ORIGINAL ARTICLE

# Can the Inflammatory Cell Ratio NLR and PLR be Used as a Reliable Marker in Colon Cancer? A Prospective Study

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## Microabstract

In recent years, the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) have been used in diagnosis, staging, and determination of long-term prognosis of various cancers. The study involved 90 colon cancer patients diagnosed between July 2021 and December 2022. The relationship between NLR/PLR and tumor features was investigated. In predicting colon cancer tumor depth/invasion, PLR was found to be significantly more precise than NLR.

## Abstract

**Background:** Simple approaches for detecting the tumor stage of colon cancer patients are required during the preoperative period. In recent years, the neutrophil-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) have been employed as predictive parameters for systemic inflammatory response and long-term prognosis in a variety of malignancies. The purpose of this study was to determine whether the NLR and PLR correspond with tumor characteristics in colon cancer patients.

**Materials and methods:** About 90 patients with colon cancer who reported to our institute during the time interval July 2021 to December 2022 were included in the study. The NLR and PLR were calculated using data obtained from a complete blood count evaluation. The relationship between inflammatory cell ratio and tumor-specific characteristics were analyzed.

**Results:** Neutrophil–lymphocyte ratio and PLR correlated with pTNM staging in 88 patients. Two patients exhibited diffuse peritoneal metastasis. A significant association was found between PLR and early (Tis + T1 + T2) and advanced (T3 + T4) groups. Although the difference was not statistically significant, patients with lymphovascular invasion (LVI) and perineural invasion (PNI) had greater mean NLR and PLR.

**Conclusion:** Platelet–lymphocyte ratio was found to be more accurate than NLR in predicting colon cancer tumor depth/invasion. A high PLR value aids in prognosticating advanced T-stage colon cancer patients and can be used as a valuable tool for preoperative counseling, but it must be validated with a survival analysis.

**Clinical practice points:** The tumor microenvironment contains a variety of inflammatory cells that contribute to the growth and spread of the neoplasm. The NLR and PLR have been shown to be clinically and prognostically important in a variety of gastrointestinal cancers. The results of this study demonstrate that PLR was more accurate than NLR in predicting colon cancer tumor depth/invasion. Also, a high PLR value aids in prognosticating advanced T-stage colon cancer patients and may be used as a valuable tool for preoperative counseling.

**Keywords:** Colorectal cancer, Gastrointestinal malignancies, Neutrophil–leukocyte ratio, Platelet–lymphocyte ratio, Serum biomarkers.

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## Introduction

Colon cancer is one of the most common types of cancer worldwide. Over the previous decade, there has been a 30% increase in the prevalence of colon cancer among individuals of all ages.[1] Several studies have shown that inflammation plays a major role in tumor development. The tumor microenvironment contains a variety of inflammatory cells that contribute to the growth and spread of the neoplasm. In 1863, Rudolf Virchow proposed that tumor growth occurs at the site of chronic inflammation.[2] This served as the basis for evaluation of association of different systemic inflammatory markers, such as interleukin 6 (IL-6), neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR) with malignancies. Inflammatory mediators/cytokines in plasma/serum have been linked to cancer risk, stage, and prognosis. Serum IL-6 and tumor necrosis factor levels in prostate cancer patients correlate with clinical, pathological, and patient survival.[3] Interleukin-8 (IL-8) levels are linked to lung cancer risk several years prior to diagnosis, and elevated IL-8 and C-reactive protein aid in the prediction of future lung cancer.[4] The NLR and PLR have been shown to be clinically and prognostically important in a variety of gastrointestinal cancers, including esophageal, gastric, and hepatopancreaticobiliary cancers.[5–7] Previous research additionally identified a strong link between the NLR/PLR ratio and colorectal cancer prognosis, stage, and responsiveness to treatment.[8,9]

The primary objective of this study was to examine at the relationship between inflammatory cell ratios (PLR and NLR) and pathological (pTNM) staging, and tumor characteristics in patients with colon cancer. The goal of this study was to determine whether

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these ratios may be employed as prognostic indicators in the ongoing management of colon cancer patients because they are low-cost tests with readily measured parameters.

