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Immunohistochemical Evaluation of Cytokeratin 17 Expression in Oral Squamous Cell Carcinoma

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Abstract: Oral squamous cell carcinoma (OSCC), which makes up 80–90% of all malignant neoplasms of the mouth, is the most common type of oral cancer. Immunohistochemistry plays a crucial role in diagnostic pathology by aiding in identifying and classifying tumors IHC is utilized to study the distribution and localization of specific proteins. Identifying diagnostic markers for OSCC is essential for early diagnosis and patient-specific treatment. Cytokeratins (CK) are a family of intermediate filaments predominantly expressed in epithelial cells. The study aimed to evaluate immunohistochemical expression cytokeratin 17 in 50 cases of microscopically confirmed OSCC. The present study was observational, with retrospective and prospective sampling. The study was carried out for two years, from 2020 to 2022. The present study was designed to determine CK 17 expression by IHC and to correlate CK 17 expression with Broders grading of OSCC and other clinical pathologic parameters. Immunostaining for CK 17 was performed. The statistical analysis was done by chi-square test. In this study, there was a significant correlation between CK 17 expression and Broders grading, and CK 17, when correlated with other clinic pathologic parameters, showed no significant correlation. It was concluded that Cytokeratin17 expression could correlate with the Broders' Grading, thus contributing to early detection and more accurate determination of tumor aggressiveness to determine appropriate therapy.

Keywords: Oral Squamous Cell Carcinoma, Cytokeratin 17, Immunohistochemistry, Broders Grading, Clinicopathologic parameters.

