European Review for Medical and Pharmacological Sciences 2022; 26: 820-827

Significance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, serum albumin and prognostic nutritional index as predictors of morbidity in super-elderly patients operated on for acute appendicitis

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Abstract. – OBJECTIVE: Both life expectancy and the proportion of the population in elderly are increasing. Therefore, the number of cases of acute appendicitis (AA) among the super-elderly population is increasing. In this study, it is aimed to find the correlations between morbidity and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin and prognostic nutritional index (PNI) in super-elderly patients.

PATIENTS AND METHODS: In this retrospective study, we studied super-elderly patients (85 years old and above) who were operated on due to AA between January 2015 and January 2020 at a tertiary health center. After approval by the ethics committee, patients' preoperative, peroperative and postoperative data were collected. Patients were divided into two groups: the morbidity-positive (+) group and the morbidity-negative (-) group. The differences between the two groups regarding the parameters investigated were evaluated.

RESULTS: 25 super-elderly patients were operated on for AA. There were 7 patients in the morbidity (+) group and 18 in the morbidity (-) group. The area under the curve (AUC) for NLR was 0.476 ([95% CI: 0.215-0.738]; p = 0.856), and the AUC for PLR was 0.444 ([95% CI: 0.193-0.696]; p = 0.672). However, the AUC for PNI was 0.810 ([95% CI: 0.569-1.000]; p = 0.018), and the AUC for albumin was 0.845 ([95% CI: 0.601-1.000]; p = 0.008). At the cut-off value of 3.35 g/dL, albumin's sensitivity was 88.9% and its specificity was 85.7%. At the cut-off value of 38, PNI's sensitivity was 94.4% and its specificity was 71.4%.

CONCLUSIONS: The present study found that PNI and albumin values can be used as prognostic factors and have high sensitivity and specificity. Therefore, this study is a leader study in identifying prognostic factors for AA that can be used in the super-elderly geriatric population. However, the possibility of statistical error should be minimized by conducting studies involving more patients.

Key Words:
Appendicitis, Morbidity, Albumin, Prognostic nutritional index, Super-elderly.

Introduction

Acute appendicitis (AA) is the most common cause of acute abdominal pain in patients in all age groups who were admitted to emergency departments. The clinical signs and symptoms of AA begin with visceral peritoneum sensitivity, and parietal peritoneum sensitivity is added to the clinical picture with increased inflammation. As infection in the body increases, it is expected that inflammatory parameters, including leucocyte count and C-reactive protein, will also increase[1,2].

If the diagnosis of AA or the performance of surgery are delayed, both morbidity and mortality increase. The literature indicates a morbidity rate for AA of up to 10% and a mortality rate of up to 5%[3]. Careful examination of elderly patients is required because they are difficult to diagnose and have a high number of comorbid diseases and high rates of complications[4]. Also, as age increases, so does the possibility of early perforation, as the muscular layer of the appendix is thinner than in the young. Luckily, surgical treatments and the rates of postoperative morbidity and death for elderly patients

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have improved in accordance with developments in perioperative management, anesthesia, and surgical methods[5].

The prolongation of lifespan has changed the definition of 'old age', which according to the World Health Organization (WHO) is divided into three subgroups: early senility, between the ages of 65 and 74; old age, between the ages of 75 and 84; and advanced old age (super-elderly), at ages 85 and older. Thanks to developments in and the increased availability of healthcare, as well as improvements in healthcare delivery globally, both life expectancy and the proportion of the population that is elderly are increasing[4]. Therefore, the number of cases of AA among the super-elderly population is increasing. In addition, surgeons are more likely to encounter morbidity and mortality after appendectomies. To decrease morbidity and mortality, new markers are needed, and the super-elderly population is unexplored regarding this issue. To fill this gap in the literature, we conducted a study aimed to find identifying new parameters.

In this study, we aimed to find the correlations between morbidity and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin and prognostic nutritional index (PNI) at super-elderly patients.

