ORIGINAL ARTICLE

The role of neutrophil–albumin ratio in the diagnosis of acute appendicitis and its efficacy in predicting perforation

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ABSTRACT

BACKGROUND: Acute appendicitis (AA) is one of the most common causes of abdominal pain in patients presenting to the emergency department with abdominal pain, and despite developments in radiological imaging for its diagnosis, researchers are still in pursuit of a simpler, cheaper, and safer biomarker. Our study investigated the usability of the neutrophil–albumin ratio, a biomarker that predicts prognosis in cases with severe inflammation, in diagnosing AA and anticipating perforation.

METHODS: Our study is a retrospective and cross-sectional study. The study was conducted with patients who presented to the emergency department between January 2018 and December 2020 and were hospitalized with a preliminary diagnosis of AA. The cases were first divided into two groups as "Not appendicitis" and "AA," and then the patients with "AA" were divided into two subgroups as "Perforated" and "Non-perforated." The demographic data of the patients, their symptoms, physical examination findings, and the decision-making process for surgery were noted. The neutrophil count and albumin levels detected in the blood samples obtained at the time of admission to the emergency department were noted. Afterward, the neutrophil-albumin ratio (NAR) was calculated and the cutoff level was determined to predict the diagnosis of AA and the development of perforation.

RESULTS: The rate of complaints of pain in the periumbilical region was significantly higher in the patient group without AA compared to the patients in the AA group (70.6% and 40.3%, p=0.034). Although the leukocyte count, neutrophil count and percentage, and NAR were significantly higher in the AA group, the lymphocyte count was found to be significantly lower (p=0.005). However, no significant correlation was found between the NAR and the development of perforation (p=0.697).

CONCLUSION: The NAR is useful for the diagnosis of AA. Nevertheless, it is not a sufficient biomarker for detecting perforation.

Keywords: Albumin; appendicitis; biomarker; intestinal perforation; neutrophil.

INTRODUCTION

Acute appendicitis (AA) is one of the most important and common causes of acute abdominal pain in emergency departments. The lifetime incidence of AA is reported to be around 7% in the literature, and perforation has been reported in 17–20% of these patients.[1,2] Early detection of perforation among patients admitted to the emergency department with AA is important. Perforation leads to increased length of hospital stay, mortality, and cost. In addition, increased need for broad-spectrum antibiotics is another problem caused by perforation.[3,4] Despite an increasing number of radiological imaging options, researchers are still looking for simpler, cheaper, and safer diagnostic tools for clinicians.[5]

The number and ratio of neutrophils increase in infectious conditions, such as AA. In addition, albumin levels, a negative acute-phase reactant, decrease. The severity of inflammation increases following perforation. The importance of the neutrophil-albumin ratio (NAR) as a biomarker in predicting prognosis in the presence of severe inflammation has been frequently discussed in recent years.[6,7]

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This study aimed to determine the usability of NAR as an inflammation-based prognostic biomarker for AA-associated perforation.

MATERIALS AND METHODS

Study Design

Our study is a retrospective and cross-sectional study. The study was conducted with patients who presented to the Karabük University Training and Research Hospital emergency department between January 2018 and December 2020 and were hospitalized with a preliminary diagnosis of AA. The study was approved by the Ethics Committee of Karabük University (25/02/2021-499) and followed the ethical principles in the Declaration of Helsinki for medical research involving human subjects.

Patient Distribution

Abdominal ultrasonography, computed tomography results, and operation notes of patients who were hospitalized with a preliminary diagnosis of AA and underwent surgery were analyzed. Based on these results, the cases were first divided into two groups as "Not Appendicitis" and "AA," and then the patients in the AA group were further divided into two subgroups as "Perforated" and "Non-perforated." The study included patients who were over the age of 18 years and not pregnant. Patients with incomplete information and data in the electronic hospital record system and files were excluded from the study.

Data Collection

Demographic data of the patients, such as age; gender; comorbidity; symptoms such as abdominal pain, nausea, and vomiting; physical examination findings; and the decision-making process for the surgery were extracted from the patient files and electronic hospital record system. The neutrophil count and albumin levels detected in the blood samples obtained at the time of admission to the emergency department were recorded. In addition to these, white blood cell count; lymphocyte count and percentage; and hemoglobin, C-reactive protein (CRP), urea, and creatinine levels were also examined. NAR was calculated and the cutoff level was determined with an aim to predict the development of perforation for the determined values.