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1. INTRODUCTION

A group of tumours called oral cancer can develop anywhere in the mouth, pharynx, or salivary glands. More than ninety percent of oral cancers are estimated to be OSCC-related. Despite advances in therapeutic methods, OSCC morbidness and fatality rates have remained mostly constant for the past thirty years. Men experience rates of morbidity and death of 6.6/100,000 and 3.1/100,000, respectively, whereas women experience rates of 2.9/100,000 and 1.4/100,000. According to current studies, oral carcinoma is a significant cause of cancer in some parts of India. [1]In contrast to other malignant tumours, OSCC has not seen a great increase in survival rates due to advances in detection and treatment. Oral squamous cell carcinoma is increasing in both incidence and mortality, with males experiencing a higher rate of death (6.6/100,000) and higher rates of morbidity (3.1/100,000) than females, which is 2.9/100,000 and 1.4/100,000 in women, are all on the rise. [2]Use of alcoholic beverages and tobacco products is a major risk factor. Seventy-five percent of all cases of oral cavity carcinoma are associated with tobacco use. Smokers are six times more likely than non-smokers to receive a mouth cancer diagnosis. Also, heavy drinkers have a six-fold higher chance of acquiring mouth cancer than social drinkers. Together Users of tobacco and alcohol are exposed to a risk of cancer 15 times that of non-users. [1] In some culturally predisposed populations, betel nut chewing may play a role along with alcohol and tobacco usage. [1]OSCC is common in older people, those from lower socioeconomic backgrounds, and those from some culturally biased groups. Other factors include the inability to repair mutagen-damaged DNA, metabolizing carcinogens, and impaired immunity. People with HIV, those with an organ transplant, and those on immunosuppressants are more prone to developing OSCC. [1] Consequently, it is necessary to perform a complete physical examination, including palpation of the lymph nodes, to make an accurate diagnosis. Diagnostic techniques such as vital staining, histology, immunohistochemistry (IHC), cytopathology, and molecular investigations are used. Histopathological analysis, however, is the pathologist's secret weapon for combating oral squamous cell cancer. [3]Squamous cell carcinomas of the head and neck are graded by various methods, including TNM classification, Broders' grading, Fisher, and various other systems.[4]Broders put forth a histological categorization for OSCC. In 1920, a classification system was established; by 1925, it had been broken down and examined based on cell differentiation. There are four distinct categories for carcinomas, numbered from one to four. grade I carcinomas (Well Differentiated) have up to 25% of undifferentiated cells. 25%-50% of the cells in grade 2 (moderately differentiated) are undifferentiated. In grade 3 (Poorly Differentiated), the percentage of undifferentiated cells is between 50 and 75 percent, while in grade 4 (Anaplastic), it's between 75 and 100 percent. [5]IHC markers are used since there is always some subjectivity involved in distinguishing between well-, moderately-, and poorly-differentiated carcinomas. immunohistochemistry can be used to detect and identify antigens using antigen-antibody interactions. It serves as a diagnostic tool in the field of histopathology. Immunohistochemistry is reliable enough to be used frequently. It is possible to use it to analyze data collected in the past from stored information. It works for molecules of any immunological origin and can be applied to any morphological metric. [6]In order to determine where an antigen is located in the body, both healthy and diseased, immunohistochemistry uses specific antibodies. Immunohistochemistry (IHC) is a widely used biological and medical research technique that combines immunological principles with histological staining. It involves using antibodies to detect specific antigens within tissue sections, allowing researchers to visualize the distribution, localization, and relative abundance of target proteins or molecules in situ. IHC has numerous applications across various fields, including.[7] OSCC is associated with high expression of cytokeratins, intermediate filaments of the cytoskeleton, compared to normal oral mucosa. The five-year survival rate remains 70-80% because the cancer is diagnosed very late and also due to resistance to chemotherapy or radiation therapy, despite advances in diagnostics and therapies like surgery, radiation therapy, and chemotherapy with the introduction of therapy, a combination of both. Therefore, it is crucial to identify diagnostic indicators of oral squamous cell carcinoma to enable early, accurate diagnosis and successful treatment of patients. OSCC is a serious disease; hence, discovering diagnostic markers is crucial. Although cancerization of normally differentiated epithelium can result in a wide range of phenotypes, biochemical investigations and immunohistochemistry have demonstrated that OSCC exhibits a more diverse set of Cytokeratins. [8] Type I Cytokeratins (CK) are either light in weight or acidic. In contrast, type 2 Cytokeratins are either heavy, basic, or neutral. Neutral cytokeratins have several subtypes, including starting CK 1 to CK 9. The cytokeratins from CK10 to CK20 are classified as acidic cytokeratins. [9] Cytokeratin 17 (CK 17) should be prioritized as a diagnostic marker of OSCC among CKs since it has been shown in numerous studies to be overexpressed in malignant tissues relative to normal tissues in squamous cell carcinoma. One form of basal cytokeratin is cytokeratin 17. This stain is present in many normal tissues, which include basal cells of the complex epithelium, myoepithelial cells of the breast, metaplastic cells of the cervix, and epithelium of the hair shaft. Basal cells of neoplastic tissues are positively stained for cytokeratin 17 (CK17). These include the skin tissue, breast tissue, CSIL, cholangiocarcinoma, premalignant changes of the larynx or SCC, pancreaticobiliary, SCC of head and neck, thyroid, and urothelial carcinoma. Gastric adenocarcinoma typically has a lack of staining. [10] Surface boundary cells, invading parabasal cells, and pearl nests of oral squamous cell carcinoma all express cytokeratin 17. [11] Broders are classified based on the degree to which their cells have differentiated. The expression of cytokeratin 17 is linked to histopathological grade, and it is demonstrated to be significantly higher in grades 1 and 4 than in grades 2, 3, and 4. It follows that Cytokeratin 17 expression decreases with tumour grade; however, it did not show any significant correlation between cytokeratin 17 immunohistochemical expression and clinicopathologic variables of OSCC.[8]The current study aims to establish a relationship between CK 17immunohistochemical expression and the histopathological grading of OSCC as well as other clinicopathologic parameters.

2. MATERIALS AND METHODS

The present study is described below for its material and methods.

2.1. Place of study

Department of Pathology, Jawaharlal Nehru Medical College, DattaMeghe Institute of Higher Education and Research (DMIHER), Sawangi (Meghe), Wardha, Maharashtra.

2.2. Duration of study

The study was carried out for 2 years period of 2020 to 2022.

2.3. Ethics clearance

The protocol was scrutinized by Institutional Ethics Clearance (IEC) and certified. The IEC number was DMIMS(DU)/IEC/2020-21/9266

2.4. Study Design

The Observational study design was adopted with prospective and retrospective sampling.

2.5. Sample Size

50 cases.

- Cases were confirmed on histological examination as OSCC was operated upon, and the resected specimens were received in the Departments of Histopathology in a ten percent neutral buffered formalin solution. The resected specimens were kept for overnight fixation (12 hours).
- Grossing of the specimens was done, and appropriate sections from the margins, tumor mass, and lymph nodes were taken.
- The resected specimens were put through routine tissue processing. After the processing, routine H & E staining was performed.
- The histopathological grade of the tumor was evaluated by employing the Broders grading system for squamous cell carcinoma.
- To determine CK 17 expression by IHC and to correlate CK 17 expression with Broders grading of OSCC and other clinic pathologic parameters, immunostaining for CK 17 was performed.

