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Research Article

Prognostic impact of stage, chronic obstructive pulmonary disease and second primary malignancies in laryngeal cancer: a single-center retrospective cohort study

Laringeal kanserde evre, kronik obstrüktif akciğer hastalığı ve ikinci primer malignitelerin prognostik etkisi: tek merkezli retrospektif kohort çalışması

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Abstract

Aim: Tumor stage and comorbid conditions are well-established prognostic factors in laryngeal cancer (LC); however, their combined impact on survival has not been comprehensively evaluated in real-world settings. This study aimed to assess the effects of tumor stage, comorbidities, and second primary malignancies (SPMs) on long-term survival in patients with LC.

Material and Methods: We retrospectively analyzed data from 130 patients with histologically confirmed laryngeal squamous cell carcinoma who were treated and followed at our institution between 2010 and 2023. Survival outcomes were assessed using the Kaplan--Meier method and Cox proportional hazards regression. The prognostic impact of comorbidities, COPD, and SPMs was specifically evaluated.

Results: The mean overall survival (OS) for the entire cohort was 87.1 months (95% CI: 72.2--101.9). Patients with metastatic disease had significantly shorter OS (mean: 10.2 months; $p < 0.001$), and those with at least one comorbidity had a reduced OS of 70.2 months ($p = 0.004$). Metastatic disease was associated with a 4.9-fold increased risk of mortality (HR = 4.92; $p < 0.001$). SPMs occurred in 15 patients (11.5%), and three patients (2.3%) died due to SPMs. In multivariate analysis, both SPMs (HR = 2.37; 95% CI: 1.48--3.79; $p = 0.002$) and COPD (HR = 1.88; 95% CI: 1.22--2.90; $p = 0.008$) were identified as independent predictors of worse survival.

Conclusion: Tumor stage, comorbidities, and second primary malignancies independently and synergistically impact survival outcomes in patients with laryngeal cancer. These findings underscore the importance of a multidisciplinary care model that integrates oncologic treatment with comorbidity management and vigilant follow-up.

Keywords: laryngeal cancer, overall survival, second primary malignancy, tumor stage

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Öz

Amaç: Laringeal kanserde (LK) tümör evresi ve komorbid durumlar, iyi bilinen prognostik faktörlerdir; ancak bu değişkenlerin sağkalım üzerindeki kombine etkisi gerçek yaşam verilerinde yeterince kapsamlı şekilde araştırılmamıştır. Bu çalışmanın amacı, LK hastalarında tümörün evresi, komorbiditeler ve ikinci primer malignitelerin (İPM) uzun dönem sağkalım üzerine etkilerini değerlendirmektir.

Gereç ve Yöntemler: 2010–2023 yılları arasında kurumumuzda tedavi edilip takip edilen, histopatolojik olarak doğrulanmış laringeal skuamöz hücreli karsinom tanılı 130 hasta retrospektif olarak incelendi. Sağkalım analizleri Kaplan–Meier yöntemi ile yapıldı; prognostik faktörler Cox orantısal risk regresyon modeli kullanılarak değerlendirildi. Özellikle komorbiditelerin, KOAH'ın ve İPM'lerin prognostik etkileri araştırıldı.

Bulgular: Tüm kohortta ortalama genel sağkalım (OS) 87,1 ay olarak hesaplandı (%95 GA: 72,2–101,9). Metastatik hastalığı bulunanlarda OS anlamlı derecede daha kısa bulundu (ortalama: 10,2 ay; $p < 0,001$). En az bir komorbiditesi olanlarda OS 70,2 aya düşmüştü ($p = 0,004$). Metastatik hastalık, mortalite riskinde 4,9 kat artış ile ilişkiliydi (HR = 4,92; $p < 0,001$). SPM, 15 hastada (%11,5) saptandı ve üç hasta (%2,3) SPM nedeniyle kaybedildi. Çok değişkenli analizde, SPM (HR = 2,37; %95 GA: 1,48–3,79; $p = 0,002$) ve KOAH (HR = 1,88; %95 GA: 1,22–2,90; $p = 0,008$) bağımsız olarak olumsuz sağkalım öngördürücüleri olarak belirlendi.