Statistical Analysis

For summarizing the data obtained from the study, descriptive statistics were expressed in mean±standard deviation or median, minimum, and maximum, according to the distribution for continuous (numeric) variables and in number and percentage for categorical variables. Normality of numeric variables was checked using Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests.

Mann–Whitney U test was used to compare two independent groups when numerical variables did not show normal distribution and the assumptions of parametric test methods were not met. Pearson Chi-square test was used in 2×2 tables with 5 or more expected cells and Fisher's exact was used in tables with below 5 expected cells in the comparison of differences between categorical variables based on groups.

Pearson correlation coefficient was used to evaluate the correlation between NAR, length of stay, and appendicitis diameter. The Kruskal–Wallis test was used for NAR comparisons in more than two groups. Differences between the groups were evaluated using the Dwass–Steel–Critchlow–Fligner test.

The ability of NAR in predicting AA-associated perforation was investigated using receiver operating characteristic (ROC) curve analysis, which was performed using MedCalc Statistical Software Trial version (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015) with an optimal cutoff value and a 95% confidence interval, and the area under the curve with Youden's index was calculated using the DeLong method.

All other statistical analyses were performed using Jamoviproject (2020), Jamovi (Version 1.8.4; Retrieved from https://www.jamovi.org), and JASP (Version 0.14.1.0; Retrieved from https://jasp-stats.org), and the level of significance was set at $p<0.05$.

RESULTS

The study was carried out with a total of 161 patients, of whom 144 belonged to the AA group and 17 to the NA group. The mean age of the patients was 34.96±15.89 years. There was no significant difference between the groups in terms of age, gender, and comorbidity distribution ($p>0.05$). Evaluation of complaints at initial admission showed that the rate of complaints of periumbilical pain was significantly higher in patients in the NA group compared to those in the AA group (70.6% and 40.3%, $p=0.034$). Although leukocyte count, neutrophil count and percentage, and NAR were significantly higher in the AA group, lymphocyte count was found to be significantly lower ($p=0.005$). Further, although the median diameter of the vermiform appendix was 10 mm in the AA group, it was 7 mm in the NA group, indicating a significant difference between them ($p<0.001$). The demographic and clinical characteristics of the patients based on groups, their complaints, laboratory data, length of hospital stay, appendicitis diameter, and methods used for diagnosis are given in Table 1.

AA-associated perforation was detected in a total of 22 patients (15.3%). The rate of comorbidities was significantly higher in patients who did not develop perforation (76.3% vs. 45.5%, $p=0.007$). On the other hand, the rate of hypertension was significantly higher in patients with perforation ($p=0.004$). Initial complaints at admission and diagnostic

Table 1. Demographic and clinical characteristics of patients based on clinical–pathological acute appendicitis status

