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Systemic inflammatory markers for distinguishing uncomplicated and complicated acute appendicitis in adult patients

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ABSTRACT

OBJECTIVE: This study aimed to investigate the predictive power of serum systemic inflammatory markers including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-eosinophil ratio (MER), and C-reactive protein (CRP) levels for distinguishing uncomplicated and complicated acute appendicitis in adult patients admitted to the emergency department (ED).

METHODS: This retrospective, cross-sectional, observational, and single-center study enrolled 212 consecutive adult patients with acute appendicitis who were admitted to the ED of our tertiary care university hospital between January 1, 2019 and December 31 2021. Patients were divided into two groups (Group I, uncomplicated acute appendicitis; Group II, complicated appendicitis) according to their surgical findings and histopathological examination. Systemic inflammatory markers measured on admission were compared among patients to identify factors associated with complicated acute appendicitis.

RESULTS: A total of 132 patients, 83 male (62.9%) and 49 female (37.1%), were included in the study. The mean age was 34.7±13.40 years. Based on the histopathological examination, the number of patients in Group I was 103 (78.03%) and 29 (21.96%) in Group II. Laboratory findings on admission revealed no significant differences between Groups I and II patients in terms of mean serum NLR, MER, and CRP values (p=0.096, p=0.248, and p=0.297, respectively). However, the mean serum PLR in Group II patients was statistically significantly higher than those in Group I (p=0.032). The mean serum monocyte and monocyte fraction (%) values were significantly lower, and the mean serum neutrophil fraction (%) value was higher in Group II patients compared to those with Group I. Receiving operator characteristic (ROC) analysis identified a serum PLR cutoff value of ≥133.73 for distinguishing uncomplicated and complicated acute appendicitis in adult patients, with 60% sensitivity and 58.4% specificity. In addition, ROC analysis revealed a cutoff monocyte fraction (%) level of ≤6, with 72% sensitivity and 64% specificity, for distinguishing uncomplicated and complicated acute appendicitis in adult patients.

CONCLUSION: Our findings indicate that the mean serum NLR, MER, and CRP values measured on admission to ED in adult patients with acute appendicitis could not predict complicated acute appendicitis. However, mean serum PLR and neutrophil and monocyte counts can be useful in distinguishing complicated cases.

Keywords: Complicated acute appendicitis; c-reactive protein; hemogram; markers of inflammation; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio.

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Acute appendicitis is the most common cause of acute abdomen in the emergency department (ED). The lifetime risk of acute appendicitis is 8.6% in men and 6.9% in women [1]. Late intervention is associated with complications, prolonged hospital stay, and increased morbidity and mortality. Early diagnosis and treatment may prevent the development of complications in patients with acute appendicitis [2, 3].

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Among the systemic inflammatory parameters, the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte eosinophil ratio (MER), and C-reactive protein (CRP) value were found to be associated with the disease severity in critical illness [4–6]. In a retrospective study of 162 patients who underwent an appendectomy, Eren et al. [7] noted that NLR can be used with a physical examination as a diagnostic marker for acute appendicitis and predict perforated appendicitis. In addition, in another study of 520 patients who were operated on due to appendicitis, Kapci et al. [8] reported that the hemogram parameters such as leukocyte count, neutrophil count, and NLR are beneficial in the diagnosis of acute appendicitis when used with the physical examination. However, in the research of 101 patients with acute appendicitis, Guler et al. [9] observed no significant difference in terms of leukocyte counts and CRP values between perforated and non-perforated acute appendicitis patients.

In this study, we investigated the predictive power of serum systemic inflammatory markers including NLR, PLR, MER, and CRP levels for distinguishing uncomplicated and complicated acute appendicitis in adult patients admitted to the ED.

Highlight key points

- The incidence of complicated acute appendicitis increases with aging.
- The systemic inflammatory markers including mean serum NLR, PLR, MER values, and CRP levels could not predict complicated acute appendicitis.
- PLR can be useful in distinguishing complicated appendicitis from the uncomplicated appendicitis.
- To identify the patient with complicated appendicitis, a monocyte fraction (%) level of ≤6 was found to be a cut-off with 72% sensitivity and 64% specificity.
- Moreover, to identify the patient with complicated appendicitis, a PLR value of ≥133.73 was found to be a cut-off with 60% sensitivity and 58.4% specificity.

