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Salivary Chemerin in Oral Leukoplakia and Oral Squamous Cell Carcinoma: A Case-Control Study

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ABSTRACT

The objective of this study was to evaluate salivary levels of chemerin as early prognostic, diagnostic biomarkers for patients with oral leukoplakia and oral squamous cell carcinoma. Case control study was designed that included 20 patients with oral leukoplakia, 20 patients with oral squamous cell carcinoma and 20 were healthy controls. Salivary chemerin was analyzed using ELISA. Salivary chemerin levels were significantly higher in OSCC group than Oral Leukoplakia and healthy controls. The mean salivary in Group 2: Squamous Cell Carcinoma was 10.32 ng/mL as compared to Group 1:Oral Leukoplakia (8.41 ng/mL) and Group 3:Healthy controls (2.7180 ng/mL) with p value of 0.001. ROC curve revealed 100% sensitivity and 90% specificity in detecting early stage Oral squamous cell carcinoma. The cut off value of 9.66mg/mL was obtained in distinguishing oral squamous cell carcinoma from Oral leukoplakia. Salivary chemerin can be used as a diagnostic biomarker in detecting early stage oral squamous cell carcinoma and preventing the malignant transformation in precancerous stage (Oral Leukolapkia)
Keywords: *Salivary biomarker, chemerin, oral squamous cell carcinoma, oral leukoplakia*

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INTRODUCTION

OSCCs account for 40% of all cancers in Southeast Asia with approximately 4% in affluent developed countries [1]. Squamous cell carcinomas account for more than 90% of oral and pharyngeal cancers. In India, oral cancer is the most common cancer amongst men (16.1 % of all cancers). The Whites shows 58% survival rate of 5 years while it is 31% in blacks. The male to female ratio diagnosed with oral and pharyngeal cancer is 2:1, but as the age increases the ratio comes to 1:1. Carcinoma of the oral cavity begins as preneoplastic lesions in the form of inflammatory lesions such as leukoplakia, erythroplakia, and erythroleukoplakia. There is approximately a 5% - 17% risk and likelihood of malignant transformation of leukoplakia to squamous cell carcinoma. Some of the prominent clinical features such as alterations in host immunity, inflammation, angiogenesis, and metabolism have been seen in oral cancer. Various factors such as tumor-induced T-lymphocyte, granulocyte, and neoangiogenic responses in the local tumor microenvironment might be responsible for increased tumor growth and metastasis and decreased survival rates [2].

The capacity of tumour angiogenesis is another factor to take into account while thinking about tumour invasion. The development and dissemination of tumour cells depend on the process of angiogenesis. [3] Because the walls of newly created vessels in tumours are weaker than those of normal vessels, tumour cells can invade these vessels more easily, which opens the door for lymph node metastasis. One of the key steps in the transformation of epithelial dysplasia into OSCC is angiogenesis. Cancer is characterised by angiogensis, which is controlled by pro- and anti-angiogenic molecules, one of which is chemerin.The retinoic acid receptor responder 2 (RARRES2) gene, also known as tazarotene-induced gene 2, encodes the chemoattractant protein chemerin (TIG2). White adipose tissue, the liver, the lung, and immune cells all have high levels of the receptor for chemerin, CMKLR1. Chemerin binds to the ChemR23 receptor, which controls inflammation and functions as a chemotactic factor for macrophages and dendritic cells

[5-7]. Variants in genes responsible for angiogenesis were significantly associated with plasma chemerin levels, suggesting a functional correlation between chemerin and angiogenesis Chemerin is also widely overexpressed in several malignant tumors [8]. A possible biomarker for the detection of cancer is chemerin. Chemerin expression was seen to be down regulated in some tumours, whilst the levels of chemerin were seen to be up regulated in some cancer tissues. These discrepancies are most likely caused by the fact that different cancer types may express chemerin differently, which is a common occurrence in tumourbiology [9].

Since the entire saliva is a complex mixture made up of fluid produced by major, minor salivary glands, and gingival crevicular fluid, salivary diagnostics, which is non-invasively collected, is one of the emerging fields that uses nanotechnology and molecular diagnostics to help in the diagnosis of oral diseases. Therefore, early detection of oral squamous cell carcinoma can be crucial in halting the growth of precancerous lesions and avoiding invasive therapy [10]. Hence this study was done to estimate the salivary chemerin levels in patients with histologically proven Oral Leukoplakia and Oral Squamous Cell Carcinoma.

