RESEARCH ARTICLE

Prognostic Significance of Preoperative Lymphocyte-Monocyte Ratio in Patients with Resectable Esophageal Squamous Cell Carcinoma

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Abstract

Background: The interaction between tumor cells and inflammatory cells has not been systematically investigated in esophageal squamous cell carcinoma (ESCC). The aim of the present study was to evaluate whether preoperative the lymphocyte-monocyte ratio (LMR), the neutrophil-lymphocyte ratio (NLR), and the platelet-lymphocyte ratio (PLR) could predict the prognosis of ESCC patients undergoing esophagectomy. Materials and Methods: Records from 218 patients with histologically diagnosed ESCC who underwent attempted curative surgery from January 2007 to December 2008 were retrospectively reviewed. Besides clinicopathological prognostic factors, we evaluated the prognostic value of the LMR, the NLR, and the PLR using Kaplan-Meier curves and Cox regression models. Results: The median follow-up was 38.6 months (range 3-71 months). The cut-off values of 2.57 for the LMR, 2.60 for the NLR and 244 for the PLR were chosen as optimal to discriminate between survival and death by applying receiver operating curve (ROC) analysis. Kaplan-Meier survival analysis of patients with low preoperative LMR demonstrated a significant worse prognosis for DFS (p=0.004) and OS (p=0.002) than those with high preoperative LMR. The high NLR cohort had lower DFS (p=0.004) and OS (p=0.011). Marginally reduced DFS (p=0.068) and lower OS (p=0.039) were found in the high PLR cohort. On multivariate analysis, only preoperative LMR was an independent prognostic factor for both DFS (p=0.009, HR=1.639, 95% CI 1.129-2.381) and OS (p=0.004, HR=1.759, 95% CI 1.201-2.576) in ESCC patients. Conclusions: Preoperative LMR better predicts cancer survival compared with the cellular components of systemic inflammation in patients with ESCC undergoing esophagectomy.

Keywords: Esophageal squamous cell carcinoma - lymphocyte-monocyte ratio - clinical outcome

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Introduction

Esophageal carcinoma (EC) ranked the eighth most common cancer and the sixth leading cause of cancer-related death all around the world. In east Asia, especially in China, Esophageal squamous cell carcinoma (ESCC) is the predominant histological type of EC, affecting more than 100 cases per 100,000 population annually (Pennathur et al.). Despite multidisciplinary treatment for ESCC, surgical resection remains the primary treatment for non-metastatic disease. Unfortunately, even after potentially curative surgery, the 5-year survival rate is only 26.2% to 49.4%, mainly due to local or distant recurrences (Liu et al., 2012). Therefore, it is imperative to identify novel prognostic markers that will improve clinical outcome through identifying ESCC patients with high risk of tumor recurrence and poor prognosis.

Nowadays, it is widely accepted that there is a causal relationship between inflammation, innate immunity and cancer. Cancer-related inflammation affects many aspects of the neoplastic process by promoting or restraining progression, angiogenesis and metastasis, suppressing antitumor immunity and impacting response to systemic therapies (Mantovani et al., 2008; Colotta et al., 2009). Inflammatory component of a developing neoplasm includes a diverse leukocyte population, for example, neutrophils, macrophages, dendritic cells, eosinophils and mast cells, as well as lymphocytes. In the last decades, there is a growing interest for clinical interpretation of inflammatory-related factors' interactions in various solid tumors. Neutrophil-lymphocyte ratio (NLR) has been proved to be an independent prognostic factor for survival in various solid tumors, including esophageal carcinoma, colorectal carcinoma, hepatocellular carcinoma, gastric cancer, and renal cell carcinoma (Sharaiha et al., 2011; Templeton et al., 2014b). Platelets-lymphocyte ratio (PLR), based on circulating platelets and lymphocytes, has also been proved to be a prognostic factor in various solid tumors (Templeton et al., 2014a). However, studies available regarding NLR, PLR in EC are limited, especially in ESCC, and the results are controversial. Recently, lymphocyte-monocyte ratio (LMR) was found that could act as a convenient and inexpensive prognostic factor in some hematologic malignancies and solid tumors,

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such as diffuse large B-cell lymphoma (Li et al., 2014), soft tissue sarcomas (Szkandera et al., 2014), gastric cancer (Zhou et al., 2014) and colon cancer (Stotz et al., 2014). To the best of our knowledge, no studies regarding the preoperative LMR as a prognostic factor in patients with esophageal carcinoma have been published so far.