2.6. Methods

2.7. Immunohistochemistry

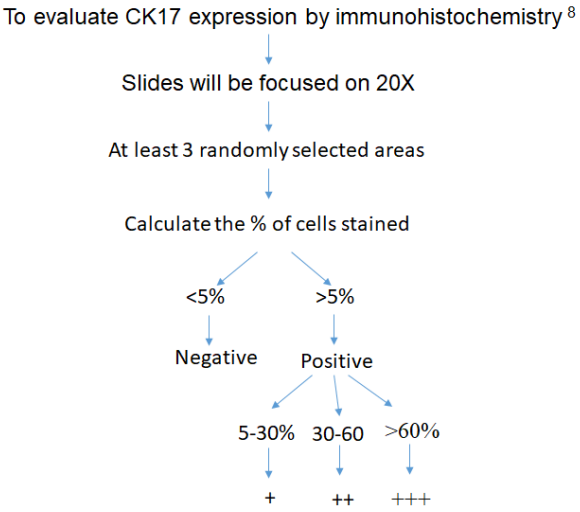
In brief, antigen sites were exposed by microwave heating in citrate buffer. Mouse monoclonal anti-cytokeratin 17 antibody (pathnsitu brand dilution 1:400) was used. The normal oral mucosa was employed as a negative control.

2.8. Immunohistochemical staining [12]

- Tissue Preparation: The tissue samples are first collected and fixed in formalin to preserve their structure. After fixation, the tissue is embedded in paraffin wax and cut into thin sections.
- Deparaffinization: Paraffin wax is removed from the tissue sections by immersing them in xylene or other similar solvents.
- Rehydration: The tissue sections are then rehydrated by passing them through a series of graded alcohols to remove any remaining solvents.
- Antigen Retrieval: The epitopes of the target protein are often masked by the fixation process. Antigen retrieval can be used to expose the target protein. This can be done by heat-induced antigen retrieval, enzymatic retrieval, or chemical retrieval.
- Blocking: The tissue sections are treated with a blocking solution, typically consisting of a protein such as BSA.
- Primary Antibody Incubation: The antibody cytokeratin Brand- Pathnsitu diluted 1:400 is applied at room temperature for 1 hour.
- Secondary Antibody Incubation: A secondary antibody labeled with an enzyme such as horseradish peroxidase (HRPis) is then applied to the tissue sections. This secondary antibody binds to CK 17
- Chromogenic Substrate: A chromogenic substrate, such as diaminobenzidine (DAB), is added to the tissue sections. The chromogenic substrate reacts with the enzyme-labeled secondary antibody to produce a visible color change.
- Counterstaining: To visualize the tissue morphology and to distinguish the different cell types, a counterstain, such as hematoxylin, is applied to the tissue sections.
- Mounting:
- Finally, the tissue sections are mounted on a glass slide with DPX, and a coverslip is placed over the section.

2.9. Analysis of Immunohistochemical Expression of CK17

Cells that showed brown color were treated as positive. To evaluate the expression of cytokeratin 17 by immunohistochemistry, slides will be focused on 200 magnifications. At least 3-5 fields will be randomly selected. The percentage of cells stained will be calculated. Sections with <5% cells stained will be considered negative, while those with >5% cells stained will be considered positive[8].



More than 60% of stained cells were considered strong Cytokeratin 17 expression, and less than 60% were weak cytokeratin 17.

2.10. Statistical analysis

The chi-square test for univariate analyses determined the statistical significance of the differences between the groups. p values of < 0.05 were considered to be significant.

3. RESULTS

A total of 50 cases were included in the study.

Table 1- Demographic data of Oral Squamous Cell Carcinoma:

Characteristic	Category	Cases (%)
Gender	Male	37 (74)
	Female	13 (26)
Age	< 60 years	45 (90%)
	>60 years	05 (10%)
Histopathological differentiation according to Broder grading	Well Differentiated (WDSCC)	18 (36%)
	Moderately Differentiated (MDSCC)	26 (52%)
	Poorly differentiated (PDSCC)	06 (12%)
Lymph nodal Status	Positive	13 (26%)
	Negative	37 (74%)
T stage	T2	29 (58%)
	T3	16 (32%)
	T4	05 (10%)
Stage	Stage II	26 (52%)
	Stage III	10 (20%)
	Stage IV	14 (28%)
Site	Tongue	13 (26%)
	Buccal mucosa	10 (20%)
	Gingivobuccal sulcus	18 (36%)
	Other sites	09 (18%)
Cytokeratin 17 expression	Strong	24 (48%)
	Weak	24 (48%)
	Negative	02 (04%)

