

Clinicopathological characteristics and prognostic risk factors of cervical cancer patients aged ≤35 years old

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Abstract

We aimed to explore the clinicopathological characteristics and prognostic risk factors of cervical cancer in patients aged ≤35 years. A total of 256 cervical cancer patients treated at Anhui Medical University Affiliated Maternity and Child Health Hospital and The First Affiliated Hospital of Anhui Medical University from January 2016 to October 2018 were divided into ≤35-year-old (n = 136) and >35-year-old (n = 120) groups. Their clinicopathological characteristics and 3-year cumulative disease-free survival (DFS) and overall survival (OS) rates were compared. The factors influencing the 3-year cumulative DFS rate of patients in the ≤35-year-old group were analyzed using univariate and multivariate Cox regression models. The human papillomavirus (HPV) infection rate, incidence rate of contact vaginal bleeding, depth of cervical interstitial infiltration, and incidence rates of parametrial metastasis and vascular infiltration were all significantly higher in the ≤35-year-old group than in the >35-year-old group. The 3-year cumulative DFS rates of all patients and those with HPV infection and contact vaginal bleeding were significantly lower in the ≤35-year-old group than in the >35-year-old group (69.12% vs. 77.50%, 68.29% vs. 80.85%, and 66.04% vs. 81.48%) (log-rank $\chi^2 = 7.429, 4.339, \text{ and } 4.276, P < .05$). Depth of cervical interstitial infiltration >4 mm, parametrial metastasis, lymph node metastasis, and vascular infiltration were independent risk factors for the prognosis of cervical cancer patients aged ≤35 years ($P < .05$). Cervical cancer aged ≤35 years have a worse postoperative prognosis than those aged >35 years, which is affected by the depth of cervical interstitial infiltration >4 mm, parametrial metastasis, lymph node metastasis, and vascular infiltration. Therefore, it is necessary to identify more effective treatment methods for young patients with cervical cancer to improve the therapeutic effect and reduce the risk of recurrence and metastasis.

Abbreviations: DFS = disease-free survival, HPV = human papillomavirus, OS = overall survival, TNM = tumor-node-metastasis.

Keywords: age, cervical cancer, clinicopathological characteristic, prognostic risk factor

1. Introduction

Cervical cancer is a common malignancy of the female genital tract, with approximately 530,000 new cases annually. In recent years, the incidence of cervical cancer has shown a trend toward younger age, and its mortality rate remains high, seriously threatening the health of female patients.^[1] The clinical characteristics of patients with cervical cancer aged ≤35 years are different from those of patients aged >35 years, and the disease develops rapidly in young patients, with a worse prognosis than that of elderly patients.^[2] The risk factors for the prognosis of patients with cervical cancer have been a research hotspot in the field of gynecological tumors. According to previous studies,^[3,4] the pathological type, stage, and lymph node metastasis of tumors are all factors influencing the prognosis of cervical cancer patients. Currently, 20 to 40% of cervical cancer patients are aged ≤35 years,^[5] but

there are few studies on the factors influencing the prognosis of these patients. Moreover, the boundary age of young patients with cervical cancer is 35 years in the Chinese literature. In the present study, therefore, the differences in clinical characteristics of cervical cancer patients aged above and below 35 years and the factors influencing the prognosis were mainly explored, aiming to provide references for the prevention, diagnosis, and treatment of cervical cancer, improving the prognosis of young patients, and reducing the recurrence and mortality rates.

2. Materials and methods

2.1. Clinical data

A total of 256 patients with cervical cancer treated at Anhui Medical University Affiliated Maternity and Child Health Hospital

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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and The First Affiliated Hospital of Anhui Medical University between January 2016 and October 2018 were selected. They were aged 23 to 73 years, with an average of (47.52 ± 7.92) years, and the body mass index (BMI) was (21.02 ± 1.36) kg/m². The patients were divided into ≤ 35 -year-old ($n = 136$) and > 35 -year-old ($n = 120$) groups according to their age. This study was approved by the ethics committee of our hospital, and the test methods were strictly in accordance with the relevant regulations. All participants and their families were informed of the relevant rights and risks, and they voluntarily participated in the study and signed an informed consent form.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

- 1) patients diagnosed with primary cervical cancer by histopathology, with complete pathological results and clear tumor type and grade,
- 2) patients initially treated by surgery, and
- 3) patients who could receive regular follow-up at our hospital.

