

## Prognostic importance of serum CRP, prealbumin, and transferrin levels in patients with advanced stage esophageal cancer

*İleri evre özofagus kanserli hastalarda serum CRP, prealbumin ve transferrin düzeylerinin prognostik önemi*

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**Background:** This study investigated the prognostic value of serum C-reactive protein (CRP), prealbumin, and transferrin levels in patients with advanced stage esophageal cancers treated with stent placement.

**Methods:** In a prospective, randomized study conducted between July 2007 and December 2008, serum CRP, prealbumin, and transferrin levels were determined 1-3 days prior to stent placement in 61 consecutive patients who underwent stent placement due to locally advanced disease or distant organ metastasis. All patients were followed until death.

**Results:** The stent was successfully placed in all patients and oral intake was restored. There was no procedure-related mortality. The mean survival period of the patients was 164.3±120.3 days (range 15 to 450 days). Whereas the mean survival period was 103.2±82.3 days in patients with a serum CRP level ≥10 mg/L (n=38), it was 265.4±121.2 days in patients with a serum CRP level <10 mg/L (n=23). While the mean survival period was 237.5±132.7 days in patients with a serum prealbumin level ≥15 mg/L (n=28), the mean survival period was 102.3±79.6 days in patients with a serum prealbumin level <15 mg/L (n=33). The mean survival period was 211.6±130.2 days in patients with a serum transferrin level ≥200 mg/L (n=25) while the mean survival period was 131.5±113.8 days in patients with a serum transferrin level <200 mg/L (n=36). The relationship between serum CRP, prealbumin, and transferrin levels in reference to survival was statistically significant (p<0.001, p<0.001, and p=0.003, respectively).

**Conclusion:** Serum CRP, prealbumin, and transferrin levels can easily be measured prior to esophageal stent placement in patients with advanced stage esophageal cancer and the results may give an idea on the prognosis of the patients.

**Key words:** C-reactive protein; esophageal carcinoma; prealbumin; survey; transferrin.

**Amaç:** Bu çalışmada stent takılarak tedavi edilen ileri evre özofagus kanserli hastalarda serum C-reaktif protein (CRP), prealbumin ve transferrin düzeylerinin prognostik değeri araştırıldı.

**Çalışma planı:** Temmuz 2007 ve Aralık 2008 tarihleri arasında gerçekleştirilen prospektif randomize bir çalışmada lokal olarak ilerlemiş hastalık veya uzak organ metastazı nedeniyle stent takılarak tedavi edilen ardışık 61 hastada, stent takılmadan 1-3 gün önce serum CRP, prealbumin ve transferrin düzeyleri çalışıldı. Tüm hastalar ölünceye kadar takip edildi.

**Bulgular:** Stent tüm hastalarda başarı ile takılarak oral alım tekrar sağlandı. İşleme bağlı mortalite gözlenmedi. Hastaların ortalama sağkalım süresi 164.3±120.3 gün (dağılım 15-450 gün) idi. Serum CRP seviyesi ≥10 mg/L olan hastalarda (n=38) ortalama sağkalım 103.2±82.3 gün iken serum CRP seviyesi <10 mg/L olan hastalarda (n=23) ortalama sağkalım 265.4±121.2 gün idi. Serum prealbumin seviyesi ≥15 mg/L olan hastalarda (n=28) ortalama sağkalım 237.5±132.7 gün iken serum prealbumin seviyesi <15 mg/L olan hastalarda (n=33) ortalama sağkalım 102.3±79.6 gün idi. Serum transferrin seviyesi ≥200 mg/L olan hastalarda (n=25) ortalama sağkalım 211.6±130.2 gün iken serum transferrin seviyesi <200 mg/L olan hastalarda (n=36) ortalama sağkalım 131.5±113.8 gün idi. Referans serum CRP, prealbumin ve transferrin seviyelerinin sağkalımla ilişkisi istatistiksel olarak anlamlı idi (sırasıyla p<0.001, p<0.001 ve p=0.003).

**Sonuç:** İleri evre özofagus kanserli hastalarda özofageal stent uygulamasından önce serum CRP, prealbumin ve transferrin düzeyleri kolaylıkla saptanabilir ve hastaların prognozları hakkında fikir elde edilebilir.

