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# Evaluation of Salivary CA 125 Antigen in Patients with Oral Cancer, Oral Potentially Malignant Disorders and in Comparison, with Healthy Controls - A cross sectional study

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## Abstract

**Background:** Oral squamous cell carcinomas (OSCC) account for more than 90% of all oral malignancies. The primary risk factors of significant concern are smoking and drinking alcohol, and their combined impact is greater than their individual effects. Oral potentially malignant disorders (OPMD) establishes clinical presentations that carry an increased risk to develop into OSCC. Achieving early detection of these conditions requires thorough examinations, where biopsy serves as the primary diagnostic tool for oral cancer. Recently, numerous studies have focused on early diagnosis and prognostic assessment of the disease through the analysis of serum and salivary biomarkers. Cancer Antigen 125 (CA 125) is one such biomarker, also known as Mucin 16, is a human protein encoded by the MUC16 gene. It is part of the mucosal glycoproteins family typically present on the cell surface of normal cells. CA 125 is secreted from cancer cell surfaces and can be detected in saliva or blood, serving as a significant cancer marker that may be increased in individuals with epithelial neoplasms like ovarian, breast, and oral carcinoma.

**Aim & Objectives**

- To estimate the salivary levels of CA 125 antigen in Individuals with OPMDs, OSCC and in healthy controls.
- To compare the estimated levels of CA125 antigen in Individuals with OPMDs, OSCC with healthy controls.
- To compare the estimated levels of CA125 antigen with histopathological stage of differentiation of OSCC.

**Materials and methods:** Totally, 45 cases separated into three categories, Group 1 – OSCC, Group 2 - OPMDs and Group 3 – Healthy controls which included 15 participants in each group. Saliva was collected from the subjects using the simple drooling method to obtain whole saliva. The saliva samples were centrifuged at 3000 rpm for 10 minutes. The concentration of CA 125 antigen was determined by using Quantitative sandwich ELISA (Enzyme linked immunosorbent assay) technique.

**Results:** Our study had highest salivary CA 125 antigen levels in OSCC group (7684.40U/L) and followed by OPMD group (4949.53 U/L) and lowest in healthy control group (3009.2U/L). The intergroup comparison of the concentration values was found to be statistically significant between the groups with the p value <0.001. In the present study in Oral cancer patients, the mean concentration was more in moderately differentiated OSCC and statistically significant differences between the type of differentiations against the concentration (p<0.001) were seen.

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**Summary and Conclusion:** Our study shows that there is significant increase in salivary CA-125 antigen levels in OSCC and OPMD group compared to healthy controls. The salivary levels of CA-125 antigen also shows significant increase among type of differentiation of OSCC particularly in moderately differentiated OSCC and OPMDs.

Thus, it can be inferred that salivary CA-125 antigen can be a potential diagnostic biomarker for Oral cancer and OPMD and comparing with healthy individuals. Further studies with larger cohorts are necessary to establish the clinical effectiveness of salivary CA 125 antigen in OSCC detection and malignant potential risk of OPMDs.

**Keywords:** Cancer Antigen 125; OPMDs; OSCC; Salivary biomarkers; MUC16

**Abbreviations:** Oral squamous cell carcinomas (OSCC), Oral potentially malignant disorders (OPMDs), Cancer Antigen 125 (CA 125).

## Introduction

Oral cancer is usually referred as squamous cell carcinoma of the lip, oral cavity and oropharynx, with a higher prevalence among males than females [1]. Head and neck cancers rank as the sixth most prevalent cancer globally and are the leading cancer type in developing nations [2]. According to Globocan 2020 which reveals that the carcinoma of lip and oral cavity accounts for about 377,713 new cases 177,757 deaths [3]. The most important risk factors are tobacco and alcohol consumption, which is likely to have a synergistic effect [4,5]. Oral potentially malignant disorders (OPMD) establishes clinical manifestations with a heightened likelihood of progressing into OSCC [5]. Commonly occurring OPMDs include leukoplakia, erythroleukoplakia, oral lichen planus (OLP), and oral submucous fibrosis (OSMF) [6].