As in the above Table -1, Out of 50 cases, 45 cases were in the age range of < 60 years and only 5 were in the age range of >60 years. A total of 12 cases were female, and 38 cases were male. According to the site, the most common amongst the study population was Gingivobuccal sulcus (36%), followed by Tongue (26%) and Buccal mucosa (20%). In our study population, lymph nodal status was positive in 26% of cases; the most common T stage amongst the study population was Stage T2 (58%), followed by Stage T3 (32%) and T4 (10%). The most common stage of cancer amongst the study population was Stage II (52%), followed by Stage IV (28%) and Stage III (20%). According to Broders grading in our study majority of cases were Moderately Differentiated (MDSCC) (52%), followed by Well Differentiated (WDSCC) (36%) and Poorly Differentiated (PDSCC) (12%).In this study, Cytokeratin 17 expression on cancer was Strong in 48% of cases, weak in 48%, and Negative in 4%. as shown in Table 1.

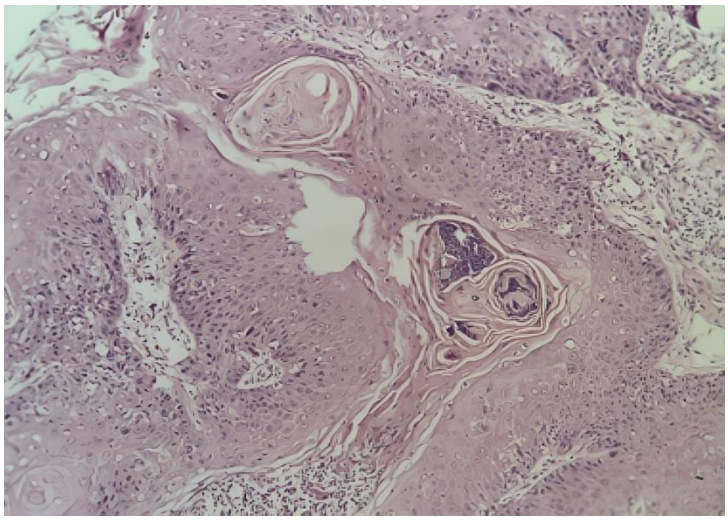


Fig 1: High power well differentiated squamous cell carcinoma (40x, H&E stain)

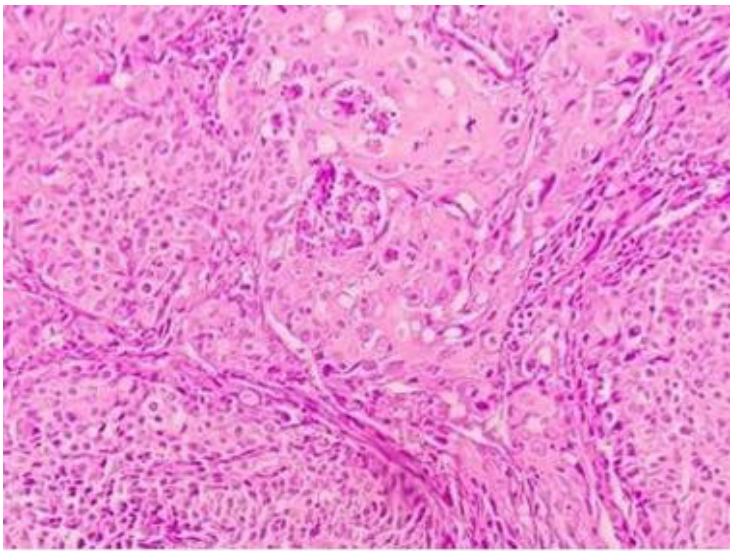


Fig 2: High power Moderately Differentiated Squamous Cell Carcinoma (40x, H&E stain)