Patients and Methods

This retrospective study included super-elderly patients who were operated on due to AA between January 2015 and January 2020 at Erzurum Regional Education and Research Hospital, Erzurum, Turkey. Patients' hospital records, consultation and operation notes, pathology reports and clinical charts were used.

The study excluded patients under 85 years of age and those who were operated on at external centers and then admitted to our center due to complications. After approval by the ethics committee, patients' preoperative, peroperative and postoperative data were collected, and patients were divided into two groups: patients who developed complications in the 30 days after surgery were considered as the morbidity-positive group, and those without complications were considered as the morbidity-negative group. The differences between the two groups regarding the parameters investigated were evaluated.

The preoperative factors included patients' ages, gender, comorbidities, previous surgical history, laboratory parameters and the additional diagnostic tools (ultrasonography or computed tomography) were used. The basic hematological parameters and serum albumin levels were identified, and the NLR, PLR and PNI values were calculated. The NLR is calculated by dividing the number of neutrophils by the number of lymphocytes. The PLR is calculated by dividing the number of platelets by the number of lymphocytes. The PNI is calculated using a simple mathematical formula: PNI = (10 × serum albumin [g/dL]) + (0.005 × lymphocytes/μL).

The peroperative factors evaluated included surgery type and incision type. All the surgeries were performed using general anesthesia. Laparoscopic surgery and open surgery were used for treatment. All laparoscopic appendectomies were performed using three trocar methods: supra-umbilical, supra-pubical and left pararectal. All open surgeries were performed *via* a McBurney incision.

In addition, postoperative complications and pathological diagnoses of appendix specimens were evaluated. Phlegmonous appendicitis, catarrhal appendicitis, suppurative appendicitis) were evaluated as non-complicated appendicitis, while gangrenous appendicitis, perforated appendicitis, plastron appendicitis were evaluated as complicated appendicitis. The lengths of hospital stay of those in the two morbidity groups were compared.

Statistical Analysis

The statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). A Shapiro-Wilk test was used to assess the normality distribution of the quantitative variables. According to the results of the Shapiro-Wilk test, an Independent-Samples *t*-test or Mann-Whitney U test was used to compare the morbidity groups. Chi-square tests were used to compare the qualitative variables. A p-value < 0.05 was considered statistically significant. In addition, the area under the curve (AUC) and the sensitivities and specificities of NLR, PLR, albumin and PNI were calculated using the receiver operating characteristic (ROC) curve.

Ethics committee approval was received from Non-invasive Clinical Research Ethics Committee of Erzurum Regional Education and Research Hospital, Erzurum, Turkey (Decision: 2021/12-205).

Results

Between January 2015 and January 2020, 25 super-elderly patients were operated on for AA. These patients were divided into two groups: the morbidity-positive (+) group and the morbidity-negative (-) group. There were 7 patients in the morbidity (+) group and 18 in the morbidity (-) group.

Of the 25 patients, 15 (60%) were female, and the mean age was 88.92 ± 4.5 (range: 85-104). Table I shows patients' preoperative, peroperative and postoperative data. The patients' histories showed that 20 (80%) had at least one comorbid disease and that 4 (16%) had a history of cholecystectomy. Mean rank of NLR (13.00 *vs.* 13.00; $p>0.999$), PLR (13.60 *vs.* 10.60; $p=0.447$), albumin (13.35 *vs.* 11.60; $p=0.668$) and PNI (12.88 *vs.* 13.50, $p=0.869$) were statistically same in patients with and without comorbidity.

23 (92%) surgeries were open surgeries performed *via* a McBurney incision. Postoperative complications were seen in 7 (28%) patients, 6 of 7 after open surgeries. Wound abscess was seen in three patients, wound hematoma in two patients, wound seroma in one patient and intra-abdominal (peri-cecal) abscess in one patient. All wound complications were treated using drainage and daily cleaning. The abdominal abscess was treated using 1 gram of intravenous ertapenem (1 vial) per day for 7 days. The abscess regressed after antibiotherapy.