MATERIALS AND METHODS

Ethics Committee Approval and Patient Consent

This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Haseki Research and Training Hospital in March 09, 2022 (no. 49/2022). Patient consent to review their medical records was not required by the IRB, because there were no potentially identifying marks and no patient identifiers in the images or accompanying text.

Study Design and Setting

This retrospective, cross-sectional, observational, and single-center study included consecutive 212 adult patients aged ≥18 years who were diagnosed with acute appendicitis in ED and underwent an appendectomy at the surgical clinic between January 1, 2019 and December 31, 2021. Data were collected by searching for K35 International Classification of Disease codes in the hospital's automation system and hospital archive.

Study Population and Sampling

We enrolled a total of 212 patients who were diagnosed with acute appendicitis in ED and underwent an appendectomy at the surgical clinic. Of these patients, 4 were excluded because their post-operative pathology report was noted as negative appendicitis. Eight patients were excluded because they had unusual findings in their appendectomy specimen (e.g., mucoceles of the appendix, neoplasm, and lymphadenopathy). Thirty-five patients were excluded, while their data could not be accessed through the automation system or hospital archive. Two patients under the age of 18 were excluded from the study. Eighteen patients were excluded because they had a history of hematological disease. Thirteen other patients who within the last 1 week took medications that may affect the level of serum systemic inflammatory markers including NLR, PLR, MER values, and CRP levels (anti-inflammatory, antibiotic, and statins) were excluded from the study. Finally, 132 patients with positive appendicitis confirmed with post-operative reports were included in the study.

We assessed patients' demographics (age and sex), systemic inflammatory parameters including leukocyte (n=4.5–10.0 10^3/uL), neutrophil (n=1.5–8.0 10^3/uL), lymphocyte (n=0.8–5.0 10^3/uL), eosinophil (n=0.01–0.40 10^3/uL), and platelet counts (n=150–450 10^3/uL), monocyte (n=4.2–11.8%), neutrophil (n=42.9–74.3%), eosinophil (n=0.2–5.3%) and lymphocyte (n=18.3–45.7%) levels, NLR, PLR, MER, and CRP (n<5 mg/L) values measured on admission, and radiological findings.

Patients were divided into two groups according to their surgical findings and histopathological examination. Group I included patients with uncomplicated

acute appendicitis (cases presenting without surgical or histopathological signs of perforation) and Group II included patients with complicated appendicitis (cases with perforation, necrosis, abscess, or generalized peritonitis). Systemic inflammatory markers measured in serum on admission were compared among patient groups to identify factors associated with complicated acute appendicitis.

Outcome Definition

We evaluated the systemic inflammatory parameters for predicting patients with complicated acute appendicitis from the uncomplicated acute appendicitis.

Statistical Analysis

All data analyses were conducted using SPSS statistical software (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA). Categorical variables (sex and age) were expressed as numbers of patients (n) and percentages (%). Numerical data were expressed as mean, standard deviation, minimum, maximum, and median values. Intergroup comparisons (Group I vs. Group II) were conducted using Chi-squared and Student's independent t-tests for normally distributed data (e.g., gender and age) and the Mann–Whitney U test for non-normally distributed data (e.g., leukocyte, hemoglobin neutrophil, lymphocyte, and thrombocyte counts; CRP). The numerical variables in the patient groups were compared using the Mann–Whitney U test when the data conformed to non-normal distribution. The decisive factor was analyzed using the receiving operator characteristic (ROC) analysis to determine the cutoff value for PLR, monocyte, and monocyte fraction. The alpha significance level was set at $p<0.05$.