Despite decades of research and development in managing oral cancer, the survival rates for treated cases have not still improved. In most of the countries, the 5-year survival rates remain under 50%, and approximately half of oral cancers are thought to originate from precursor lesions [7-10]. Hence, early diagnosis and appropriate management is essential for improving the survival rates of patients with oral cancer.

Achieving early detection of these conditions requires thorough examinations, where biopsy serves as the primary diagnostic tool for oral cancer. Recently, many studies have concentrated on the early detection and prognostic evaluation of the condition by examining biomarkers in both blood and saliva.

Saliva is a potent body fluid that mirrors the normal internal attributes and health status of an individual [11,12]. As a fluid with multiple components, the process of collecting saliva is convenient, safe, non-invasive, readily accessible, and possesses broader applications in both experimental research and clinical practice [13]. It proves particularly beneficial for conditions such as OPMDs and oral carcinoma lesions, as it maintains direct tactile interaction with these lesions [14].

The biomarkers for oral carcinoma found in saliva are categorized into biomarkers derived from proteins and RNA based [17]. There have been various biomarkers for cancer found in saliva, one such biomarker is CA 125, whose role as a biomarker is well established in other cancers like ovarian, breast, and oral carcinoma.It is crucial that these salivary diagnostic markers be developed, particularly for individuals who have OPMDs and oral cancer. Hence, the current study aims at evaluating the reliability of CA 125 antigen, as a diagnostic biomarker in OPMDs and OSCC.

## Aim

To evaluate the reliability of salivary expression of CA 125 antigen as a diagnostic biomarker in OPMDs and Oral cancers in comparison with healthy individuals.

## Objectives

- To estimate the salivary levels of CA 125 antigen in Individuals with OPMDs, OSCC and in healthy controls.
- To compare the estimated levels of CA125 antigen in Individuals with OPMDs, OSCC with healthy controls.
- To compare the estimated levels of CA125 antigen with histopathological stage of differentiation of OSCC.

## Materials and Method

This was a Prospective Case Control study on patients with OPMD and OSCC in comparison with healthy controls. Study subject recruitment was done from the outpatient department of private dental college from a South-Indian population in Chennai. Sample size calculation was done using G Power software. Totally, 45 patients divided into three groups consisting of 15 patients in each group were included under the study. The study was conducted for a period of 6 months. Random selection procedure was used to choose participants. This study was approved by the Ethical Committee.

### Inclusion criteria:

- Individuals with willingness to participate in the study
- Individuals with willingness to quit the habit that caused the disease.

### Group I: OSCC

- Patients with clinically and histopathologically diagnosed with OSCC.

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- **Group II: OPMD**

  Patients clinically diagnosed with OSMF.

  Patients with clinically and histopathologically diagnosed with lichen planus and leukoplakia.

- **Group III: Healthy individuals (control group)**

  Healthy individuals free of any habits and systemic disease.

### Exclusion criteria:

- Patients with history of ovarian cancer
- Pregnant and lactating women
- Currently undergoing or having undergone any form of definitive therapy for OSCC.
- Dry mouth syndrome and patient's inability to collect sufficient saliva samples on a reliable basis.

### Method:

- Individuals were clinically diagnosed by the principal investigator and two senior professors to confirm the diagnosis clinically.
- A detailed history of the habits and disease were elicited.
- Patient education and counselling regarding the habits were done.
- The nature of the study was explained to the patient and an informed consent were obtained.

Subjects was made to rinse their mouth with water and also strictly restrained from eating and drinking for at least one hour before sample collection. Saliva was collected from the subjects using the simple drooling method to obtain whole saliva. Individuals were asked to swallow first, and to collect the saliva in the mouth for 5 minutes without swallowing and expectorate it into a sterile - wide mouthed container. Refrigerating the samples immediately or freezing at or below -20°c and later transferred to laboratory. Then the samples were then centrifuged at 3000 rpm for 10min.

The supernatants were collected carefully using micropipette and then transferred to Eppendorf tubes and stored at a temperature of -20°c until unit analysis.

The CA 125 Estimation was done using Quantitative sandwich ELISA (Enzyme linked immunosorbent assay) technique.