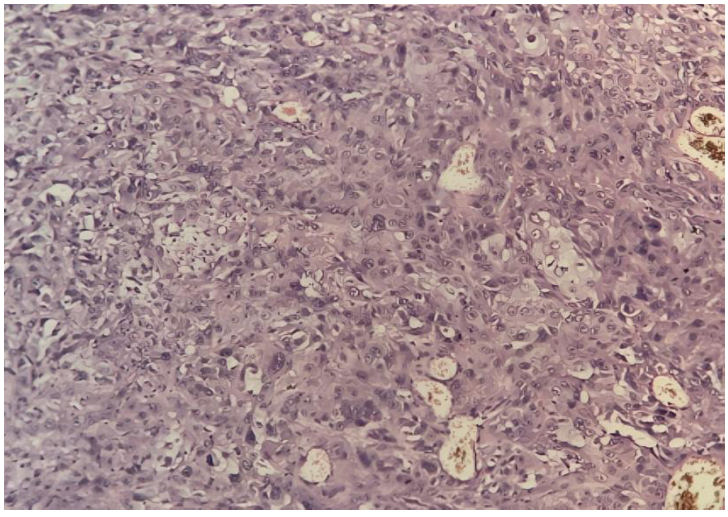


Fig 3: High power poorly differentiated squamous cell carcinoma (40x, H&E stain)

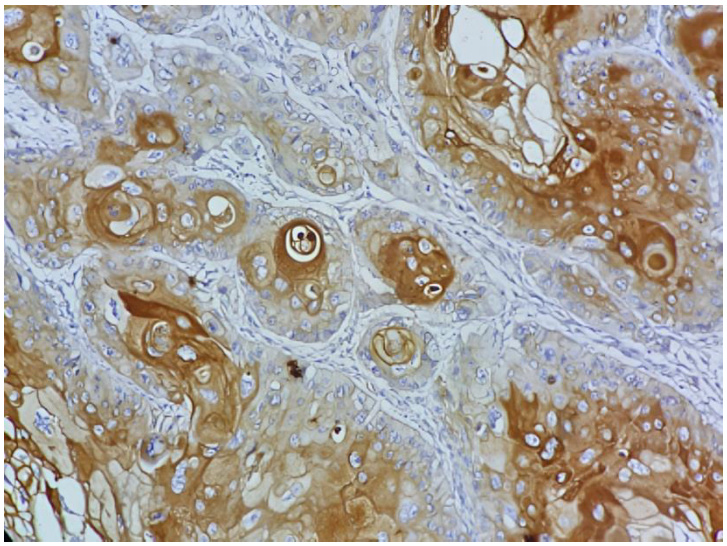


Fig 4- Well Differentiated Squamous Cell Carcinoma with Immunohistochemical stain showing more than 60% positive cells (+++) (20x) (strong Cytokeratin 17 expression)

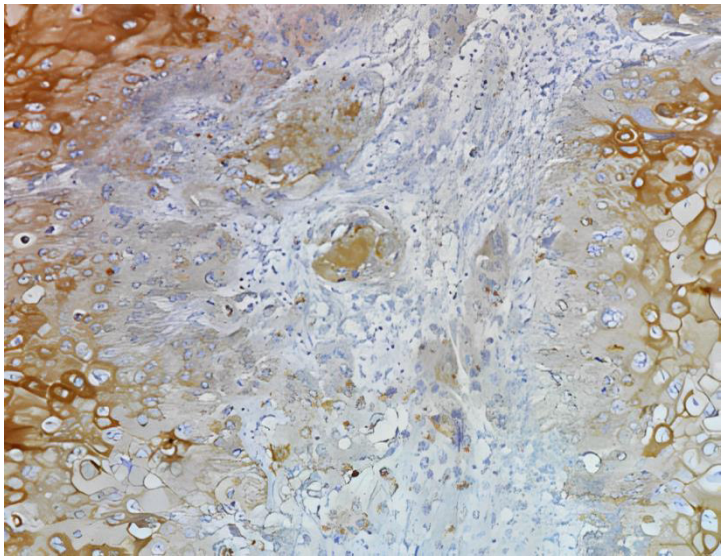


Fig 5: Moderately Differentiated Squamous Cell Carcinoma with Immunohistochemical stain showing more than 30-60% positive cells (++) (20x)(weak Cytokeratin 17 expression)

