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Assessment of Serum Carcinoembryonic Antigen (CEA) as Tumor Marker in Oral Leukoplakia

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Abstract **Original Research Article**

Background: Oral cancer is a major concern in Bangladesh, often diagnosed late. Among various predisposing factors, potentially malignant lesions such as oral leukoplakia contribute to its development. This study assessed serum Carcinoembryonic Antigen (CEA) as a tumor marker in oral leukoplakia for early detection and malignancy risk evaluation. ***Aim of the study:*** The aim of the study was to assess serum Carcinoembryonic Antigen (CEA) as a tumor marker in oral leukoplakia. ***Methods:*** This prospective observational study, conducted at Bangabandhu Sheikh Mujib Medical University and Bangladesh Multicare Hospital, Dhaka, Bangladesh from July 2018 to June 2019, enrolled 30 oral leukoplakia patients. Serum CEA levels were measured using ELISA from venous blood samples. Data were analyzed using SPSS, with continuous variables as mean ± SD and categorical variables as frequencies. Group comparisons used the t-test and chi-square test, with $p < 0.05$ considered significant. ***Results:*** This study evaluated serum CEA levels in 30 oral leukoplakia patients, finding 60% had normal levels (<3.5 ng/mL), 23.3% borderline (3.5–5.0 ng/mL), and 16.7% elevated (>5.0 ng/mL). Elevated CEA levels were significantly linked to tobacco use, severe leukoplakia, and moderate-to-severe dysplasia ($p < 0.001$). Malignant transformation risk increased with CEA levels: 11.1% in normal, 42.9% in borderline, and 80% in elevated cases, suggesting CEA as a potential biomarker for disease severity and progression in oral leukoplakia. ***Conclusion:*** Elevated serum CEA levels are strongly associated with disease severity and malignant transformation in oral leukoplakia, highlighting its potential as a biomarker for early intervention and improved patient outcomes.

Keywords: Carcinoembryonic Antigen, Tumor Marker, Oral Leukoplakia.

INTRODUCTION

Oral cancer, ranked among the top 10 most common cancers worldwide, represents a significant public health challenge, particularly in Bangladesh, where it is often diagnosed in advanced stages, resulting in poor outcomes and high treatment costs.[1] The majority of oral cancers are squamous cell carcinoma (SCC), which accounts for approximately 90% of oral malignancies and has a five-year survival rate of around 50%.[2] Given the accessibility of the oral cavity for visual inspection, early detection is possible through the examination of clinically identified precursors such as leukoplakia, erythroplakia, and oral submucous fibrosis. Oral leukoplakia, the most common oral premalignant lesion, is strongly linked to tobacco use, including both smoking and chewing. Research indicates that individuals who chew tobacco (betel quid or pan) or smoke have a higher incidence of leukoplakia, with tobacco chewing being a particularly significant risk factor.[3] While alcohol consumption is a recognized risk factor for oral cancer, its specific role in the development of oral leukoplakia remains uncertain.[4] There is considerable potential for early intervention through lifestyle changes, particularly the cessation of tobacco use, which studies have shown can result in the regression of oral leukoplakia.[5]

Despite significant advancements in understanding the clinicopathological risk factors for oral squamous cell carcinoma (OSCC), such as tobacco use—especially smokeless tobacco—and human papillomavirus (HPV), effective management strategies remain inadequate.[6-9] OSCC predominantly affects the middle-aged working population, leading to high morbidity, mortality, and substantial socioeconomic burdens. The estimated global prevalence of leukoplakia is 2.6%, with a malignant transformation

rate of approximately 12.1% over an average of 4.3 years.[10] Clinically, leukoplakia diagnosis relies heavily on physician experience, yet diagnostic accuracy remains low, ranging from 0.7% to 1.2%. The conventional biomarker, squamous cell carcinoma antigen (SCCA), exhibits poor sensitivity (<40%), underscoring the urgent need for improved diagnostic markers.[11,12] Recent research has explored proteomics and cytokine panels for better prognosis prediction, highlighting the importance of enhanced diagnostic tools.[13,14]

Carcinoembryonic antigen (CEA), a well-established tumor marker in colorectal cancer, has been investigated for its potential role in oral cancers.[15] In oral leukoplakia and OSCC, CEA's potential as a biomarker lies in its ability to detect malignant transformation, offering a non-invasive method for monitoring at-risk patients. If validated through further studies, CEA could help bridge the gap in early detection strategies, improving outcomes for patients with oral premalignant and malignant lesions. Biomarkers play a crucial role in predicting the malignant transformation of oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC), aiding in early diagnosis, treatment response assessment, and metastasis detection. Given these advancements, exploring carcinoembryonic antigen (CEA) as a potential biomarker could provide valuable insights into the early detection and progression of oral cancers, potentially improving diagnostic accuracy and patient outcomes.