## Materials and Methods

This study was designed as a prospective observational study, and was approved by the Institutional Ethics Committee (AMH-DNB-072/07-21). All patients admitted to Apollo Hospital, Chennai, for elective colon cancer surgery from July 2021 to December 2022 were included in the study. Patients receiving preoperative radiation and/or chemotherapy, emergency colonic malignancy procedures, recurrent colon cancers, blood cancers, or multiple myeloma, concurrent and recent abdominal, lung, intestinal, and other systemic infections, or blood transfusions and patients on antiplatelet therapy, steroid therapy, or a combination of the two were excluded.

Preoperative parameters that were recorded included comprehensive demographic profile, clinical symptoms with duration, clinical findings, and prior medical history. Colonoscopic findings, biopsy report, preoperative contrast-enhanced computed tomography findings were documented for all patients. Preoperative blood samples were collected 1 week before surgery. NLR was computed by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was calculated by dividing the platelet count by the absolute lymphocyte count. The relationship between the inflammatory cell ratio and the tumor depth, node, metastasis, pTNM stage, lymphovascular invasion (LVI), perineural invasion (PNI), and tumor grade of the resected material were analyzed.

### Statistical Analysis

Data analysis was performed using SPSS version 25. For qualitative data, descriptive statistics were expressed as percentages, while quantitative data were represented as mean with standard deviation or median with interquartile range. The Shapiro-Wilk test was used to determine normality. The Kruskal–Wallis and Man–Whitney *U* tests were used to compare medians. A receiver operating characteristic (ROC) curve was generated, and the area under the curve was calculated. The ROC curve was utilized to determine the cutoff value of NLR and PLR in differentiating between early and advanced groups, tumor depth (T1 + T2 vs T3 + T4), nodal groups (N0 vs N1 + N2), and distant metastasis (M0 vs M1). NLR and PLR sensitivity and specificity for colon cancer staging were determined. *P*-values <0.05 were deemed statistically significant.

## Results

Our study included 90 patients, with 88 undergoing tumor excision and final histological investigation. Because of the existence of diffuse peritoneal metastases, two patients received solely a bypass procedure. In 88 individuals, NLR and PLR were correlated with pTNM staging. Majority of the patients were between the ages 30 and 80. There were 68 males (75.6%) and 22 females (24.4%). The male to female ratio was 3:1.

Table 1 represents stratification of the patient population based on diagnosis. The most common diagnoses were ascending colon carcinoma followed by sigmoid colon carcinoma, and cecal carcinoma. One patient with hepatic flexure adenocarcinoma had synchronous sigmoid polyp with low-grade dysplasia. Another patient had multiple[3] polyps in the right colon with high-grade dysplasia. On preoperative computed tomography, five patients were found to have liver metastasis, of which two had widespread peritoneal metastases, which was discovered intraoperatively. About 30 (33.3%) patients were operated on using open laparotomy, 23 (25.6%) via laparoscopic method, and the remaining 37 (41.1%) via robotic approach. All patients with solitary liver metastases had metastasectomy with tumor resection. Patients with metastases to the liver and peritoneum underwent laparotomy and bypass procedure.

**Table 1:** Tumor location with frequency

| *Diagnosis* | *Frequency n (%)* |
|---|---|
| Ascending colon carcinoma | 31 (34.4%) |
| Cecal carcinoma | 11 (12.2%) |
| Cecal carcinoma with metastasis | 2 (2.2%) |
| Hepatic flexure carcinoma | 10 (11.1%) |
| Transverse colon carcinoma | 4 (4.4%) |
| Transverse colon carcinoma with metastasis | 2 (2.2%) |
| Splenic flexure carcinoma | 4 (4.4%) |
| Descending colon carcinoma | 10 (11.1%) |
| Sigmoid colon carcinoma | 14 (15.5%) |
| Sigmoid colon carcinoma with metastasis | 1 (1.1%) |
| Multiple polypoidal growths involving right colon | 1 (1.1%) |

Tables 2 and 3 represent correlation of tumor characteristics with NLR and PLR, respectively. Patients with carcinoma in situ (Tis) had slightly higher mean NLR, PLR than those with T1 tumor, and those with T2 tumors had a slightly higher mean NLR, PLR than T3 tumors. The mean NLR/PLR for advanced tumors was higher than the early groups. Statistically significant association was noted with PLR and tumor groups.