Sonuç: Tümör evresi, komorbiditeler ve ikinci primer maligniteler, laringeal kanserli hastalarda sağkalımı hem bağımsız hem de sinerjistik olarak etkilemektedir. Bu bulgular, onkolojik tedaviyi komorbidite yönetimi ve dikkatli izlemle entegre eden multidisipliner bir yaklaşımın önemini ortaya koymaktadır.

Anahtar kelimeler: laringeal kanser, genel sağkalım, ikinci primer malignite, tümör evresi

Introduction

Laryngeal cancer (LC) accounts for approximately 1-2% of all malignancies and nearly one-third of head and neck cancers, with over 190,000 new cases and 100,000 deaths reported globally each year [1,2]. In Türkiye, its incidence is approximately 7 per 100,000 [3]. Due to its location in the upper aerodigestive tract, LC frequently compromises vital functions such as speech, swallowing, and breathing, contributing to substantial morbidity [3].

Despite advances in diagnostics and therapy, survival outcomes for LC have seen little improvement over recent decades, with five-year OS rates stagnating around 60% [4]. Tumor stage is universally recognized as the most decisive prognostic factor; early-stage glottic tumors typically demonstrate favorable outcomes, whereas advanced or metastatic disease portends a poor prognosis [5,6].

In addition to tumor burden, comorbidities are prevalent in LC patients, often due to shared risk factors like smoking. Chronic conditions such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, and diabetes may impair treatment tolerance and survival, yet their independent prognostic significance remains insufficiently clarified [7–9,10]. Furthermore, field cancerization exposes these patients to SPMs, complicating long-term outcomes [11,12].

Although the prognostic relevance of stage, comorbidities, and SPMs has been previously noted, few real-world studies have evaluated their combined impact on survival. In this retrospective cohort study, we investigated how these key factors influence long-term outcomes in laryngeal cancer patients, using survival data from a single-center cohort with extended follow-up.

Material and Methods

Study design and patient selection

This was a retrospective, single-center cohort study conducted at a tertiary university-affiliated oncology center. A total of 130 consecutive patients diagnosed with histologically confirmed laryngeal squamous cell carcinoma between January 2010 and December 2023 were included. Eligibility criteria required complete clinical, pathological, and follow-up data. All patients were treated and monitored within the medical oncology service of the same institution. Ethical approval for this study was obtained from the local institutional review board.

Demographic and clinical parameters collected included age, sex, smoking status (classified as current, former, or never), tumor localization, TNM stage at initial diagnosis (based on the AJCC 8th edition), treatment modality, presence of comorbid conditions, occurrence of second primary malignancies (SPMs),

recurrence, and vital status. Due to inconsistent documentation of smoking burden, pack-year data were not analyzed. Comorbidities were extracted from clinical records and coded as binary variables; no formal comorbidity index (e.g., ACE-27, Charlson) was applied due to heterogeneity in historical data and insufficient granularity for retrospective scoring [13].

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviation (SD) and medians with range; categorical variables were summarized as counts and percentages. The Kolmogorov--Smirnov test was used to assess normality of distributions for continuous variables.

The primary endpoint was OS, defined as the interval from histological diagnosis to death from any cause or last follow-up. PFS was evaluated as a secondary endpoint and defined as the time from diagnosis to documented disease progression, recurrence, or death. Survival probabilities were estimated using the Kaplan--Meier method, and survival differences between groups were assessed using the log-rank test.

To identify independent prognostic factors, a multivariate Cox proportional hazards regression model was constructed. Variables demonstrating a statistically significant association with OS in univariate (Kaplan--Meier) analysis were entered into the multivariate model. In addition, variables deemed clinically relevant based on prior literature and biological plausibility---such as the presence of COPD and second primary malignancy---were retained in the model regardless of univariate significance. This approach was adopted to account for potential confounding and to avoid underfitting due to sample size constraints. The proportional hazards assumption was visually assessed using log-minus-log plots, and no violations were observed.

Given the limited number of covariates and the lack of strong clinical collinearity between them, formal multicollinearity testing (e.g., variance inflation factor [VIF]) was not performed. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered the threshold for statistical significance.