**Anahtar sözcükler:** C-reaktif protein; özofagus kanseri; prealbumin; sağkalım; transferrin.

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Esophageal cancer is one of the most fatal malignant tumors. Since the majority of the patients are diagnosed in advanced stages, a curative surgical intervention cannot be planned. In such patients, stent placement for restoring the swallowing function is one of the most commonly used palliative methods. Self-expandable metallic stents can be placed with a 95% success rate, and the procedure-related mortality rate is <1.5 percent.<sup>[1]</sup> An improvement in dysphagia can be achieved in the majority of patients, and even solid foods can be tolerated.

Various markers have been studied in the diagnosis and monitoring of patients with esophageal cancer. However, no independent predictive marker which indicates the general status of the patient prior to treatment, facilitates selection of the appropriate treatment option, or suggests an opinion about the possible survival period of the patient has been demonstrated. In several studies, increased serum C-reactive protein (CRP) levels have been shown to be associated with poor prognosis in patients with esophageal cancer.<sup>[2-5]</sup> Prealbumin and transferrin are negative acute phase reactants whose serum levels decrease in patients with malignancy and malnutrition.<sup>[6]</sup> The aim of this study was to investigate the prognostic value of serum CRP, prealbumin, and transferrin levels in patients with advanced stage esophageal cancer treated with stent placement.

## PATIENTS AND METHODS

### Patients

In a prospective randomized study conducted between July 2007 and December 2008 in the Thoracic Surgery Department of the Atatürk University Faculty of Medicine, serum CRP, prealbumin, and transferrin levels were studied in 61 consecutive patients (32 females, 29 males; mean age 63.9±13.5 years; range 34 to 94 years) who underwent esophageal stent placement due to inoperable esophageal carcinoma. The age, gender, symptoms and signs of the patients, localization and pathologic type of the tumor, and survival outcomes were evaluated.

The tumor was localized in the mid-esophagus in 31 (50.8%) patients and localized in the distal esophagus and cardia in 30 (49.2%) patients. The histologic type was squamous cell carcinoma in 47 (77.0%) patients and adenocarcinoma in 14 (23.0%) patients. The characteristics of the patients are presented in table 1.

Dysphagia was present in 59 (96.7%) of the patients. Fifty-three (86.9%) of the patients had a history of weight loss, and 43 (70.5%) were cachectic. Other symptoms

were retrosternal and epigastric pain in 29 (47.5%) patients, weakness and loss of appetite in 13 (21.3%) patients, regurgitation or vomiting in four (6.5%) patients, cough in two (3.3%) patients, fever in one patient (1.6%), and hematemesis in one patient (1.6%).

The diagnosis of esophageal cancer was confirmed in all patients with a histopathologic examination of endoscopic biopsies. All the patients were evaluated by abdominal ultrasonography (US) as well as thoracic and abdominal computed tomography (CT). In addition, four patients were evaluated by positron emission tomography-computed tomography (PET-CT), and three patients were evaluated by bone scintigraphy. Seven (11.4%) patients had liver metastasis, six (9.8%) patients had pulmonary metastasis, and one (1.6%) patient had bone metastasis. Left atrial invasion was shown in four (6.5%) patients on radiologic examination, and tracheal invasion was demonstrated in two (3.3%) patients on bronchoscopy.

Only four (6.6%) patients received chemoradiotherapy prior to the stent placement. None of the patients who underwent stent placement received chemoradiotherapy afterwards.

### Esophageal stent placement

Before the stent was placed, the size of the stenosis was evaluated via endoscopy, barium X-ray of the esophagus, and CT, and then the stent size was selected. Following basic procedure, the stents were placed 2-2.5 cm from the upper and lower margins of the tumor under direct esophagoscopy and fluoroscopic visualization. Of the 61 stents, 56 (91.8%) were placed via rigid esophagoscopy, and five (8.2%) were placed via flexible esophagoscopy. A covered self-expandable metallic Ultraflex esophageal stent (Boston Scientific,

**Table 1. Characteristics of patients**

Variables	n	%
Gender		
Male	29	47.5
Female	32	52.5
Histology		
Squamous cell carcinoma	47	77
Adenocarcinoma	14	23
Tumor localization		
Middle esophagus	31	50.8
Lower esophagus and gastroesophageal junction	30	49.2
Initial radiochemotherapy		
Yes	4	6.6
No	57	93.4
Total number of the patients	61	100

Natick, MA, USA) was used in all patients. No mortal complications (bleeding, aspiration pneumonia, tracheal compressions, perforations, esophagorespiratory fistulas) due to stent placement occurred. Three patients underwent a second stent placement due to tumor overgrowth.