MATERIAL AND METHODS

The study sample comprised 60 individuals and was allocated into three study groups. 20 subjects were histologically diagnosed with Oral leukoplakia (Group 1), 20 with Oral squamous cell carcinoma (Group 2), and 20 were age and sex-matched subjects that comprised the control group (Group 3). All participants enrolled in the study were taken from the outpatient department of Oral Medicine and Radiology, Faculty of Dental Sciences, SGT University from June 2019 to June 2020. The study protocol was explained to the patients after whom informed written consent was obtained from them. A detailed clinical oral examination was done for each subject and all the details were entered in a proforma. Inclusion criteria include subjects clinically and histologically diagnosed with leukoplakia (homogenous and non-homogenous) and squamous cell carcinoma. Patients with any other systemic disease such as diabetes, obesity, hypertension, inflammatory disease, patient having any other cancer elsewhere in the body, autoimmune disorder and patient had not gone for surgery, chemotherapy or radiotherapy were excluded from the study. After clinical examination, patients were subjected to oral prophylaxis. Incisional biopsies were taken for all the lesions in order to confirm the clinical diagnosis. Patient was recalled after 7-10 days following oral prophylaxis.

For saliva collection, patients were told to sit in an erect posture, with the head bent down and the mouth was open to allow the unstimulated whole saliva to drip passively from the lower lip into a sterile container until the desired amount of saliva was collected which was then transferred to Eppendorf tubes (Draining method) [11]. Collection was made at a standard time, preferably between 9 am to 11 am to avoid diurnal variation. Visibly contaminated samples with blood were discarded. After collection, the salivary samples were immediately centrifuged for 2 min at 10,000×g and frozen at -80 °C until assayed.

The salivary levels of chemerin were evaluated using Human Chemerin ELISA. The kit consists of **s**tandards, controls, and samples were incubated in microtitration wells precoated with polycolonal anti-human chemerin antibody. The procedure was done as per the instructions mentioned.The absorbance of each well on a microplate reader was set to 450nm, preferably with the reference wavelength set to 630 nm (acceptable range: 550-650nm) was determined. Readings were subtracted at 630 nm (550-650nm) from the readings at 450 nm. The absorbance was read within 5 minutes of the final step.

RESULTS

The data was compiled, tabulated, and subjected to statistical analysis using SPSS (21.0 version). Shapiro Wilk test was used,(the p-value was less than 0.05). Therefore, bivariate analyses were performed using the nonparametric tests i.e Mann-Whitney U and Kruskal-Wallis test. The Chi-square test was used for categorical variables. The spearmen correlation coefficient was used to find an association between variables. Table 1 & 2 shows the demographic data of the subjects enrolled in the study. The mean age of patients with Oral leukoplakia was 46.8 years while the age of patients with OSCC was 43.9 years. Table 3 depicts the involvement of the site in which mandible alveolus was the most prevalent site in patients having squamous cell carcinoma. Table 4 depicts the comparison of mean salivary chemerin levels according to habits and maximum levels were reported in the group that consumed gutka. The mean salivary chemerin levels were 3.77 ng/ml, 2.05 ng/ml, 5.63 ng/ml, and 2.20 ng/ml in participants consuming bidi, cigarette, gutka, and hookah groups respectively

Table 5 shows the mean salivary chemerin levels and maximum levels observed in patients having squamous cell carcinoma (10.32 ng/ml with SD of 1.72) followed by patients with Oral Leukoplakia (8.41 ng/ml with SD of 0.94) and least levels were noted in the control group (2.71 ng/ml with SD of 0.57). On pairwise comparison of mean salivary chemerin levels among the groups, it was found to be statistically

significant with a p-value of 0.001. There was a strong positive linear significant correlation of salivary chemerin levels with histopathological grading of leukoplakia (Correlation coefficient of 0.803) and oral squamous cell carcinoma (Correlation coefficient of 0.863) and the p-value was found to be significant (Graph 1&2). The area under the ROC curve for chemerin levels and histopathological grading in Group 1 was found to be significant, 0.017* with an excellent measure of the accuracy of 0.941 with 97.6% sensitivity and 66.7% specificity (Graph 3). The cut-off value of 7.94 ng/mL was found. Similarly, the area under ROC curve for chemerin levels and histopathological grading in Group 2 was found to be significant with an excellent measure of the accuracy of 0.001* with 100% sensitivity and 90% specificity (Graph 4) and the cut-off value was 9.66ng/ml.

