

Recurrent Vocal Fold Leukoplakia: Incidence and Risk Factors

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ABSTRACT

Background: Vocal fold leukoplakia (VFL) is a benign lesion of the vocal folds, that if left untreated, possesses the potential to develop into a malignant, high-risk carcinoma of the larynx. There are several risk factors, such as smoking, alcohol consumption, and exposure to chemical irritants affecting the disease severity and recurrence post-surgical intervention.

Objectives: To examine the demographic and clinical characteristics associated with VFL, to investigate the recurrence of VFL following surgical removal, and to identify prognostic factors that can predict lesion recurrence.

Materials and methods: In the current prospective cohort study, 85 adult patients with VFL were recruited. The selected patients underwent a direct laryngoscope, followed by surgical stripping and biopsy sampling for histopathological examination, with subsequent one-year follow-up.

Results: Out of 85 patients with VFL, there were 29 patients (34.11%) with recurrence. There were 67 (78.8%) males. The mean age of men was 63.0 ± 6.6 years, compared to 61.1 ± 7.0 years for women. Sixty percent (51) of the cases had a history of smoking. There was no significant impact of sex, age, and smoking on VFL recurrence (P -value > 0.05). However, high-risk histopathological grades and bilateral VFL with involvement of the anterior commissure were significantly correlated with recurrence (P -values of 0.001 and 0.012, respectively). Univariate analysis presented a significant association between high-risk histopathological grade (P -value = 0.001) and bilateral VFL (P -value = 0.012) and recurrence. The high-risk histopathological grade was found to be independently effective in predicting the recurrence of VFL after treatment by utilizing multivariate analysis.

Conclusion: VFL had a high recurrence rate. Findings from a high-risk histopathological grade and bilateral VFL with involvement of the anterior commissure can be employed to predict VFL recurrence after surgery. Embracing a healthy and conscious lifestyle by minimizing exposure to risk factors could impede the progression and recurrence of VFL, specifically among individuals who are at higher risk of developing the aggressive form of the disease.

Keywords: Vocal fold leukoplakia; Recurrent vocal fold leukoplakia; Larynx; Malignant high-risk carcinoma.

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INTRODUCTION

Vocal fold leukoplakia (VFL) is characterized by white patches or plaques on the mucosal surface of the vocal folds [1]. It is estimated that less than 1% of the general population is affected by

the condition. However, higher incidence rates are reported among specific high-risk cohorts, such as tobacco smokers, alcohol consumers, individuals with high voice demands, and individuals with chronic laryngitis [2]. Furthermore, genetic studies showed that single nucleotide polymorphisms and altered protein expression levels were also found to play a significant role in the pathogenesis of VFL [3].

If left untreated, leukoplakia, a precancerous low-risk (non-dysplastic) lesion, can develop into a high-risk laryngeal cancer (squamous cell carcinoma) [4, 5]. The management of VFL

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can be influenced by a range of factors, including the patient's characteristics and the histopathological characteristics of the disease [6]. Therefore, histopathological examination of VFL is crucial in VFL treatment and prevention of potential recurrence, specifically among high-risk patients [5, 7]. Low-risk VFL can simply be treated by surgically removing the affected tissues, maintaining regular follow-up, and limiting exposure to risk factors [4, 8].

Recently, a novel approach to utilizing photoangiolytic lasers in in-office setups has proven effective in treating low to mild types of VFL through the ablative approach, which showed beneficial effects in preventing scarring as well as protecting voice quality [9]. In contrast, extensive surgical considerations and/or radiotherapy are mostly recommended for individuals with high-risk VFL, which involves malignant tissue transformation [10]. Moreover, studies have reported the highest VFL recurrence rates among patients with high-risk VFL [4, 11, 12].

The pathological nature of VFL is very important in predicting the long-term implications of the disease for patients [13]. Hence, it is critical to pay close attention to VFL that is accompanied by any form of atypical hyperplasia, as the disease has the potential to progress to a higher malignant grade and recur after treatment [14, 15].

