated appendicitis group. While the mean of RDW [13.4 (1.0) in complicated vs. 13.7 (1.3) in non-complicated group (p=0.021)] was significantly lower in complicated appendicitis group. The detailed laboratory findings of enrolled patients are presented in **Table 2**.

### The Predictors of Complicated Appendicitis

In backward stepwise regression, age (OR, 1.026; 95% CI, 1.006-1.046; p=0.010), male gender (OR, 1.837; 95% CI, 1.017-3.318; p=0.044), the mean levels of LUC (OR, 19.868; 95% CI, 1.260-313.243; p=0.034) and GGT (OR, 1.013; 95% CI, 1.003-1.023; p=0.013) were associated with a higher risk of complicated appendicitis. In addition, the monocyte to platelet ratio (OR, 0.920; 95% CI, 0.847-0.999; p=0.047) was associated with a lower risk of complicated appendicitis (**Table 3**). In the ROC curve analysis of stepwise backward model AUC was 0.69 (95% CI, 0.64-0.72; p<0.001) (**Figure 2**).

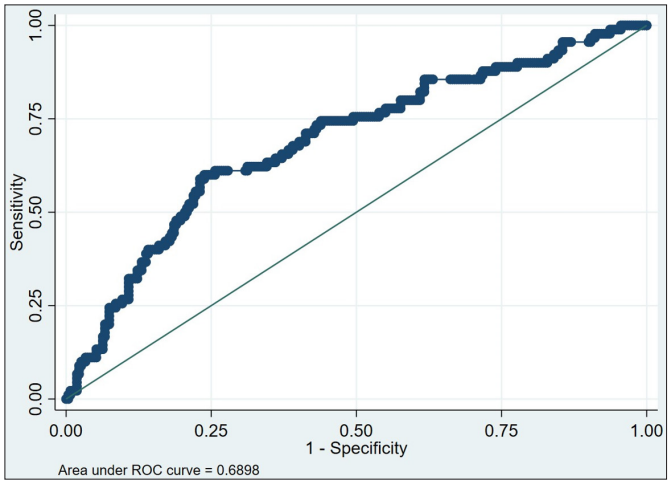


**Figure 2.** ROC curve of regression model for predicting complicated acute appendicitis

**Table 1.** Baseline characteristics of patients in complicated vs. non-complicated groups

| | Total n=575 | Non-complicated n=432 | Complicated n=143 | p |
|---|---|---|---|---|
| Age, mean (SD) | 34.2 (14.2) | 33.6 (14.1) | 36.0 (14.3) | 0.078 |
| Male, n (%) | 343 (59.7%) | 244 (56.4%) | 99 (68.5%) | 0.011 |
| Hypertension, n (%) | 43 (7.5%) | 32 (7.4%) | 11 (7.7%) | 0.91 |
| Diabetes mellitus, n (%) | 27 (4.7%) | 22 (5.1%) | 5 (3.5%) | 0.43 |
| Chronic obstructive pulmonary disease, n (%) | 5 (0.9%) | 4 (0.9%) | 1 (0.7%) | 0.81 |
| Coronary artery disease, n (%) | 15 (2.6%) | 11 (2.5%) | 4 (2.8%) | 0.87 |
| Congestive heart failure, n (%) | 4 (0.7%) | 3 (0.7%) | 1 (0.7%) | 0.99 |
| Peripheral arterial disease, n (%) | 1 (0.2%) | 0 (0.0%) | 1 (0.7%) | 0.082 |
| Hyperlipidemia, n (%) | 3 (0.5%) | 1 (0.2%) | 2 (1.4%) | 0.093 |
| Cerebrovascular disease, n (%) | 2 (0.3%) | 0 (0.0%) | 2 (1.4%) | 0.014 |
| Rheumatoid disease, n (%) | 11 (1.9%) | 9 (2.1%) | 2 (1.4%) | 0.60 |
| Hypothyroidism, n (%) | 22 (3.8%) | 16 (3.7%) | 6 (4.2%) | 0.79 |
| Hyperthyroidism, n (%) | 2 (0.3%) | 2 (0.5%) | 0 (0.0%) | 0.42 |
| Osteoporosis, n (%) | 1 (0.2%) | 1 (0.2%) | 0 (0.0%) | 0.57 |
| Cancer, n (%) | 2 (0.3%) | 1 (0.2%) | 1 (0.7%) | 0.82 |
| Hyperprolactinemia, n (%) | 1 (0.2%) | 1 (0.2%) | 0 (0.0%) | 0.57 |
| Polycystic ovarian syndrome, n (%) | 1 (0.2%) | 1 (0.2%) | 0 (0.0%) | 0.57 |
| Benign prostate hyperplasia, n (%) | 3 (0.5%) | 2 (0.5%) | 1 (0.7%) | 0.73 |
| History of organ transplantation, n (%) | 1 (0.2%) | 0 (0.0%) | 1 (0.7%) | 0.082 |