Mortality was seen in only 1 (4%) patient who had 3 comorbid diseases (severe chronic obstructive pulmonary disease, congestive heart failure and hypertension), and this mortality occurred on postoperative day 1 due to severe comorbid diseases. This patient's PNI levels and serum albumin levels were 39.5 and 3.2 g/dL, respectively.

The most common pathological diagnosis was non-complicated appendicitis in 19 (76%) patients. Albumin level was significantly higher at the patients with non-complicated appendicitis (14.61 *vs.* 7.92, $p=0.050$). However, PNI was not higher significantly at the patients with non-complicated appendicitis (14.55 *vs.* 8.08, $p=0.059$). Similarly, there was no significant difference in the comparison of NLR and PLR levels of patients with complicated and non-complicated appendicitis, $p=0.926$ and $p=0.642$, respectively.

The mean length of hospital stay was 2.76 ± 1.85 days (range: 1-8) without a difference between the morbidity groups. Among the parameters evaluated, only albumin and PNI differed statistically between the two morbid-

Table I. Patients' preoperative, peroperative and postoperative data.

Variables	N (%) or value
Preoperative Factors	
Age (mean + sd, year)	88.92 ± 4.5 (85-104)
Gender	
• Female	15 (60%)
• Male	10 (40%)
Comorbidity	
• One comorbid disease	
HT	6 (24%)
COPD	3 (12%)
• Two comorbid diseases	
HT and COPD	4 (16%)
HT and CHF	3 (12%)
HT and DM	1 (4%)
• Three comorbid diseases	
HT, COPD and CHF	3 (12%)
• None	5 (20%)
Previous Operation	
• Yes	4 (16%)
• No	21 (84%)
Laboratory Parameters (mean+sd)	
• Wbc ($10^3/mm^3$)	11.67 ± 6.41 (4.3-32.9)
• Hb (g/dL)	13.34 ± 1.98 (8.1-16.8)
• Plt ($10^3/mm^3$)	241.8 ± 59.48 (125-401)
• Neutrophil (Neu) ($10^3/mm^3$)	9.31 ± 6.49 (2.76-30.5)
• Neu %	76.42 ± 13.24 (52.4-97.4)
• Lymphocyte (Lym) ($10^3/mm^3$)	1.5 ± 0.93 (0.2-3.7)
• Lym %	16.46 ± 10.4 (1.8-36.8)
• NLR	10.75 ± 14.46 (1.44-54.1)
• PLR	248.98 ± 231.34 (50-1220)
• Albumin (g/dL)	3.64 ± 0.63 (2.1-4.5)
• PNI	43.98 ± 8.41 (25-62.5)
Diagnose	
• Clinically	9 (36%)
• USG	6 (24%)
• CT	5 (20%)
• USG and CT	5 (20%)
Peroperative Factors	
Type of Surgery	
• Laparoscopic	2 (8%)
• Open	23 (92%)
Type of Incision	
• McBurney incision	23 (92%)
• Three trocar method	2 (8%)
Postoperative Factors	
Pathological Evaluation	
• Non-complicated appendicitis	19 (76%)
• Complicated appendicitis	6 (24%)
Overall Morbidity	7 (%28)
Overall Mortality	1 (4%)
LOS (Mean+sd, days)	2.76 ± 1.85 (1-8)

HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, DM: Diabetes mellitus, Wbc: White blood cell, Hb: Hemoglobin, Plt: Platelet, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, USG: Ultrasonography, CT: Computed tomography, LOS: Length of stay.

ity groups. Both the albumin and PNI values were lower in the morbidity (+) group and had p=0.006 and p=0.017, respectively. Table II groups the patients' preoperative, peroperative and postoperative parameters according to morbidity.