Patients with missing survival or follow-up data were excluded from the analysis; no imputation techniques were applied.

Results

A total of 130 patients diagnosed with laryngeal cancer were included in the study. The median age was 66.2 years (range: 19.4--99.4), and the mean age was 65.5 ± 11.6 years. Most patients were male (89.2%), and over half (56.2%) had at least one documented comorbidity. In terms of disease stage at diagnosis, 52 patients (40%) had early-stage (Stage I--II), 52 (40%) had locally advanced (Stage III), and 26 (20%) presented with metastatic disease. The most common tumor location was the glottis (data not shown in table). Detailed baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

Characteristics	n = 130 (%)
Age (years) (median, min-max)	66.2 (19–99)
Age (Categorical)	
≤ 65 years	60 (46.2)
> 65 years	70 (53.8)
Sex	
Male	116 (89.2)
Female	14 (10.8)
Smoking Status	
Never	18 (13.8)
Former	67 (51.5)
Current	45 (34.7)
Tumor Stage	
Stage I–II (Localized)	52 (40.0)
Stage III (Locally Advanced)	52 (40.0)
Stage IV (Metastatic)	26 (20.0)
Comorbidity Status	
Any Comorbidity	73 (56.2)
Hypertension	33 (25.4)
Diabetes Mellitus	20 (15.4)
Coronary Artery Disease	28 (21.5)
Chronic Obstructive Pulmonary Disease	43 (33.1)
Other Comorbidities	2 (1.5)
Clinical Outcomes	
Recurrence	16 (12.3)
Death (All-cause)	62 (47.7)

The most frequent comorbid conditions were COPD in 43 patients (33.1%), hypertension in 33 (25.4%), coronary artery disease in 28 (21.5%), and diabetes mellitus in 20 (15.4%). Other less common comorbidities included chronic kidney disease and prior stroke. Many patients had multiple co-existing conditions, particularly older individuals with a history of heavy smoking.

Over a median follow-up of 55.3 months, 62 patients (47.7%) died and 16 patients (12.3%) experienced recurrence. Among the deaths, 49 (37.7%) were due to laryngeal cancer progression. Non-cancer-related causes included cardiac events (5.4%), pneumonia (3.1%), COVID-19 (2.3%), second

primary malignancies (2.3%), and other causes such as chronic organ failure or trauma (5.4%). Notably, many non-cancer deaths occurred in patients with significant comorbidities.

The OS for the entire cohort was 87.1 ± 7.6 months (95% CI: 72.2--101.9). Kaplan--Meier analysis revealed a strong association between disease stage and survival (log-rank p < 0.001). Patients with Stage I--II disease had excellent long-term outcomes, with a mean OS of 130.1 months (95% CI: 107.0--153.3) and an estimated 5-year survival of 82%. Median OS was not reached in this group. In contrast, patients with Stage III disease had intermediate outcomes (mean OS: 83.9 months; 95% CI: 65.7--102.1), with a 5-year survival rate of approximately 58%. Those with Stage IV disease had a poor prognosis, with a mean OS of only 10.2 months (95% CI: 7.9--12.5), and a 5-year survival rate of ~12%. These findings are illustrated in Figure 1.