**Table 2.** Admission laboratory findings of the study population in complicated vs. non-complicated groups

| | Total n=575 | Non-Complicated n=432 | Complicated n=143 | p |
|---|---|---|---|---|
| White blood cell, (x109/L) | 13.6 (4.2) | 13.4 (4.3) | 13.9 (3.8) | 0.28 |
| Neutrophil, (x109/L) | 11.0 (4.2) | 10.9 (4.3) | 11.3 (3.9) | 0.32 |
| Lymphocyte, (x109/L) | 1.7 (0.8) | 1.7 (0.8) | 1.7 (0.8) | 0.90 |
| Monocyte, (x109/L) | 0.6 (0.3) | 0.6 (0.3) | 0.7 (0.3) | 0.031 |
| Eosinophil, (x109/L) | 0.1 (0.1) | 0.1 (0.1) | 0.1 (0.1) | 0.060 |
| Basophil, (x109/L) | 0.0 (0.1) | 0.0 (0.1) | 0.0 (0.0) | 0.49 |
| Red blood cell, (x1012/L) | 4.9 (0.5) | 4.9 (0.5) | 4.9 (0.5) | 0.13 |
| HGB, (g/dL) | 14.2 (1.8) | 14.2 (1.9) | 14.4 (1.6) | 0.25 |
| HCT, (%) | 42.4 (5.1) | 42.3 (5.3) | 42.8 (4.4) | 0.30 |
| MCV, (fL) | 87.0 (6.4) | 87.1 (6.7) | 86.8 (5.2) | 0.57 |
| MCH, (pg/cell) | 29.2 (2.5) | 29.2 (2.5) | 29.2 (2.2) | 0.90 |
| MCHC, (g/dL) | 33.5 (1.3) | 33.5 (1.3) | 33.6 (1.4) | 0.43 |
| RDW, (%) | 13.6 (1.3) | 13.7 (1.3) | 13.4 (1.0) | 0.021 |
| PLT, (x109/L) | 265.9 (66.4) | 266.0 (68.7) | 265.9 (59.1) | 0.99 |
| MPV, (fL) | 7.7 (0.9) | 7.7 (0.9) | 7.8 (0.9) | 0.49 |
| PCT, (%) | 0.2 (0.1) | 0.2 (0.1) | 0.2 (0.0) | 0.69 |
| PDW, (%) | 55.2 (9.8) | 55.3 (10.2) | 55.0 (8.4) | 0.74 |
| LUC, (x109/L) | 0.1 (0.1) | 0.1 (0.1) | 0.2 (0.1) | 0.27 |
| Urea, (mg/dL) | 27.6 (8.8) | 27.6 (9.2) | 27.7 (7.5) | 0.95 |
| Creatinine, (mg/dL) | 0.8 (0.8) | 0.9 (0.9) | 0.8 (0.2) | 0.60 |
| C-reactive protein, (g/L) | 72.1 (81.1) | 61.6 (76.5) | 105.8 (86.6) | <0.001 |
| LDH, (U/L) | 208.5 (56.6) | 208.2 (56.4) | 209.4 (57.4) | 0.84 |
| Sodium, (mEq/L) | 138.9 (2.4) | 139.0 (2.4) | 138.9 (2.6) | 0.59 |
| Potassium, (mEq/L) | 4.1 (0.3) | 4.1 (0.3) | 4.1 (0.3) | 0.63 |
| Direct Bilirubin, (mg/dL) | 0.4 (4.2) | 0.5 (4.8) | 0.3 (0.2) | 0.61 |
| Indirect Bilirubin, (mg/dL) | 0.8 (0.7) | 0.8 (0.7) | 0.7 (0.6) | 0.59 |
| Total Bilirubin, (mg/dL) | 1.1 (0.8) | 1.1 (0.9) | 1.1 (0.7) | 0.87 |
| AST, (U/L) | 23.3 (10.8) | 23.1 (10.7) | 24.0 (11.0) | 0.41 |
| ALT, (U/L) | 24.2 (18.1) | 23.1 (17.5) | 27.4 (19.6) | 0.016 |
| GGT, (U/L) | 24.4 (22.0) | 22.5 (19.0) | 30.3 (28.4) | <0.001 |
| ALP, (U/L) | 78.7 (26.2) | 77.8 (26.9) | 81.2 (23.7) | 0.18 |
| Albumin, (g/L) | 45.7 (3.3) | 45.7 (3.3) | 45.7 (3.3) | 0.99 |
| Total Protein, (g/L) | 70.2 (4.9) | 70.2 (4.7) | 70.2 (5.5) | 0.96 |
| NLPR Index | 3.4 (2.9) | 3.3 (2.6) | 3.6 (3.8) | 0.19 |
| MPR Index | 40.2 (12.7) | 40.3 (13.1) | 39.9 (11.3) | 0.73 |
| LMR Index | 3.2 (2.1) | 3.3 (1.9) | 3.1 (2.6) | 0.31 |
| SII Index | 2154.2 (1595.1) | 2132.5 (1632.5) | 2219.7 (1479.7) | 0.57 |
| PNI Index | 450.9 (62.9) | 449.9 (66.6) | 454.1 (50.3) | 0.49 |