NLR, PLR, albumin, and PNI were evaluated using the ROC curve. The AUC for NLR was 0.476 ([95% CI: 0.215-0.738]; p = 0.856), and the AUC for PLR was 0.444 ([95% CI: 0.193-0.696]; p = 0.672). These two factors were not suitable for predicting morbidity. However, the AUC for PNI was 0.810 ([95% CI: 0.569-1.000]; p = 0.018), and the AUC for albumin was 0.845 ([95% CI: 0.601-1.000]; p = 0.008). At the cut-off value of 3.35 g/dL, albumin's sensitivity was 88.9% and its specificity was 85.7%. At the cut-off value of 38, PNI's sensitivity was 94.4% and its specificity was 71.4%. Figure 1 shows ROC curves of NLR, PLR, albumin, and PNI.

Table II. The patients' preoperative, peroperative and postoperative parameters according to morbidity.

Parameters	Morbidity (+) (n = 7)	Morbidity (-) (n = 18)	p-value
Preoperative Factors			
Age (mean rank)	14.29	12.50	0.615*
Gender			0.179**
• Female	6 (40%)	9 (60%)	
• Male	1 (10%)	9 (90%)	
Comorbidity			> 0.999**
• Yes	1 (20%)	4 (80%)	
• No	6 (30%)	14 (70%)	
Previous Operation			0.548**
• Yes	5 (23.8%)	16 (76.2%)	
• No	2 (50%)	2 (50%)	
Laboratory Parameters			
• WBC (mean rank)	13.14	12.94	0.976*
• Hb (mean, g/dL)	12.90	13.51	0.501***
• PLT (mean, $10^3/mm^3$)	240.42	242.33	0.944***
• Neutrophil (Neu) (mean rank)	13.57	12.78	0.836*
• Neu % (mean)	78.58	75.58	0.622***
• Lymphocyte (Lym) (mean rank)	12.00	13.39	0.701*
• Lym % (mean)	15.14	16.98	0.700***
• NLR (mean rank)	13.43	12.83	0.883*
• PLR (mean rank)	14.00	12.61	0.701*
• Albumin (mean rank)	6.79	15.42	0.006*
• PNI (mean rank)	7.43	15.17	0.017*
Diagnose			0.084****
• Clinically	2 (22.2%)	7 (77.8%)	
• USG	0 (0%)	6 (100%)	
• CT	2 (40%)	3 (60%)	
• USG and CT	3 (60%)	2 (40%)	
Peroperative Factors			
Type of Surgery			0.490**
• Laparoscopic	1 (50%)	1 (50%)	
• Open	6 (26.1%)	17 (73.9%)	
Type of Incision			0.490**
• McBurney incision	6 (26.1%)	17 (73.9%)	
• Three trocar method	1 (50%)	1 (50%)	
Postoperative Factors			
Pathological Evaluation			0.298****
• Non- complicated	4 (21.1%)	15 (78.9%)	
• Complicated	3 (50%)	3 (50%)	
LOS (mean rank)	16.79	11.53	0.110

Wbc: White blood cell, Hb: Hemoglobin, Plt: Platelet, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, USG: Ultrasonography, CT: Computed tomography, LOS: Length of stay. *Mann Whitney U-Test,**Chi-Square Test, ***Independent t-test, ****Likelihood Ratio Test.