Therefore, we conducted a retrospective study on ESCC, attempting to evaluate the prognostic value of cellular components of the systemic inflammatory response, including the preoperative LMR, the NLR and the PLR for the disease.

Materials and Methods

Patients and follow up

A retrospective analysis was conducted of 459 patients underwent esophagectomy at the Department of Thoracic Surgery, Qilu Hospital of Shandong University between January 2007 and December 2008.

Patients were included if they underwent radical surgery for pathologically proven ESCC. The exclusion criteria comprised neoadjuvant treatment, distal metastasis, perioperative mortality, lost to follow up, without pre-operative blood cell counts records or with concurrent infection and autoimmune diseases. Finally, 218 patients (177 male, 41 female) were included.

Clinicopathological characteristics and laboratory data were retrospectively obtained from the patient records. Types of esophagectomy included Ivor-Lewis and the three-stage (right thoracotomy, midline laparotomy and left cervical incisions) esophagectomy. All tumors were staged according to the American Joint Committee on Cancer staging manual (7th edition, 2010). This study was approved by the Ethics Committee of Qilu Hospital of Shandong University.

The patients were followed up in our outpatient clinics every 3 months for the first 2 years after surgery and thereafter every 6 months interval or until death. Follow-up investigations included regular history and physical examinations in all patients at each visit. Routing diagnostic imaging methods included tumor marker assays, such as squamous cell carcinoma antigen, barium meal fluoroscopy and computer tomography. The last follow up was on November 2013.

LMR, NLR and PLR evaluation

As part of the physical examinations, a complete blood count (CBC) was collected in all patients within one week prior to surgery. The LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. Similarly, NLR was calculated as the ratio of total neutrophils count divided by the total lymphocyte count. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Science (SPSS for Windows, version 17.0, SPSS Inc, Chicago, IL) program. A 2-sided P values <0.05 indicated statistical significant.

The end points for this study were disease-free survival (DFS) and Overall survival (OS). DFS was defined as the length of time (in months) after surgery during which the patient survived with no sign of tumor recurrence. OS was defined as the time (in months) from the date of surgery to individuals' death of any cause or the last follow-up. The possible cut-off levels for these continuous LMR, NLR and PLR were calculated by applying receiver operating curve (ROC) analysis. The optimal cut-off value that would discriminated between survival and death (i.e., which had the most significant P-value on a log-rank test) were determined by testing all possible cut-offs as previously described (Szkandera et al., 2014).

Spearman's rank correlation coefficient was used to describe the correlation between LMR, NLR and PLR. The relationships between LMR, NLR and PLR and clinicopathological parameters were evaluated by the Chi square test. Kaplan-Meier curves and log-rank tests were used for DFS and OS analyses. Backward stepwise multivariate Cox proportion analysis was used to test independence, significance, and hazard discrimination, respectively.

Results

Patient characteristics

Among the 218 patients, 41 (18.8%) were women and 177 (81.2%) were men. The median age of the entire cohort at the time of diagnosis was 60.5 years (range 32-84 years). The median follow-up was 38.6 months (range 3-71months). None of them received neoadjuvant treatments preceded surgery. Postoperative treatment was used in 82 (37.6%) cases where 17 (20.7%) cases with chemotherapy, 41 (50.0%) cases with radiotherapy, and 24 (29.3%) cases with chemoradiotherapy, respectively. Within the follow-up period, a total of 96 (44.0%) patients developed tumor recurrences and 138 (63.3%) patients died. Of these patients who suffered recurrence, 6 were surgical anastomosis recurrences, 38 were local recurrences and 52 were distant recurrences.