The mean NLR for N0 stage was higher than for N1 stage. The pN1 stage had a greater mean PLR than the pN2 stage. N0 tumors were included in the early pN group, whereas N1 + N2 tumors were included in the advanced pN group.

The advanced tumor group had higher mean NLR and PLR values than the early group, but the difference was not statistically significant. The mean NLR was higher in patients without distant metastasis (M0) than in patients with metastasis (M1). The mean PLR for the pM1 stage was greater than that of the pM0 stage.

Lymphovascular invasion was found to be positive in 50%, and PNI was positive in 12.5% of the patients in our study. LVI/PNI-positive patients had higher mean NLR and PLR values than LVI/PNI-negative patients.

Mean PLR increased with lower grade/differentiation (poor differentiation > moderate differentiation > well differentiation > HGD). However, the mean NLR was lower in poorly differentiated tumors than in well and moderately differentiated adenocarcinomas. There was no correlation was seen between NLR and PLR and pTNM stage. The mean NLR and PLR were higher in stage II than in stages III and IV (Table 4).

Statistically significant correlation was noted only between PLR and pathological T (pT) stage, hence ROC curve analysis (Fig. 1) and the cutoff value for differentiating early and advanced T (Tis + T1 + T2, and T3 + T4) stage was derived. The cutoff value was 143.73, based on the most prominent point for sensitivity (66.2%) and specificity (70%) (Table 5). The area under the ROC curve was 0.677 (95% CI: 0.547-0.807, P=0.012). PLR > 143.73 indicated advanced pT stage.

**Table 2:** Correlation between NLR and tumor characteristics

| | *Correlation of NLR with tumor characteristics of colon cancer* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Frequency* | *Minimum* | *Maximun* | *Mean* | *SD* | *Median* | *IQR* | *p-value* |
| Tis | 8 (9.1%) | 1.17 | 3.70 | 2.46 | 0.96 | 2.42 | 1.89 | 0.22 |
| T1 | 4 (4.5%) | 1.42 | 2.25 | 1.93 | 0.40 | 2.03 | 0.73 | |
| T2 | 11(12.5%) | 1.46 | 6.58 | 3.57 | 1.76 | 2.57 | 2.88 | |
| T3 | 44 (50%) | 0.86 | 8.70 | 3.33 | 1.91 | 2.73 | 1.75 | |
| T4 | 21 (23.9%) | 1.47 | 14.00 | 4.03 | 2.99 | 2.84 | 3.37 | |
| Tis + T1 + T2 | 23 (26.1%) | 1.17 | 6.58 | 2.9 | 1.48 | 2.53 | 1.51 | 0.28 |
| T3 + T4 | 65 (73.9%) | 0.86 | 14.00 | 3.55 | 2.32 | 2.75 | 2.04 | |
| N0 | 45 (51.1%) | 1.17 | 8.70 | 3.33 | 1.97 | 2.56 | 1.72 | 0.96 |
| N1 | 28 (31.8%) | 0.86 | 7.63 | 3.30 | 1.78 | 2.83 | 2.44 | |
| N2 | 15 (17%) | 1.47 | 14.00 | 3.69 | 3.17 | 2.27 | 2.21 | |
| N0 | 45 (51.1%) | 1.17 | 8.70 | 3.33 | 1.97 | 2.56 | 1.72 | 0.97 |
| N1 + N2 | 43 (48.9%) | 0.86 | 14 | 3.44 | 2.33 | 2.79 | 2.21 | |
| M0 | 85 (96.6%) | 0.86 | 14 | 3.42 | 2.17 | 2.57 | 1.94 | 0.34 |
| M1 | 3 (3.4%) | 2.11 | 2.79 | 2.35 | 0.38 | 2.14 | | |
| LVI present | 44 (50%) | 0.86 | 14.00 | 3.62 | 2.63 | 2.42 | 3.05 | 0.62 |
| LVI absent | 44 (50%) | 1.17 | 8.70 | 3.14 | 1.50 | 2.64 | 1.39 | |
| PNI present | 11 (12.5%) | 1.47 | 7.63 | 4.59 | 2.19 | 5.20 | 4.12 | 0.054 |
| PNI absent | 77 (87.5%) | 0.86 | 14.00 | 3.21 | 2.09 | 2.56 | 1.41 | |
| Tumor grade | | | | | | | | 0.57 |
| High-grade dysplasia | 8 (8.9%) | 1.17 | 3.70 | 2.46 | 0.96 | 2.42 | 2.42 | |
| Well-differentiated | 4 (4.4%) | 1.42 | 6.17 | 3.15 | 2.07 | 2.52 | 3.59 | |
| Mod differentiated | 64 (71.1%) | 1.46 | 14.00 | 3.65 | 2.33 | 2.71 | 2.40 | |
| Poorly differentiated | 10 (11.1%) | 0.86 | 5.40 | 2.80 | 1.59 | 2.51 | 2.84 | |
| Signet ring | 3 (3.3%) | 2.18 | 2.84 | 2.41 | 0.37 | 2.21 | 2.21 | |
| NET | 1 (1.1%) | | | 4.11 | | | | |