The exclusion criteria were as follows:

- 1) patients with distal lymph node metastasis.
- 2) those complicated with other malignant tumors,
- 3) those complicated with failure and dysfunction of the heart, brain, liver, kidney, or other vital organs,
- 4) those in pregnancy, and
- 5) those with incomplete data or those lost to follow-up.

2.3. Collection of baseline clinical data

Baseline data were collected, and relevant indices were measured by all medical staff in our department. All participating researchers received unified training and passed the training exam before the study to ensure a unified standard in the index evaluation. Baseline data were collected in the 2 groups, including age, height, weight (body mass index [BMI] = weight [kg]/height² [m²]), parity, presence or absence of a history of abnormal pregnancy, HPV infection, family history of cervical cancer, clinical symptoms, tumor diameter, pathological type, tumor-node-metastasis (TNM) stage, differentiation degree, depth of cervical interstitial infiltration, parametrial metastasis, and vascular infiltration.

2.4. Treatment methods

The patients were treated with surgery and chemoradiotherapy. Among those undergoing surgery, 193 underwent extensive hysterectomy + pelvic lymph node dissection, and 63 underwent extensive hysterectomy + unilateral adnexectomy/bilateral adnexectomy/unilateral ovariectomy + pelvic lymph node dissection. After surgery, 79 patients underwent radiotherapy (41 cases of intraluminal radiotherapy and 38 cases of external radiotherapy) and 52 patients underwent chemotherapy. Chemotherapy regimens included cisplatin + 5-fluorouracil ($n = 23$) and cisplatin + bleomycin + vincristine ($n = 15$).

2.5. Follow-up

All patients were followed up by telephone, outpatient review, and hospitalization for 3 years from the end of surgery to October 31, 2021. They received outpatient reviews within 1 month after discharge and then once every 3 months. The follow-up included the presence or absence of local recurrence, distant metastasis, and survival status. In case of death, the time and cause of death were recorded. OS and DFS rates were calculated. OS refers to the duration from the date of surgery to the date of death or the end date of the follow-up period. DFS

(months) was defined as the duration from the date of surgery to the date of recurrence. Recurrence or metastasis was confirmed based on the results of B-ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)-CT, and other imaging examinations.

2.6. Statistical analysis

SPSS 19.0 software was used for statistical analysis. Measurement data were expressed as mean \pm standard deviation, comparisons between 2 groups were performed by independent-samples *t* test, and comparisons among groups were conducted by analysis of variance. Numerical data are expressed as *n*, and comparisons between groups were performed using the χ^2 test. Survival curves were plotted using the Kaplan–Meier method, and DFS and OS were calculated and compared using the log-rank test. Factors influencing prognosis were analyzed using univariate and multivariate Cox proportional hazards models. A two-tailed $P < .05$ suggested a statistically significant difference.

3. Results

3.1. Clinical characteristics of 2 groups

The HPV infection rate, incidence rate of contact vaginal bleeding, depth of cervical interstitial infiltration, and incidence rates of parametrial metastasis and vascular infiltration were all significantly higher in ≤ 35 -year-old group than those in > 35 -year-old group, showing statistically significant differences ($P < .05$) (Table 1).

3.2. Three-year cumulative DFS and OS curves of 2 groups

At the end of the follow-up period, the disease recurred in 69 patients, including 44 cases of pelvic recurrence and 25 cases of distant lymph node metastasis (lung metastasis in 10 cases, bone metastasis in 8 cases, and liver metastasis in 7 cases), and 46 patients died. The 3-year cumulative DFS and OS rates were 73.05% and 82.42%, respectively. There were 42 cases of recurrence and metastasis, 24 of death in the ≤ 35 -year-old group, 27 of recurrence and metastasis, and 22 of death in the > 35 -year-old group. The 3-year cumulative DFS rate in the ≤ 35 -year-old group was significantly lower than that in the > 35 -year-old group [69.12% (94/136) vs. 77.50% (93/120)] (log-rank $\chi^2 = 7.429$, $P < .05$), while the cumulative OS rate was not significantly different between the 2 groups [82.35% (112/136) vs. 81.67% (98/120)] (log-rank $\chi^2 = 0.020$, $P > .05$) (Fig. 1).