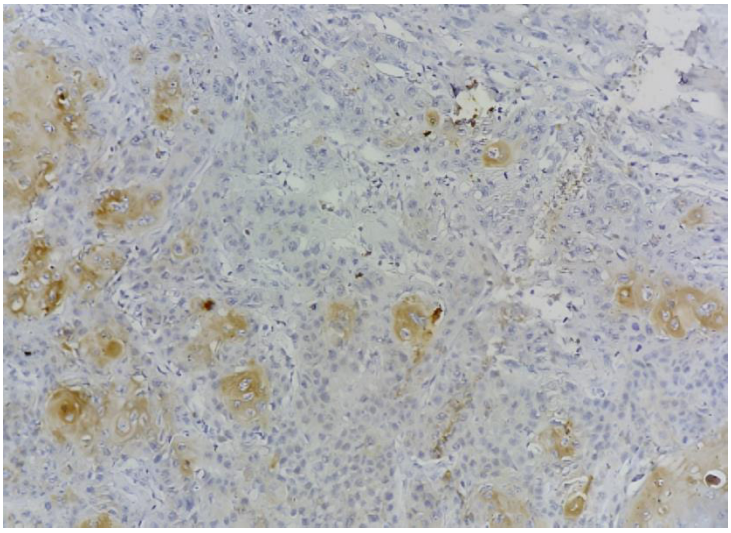


Fig6: Moderately Differentiated Squamous Cell Carcinoma with Immunohistochemical stain showing more than 5-30% positive cells (+) (20x)(weak Cytokeratin 17 expression)

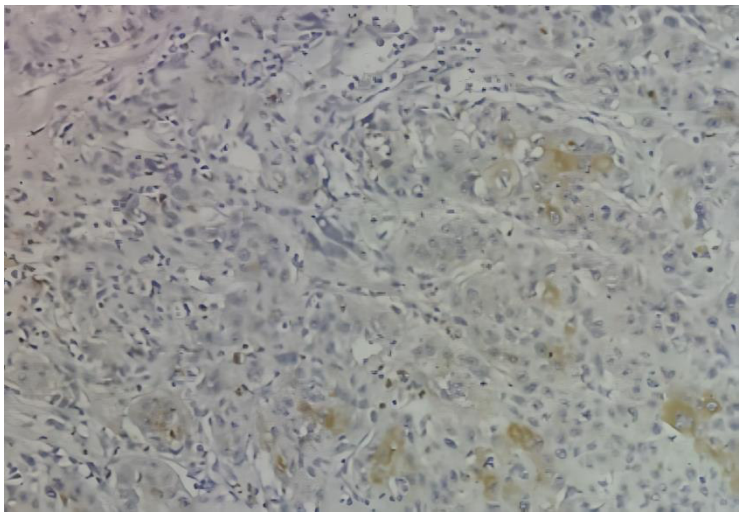


Fig 7: Poorly Differentiated Squamous Cell Carcinoma with Immunohistochemical stain showing <5% positive cells (20x) (Negative cytokeratin 17 expression)

Table 2 -Correlation of cytokeratin 17 with Broders grading and other clinicopathologic parameters

Clinicopathologic parameters	Cytokeratin 17 expression			p value (chi square test)
	Strong	weak	Negative	
Gender				
Male	19	17	02	0.573
Female	05	07	00	
Age				
< 60 years	21	22	02	0.374
>60 years	03	02	00	
Site				
Tongue	05	06	02	
Gingivobuccal sulcus	08	10	00	0.725
Buccal mucosa	03	07	00	
Others	08	01	00	
T stage				
T2	14	14	01	
T3	06	09	01	0.574
T4	04	01	00	
Lymph node metastasis				
Positive	06	06	01	0.732
Negative	18	18	01	
Stage				
II	12	13	01	
III	05	05	00	0.137
IV	07	06	01	
Histopathological differentiation according to Broders Grading				
Moderately Differentiated	07	19	00	
Poorly Differentiated	00	04	02	0.001
Well Differentiated	17	01	00	

Table 2 shows the correlation of CK 17 expression with Broders grading and other clinicopathological parameters. The cytokeratin 17 expression with Broders grading showed a positive correlation, and CK 17, when correlated with other clinicopathological parameters, showed no statistically significant correlation.

3.1. Correlation of cytokeratin 17 with age

Amongst strong cytokeratin 17 expressions, 87.5 % of patients were in the age range of < 60 years, 91.6% of patients showed weak cytokeratin 17 expression, and 100% of negative cytokeratin 17 expression were in the age range of < 60 years (Table 2). The P value was 0.374, which was statistically insignificant.

3.2. Correlation of cytokeratin 17 with gender

The male population had 79.2% strong, 70.8% weak, and 100% of negative cytokeratin 17 expressions (Table 2), and the p-value was 0.573; thus, the difference was statistically insignificant.