The overall median (range) white blood cell, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, and absolute platelet count in our cohort were 6.42 (3.23-13.20)$\times 10^9$/l, 4.02 (1.62-10.13)$\times 10^9$/l, 1.66 (0.39-4.04)$\times 10^9$/l, 0.46 (0.18-1.07)$\times 10^9$/l and 240 (78-652)$\times 10^9$/l, respectively. To investigate the most promising inflammatory biomarker, we determined the cut-off value of 2.57 for the LMR, 2.60 for the NLR and 244 for the PLR as optimal to discriminate between survival and death. In addition, LMR was in negative correlation with NLR (ϱ=-0.681, p<0.001) and PLR (ϱ=-0.505, p<0.001). NLR was in positive correlation with PLR (ϱ=0.639, p<0.001).

The clinical characteristics of 218 ESCC patients were comparable between patients grouped by LMR, NLR and PLR, as presented in Table 1. Based on the cutoff value of LMR, 45 patients were included in the low LMR group (<2.57), whereas the other 173 patients were in the high LMR group (≥2.57). No significant difference was identified regarding gender, age, tumor length, tumor location, differential grade, pT status, pN status, pTNM stage and the treatment regimen between the two groups.

Table 1. The Characteristics of 218 ESCC Patients Grouped by LMR, NLR and PLR

Characteristic		Cases	LMR		*P* value	NLR		*P* value	PLR		*P*value
		(n =218)	Low	High		Low	High		Low	High	
Gender	Female	41 (18.8%)	5	36	0.138	31	10	0.012*	37	4	0.571
	Male	177 (81.2%)	40	137		96	81		154	23	
Ages (years)	≤60	109 (50.0%)	22	87	0.939	62	47	0.680	93	16	0.304
	>60	109 (50.0%)	23	86		65	44		98	11	
Tumor length (cm)	≤3	65 (29.8%)	12	53	0.193	46	19	0.015*	59	6	0.357
	>3	153 (70.2%)	33	120		81	72		132	21	
Tumor location	Upper	23 (10.6%)	6	17	0.217	15	8	0.259	18	5	0.036*
	Middle	122 (56.0%)	20	102		75	47		113	9	
	Lower	73 (33.5%)	19	54		37	36		60	13	
Differential grade	Well	55 (25.2%)	15	40	0.312	34	21	0.642	47	8	0.853
	Middle	95 (43.6%)	19	76		52	43		84	11	
	Poor	68 (31.2%)	11	57		41	27		60	8	
pT status	T1-2	86 (39.4%)	14	72	0.199	58	28	0.026*	78	8	0.265
	T3-4	132 (60.6%)	31	101		69	63		113	19	
pN status	N0	128 (58.7%)	23	106	0.245	75	53	0.904	116	12	0.108
	N1-3	90 (41.3%)	22	68		52	38		75	15	
pTNM stage	I+II	133 (61.0%)	24	109	0.236	81	52	0.322	119	14	0.297
	III	85 (39.0%)	21	64		46	39		72	13	
Adjuvant therapy	No	136 (62.4%)	26	110	0.745	79	57	0.948	123	13	0.103
	Yes	82 (37.6%)	19	63		48	34		68	14	
Recurrence	No	122 (56.0%)	19	103	0.037*	76	46	0.173	112	10	0.034*
	Yes	96 (44.0%)	26	70		51	45		79	17	

ESCC esophageal squamous cell carcinoma, LMR lymphocyte-monocyte ratio, NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, pT pathological tumor stage, pN pathological node stage, pTNM pathological tumor node metastasis stage; *p<0.05

Table 2. Univariate and Multivariate Analyses of Prognostic Factors in ESCC With Respect to Disease-free Survival

Disease-free Survival	Univariate analysis			Multivariate Analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Female	0.133	1.390	0.904-2.135			
Age ≤ 60	0.614	0.921	0.670-1.266			
Tumor length ≤ 3	0.065	1.398	0979-1.996	0.046*	1.639	1.129-2.120
Tumor location: Upper/middle/lower	0.977	1.004	0.780-1.292			
Differential Grade: Well/middle/poor	0.994	1.001	0.805-1.672			
pT status: T1-2/T3-4	0.009*	1.566	1.120-2.188	0.989	1.003	0.689-1.459
pN status: N0/ N1-3	<0.001*	1.879	1.364-2.589	0.672	1.130	0.641-1.809
pTNM stage:I-II/III	<0.001*	2.143	1.553-2.955	<0.001*	1.829	1.317-2.541
Treatment regimens: Surgery alone	0.272	1.203	0.865-1.678			
NLR<2.60	0.004*	1.577	1.145-2.170	0.295	1.229	0.836-1.809
PLR<244	0.068	1.516	0.964-2.385	0.722	0.905	0.523-1.568
LMR≥2.57	0.004*	1.717	1.184-2.292	0.009*	1.639	1.129-2.381

