Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 15 [2] January 2026. 01-07

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Analysis of Angiogenic marker CD34 in Oral Squamous Cell Carcinoma and Normal Mucosa at Pakistan Institute of Science and Medicine (PISM)

Waqas Ejaz[1], Sarosh Salaria[2], Wajih Malik[3], Shahzaib Wazir[4], Sarmad Saif[5], Usman Rashid[6]
[1] Department of Oral and Maxillofacial Pathology, Superior University, Lahore, Pakistan
[2] Department of Pathology, Superior University, Lahore, Pakistan
[3] Department of Physiology, Sharif Medical and Dental College, Lahore, Pakistan
[4] Department of Periodontology, Lahore Medical and Dental College, Lahore, Pakistan
[5] Assistant Professor, Periodontology, Sharif Medical and Dental College, Lahore, Pakistan
[6] Assistant Professor, Periodontology, Sharif Medical and Dental College, Lahore, Pakistan
Corresponding author : **Waqas Ejaz**
Orchid id 0009-0001-3080-3555

ABSTRACT
The most prevalent malignant neoplasm of the oral cavity is oral squamous cell carcinoma (OSCC), and it is one of the major health challenges in the world, especially in the developing nations where tobacco consumption is very rampant. Regardless of the improvements in diagnostic methods and treatment approaches, the general prognosis of OSCC has not changed significantly in the past decades. This demonstrates the necessity of better knowledge of the molecular pathways of oral carcinogenesis and to find good biomarkers, which can help in diagnosis, prognostication, and decision making in treatment. Angiogenesis is among the most important biological mechanisms that are involved in cancer progression and are interconnected. The current work was performed to measure and compare the expressions of an angiogenic marker, CD34 in oral squamous cell carcinoma and normal oral mucosa. A cross-sectional study design across time was chosen. The number of tissue samples was 50 (25 OSCC cases with histopathological confirmation and 25 samples of normal oral mucosa, which are used as controls). The antibodies against CD34 were used to perform the immunohistochemical staining. Micro vessel density was assessed in measuring CD34 expression. The SPSS software was used to conduct statistical analysis. These findings indicated that there was a significant increase in CD34 micro vessel density when comparing OSCC and normal oral mucosa. In OSCC and control groups, the micro vessel density of CD34 was much higher in OSCC group. The expression of CD34 grew progressively as the histopathological grade of OSCC became more aggressive. Moreover, positive relationship between CD34 micro vessel density was found to be statistically significant, indicating that angiogenesis is closely interacting in carcinogenesis of the mouth. The research affirms that angiogenesis is among the essential processes related to oral squamous cell carcinoma, and the CD34 is a significant biomarker. It was also discovered that smoking caused a considerable increase in angiogenic. Such results indicate the prognostic and therapeutic potential of CD34 and the significance of tobacco cessation in prevention and treatment of OSCC.
Keywords*: Angiogenic marker CD34, Carcinogenesis, OSCC, Oral Mucosa*

Received 02.12.2025 Revised 20.12.2025 Accepted 10.01.2026

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the predominant neoplastic disease of the oral cavity as it has over 90 percent of all oral cancers. It is a major global public health issue because it has a high incidence, morbidity, and mortality(1). OSCC is one of the ten most prevalent cancers in most of the developing countries, especially in South Asia, where cultural, social, and behavioural practises contribute greatly to the prevalence of the disease (1,2). Although new diagnostic imaging, surgical procedures, radiotherapy and chemotherapy regimens have been developed, the overall five-year survival rate of OSCC has not improved significantly over the past few decades, which is around 50-60% implying that there is not a significant improvement in patient outcomes (3).

Carcinogenic insults particularly in the oral cavity are unique because the mouth cavity is constantly exposed to tobacco smoke, alcohol, betel quid, and other environmental carcinogens(4). The issue of OSCC being multifocal and its likelihood of local recurrence and second primary tumours complicate further the management of the disease(5, 6). These issues highlight the necessity to learn more about the biological

processes of the formation and progression of OSCC to enhance the processes of early diagnosis, prognosis, and treatment approaches(7,8).