3.3. Correlation of cytokeratin 17 with site

Strong cytokeratin 17 expressions were observed most commonly in Gingivobuccal sulcus (33.3%) followed by Others (33.3%), weak cytokeratin 17 expressions were observed most commonly in Gingivobuccal sulcus (41.7%) followed by Buccal mucosa (29.2%) and tongue (25%) and the p-value was 0.725 (Table 2) which was statistically insignificant.

3.4. Correlation of cytokeratin 17 with T stage

Strong cytokeratin 17 expressions were observed most commonly in the T2 stage(58.3%), followed by the T3 stage (25%) and T4 stage (16.7%), weak cytokeratin 17 expression was observed most commonly in the T2 stage (58.3%) followed by T3 stage (37.5%) and T4 stage (4.2%), negative cytokeratin 17 expression was observed most commonly in T2 stage (50%) followed by T3 stage (50%) and the p-value was 0.574 (Table 2) and the difference was statistically insignificant.

3.5. Correlation of cytokeratin 17 with lymph node metastasis

Lymph nodal metastasis was positive in 25.0% of strong, 25% of weak, and 50% of negative strong cytokeratin 17 expression (Table 2), and the difference was statistically insignificant.

3.6. Correlation of cytokeratin 17 with stage

Strong cytokeratin 17 expressions were commonly observed in Stage II cancer (50%), followed by Stage IV (29.2%), and weak cytokeratin 17 expressions were commonly observed in Stage II (54.2%), followed by Stage IV (25%). Negative cytokeratin 17 expression was commonly observed in Stages II&IV (50% each). The p-value came out to be 0.137, as shown in (Table 2) which was statistically insignificant.

3.7. Correlation of cytokeratin 17 with Broder grading

Strong cytokeratin 17 expressions were commonly observed in WDSCC (Grade I) (70.8%), followed by MDSCC (Grade II) (29.2%), weak cytokeratin 17 expression was commonly observed in MDSCC (Grade II) (79.2%). Negative cytokeratin 17 expressions were commonly observed in PDSCC (Grade III) (100%); the p-value was 0.001, as shown in (Table 2) which was statistically significant.

4. DISCUSSION

This study evaluated the immunohistochemical expression of CK 17 and correlated CK 17 expression with Broders grading and other clinicopathologic parameters. In the present study, the normal oral mucosa, used as control, showed negative immunohistochemical expression of CK17. This concurs with the finding obtained by Kitamura et al. [8] and Noguchi et al.[13] that there were no positives for CK17 in normal oral epithelium. The present study showed overexpression or even de novo expression of CK17 in oral squamous cancerous tissue compared to normal and adjacent nonmalignant epithelium. This finding strongly suggested that the overexpression of CK17 could be associated with malignant transformation. This was found to be consistent with the findings of many studies, such as that of Moll et al [14], who stated that as mostly normal stratified squamous epithelia do not show any expression of CK 17, its presence in the corresponding malignancies can be regarded as neo-expression during carcinogenesis. Also, Kitamura et al.[8], Wei et al.[15], and Noguchi et al.[13] observed overexpression of CK17 in human oral cancer tissue compared to normal epithelium, adjacent non-malignant epithelium, and dysplastic epithelium, respectively. Linear with these data, CK17 has been reported to demonstrate higher expression in malignant tissues in comparison with normal tissues in cervical[16], laryngeal [17], esophageal, [18] and Lung SCCs [19]In our study, there was no significant correlation between age, gender, site of patients of Oral Squamous Cell Carcinoma and cytokeratin 17 expression and the results were in concordance to those obtained by Kitamura et al, [8] Sirima et al [20]Enny –Sonia et al.[21]In the present study there was no significant correlation between T stage, lymph node metastasis, stage and cytokeratin 17 expressions of oral squamous cell carcinoma and the results are in concordance to those obtained by Ryoji Kitamura et al [8], Sirima et al [20], B. A Coelho et al.[22]In our study, the most common Histopathological diagnosis of cancer was MDSCC(52%), followed by WDSCC (36%) and PDSCC (12%). In the present study, strong cytokeratin 17 expression was commonly observed in WDSCC (70.8%) followed by MDSCC (29.2%), weak cytokeratin 17 expressions was commonly observed in MDSCC(79.2%), and negative cytokeratin 17 expression was commonly observed in PDSCC(100%) the difference was statistically significant.An overview of the immunohistochemical results showed that the expression of CK17 became less pronounced as the grade worsened, i.e., down-regulated from well-differentiated, through moderately differentiated, to poorly differentiated OSCC. There was a statistically significant correlation between CK 17 immunohistohistochemical expression and Broders Grading. Correlation of CK 17 with Broders grading in other studies. Ryoji Kitamura et al. conducted a study on cytokeratin 17 expression in 105 cases of OSCC. In that study, out of 105 patients, 72 cases were well differentiated. Of 72 cases, 49 showed cytokeratin, 17 showed weak positivity, and 23 showed strong positivity. Moderate and poorly differentiated comprised 33 cases, out of which 32 cases showed weak positivity for cytokeratin 17 and one showed strong positivity for cytokeratin 17. It was found that The results of CK17 indicate a significant expression in WDSCC and the decreasing expression in MDSCC and PDSCC.This study showed a statistically significant correlation between cytokeratin 17 expression with histologic grade. [8]B.A. Coelho et al. studied cytokeratin 17 and cytokeratin 19 expression in OSCC .67 tumor tissue and 67 non-tumor tissues were obtained and used for immunohistochemical evaluation of keratin 17 and keratin19. Of 67 cases of oral squamous cell carcinoma, 30 were WDSCC, 32 were MDSCC, and only 5 were PDSCC. Out of 30 cases of WDSCC, 6 cases showed negative cytokeratin 17 expression, and 24 showed positive cytokeratin 17 expression. Out of 32 cases of MDSCC, 5 cases showed negative cytokeratin 17 expression, 5 cases of poorly differentiated, 3 cases showed negative cytokeratin 17 expression, and 2 positive cytokeratins 17 expressions. There was a statistically significant correlation between cytokeratin 17 expression with histopathological grade. [22] Sirima et al conducted a study on cytokeratin 17 expression during oral carcinogenesis in 186 cases, of which 83 cases of oral squamous cell carcinoma. Of 83 cases, 44 were of well-