**Serum CRP, prealbumin and transferrin level measurements**

Serum CRP, prealbumin, and transferrin levels were evaluated in blood samples obtained 1-3 days prior to stent placement. Five ml blood samples were obtained on the morning following a fast. Serum CRP, prealbumin, and transferrin levels were determined by the nephelometric method (Image Immunochemistry System, Beckman Coulter, Fullerton, CA, USA). Normal reference ranges for serum CRP, prealbumin, and transferrin were 0-5, 20-40, and 200-360 mg/L, respectively.

**Statistical analysis**

Statistical analysis was performed using SPSS for Windows 10.0 version software (SPSS Inc., Chicago, Illinois, USA). Data is presented as the mean ± standard deviation (mean±SD) and standard error (SE). The results were compared by the Durbin-Watson statistics, and a p<0.05 was considered statistically significant.

**RESULTS**

The mean survival in patients with a serum CRP level ≥10 mg/L (n=38) was 103.2±82.3 days; however, the

mean survival was 265.4±121.2 days in patients with a serum CRP level <10 mg/L (n=23; Figure 1).

The mean survival in patients with a serum prealbumin level ≥15 mg/L (n=28) was 237.5±132.7 days; however, the mean survival was 102.3±79.6 days in patients with a serum prealbumin level <15 mg/L (n=33; Figure 2).

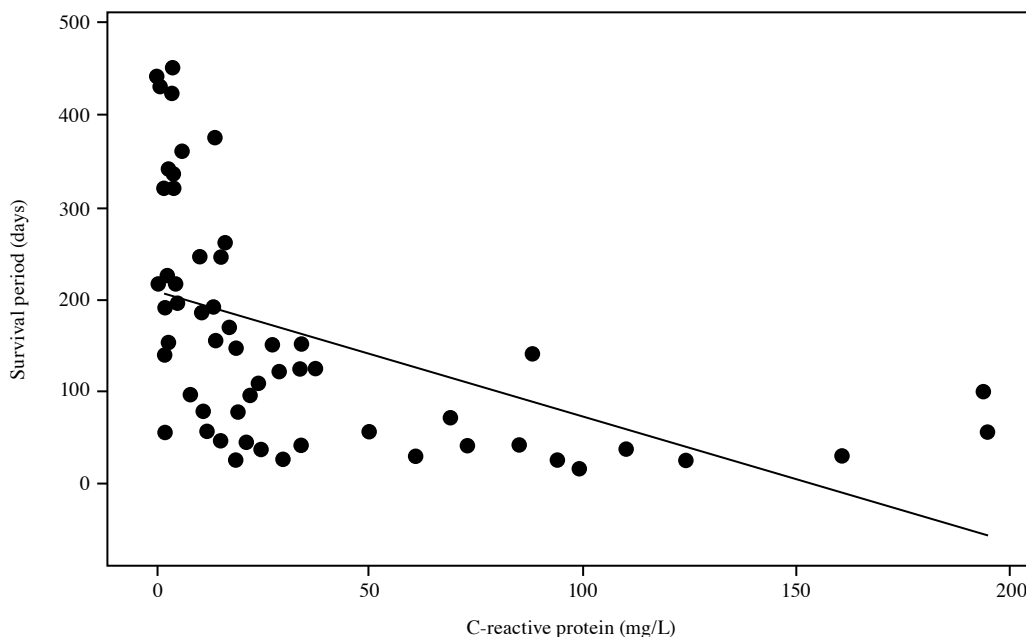
The mean survival in patients with a serum transferrin level ≥200 mg/L (n=25) was 211.6±130.2 days; however, the mean survival was 131.5±113.8 days in patients with a serum transferrin level <200 mg/L (n=36; Figure 3).

The relationship between serum CRP, prealbumin, and transferrin levels and survival was statistically significant (p<0.001, p<0.001, and p=0.003, respectively).