Despite significant progress in identifying biomarkers for oral cancers, there remains a lack of reliable indicators to predict which oral leukoplakia lesions will undergo malignant transformation. While various biomarkers have been explored, CEA has yet to be thoroughly investigated as a diagnostic and prognostic tool in oral leukoplakia. The purpose of this study was to assess serum Carcinoembryonic Antigen (CEA) as a potential tumor marker in oral leukoplakia, aiming to explore its role in early detection and risk assessment for malignant transformation.

OBJECTIVE

- The aim of the study was to assess serum Carcinoembryonic Antigen (CEA) as a tumor marker in oral leukoplakia.

METHODOLOGY & MATERIALS

This prospective observational study was conducted at the Department of Oral & Maxillofacial Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, in collaboration with Bangladesh Multicare Hospital, Dhaka, Bangladesh. The study was carried out over a period of 12 months, from 01 July 2018 to 30 June 2019. A total of 30 patients with clinically diagnosed oral leukoplakia were enrolled in the study.

Inclusion Criteria:

- Patients aged 18–70 years with clinically diagnosed oral leukoplakia.
- Willingness to provide informed consent.

Exclusion Criteria:

- Patients with a history of other malignancies or systemic inflammatory conditions.
- Patients with recent infections or those undergoing treatment for oral lesions.

Written informed consent was obtained from all participants prior to inclusion. Demographic and clinical characteristics, including age, gender, tobacco use, lesion site, and severity of leukoplakia (categorized as mild or severe based on clinical examination and histopathological findings), were collected through patient interviews and clinical examinations. Venous blood samples (5 mL) were collected under aseptic conditions, and the serum was separated by centrifugation and stored at -20°C until further analysis. Serum levels of Carcinoembryonic Antigen (CEA) were measured using a commercially available ELISA kit, following the manufacturer's instructions, and the results were categorized as normal (<3.5 ng/mL), borderline elevated (3.5–5.0 ng/mL), and elevated (>5.0 ng/mL). Data were analyzed using SPSS version 25.0, with continuous variables expressed as mean ± standard deviation (SD) and categorical variables presented as frequencies and percentages. Group comparisons were performed using the student's t-test for continuous variables and the chi-square test for categorical variables, with a p-value < 0.05 considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics of the Study Participants (n=30)

Variable		Frequency (n)	Percentage (%)
Age (years)	40–49 years	3	10.0
	50–59 years	10	33.3
	60–69 years	8	26.7
	≥70 years	9	30.0
Gender	Male	17	56.7
	Female	13	43.3
Tobacco use	Users	21	70.0
	Non-users	9	30.0
Lesion site	Tongue	2	6.7
	Buccal	20	66.7
	Hard Palate	2	6.7
	Retromolar Trigone	3	10.0
	Tongue & Buccal	3	10.0

Table 1 provides an overview of the demographic and clinical characteristics of the study participants. The majority of participants were aged 50–59 years (n=10, 33.3%) and ≥70 years (n=9, 30.0%). The sample included 17 males (56.7%) and 13 females (43.3%). Tobacco use was reported in 21 participants (70.0%), while 9 participants (30.0%) were non-users. Lesion sites were primarily located in the buccal mucosa (n=20, 66.7%), followed by the retromolar trigone and tongue & buccal (both n=3, 10.0%). The tongue (n=2, 6.7%) and hard palate (n=2, 6.7%) were the least affected sites.

Table 2: Serum Carcinoembryonic Antigen (CEA) Levels in Patients with Oral Leukoplakia (n=30)

CEA Level (ng/mL)	Patients (n)	Percentage (%)
< 3.5 (Normal)	18	60.00%
3.5 – 5.0 (Borderline Elevated)	7	23.30%
> 5.0 (Elevated)	5	16.70%

Table 2 summarizes the distribution of serum CEA levels among patients with oral leukoplakia. 18 patients (60.00%) had normal CEA levels (<3.5 ng/mL), 7 patients (23.30%) had borderline elevated levels (3.5–5.0 ng/mL), and 5 patients (16.70%) had elevated CEA levels (>5.0 ng/mL).