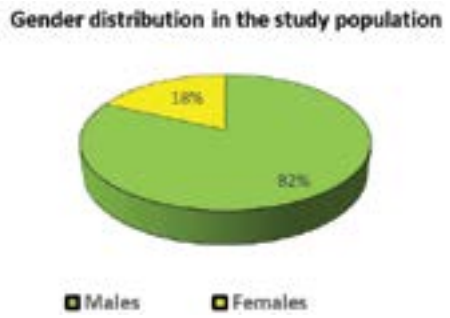
### Statistical analyses

The study data was entered in Microsoft Excel Spreadsheet and was subjected to statistical analysis using Statistical Package for Social Sciences (version 21, IBM, Chicago, USA). Categorical variables were expressed as numbers (n) and percentage (%). Continuous variables were expressed as Mean and Standard deviations. The data was subjected to normality test using Shapiro Wilk test. The level of significance was set at 0.05.

## Results

**Table 1:** Frequency distribution of gender

| Gender | | Frequency (n) | Percent (%) |
|---|---|---|---|
| Valid | Males | 37 | 82.2 |
| | Females | 8 | 17.8 |
| | Total | 45 | 100 |




**Graph 1:** Pie diagram representing the gender distribution

The frequency distribution of gender was given in table 1 and depicted in graph 1. The males constituted up to 37 (82%) and females constituted up to 8 (18%).

**Table 2:** Frequency distribution of diagnosis with respect to groups.

| Diagnosis among the study population | | Frequency (n) | Percent (%) |
|---|---|---|---|
| **Group 1** | Carcinoma of buccal mucosa and retromolar area | 2 | 13.33 |
| (OSCC) | Carcinoma of gingivobuccal sulcus | 2 | 13.33 |
| | Carcinoma of tongue | 7 | 46.67 |
| | Oral Squamous cell carcinoma of alveolus | 3 | 20 |
| | Oral squamous cell carcinoma of the soft palate | 1 | 6.67 |
| | Total | 15 | 100 |
| **Group** 2 (OPMDs) | Grade 4 OSMF | 5 | 33.33 |
| | Lichenoid dysplasia | 2 | 13.33 |
| | Oral Leukoplakia | 5 | 33.33 |
| | Oral Lichen planus | 3 | 20 |
| | Total | 15 | 100 |
| **Group 3** (Healthy controls) | Healthy | 15 | 100 |

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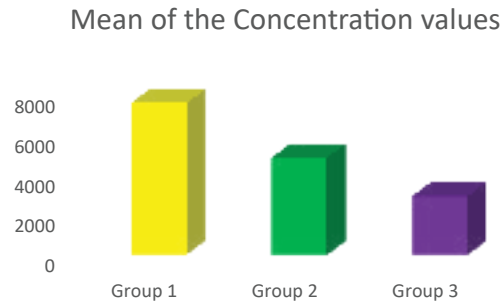
Frequency distribution of diagnosis with respect to groups was depicted in table 2. In group 1(OSCC), Carcinoma of buccal mucosa and retromolar area up to 2(13.3%), Carcinoma of gingivobuccal sulcus up to 2(13.33%), Carcinoma of tongue constituted up to 7 (46.67%), Oral Squamous cell carcinoma of alveolus constituted up to 3(20%), Oral squamous cell carcinoma of the soft palate constituted up to 1(6.67%).

In group 2(OPMDs), Grade 4 OSMF constituted up to 5(33.33%), Lichenoid dysplasia constituted up to 2(13.33%), Oral Leukoplakia constituted up to 5(33.33%), and oral lichen planus constituted up to 3(20%). In group 3(Healthy controls), all the 15 (100%) study people were healthy participants.