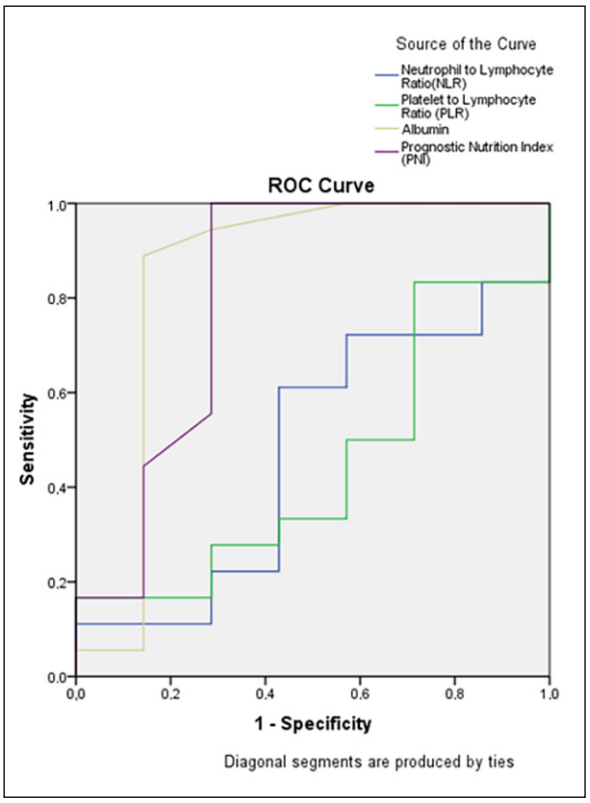

Figure 1. ROC curves of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, Serum Albumin and Prognostic Nutritional Index.

Discussion

AA's epidemiology and outcomes are different in elderly patients than in younger ones. First, although the elderly has fewer incidents of AA, they experience both higher morbidity and higher mortality[6]. At geriatric ages, the incidence of perforated appendicitis is 7% and has a morbidity rate approaching 17-20%[7]. In a population-based AA study conducted in Finland, those older than 65 were at significant risk of mortality[8]. Compared to young appendectomy patients, elderly patients are burdened with higher postoperative mortality and morbidity[9].

Morbidity and mortality due to AA are important problems, and although many studies have addressed preventing both, only a limited number have included patients of advanced geriatric age. Factors such as NLR and PLR have been investigated in all age groups. The present study investigated these two commonly used ratios along with PNI and albumin levels, thereby bringing a different perspective to the subject of morbidity in patients undergoing appendectomy at super-elderly ages.

The first clinical study of NLR in humans was by Goodman et al[10] in 1995 and found that NLR was a useful marker for AA, with a cut-off value of 3.5 and high sensitivity. Over time, studies showed the uses of NLR as a cancer biomarker[11,12] and later determined the usability of NLR outside the surgical field. Yavuz et al[13] found that NLR had a 92.5% sensitivity and a 59.3% specificity in those 65 years and older with a cut-off value of 3.93. However, Cigsar et al[14] found that NLR could not predict geriatric positive appendectomies at a cut-off value of 5.35. In the present study, the AUC for NLR was 0.476 ([95% CI: 0.215-0.738]; $p = 0.856$), meaning that NLR is not a marker of AA in the super-elderly geriatric population.

PLR is a recently discovered marker, and its first use was in periampullary tumours[15]. In 2012, other studies showed a correlation between PLR and cardiovascular diseases[16]. In addition, PLR has been shown to be a good prognostic marker in various cancer types, including hepatic, colorectal, pancreatic, gastroesophageal and breast cancer[17]. Kahramanca et al[18] demonstrated the utility of PLR in diagnosing AA [cut-off value: 136.5, AUC: 0.568; $p = 0.036$ (CI% 95: 0.508-0.628)][18]. Pehlivanli et al[19] found PLR useful as a prognostic biomarker in differentiating AA from perforated appendicitis, regardless of age group. In contrast, Topal et al[20] found that PLR was not useful in any age group: in the 18–39 age group, the AUC was 0.654, $p < 0.001$; in the 40-59 age group, the AUC was 0.612, $p = 0.001$; and in age groups ≥ 60, the AUC was 0.561, $p = 0.134$[20]. In the present study, the AUC for PLR was 0.444 ([95% CI: 0.193–0.696]; $p = 0.672$), meaning that PLR was not a marker of AA in the super-elderly geriatric population.

Serum albumin is an inflammatory marker and a negative acute phase protein that can be used as a marker for all inflammatory diseases. Regardless of the localized or generalized nature of the disease, the acute phase response is a general host reaction. The clinical symptoms of AA begin with visceral peritoneum sensitivity, and parietal peritoneum sensitivity is added to the clinical picture with increased inflammation. As inflammation increases, negative acute phase proteins decrease. Therefore, in advanced inflammation, serum albumin levels decrease.