	Presence of appendicitis		p-value
	Acute appendicitis (n=144)	No appendicitis (n=17)	
Demographic features			
Age (years)†	32.5 [10.0–94.0]	25.0 [18.0–66.0]	0.161*
Gender‡			
Female	58 (40.3)	7 (41.2)	0.999**
Male	86 (59.7)	10 (58.8)	
Comorbidity‡	103 (71.5)	13 (76.5)	0.781**
Coronary artery disease	3 (2.1)	0 (0.0)	0.999**
Hypertension	30 (20.8)	4 (23.5)	0.759**
Diabetes mellitus	15 (10.4)	1 (5.9)	0.999**
Cerebrovascular disease	2 (1.4)	0 (0.0)	0.999**
Cancer (%)	1 (0.7)	0 (0.0)	0.999**
Chronic renal failure	2 (1.4)	0 (0.0)	0.999**
Dyslipidemia	1 (0.7)	0 (0.0)	0.999**
Other	9 (6.2)	1 (5.9)	0.999**
Symptoms‡			
Right lower quadrant pain	89 (61.8)	6 (35.3)	0.066**
Periumbilical pain	58 (40.3)	12 (70.6)	0.034**
Vomiting	23 (16.0)	0 (0.0)	0.135**
Fever	6 (4.2)	0 (0.0)	0.999**
Anorexia	3 (2.1)	0 (0.0)	0.999**
Diagnosis‡			
USG	27 (18.8)	4 (23.5)	0.744**
CT	116 (80.6)	11 (64.7)	0.204**
Clinical	10 (6.9)	2 (11.8)	0.618**
Laboratory parameters†			
Leukocyte count (x10^9)	14.5 [4.2–24.9]	9.2 [4.7–25.5]	<0.001*
Hemoglobin (g/dL)	13.7 [9.2–17.6]	13.6 [9.5–16.8]	0.919*
Neutrophil count (x10^9)	11.4 [2.0–22.4]	6.2 [2.8–24.0]	<0.001*
Neutrophil rate (%)	79.8 [8.9–95.8]	65.9 [55.7–94.1]	0.002*
Lymphocyte count (x10^9)	2.0 [0.5–6.5]	1.8 [1.0–4.5]	0.613*
Lymphocyte rate (%)	13.4 [3.1–47.9]	23.3 [4.0–35.2]	0.005*
Urea (mg/dL)	27.0 [12.7–75.0]	29.0 [14.8–40.0]	0.917*
Creatinine (mg/dL)	0.8 [0.5–1.3]	0.7 [0.6–1.1]	0.658*
Albumin (g/dL)	4.6 [1.3–5.4]	4.4 [3.8–45.5]	0.412*
Total bilirubin (mg/dL)	0.7 [0.2–6.5]	0.7 [0.2–1.4]	0.708*
CRP (mg/dL)	12.4 [0.2–326.0]	10.5 [0.9–123.7]	0.478*
Neutrophil/albumin	2.6 [2.0–3.0]	1.3 [1.0–1.9]	<0.001*
Vermiform appendix diameter (mm)†	10.0 [5.0–20.0]	7.0 [5.0–13.0]	<0.001*
Length of hospital stay (days)†	2.0 [1.0–18.0]	2.0 [1.0–9.0]	0.938*

†Median [min–max], ‡n (%). USG: Ultrasonography; CT: Computed tomography; CRP: C-reactive protein. *The Mann–Whitney U test was used. **Pearson Chi-square or Fisher Exact test was used.

methods did not demonstrate a significant relationship with the development of perforation (p>0.05). The CRP value of the patients with perforation was 74 mg/dL, which was significantly higher than that of the patients without perforation

Table 2. Demographic and clinical characteristics of patients depending on the development of perforation in cases with clinical–pathological acute appendicitis