**Table 3:** Mean values of Concentration of CA 125 antigen among the study group.

| Groups | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| 1 (OSCC) | 15 | 6722 | 8833 | 7684.4 | 754.33005 |
| 2 (OPMDs) | 15 | 4194 | 5972 | 4949.5333 | 635.96944 |
| 3 (Healthy controls) | 15 | 2083 | 3777 | 3009.2667 | 473.79719 |




**Graph 3:** Bar graph depicting the mean values of the concentration of CA 125 antigen levels in each group.

**Table 4:** Intergroup comparison of Mean values of Concentration of CA 125 antigen levels with respect to each group.

| Concentration values | N | Mean | Std. Deviation | F value | P value |
|---|---|---|---|---|---|
| Group 1(OSCC) | 15 | 7684.4 | 754.33005 | 289.462 | <0.001*** |
| Group 2(OPMDs) | 15 | 4949.5333 | 635.96944 | | |
| Group 3(Healthy controls) | 15 | 3009.2667 | 473.79719 | | |

The mean values of concentration in group 1(OSCC), the mean values of concentration were 7684.40 ± 754.33, in group 2(OPMDs) it was 4949.53 ± 635.96, in group 3(Healthy controls), it was 3009.26 ± 473.79 (Table 3, Graph 3).

The concentration values were found to be more in group 1 - Oral cancer on comparison with other two groups. The concentration values of group 2 - OPMDs were found to be more than concentration values of healthy control group. The intergroup comparison of the concentration values was done among the three groups. It was found that there was a statistically very highly significant difference found between the groups (p<0.001). (Table 4)

The post hoc tukey's test was done for multiple comparisons with concentration values among the study groups. From the results, it was found out that there was a very high statistical significance observed for concentration of Oral cancer on comparison with other two groups. It was inferred that concentration values were higher for OSCC group than other two groups and this was found to be very highly statistically significant. (p value<0.001). The concentration values of OPMDs were found to be higher than healthy Control groups and this was also found to be very highly statistically significant. (p value < 0.001). It must be noted that, though concentration values of OPMD is more than healthy control group.

It was found that Group 1(OSCC) vs Group 2 (OPMDs), Group 1 (Oral cancer) vs group 3(healthy controls), group 2 (OPMDs) vs group 3 (healthy controls) was very highly statistically significant (p<0.001). (Table 5)

**Table 5:** Post Hoc tukey test for multiple comparisons with concentration of CA 125 antigen levels among the study groups

| (I) Groups | (J) Groups | Mean Difference (I-J) | Std. Error | P value |
|---|---|---|---|---|
| Group 1 (OSCC) | Group 2 (OPMDs) | 2734.86667* | 230.7432 | <0.001*** |
| | Group 3 (Healthy controls) | 4675.13333* | 230.7432 | <0.001*** |
| Group 2 (OPMDs) | Group 1 (OSCC) | -2734.86667* | 230.7432 | <0.001*** |
| | Group 3 (Healthy controls) | 1940.26667* | 230.7432 | <0.001*** |
| Group 3 (Healthy controls) | Group 1 (OSCC) | -4675.13333* | 230.7432 | <0.001*** |
| | Group 2 (OPMDs) | -1940.26667* | 230.7432 | <0.001*** |

The Mean values of concentration of Early invasive Squamous cell carcinoma was 6944 ± 156.97, Well-differentiated Squamous cell carcinoma was 7143 ± 380.66, Moderately differentiated Squamous cell carcinoma 8174.14 ± 651.15 and Verrucous carcinoma with severe dysplasia 8444. The intragroup comparison of the type of differentiation against concentration values in group 1 (Oral cancer) was done among the study group and it was found that there were very high statistically significant differences observed between the type of differentiations against the concentration (p<0.001). The most common pattern was moderately differentiated squamous cell carcinoma and mean concentration was increased in Moderately differentiated and Verrucous carcinoma with severe dysplasia. (table 6).

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## Discussion

Oral cancer is a significant global public health concern, with rising rates of both incidence and mortality worldwide. Males are often more affected compared to women due to increased consumption of chewing tobacco, alcohol, and smoking. Oral mucosal changes occur due to chronic consumption of tobacco-related products, leading to potentially malignant diseases and consequently, oral squamous cell carcinoma. Detecting cancer in its initial stages is crucial to mitigate morbidity and mortality associated with this condition. Conventional screening methods are essential in diagnosing oral cancer. Newer screening techniques are emerging to reduce the delay in the prediction of the condition, thereby facilitating the utilization of sensitive and specific biomarkers for screening, diagnosis, staging, and monitoring of this formidable malignancy.

