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Retrospective Study

Identification of multiple risk factors for colorectal cancer relapse after laparoscopic radical resection

Jun Luo *et al*.Colorectal cancer relapse risk factors identified

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a common and deadly disease that often requires surgical intervention, such as laparoscopic radical resection. However, despite successful surgery, some patients experience disease relapse. Identifying risk factors for CRC relapse can help guide clinical interventions and improve patient outcomes.

AIM

Comparative analysis of the baseline data of patients with colorectal cancer (CRC) to determine the risk factors that may lead to CRC relapse after laparoscopic radical resection, so as to guide clinical interventions and reduce the risk of relapse in patients.

METHODS

A retrospective analysis was performed on the baseline data of 140 CRC patients who were admitted to our hospital from January 2018 to January 2020. All included subjects were followed up until death or for a maximum of three years. The baseline data and laboratory indicators of relapsed and non-relapsed patients were compared.

RESULTS

Among the 140 CRC patients included in the study, 30 cases relapsed within three years after laparoscopic radical resection (21.43% relapse rate), and 110 patients did not relapse (78.57% non-relapse rate). The relapse group showed higher frequency of tumors located in rectum with low differentiation and lymphatic vessel invasion than those in the non-relapse group. Expressions of serum markers such as the $CD4^+/CD8^+$ ratio, immunoglobulin (IgG, IgA, and IgM) levels, albumin-globulin ratio (AGR), and prognostic nutritional index (PNI) were lower in the relapse group than the non-relapse group, while the neutrophils to lymphocytes ratio (NLR), expressions of cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), vascular endothelial growth factor (VEGF), and YKL-40 were higher than those in the non-relapse group, and the differences are statistically significant ($P<0.05$). There is no significant difference in other data between the groups ($P>0.05$). Logistics regression showed that all the above significantly altered factors are independent risk factors for CRC relapse after laparoscopic radical surgery ($OR>1$, $P<0.05$).

CONCLUSION

We have identified multiple risk factors for relapse of CRC following surgery, which can be considered for clinical monitoring of patients to reduce disease recurrence and improve patient survival.

Key Words: Colorectal cancer; laparoscopic radical surgery; relapse; risk factors.

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Core Tip: This study aimed to identify risk factors for colorectal cancer (CRC) relapse after laparoscopic radical resection by comparing the baseline data and laboratory

indicators of 140 CRC patients, of which 30 relapsed within three years. The results showed that tumors located in rectum with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Lower levels of CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, and PNI, and higher levels of NLR, CYFRA21-1, VEGF, and YKL-40 were also identified as independent risk factors for CRC relapse following surgery. These findings suggest that monitoring these factors could help reduce the risk of disease recurrence and improve patient outcomes.

INTRODUCTION

Colorectal cancer (CRC) is a malignant disease of the digestive tract with high incidence that is closely related to the living environment and lifestyle. The lack of specific symptoms at the early stage of onset leads to a low early detection rate. Thus, many patients are in the advanced stage when diagnosed, and the prognosis of these patients is often unsatisfactory [1-2]. Treatments for CRC has progressed rapidly, and the overall principle is to adopt surgical intervention supplemented by comprehensive standardized treatments, such as radiotherapy and targeted therapy. Currently, endoscopic technology has gradually replaced the traditional laparotomy and is the first choice and main intervention means for the treatment of CRC [3-4]. Although CRC patients receive timely consolidation treatment with adjuvant therapies, such as chemoradiotherapy and molecular targeted therapy after surgery, the risk of postoperative relapse remains high, leading to high mortality rate in these patients [5-6]. About 30% of CRC patients who have undergone laparoscopic radical surgery showed risk of metastasis or relapse after surgery, and the five-year survival rate of such patients is only about 19%. Metastasis to the liver, in particular, is a major clinical challenge. Therefore, exploring the factors that may lead to postoperative relapse is particularly necessary to enhance vigilance of patients at high-risk of relapse and guide more appropriate clinical interventions, ultimately reducing the risk of postoperative relapse and enhance prognosis of patients [7-8]. A search for clinical literature related to the exploration of factors that may affect the relapse of laparoscopic radical resection for

patients with CRC highlighted factors such as patient age, tumor stage, and tumor size, with no firm consensus [9-11]. In view of this, in this study, we compared and analyzed the baseline data of included subjects to identify the influencing factors that may lead to the relapse of CRC patients after laparoscopic radical resection, so as to guide future interventions and reduce the risk of relapse in CRC patients after surgery.