Cases with low albumin may be more inflamed and more likely to have complicated appendicitis.

Ishizuka et al[21] found that serum albumin levels were lower in patients who had gangrenous appendicitis than in patients who had catarrhal appendicitis (p = 0.004). Also, the same study found a relationship between albumin levels and gangrenous appendicitis using univariate analysis (p < 0.001, OR: 0.431 [95% CI: 0.267-0.694]) but no correlation when using multivariate analysis (p = 0.544, OR: 0.770 [95% CI: 0.331-0.793]). In the present study, the AUC for albumin was 0.845 ([95% CI: 0.601-1.000]; p = 0.008), which is similar to the results in the literature. In addition, at a cut-off value of 3.35 g/dL, albumin's sensitivity was 88.9% and its specificity was 85.7%. Therefore, lower albumin level is an important marker for AA in the super-elderly geriatric population regardless of the presence of comorbid disease.

PNI is an effective parameter for evaluating preoperative nutritional conditions and surgical risk. Recently, it has been found to be associated with outcomes in various malignancies and inflammatory diseases. PNI is calculated using only two values: serum albumin concentration and lymphocyte count. Serum albumin concentration is lower in cases of infectious disease, including AA. In addition, because AA is a bacterial infectious disease, the neutrophil count is increased, and the lymphocyte count is decreased. Therefore, in infectious diseases, the PNI is expected to be low. In fact, the lower the PNI value, the more severe the infection.

PNI is a relatively new topic of research, and studies regarding it are limited. A study that compared interval laparoscopic appendectomy and non-interval laparoscopic appendectomy found no difference between the two techniques in terms of PNI (p = 0.82)[22]. Ikeguchi et al[23] found that patients who had colorectal perforation and low preoperative PNIs required special attention to prevent the occurrence of postoperative wound complications. In the present study, the AUC for PNI was 0.810 ([95% CI: 0.569-1.000]; p = 0.018). For the cut-off value of 38, PNI's sensitivity was 94.4%, and its specificity was 71.4%. PNI is an important marker of AA in the super-elderly geriatric population regardless of the presence of comorbid disease.

Limitations

Our study is a retrospective study, and due to the limited data obtained, it prevented the examination of more parameters. In addition, the number of patients included in the study was also limited, as a very specific age group (85 years old and above) was examined. This is an important obstacle to reach a large number of patients. Therefore, the possibility of statistical error should be minimized, and more accurate results should be obtained by conducting studies involving more patients.

Today, laparoscopic surgery is at the forefront in the surgical treatment of acute appendicitis, and the use of laparoscopic surgery was limited in our study due to surgeon preference and accompanying comorbid diseases. Therefore, more data are needed on laparoscopic appendectomy in super-elderly patients.

Conclusions

AA is a worldwide problem that can occur at any age, but its morbidity and mortality increase in geriatric patients. Furthermore, studies on AA in the super-elderly (85 years and older) geriatric population are limited. More studies are needed on ways to prevent morbidity and mortality and find prognostic factors for use in the elderly population. The present study found that PNI and albumin values can be used as prognostic factors and have high sensitivity and specificity. Therefore, this study is a very important research aimed at identifying prognostic factors for AA that can be used in the super-elderly geriatric population.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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Authors' Contribution

Concept: T.K, M.K., Design: T.K, M.K., Data Collection or Processing: T.K, M.K., Analysis or Interpretation: T.K., Writing: T.K, M.K.

Availability of Data

Primary data used in this research article will be available on request.

Informed Consent
Informed consent was not sought for the present study because the retrospective data retrieval would not affect patients' clinical management.

Ethical Approval
Ethics committee approval was received from Non-invasive Clinical Research Ethics Committee of Erzurum Regional Education and Research Hospital, Erzurum, Turkey (Decision: 2021/12-205).

Human Rights Statement
This study was completed in accordance with the Helsinki Declaration.

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