**Table 3:** Correlation between PLR and tumor characteristics

| | *Correlation of PLR with tumor characteristics of colon cancer* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Frequency* | *Minimum* | *Maximum* | *Mean* | *SD* | *Median* | *IQR* | *p-value* |
| Tis | 8 (9.1%) | 93.90 | 143.35 | 122.78 | 20.25 | 131.55 | 39.68 | 0.008 |
| T1 | 4 (4.5%) | 48.20 | 111.90 | 86.64 | 31.09 | 93.24 | 57.11 | |
| T2 | 11(12.5%) | 92.12 | 484.00 | 200.77 | 113.54 | 189.70 | 119.38 | |
| T3 | 44 (50%) | 77.50 | 531.40 | 198.18 | 105.79 | 172.05 | 127.35 | |
| T4 | 21 (23.9%) | 95.10 | 424.80 | 196.63 | 74.10 | 187.70 | 95.85 | |
| Tis + T1 + T2 | 23 (26.1%) | 48.2 | 484 | 153.79 | 91.62 | 126.7 | 85.44 | 0.012 |
| T3 + T4 | 65 (73.9%) | 77.5 | 531.4 | 197.68 | 96.1 | 183.5 | 107.05 | |
| N0 | 45 (51.1%) | 48.2 | 531.4 | 184.09 | 108.88 | 143.35 | 116.95 | 0.44 |
| N1 | 28 (31.8%) | 92.12 | 484.00 | 198.41 | 88.49 | 183.20 | 98.38 | |
| N2 | 15 (17%) | 80.57 | 278.00 | 169.80 | 69.22 | 147.30 | 141.10 | |
| N0 | 45 (51.1%) | 48.2 | 531.4 | 184.09 | 108.88 | 143.35 | 116.95 | 0.33 |
| N1 + N2 | 43 (48.9%) | 80.57 | 484 | 188.43 | 82.59 | 182.9 | 110 | |
| M0 | 85 (96.6%) | 48.2 | 531.4 | 186.14 | 97.81 | 167.5 | 116.54 | 0.63 |
| M1 | 3 (3.4%) | 135 | 232.9 | 188.17 | 49.49 | 196.62 | | |
| LVI present | 44 (50%) | 80.57 | 531.40 | 190.32 | 92.27 | 183.90 | 117.70 | 0.43 |
| LVI absent | 44 (50%) | 48.20 | 519.60 | 182.10 | 101.26 | 167.10 | 90.50 | |
| PNI present | 11 (12.5%) | 111.80 | 307.30 | 210.33 | 64.74 | 232.90 | 118.20 | 0.07 |
| PNI absent | 77 (87.5%) | 48.20 | 531.40 | 182.76 | 99.95 | 164.10 | 100.10 | |
| Tumor grade | | | | | | | | 0.23 |
| High-grade dysplasia | 8 (8.9%) | 93.90 | 143.35 | 122.78 | 20.25 | 131.55 | 39.68 | |
| Well-differentiated | 4 (4.4%) | 48.20 | 233.58 | 151.77 | 80.75 | 162.65 | 154.46 | |
| Moderately differentiated | 64 (71.1%) | 73.10 | 531.40 | 193.55 | 100.28 | 179.70 | 115.18 | |
| Poorly differentiated | 10 (11.1%) | 96.70 | 424.80 | 210.03 | 113.45 | 175.90 | 203.09 | |
| Signet ring | 3 (3.3%) | 109.00 | 298.20 | 198.30 | 95.04 | 187.70 | | |
| NET | 1 (1.1%) | | | 115.4 | | | | |