RESULTS

Table 1 presents the demographic characteristics of the patients in this study. A total of 132 patients, 83 male (62.9%) and 49 female (37.1%) were included in the study. The mean age was 34.7±13.40 years. We categorized the patients into two groups based on the surgical findings and histopathological examination. Group I included patients with uncomplicated acute appendicitis and Group II included patients with complicated appendicitis. The number of patients in group I was 103 (78.03%) and 29 (21.96%) in group II. The mean age of group II patients was statistically significantly higher than those in Group I (41.80±16.40 vs. 32.70±12.30; p=0.005). However, no statistically significant difference was found between Group I and II patients in terms of gender (p=0.297).

Table 1. Comparison of demographic characteristics (age, gender) among patient groups separated based on histopathological examination

	Group I (n=103)	Group II (n=29)	p*
Age			**0.005**
Mean±SD	32.70±12.30	41.80±16.40	
Min–Max	18–71	19–88	
Gender			0.297
Male, (%)	63.10	55.17	
Female, (%)	36.90	44.83	

*: Subgroup analyses (noncomplicated appendicitis vs. complicated appendicitis) were conducted using Chi-squared and Student's independent t-tests, as appropriate. Group I: Patients with uncomplicated appendicitis; Group II: Patients with complicated appendicitis; SD: Standard deviation; Min: Minimum; Max: Maximum.

Laboratory findings on admission revealed no significant differences between Groups I and II patients in terms of mean serum NLR, MER, and CRP values (p=0.096, p=0.248, and p=0.297, Table 2, respectively). However, we observed that the mean serum PLR in Group II patients was statistically significantly higher than those in Group I (162.80±208.30 vs. 196.40±111.60, p=0.032; Table 2). In addition, mean serum monocyte and monocyte fraction (%) values were found to be significantly lower in Group II patients compared to Group I (p=0.032 and p=0.012, respectively, Table 3). Furthermore, the mean serum neutrophil fraction (%) value was found to be statistically significantly higher in the Group II patients (p=0.047). Finally, no significant difference was found between the patient groups in terms of mean serum leukocyte, neutrophil, lymphocyte, platelet, and eosinophil counts (p=0.881, p=0.377, p=0.100, p=0.307, and p=0.174, respectively, Table 3).

ROC analysis identified a serum PLR cutoff value of ≥133.73 for distinguishing patients with complicated appendicitis from patients with non-complicated appendicitis, with 60% sensitivity and 58.4% specificity (Area under the curve [AUC]: 0.639, 95% confidence interval [CI] 0.513–0.764, p=0.032; Table 3 and Fig. 1). In addition, ROC analysis revealed a cutoff monocyte fraction (%) level of ≤6, with 72% sensitivity and

Table 2. Comparison of laboratory findings among patient groups separated based on histopathological examination

	Group I (n=103)		Group II (n=29)		p*
Laboratory findings	Mean±SD	Min–Max	Mean±SD	Min–Max	
Leukocyte (10^3/uL)	12.8±4.1	5.22–27.7	13.1±4.9	6.35–28.21	0.881
Platelet (10^3/uL)	247.5±97.6	82.5–78.5	254.4±84.0	109–485	0.307
Neutrophil (10^3/uL)	9.79±3.77	1.73–25.61	10.6±4.8	3.8–26.09	0.377
Lymphocyte (10^3/uL)	1.96±0.81	0.04–5.1	1.69±0.98	0.32–3.84	0.100
Eosinophil (10^3/uL)	0.15±0.25	0–1.87	0.09±0.09	0–0.38	0.174
Monocyte (10^3/uL)	0.86±0.35	0.03–2.02	0.70±0.32	0.19–1.43	0.032
Neutrophil fraction (%)	74.8±10.2	17.4–92.5	79.2±10.5	50–94	0.047
Lymphocyte fraction (%)	16.1±6.8	0.4–40.5	14.3±9.3	2.2–42	0.136
Eosinophil fraction (%)	1.28±1.91	0–12.6	0.78±0.85	0–3.3	0.248
Monocyte fraction (%)	6.88±2.35	0.30–15.5	5.54±2.23	2–10.7	0.012
CRP (mg/L)	46.8±57.0	0.30–296.3	77.9±103.9	1.4–412.4	0.297
NLR	6.15±5.13	1.22–43.25	9.75±9.51	1.19–42.19	0.096
PLR	162.8±208.3	53.7–2062.5	196.4±111.6	72.3–507	0.032
MER	17.9±30.2	0–192	13.8±29.1	0–143	0.248

