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Salivary Interleukin 17a and IL1 as a Dependent Positive Predictive Biomarker for Oral Squamous Cell Carcinomas in Iraqi Patients

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ABSTRACT

Background: Head and neck cancer is the sixth most common cancer in human. Over 90% of malignant neoplasms of the head and neck are diagnosed as squamous cell carcinomas of oral cavity. In addition, its diagnosis is often late due to unavailability of predictive reliable measurable biomarkers. Interleukin 17 is one of pro-inflammatory cytokines manufactured by T-helper cells. It usually binds to type I cell-surface receptor named interleukin. Interleukin-1 (IL-1) represents a master cytokine of local and systemic inflammation. It exerts both beneficial, promoting innate immunity against invading microorganisms, and harmful roles in a plethora of autoimmune and autoinflammatory diseases including cancer. The purpose of the current study was to explore the predictive role of salivary interleukin 17 and IL1 in the diagnosis of oral squamous cell carcinoma in comparison with healthy individuals. Method: Patients with histopathologic ally-confirmed oral squamous cell carcinoma (40 patients) and 40 normal healthy subjects (controls) were involved in this study. Unstimulated saliva was collected from each individual. Salivary interleukin-17 and IL1 levels were evaluated for both groups using Enzyme-Linked Immuno-Sorbent Assay (ELISA) technique. Results: Mean value of IL-17 and IL1 levels were significantly increased in oral squamous cell carcinoma patients as compared to controls. Conclusion: Interleukin-17 and IL1 has particular advantage to be used as a positive predictive factor for prognosis and diagnosis of OSCC.

Keywords: Interleukin-1, Interleukin-17, Oral Squamous Cell Carcinoma

1 Introduction

A poor prognosis of oral cavity and oropharyngeal cancer is associated with delayed diagnosis, and there is a lack of reliable biomarkers for these diseases. Each year, over 350,000 new cases are diagnosed and almost 180,000 deaths are reported due to oral cancer, making this disease a significant worldwide health problem [1]. Delayed cancer diagnosis is a factor contributing to the low survival rate. Patients with specific risk factors for oral cancer, such as smoking, excessive alcohol consumption, and human papillomavirus infection, should regularly assess their oral condition as a part of preventive examinations. Oral squamous cell carcinoma (OSCC) is the most commonly diagnosed head and neck cancer and its incidence has increased in recent decades. OSCC prevalence among women and young or middle age men has also been increasing [2]. OSCC is the most prevalent cancer in the oral cavity, accounting for more than 90% of oral malignancies [3]. Despite recent advances in the detection, prevention, and treatment of OSCC, this highly aggressive cancer remains associated with a poor 5-year

patient survival rate [1]. Approximately, one-third of treated patients experience local or regional recurrence and/or distant metastasis. This poor prognosis can be attributed to the notion that about two-thirds of patients with OSCC are already at an advanced stage of the disease at the time of diagnosis. The main risk factors for oral cancer are exposure to exogenous carcinogens, such as tobacco smoke, smokeless tobacco, excess alcohol, and the presence of human papillomavirus (HPV) [4]. In the past, approaches using saliva samples in the diagnostic process of an early detection of oral and oropharyngeal cancer were made. Elevated concentrations of various active compounds in saliva samples indicate the possibility of using them as potential biomarkers [5]. Inflammation, and cytokines, plays a crucial role in various stages of cancer, as a group of host immune system products, are involved. Cytokines in the tumor microenvironment (TME) play a critical role in processes related to cancer progression, such as invasion and metastasis [6,7]. Inflammatory cytokines, especially those secreted by tumor cells, play an essential role in the TME [8]. Pro-inflammatory cytokines present in the tumor microenvironment (TME) can have dual effects; they can stimulate inflammation to decrease tumor progression; or they can stimulate inflammation favoring carcinogenesis, tumor growth and metastasis [9].

The IL-17 family consists of six cytokines (from IL- 17A to IL-17F), which are produced mainly by Th17 cells. IL-17 plays an active role in autoimmune diseases and rejection of transplanted organs and has anticancer effects. On the other hand, Th17-related cytokines can initiate tumor progression, angiogenesis, and metastasis. IL-17A has been found in many types of cancer, e.g., ovarian cancer and pancreatic cancer [10, 11].