differentiated oral squamous cell carcinoma, and 39 were moderate and poorly differentiated carcinoma. Out of 44 cases, 03 cases showed a score of 0, which is less than 5 % immunoreactive cells; 19 cases had a score of 1, that is 6-25% of immunoreactive cells; 17 cases had a score of 2, that is 26-50% of immunoreactive cells and 9 cases had a score of 3 that is more than 50% of immunoreactive cells. This study showed a statistically significant correlation between cytokeratin 17 expression with histological grade. [20] The results of our study showed the association between Broders grading and cytokeratin 17 expressions are those obtained by Ryoji Kitamura et al, and Sirima et al. concluding that there was a statistically significant correlation between Broders grading and cytokeratin 17 expressions in OSCC. Moreover, Ikeda et al.[16] revealed a significant correlation between the immunostaining of CK17 and the rising grade of cervical intraepithelial neoplasia and SCC in the cervix. The argument made by Poschmann et al.[23] that during the cell transition from bronchial epithelium to moderately differentiated squamous cell lung cancer, the expression of CK17 is initially induced and decreases with further differentiation of tumor cells, may help to explain the variation in CK17 expression between the various histopathological grades of OSCC in the present study. As a result, the pattern of CK17 protein expression may significantly and objectively aid in differentiating tumour grades.

5. CONCLUSION

The prognosis for OSCC, a widespread health issue, is dismal. The buccal cavity can be easily accessed for a clinical examination, but OSCC is often identified when it has advanced. Common reasons include inaccurate initial diagnosis and ignorance of the patient or treating physician. Recently, immunohistochemistry markers (IHC) as a trustworthy diagnostic tool has grown in favour. Cytokeratin, 17 immunohistochemical expressions in diagnosing Oral cancer, may be used to grade OSCC that correlates with Broders' system**.** Cytokeratin 17 expression also correlated with other clinicopathologic parameters, but there was no statistically significant correlation between cytokeratin 17 expression and other clinicopathologic parameters. Cytokeratin17 expression can correlate with the Broders' Grading, thus contributing to early detection and more accurate determination of tumor aggressiveness to determine appropriate therapy.

6. ACKNOWLEDGEMENTS

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7. AUTHORS CONTRIBUTION STATEMENT

Dr.Ankita Gyanchandani prepared the whole manuscript and collected all the data required. Dr. Samarth Shukla gave all the necessary inputs required for this manuscript and reviewed the manuscript. Dr.Ravindra Kadu reviewed the manuscript. All authors discussed and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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