**Table 4:** NLR and PLR correlation with tumor (pT) stage

| | *pTNM stage* | *Frequency* | *Minimum* | *Maximum* | *Mean* | *SD* | *Median* | *IQR* | *p-value* |
|---|---|---|---|---|---|---|---|---|---|
| NLR | 0 | 8 (9.1%) | 1.17 | 3.70 | 2.46 | 0.96 | 2.42 | 1.89 | 0.64 |
| | I | 12 (13.6%) | 1.42 | 6.58 | 2.98 | 1.64 | 2.43 | 0.77 | |
| | II | 25 (28.4%) | 1.63 | 8.70 | 3.78 | 2.26 | 2.75 | 2.59 | |
| | III | 40 (45.45%) | 0.86 | 14.00 | 3.45 | 2.38 | 2.84 | 2.17 | |
| | IV | 3 (3.4%) | 2.11 | 6.30 | 3.33 | 2.01 | 2.46 | 3.31 | |
| PLR | 0 | 8 (9.1%) | 93.90 | 143.35 | 122.78 | 20.25 | 131.55 | 39.68 | 0.02 |
| | I | 12 (13.6%) | 48.20 | 233.58 | 139.30 | 56.56 | 116.10 | 86.38 | |
| | II | 25 (28.4%) | 77.50 | 531.40 | 225.20 | 127.01 | 197.80 | 132.90 | |
| | III | 40 (45.45%) | 80.57 | 484.00 | 184.91 | 85.21 | 174.30 | 114.60 | |
| | IV | 3 (3.4%) | 183.50 | 278.00 | 222.76 | 42.34 | 214.76 | 79.95 | |

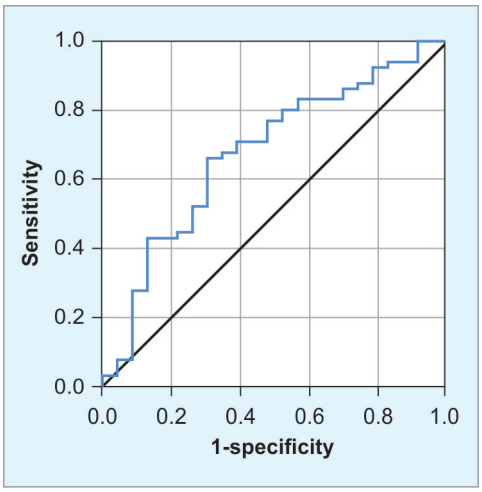


**Fig. 1:** Receiver operating characteristic curve analysis for pathological T (pT) group

(SII), Glasgow Prognostic Score (GPS) are commonly measured for the assessment of systemic inflammatory response, and for the prognostication of different malignant and non-malignant conditions.

In the past, studies on the significance of NLR and PLR in various facets of malignancy management, such as diagnosis, staging correlation, and outcomes, have been conducted. Tianyi Fang et al.[11] in their study demonstrated mean NLR of 3.15 ± 4.84 in patients with gastric cancer in comparison to 1.73 ± 0.62 among healthy individuals. The NLR and PLR were discovered to have more diagnostic utility in gastric cancer patients than standard tumor markers like CEA and CA19-9. Stojkovic Lalosevic M et al.[12] demonstrated higher mean NLR and PLR values among patients with colorectal cancer than the healthy volunteers. The results of the study showed that diagnostic efficacy of combined markers was superior to individual markers. According to the results of a systematic review and meta-analysis conducted by Naszai et al., NLR is a readily available prognostic biomarker in colorectal cancer and should be collected in prospective studies.[13] Another meta-