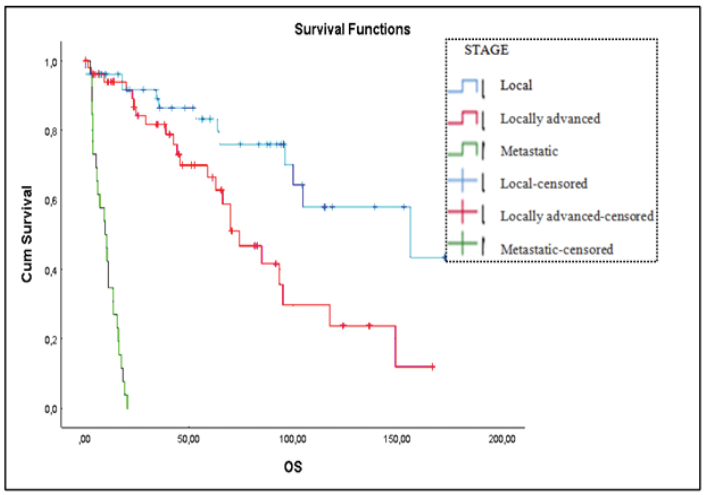

Figure 1. Kaplan–Meier overall survival curves by tumor stage (N=130). Patients with localized (Stage I–II) laryngeal cancer show much better survival than those with locally advanced (Stage III) or metastatic disease (Stage IV) (log-rank p<0.001). At 5 years, ~82% of stage I–II patients were alive, compared to ~58% of stage III and ~12% of stage IV patients.

Comorbidity status also significantly influenced survival outcomes. Patients without comorbidities had a mean OS of 105.9 months (95% CI: 85.2--126.8), compared to 70.2 months (95% CI: 51.9--88.4) in those with at least one comorbidity (log-rank p = 0.004). At 5 years, approximately 73% of patients without comorbidities were alive, versus 50% among those with comorbidities. The survival gap widened further at 10 years, emphasizing the long-term impact of co-existing illnesses (Figure 2).

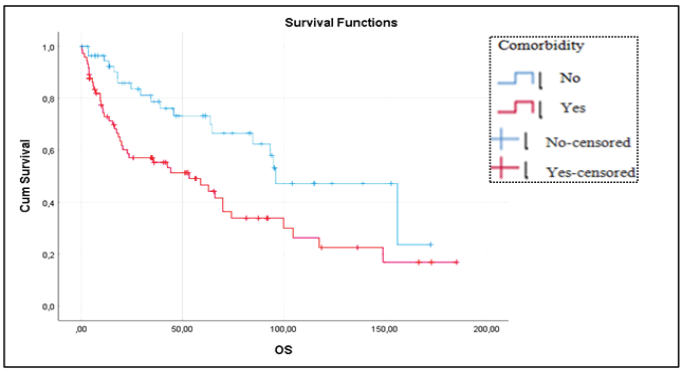

Figure 2. Kaplan–Meier overall survival by comorbidity status. Patients without any major comorbidity (blue curve) had better survival than those with at least one comorbid condition (red curve) (p=0.004 by log-rank test). At 5 years, approximately 70% of patients without comorbidities were alive, versus ~50% with comorbidities.

No significant differences in OS were observed by sex or age. The mean OS was 90.0 months for males and 60.1 months for females (log-rank p = 0.277), though the female sample size was limited (n = 14). Similarly, survival outcomes were nearly identical between patients aged ≤65 years (mean OS: 86.6 months) and >65 years (85.6 months) (p = 0.985).

A total of 15 patients (11.5%) developed a second primary malignancy, most frequently esophageal (33.3%), bladder (26.7%), gastric (20.0%), or lung cancer (20.0%) [14]. These patients had significantly shorter survival than those without a second primary (median OS: 48 vs. 96 months; p = 0.009).

PFS was also evaluated as a secondary endpoint. The mean PFS for the overall cohort was 8.5 ± 1.9 months (95% CI: 4.9--12.2). While there was a numerical trend toward longer PFS in early-stage disease (14.9 vs. 7.0 months for Stage I--II vs. III), the difference was not statistically significant (p = 0.166). No significant PFS differences were observed by age, sex, or comorbidity. These findings suggest that while PFS patterns followed stage distribution, OS remained the more clinically meaningful endpoint in this cohort. The lack of statistically significant differences in PFS across tumor stages may be attributable to several factors. These include the relatively small number of patients within certain stage subgroups, shorter follow-up durations in some cases, and the influence of competing risks such as non-cancer-related deaths, particularly among patients with significant comorbidities.

Univariate and multivariate analyses of factors associated with OS are presented in Table 2. In univariate analysis, tumor stage, comorbidity status, presence of a second primary malignancy, and COPD were significantly associated with OS. In the multivariate Cox regression model, three independent predictors of mortality were identified: metastatic disease (HR: 4.92; 95% CI: 3.21--7.54; p < 0.001), presence of a second primary malignancy (HR: 2.37; 95% CI: 1.48--3.79; p = 0.002), and COPD (HR: 1.88; 95% CI: 1.22--2.90; p = 0.008).