The aetiology of OSCC is complex and a complex interaction between genetic susceptibility and environmental exposures leads to the disease. The most vital and commonly accepted risk factor among them is tobacco use(9, 10). The use of tobacco takes a number of different forms such as cigarettes, hookah, cigar, smokeless tobacco, naswar, and betel quid preparations all of which have been violently linked to the growth of oral cancer(10). Tobacco smoke also harbours several carcinogenic constituents like nitrosamines, polycyclic aromatic hydrocarbons, as well as reactive oxygen species, which cause DNA damage and genetic mutations in the oral epithelial cells(11).

Any chronic tobacco encounter produces lasting mucosal irritation and inflammation with epithelial dysplasia and ultimate malignant change. Smoking has been also identified to affect immune surveillance, favour oxidative stress, and modify cellular signalling pathways that regulate cell proliferation and cell apoptosis(12).

Angiogenesis is the process of developing new blood vessels using the already-existing ones, which is a basic biological process without which tumours cannot grow and survive. When a tumour grows beyond a certain threshold, the diffusion is no longer adequate to provide oxygen and nutrients, thus angiogenesis is required to maintain the further growth of the tumour(13). Angiogenesis in OSCC is important in promoting tumour growth, invasion, and metastasis.

A complex set of pro-angiogenic and anti-angiogenic factors generated by tumour cells, stromal cell, and inflammatory cells mediates tumour-induced angiogenesis(14). Endothelial cell markers are among them, and they are regularly employed to determine the level of angiogenic activity of tumours(15). Microvessel density (MVD) is now recognised as a quantitative surrogate endpoint of angiogenesis, and its measurement can be used to learn important information about tumour vascularity(16).

CD34 is a transmembrane glycoprotein that is expressed on endothelial cells and hematopoietic progenitor cells and is regarded as one of the most sensitive pan-endothelial markers(17). Micro vessels in tumour tissue can be visualised and quantified with immunohistochemical analysis of CD34. Many studies have also shown a substantially higher microvessel density of CD34 in OSCC than in normal oral mucosa and premalignant lesions(18,19).

Aggressive tumour behaviour has been linked with increased angiogenesis in OSCC such as increased tumour size, deeper tumour invasion, lymph node metastasis, and worse prognosis. Higher microvessel density in OSCCs was associated with lower survival rates, which emphasises the prognostic relevance of angiogenesis(20). Moreover, malignant transformation has been associated with changes in stromal CD34 expression, where low stromal fibroblast positivity in poorly differentiated tumors has been demonstrated as a result of stromal remodelling and tumor stroma interactions(21,22).

Although a lot of research has been conducted on OSCC, there is still a gap in research that can simultaneously test angiogenic markers. The current paper was thus aimed at determining the expression and comparison of CD34 healthy oral mucosa and cancerous oral mucosa. The importance of the study is that it has potential clinical and public health implications. Discovery of biomarkers related to angiogenesis can be useful in risk stratification, prognostication and targeted therapy.

MATERIAL AND METHODS

Research Framework, Research Study Design, and Rationale.

The current study was developed as a comparative cross-sectional analytical study to assess the presence of an angiogenic marker, CD34 in oral squamous cell carcinoma (OSCC) and normal oral mucosa. The choice of cross-sectional design was dictated by the fact that it provides simultaneous evaluation of disease status and biomarker expression in a single point in time which is especially appropriate in immunohistochemical research of tissue samples. This design made it possible to compare directly the tissues of OSCC with normal mucosa. Moreover, cross-sectional studies of analysis are common in pathology-based research in which tissue biomarkers are assessed either diagnostically or prognostically or mechanistically.