IL-17 is mainly produced by a large variety of innate immune cells and exerts its most significant biological functions at the interface of the organism with its environment [12] IL-17A, the link between natural immunity and adaptive immunity, also plays a pivotal role in tumor progression. Initial stage carcinogenesis in the oral cavity was exacerbated via inflammation, ROS and depletion of antioxidant enzymes, in which IL-17A expressions are significantly increased [13]. Accumulating evidences have shown that overexpressed IL-17A occur in many types of cancer, including OSCC [14]. Besides, IL-17A has been detected in multiple cancer entities, such as pancreatic cancer and ovarian cancer [12, 11]. Moreover, IL-17A and other cytokines cooperated to augment the protumor functions of neutrophils, thereby promoting the progression of OSCC cells. Bioinformatic analysis on OSCC illustrated IL-17 signaling pathway is one of the key pathways]. Hence, IL-17A is one of the most important markers in OSCC progression [15]. Therefore, to clarify the particular role of IL-17A in cancer biology is very important. Cytokines are produced by host cells in response to factors secreted by the tumor cells or by the tumor itself [16, 17]. Interleukin-1 (IL-1) is commonly found at tumor sites and is considered one of the most important cytokines of the TME, where it plays a key role in carcinogenesis and tumor progression [18], and its expression has been associated with poor prognosis in cancer patients [19]. There is a growing association linking head and neck squamous cell carcinoma (HNSCC) with chronic inflammation [20, 21], in which IL-1/IL-1R signaling seems to be a key player [22].

Various polymorphisms and combinations of specific genetic mutations have been reported to be associated with an increased risk for development of OSCC [23]. Interleukin 17A and IL-17F polymorphisms are associated with increased risk for OSCC and are related to tumor stage and differentiation. In addition, it has been shown that the IL-17A and IL-17F polymorphisms increase the risk of OSCC developing in a population exposed to two other risk factors, smoking and alcohol [24]. Development and progression of OSCC are strongly affected by different components of the immune system [25]. Interleukin-1 (IL-1) represents a master cytokine of local and systemic inflammation. It exerts both beneficial, promoting innate immunity against invading microorganisms, and harmful roles in a plethora of autoimmune and autoinflammatory diseases including cancer. A causal relation between inflammation and cancer has been proposed by Virchow in 1863, who hypothesized that malignant neoplasms arise within a region of chronic inflammation causing tissue injuries and increased cell growth [26]. During the last two decades, clinical and epidemiological observations strongly supported Virchow's hypothesis; it is now clear that inflammation is a key factor involved in all aspects of carcinogenesis mediating initiation, uncontrolled cells proliferation, invasion, angiogenesis and metastasis [27-29].

However, the impact of IL-17 and IL1, an inflammatory cytokine that closely contributes to the development, progression and metastasis of various tumors and affects the sensitivity to chemotherapy and radiation therapy on OSCC formation and progression requires further elucidation. Therefore, the aim of current study was to evaluate the levels and diagnostic validity of cytokines in saliva of patients with oral squamous cell carcinoma in comparison with apparently healthy subjects. In this review, the possible roles of IL-17and IL1 in OSCC development will be discussed.

2 Materials and Methods

Study Participants, Saliva Sample Collection and Immunoassay: This cross- section study was conducted at department of maxillofacial surgery in different hospitals in Baghdad, Iraq and also from the specialized dental center in the Ba'aquba, Diyala governorate. The study samples were obtained from 80 volunteers, 40 patients who had histopathological-established untreated oral squamous cell carcinoma of both sexes. and the control group included 40

healthy individuals. The diagnosis was based on histopathological analysis from a tissue biopsy and staged according to the TNM classification system [30]. The patients were free from any other oral or systemic illness. Unstimulated saliva was collected in the morning between 8 am. and 11 am [31]. All the participants were asked to refrain from eating, drinking, smoking, and using oral hygiene products for at least 1 h prior to sample collection, done by expectoration into 15 mL sterile tubes for 5 min. Specimens with visible blood traces were discarded from the study. Salivary samples were centrifuged at 4000 rpm for 10 minutes then 100 µl of supernatant was withdrawn and stored in sterile Eppendorf tubes at (-20^{C}) for analysis of IL-17A and IL 1. Interleukin 17 production was measured using ELISA kits (IL-17 ELISA Kit) Shanghai Yehua Biological Technology/China.