ESCC esophageal squamous cell carcinoma, NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, LMR lymphocyte-monocyte ratio
*p<0.05

However, the incidence of locoregional recurrences among patients with low LMR was 57.8%, significantly higher than those with high LMR (40.5%) (p=0.037).

Based on the cutoff value of NLR, 91 patients were separated into the high NLR group (≥2.60). Significant difference between the patients with NLR values <2.60 and ≥2.60 has been found regarding gender (p=0.012), tumor length (p=0.015), and pT status (p=0.026).

Based on the cutoff value of PLR, 27 patients were separated into the high PLR group (≥244). Significant difference between the patients with PLR values <244 and ≥244 was found regarding tumor location (p=0.015), and the incidence of locoregional recurrences (p=0.034).

Survival and prognostic value of LMR, NLR and PLR in ESCC

The median follow-up was 38.6 months (range 3-71 months). The median DFS was 29.0 months, while the median overall survival was 35.0 months. In our cohort, the 5-year DFS and 5-year OS of patients treated by esophagectomy were 21.4% and 37.6%.

Kaplan-Meier curves of DFS and OS based on preoperative LMR, NLR and PLR are shown in Figure 1. The DFS and OS for patients with low LMR were 16.7% and 20.0%, compared with 34.6% and 40.9% for patients with high LMR, respectively. Patients with low preoperative LMR had a significant worse prognosis for DFS (mean 24.7 *vs* 26.5 months, p=0.004) and OS (mean 29.2 *vs* 41.3 months, p=0.002) than those with high preoperative LMR. In comparison with the low NLR

Table 3. Univariate and Multivariate Analyses of Prognostic Factors in ESCC With Respect to Overall Survival

Overall Survival	Univariate Analysis			Multivariate Analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Female	0.208	1.326	0.855-2.058			
Age ≤ 60	0.745	0.947	0.681-1.316			
Tumor length ≤ 3	0.017*	1.583	1.084-2.311	0.028*	1.546	1.048-2.281
Tumor location: Upper/middle/lower	0.772	0.912	0.742-1.248			
Differential Grade: Well/middle/poor	0.766	1.035	0.825-1.300			
pT status: T1-2/T3-4	0.007*	1.606	1.136-2.273	0.734	1.069	0.726-1.576
pN status: N0/ N1-3	<0.001*	1.849	1.329-2.574	0.67	1.137	0.630-2.058
pTNM stage:I-II/I	<0.001*	2.045	1.468-2.850	0.006*	1.602	1.142 -2.247
Treatment regimens: Surgery alone	0.311	1.193	0.848-1.678			
NLR < 2.60	0.011*	1.52	1.092-2.116	0.538	1.133	0.762-1.685
PLR < 244	0.039*	1.624	1.020-2.584	0.96	1.014	0.582-1.769
LMR < 2.57	0.002*	1.817	1.242-2.657	0.004*	1.759	1.201-2.576

ESCC esophageal squamous cell carcinoma, NLR neutrophil-lymphocyt ratio, PLR platelet-lymphocyte ratio, LMR lymphocyte-monocyte ratio *p<0.05

cohort, the high NLR cohort had lower DFS (mean 29.0 *vs* 37.8 months, p=0.004) and OS (mean 33.7 *vs* 42.6 months, p=0.011). Only marginally reduced DFS (mean 26.2 *vs* 35.2 months, p=0.068) was found in the high PLR cohort versus the low PLR cohort. OS (mean 29.9 *vs* 40.0 months, p=0.039) was significantly worse in the high PLR cohort versus the low PLR cohort.