3.3. DFS rates of 2 groups with different pathological characteristics

The 3-year cumulative DFS rate was compared between patients with HPV infection, contact vaginal bleeding, depth of cervical interstitial infiltration > 4 mm, parametrial metastasis, and vascular infiltration between the 2 groups. The DFS rates of patients with HPV infection and contact vaginal bleeding were significantly lower in the ≤ 35 -year-old group than in the > 35 -year-old group (68.29% vs. 80.85%, 66.04% vs. 81.48%) (log-rank $\chi^2 = 4.339$ and 4.276, $P < .05$). Patients with a depth of cervical interstitial infiltration > 4 mm, parametrial metastasis, and vascular infiltration had no statistically significant difference in the 3-year cumulative DFS rate between the 2 groups ($P > .05$) (Table 2 and Fig. 2).

3.4. Univariate Cox proportional hazard analysis results of influencing factors for DFS of cervical cancer patients aged ≤ 35 years

The treatment method, tumor pathological type, depth of cervical interstitial infiltration, TNM stage, parametrial

Table 1
Clinical characteristics of 2 groups.

Index		≤35-year-old group (n = 136)	>35-year-old group (n = 120)	t/χ ²	P
Age (yrs)		31.62 ± 7.53	55.03 ± 7.66	24.622	.000
Weight (kg)		54.85 ± 6.28	56.32 ± 7.02	1.768	.078
BMI (kg/m ²)		20.92 ± 2.36	21.23 ± 1.82	1.165	.245
Parity	≤1	78	69	0.001	.981
	>1	58	51		
History of abnormal pregnancy	Yes	61	58	0.310	.577
	No	75	62		
HPV infection	Yes	123	94	7.237	.007
	No	13	26		
Family history of cervical cancer	Yes	44	27	3.088	.079
	No	92	93		
Clinical symptoms	Contact vaginal bleeding	106	54	30.647	.000
	Irregular vaginal bleeding	16	41		
	Irregular vaginal discharge	9	19		
	Others	5	6		
Tumor diameter	≤5 cm	59	59	0.858	.354
	>5 cm	77	61		
Pathological type	Squamous carcinoma	104	105	5.295	.071
	Adenocarcinoma	27	12		
	Others	5	3		
Depth of cervical interstitial infiltration	≤4 mm	58	68	5.013	.025
	>4 mm	78	52		
TNM stage	I-II	76	53	3.500	.061
	III-IV	60	67		
Differentiation degree	High	44	54		
	Moderate	50	42	5.647	.059
	Low	42	24		
Parametrial metastasis	Yes	79	50		
	No	57	70		
Vascular infiltration	Yes	84	52	8.697	.003
	No	52	68		

BMI = body mass index, HPV = human papillomavirus, TNM = tumor-node-metastasis.

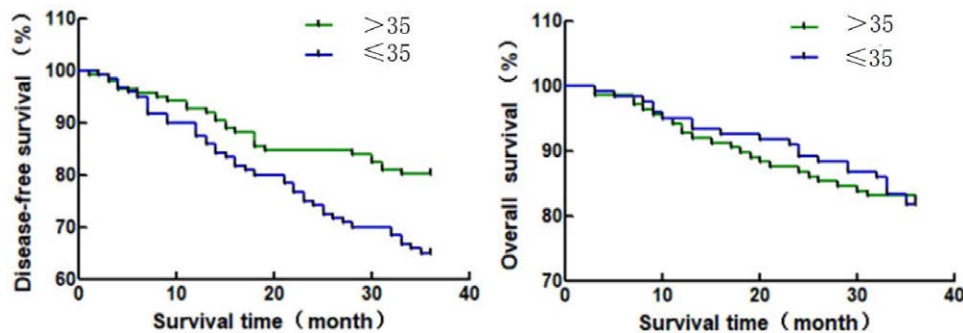


Figure 1. Three-year cumulative DFS and OS curves of 2 groups. DFS = disease-free survival, OS = overall survival.

metastasis, lymph node metastasis, and vascular infiltration were all influencing factors for the 3-year cumulative DFS rate of patients with cervical cancer aged ≤35 years (Table 3).