The choice of the study markers of CD34 was prompted by their known involvement in oral carcinogenesis. Angiogenesis is a critical need of tumour growth and metastasis, and CD34 is a sensitive pan-endothelial marker that is widely used to measure microvessel density.

Study Location and Laboratory Conditions and Time.

The research was carried out at the Department of Oral Pathology, Pakistan Institute of Science and Medicine (PiSM), a tertiary care and academic facility in Islamabad, Pakistan, where the medical institution has all the necessary histopathology and immunohistochemistry services and equipment. The institution gets a substantial volume of oral biopsy materials and therefore it is the right place to carry out a study that involves pathological research about oral malignancies.

Ethical Approval, Consent and Confidentiality measures.

The study was given ethical approval by the Ethical Review Board of Superior University, Lahore before the research activities started. The research was conducted in accordance with all the institutional ethical regulations and international standards of conducting biomedical research with human subjects.

All participants were clearly told about the objectives, methodology, possible benefits, and the least threatening risks in the study. Each participant signed an informed consent written form prior to the collection of the sample. Consent to have the excess tissues used in the research was also noted in instances where the tissue samples were taken as a routine diagnostic or treatment procedure.

Sample Size Calculation and Sampling Method, Study Population.

Sample Size Determination

A total of 50 tissue samples were used in the study (25 cases and 25 controls of the normal oral mucosa). To compare two means, the World Health Organisation (WHO) formula for calculating the sample size was used, which ensured that the statistical power was sufficient to identify significant differences in marker expression between groups. The sample size was determined as final because of the feasibility, availability of biopsy material, laboratory capacity and time. Equal distribution between study groups was observed to ensure the comparisons were balanced.

Table 1: Sample Size

Group	Description	Number of Samples
Group I	Oral Squamous Cell Carcinoma	25
Group II	Normal Oral Mucosa	25
Total		**50**

Sampling Technique

The sampling method was a non-probability convenient sampling method. During the study period, patients who came to the oral surgery and oral pathology departments were recruited consecutively until the needed sample size had been attained and they fulfilled the eligibility criteria. It is generally a sampling method in hospital-based pathology research in which tissue samples are available based on the clinical presentation.

Study Population

The population that was taken part in the study included the adult population aged 18 years and above. The OSCC patients were a group of patients with histopathically confirmed oral squamous cell carcinoma and the control group comprised of healthy patients with clinically normal oral mucosa.

Inclusion and Exclusion Criteria.

Inclusion Criteria

The following criteria were used to include the participants in the study:

- Oral squamous cell carcinoma (in the case of the OSCC group) histopathologically confirmed diagnosis.
- Oral mucosa clinically appears normal, without finding of inflammation or dysplasia (control group).
- Age 18 years or above
- Availability of informed consent.

Exclusion Criteria

The participants could not be included in the study in case they fulfilled the following conditions:

- Systemic inflammatory, autoimmune or immunosuppressive disease history.
- Past experience of chemotherapy or radiotherapy.
- Recurrent/treated OSCC.
- Poor- or poor-quality tissue samples that cannot be used in immunohistochemical studies.

Collection, fixing, and processing of samples.

Collection of OSCC Samples

Samples of oral squamous cell carcinoma with different grades were collected at the actual sites of the tumour by standard diagnostic biopsy procedure. Sites which were involved for collection of sample were buccal mucosa and tongue and incisional biopsy was performed by qualified oral surgeons and pathologists using standardised method. It was done carefully to make sure that sufficient tissue samples were obtained covering representative parts of the tumour.

Normal Oral Mucosa Collection. This includes using swabs to collect mucous material from the very same site which we used for OSCC sample i.e. buccal mucosa and tongue, which is then moved into a bottle and labelled with specific MR number.

The samples of control were healthy persons who had minor oral surgeries. Normal mucosal tissue was taken as extra tissue on clinically non-pathological regions of the oral cavity i.e buccal mucosa and tongue and was taken care of to ensure that the tissue was devoid of pathological alterations.