*: Subgroup analyses (noncomplicated appendicitis vs. complicated appendicitis) were conducted using the Mann-Whitney U test. NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MER: Monocyte eosinophil ratio; CRP: C-reactive protein; Group I: Patients with uncomplicated appendicitis; Group II: Patients with complicated appendicitis; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 3. Inflammatory markers in identifying the patient with complicated appendicitis

	AUC	SE	p	95% CI	
CRP (mg/L)	0.568	0.067	0.297	0.437	0.698
NLR	0.608	0.070	0.096	0.472	0.744
PLR	0.639	0.064	0.032	0.513	0.764
MER	0.425	0.063	0.249	0.301	0.549
Monocyte (10^3/uL)	0.361	0.067	0.032	0.229	0.493
Monocyte fraction (%)	0.325	0.064	0.007	0.199	0.450

AUC: Area under the curve; SE: Standard error; CI: Confidence interval; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MER: Monocyte eosinophil ratio; CRP: C-reactive protein.

64% specificity, for distinguishing patients with complicated appendicitis from patients with noncomplicated appendicitis (AUC 0.325, 95% CI 0.199–0.450, p=0.007, Table 3 and Fig. 2). Finally, ROC analysis revealed a cutoff monocyte count of ≤0.74 10^3/μL, with 60% sensitivity and 58.4% specificity, for distinguishing patients with complicated appendicitis from patients with non-complicated appendicitis (AUC:0.361, 95% CI 0.229–0.493, p=0.032, Table 3 and Fig. 2).

DISCUSSION

This study investigated the role of systemic inflammatory markers such as NLR, PLR, MER, and CRP levels in the preoperative diagnosis of complicated appendicitis in adult patients admitted to the ED and operated on for acute appendicitis.

The key findings we found were as follows. First, 78% of patients had uncomplicated appendicitis and 22% had complicated appendicitis. Second, the mean age of the patients with complicated appendicitis was found significantly higher than those with uncomplicated appendicitis. However, no significant difference was observed between the groups in terms of gender. Third, there were no statistically significant differences between the patient groups in terms of mean NLR, MER, and CRP values. However, the mean serum PLR value was statistically significantly higher in the patients with complicated appendicitis. Fourth, mean serum monocyte and monocyte fraction (%) values were found significantly lower and the mean serum neutrophil fraction (%) value was higher in patients with uncomplicated appendicitis. Finally, in identifying the patient with complicated appendicitis, a PLR value

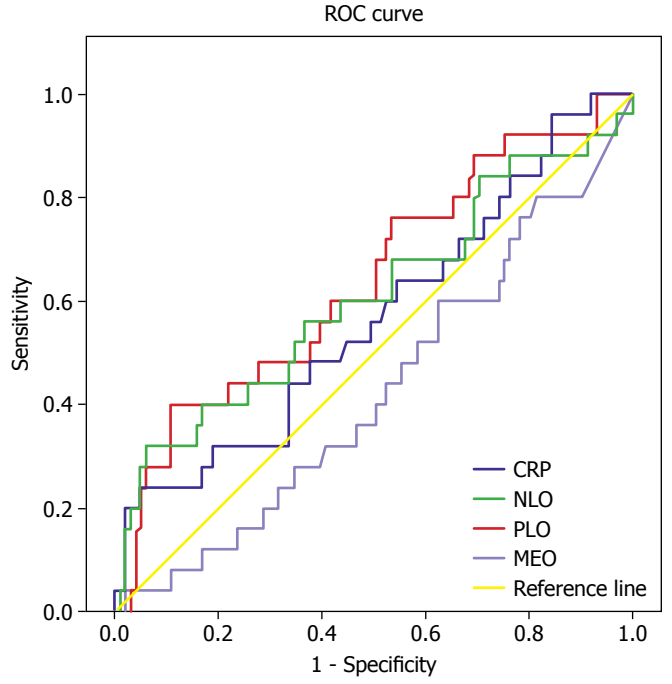

FIGURE 1. Specificity and sensitivity of serum PRL value for distinguishing patients with complicated appendicitis from those with noncomplicated appendicitis using receiver operating characteristic curves (area under the curve, 0.639; 95% confidence interval 0.513–0.764).