MATERIALS AND METHODS

2.1 Included subjects Baseline data were collected from 140 CRC patients who were admitted to our hospital Peking University Shenzhen Hospital from January 2018 to January 2020, including 80 males and 60 females. All enrolled subjects met the following requirements:

Inclusion criteria: ①patients with CRC that met the diagnostic requirements in the "Clinical Guideline for Diagnosis and Treatment of Tumor" [12] and were confirmed by clinical pathological biopsy; ② all included subjects successfully underwent laparoscopic radical resection; ③patient baseline data and laboratory test results are complete.

Exclusion criteria: ①patients with other cancerous lesions; ②patients with metastasis diagnosed before or during the operation; ③patients who have received targeted therapy, chemoradiotherapy and other adjuvant treatments before operation; ④patients with reduced compliance due to psychological disorders; ⑤presence of acute or chronic diseases such as decreased liver and kidney functions, pulmonary diseases, cardiovascular and cerebrovascular diseases, hematological diseases or coagulation disorders, intestinal diseases such as intestinal obstruction and intestinal perforation, and acute and chronic infections or active inflammations that may affect the prognosis of the patient.

2.2 Methods

A retrospective analysis was performed on the baseline data of the above patient cohort.

2.2.1 Diagnostic criteria for relapse Included patients underwent effective follow-up until death or up to a maximum of three years (until January 31, 2023). Relapse is defined as detection of pathological lesions similar to the primary lesions regrowing around the sites of the primary lesion, intestinal anastomosis, peri-intestinal tissue, mesentery and its lymph node regions through clinical imaging (B-scan ultrasonography, X-ray, CT), and further confirmation by tissue biopsy for patients suspected of relapse.

2.2.2 Baseline data collection The following baseline data were collected: gender; age (≥60 years, <60 years); Tumor Node Metastasis (TNM) [13] stage (stage I-II, stage III-IV); degree of differentiation (with reference to the Edmondson-Stener classification of tumor pathological grade [14], stage I: highly differentiated carcinoma, stage II: moderately differentiated carcinoma; stage III and IV: poorly differentiated carcinoma); maximum tumor diameter (≥5 cm, <5 cm); location of the lesion (rectum, left/right hemicolon); lymphovascular invasion (present, absent); pathological type (glandular cancer, mucinous adenocarcinoma, Indian cell carcinoma); depth of invasion (T1+T2, T3+T4); serum tumor and immune indicators (lymphocytes ($CD4^+/CD8^+$), immunoglobulins (IgA, IgG, IgM), neutrophils to lymphocytes ratio (NLR), albumin-globulin ratio (AGR), cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), vascular endothelial growth factor (VEGF), prognostic nutritional index (PNI), and the inflammatory biomarker YKL-40).

2.2.3 Detection of serum indicators Fasting peripheral blood was collected in anticoagulation tubes and used for the following assays: absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) using the XE-2100 blood cell analyzer (SYSMEX Corporation, Japan; NLR = PLT/ALC); enzyme-linked immunosorbent assay (ELISA) detections of immunoglobulins, VEGF and YKL-40 , Huamei, and Zhenke Biotechnology, China, respectively); total serum protein and albumin detection by an auto chemistry analyzer (BK-400, Jinan Olebo Electronic Commerce, China; globulin =

total protein – albumin, AGR = albumin/globulin); CYFRA 21-1 detection by electrochemical luminescence; PNI determination by calculating the albumin concentration and lymphocyte counts with the AU680 automatic biochemical analyzer (Beckman Coulter, USA; PNI = albumin (mg/L) + 5 x lymphocyte counts ($x10^9$/L)).