	Perforation development status		p-value
	Perforation developed (n=22)	No perforation (n=122)	
Demographic features			
Age (years)†	47.0 [18.0–80.0]	30.0 [10.0–94.0]	0.003*
Gender‡			
Female	9 (40.9)	49 (40.2)	0.999**
Male	13 (59.1)	73 (59.8)	
Comorbidity‡	10 (45.5)	93 (76.2)	0.007**
Coronary artery disease	1 (4.5)	2 (1.6)	0.394**
Hypertension	10 (45.5)	20 (16.4)	0.004**
Diabetes mellitus	5 (22.7)	10 (8.2)	0.055**
Cerebrovascular disease	1 (4.5)	1 (0.8)	0.283**
Cancer (%)	1 (4.5)	0 (0.0)	0.153**
Chronic renal failure	1 (4.5)	1 (0.8)	0.283**
Dyslipidemia	0 (0.0)	1 (0.8)	0.999**
Other	2 (9.1)	7 (5.7)	0.627**
Symptoms‡			
Right lower quadrant pain	17 (77.3)	72 (59.0)	0.166**
Periumbilical pain	8 (36.4)	50 (41.0)	0.865**
Vomiting	5 (22.7)	18 (14.8)	0.350**
Fever	2 (9.1)	4 (3.3)	0.228**
Anorexia	0 (0.0)	3 (2.5)	0.999**
Diagnosis‡			
USG	3 (13.6)	24 (19.7)	0.767**
CT	19 (86.4)	97 (79.5)	0.569**
Clinical	1 (4.5)	9 (7.4)	0.999**
Laboratory parameters			
Leukocyte count (x10^9)	14.6 [5.7–21.0]	14.5 [4.2–24.9]	0.575*
Hemoglobin (g/dL)	13.8 [9.2–16.7]	13.7 [10.3–17.6]	0.364*
Neutrophil count (x10^9)	11.3 [3.8–16.9]	11.5 [2.0–22.4]	0.752*
Neutrophil rate (%)	80.6 [57.9–93.8]	79.4 [8.9–95.8]	0.602*
Lymphocyte count (x10^9)	1.8 [0.5–4.2]	2.1 [0.6–6.5]	0.234*
Lymphocyte rate (%)	12.7 [3.4–33.3]	13.8 [3.1–47.9]	0.562*
Urea (mg/dL)	32.5 [15.9–75.0]	27.0 [12.7–59.8]	0.029*
Creatinine (mg/dL)	0.9 [0.5–1.3]	0.8 [0.5–1.2]	0.017*
Albumin (g/dL)	4.5 [1.3–5.0]	4.6 [3.2–5.4]	0.056*
Total bilirubin (mg/dL)	0.6 [0.2–2.0]	0.7 [0.2–6.5]	0.428*
CRP (mg/dL)	74.2 [1.1–326.0]	10.8 [0.2–266.0]	<0.001*
Neutrophil/albumin	2.6 [1.0–10.4]	2.5 [0.4–5.3]	0.697*
Vermiform appendix diameter (mm)†	10.5 [7.0–20.0]	9.0 [5.0–20.0]	0.007*
Length of hospital stay (days)†	3.5 [1.0–18.0]	2.0 [1.0–6.0]	<0.001*

†Median [min–max], ‡n (%). USG: Ultrasonography; CT: Computed tomography; CRP: C-reactive protein. *The Mann–Whitney U test was used. **Pearson Chi-square or Fisher Exact test was used.

Table 3. Multi-group analysis of neutrophil/albumin ratio based on the development of acute appendicitis and perforation

	Acute appendicitis group (n=144)			p-value
	Not appendicitis group (n=17)	Perforation developed (n=22)	No perforation (n=122)	
Neutrophil/albumin†	1.3 [1.0–1.9]	2.6 [2.3–3.0]	2.5 [1.9–3.0]	0.001

†Median [min–max]. Kruskal–Wallis test was used.

Table 4. Correlation of neutrophil/albumin ratio with the vermiform appendix diameter and length of hospital stay in patients in the acute appendicitis group (n=144)

		r	p
Neutrophil/albumin	Vermiform appendix diameter (mm)	0.213	0.010
Neutrophil/albumin	Length of hospital stay (days)	0.232	0.005

Pearson correlation coefficient was used.

(10.8 mg/dL) (p<0.001). No significant correlation was found between NAR and the development of perforation (p=0.697). The demographic and clinical characteristics of the patients and the distribution of laboratory variables depending on the development of perforation in cases with clinical-pathological AA are given in Table 2.

The vermiform appendix diameter and length of hospital stay were found to be significantly higher in patients with perfora-

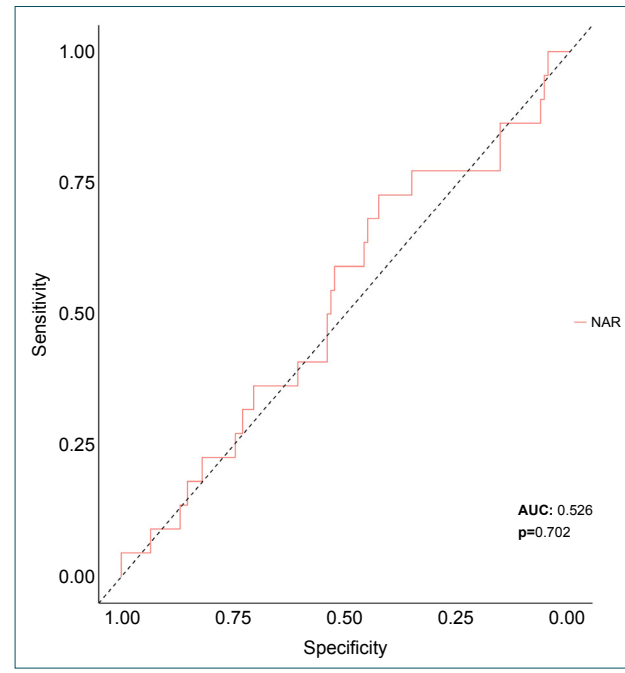

Figure 2. Receiver operating characteristic analysis of the ability of the neutrophil/albumin value in predicting perforation in patients with acute appendicitis.