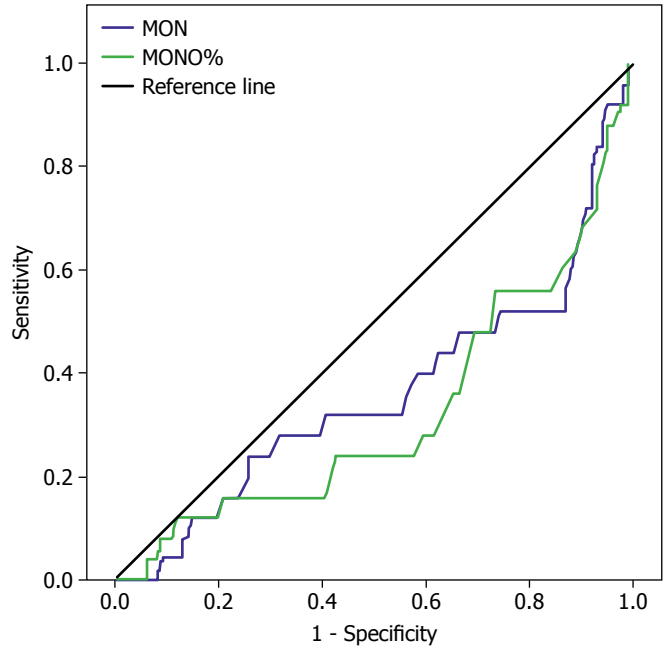

FIGURE 2. Specificity and sensitivity of serum monocyte fraction (%) and monocyte level for distinguishing patients with complicated appendicitis from those with non-complicated appendicitis using receiver operating characteristic curves (area under the curve [AUC], 0.325; 95% confidence interval [CI] 0.199–0.450 and AUC, 0.361; 95% CI 0.229–0.493, respectively).

of ≥133.73 was found to be the cutoff with 60% sensitivity and 58.4% specificity, and a monocyte fraction (%) value of ≤6 was determined as the cutoff with 72% sensitivity and 64% specificity.

Acute appendicitis occurs as a result of obstruction of the appendiceal lumen which is the most common cause of acute abdomen in patients admitted to ED worldwide. It's surgery should be performed quickly and urgently. Delayed intervention causes complications and also increased morbidity and mortality rates [2, 3]. Especially, the detection of complicated appendicitis in the early stage of the disease is critical to improving the patient's prognosis. Therefore, fast, simple, inexpensive, and widely available indicators are required that can easily predict the patient's prognosis on admission to ED. There are clinical studies examining various imaging modalities and biomarkers to distinguish between preoperatively uncomplicated and complicated cases in patients with acute appendicitis [10–12]. However, many of these imaging modalities and biomarkers have limitations in actual application since they are not effective and easily accessible during hospitalization at the current time. In their retrospective study of appendicitis cases, Borushok et al. [13] stated that the specificity of any ultrasonography finding alone could not exceed 59% in determining the complicated cases. In the same study, it was reported that the specificity of ultrasonography could reach 86% by evaluating different findings such as pericecal fluid, appendicitis wall thickness, and contamination of the fatty planes, which indicate appendicitis [13]. In another study of 94 cases with appendicitis, Horrow et al. [14] reported that computed tomography has a specificity of up to 94.4% in diagnosing complicated and perforated appendicitis. Since the ultrasound results are operator-depending, CT causes radiation exposure, and both imaging methods are not easily accessible, we need other markers to diagnose complicated cases preoperatively. Hemogram is always an important component of diagnosis in patients with acute abdominal pain in ED. Researchers note that some hemogram parameters such as leukocyte and neutrophil count or NLR can predict critical illness [4–6].