3.5. Multivariate Cox regression model analysis results of DFS of cervical cancer patients aged ≤35 years

With DFS as the dependent variable and factors with statistically significant differences in univariate analysis as independent variables, the influencing factors for DFS in cervical cancer patients aged ≤35 years were assessed using the Cox regression model. The results showed that a depth of cervical interstitial infiltration >4 mm, parametrial metastasis, lymph node metastasis, and vascular infiltration were all independent risk factors for the prognosis of cervical cancer patients aged ≤35 years (Table 4).

4. Discussion

In recent years, with the improvement in cervical cancer screening, the incidence of cervical cancer has shown a younger trend, and the mortality rate of cervical cancer patients has also been reduced by early diagnosis and treatment.^[4] There has been insufficient understanding of malignant tumors, so it is generally believed that malignant tumors frequently occur in middle-aged and elderly patients, and related clinical symptoms in young patients are often ignored, thus delaying treatment.^[6] In this study, we found that the prognosis of young patients was poor, and the factors affecting the prognosis of young patients were explored.

In this study, the clinical characteristics of patients aged ≤35-year-old group and >35-year-old group. The HPV infection rate, incidence rate of contact vaginal bleeding, depth of cervical interstitial infiltration, and incidence rates of parametrial metastasis and vascular infiltration were

Table 2**DFS rates of 2 groups with different pathological characteristics.**

Index	Recurrence and metastasis	n	≤35-year-old group	>35-year-old group	χ^2	P
HPV infection	Yes	57	39	18	4.339	.037
	No	160	84	76		
Contact vaginal bleeding	Yes	46	36	10	4.276	.039
	No	114	70	44		
Depth of cervical interstitial infiltration >4 mm	Yes	45	30	15	1.275	.259
	No	85	48	37		
Parametrial metastasis	Yes	47	31	16	0.693	.405
	No	82	48	34		
Vascular infiltration	Yes	50	33	17	0.601	.438
	No	86	51	35		

HPV = human papillomavirus.