2.1 Statistical Analysis

Data description, analysis and presentation were performed using Statistical Package for social Science (SPSS version-22, Chicago, Illionis, USA), Simple and cluster chart bars, frequency, percentage, minimum, maximum, mean, standard deviation, Pearson chi square, Pearson correlation, Un-paired T test, One Way ANOVA with Hochberg GT2, level of significance is when p value less than 0.05.

3 Result

3.1 Clinical Description

The clinical features of 80 subjects participate in this study aged range 33-84 years old with mean ± SD as 58.96 ± 13.015, 41 males and 39 females distributed into 40 subjects for study and 40 subjects for control, mean of age in the study group is higher than that in the control but with no significant difference, males is higher in control than those in the study while females is higher in the study than those in the control but also no significant association (Figure 1).

3.2 Descriptive and Statistical Test of Il-17a Among Groups

With the use of Un-paired T test, it is found IL-17a is higher in the study group than that in the control group with significant difference (Table 1).

Table 1. Comparison of IL17a between study group and control group.

	Control	Study	Un-paired T test	p value
Minimum	230.000	351.000	7.132	0.000 Sig.
Maximum	641.000	1052.000		
Mean	381.150	602.125		
±SD	105.481	165.135		

3.3 Statistical Analysis of IL-1 Among Groups

Results below show that IL-1 is higher in the study group than that in the control group with significant difference (Table 2).

Table 2. Comparison of IL1 between study group and control group.

	Control	Study	Un-paired T test	p value
Minimum	13.440	28.300	9.859	0.000 Sig.
Maximum	59.000	97.880		
Mean	32.954	60.143		
±SD	8.339	15.320		

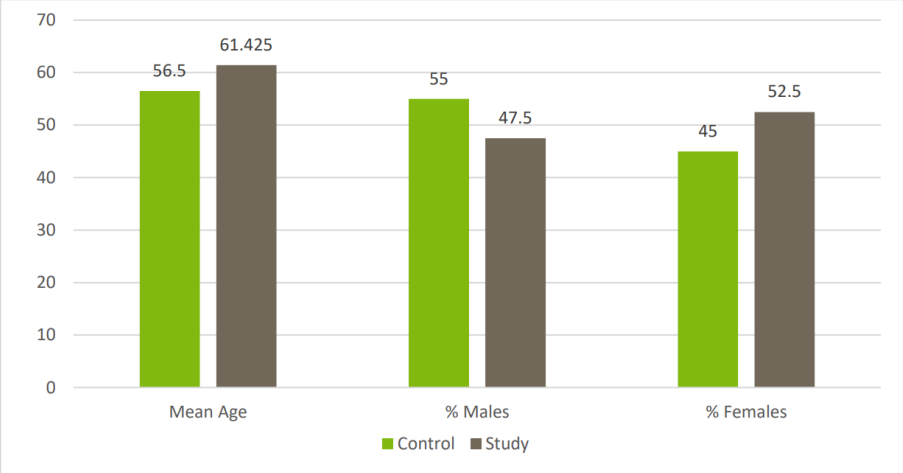

Fig. 1. Comparison between the study and control groups by clinical characteristics.

3.4 Distribution of OSCC by Site, Histopathology and TNM

According to the site, OSCC is spread in tongue border highest (14 patient) followed by Lip and tongue tip (10, 9 patients respectively) while little in buccal mucosa (7 patient). Histopathology, moderate differentiated is commonest (19 patient) followed by well differentiated (14 patient) with little in poorly differentiated (7 patient). In TNM, Stage I is higher than Stage II (Table 3).

3.5 Descriptive and Statistical Test of Il-17a Among Site, Histopathology and TNM

Regarding site, Il-17 a is higher in tongue border followed by tongue tip and buccal mucosa while lower in lip but with no significant difference, IL_17a is higher in poorly followed by well and lower in moderate with significant difference furthermore using HochberGT2, all results between histopathological views are significant except between well and moderate, its result is not significant., IL- 17 a is higher in Stage I than in Stage II but with no significant difference (Tables 4 and 5).