**Table 5:** Cutoff and area under curve for pT staging

| | *Area under curve* | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | *Asymptotic 95% CI* | |
| *Variable* | *Cutoff* | *Area* | *Sensitivity* | *Specificity* | *p-value* | *Lower bound* | *Upper bound* |
| PLR | 143.73 | 0.677 | 66.2 | 70.0 | 0.012 | 0.547 | 0.807 |

## Discussion

Neutrophils and platelets have pro-tumor property, whereas lymphocytes have antitumor property. Neutrophilia and thrombocytosis promote tumor development, whereas lymphocytopenia leads to decreased anticancer activity. The majority of cancers exhibit neutrophilia. Neutrophilia is caused by tumor cells producing granulocyte monocyte colony stimulating factor (GM-CSF), interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and other inflammatory markers. Interleukin-10 and transforming growth factor-β, are inhibitory inflammatory mediators causing altered lymphocyte function and immunosuppression. Thrombocytosis is also a prevalent feature in the majority of cancers, owing to the stimulatory influence of proinflammatory mediators on megakaryocytes.[10]

Blood parameters including CRP, IL-6, neutrophil levels, lymphocyte levels, tumor infiltrating lymphocytes (TIL), platelets count, mean platelet volume (MPV), NLR, PLR, lymphocyte monocyte ratio (LMR), systemic immune-inflammation index

analysis by Tan et al. suggested that increased peripheral blood PLR is a predictor for overall survival and was associated with clinicopathological findings in patients with colorectal cancer.[14]

NLR and PLR are two novel tumor markers that have been linked to tumor stage and are thought to be indirect indicators of cancer aggressiveness. The most commonly used tumor marker for colon cancer is carcinoembryonic antigen, which has limited sensitivity and specificity. An additional prognostic indicator is necessary in the preoperative scenario to gauge the gross stage of the tumor. High NLR and PLR levels have been linked to advanced tumor stages.[15,16] According to existing research, patients with high preoperative NLR and PLR values have a worse overall survival than those with low NLR and PLR values.[10,17]

Results of our study indicate higher NLR for patients with advanced tumors ($p = 0.28$) which is similar to the findings of the study by Özgehan G et al.,[18] and Li et al.[19] The same trend was observed with PLR ($p = 0.012$), which is supported by results of studies by Li et al.,[19] and Uludag SS et al.[20]

Although the advanced (pN) group exhibited higher mean NLR and PLR values than the early (pN) group, the difference was not statistically significant. Khan et al.[21] exhibited a statistically significant difference in NLR with regard to nodal staging, while Li et al.[19] demonstrated a statistically significant difference in PLR.

The mean NLR and PLR were higher in stage II tumors than in stage III and IV tumors (stage II > stages III and IV). A similar result was noted Jia et al.,[8] and Kilincalp et al.[22]

Poorly differentiated tumors showed greater mean PLR than well-differentiated tumors in our study, although the difference was not statistically significant. A similar result was observed in a study by Zou et al.,[23] which demonstrated that increased PLR was related with poorer tumor differentiation.

There was an association between LVI/PNI positivity and NLR/PLR values similar to the results given by Dimitriou et al.[24] In our study, PLR > 143.73 indicated advanced tumors.

Preoperative tumor marker assessment aid in tumor prognosis, tumor control and may improve the overall patient outcomes. Our study showed a statistically significant association between PLR and tumor depth groups. Although NLR exhibited an association with tumor depth, it was not statistically significant ($p = 0.05$). The study's shortcomings included the fact that NLR and PLR association for stage IV cancers was difficult due to the small number of patients. Also, NLR/PLR values are easily influenced by a variety of other factors. Studies with large sample size, and long-term follow-up are required.

## Conclusion

The NLR and PLR values are low-cost, simple, and noninvasive assays that can be used as potential biomarkers for colon cancer. The PLR score was found to be more accurate than NLR for predicting tumor depth/invasion. A high PLR score may help predict the prognosis of patients with advanced T stage colon cancer and may be beneficial in preoperative counseling, but it must be validated with a survival study.

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