2.3 ***Statistical analysis*** SPSS25.0 was used to process the data. The Shapiro-Wilk test was used to determine the normality of the measurement data, and $\pm s$ meant the measurement data conformed to normal distribution. Independent sample t test was used for inter-group comparison; n (%) represented the count data, and χ^2 test was used. Logistic regression analysis was used to analyze the risk factors for relapse in patients with CRC after laparoscopic radical resection; inspection level α=0.05.

RESULTS

2.1 Relapse status of patients after radical resection of CRC

Among the 140 patients with CRC included in the study, 30 cases relapsed within three years after laparoscopic radical resection, while 110 cases did not relapse. The relapse rate is therefore 21.43% (30/140) and the non-relapse rate 78.57% (110/140). We analyzed the baseline data of the relapse and non-relapse groups below.

2.2 Comparison of baseline data between the two groups

The relapse and non-relapse groups are comparable in many of the baseline characteristics. However, significant differences between the two groups can be found in the differentiation degree of the tumor, lesion location, lymphatic vessel invasion, and a number of serum indicators. Majority of patients in the relapse group had tumors in the rectum that showed low differentiation, and had lymphatic vessel invasion, while tumors of the non-relapse patients tended to be located in the left/right hemicolon, more differentiated, and absent for lymphatic invasion (Table 1). The $CD4^+/CD8^+$ ratio, levels of IgG, IgA, IgM, AGR, and PNI in the relapse group were lower than those in the non-relapse group, while the expressions of NLR, CYFRA21-1, VEGF, and YKL-40 were

higher than those in the non-relapse group, and the differences are statistically significant ($P<0.05$).

2.3 *Logistic regression analysis of relapse after laparoscopic radical resection of CRC*

To determine whether the factors that are significantly different between the relapse and no-relapse patients are significant risk factors for relapse after laparoscopic radical resection, we performed logistic regression analysis with relapse after surgery as the dependent variable (1 = relapse, 0 = non-relapse), and indicators with significant differences in Table 1 as the independent variables (assignments are shown in Table 2-1). The results showed that the degree of differentiation (low differentiation), location of the lesion (rectum), lymphatic vessel invasion (present), low expression of serum $CD4^+/CD8^+$, IgG, IgA, IgM, AGR, and PNI, and high expression of serum NLR, CYFRA21-1, VEGF, and YKL-40 are all independent risk factors for relapse in CRC patients after laparoscopic radical surgery ($OR > 1$, $P < 0.05$; Table 2-2).

DISCUSSION

Laparoscopic radical resection can significantly improve the overall outcome of patients and reduce the impact of open surgery on the immune function of the body. However, the risk of relapse in CRC patients after radical resection is still high. Our current study supports this conclusion with an observed relapse rate of 21.43% in our cohort of 140 patients. This has serious impact on patients' quality of life and overall survival rate. Therefore, for patients with CRC, early detection of relapse after surgery and exploring the risk factors that may lead to relapse are particularly crucial for guiding further treatments for patients, prolonging survival time and improving life quality [15-16].

The results of this study showed that patients with tumors in the rectum with low degree of differentiation, and presence of lymphatic vessel invasion are more at risk of postsurgical relapse than patients with more differentiated tumor located within the colon and absence of lymphatic vessel invasion. Other immune/tumor-related risk

factors for relapse include lower expressions of $CD4^+/CD8^+$, IgG, IgA, IgM, AGR, and PNI, and higher expressions of NLR, CYFRA21-1, VEGF, and YKL-40. Logistics regression analysis supports that all these variables are independent risk factors for CRC relapse after laparoscopic radical resection.

A possible reason for the higher relapse rate in patients with tumors in the rectum may be because of the complex rectal lymphatic drainage system. The absence of serosal in the lower rectal cancer tube may allow the lesions to easily adhere to the surrounding tissues, increasing the difficulty of complete surgical removal and the risk of postoperative relapse [17]. The degree of tissue differentiation has a significant effect on the biological behavior of the tumor. A lower degree of differentiation indicates that the tumor tissue has strong regenerative ability, fast growth rate due to rapid cell division and proliferation, and high migration and invasiveness into the surrounding tissues, lymphatic vessels, and capillaries, contributing to a high probability of postoperative relapse [36-37].