Obsession and Transit.

All the tissue specimens were put in 10 % neutral buffered formalin solution immediately after the excision to maintain cellular morphology and to inhibit cellular autolysis for 24 hours. Samples were then brought to the Oral Pathology laboratory to be further processed and labelled with specific numbers for identification.

Processing and Embedding of Tissues.

Further histopathological procedures were used to process the formalin-fixed tissues. This involved dehydration using a graded concentration of alcohol, clearing with xylene, paraffin wax infiltration with molten paraffin wax. The tissues were fixed on paraffin blocks to support the microtomy.

Sectioning, Immunohistochemical Procedure, and Evaluation.

A rotary microtome was used to cut paraffin-embedded tissue blocks. Sections with 3-4 um thickness were taken and placed on clean labelled glass slides. Before staining, slides were dried in a hot air oven. To assess the expression of CD34, immunohistochemistry was done. The slides were deparaffinized using xylene and rehydrated using alcohol decreasing in concentration from 100% to 95% to 70%. Through heat-induced epitope retrieval, antigen retrieval was done using citrate buffer (pH 6.0).

To prevent non-specific staining, the activity of endogenous peroxidases was inhibited with hydrogen peroxide. The antibodies used were CD34 primary, and after incubating, a horseradish peroxidase (HRP) polymer detection system as a secondary antibody was utilised. DAB chromogen was used to visualise it, and the slides were counterstained with haematoxylin staining.

The endothelial cells that were positive to CD34 were brown-stained. Micro vessel density was measured through the process of determining vascular hot spots and the number of micro vessels in three high-power fields under x400 magnification. Each case was counted in mean micro vessel and evaluation of CD34 expression indicates angiogenesis. With increased CD34 expression, tumor angiogenesis is increased.

Statistical Analysis

All the data were inputted in the Microsoft Excel and analysed with the help of Statistical Package of Social Sciences (SPSS) software. Quantitative variables were presented in terms of mean and standard deviation, and qualitative variables presented in terms of frequencies and percentages. The main outcome measures were the micro vessel density of CD34.

RESULTS

All the OSCC cases used in the study were histopathologically verified before inclusion. The control group involved the normal oral mucosal tissues of healthy subjects in undergoing minor oral surgery. There was good tissue preservation and staining quality in all the samples and none of the samples was excluded based on technical failure.

Demographic data, including the age and gender, were collected, but the main emphasis on analysis was laid on the histopathological diagnosis and the microvessels density of CD34.

Table 2: Distribution of Study Samples According to Diagnostic Groups

Diagnostic Group	Number of Samples	Percentage (%)
Oral Squamous Cell Carcinoma	25	50.0
Normal Oral Mucosa	25	50.0
Total	**50**	**100**