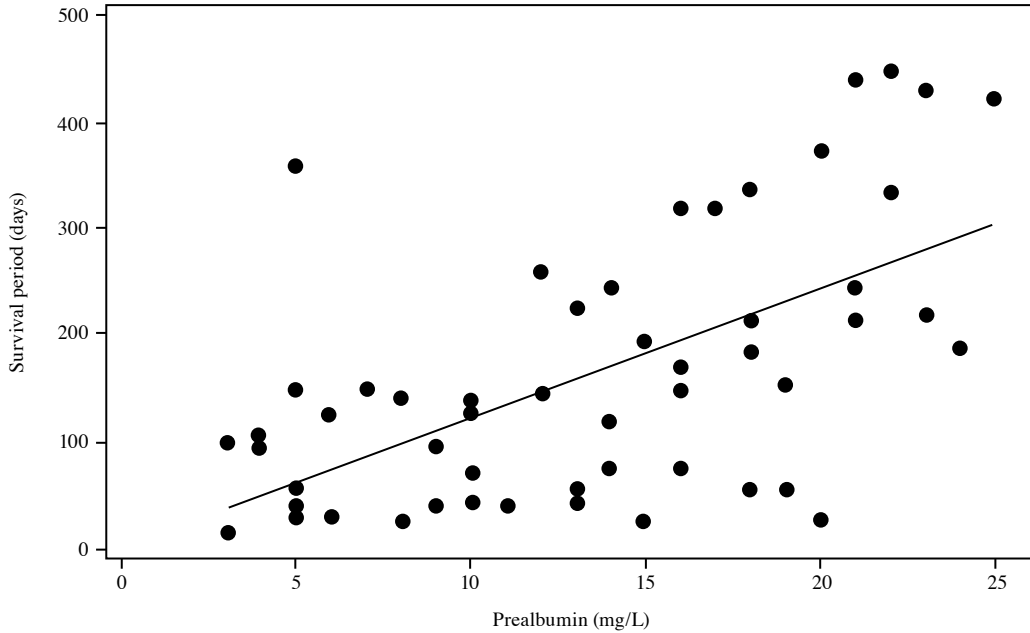
The mean duration of hospital stay after the procedure was 2.1 days (range 1-5 days). All patients died during the course of follow-up. The mean survival of the patients was 164.3±120.3 days with a range of between 15 and 450 days.

**DISCUSSION**

The mediators interleukin 1 (IL-1) and tumor necrosis factor (TNF) are involved in the acute phase response. These substances are synthesized in and released from both the activated monocytes in the blood and the macrophages in various organs. Due to the triggering of some reactions by certain substances such as IL-1 and TNF, the plasma levels of some proteins, known as acute phase reactants, increase. However, the



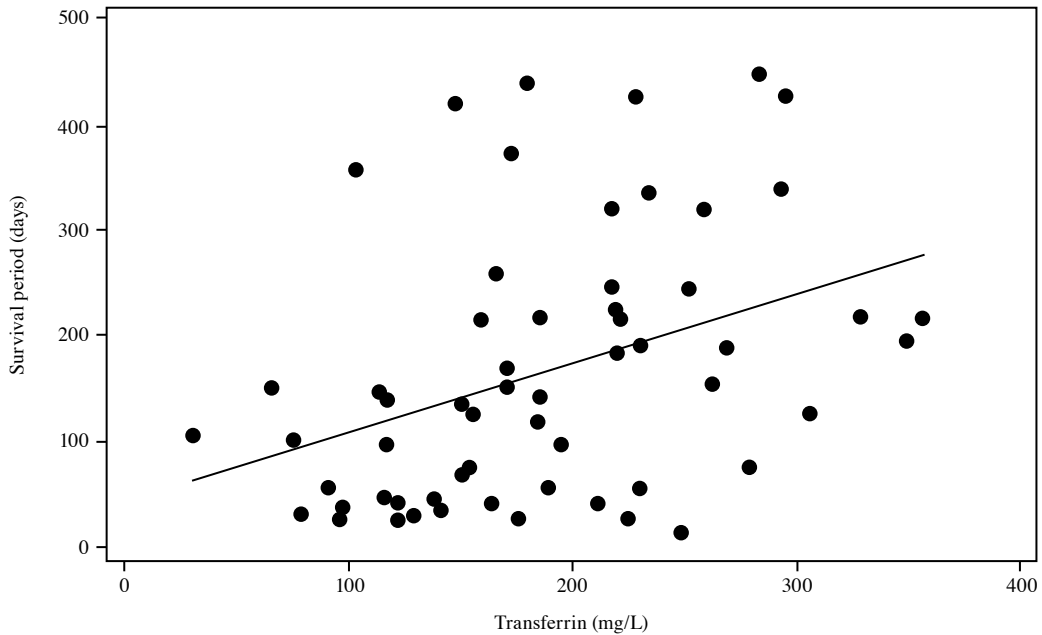
**Figure 1.** The relationship between serum C-reactive protein levels and survival.