3.6 Descriptive and Statistical Test of IL-1 Among Site, Histopatho and TNM

Regarding site, IL-1 is higher in tongue tip followed by lip and tongue border with lower in buccal mucosa but with no significant difference, IL-1 is higher in poorly followed by well and lower in moderate with no significant difference., IL-1 is higher in Stage II than in Stage I with significant difference.

3.7 Descriptive and Statistical Test of Il-17a Among Age and Gender

Findings show that IL-17 a increases with age with significant difference, IL-17 A is higher in females than in males but with no significant difference (Table 6).

Table 3. Il-17a among site, histopatho and TNM.

Vars.		Minimum	Maximum	Mean	± SD	Statistics	p value
Site [a]	Lip	351.000	709.000	514.000	111.541	1.483	0.236 NS
	Tongue border	374.000	1052.000	653.929	199.624		
	Tongue tip	359.000	786.000	615.111	146.305		
	Buccal mucosa	421.000	789.000	607.714	155.612		
Histopatho[a]	Well	359.000	705.000	565.500	114.875	8.936	0.001 Sig.
	Moderate	351.000	848.000	557.158	160.712		
	Poorly	677.000	1052.000	797.429	130.929		
TNM[b]	Stage I	359.000	1052.000	609.360	178.505	0.354	0.726 NS
	Stage II	351.000	789.000	590.067	145.233		

A=One way ANOVA, b= Un-paired T test.

Table 4. Multiple comparisons of Il-17a using Hochberg GT2.

Vars.		Mean Difference (I-J)	p value
Well	Moderate	8.34211	0.998
	Poorly	-231.92857	0.003
Moderate	Poorly	-240.27068	0.001

Table 5. IL-1 among site, histopathology and TNM.

Vars.		Minimum	Maximum	Mean	±SD	Statistics	p value
Site [a]	Lip	28.300	97.880	60.453	18.512	0.628	0.602 NS
	Tongue border	44.800	86.400	59.746	13.330		
	Tongue tip	33.400	87.500	64.982	17.122		
	Buccal mucosa	42.900	76.880	54.273	12.642		
Histopatho[a]	Well	33.400	86.400	58.219	13.826	1.807	0.178 NS
	Moderate	28.300	97.880	57.952	15.999		
	Poorly	50.500	87.500	69.937	14.415		
TNM[b]	Stage I	28.300	75.300	53.544	11.819	4.201	0.000 Sig.
	Stage II	43.700	97.880	71.141	14.389		

A=One way ANOVA, b= Un-paired T test.

Table 6. Il-17a among age and gender.

Vars.	Cats.		IL-17a	Un-paired T test	p value
Age (years)	<=60y	Minimum	230.000	3.285	0.002 Sig.
		Maximum	1052.000		
		Mean	436.182		
		±SD	155.736		
	60y+	Minimum	284.000		
		Maximum	881.000		
		Mean	559.417		
		±SD	179.717		
Gender	Malse	Minimum	230.000	0.534	0.595 NS
		Maximum	787.000		
		Mean	481.293		
		±SD	156.993		
	Females	Minimum	234.000		
		Maximum	1052.000		
		Mean	502.513		
		±SD	197.296		

3.8 Descriptive and Statistical Test of IL-1 Among Age and Gender

Findings show that IL-1 a increases with age with significant difference, IL-1 is higher in females than in males but with no significant difference (Table 7).

Findings show that Il-17 A is very good in differentiation between study case and control with significant result (Figure 2).

Findings show that Il-1 is excellent in differentiation between study cases and control with significant result (Figure 3).

Results show that there is weak positive not significant correlation between IL-1 and IL- 17 A in both groups (Table 8).

Table 8. Correlation between IL-1 and IL- 17 A in both groups

Groups	r	p value
Control IL17a	0.029	0.861
Study IL17a	0.094	0.565

Table 7. IL-1 among age and gender.