**Bast et al** were the pioneers in the study of CA125, introducing it in 1981 [18]. They devised a radioimmunoassay for CA125 and discovered that over 80 percent of women diagnosed with ovarian cancer had higher levels of CA -125 in their blood compared to < 1% of healthy individuals. Subsequently, in 2001, the gene responsible for encoding CA125 was identified to be situated on chromosome 17 [19].

Salivary levels of CA 125 are observed in cases of OSCC, perhaps as a result of an increased discharge of cancer cells. It is more practical to use saliva because it is easier to collect and guarantees consistent and trustworthy findings. A further advantage is patient compliance, which can be used for mass screening [16].

The present study was intended to evaluate the reliability of CA 125 antigen in saliva as a diagnostic indicator for OPMDs and OSCC, comparing it with healthy controls.

In our study OSCC displayed a predominance among males. Similar findings were noted in previous studies by **Araft Ahmad et al** 2021 [22] in 56 subjects (75% were males and 25% were females), **Shumaila Younus et al** in 2018 [23] in 138 patients (78.3% were male and 21.7% were female), **Yadav Shw et al** 2018 [24] in 150 subjects (71 % were males and 29% were females) noted a greater frequency of males compared to females in their investigations. This observation may be attributed to the increased prevalence of tobacco consumption among males in contrast to females in the study.

Our study also observed a greater prevalence of males among individuals with OPMDs in the oral cavity. This aligns with other research indicating a notable male predominance of oral cancer having the highest incidence globally, similar to our findings [25]. **Yadav Shweta et al** 2018 [24] also observed a greater prevalence of males among individuals with pre-malignant and malignant lesions in the oral cavity which was in accordance to our study.

According to our study, the most prevalent site of carcinoma include tongue (46.6%) followed by alveolus (20%), buccal mucosa and retromolar area (13.3%), gingivobuccal sulcus (13.3%) and soft palate (6.67%). A study done by **Araft Ahmad et al** 2021 **[**21] revealed that the most frequent sites of occurrence were the buccal mucosa in 57.1% of cases, the tongue was affected in 26.7%, followed by the labial mucosa - 5.3%, the alveolar ridge - 5.3%, the palate - 3.6%, and the lips - 1.8% which was not in accordance to our study.

Similarly, **Shumaila Younus et al** in 2018 [23] found that the buccal mucosa was the most prevalent site in 58% of cases and **Balan et al in 2012** [16**]** observed that the frequently affected areas of OSCC were the buccal mucosa, tongue, palate, labial mucosa, floor of the mouth, and alveolar ridge which was also not in concordance to our study.

In the present study moderately, differentiated carcinoma (46.7%) was predominant which is in accordance to the study done by **Shumaila Younus et al** in 2018 [23] and **Araft Ahmad et al** 2021 [22] showed (43.5%) and 46.4 % of moderately differentiated OSCC cases were seen among the subjects.

Our study had highest salivary CA 125 antigen levels in OSCC group (7684.40U/L) and followed by OPMD group (4949.53 U/L) and lowest in healthy controls group (3009.2U/L). There was a statistically significant contrast between the concentration values when comparing within the groups, with a p-value of less than 0.001. The intergroup comparison of the concentration values was found to be statistically highly significant difference between the groups with the p value <0.001 which is in accordance to the study done by **Araft Ahmad et al** [22] **2021** revealed that CA-125 level among OSCC patients averaged 428.5 ± 110.2 U/mL, whereas in the control group, it averaged 132.4 ± 58.6 U/mL and also showed elevated levels of salivary CA 125 in poorly differentiated SCC (514.2±132.6 U/mL), which was consistent with our study.

**Marieh Honarmand** 2021 [26] observed that the levels of Salivary CA125 levels in individuals with OSCC 18.96±4.01 (kU/L), OLP 16 ±1.87(kU/L), and controls 6.9±4.16 (kU/L) and they showed significant difference between the groups which was also in accordance to our study.