Univariate and multivariate analyses of disease-free and overall survival

Tables 2 and Table 3 show the results of univariate and multivariate analyses of the factors related to DFS and OS. Univariate analysis revealed that pT status (p=0.009), pN status (p<0.001), pTNM stage (p<0.001), NLR (p=0.004) and LMR (p=0.004) were significantly associated with DFS. Tumor length (p=0.065) and PLR (p=0.068), which were found to be associated with DFS but without reaching the significant level, were also enrolled in multivariate analysis. By multivariate analysis, tumor length, pTNM stage and LMR were also significantly associated with DFS (for the LMR: p=0.009, HR=1.639, 95% CI 1.129-2.381).

Univariate analysis demonstrated that tumor length (p=0.017), pT status (p=0.007), pN status (p<0.001), pTNM stage (P<0.001), NLR (p=0.011), PLR (p=0.039) and LMR (p=0.002) were significantly associated with OS. Multivariate analysis showed that tumor length, pTNM stage, LMR were independently associated with unfavorable OS (for the LMR: p=0.004, HR=1.759, 95% CI 1.201-2.576).

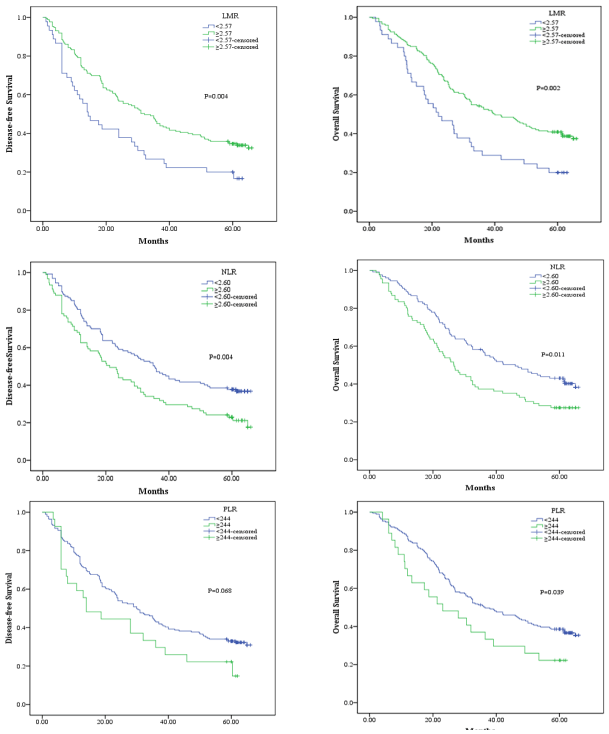

Figure 1. Kaplan-Meier Survival Curves of Disease-free Survival and Survival Rates in 218 Patients with Esophageal Squaeal Squamous Cell Carcinoma Classified into 2 Group According to Lymphocyte-monocyte Ratio (LMR), Neutrophil-monocyte ratio (NLR) and plateletelymphocyte retio (PLR)

Discussion

Since Virchow first hypothesized that many cancers arise from sites of chronic inflammation in 1863, it is now becoming clear that inflammation and innate immunity have a strong link with cancer development and progression (Mantovani et al., 2008). In the present study, we performed a retrospective study including 218 ESCC patients who underwent attempted curative surgery and evaluated the relationship of various cellular components of systemic inflammation and the clinical outcome. Amongst the inflammation-based prognostic scores, i.e., the LMR, NLR, and PLR, only LMR was a prognostic factor independent of the tumor length and pTNM stage.

Recently, great interests have been focused on elucidating the role of LMR in predicating cancer recurrence and death. Porrata et al. found that a high peripheral blood LMR at diagnosis was associated with superior overall survival, lymphoma-specific survival, progression-free survival, and time to progression in classical Hodgkin's lymphoma (cHL) (Porrata et al., 2012). Then, they started further research and found that in cHL patients who maintaining a high peripheral blood LMR during treatment cycles experienced better clinical outcomes compared with those who did not (Porrata et al., 2013). Szkandera et al. reported that the

low LMR predicted poor clinical outcome and improved the predictive accuracy in patients with soft tissue sarcomas (Szkandera et al., 2014). Stotz et al. analyzed data from 372 stage II and III colon cancer and found that low LMR is a negative prognostic marker in stage III colon cancer patients, and patients with low LMR do not benefit from adjuvant chemotherapy (Stotz et al., 2014). Similar results were showed in gastric cancer and pancreatic adenocarcinoma (Fujiwara et al., 2014; Zhou et al., 2014). Consistent with previous studies, we found that an increased LMR was significantly associated with increased DFS and OS in patients with resectable ESCC.