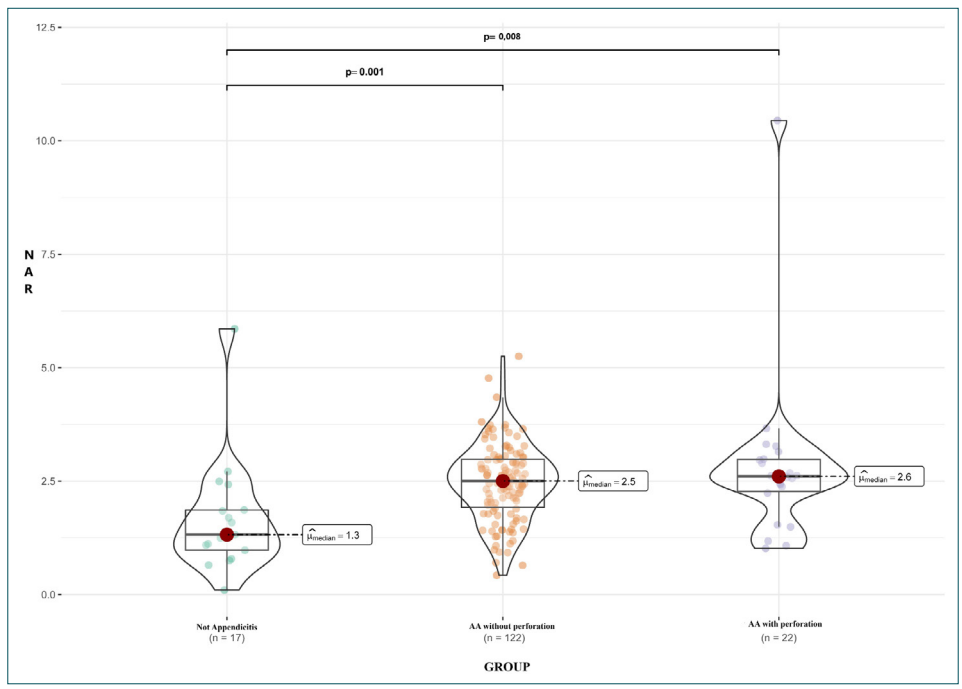

Figure 1. Graphical representation of neutrophil/albumin value per group.

tion compared to patients without perforation (p=0.007 and p<0.001, respectively).

There were significant differences in the comparison of NAR depending on whether there was AA and perforation or NA group (p=0.001). Multiple comparisons showed that patients in NA group had significantly lower NAR than patients with AA with and without perforation (p<0.001 and p=0.008, respectively) (Table 3 and Fig. 1).

There was a positive and significant correlation between NAR and the vermiform appendix diameter and hospital stay (Table 4).

In the ROC analysis performed to identify NAR's ability to predict the development of perforation in patients in the AA group, the optimum cutoff value was found to be >2.38. A neutrophil/albumin ratio of >2.38% predicted the development of perforation with a sensitivity of 73.73% and a specificity of 42.62%. However, the area under the ROC curve was found to be 0.526, which was not statistically significant (p=0.702) (Fig. 2).

DISCUSSION

Meta-analyses in laboratory studies on AA suggest that NAR can be used to differentiate patients with and without AA.[8] NAR, on the other hand, has previously been shown to be useful in predicting mortality in patients with COVID-19 disease and sepsis.[9,10] In literature, there are no studies on the use of NAR for the differentiation of AA. In this regard, our study is the first to compare the relationship between NAR and AA. In paired group comparisons of NAR for the presence of AA and perforation status, the results of our study showed that NAR was significantly lower in patients without AA compared to patients with AA with and without perforation. This suggests that NAR may be useful in the diagnosis of appendicitis. However, no significant relationship was found between NAR and the development of perforation, and no statistical significance was found in the ROC curve that determined the NAR cutoff value. This can be interpreted as an indication that NAR is insufficient to detect perforation among patients with appendicitis.