DISCUSSION

The sixth most frequent cancer worldwide, oral squamous cell carcinoma is one of the significant issues for global health [11]. A precancerous lesion exhibiting dysplasia always precedes oral squamous cell carcinoma (OSCC). According to the American Dental Association, "one of the most effective approaches for reducing the incidence and mortality of cancer has shown to be identifying white and red lesions that signal dysplasia and removing them before they develop to malignancy [12]." Unpredictable malignant transformation of a dysplastic lesion takes place over a few years, during which the lesion can be treated to stop the growth of oral cancer. Therefore, despite numerous advances in preventive measures, significant mortality and morbidity have been linked to a delay in the diagnosis of OSCC [13]. With advancements in technology, many non-invasive techniques such as liquid biopsy have been proposed as a new diagnostic aid for early diagnosis, prognosis, and follow-up of OSCC. Earlier extensive research has been done on various serum biomarkers in the early detection of OSCC such as adiponectin, VEGF, MMP-9, MMP-6, IL-6 etc. because there are quantitative changes happening in the serum before the morphological alterations are seen in the body during the tumor development [14].

Additionally, OSCC is solely linked to the oral microenvironment, resulting in close contact with the acidic biological substance known as saliva that is engaged in a number of physiological and pathological processes. The use of saliva in liquid biopsy offers various benefits over other specimens (tissue/serum) for OSCC diagnosis and management. Saliva is regarded as "the mirror of the body," reflecting any physiological or pathological change in the local microenvironment and distant sites of the body; (ii) it is a quicker, easier screening tool; (iii) it is cost-effective and can be used for a larger population; and (iv) it allows for the collection of larger volumes of samples for examination, the ability to repeat analysis with ease, and the ability to track OSCC over time [12, 15].

Several adipokines (such as leptin, resistin, apelin, visfatin, and chemerin) have been studied in cancer development. Chemerin is secreted from white adipose tissue (WAT) [16]. Chemerin is a recently identified adipokine and chemoattractant protein that serves as a ligand for the G-protein coupled receptors such as CMKLR1 (ChemR23), GPR1, and CCRL2. Chemerin (146 amino acid chain) which is an active form initially secreted as prochemerin (163 amino acid chain) gets activated by cleavage at the C terminal of the amino acid chain with the help of proteases [17]. It has an important role in chemoattraction of the innate cells that include: natural killer cells, macrophages, and dendritic cells; inflammation, glucose, and lipid metabolism and is responsible for tumor angiogenesis, invasion, differentiation, and progression. Chemerin promotes angiogenesis by increasing the activity of MMPs [18].

Chemerin has been found to have an important role in cancer progression. Chemerin receptors are expressed on malignant tumor cells and their expression is different in various types of cancer. The conversion of the premalignant lesion into malignancy depends on various factors and one such factor is angiogenesis as it serves as a pro-angiogenic molecule [4]. Earlier studies have used serum to evaluate the chemerin levels in various cancers. Limited data is present on the association of salivary chemerin levels in leukoplakia (homogenous and non-homogenous) and oral squamous cell carcinoma.

In the present study, the mean age in Group 1 was 46.8 years whereas in Group 2 was 43.9 years. This shows that the mean age of patients having oral squamous cell carcinoma was less than the mean age of patients with oral leukoplakia. In India, the use of hookah/ tobacco products has increased dramatically among the youth and considered as second global tobacco pandemic.[20]Using different vaping devices such as e-cigarettes became fun and fashionable and they have a similar sensation to smoking cigarettes. Studies on OCC (Oral cavity cancer) risk factors in younger patients have yielded mixed results.

In the present study, in Group 2, the most common site involved was the mandibular alveolus (N-7), followed by the lateral border of the tongue (N-2) and hard palate (N-2). Other sites involved were the Retromolar trigone area, buccal mucosa, the floor of the mouth, and lower labial mucosa. Similar results were reported byShenoi R et alin which mandibular alveolus was the most prevalent site and Tandon P et al found mandibular alveolus as the second most common site after buccal mucosa [22, 23].

On comparing the mean salivary chemerin levels according to habits among three groups, the participants who chewed gutka (5.63ng/mL) had the highest levels of chemerin. This is the first study in which type of tobacco usage is compared with salivary chemerin levels. One possible reason for the elevated levels of salivary chemerin in gutka chewers might be due to the increased amount of dry tobacco used in gutka, slaked lime, and areca nut. The chemical composition of these ingredients is highly genotoxic and cytotoxic and these substances are in contact with the oral cavity for a longer duration of time. The slaked lime which is mixed with tobacco causes an exothermic reaction in the buccal mucosa and makes buccal mucosa more susceptible to various carcinogens [24, 25].