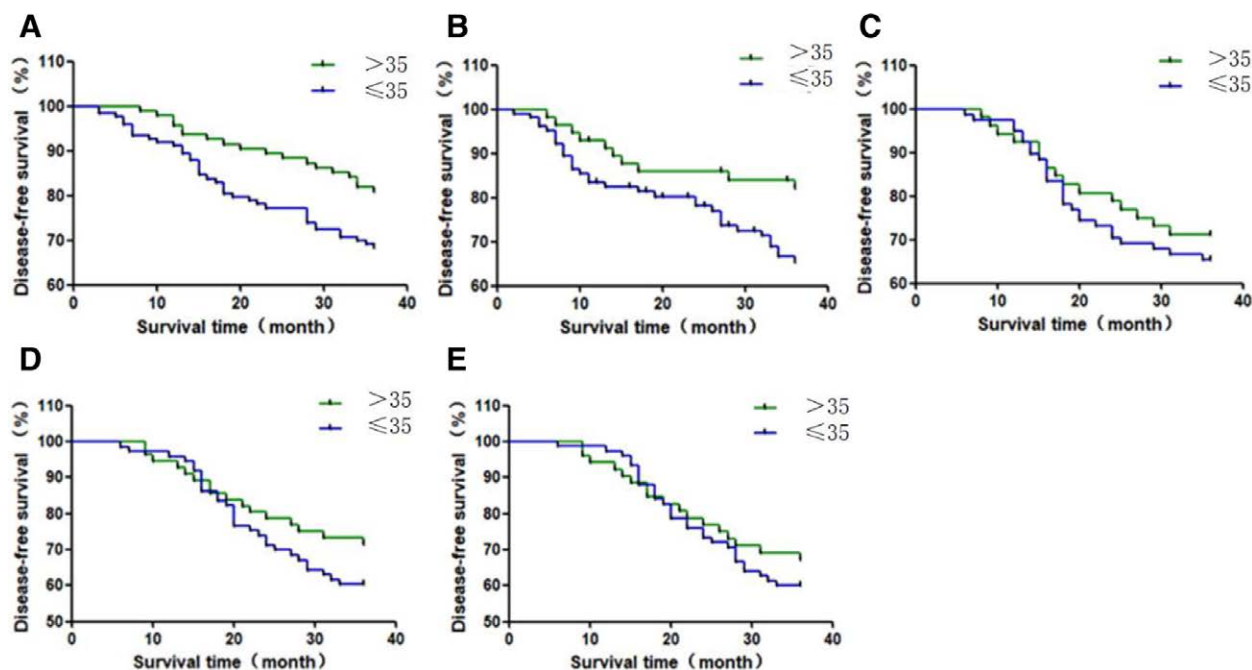


Figure 2. Three-year cumulative DFS rates of 2 groups with different pathological characteristics. (A) Three-year cumulative DFS rate of patients with HPV infection. (B) Three-year cumulative DFS rate of patients with contact vaginal bleeding. (C) Three-year cumulative DFS rate of patients with the depth of cervical interstitial infiltration >4 mm. (D) Three-year cumulative DFS rate of patients with parametrial metastasis. (E) Three-year cumulative DFS rate of patients with vascular infiltration. DFS = disease-free survival, HPV = human papillomavirus.

all significantly higher in the ≤35-year-old group than in the >35-year-old group. HPV infection is an independent risk factor for cervical cancer, and the higher rate of HPV infection in young patients with cervical cancer may be related to frequent and unclean intercourse.^[7] Talía et al found that approximately 85% of young patients had HPV infection.^[8] Therefore, routine HPV screening should be adopted in young women to reduce the risk of cervical cancer through early diagnosis. Peng et al reported that contact vaginal bleeding occurred more frequently in young patients, which might be related to their more active sex lives.^[9] In this study, the incidence rates of parametrial metastasis and vascular infiltration were higher in the ≤35-year-old group than in the >35-year-old group, consistent with the findings of Bergengren et al.^[10] In addition, it was also found that the depth of cervical interstitial infiltration was larger in ≤35-year-old group, which may be related to the stronger immune function and vigorous metabolism of young patients.

Age is an influencing factor in the therapeutic effect and prognosis of patients with cervical cancer.^[11] In this study, the DFS rate of cervical cancer patients in the ≤35-year-old group was significantly lower than that in the >35-year-old

group, suggesting that young patients are more prone to tumor recurrence and metastasis after treatment. Simopekka et al also reported that the age of cervical cancer patients was correlated with tumor malignancy and metastasis, and a lower age corresponded to a higher tumor malignancy and metastasis rate.^[12] In this study, the 3-year cumulative DFS rates of patients with different pathological characteristics were compared between the 2 groups. The results revealed that the 3-year cumulative DFS rate of patients with HPV infection and contact vaginal bleeding was significantly different between the 2 groups, and the recurrence and metastasis rates were higher in the ≤35-year-old group, consistent with the conclusion of the overall comparison. However, patients with a depth of cervical interstitial infiltration >4 mm, parametrial metastasis, and vascular infiltration did not have a worse prognosis in the ≤35-year-old group, demonstrating that the depth of cervical interstitial infiltration, parametrial metastasis, and vascular infiltration may be the main factors influencing the prognosis of patients.

In this study, the factors influencing the prognosis of patients aged ≤35-year-old group were analyzed. The treatment method, tumor pathological type, depth of cervical interstitial infiltration,

Table 3
Univariate Cox proportional hazard analysis results of influencing factors for DFS of cervical cancer patients aged ≤35 years.