Considering the absence of a unified medical agreement about the management and treatment of VFL, and the fact that most of our understanding regarding this condition comes from retrospective studies, it is imperative to examine the incidence and risk factors associated with VFL through prospective cohort investigation. Additionally, there is a lack of relevant local studies from Iraq on this issue, indicating a significant gap in understanding the disease within this population. Such studies would offer insightful information on improving patient outcomes and customizing treatment plans. So, the study's goals were to look into the demographic and clinical factors linked to VFL, the rate of VFL recurrence after surgery, and the development and recurrence of lesions during the follow-up period.

MATERIALS AND METHODS

In the current prospective cohort study, 85 adult patients with VFL were recruited from the Department of Otorhinolaryngology of Al-Diwaniyah and Al-Kut teaching hospitals from January 2019 to May 2023.

The study was approved by the ethical and scientific research committees at the Department of Surgery, College of Medicine, University of Wasit, Iraq, (No. 167) and at the Department of Surgery, College of Medicine, University of Al-Qadisiyah, Iraq, (No. 320) on January 7th, 2019, and January 16th, 2019, respectively. We formally informed the patients about the study's purpose and obtained written consent from all participants. Our patients' confidentiality was protected during the entirety of the study process.

Patients with whitish lesions on vocal cords that proved to be VFL on histopathological examination were enrolled in the present study. The exclusion criteria included patients with medical history or with current signs of laryngeal candidiasis, reflux laryngitis, chronic Reinke's edema, gastroesophageal reflux symptoms, or a compromised immune system. Additionally, patients who declined to participate were excluded.

All selected individuals underwent direct laryngoscope procedures under general anesthesia for VFL cold steel excision and biopsy sampling for histopathological examination. The

grading and severity of histopathological findings were interpreted by specialized pathologists at Al-Diwaniyah and at Al-Kut teaching hospitals, into five distinct features, "nondysplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma" according to Lee et al. [11]. High-risk patients who showed histopathological characteristics of severe dysplasia and malignant carcinoma were referred to the Department of Oncology to provide the appropriate intervention. The recurrence of VFL was assessed one-year following the surgical intervention. Figures 1 and 2 are two examples of our patients.

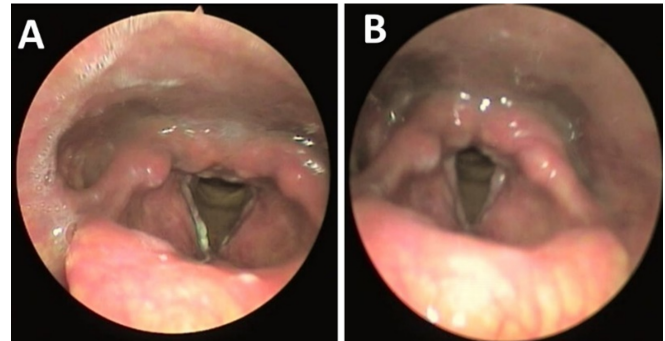


Figure 1. A 58-year-old gentleman with a history of smoking presented with vocal fold leukoplakia before (A) and after (B) surgical removal of the lesion.

Data processing for statistical evaluation and level of significance was performed on a statistical package for the social sciences (SPSS) software (version 28, IBM-USA). Power analysis was performed to determine the total sample size required for the study, where the power value was set at (0.80),

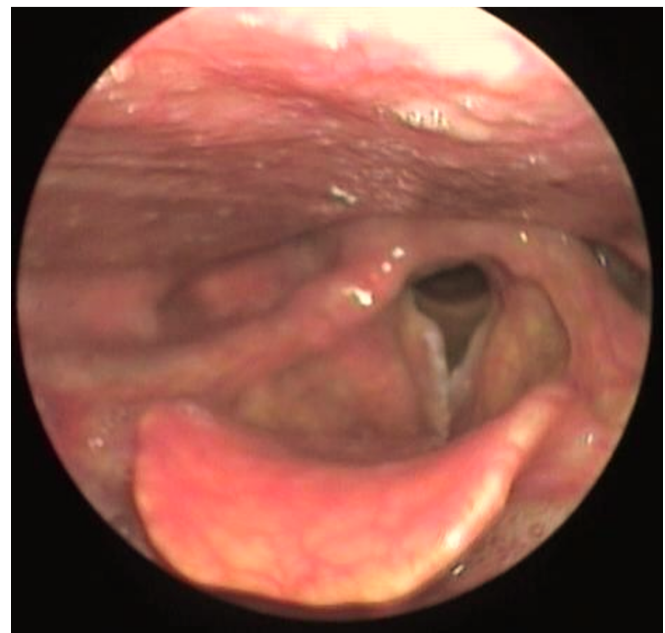


Figure 2. A 64-year-old male with a history of smoking presented with postoperative bilateral recurrent vocal fold leukoplakia. The lesion spanned the full length of the vocal folds.