As an important immune organ, the lymph node is the switch that activates the immune response of the body. Because of the abundant lymphatic and blood vessels in the mesorectum, cancer cells can easily invade these circulatory systems, forming circulating tumor cells that are resistant to apoptosis and attacks from the immune system and many other environmental factors, eventually invading new tissues to form metastases, thus increasing the relapse rate of patients after surgery [43-44]. The body's immune function is essential for monitoring and inhibiting tumor progression, of which T cells and their subsets are particularly related to the progression of malignant diseases. $CD8^+$ T cells can directly act as effector cells to kill tumor cells, while $CD4^+$ T cells mainly inhibit inflammatory factors, secrete specific cytokines to assist other immune cells, regulate the body's immune function against tumor, and increase the body's immune tolerance to achieve antitumor immunity. Thus, the changes in $CD8^+/CD4^+$ ratio directly affect the body's ability to resist tumor cells [18-20]. Regulatory T cells contributes to the mechanism of immune escape of cancer lesions. When the $CD4^+/CD8^+$ value is high, a large number of regulatory T cells infiltrate the tumor and

illicit a significant immunosuppressive effect that contributes to tumor occurrence, progression and metastasis. When the $CD4^+/CD8^+$ value is increased for various reasons, it indicates that the immune function is in an inhibitory state with decreased immunity and increased tolerance, the antitumor immune response is also damaged, leading to the proliferation and progression of cancerous lesions, and directly increases the risk of postoperative relapse. When a patient relapses after surgery, many soluble immunosuppressive factors are also produced in the process of tumor regeneration and progression, which hinders the maturation of $CD4^+$ cells, inhibits the body's immune system, and promotes disease progression. This forms a vicious cycle and leads to poor prognosis for patients [21-23]. Immunoglobulins such as IgG, IgA, and IgM are all important parts of the immune system. They mainly activate the complement system by specifically binding to antigens, accelerate cell lysis and enhance antibody regulation to achieve antitumor immune effects. Abnormal expression of immunoglobulins is a manifestation of impaired humoral immune function. A decreased expression of IgG, IgA, and IgM indicates decreased mucosal defense and weakened complement-mediated phagocytosis. Reduced phagocytic removal of cancer cells is thus likely to increased risk of postoperative relapse in patients [24-26].

The AGR and NLR are both markers of inflammation that indicate the systemic inflammatory response state and immunosuppressive function of the body. Inflammatory responses are triggered when the body suffers from infection and other factors. But unregulated inflammation can cause significant damage to the body and a chronic inflammatory state will retard immune infiltration and increase angiogenesis, providing an ideal environment for the growth and reproduction of cancer cells and promotes the generation and spread of cancerous lesions. Relapsing tumors aggravates the inflammatory response in the body and forms a negative feedback that leads to an increased risk of postoperative relapse in patients [27-29].

In addition to the AGR, a combination of albumin and lymphocyte count readouts in the form of PNI may also be a useful marker in cancer biology. Lymphocytes are important components of the immune system but are also involved in protein recovery

and nutrient transport, so PNI can highlight the nutritional status of individuals. Reduced PNI values indicate decreased lymphocyte counts and albumin levels, and possible inflammation and malnutrition in the body. This can lead to treatment intolerance and decline in antitumor immune functions, resulting in increased cancer cell proliferation and risk of postoperative relapse [38-40].

The protein antigen of CYFRA21-1 is mainly present in the lymph nodes, bone marrow and epithelium in the healthy state. When cells become cancerous, protease is activated and normal colorectal epithelial tissues are damaged. When cells die, the activated protease accelerates the dissolution rate, large amount of CYFRA21-1 is released into blood, and the expression of CYFRA21-1 in serum is increased. Thus, high expression of CYFRA21-1 indicates extensive cell death or damaged. We should be alert to the re-invasion of cancer lesions, indicating that patients have a high risk of relapse [30-32].