Diagnosis of AA and AA-associated perforation that may develop later on remains challenging for emergency physicians and surgeons. Due to possible uncertainty in terms of the early diagnosis, and the decision of observation for surgery or operation before the perforation constitutes a surgical dilemma.[10] Despite developments in imaging methods and the ease of access to these methods, the need for diagnostic and prognostic markers has remained constant. Although there are claims in the literature that some biomarkers such as CRP, WBC, and bilirubin can be used in the prediction of perforation, these markers are not sufficient for diagnosis.[11] In our study, CRP, creatinine, and urea levels were statistically significantly higher in patients who developed perforation compared to those in patients who did not.

In a study published in 2020, Hanson et al.[12] evaluated the correlation between perforation status and patient age and found that the diagnosis of intraoperative perforated appendicitis was 4 times higher in patients above 46 years of age. Our study found that perforation developed in 15.3% of the patients, and the median age of the patients who developed perforation was 47 years. This suggests that our study is consistent with the findings of other studies in the literature.

Conclusion

NAR is useful for the diagnosis of AA. However, it is not a useful biomarker for detecting perforation.

Ethics Committee Approval: This study was approved by the Karabük University Non-interventional Clinical Research Ethics Committee (Date: 25.02.2021, Decision No: 2021/499).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Nötrofil/albümin oranının akut apandisit tanısındaki yeri ve perforasyonu öngörmedeki etkinliği

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AMAÇ: Akut apandisit karın ağrısı ile acile başvuruların sık sebeplerinden biri olup, tanısında radyolojik görüntülemelerde ilerlemelere rağmen, daha basit, ucuz ve güvenli bir biyobelirteç arayşı devam etmektedir. Bizde çalışmamızda akut apandisit perforasyonunda, şiddetli enflamatuvar süreçlerde prognozu ön gören bir biyobelirteç olan nötrofil sayısı ile albümin oranının biyobelirteç olarak kullanılabilirliğini saptamaktadır.
GEREÇ VE YÖNTEM: Çalışmamız geriye dönük, kesitsel bir çalışmadır. Çalışmaya Ocak 2018–Aralık 2020 tarihleri arasında acil servisine başvuran ve akut apandisit ön tanısı ile hastaneye yatırılan hastalar arasında yapıldı. Olgular önce "apandisit değil" ve "akut apandisit" şeklinde iki gruba ayrıldı, ardından "akut apandisit" olduğu saptanan hastalar "perfore olan" ve "perfore olmayan" şeklinde iki alt gruba ayrıldı. Hastaların demografik verileri, semptomları, fizik muayene bulguları, operasyon kararının hangi şekilde verildiği not edildi. Olguların acil servise başvuru anında alınan kan örneklerinde saptanan nötrofil sayısı ve albümin seviyeleri kaydedildi. Sonrasında nötrofil/albümin oranı hesaplandı ve saptanan değerler için akut apandisit tanısını öngörmedeki yeri ile perforasyon gelişimini öngörmede kestirim seviyesi belirlendi.
BULGULAR: Akut apandisit gelişmeyen hasta grubundaki peri-umbilikal bölgede ağrı şikâyeti olma oranı akut apandisit grubundaki hastalara göre anlamlı olarak daha fazla idi (%70.6 ve %40.3, p=0.034). Lökosit sayısı, nötrofil sayı ve yüzdesi ve nötrofil/albümin oranı akut apandisit grubunda anlamlı olarak daha yüksek iken lenfosit sayısı anlamlı olarak daha düşük olarak bulundu (p=0.005). Buna karışın nötrofil/albumin oranı ile perforasyon gelişimi arasında anlamlı bir ilişki tespit edilmedi (p=0.697).
TARTIŞMA: Nötrofil/albümin oranı akut apandisit tanısında kullanılabilir bir orandır. Bununla birlikte perforasyonu saptamada yeterli bir biyobelirteç değildir.
Anahtar sözcükler: Albümin; apandisit; biyobelirteç; intestinal perforasyon; nötrofil.

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