the value of the effect size was (0.15), and there was a total of five independent predictors at a significance level of (0.05). To statistically examine the association between patient's characteristics and VFL recurrence after surgery, data variables were statistically evaluated by employing either a Fisher's exact test or Chi-square test (χ^2) for categorical variables or the following independent sample t-test for continuous data. Univariate and multivariate logistic regression was performed to assess the association between patients' prognostic factors and VFL recurrence. Odd ratio (OD) and 95% confidence interval (CI) were calculated to measure the strength of the association, and P-values of less than 0.05 was considered to be significant.

RESULTS

Of 85 patients with VFL, 29 (34.11%) revealed recurrence during a one-year follow-up. The study included a total of 85 patients diagnosed with VFL, comprising 67 men (78.8%) and 18 women (21.2%). All patients had a mean age of 60.8 ± 7.8 years (age range of 39 to 74 years). Histopathological findings acquired from direct biopsies of the vocal folds showed various degrees of dysplastic developments, specifically in patients with a severe form of dysplasia ($n = 19$, 22.4%), and malignant carcinoma ($n = 19$, 22.4%). Fifty-one (60%) patients were tobacco smokers, and 48 (56.5%) had bilateral VFL (Table 1).

Results showed that patients' demographic variables such as, sex, age, and tobacco smoking did not present a significant association with VFL recurrence (P-value > 0.05). However, high-risk histopathological findings (Severe dysplasia and carcinoma), as well as bilateral VFL (with involvement of the anterior commissure) were the only factors that were significantly (P-value = 0.001 and 0.012, respectively) associated with recurrence post treatment (Table 1).

Univariate analysis revealed that high-risk histological findings (OR: 8.590, 95% CI (3.049-24.206), P-value = 0.001), and bilateral (with involvement of the anterior commissure) VFL (OR: 3.626, 95% CI (1.335-9.854), and P-value of 0.012) were related to VFL recurrence. Moreover, multivariate analysis showed high-risk histological grade of VFL lesion was the independent prognostic factor (OR: 1.465, 95% CI (2.499-35.775), P-value = 0.001) that can predict VFL recurrence post treatment. However, sex, age, smoking status, and side of VFL (with involvement of the anterior commissure) did not present any significant prognostic ability following the same analysis (Table 2).

DISCUSSION

Vocal fold leukoplakia is characterized by white patches on the mucous membranes of the vocal cords. This condition is of particular concern since it might indicate the existence of pre-malignant alterations [1]. The disease also presents clinical difficulty due to the inherent limitations of standard diagnostic procedures and the lack of comprehensive knowledge regarding prognostic classifications [8]. Therefore, early diagnosis and effective treatments are imperative in preventing the development of laryngeal cancer. Furthermore, no available reports from Iraq have specifically investigated this condition among Iraqis or examined how patients' demographic and clinical characteristics can be used to predict VFL recurrence. Such information is crucial for understanding the context of VFL in at least this specific group of individuals.

The current analysis first examined the histopathological features of the collected VFL lesions in the study group and found that nearly half of the patients ($n = 38$, 48%) were diagnosed with the high-risk pathological grade (severe dysplasia and carcinoma) of the disease. The extent of the lesion and the degree of dysplastic tissue transformation are primary factors that could influence VFL recurrence [11]. Indeed, high-risk histopathological changes that are associated with poor prognosis were found to have a positive correlation with VFL recurrence. Comparable outcomes have been reported in various studies [2, 13]. However, even lesions defined as having no dysplasia or mild dysplastic changes were found to be associated with an elevated risk of developing carcinoma and recurrence in the later stages of the disease [5]. The current analysis supports these findings, showing that 6.9% of nondysplasia lesions and 10.3% of mild dysplasia lesions recurred over the follow-up period. These data emphasize the crucial requirement for careful observation and subsequent action in patients with even milder types of dysplasia, since detecting and intervening early can greatly influence long-term results.