The mean salivary chemerin levels were assessed and we found that salivary chemerin levels were elevated in Group 2: Squamous Cell Carcinoma (10.32 ng/mL with SD of 1.72) as compared to Group 1: Oral Leukoplakia (8.41 ng/mL with SD of 0.94) and Group 3: Healthy controls (2.7180 ng/mL with SD of 0.57).with a p-value of 0.001. The findings were in agreement with the study done byGhallab NA, and Shaker OG on OPMLs and OSCC. Ghallab in his study enrolled patients who had speckled leukoplakia, atrophic lichen planus, and actinic keratosis.[26] It is well established that speckled leukoplakia has the highest rate of malignant transformation but with the use of this salivary biomarker, we can detect the lesion at an early stage before it manifests in the oral cavity as biochemical changes precede the morphological alterations.

Wang N et al investigated the expression of chemerin in 19 SCOTT patients by immunohistochemistry and they observed a significant difference in chemerin expression between SCCOT and peritumoral tissues ($P<0.01$). Lu Z et alin their study concluded that serum chemerin levels were considerably greater in patients with OSCC than in healthy controls. The serum chemerin levels also increased with the advanced stage of the disease and the levels decreased after the tumor resection [27-28].

The reason for the higher expression of chemerin has been attributed to its tumor-promoting effects in which angiogenesis is one of the important steps.VEGF is regarded as a crucial component of angiogenesis because it stimulates endothelial cell motility, mitosis, and MMP production. Chemerin's ability to bind to the endothelial cells' CMKLR1 and increase the activity of MMP-2 and MMP-9 in these cells demonstrated its robust angiogenesis. In another study similar effect of chemerin on angiogenesis demonstrated that it mediated the formation of blood vessels to a similar extent as VEGF.[29]Chemerin increases migration, invasion, and proliferation in OSCC cells and the knockdown of chemerin receptor RARRES2 substantially inhibits tumorigenesis and metastasis in OSCC [28].

The mean salivary chemerin levels were also compared with histological grading of Oral Leukoplakia and Squamous cell carcinoma and we found there was a strong positive linear significant correlation between them with a correlation coefficient of 0.803 and 0.0863 respectively and to determine the accuracy of the salivary chemerin as a biomarker, ROC analysis was done and area under the curve (AUC) was calculated by using logistic regression analysis. Salivary chemerin showed AUC of 0.94 and 0.950 for Oral Leukoplakia and Oral Squamous Cell Carcinoma respectively. It showed 100% sensitivity and 90% specificity in distinguishing patients with oral squamous cell carcinoma from patients with oral leukoplakia with a cut-off value of 9.66gm/dl. The cut-off value of 7.94gm/dl was obtained in distinguishing oral leukoplakia from the healthy group with sensitivity and specificity of 97.6% and 66.7% respectively Lu Z et al observed sensitivity and specificity of serum chemerin (79.2% & 91.2%) respectively with a cut-off value of 60.35 ng/mL which was used to differentiate patients with OSCC from healthy controls.[28] A study done by Ghallabobtained 100 % sensitivity and specificity in distinguishing OSCC patients as well as patients with OPMLs from healthy controls [26]. So our study suggests that salivary chemerin can be used as one of the diagnostic tools in the early detection of oral cancer and can predict the malignant transformation in the pre-cancerous state i.e. leukoplakia.

CONCLUSION

Salivary chemerin can serve as a diagnostic biomarker in detecting the malignant transformation of the precancerous lesion (oral leukoplakia) to an advanced one as it shows 100% sensitivity and 90% specificity. Chemerin can serve as a novel approach in cancer treatment by inhibiting angiogenesis hence inhibiting the progression of cancer at early stages or useful in recognizing patients with malignant potential for early interventional modalities. Hence there is a need for more comprehensive studies with larger sample sizes to determine the diagnostic and prognostic value of salivary chemerin in oral squamous cell carcinoma.