Many vascular stimulation factors can stimulate cancer cells to release a large number of angiogenic factors that promote angiogenesis within the tumor. VEGF has a strong induction effect, which can accelerate the abnormalities and rapid growth of tumors. High levels of serum VEGF can promote the abnormal proliferation of tumor cells, accelerate the transformation of cancer cells into solid tumors, stimulate their migration and invasion to the surrounding tissues and organs, destroy the normal colorectal epithelial tissues and cells, accelerate neoangiogenesis, change the microenvironment, and increase the chance of relapse [33-35].

YKL-40 is a secretory glycoprotein mainly produced by chondrocytes, neutrophils, and other cells under the influence of inflammation. YKL-40 has many biological functions and signals *via* multiple pathways involved in angiogenesis, cell proliferation and differentiation, and immune and inflammatory responses. High expression of YKL-40 may accelerate colorectal epithelial-mesenchymal transition (EMT) by up-regulating vimentin and N-cadherin, and down-regulating E-cadherin. As EMT is an important property for tumor migration and invasion, increased YKL-40 expression may increased risk of relapse in patients with CRC after radical surgery [41-42].

CONCLUSION

In this study, we have highlighted a number of risk factors for relapse in CRC patients after surgery, which will enable targeted interventions to be adopted in clinical practice depending on the combination of risk factors present. These factors can serve as a monitoring strategy to identify patient at high risk and detect early disease recurrence. Direct interventions to reduce the abnormal expression of these serum indicators may also reduce the risk of relapse after radical surgery. However, due to the retrospective nature of this study and the limited sampling within a single-center, the reproducibility and generalizability of our research conclusions need to be verified by further exploration in the future. In addition, the results of this study show that TNM stage is not a risk factor for postoperative recurrence in patients with CRC, which is inconsistent with the results of Zhang[45] et al. However, the reasons for the inconsistent results are not discussed in depth in this paper. Further research is needed on the impact of TNM stage on postoperative recurrence in patients with CRC.

In summary, we have identified a number of risk factors for CRC relapse following laparoscopic radical resection, including tumors located in the rectum with low differentiation and lymphatic vessel invasion, low serum expression of $CD4^+/CD8^+$, IgG, IgA, IgM, AGR, and PNI, and high serum expression of NLR, CYFRA21-1, VEGF, and YKL-40. Monitoring these risk factors will help us to enhance vigilance for the risk of CRC relapse after laparoscopic radical surgery.

ARTICLE HIGHLIGHTS

Research background

+ADw-html+AD4APA-p+AD4-Colorectal cancer (CRC) is a prevalent and life-threatening disease that often necessitates surgical intervention, such as laparoscopic radical resection. However, despite successful surgical procedures, a subset of patients experiences relapse. The identification of risk factors associated with CRC relapse is crucial for guiding clinical interventions and enhancing patient outcomes. This study

aimed to conduct a comparative analysis of baseline data and laboratory indicators in CRC patients to determine the risk factors contributing to relapse following laparoscopic radical resection. A retrospective analysis was performed on 140 CRC patients, of which 30 experienced relapse within three years after surgery. The study revealed that tumors located in the rectum with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Additionally, specific serum markers, including CD4+-/CD8+- ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40, were identified as independent risk factors for CRC relapse. These findings underscore the importance of monitoring these factors to reduce the risk of disease recurrence and improve patient outcomes.+ADw-/p+AD4APA-/html+AD4-

Research motivation

+ADw-html+AD4APA-p+AD4-Colorectal cancer (CRC) is a significant health burden with the potential for relapse even after successful surgical intervention. The identification of risk factors associated with CRC relapse is crucial to guide clinical interventions and enhance patient outcomes. This study aimed to analyze the baseline data and laboratory indicators of CRC patients who underwent laparoscopic radical resection, with the objective of determining the risk factors contributing to relapse. The findings highlighted several key factors, including tumor location, differentiation, lymphatic vessel invasion, as well as serum markers such as CD4+-/CD8+- ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40. Understanding these risk factors can aid in identifying high-risk patients and implementing proactive measures for monitoring and intervention, ultimately reducing the risk of relapse and improving the long-term survival prospects for CRC patients.+ADw-/p+AD4APA-/html+AD4-