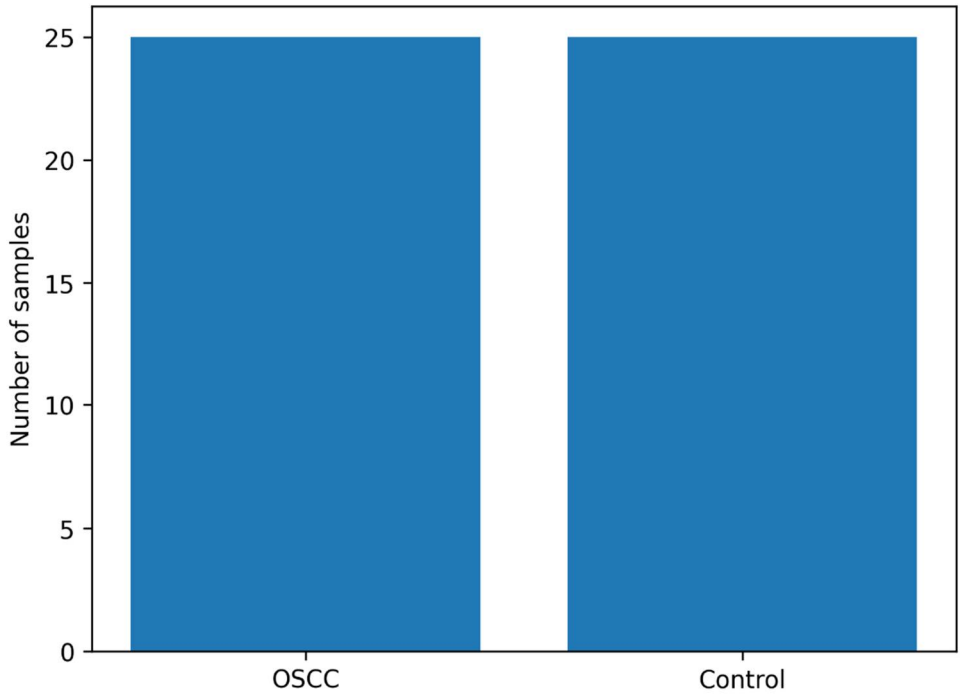

Figure 1: Distribution of Study Samples According to Diagnostic Groups

The immunohistochemical staining of CD34 showed clear variation in the density of microvessels in OSCC tissues and controls (normal oral mucosa). The detection of CD34 was found as a brown endothelial cell cytoplasmic staining of blood vessels. Increased vascularity regions were easily detected in the sections of OSCC, especially in the stromal regions near tumour islands. Conversely, normal oral mucosa had fewer comparatively CD34-positive micro vessels. Vascular architecture in control tissues was observed to be evenly distributed and of less density when compared to those of OSCC specimens. Micro vessel density (MVD) was estimated, using three vascular hot spots in each slide and the number of CD34-positive vessels using high-power magnification (x400). The average count of microvessels per case was noted and statistically analysed.

Quantitative analysis revealed that the mean CD34 microvessel density was much greater in the OSCC cases than normal oral mucosa.

Table 3: Comparison of Mean CD34 Microvessel Density Between OSCC and Control Groups

Group	**Mean MVD ± SD**
OSCC	34.72 ± 6.15
Control	14.68 ± 3.82

A distinct t-test was used to show that the difference between OSCC and control groups in terms of CD34 microvessel density is statistically significant ($p < 0.001$).

DISCUSSION

The current research was conducted to examine the level of the angiogenic marker of CD34 in oral squamous cell carcinoma and normal oral mucosa. Oral squamous cell carcinoma has been a significant social health issue among the global population but particularly among the South Asians whereby tobacco consumption is very rife. Although there is an improvement in the diagnostic and treatment modalities, the survival rates of the OSCC patients have recorded a slight improvement over the years necessitating a deeper insight into the molecular pathways involved in tumour development, growth, and aggressiveness. Angiogenesis and inflammation have now been considered as two key and interdependent pathways in carcinogenesis and biomarkers of these pathways have the potential to provide useful information on tumour behaviour and prognosis.

Results of the current study revealed that, the microvessel density CD34 was significantly greater in the OSCC tissues than in normal oral mucosa. This finding confirms the long-standing idea that angiogenesis is an essential condition of the further enlargement of the tumour beyond a certain minimum size. The provision of sufficient supply of blood is essential to the tumour cells to sustain augmented metabolic rates

and to support the process of invasion-metastasis. Higher microvessel density of the OSCC samples shows that the angiogenic process is active in the tumour microenvironment. These findings align with many earlier researches which have also found high levels of CD34 and high microvessel density in OSCC compared with normal mucosa and premalignant lesions. Other investigators including Mishra and Sangamesh and Singh have also shown that OSCC tissues have higher vascular density significantly highlighting the contribution of angiogenesis to oral carcinogenesis.