Due to the reported recurrent nature of VFL and its ability to transform from a low-risk beginning lesion to a highly invasive laryngeal cancer [12], our patients were followed up for one year after surgery. Our results presented effective clinical responses to the surgical removal of VFL after the follow-up period, and that was recorded in 56 patients, compared to 29 patients who presented with symptoms of VFL recurrence. Cui et al. (2016) reported a similar rate of recurrence and found the site of the lesion (bilateral, - with involvement of the anterior commissure), among other factors, to increase the likelihood of lesion relapse [16]. Others, in contrast, reported relatively lower incidence rates of lesion recurrence after surgery compared to our findings [2, 4].

Moreover, the statistical analysis presented a significant association between high-risk histopathological grades and the site of lesion (bilateral - with involvement of the anterior commissure) to VFL recurrence. Univariate analyses revealed that histopathological grade and site of lesion can be used as reliable predictors for the recurrence of VFL. In multivariate analysis, however, the site of the lesion was found not to be considered as an independent prognostic factor for recurrence. Only the histopathological grade of tissue biopsies presented a significant correlation in this regard. In line with these findings, studies by Kizil et al. (2012) and Yang, et al. (2016) reported a significant association between VFL high-risk carcinoma and VFL recurrence post-surgery [17]. Lee et al. (2014) demonstrated a strong association between the degree of dysplasia and the risk linked to recurrence [11]. These findings are clearly state that surgical removal of VFL is not completely risk-free, and long-term follow-up is still required.

Several risk factors can play a significant role in the progression and recurrence of VFL, such as sex, age, tobacco smoking, alcohol consumption, voice abuse, and genetic predisposition [2, 3, 11]. Many studies widely recommend monitoring these factors for their prognostic significance [11, 18]. In our analysis, sex and age did not present significant contributions to recurrence. These findings align with the previous report [11] and contradict others who indicated a strong relationship between being male and old age and recurrence after treatment [6, 15]. On the other hand, studies by Lee et al. (2015), Li et al. (2021), and Pietruszewska et al. (2021) reported a higher prevalence of VFL among men compared to women [13, 18, 19], also men, were found to be at higher risk for developing laryngeal tissue transformation [20]. The

Table 1. Demographic and clinical characteristics of 85 patients were presented as counts (%) according to recurrent vocal fold leukoplakia after one-year of surgical removal of the lesion *.

Patients' characteristics		Total Count(%)	VFL recurrence		P-value
			No Count (%)	Yes Count (%)	
Sex	Female	18 (21.2%)	14 (25.0%)	4 (13.8%)	0.275†
	Male	67 (78.8%)	42 (75.0%)	25 (86.2%)	
Age (Years)		60.80 ± 7.85	60.70 ± 7.44	61.00 ± 8.71	0.867‡
Smoking	No	34 (40.0%)	25 (44.6%)	9 (31.0%)	0.252†
	Yes	51 (60.0%)	31 (55.4%)	20 (69.0%)	
Histopathology	Nondysplasia	16 (18.8%)	14 (25.0%)	2 (6.9%)	0.001§*
	Mild dysplasia	14 (16.5%)	11 (19.6%)	3 (10.3%)	
	Moderate dysplasia	17 (20.0%)	15 (26.8%)	2 (6.9%)	
	Severe dysplasia	19 (22.4%)	7 (12.5%)	12 (41.4%)	
	Carcinoma	19 (22.4%)	9 (16.1%)	10 (34.5%)	
Side of VFL	Unilateral	37 (43.5%)	30 (53.6%)	7 (24.1%)	0.012†*
	Bilateral	48 (56.5%)	26 (46.4%)	22 (75.9%)	

* Significant at P-values <0.05, † Fisher's exact test, ‡ t-test for independent samples, § Chi-square test.

Table 2. Univariate and multivariate logistic regression analysis of patients' prognostic factors for vocal fold leukoplakia recurrence *.