Table 1: Gender wise distribution of study population

		Sex		Total
		F	M	
Group 1: Oral Leukoplakia	N	7 (35%)	13 (65%)	20
Group 2: Squamous Cell Carcinoma	N	5 (25%)	15 (75%)	20
Group 3: Healthy Controls	N	7 (35%)	13(65%)	20
P VALUE - 0.735				

Table 2: Comparison of mean age among three groups

	N	Mean (in years)	Std. Deviation
Group 1: Oral Leukoplakia	20	46.8000	11.88365
Group 2: Squamous Cell Carcinoma	20	43.9000	14.57792
Group 3: Healthy Controls	20	46.0000	5.58193
P VALUE – 0.706			

Table 3: Distribution of patients of Squamous Cell Carcinoma according to the site involved.

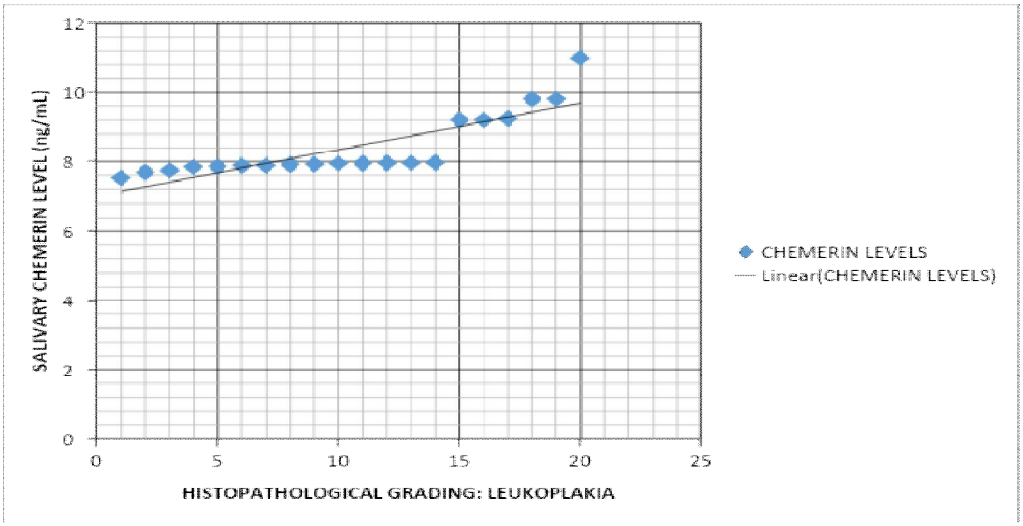
	N	%
Lower labial mucosa	1	5
Buccal Vestibule	1	5
Buccal mucosa, alveolus	1	5
Lower alveolus	7	35
Floor of mouth	1	5
Lateral border of the tongue	2	10
Oropharynx, Base of tongue	1	5
Retromolar trigone area	1	5
Rt Buccal Mucosa	1	5
Left buccal mucosa	1	5
Hard Palate	2	10
Soft palate	1	5
TOTAL	20	100

Table 4: Comparison of mean salivary chemerin levels according to habits among three groups

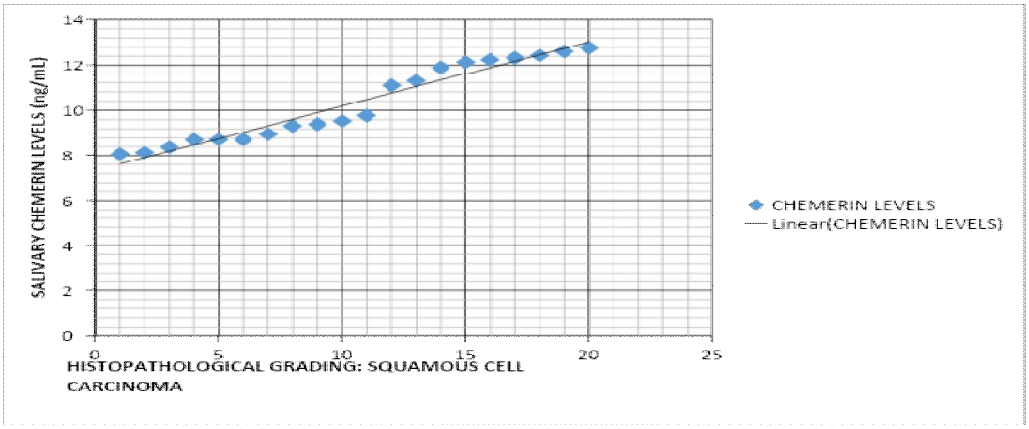
HABIT	N	MEAN (in ng/mL)	STD. DEVIATION	P VALUE
Bidi	19	3.7747	2.42623	0.038,SIG
Cigarette	7	2.0500	.71910	
Gutka	13	5.6377	3.45504	
Hookah	1	2.2000		