**Figure 2.** The relationship between prealbumin levels and survival.

plasma levels of other proteins, known as negative acute phase reactants, decrease during the acute phase response. The primary negative acute phase reactants are prealbumin, albumin, and transferrin. The proteins with increased plasma levels, such as CRP, alpha 1-antichymotripsin, alpha 1-acid glycoprotein, alpha 1-antitrypsin, haptoglobin, fibrinogen, ceruloplasmin, and complement components C3 and C4, are called positive acute phase reactants.<sup>[7]</sup>

In patients with esophageal cancers, serum CRP levels increase with tumor progression resulting in a poor prognosis.<sup>[3]</sup> C-reactive protein is produced by hepatocytes and has been suggested to be associated with inflammatory cytokines produced by tumor cells.<sup>[8,9]</sup> Overproduction of inflammatory cytokines by tumor cells in patients with advanced cancer may lead to the gradual increase in CRP levels that are observed with increased tumor size and progression.



**Figure 3.** The relationship between the transferrin levels and survival.

This association has been verified by demonstrating the correlation between CRP levels and the invasion depth of the tumor as well as the presence of lymph node and distant metastases. It can thus be suggested that both the tumor volume and the advanced stage contribute to the CRP levels.<sup>[3]</sup>

The mechanism of increased CRP levels in cancer is unknown. CRP, which is strongly induced by cytokines like IL-1, TNF, and IL-6, is produced in the liver. Also, CRP is frequently overproduced by tumor cells.<sup>[8]</sup>

In a few studies conducted on patients with esophageal cancer, encouraging results with respect to pre-treatment CRP levels have been obtained when determining the prognosis.<sup>[2-4,9]</sup> Guillem and Triboulet<sup>[2]</sup> did not find a correlation between the serum CRP levels and the age, gender, histologic type, tumor localization, and TNM stage. In contrast, higher rates of unresponsiveness to chemoradiotherapy have been observed in patients with CRP levels >6 mg/L compared to those with normal CRP levels.

Nozoe et al.<sup>[9]</sup> reported that the increased serum CRP level is an independent prognostic factor in patients with esophageal carcinoma. In their study, they also included patients who underwent preoperative treatment and non-curative surgery since both the preoperative treatment and the surgical curability can considerably affect the prognosis. In the present study, we particularly focused on the patients who were treated with an esophageal stent and those for whom oral intake was restored.

As in the patients with esophageal cancer and poor immunity, a correlation has been shown between malnutrition and high serum CRP concentrations.<sup>[9]</sup> In the present study, a close relationship was found between the serum CRP levels and survival. The mean survival period was 103.2±82.3 days in patients with a serum CRP level ≥10 mg/L (n=38) whereas the mean survival period was 265.4±121.2 days in patients with a serum CRP level <10 mg/L (n=23; p<0.001).

Protein-calorie malnutrition is observed in approximately 80% of the patients with esophageal cancer.<sup>[10]</sup> Malnutrition can be prevented or improved by nutritional support, and this is associated with a better response to the cancer therapy. Serum proteins provide indirect information about the visceral protein levels. A decrease in protein levels indicates low hepatic synthesis and is generally associated with inadequate intake. The half-life of serum transferrin is eight days while the half-life of serum prealbumin is 2-3 days. These proteins are affected earlier by the acute alterations in protein balance and respond to nutritional support

more rapidly.<sup>[10]</sup> Serum transferrin and prealbumin levels have been proved to be significant as indicators for the response to nutritional support in patients with esophageal cancer.<sup>[10]</sup>