Vars.	Cats.		IL-17a	Un-paired T test	P value
Age (years)	<=60y	Minimum	13.440	3.395	0.002 Sig.
		Maximum	74.400		
		Mean	40.624		
		±SD	15.143		
	60y+	Minimum	18.500		
		Maximum	97.880		
		Mean	53.789		
		±SD	19.537		
Gender	Malse	Minimum	13.440	0.608	0.545 NS
		Maximum	97.880		
		Mean	45.326		
		±SD	18.025		
	Females	Minimum	18.500		
		Maximum	87.500		
		Mean	47.833		
		±SD	18.868		

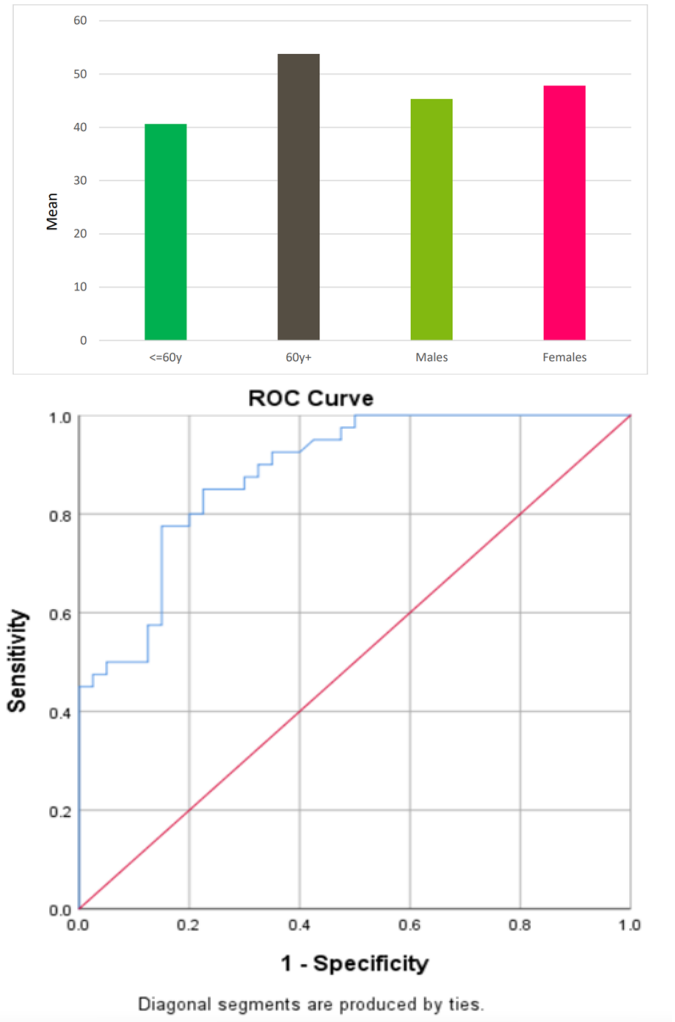

Fig. 2. Il-17a, area under curve = 0.883, p value = 0.000 Sig., sensitivity = 82.5%, specificity = 78.5%, optimal cutoff point = 455.000.

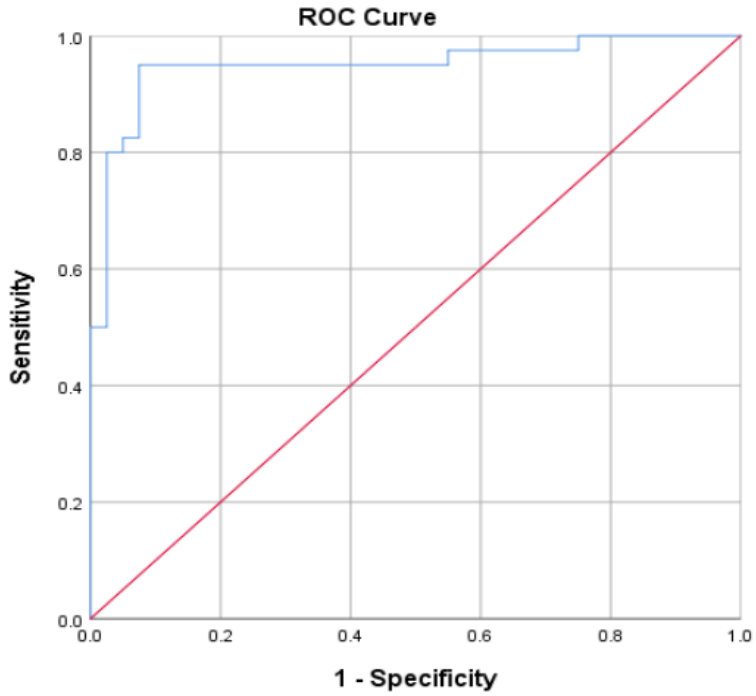

Fig. 3. IL-1, area under curve = 0.949, p value = 0.000 Sig., sensitivity = 92.5%, specificity = 92.5%, optimal cutoff point = 43.15

4 Discussion

The delayed diagnosis of OSCC at advanced stages is the main contributing factor to the poor 5-year survival rate. Currently used clinical strategies such as biopsy, vital tissue staining and exfoliative cytology will only be applicable to small patient groups and have clear limitations [32].