Table 2. Univariate and multivariate analyses of OS.

Variable	n (%)	Mean OS (months)	SE	95% CI	Univariate HR (95% CI) p-value		Multivariate HR (95% CI) p-value	
Gender								
Male	116 (89.2%)	90.0	8.2	74.1 – 106.0	1.24			
Female	14 (10.8%)	60.1	17.1	26.6 – 93.6	(0.63–2.45)	0.277		
Age Group								
≤ 65 years	60 (46.2%)	86.6	11.8	63.6 – 109.7	1.01			
> 65 years	70 (53.8%)	85.6	9.4	67.3 – 103.9	(0.65–1.57)	0.985		
Tumor Stage								
Stage I–II	52 (40.0%)	130.1	11.8	107.0 – 153.3	Reference	–		
Stage III	52 (40.0%)	83.9	9.3	65.7 – 102.1	2.13 (1.21–3.76)	0.009	4.92	Ns
Stage IV	26 (20.0%)	10.2	1.1	7.9 – 12.4	5.72 (2.90–11.30)	<0.001	(3.21–7.54)	<0.001
Comorbidity								
No	57 (43.8%)	105.9	10.6	85.2 – 126.8				
Yes	73 (56.2%)	70.2	9.3	51.9 – 88.4	1.76 (1.20–2.56)	0.004		
COPD								
No	87 (66.9%)	105.9	10.0	86.2 – 125.6	Reference		1.88	
Yes	43 (33.1%)	70.2	9.0	52.1 – 88.3	1.85 (1.17–2.91)	0.008	(1.22-2.90)	0.008
Second Primary								
No	115 (88.5%)	96.0	8.1	80.1 – 111.9	Reference		2.37	
Yes	15 (11.5%)	48.0	10.2	27.9 – 68.1	2.04 (1.20–3.45)	0.009	(1.48-3.79)	0.002

HR: Hazard ratio; CI: Confidence interval; NS: not significant; SE: standard error of the mean.

Discussion

This retrospective analysis of 130 patients with laryngeal cancer identifies a triad of independent prognostic factors---tumor stage, comorbidities (notably COPD), and second primary malignancies (SPMs)---that significantly influence OS. Among these, metastatic disease emerged as the most decisive determinant, reducing mean OS to 10.2 months and increasing mortality risk nearly fivefold (HR = 4.92, $p < 0.001$) [5,6]. These findings are consistent with global data reporting 5-year survival rates below 30% for stage IV laryngeal cancer, reflecting both limited therapeutic efficacy and aggressive tumor biology [1,2,5,15].

The stark contrast between localized (82% 5-year OS) and metastatic disease (12% 5-year OS) highlights the critical importance of early diagnosis. Public health campaigns emphasizing persistent hoarseness---a frequently overlooked but early symptom---may improve stage at presentation [16]. For patients with metastatic disease, our findings reinforce current NCCN guidelines recommending early integration of palliative care with systemic therapy, given the rarity of long-term survival beyond two years [17].

Comorbid conditions were present in over half of the cohort (56.2%) and were independently associated with shorter OS. Specifically, COPD was identified as a strong negative prognostic factor (HR = 1.88, $p = 0.008$), with comorbid patients exhibiting a 35-month reduction in survival (70.2 vs. 105.9 months, $p = 0.004$). The underlying mechanisms may include impaired pulmonary reserve, increased perioperative risk, and decreased tolerance to radiotherapy due to baseline respiratory dysfunction [18,19]. Furthermore, non-cancer-related mortality accounted for 23.3% of deaths, predominantly due to pneumonia and cardiac events, suggesting that competing risks significantly contribute to outcomes. These findings align with European studies reporting increased non-oncologic mortality among head and neck cancer patients with COPD [20,21].

While female patients had numerically lower OS compared to males (60.1 vs. 90.0 months), this difference was not statistically significant, likely due to the small sample size (n

= 14). Nevertheless, the possibility of sex-based biological differences in tumor behavior and treatment response remains an open question and should be further explored in larger, gender-balanced studies [22]. The very low number of female patients in our cohort (n=14) limits the generalizability of gender-based survival comparisons, and these findings should therefore be interpreted with caution.