Esophageal cancer is particularly important among cancers associated with cachexia.<sup>[5]</sup> Cachexia is responsible for 30%-50% of cancer-related deaths among digestive tract malignancies.<sup>[11]</sup> Not only have 80% of patients newly diagnosed with gastrointestinal tract malignancies experienced substantial weight loss, but some molecularly altered characteristics of cachexia have also been observed, even in the absence of weight loss.<sup>[12]</sup> Despite intensive studies, the pathophysiology of cancer-related cachexia has not been fully elucidated. Moreover, currently available treatment modalities are not completely satisfactory. The up-regulation of cytokines may contribute to the unintended weight loss in cancer-related cachexia.<sup>[5]</sup> Although the contribution of certain cytokines varies according to the type of tumor, in experimental studies conducted on cancer-related cachexia, IL-1, tumor TNF- $\alpha$ , and particularly IL-6 have been found to be the main responsible cytokines.<sup>[13,14]</sup> Moreover, in studies about cachexia in patients with gastroesophageal cancer, it has been demonstrated that other pro-inflammatory cytokines such as IL-8 and vascular endothelial growth factor-A (VEGF-A) might be effective as well.<sup>[15]</sup> Recently, inadequate oral intake, weight loss, and systemic inflammation have been suggested to be important factors in identifying cachectic cancer patients, particularly those with esophageal carcinoma.<sup>[16]</sup> Nevertheless, the relationship between weight loss and acute phase reactants in cancer-related cachexia has been reported only in lung cancer, pancreatic cancer, and melanoma.<sup>[17]</sup>

In experimental studies, a decrease in prealbumin production after 14 days of consuming a diet that provides only 60% of the daily protein need has been observed.<sup>[18]</sup> Prealbumin production can return to normal levels within 4-8 days with adequate nutrition.<sup>[19]</sup> Therefore, prealbumin is considered to be the best indicator for nutritional status.

Krzystek-Korpacka et al.<sup>[5]</sup> have determined alterations in albumin and CRP levels in cancer patients, with further CRP elevation in those with cachexia. A decrease in transferrin has been observed only in cachectic patients. In the present study, the cachexia in gastroesophageal cancer was found to be associated with the alterations in acute phase proteins.

Transferrin and prealbumin are among the most commonly used indicators to demonstrate the protein

status of the body. The level of the circulating plasma proteins depends on the speed of synthesis, the distribution of the volume, and the speed of catabolism. These are generally used to evaluate the nutritional status. While the prealbumin levels rapidly decrease after a fast and reach a plateau in the first week, the transferrin levels demonstrate a slight decrease. Prealbumin is considered to be the most sensitive parameter in demonstrating malnutrition.<sup>[20]</sup> In a few studies, although the transferrin level has been reported to be an indicator that accompanies malnutrition, it has been stated that it was not as sensitive as prealbumin.<sup>[21]</sup> In the present study, 59 (96.7%) of the patients had dysphagia. Fifty-three patients (86.9%) had a history of weight loss while 43 (70.5%) patients had a cachectic appearance. The prealbumin level was below the normal limit in 48 (78.7%) of the patients, and the transferrin level was below the normal limit in 36 (49.0%) patients. In the present study, serum prealbumin and transferrin levels were determined to be directly associated with the prognosis. While the mean survival period was  $237.5 \pm 132.7$  days in patients with a serum prealbumin level  $\geq 15$  mg/L (n=28), the mean survival period was  $102.3 \pm 79.6$  days in patients with a serum prealbumin level  $< 15$  mg/L (n=33;  $p < 0.001$ ). Whereas the mean survival period was  $211.6 \pm 130.2$  days in patients with a serum transferrin level  $\geq 200$  mg/L (n=25), the mean survival period was  $131.5 \pm 113.8$  days in patients with a serum transferrin level  $< 200$  mg/L (n=36;  $p = 0.003$ ).

Patients with esophageal cancer treated with stents are usually in the advanced stage with almost all having malnutrition. The levels of serum CRP, prealbumin, and transferrin can easily be determined prior to the procedure in the patients with advanced stage esophageal cancer, suggesting an opinion about the prognosis of patients who have undergone esophageal stent placement.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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