Similar study by **Balan et al** 2012 [16], assessed salivary CA 125 levels among OSCC patients were 320.25, while those in the control were 33.14 ($p<0.05$) which was in concordance to our study and **Yadav Shweta et al** in 2018 [24] showed that control group exhibited the lowest levels (33.0 mg/dl), followed by healthy tobacco users (296.67 mg/dl), individuals with precancerous lesions (809.64 mg/dl), and the highest levels were seen in patients with oral carcinoma (1362.2 mg/dl) these findings were in correlation with our study.

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**Shumaila Younus et al** in 2018 [23] measured CA125 levels in the saliva of OSCC patients yielded notable findings. Salivary CA125 levels in healthy individuals [29.8 ± 9.8 U/ml] were decrease as compared to the mean salivary CA125 levels in OSCC cases [413 ±154.8 U/ml and which was in accordance to our study.

Our study shows significant difference in the salivary CA 125 antigen levels in OPMDs compared to healthy controls group, which was not in concordance to the study done by **Geng XF et al** in 2013 [27] which did not show a significant variance in CA-125 levels between patients with non-neoplastic diseases and controls.

In the present study in OSCC patients, the mean concentration was more in moderately differentiated OSCC and Verrucous carcinoma with severe dysplasia and it was found statistically significant differences between the type of differentiations against the concentration ($p<0.001$). The reason for increased concentration in OSCC with moderately differentiated is due to the limited sample size with no poorly differentiated histopathological variety of OSCC in our study.

Apart from **Geng XF et al.** in 2013 [27] and **Marieh Honarmand** 2021 [26] study, we did not encounter any other research that investigated salivary CA125 levels in individuals with OPMDs. Our study is one of the pioneer studies which has seen the salivary CA 125 levels in OPMDs, levels of which has also significantly increased when compared to healthy controls.

The previous studies did not demonstrate the levels of CA 125 antigen concentration in OPMDs, however our study showed significant increase in the concentration of CA 125 antigen, and intragroup comparison with concentration was also statistically significant, simply implicating its importance which warrants oral physicians immediate intervention of these OPMDs.

## Summary and Conclusion

OSCC is a prevalent form of oral cancer characterized by malignant growths in the oral cavity, particularly in the squamous cells lining the mouth. Frequently, it is linked with factors like tobacco consumption, heavy alcohol intake, chewing betel quid. Treatment modalities for OSCC depend on various factors including the stage, location, and extent of the tumor. Treatment choices encompasses surgical, radiation therapy, chemotherapy, targeted therapy, or a blend of these strategies. Timely identification and swift intervention are vital for improving outcomes in OSCC patients. However, newer technologies like salivary biomarkers are emerging as promising tools for early detection, offering non-invasive and cost-effective screening methods. Our study aimed to investigate the potential of salivary CA 125 antigen as a diagnostic biomarker for OSCC compared to OPMDs and healthy controls. Through our analysis, we observed significantly elevated levels of salivary CA 125 in OSCC patients and OPMD individuals compared to healthy controls. This suggests the potential usefulness of salivary CA 125 as a diagnostic marker for OSCC.

To conclude, our study provides evidence supporting the utility of salivary CA 125 antigen as a potential diagnostic biomarker for OSCC and OPMD and comparing with healthy individuals. Further validation studies with larger cohorts are warranted to confirm these findings and establish the clinical utility of salivary CA 125 in OSCC detection and malignant potential risk of Oral Potentially Malignant Disorders.