Conversely, the current study showed that normal samples of the oral mucosa had a relatively lower expression of CD34 and possess less microvessels, which represents the physiological vascular demands of normal tissue. The ordered and comparatively low density of blood vessels of normal mucosa highlights the contrast between physiological and pathological angiogenesis in tissues of malignant tissues. The apparent difference in the expression of CD34 in the OSCC and control samples provides the validity of CD34 as an effective marker to determine angiogenesis in oral cancer.

The observed greater increase in CD34 microvessel density as the histopathological grade of OSCC became more aggressive also supports the association between angiogenesis and tumour aggressiveness. The cases of OSCC that were poorly differentiated exhibited the greatest microvessel density, then moderately differentiated and well differentiated tumours. Such a gradual rise indicates that angiogenesis gains strength with the aggressive and less differentiated tumour. Angiogenesis in the poorly differentiated tumours can contribute to the rapid growth and metastasis of the tumours because it can offer more advancement in vascular support.

The current research contributes to the possible therapeutic importance of angiogenic pathway targets in OSCC as well. Antiangiogenic therapy has been studied in diverse cancers such as head and neck cancers. Despite inconsistencies in clinical outcomes, the molecular proofs that studies including the current one have been able to establish indicate that patients who are high in terms of CD34 can be subjected to targeted therapies to supplement traditional forms of treatment. More studies that use bigger cohorts and clinical trials need to be conducted to confirm these methods.

However, in spite of its merits, the current research has some limitations that are to be considered. The sample used was also quite small, so it could be a limitation to the extrapolation of the results. Also, the cross-sectional design does not allow evaluating the longitudinal alterations in the marker expression itself and their direct influence on patient survival and treatment outcomes. The status of smoking was determined by patient history and quantitative measures, including pack-years but were not involved which could have offered a greater understanding of changes with tobacco exposure. However, the same and statistically significant results in several analyses give the results credibility.

Overall, the current research showed that compared to normal oral mucosa, oral squamous cell carcinoma has a significantly higher level of CD34 expression. Angiogenesis was identified to increase with deteriorating histopathological grade of OSCC, and there was a significant positive outcome of CD34 microvessel density. The findings add to the accumulating literature on the role of molecular biomarkers in the biology of tumours and the significance of an integrated approach to preventive and therapeutic measures involving angiogenic cascades in oral squamous cell carcinoma.

REFERENCES

1. Warnakulasuriya S. (2020). Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral oncology. 102:104550.
2. Saraswat N, Pillay R, Everett B, George A. (2020). Knowledge, attitudes and practices of South Asian immigrants in developed countries regarding oral cancer: an integrative review. BMC cancer. 20(1):477.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians.71(3):209-49.
4. Chaudhari MA, Panchal M, Singh N, Fegade T, Sadhu LL. (2025). Oral Mucosal Changes Due to Smokeless Tobacco, Betel Quid and Areca Nut: A Review of Risks and Pathology. Journal of Advanced Medical and Dental Sciences Research. ;13(4):19-22.
5. Togni L, Caponio VCA, Zerman N, Troiano G, Zhurakivska K, Lo Muzio L, et al. (2022). The emerging impact of tumor budding in oral squamous cell carcinoma: main issues and clinical relevance of a new prognostic marker. Cancers.14(15):3571.
6. Badwelan M, Muaddi H, Ahmed A, Lee KT, Tran SD. (2023). Oral squamous cell carcinoma and concomitant primary tumors, what do we know? A review of the literature. Current Oncology. 30(4):3721-34.
7. Ji H, Hu C, Yang X, Liu Y, Ji G, Ge S, et al. (2023). Lymph node metastasis in cancer progression: molecular mechanisms, clinical significance and therapeutic interventions. Signal Transduction and Targeted Therapy.8(1):367.
8. Ravindran S, Ranganathan S, Kannan SK, Marri J. (2025). The role of molecular biomarkers in the diagnosis, prognosis, and treatment stratification of oral squamous cell carcinoma: A comprehensive review. The Journal of Liquid Biopsy. 100285. doi: 10.1016/j.jlb.2025.100285.