Additionally, although COPD remained an independent predictor in multivariate analysis, the absence of detailed smoking exposure data (e.g., pack-years) may have introduced residual confounding.

Second primary malignancies were identified in 11.5% of patients, with the most frequent being esophageal (33.3%) and bladder cancers (26.7%) [14]. These findings support the theory of field cancerization associated with cumulative carcinogen exposure, particularly tobacco and alcohol [11,23]. SPMs were associated with a 50% reduction in OS (48 vs. 96 months; HR = 2.37, p = 0.002), emphasizing their substantial impact on long-term prognosis. The risk of SPMs extends beyond a decade after initial diagnosis, suggesting that current surveillance guidelines may underestimate their clinical importance [12,24].

Based on our findings, we propose several practical strategies for post-treatment surveillance and risk reduction in laryngeal cancer survivors: Annual PET-CT imaging during the first five years, due to its high sensitivity (~92%) for detecting aerodigestive tract SPMs [25], quadrennial cystoscopic screening, especially in patients with risk factors such as smoking history or hematuria, given the prevalence of bladder cancer, integration of structured smoking cessation programs into follow-up care, as these have been shown to reduce the incidence of SPMs by up to 40% [26].

Limitations of the study

This study has several limitations inherent to its retrospective, single-center design. First, although the sample size (n = 130) is relatively substantial for a rare tumor site, subgroup analyses - particularly those involving sex and second primary malignancies - may be underpowered due to small absolute numbers. The markedly low number of female patients (n = 14) limits the generalizability of sex-based comparisons [22].

Second, while smoking is a well-established risk factor in laryngeal cancer, detailed smoking burden data (e.g., pack-years) were inconsistently documented in clinical charts and therefore excluded from the analysis. Similarly, due to heterogeneity in historical medical records, no formal comorbidity index (e.g., Charlson or ACE-27) was retrospectively applied; instead, comorbidities were analyzed as binary variables based on clinical relevance [13].

Third, although multicollinearity testing (e.g., VIF) was not formally performed, the included covariates were carefully selected to avoid redundancy, and no significant collinearity was observed based on clinical plausibility and statistical outputs. Finally, PFS was evaluated as a secondary endpoint but may have been underestimated in patients with limited follow-up, particularly those lost to follow-up or deceased from non-cancer causes.

Despite these limitations, the study provides valuable real-world data on the prognostic impact of tumor stage, comorbidities, and second primary malignancies in laryngeal cancer - a topic underexplored in current literature.

Moreover, comorbidities were coded only as binary variables (present/absent), which precluded the use of standardized scoring systems such as the Charlson Comorbidity Index or ACE-27. This limitation restricted a more granular assessment of comorbidity burden and may have reduced the sensitivity of the prognostic analyses. Additionally, detailed smoking exposure data, such as pack-years, were unavailable, which limited our ability to adjust for this established prognostic factor in survival analyses.

In conclusion, in this retrospective single-center study of 130 patients with laryngeal squamous cell carcinoma, we demonstrated that tumor stage, comorbidities, and second primary malignancies independently and synergistically affect long-term survival outcomes. Advanced stage disease and the presence of comorbid conditions - particularly COPD - were associated with significantly poorer prognosis. Additionally, patients who developed second primary malignancies had markedly reduced survival, underscoring the importance of long-term surveillance and oncologic vigilance beyond initial treatment.

These findings emphasize the need for a comprehensive, multidisciplinary approach in managing laryngeal cancer patients, integrating tumor-directed therapy with proactive management of comorbid conditions and secondary malignancy risk. Further prospective studies with larger, multicenter cohorts are warranted to validate these observations and refine prognostic models for individualized patient care.

Ethics Approval

This study was approved by the Ethics Committee of Van Training and Research Hospital (Approval Date: 04 July 2025; Approval Number: 2025-05-12) and conducted in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization, methodology, data curation, formal analysis, and original draft preparation, writing M.S.D.; writing---review and editing, E.H. Both authors have read and approved the final version of the manuscript.

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