## References

1. Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. European urology 53 (2008): 68-80.
2. Jeihooni AK, Jafari F. Oral Cancer: Epidemiology, Prevention, Early Detection, and Treatment. Oral Cancer-Current Concepts and Future Perspectives 18 (2021): 23-54.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 71 (2021): 209-249.
4. Badwelan M, Muaddi H, Ahmed A, et al. Oral Squamous Cell Carcinoma and Concomitant Primary Tumors, What Do We Know? A Review of the Literature. Current Oncology 30 (2023): 3721-3734.
5. Warnakulasuriya S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral oncology 102 (2020): 104550.
6. Piyarathne NS, Rasnayake RM, Angammana R, et al. Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors- A systematic review. Expert Review of Molecular Diagnostics 21 (2021): 789-807.
7. Sivapathasundharam B. Epithelial neoplasms of the oral cavity. Shafer's Textbook of Oral Pathology E-book 23 (2020): 146.
8. Glick M. Burket's oral medicine. PMPH USA (2015).
9. Kaur J, Srivastava R, Borse V. Recent advances in point-of-care diagnostics for oral cancer. Biosensors and Bioelectronics 178 (2021): 112995.
10. Sathiasekar AC, Mathew DG, Lal MJ, et al. Oral field cancerization and its clinical implications in the management in potentially malignant disorders. Journal of pharmacy & bioallied sciences 9 (2017): S23.
11. Guerra EN, Rego DF, Elias ST, et al. Diagnostic accuracy of serum biomarkers for head and neck cancer: A

Pattugayathri S, et al., Dent Res Oral Health 2024
DOI:10.26502/droh.0082

systematic review and meta-analysis. Critical reviews in oncology/hematology 101 (2016): 93-118.

12. Di Venere M, Viglio S, Cagnone M, et al. Advances in the analysis of "less-conventional" human body fluids: An overview of the CE-and HPLC-MS applications in the years 2015-2017. Electrophoresis 39 (2018): 160-178.
13. Uddin MK, Shirin T, Hossain ME, et al. Diagnostic performance of self-collected saliva versus nasopharyngeal swab for the molecular detection of SARS-CoV-2 in the clinical setting. Microbiology spectrum 9 (2021): e00468-21.
14. Panta P, Wong DT. Salivary biomarkers in oral cancer. Oral Cancer Detection: Novel Strategies and Clinical Impact 11 (2019): 265-295.
15. Panta P, Venna VR. Salivary RNA signatures in oral cancer detection. Analytical Cellular Pathology 1 (2014): 25.
16. Balan JJ, Rao RS, Premalatha BR, et al. Analysis of tumor marker CA 125 in saliva of normal and oral squamous cell carcinoma patients: a comparative study. J Contemp Dent Pract 13 (2012): 671-675.
17. Bast RC, Badgwell D, Lu Z, et al. New tumor markers: CA125 and beyond. International Journal of Gynecologic Cancer 15 (2005): 54.
18. Perez BH, Gipson IK. Focus on molecules: Human mucin MUC16. Experimental eye research 87 (2008): 400.
19. O'Brien TJ, Beard JB, Underwood LJ, et al. The CA 125 gene: an extracellular superstructure dominated by repeat sequences. Tumor Biology 22 (2001): 348-366
20. Nagler R, Bahar G, Shpitzer T, Feinmesser R. Concomitant analysis of salivary tumor markers- A new diagnostic tool for oral cancer. Clinical Cancer Research 12 (2006): 3979-3984.
21. Zhang KY, Liu CY, Hua L, et al. Clinical evaluation of salivary carbohydrate antigen 125 and leptin in controls and parotid tumours. Oral Diseases 22 (2016): 630-638.
22. Ahmad A, Ghaffar UB, Hiware SD, et al. A prospective study for Assessment of saliva CA-125 level in oral cancer patients. Age 30 (2020): 7.
23. Younus S, Younus N, Khan HM. Determination of CA 125 salivary level with clinicopathological characteristics in oral squamous cell carcinoma in Karachi. Asian Journal of Medicine and Health13 (2018): 1-9.
24. Shweta Y, Deherkar JA, Sangle AR, et al. Utility of salivary CA-125 and LDH as a tumor marker in oral malignancy. Group 2 (2018): 4-5.
25. Warnakulasuriya S. Causes of oral cancer–an appraisal of controversies. British dental journal 207 (2009): 471-475.
26. Honarmand M, Saravani R, Farhad-Mollashahi L, et al. Salivary Lactate Dehydrogenase, C-Reactive Protein, and Cancer Antigen 125 levels in patients with oral lichen planus and oral squamous cell carcinoma. International Journal of Cancer Management 14 (2021).
27. Geng XF, Du M, Han JX, et al. Saliva CA125 and TPS levels in patients with oral squamous cell carcinoma. The International journal of biological markers 28 (2013): 216-220.