Lymphocytes are considered to be a manifestation of the host immune response against cancer cells by inducing cytotoxic cell death and suppressing tumor cell proliferation and migration (Ownby et al., 1983; Rosenberg, 1996). While systemic inflammation triggered by malignant cells may suppress the cytotoxic response of lymphocytes and thereby allow tumor cells to evade immune surveillance (Ubukata et al., 2010). Lymphocytopaenia also has been found in various tumors, which may result in the depression of lymphocyte-mediated immune response to the tumor, thereby worsening their prognosis (Mlecnik et al., 2011). Tumor-associated macrophages (TAM), which are derived from circulating monocytes, are recruited to the tumor site by soluble tumor-derived chemotactic factors and constitute a significant component of the inflammatory infiltrate of several malignances (Mantovani et al., 2006). Epidemiological evidence revealed that high density of TAMs are significantly associated with poor prognosis in a wide spectrum of human cancers, such as breast, hepatocellular carcinoma and esophageal cancer (Shigeoka et al., 2013; Tang, 2013; Shen et al., 2014). Moreover, the circulating CD14+CD16+ monocytes in malignant has also been reported to exhibit pro-tumorigenic features which may facilitate tumor progression (Subimerb et al., 2010). On the other hand, the pretreatment monocytes have been shown to correlate with poor prognosis in various solid tumors (Lin et al., 2014; Shen et al., 2014; Tsai et al., 2014). Thus, the circulating level of monocytes may reflect an increased formation or presence of TAMs as a surrogate marker for high tumor burden. LMR can be considered as a potential, representative, surrogate biomarker of host immunity versus tumor microenvironment. Patients with low LMR have the balance tipped in favor of pro-tumor inflammatory statue, which is associated with poor oncologic outcome.

Moreover, we evaluated the prognostic significance of other previously reported potentially prognostic cellular ratios including NLR and PLR. Although, preoperative NLR and PLR were inversely related to prognosis in many cancers; however, their role in EC are still controversial. Sharaiha et al. and Yoo et al. found that elevated NLR was associated with worse DFS and OS in EC (Sharaiha et al., 2011; Yoo et al., 2014). Feng et al. (2014) reported that NLR and PLR were significant predictors of overall survival in patients with ESCC. However, Cihan et al. (2014) founded that NLR and PLR had no effect on prognosis in patients with breast cancer. Rashid et al. (2010) reported that preoperative elevated NLR was not significantly associated with risk of death in EC patients. Dutta et al. (2011) founded that NLR and PLR had no predictive value for cancer specific survival in esophageal cancer. In the present study, we found that preoperative NLR and PLR were associated with DFS and OS in ESCC patients. However, the elevated NLR and PLR were not found to be independent prognosticators. Reasons for the discrepant findings with regard to DFS and OS for EC patients are not clear. The reasons may come from the following respects: one is that the cut-off used to define an elevated NLR and PLR were different with each study; another may be explained by discrepancies in study population, treatment modality, and pathological type.

The major limitations of our study are the retrospective analysis, single-center design and small sample size. In addition, we calculated optimized LMR, NLR and PLR cutoff levels for DFS and OS by applying ROC curves. However, it is unclear whether a different cutoff value or a threshold level would serve as a better predictor of tumor recurrence in ESCC. Further larger prospective studies are needed to confirm these preliminary results and clarify the mechanisms.

In conclusion, LMR may serve as a reproducible, minimally invasive, and inexpensive potential prognostic biomarker for patients with ESCC who underwent attempted curative surgery. It will aid the clinician to select a suitable therapy for individual patients. Furthermore, immunotherapy targeted to LMR may also help improve the prognosis of ESCC.

Acknowledgements

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