9. Mohammadpour H, Bakhshi A, Norouzi N, Fallah A, Gharib S. (2022). Environmental and genetic risk factors of oral cancer: an updated review. Clinical Cancer Investigation Journal. ;11(1-2022):1-8.
10. Chamoli A, Gosavi AS, Shirwadkar UP, Wangdale KV, Behera SK, Kurrey NK, et al. (2021). Overview of oral cavity squamous cell carcinoma: Risk factors, mechanisms, and diagnostics. Oral oncology.121:105451.
11. Khowal S, Wajid S. (2019). Role of Smoking-Mediated molecular events in the genesis of oral cancers. Toxicology mechanisms and methods. 29(9):665-85.
12. Smok-Kalwat J, Mertowska P, Mertowski S, Smolak K, Kozińska A, Koszałka F, et al. (2-23). The importance of the immune system and molecular cell signaling pathways in the pathogenesis and progression of lung cancer. International Journal of Molecular Sciences. ;24(2):1506.
13. Dudley AC, Griffioen AW.(2023). Pathological angiogenesis: mechanisms and therapeutic strategies. Angiogenesis. 26(3):313-47.
14. Lu X, Friedrich LJ, Efferth T. (2025). Natural products targeting tumour angiogenesis. British journal of pharmacology. 182(10):2094-136.
15. Huinen ZR, Huijbers EJ, van Beijnum JR, Nowak-Sliwinska P, Griffioen AW. (2021). Anti-angiogenic agents—overcoming tumour endothelial cell anergy and improving immunotherapy outcomes. Nature Reviews Clinical Oncology.18(8):527-40.
16. Jiang J, Li J, Xiong X, Zhang S, Tan D, Yang L, et al. (2023). Different predictive values of microvessel density for biochemical recurrence among different PCa populations: A systematic review and meta-analysis. Cancer Medicine.12(3):2166-78.
17. Mahapatra N, Nithya S, Uppala D, SriNivaSaN S, DOSS D. (2024). Prognostic Significance and Therapeutic Implications of CD34, an Angiogenic Marker, in Oral Squamous Cell Carcinoma: A Narrative Review. Journal of Clinical & Diagnostic Research.18(12).90-94
18. Bavle RM, Sharada P. (2023). World Literature: Bibliography. Oral Submucous Fibrosis: A Guide to Diagnosis and Management: Springer; p. 357-76.
19. Singh A, Jagtap M, Shukla S, Vagha S. (2021). Utility of Microvessel Density (MVD) by CD34 in Different Histological Grades of Oral Squamous Cell Carcinoma. https://doi.org/10.9734/jpri/2021/v33i50A33407.
20. Alessandrini L, Astolfi L, Daloiso A, Sbaraglia M, Mondello T, Zanoletti E, et al. (2023). Diagnostic, prognostic, and therapeutic role for angiogenesis markers in head and neck squamous cell carcinoma: a narrative review. International Journal of Molecular Sciences. 24(13):10733.
21. Maqsood A, Ali A, Zaffar Z, Mokeem S, Mokeem SS, Ahmed N, et al. (2021). Expression of CD34 and α-SMA markers in oral squamous cell carcinoma differentiation. A histological and histo-chemical study. International journal of environmental research and public health. 18(1):192.
22. Ding L, Xu W-J, Tao X-Y, Zhang L, Cai Z-G. (2021). Clinicopathological features of superficial CD34-positive fibroblastic tumor. World Journal of Clinical Cases. ;9(12):2739.

CITATION OF THIS ARTICLE

Waqas E, Sarosh S, Wajih M, Shahzaib W, Sarmad S, Usman R. Analysis of Angiogenic marker CD34 in Oral Squamous Cell Carcinoma and Normal Mucosa at Pakistan Institute of Science and Medicine (PISM). Bull. Env. Pharmacol. Life Sci., Vol 15 [2] January 2026. 01-07