Table 5: Comparison of mean salivary chemerin levels among three groups

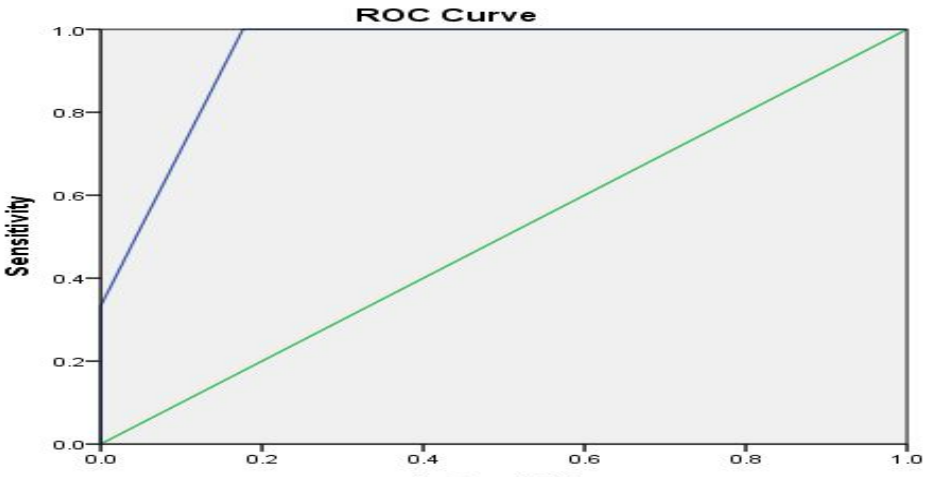
	N	Mean (ng/mL)	Std. Deviation	P Value
Group 1: Oral Leukoplakia	20	8.4105	0.94656	0.001*,SIG
Group 2: Squamous Cell Carcinoma	20	10.3275	1.72412	
Group 3: Healthy Controls	20	2.7180	0.57182	



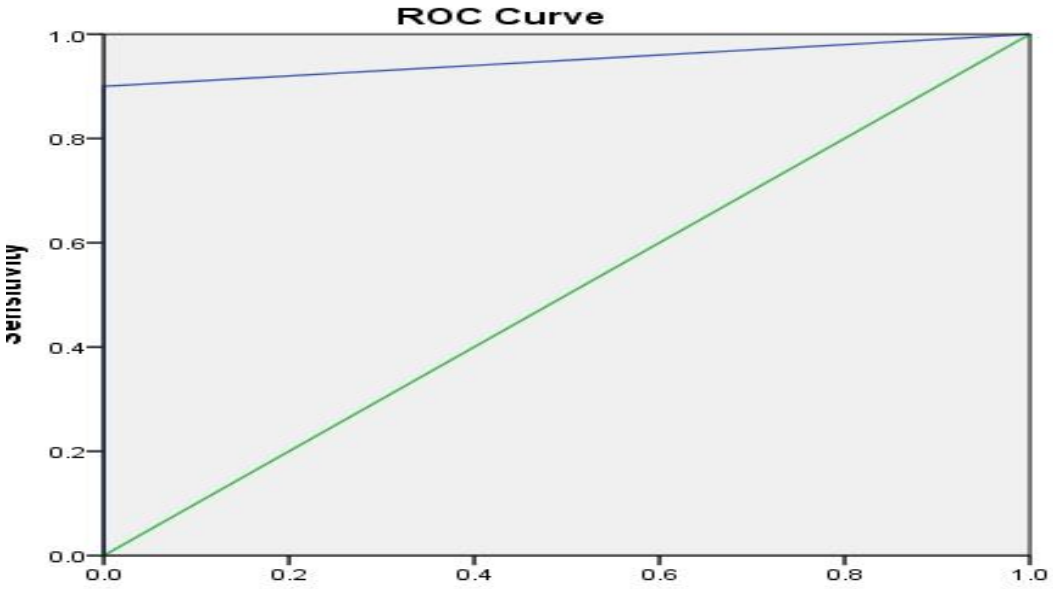
Graph 1: Correlation of chemerin levels of Group 1: Oral Leukoplakia with histo-pathological grading



Graph 2: Correlation of chemerin levels of Group 2: Squamous Cell Carcinoma with histopathological grading



Graph 3: ROC for Oral Leukoplakia



Graph 4: ROC for Oral Squamous Cell Carcinoma

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