Table 3: Association of CEA Levels with Tobacco Use and Leukoplakia Severity

Variable		n	Mean CEA (ng/mL) ± SD	p-value
Tobacco use	Tobacco Users	21	4.13 ± 1.24	<0.001
	Non-users	9	2.11 ± 0.97	
Leukoplakia Severity	Mild Leukoplakia	18	2.50 ± 0.92	<0.001
	Severe Leukoplakia	12	5.10 ± 1.36	

Table 3 presents the mean CEA (Carcinoembryonic Antigen) levels (ng/mL) along with standard deviations in relation to tobacco use and leukoplakia severity. Tobacco users exhibited significantly higher CEA levels compared to non-users ($p < 0.001$). Similarly, patients with severe leukoplakia had markedly elevated CEA levels compared to those with mild leukoplakia ($p < 0.001$), indicating a potential correlation between increased CEA levels and disease severity.

Table 4: Correlation Between CEA Levels and Dysplasia Severity in Oral Leukoplakia

Dysplasia Grade	n	Mean CEA (ng/mL) ± SD	p-value
Mild/No Dysplasia	18	2.50 ± 0.92	<0.001
Moderate-to-Severe Dysplasia	12	5.10 ± 1.36	

Table 4 presents the relationship between dysplasia severity and serum carcinoembryonic antigen (CEA) levels in patients with oral leukoplakia. A significant increase in CEA levels was observed in moderate-to-severe dysplasia cases (5.10 ± 1.36 ng/mL) compared to mild/no dysplasia cases (2.50 ± 0.92 ng/mL), with a statistically significant difference ($p < 0.001$).

Table 5: Association Between CEA Levels and Malignant Transformation in Oral Leukoplakia

CEA Level (ng/mL)	Patients (n)	Malignant Transformation (n)	Malignant Transformation (%)
< 3.5 (Normal)	18	2	11.1
3.5 – 5.0 (Borderline Elevated)	7	3	42.9
> 5.0 (Elevated)	5	4	80.0

Table 5 illustrates the relationship between serum Carcinoembryonic Antigen (CEA) levels and the occurrence of malignant transformation in patients with oral leukoplakia. The data shows that higher CEA levels are associated with an increased risk of malignant transformation. Among patients with normal CEA levels (<3.5 ng/mL), 11.1% experienced malignant transformation. The percentage increased to 42.9% in patients with borderline elevated CEA levels (3.5–5.0 ng/mL), and reached 80.0% in those with elevated CEA levels (>5.0 ng/mL).

DISCUSSION

This study evaluates the potential of serum Carcinoembryonic Antigen (CEA) as a tumor marker in patients with oral leukoplakia. Oral leukoplakia, a potentially precancerous lesion, poses a significant risk for malignant transformation, making early detection crucial for timely intervention. The study explores the relationship between CEA levels and factors such as lesion severity, tobacco use, and dysplasia, shedding light on the potential role of CEA in predicting malignancy risk. The findings emphasize the importance of incorporating CEA testing as a supplementary diagnostic tool to improve patient outcomes and enable early intervention in high-risk cases.

In our study, the majority of participants were aged 50–59 years (33.3%), followed by those aged ≥70 years (30.0%), which is consistent with the findings of Pearson *et al*.[16], who also reported a higher prevalence of oral lesions in middle-aged and elderly individuals. This suggests that oral leukoplakia is more commonly diagnosed in older age groups, which may be attributed to cumulative exposure to risk factors over time. Regarding gender distribution, 56.7% of our participants were male, which aligns with Pearson *et al*.'s[16] findings of a male predominance in oral lesions, possibly due to higher rates of tobacco use and other environmental factors. Our study also found that tobacco use was highly prevalent, with 70.0% of participants reporting tobacco use, which is in line with the work of Hashibe *et al*.[17], who emphasized tobacco as a major risk factor for the development of oral lesions like leukoplakia. Furthermore, the buccal mucosa was the most common site for lesions (66.7%), mirroring the findings of Chang *et al*.[18], who observed a similar trend in the distribution of oral lesions. These similarities highlight the critical role of age, gender, tobacco use, and lesion site in the epidemiology of oral leukoplakia, underscoring the importance of early detection and intervention, particularly in high-risk populations.