Research objectives

+ADw-html+AD4APA-p+AD4-This study aimed to compare baseline data and laboratory indicators of colorectal cancer (CRC) patients who underwent laparoscopic radical resection to identify risk factors associated with CRC relapse. The objectives

were to determine the differences in tumor characteristics, analyze serum markers, assess statistical significance, identify independent risk factors using logistic regression, and provide insights for clinical monitoring and interventions to reduce relapse risk and improve patient outcomes.+ADw-/p+AD4APA-/html+AD4-

Research methods

+ADw-html+AD4APA-p+AD4-This study utilized a retrospective analysis of baseline data from 140 colorectal cancer (CRC) patients admitted to the hospital between January 2018 and January 2020. The included subjects were followed up until death or a maximum of three years. Comparative analysis was conducted to compare the baseline data and laboratory indicators between patients who experienced relapse and those who did not. Tumor characteristics, including location, differentiation, and lymphatic vessel invasion, were assessed. Serum markers, such as CD4+-/CD8+- ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40, were measured and compared between the relapse and non-relapse groups. Statistical analyses were performed to determine the significance of the observed differences. Logistic regression was employed to identify independent risk factors associated with CRC relapse after laparoscopic radical surgery. The research methods aimed to provide valuable insights into the identification and monitoring of risk factors for disease recurrence and improving patient survival outcomes.+ADw-/p+AD4APA-/html+AD4-

Research results

Out of the 140 CRC patients included in the study, 30 cases (21.43%) experienced relapse within three years after laparoscopic radical resection, while 110 patients (78.57%) did not relapse. The relapse group exhibited a higher frequency of tumors located in the rectum with low differentiation and lymphatic vessel invasion compared to the non-relapse group. Significant differences were observed in the levels of several serum markers. The relapse group showed lower expressions of CD4+/CD8+ ratio, IgG, IgA, IgM, albumin-globulin ratio (AGR), and prognostic nutritional index (PNI).

Conversely, the relapse group had higher levels of neutrophil-to-lymphocyte ratio (NLR), cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), vascular endothelial growth factor (VEGF), and YKL-40. Logistic regression analysis confirmed that all these altered factors were independent risk factors for CRC relapse following laparoscopic radical surgery, with odds ratios greater than 1 and statistically significant values ($P<0.05$). These findings emphasize the importance of monitoring these factors for reducing disease recurrence and improving patient survival outcomes.

Research conclusions

Based on our comparative analysis of baseline data and laboratory indicators in CRC patients who underwent laparoscopic radical resection, we have identified several important conclusions. Firstly, tumors located in the rectum with low differentiation and lymphatic vessel invasion are associated with a higher risk of relapse after surgery. Additionally, lower levels of CD4+/CD8+ ratio, IgG, IgA, IgM, AGR, and PNI, along with higher levels of NLR, CYFRA21-1, VEGF, and YKL-40, serve as independent risk factors for CRC relapse following surgery. These findings highlight the significance of monitoring these factors to guide clinical interventions and reduce the risk of disease recurrence. By focusing on these risk factors, healthcare professionals can enhance patient surveillance and develop strategies to improve survival outcomes in CRC patients undergoing laparoscopic radical resection.

Research perspectives

+ADw-html+AD4APA-p+AD4-The identification of multiple risk factors for CRC relapse following laparoscopic radical surgery provides valuable insights into improving patient outcomes. Moving forward, prospective studies should focus on validating these findings in larger patient populations and diverse healthcare settings. Further investigations can explore the molecular mechanisms underlying the identified risk factors to gain a deeper understanding of their roles in disease recurrence. Additionally, the development of predictive models incorporating these risk factors

could aid in personalized treatment strategies and postoperative surveillance. Long-term follow-up studies are warranted to assess the impact of monitoring these factors on long-term survival and quality of life in CRC patients. Furthermore, intervention studies targeting modifiable risk factors may offer potential avenues for reducing disease relapse rates. Overall, continued research efforts in this field will contribute to optimizing clinical management and ultimately enhancing the prognosis of CRC patients undergoing laparoscopic radical resection.+ADw-/p+AD4APA-/html+AD4-

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