In a retrospective study of 162 patients who underwent appendectomy, Eren et al. [7] recommend NLR, together with physical examination and other diagnos-

tic methods, in the diagnosis of acute appendicitis and in predicting perforated cases. Similarly, Kapci et al. [8] evaluated retrospectively the data of 520 operated patients due to appendicitis and stated that examining the leukocyte counts, neutrophil counts, and NLR from routine hemogram parameters accompanied by physical examination findings is beneficial in the diagnosis of acute appendicitis. Similarly, also in our study, the leukocyte and neutrophil counts and NLR were higher in patients with complicated appendicitis than in those with uncomplicated appendicitis. However, there was no statistical difference between the groups in terms of the leukocyte and neutrophil counts and NLR. Our findings indicate that the leukocyte and neutrophil counts and NLR could not predict complicated appendicitis.

Acute leukocytosis occurs in the majority of patients with acute appendicitis. The studies stated that 80% of patients diagnosed with appendicitis have an increased neutrophil fraction along with leukocyte counts [15]. Coleman et al. [15] reported the sensitivity and specificity of leukocyte counts in acute appendicitis as 92% and 100%, respectively, and 69% and 75% for CRP values. However, in a study that included 101 operated appendicitis patients, Guler et al. [9] reported that leukocyte counts and CRP values were not effective in distinguishing between perforated and non-perforated cases. Similar to Guler et al., [9] we found no significant difference in terms of leukocyte counts and CRP values between the patients with uncomplicated and complicated appendicitis.

In another retrospective study of 1,067 patients who underwent an appendectomy, Kahramanca et al. [16] categorized the patients into two groups according to histopathological examination as uncomplicated and complicated appendicitis. In the study, the cutoff value of NLR was found to be 5.74 (sensitivity 70.8%; specificity 48.5%) in identifying the patient with complicated appendicitis. In our study, we found no statistically significant difference between the patient groups with uncomplicated and complicated appendicitis in terms of mean serum NLR, MER, and CRP values. However, a significant difference was observed in terms of PLR value. In the ROC curve analysis performed for identifying the patient with complicated appendicitis, the cutoff value for PLR was found to be ≥133.73, with a sensitivity of 60% and a specificity of 58.4%. In addition, a monocyte fraction value of ≤6 was observed to be the cutoff value with 72% sensitivity and 64% specificity. Finally, the cutoff value for monocyte count was ≤0.74 with 60% sensitivity and 58.4% specificity.

This study had some limitations, the most important of which were the small sample size, retrospective and single-center design. In addition, we may have denied the possibility that negative explorations, which specified in the exclusion criteria, may alter false-positive rates in reflecting the marker strength of systemic inflammatory markers including NLR, PLR, MER values, and CRP levels in the present study. Thus, a larger prospective, multicenter study involving patients with complicated and non-complicated appendicitis and including a negative appendicitis group based on post-operative pathology report is needed to overcome these issues.

Conclusion

Our findings indicate that the mean serum NLR, MER, and CRP values measured on admission to ED in adult patients with acute appendicitis, could not predict complicated acute appendicitis. However, mean serum PLR and neutrophil and monocyte counts can be useful in distinguishing complicated cases. In addition, it can be said that the incidence of complicated acute appendicitis increases with aging.

In identifying the patient with complicated appendicitis, a PLR value of ≥133.73 was found to be the cutoff with 60% sensitivity and 58.4% specificity, and a monocyte fraction (%) value of ≤6 was determined as the cut-off with 72% sensitivity and 64% specificity. The mean serum PLR and neutrophil and monocyte counts are simple, cheap, and available to carry out as diagnostic tools to distinguish complicated appendicitis from the uncomplicated appendicitis in ED. Additional randomized controlled trials with larger sample sizes are required to confirm the current findings.

Ethics Committee Approval: The Haseki Research and Training Hospital, Clinical Research Ethics Committee granted approval for this study (date: 09.03.2022, number: 49-2022).

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Authorship Contributions: Concept – SY, AA, OS; Design – SY, AA, OS; Supervision – OS, HE; Materials – HE, ID; Data collection and/or processing – SY, AA, ID; Analysis and/or interpretation – AA, OS; Literature review – SY, AA, HE; Writing – AA, OS; Critical review – OS, HE, ID.

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