Influencing factor	Assignment	n	Recurrence and metastasis (n = 42)	3-Year cumulative DFS (%)	HR	95% CI	χ ²	P	
Parity	≤1	0	78	24	69.23	0.65	0.57–1.46	0.001	.974
	>1	1	58	18	68.97				
History of abnormal pregnancy	No	0	75	20	73.33	0.86	0.42–1.75	1.392	.238
	Yes	1	61	22	63.93				
HPV infection	No	0	13	3	76.92	0.61	0.52–1.53	0.410	.522
	Yes	1	123	39	68.29				
Family history of cervical cancer	No	0	92	27	70.65	0.78	0.64–1.69	0.314	.575
	Yes	1	44	15	65.91				
Treatment method	Surgery	0	68	15	77.94	2.18	2.12–6.43	4.960	.026
	Surgery + chemoradiotherapy	1	68	27	60.29				
Tumor diameter	≤5 cm	0	59	13	77.97	0.95	0.79–1.96	3.822	.051
	>5 cm	1	77	29	62.34				
Pathological type	Squamous carcinoma	0	104	27	74.04	2.33	1.32–3.54	5.014	.025
	Others	1	32	15	53.12				
Depth of cervical interstitial infiltration	≤4 mm	0	58	11	81.03	3.85	1.25–5.33	6.728	.009
	>4 mm	1	78	31	60.26				
TNM stage	I–II	0	76	17	77.63	2.56	1.42–3.69	5.850	.016
	III–IV	1	60	25	58.33				
Differentiation degree	High	0	44	10	77.27	0.89	0.15–1.38	2.027	.155
	Moderate–low	1	92	32	65.22				
Parametrial metastasis	No	0	57	11	80.70	4.47	3.15–6.28	6.169	.013
	Yes	1	79	31	60.76				
Lymph node metastasis	No	0	69	13	81.16	5.51	3.28–6.76	9.515	.002
	Yes	1	67	29	56.72				
Vascular infiltration	No	0	52	9	82.69	5.16	4.24–8.31	9.473	.007
	Yes	1	84	33	60.71				

CI = confidence interval, HPV= human papillomavirus, HR = hazard ratio, TNM = tumor-node-metastasis.

Table 4
Multivariate Cox regression model analysis results of DFS of cervical cancer patients aged ≤35 years.

Clinicopathological characteristic	β	SE	Wald	HR	95% CI	P
Surgery + chemoradiotherapy	0.78	0.35	0.68	1.393	0.341–1.252	.133
Squamous carcinoma	0.54	0.28	0.79	1.450	0.712–1.353	.072
Depth of cervical interstitial infiltration >4 mm	1.18	0.29	10.85	2.738	1.532–2.938	.038
TNM stage III–IV	0.39	0.31	0.84	1.532	0.582–2.968	.069
Parametrial metastasis	1.16	0.33	10.48	2.503	1.231–3.945	.042
Lymph node metastasis	1.25	0.34	12.97	3.412	1.368–4.982	.011
Vascular infiltration	1.21	0.27	11.42	3.556	1.295–4.794	.016

β = model coefficient, CI = confidence interval, HR = hazard ratio, TNM = tumor-node-metastasis.

TNM stage, parametrial metastasis, lymph node metastasis, and vascular infiltration were all influencing factors for the 3-year cumulative DFS rate of cervical cancer patients aged ≤35 years. The results of multivariate Cox regression analysis revealed that a depth of cervical interstitial infiltration >4mm, parametrial metastasis, lymph node metastasis, and vascular infiltration were all independent risk factors for the DFS rate of cervical cancer patients aged ≤35 years. The pathological type and TNM stage of the tumor directly affect the occurrence and progression of the disease, and more complicated treatment has a greater impact on the normal physical function of patients. In addition, the vigorous metabolism and strong immune function of young patients create conditions for the malignant development of tumor cells, thereby increasing the metastasis and recurrence rates and affecting the prognosis of young patients. Eo et al found a significant correlation between the depth of interstitial infiltration of >4mm and lymph node metastasis.^[13] In a

retrospective study by Ryu et al,^[14] the results of multivariate analysis confirmed that a depth of interstitial infiltration >50% and parametrial involvement were both independent risk factors for the 5-year DFS rate of cervical cancer patients.

In this single-center study, the sample size was small, the analysis of prognosis might have been biased, and there were few age groups. This study had certain limitations. In the future, multi-center large-sample research with more age groups is needed to verify the results of this study.

In conclusion, patients with cervical cancer aged ≤35 years have a worse postoperative prognosis and are more prone to recurrence and metastasis than those aged >35 years, which is affected by the depth of cervical interstitial infiltration >4mm, parametrial metastasis, lymph node metastasis, and vascular infiltration. Therefore, it is necessary to develop more active and effective treatment methods for young patients with cervical cancer to improve their therapeutic effect and reduce the risk of recurrence and metastasis.

Author contributions

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