In order to improve early diagnosis and reduce mortality, there is a need to develop markers with an appropriate level of sensitivity and specificity. The aim of using salivary biomarkers for OSCC detection is the facilitation of diagnostics at a point where OSCC is still small and treatment is very likely to be successful. In order to achieve this highly desirable goal, a saliva screening method must have sufficient sensitivity and specificity, be rather inexpensive, non-invasive, have high throughput, and can be used by non-trained personnel. Using the latest advancements in technology could help put saliva in such a clinical context. Recent studies have shown that there is an abundance of accessible salivary biomarkers with highly discriminatory value for various diseases [33-37]. For this dreaded malignancy, sensitive and specific biomarkers are to be considered effective in respect to screening, diagnosis, staging and follow-up [38]. Saliva was looked upon as a true reflection of blood and its various elements and represents a true mirror for body's health. It has been used for detection of various diseases ranging from autoimmune diseases to infections and cancers [39-41]. Tow biomarkers with significantly different expression in OSCC than in controls were found in this study, IL17a and IL1.

IL-17 is a relatively novel cytokine family and it plays an important role in connecting innate and adaptive immune responses. In this study, the comparison of IL17a between study group and control group, it is higher in the study group than that in the control group with significant difference, p value = 0.000 Sig. The results between histopathological views is higher in poorly differentiation followed by well differentiation with significant difference and lower in moderate differentiation. IL17a Sensitivity = 82.5%, specificity = 78.5. These findings show that Il-17 a is very good in differentiation between study case and control with significant result, p value=0.000 Sig.

In this study IL-17 showed an increasing trend correlated with the age with significant difference (p value=0.002 Sig) this result agree with [42]. In addition, the mean values of salivary levels of IL-17A in saliva samples were significantly increased in OSCC patients in comparison to salivary levels of healthy control subjects. These results are in agreement with those presented by [43], that T helper 17 cells and IL-17 levels are increased in patients with head and neck squamous cell carcinoma. The high salivary levels of IL-17 with OSCC patients may be due to the tumor microenvironment. And also agreement with [44] which had been stated that the functions of IL-17 contribute mainly to progression of tumor as IL- 17 directly affects reproduction and survival of tumor cells.

The combination of various salivary biomarkers has improved the diagnosis of oral cancer, including OSCC. These combinations have high sensitivity and specificity that collectively have discriminatory power within detecting OSCC.

IL1 findings of the present study showed it is higher in the study group than that in the control group with significant difference, p value=0.000 Sig. IL-1 is higher in poorly differentiation followed by well differentiation with no significant difference., IL-1 is higher in Stage II than in Stage I with significant difference, p value=0.000 Sig. The area under curve=0.949, p value=0.000 Sig., Sensitivity=92.5%, specificity=92.5%, This make Il-1 is excellent in differentiation between study cases and control with significant result.

This is in agreement with previous study, as there is evidence suggesting that IL- 1α, IL-1β, and IL-1RA are involved in the pathogenesis of HNSCC and can be detected in the saliva of cancer patients [45–47],

IL-1β is overexpressed in the saliva of oral cancer patients compared to oral leukoplakia and control patients [48, 49] and IL-1β salivary levels have been shown to discriminate between OSCC subjects and controls [50–52].

5 Conclusion

From the results of the presents study, it can be concluded that cytokines are important and are detectable in saliva of patients with OSCC. IL-1 increases the pathogenicity of OSCC and prove useful as potential biomarker for diagnosis prognosis and diagnosis of OSCC.

Conflict of Interest: The authors declare no conflict of interest.
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Ethical consideration: The study was approved by Diyala University, Diyala, Iraq.

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