**Table 3.** Significant predictors of complicated acute appendicitis according to stepwise backward model

| | Odds Ratio (95% Confidence Interval) | p |
|---|---|---|
| Age | 1.026 (1.006-1.046) | 0.010 |
| Male | 1.837 (1.017-3.318) | 0.044 |
| LUC | 19.868 (1.260-313.243) | 0.034 |
| GGT | 1.013 (1.003-1.023) | 0.013 |
| Monocyte to platelet ratio (MPR) | 0.920 (0.847-0.999) | 0.047 |

## DISCUSSION

In addition to risk of surgical complications and absence from work, appendectomy, including the admission and 1-year follow-up, is known to be 1.6 times more expensive than conservative treatment (8). To avoid these disadvantages of appendectomy, non-operative treatment with antibiotics should be considered in non-complicated patients in certain circumstances.

The present retrospective cohort study was performed to evaluate the predictive factors of complicated appendicitis. Our results demonstrate that age is one of the predictors of complicated appendicitis. Similarly, in a study comparing complicated and non-complicated appendicitis based on patient characteristics and imaging features, Atema et al recently showed that the age over 45 years is associated with a higher risk of complicated appendicitis (9). In their study including 895 patients who underwent appendicectomy, Eddama et al. also reported that increased age was associated with increased risk of complicated appendicitis (10).

Even if it is known that acute appendicitis incidence is higher in male gender (11), the previous studies did not find an association between male gender and complicated appendicitis (12). In the present study after adjusting for confounding variables, we observed that male gender was associated with a higher risk of complicated appendicitis.

Several studies reported that CRP and bilirubin levels were significant predictors of complicated appendicitis (13,14). As well, in this study CRP and GGT levels were significant factors in predicting complicated appendicitis.

Although increased levels of LUC have previously been associated with leukemia, viral and fungal infections, to the best of our knowledge, this is the first study demonstrating that the increase in large unstained cells (LUC) is a statistically significantly risk factor in the prediction model of complicated appendicitis (15). The reason for this increase remains uncertain (16).

In addition to biomarkers, we compared comorbidities in patients with complicated and non-complicated appendicities and found that the rates of comorbidities did not differ significantly between the two groups. Although the rate of cerebrovascular disease seemed to be significantly higher in the complicated group, this appeared to be due to its low frequency in the study population and absence in the non-complicated group.

This study had several limitations. First, the study was a retrospective study and not randomized. Secondly, imaging methods such as CT scan and USG has not been included to analysis. Furthermore, the study does not contain the medical examination and surgical observation reports of patients.

In conclusion, in this study, it was demonstrated that, age, male gender, the mean levels of LUC, GGT and monocyte to platelet ratio were predictors of complicated appendicitis. Using these parameters, non-complicated appendicitis could be distinguished from complicated cases to be treated conservatively with antibiotics..

## ETHICAL DECLARATIONS

**Ethics Committee Approval**: Approval for the study was granted by the Ankara City Hospital No 1 Clinical Researches Ethics Committee (Date: 18.08.2020, Decision No: E1-20-977).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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