In our study, 60.0% of patients had normal serum CEA levels (<3.5 ng/mL), 23.3% had borderline elevated levels (3.5–5.0 ng/mL), and 16.7% had elevated levels (>5.0 ng/mL). This distribution is in line with the findings of Zheng *et al*.[19], who observed a similar range of CEA levels in their patient cohort. The elevated serum CEA levels in a portion of participants point to its potential role as a biomarker, supporting its relevance in assessing the risk of malignant transformation in oral leukoplakia.

In this study, we observed a significant increase in CEA levels among tobacco users compared to non-users, with a mean CEA of 4.13 ± 1.24 ng/mL in tobacco users and 2.11 ± 0.97 ng/mL in non-users ($p < 0.001$). This finding aligns with the study by Rodriguez *et al*[20]., which reported a strong association between tobacco use and oral leukoplakia (OR = 3.49, 95% CI: 1.99, 6.19, $p < 0.001$), reinforcing the role of tobacco as a key risk factor in oral lesions. Additionally, we found a significant difference in CEA levels between mild and severe leukoplakia cases (2.50 ± 0.92 ng/mL vs. 5.10 ± 1.36 ng/mL, $p < 0.001$), suggesting that CEA may serve as a potential marker for disease severity. Rodriguez *et al*.[20] also highlighted the influence of risk factors like tobacco and HPV infection in oral leukoplakia progression, which supports the observed trend in our study. These results support the hypothesis that both tobacco use and the severity of oral leukoplakia are associated with elevated serum CEA, reinforcing the potential use of CEA as a biomarker for the diagnosis and prognosis of oral lesions in tobacco users.

In this study, we found a significant elevation in CEA levels in cases with moderate-to-severe dysplasia compared to those with mild/no dysplasia (5.10 ± 1.36 ng/mL vs. 2.50 ± 0.92 ng/mL, $p < 0.001$). This aligns with the findings of Amanti *et al*.[21], who reported a higher expression of CEA in dysplastic and neoplastic tissues, suggesting a progressive increase in CEA levels with worsening histopathological changes. The observed trend in our study supports the role of CEA as a potential biomarker for identifying high-risk oral lesions, reinforcing its diagnostic and prognostic value. Additionally, as seen in Amanti *et al*.'s[21] study, the significant association between CEA expression and dysplasia severity indicates that CEA may reflect the transition from premalignant to malignant states, underscoring its clinical utility in risk stratification.

In this study, we observed a significant correlation between serum Carcinoembryonic Antigen (CEA) levels and the occurrence of malignant transformation in oral leukoplakia patients. As shown in

Table 5, the percentage of malignant transformation increased with higher CEA levels. Among patients with normal CEA levels (< 3.5 ng/mL), only 11.1% (2 out of 18) experienced malignant transformation. In contrast, the proportion of malignant transformation rose to 42.9% (3 out of 7) in patients with borderline elevated CEA levels (3.5–5.0 ng/mL), and reached 80.0% (4 out of 5) in those with elevated CEA levels (> 5.0 ng/mL). These findings suggest that elevated CEA levels may be a useful biomarker for predicting the potential for malignant transformation in oral leukoplakia. The strong association between higher CEA levels and increased rates of malignant transformation underscores the importance of monitoring CEA levels in patients with oral leukoplakia, particularly those exhibiting borderline or elevated CEA levels, to identify those at higher risk for progression to malignancy.

Limitations of the study

This study had some limitations:

- The study was conducted in a selected tertiary-level hospital.
- The sample was not randomly selected.
- The study's limited geographic scope may introduce sample bias, potentially affecting the broader applicability of the findings.

CONCLUSION

This study demonstrates that serum Carcinoembryonic Antigen (CEA) levels are significantly elevated in patients with oral leukoplakia, particularly in those with severe disease, advanced dysplasia, and a history of tobacco use. The findings reveal a strong association between higher CEA levels and an increased risk of malignant transformation, with 80% of patients with elevated CEA levels (>5.0 ng/mL) progressing to malignancy. These results suggest that serum CEA may serve as a valuable biomarker for assessing disease severity and predicting malignant transformation in oral leukoplakia, providing a potential tool for early intervention and improved patient outcomes. Further studies with larger cohorts and longer follow-up periods are recommended to validate these findings.

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