Patients' characteristics	Univariate			Multivariate		
	Odd ratio	95% CI	P-value	Odd ratio	95% CI	P-value
Sex / Male	2.083	0.617-7.032	0.237	1.666	0.425-6.521	0.464
Age (Years)	1.005	0.949-1.065	0.865	1.015	0.952-1.083	0.646
Smoking / Yes	1.792	0.695-4.619	0.227	0.516	0.132-2.013	0.341
Histopathology / High-risk (Severe dysplasia and Carcinoma)	8.590	3.049-24.206	0.001*	1.465	2.499-35.775	0.001*
Side of VFL / Bilateral (with involvement of the anterior commissure)	3.626	1.335-9.854	0.012*	0.106	0.374-5.730	0.583

* Significant at P-values < 0.05.

exact mechanism remains enigmatic. However, it could be related to these studies that men are more likely to practice harmful habits or get exposed to substances that can affect their general health, such as smoking cigarettes, voice abuse, and consuming alcohol, which is widely considered the most common risk factors shared among patients with VFL.

Furthermore, findings from our study did not correlate smoking tobacco to the recurrence of the disease after surgery. Contradicting reports from several studies described smoking as a significant risk factor associated with VFL progression and VFL recurrence as well [21]. This might be related to the relatively smaller cohort size included in the current study. The specific mechanisms through which smoking contributes to the development of VFL and the recurrence of the lesion are still poorly understood. In cases with general oral leukoplakia, frequent smoking was found to negatively impact the epithelium mucosa of the mouth, resulting in cellular morphological changes, that on examination, appear as tissue thickening and pigmentation [22]. Numerous studies have demonstrated that VFL is not exclusively associated with conventional cigarette smoking methods. Studies showed that smokers of e-cigarettes are also suffering from the negative impact of e-smoking on their vocal folds health [23].

On the other hand, the reversible nature of leukoplakia is

probable and highlighted by many studies, specifically following early diagnosis and mitigating risk factors. If not, VFL possesses the capacity to progress into a more advanced condition that may not be susceptible to medication [24].

To our knowledge, this is the first prospective cohort report examining risk factors associated with VFL recurrence after surgical removal of the lesion. However, the study encompasses several limitations that are important to be mentioned. Although the study included 85 patients, a larger sample size is recommended for better estimation of the disease incidence and severity, specifically among Iraqis. In addition, a nationwide sample collection from various geographical regions of Iraq will account for additional risk factors that were not included in the current study, such as genetic backgrounds, environmental factors, and lifestyle factors that could impact the incidence and characteristics of VFL. Moreover, the one-year follow-up period of post-surgical treatment may be deemed to be quite short. A longer follow-up period is required for future studies to thoroughly examine further risk factors related to VFL recurrence. This approach will yield a more comprehensive understanding of the pathophysiology of VFL and will improve the accuracy of risk assessment associated with progression and postoperative recurrence.

CONCLUSION

The study suggests that bilateral VFL lesions and the histopathological grade of the disease are significant risk factors that can be employed to predict lesion recurrence over time. These factors were found effective in predicting VFL recurrence over time. Therefore, regular checkups and follow-up care are important for every case diagnosed with VFL. These measurements are important for improving the long-term results and general health of patients. It is highly recommended for those at risk of developing VFL to embrace a healthy lifestyle by minimizing exposure to risk factors that could potentially lead to life-threatening conditions.

ETHICAL DECLARATIONS

Acknowledgments

We extend our sincere appreciation to every participant in the study.

Ethics Approval and Consent to Participate

The study was approved by the ethical and scientific research committees at the Department of Surgery, College of Medicine, University of Wasit, Iraq, (No. 167) and the Department of Surgery, College of Medicine, University of Al-Qadisiyah, Iraq, (No. 320) on January 7th, 2019, and January 16th, 2019, respectively. Patients were formally informed

about the purpose of the study and written consents were obtained from all participants. Our patients' confidentiality was protected during the entirety of the study process.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data are available upon reasonable request from the corresponding author.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Abd Ali MS was responsible for the design and implementation of the study, patients' selection, data collection and analysis, patient follow-up, and writing of the manuscript. Osama Awaad Ali OA was responsible for the design and implementation of the study, patients' selection, data collection, patient follow-up, and writing the manuscript. Both authors read and approved the final version of the manuscript.

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