Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Evaluation of Differential Expression of MUC20 and sprr1B in Oral Squamous Cell Carcinoma and Oral Potentially Malignant Disorder

Dr.Payal Panwar
King George's Medical University
Dr.Priyanka singh
King George's Medical University
Dr Shalini Gupta
shalni@gmail.com
King George's Medical University
Dr Uma Shanker pal
Dr. Vandana Singh
Dr. Sameer Gupta

Research Article

Keywords: MUC20, SPRR1B, Oral Squamous Cell Carcinoma, Oral Potentially Malignant Disorders, Immunohistochemistry, Biomarker

Posted Date: April 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9433889/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

EVALUATION OF DIFFERENTIAL EXPRESSION OF MUC20 AND SPRR1B IN ORAL SQUAMOUS CELL CARCINOMA AND ORAL POTENTIALLY MALIGNANT DISORDER

Author	DESIGNATION
Dr Payal Panwar Panwarpayal07@gmail.com	Senior Resident, Department of Oral Pathology & Microbiology
Dr. Shalini Gupta shalni@gmail.com	Professor & Head, Department of Oral Pathology & Microbiology
Dr. Priyanka Singh Priyanka0100@kgmcindia.edu	Additional Professor, Department of Oral Pathology & Microbiology
Dr. Uma Shanker Pal uspal@kgmcindia.edu	Professor & Head, Department of Oral & Maxillofacial Surgery
Dr. Vandana Singh drvandnasingh22@kgmcindia.edu	Professor, Department of Oral Medicine & Radiology
Dr. Sameer Gupta sameerdr79@gmail.com	Professor, Department of Surgical Oncolgy

*Dr. Shalini Gupta -Corresponding Author

Abstract

Aim: To evaluate the expression of MUC20 and SPRR1B in Oral Squamous Cell Carcinoma (OSCC), Oral Potentially Malignant Disorders (OPMDs), and normal oral mucosa, and to correlate their expression with clinicopathological parameters. Materials and Methods: A total of 108 formalin-fixed paraffin-embedded tissue samples were included, comprising 36 OSCC, 36 OPMDs (OSMF, OED, OLP), and 36 normal oral mucosa. Immunohistochemical analysis was performed using primary antibodies against MUC20 and SPRR1B. Expression levels were scored based on intensity and proportion of positively stained cells. Statistical analysis was conducted using SPSS v23, with significance set at $p < 0.05$.

Results: MUC20 and SPRR1B expression was significantly higher in OSCC compared to OPMDs and normal mucosa ($p < 0.001$). In OPMDs, MUC20 expression was highest in mild dysplasia, while SPRR1B expression increased progressively with dysplasia severity. In OSCC, higher MUC20 and SPRR1B levels were associated with poorer histological differentiation. No significant correlation was observed between expression and OSCC clinical stage.

Conclusion: Both MUC20 and SPRR1B show progressive upregulation from normal mucosa to OPMDs and OSCC, with expression correlating to histopathological grade and dysplasia severity. These findings suggest their potential utility as biomarkers for early detection and prognostic evaluation in oral carcinogenesis.

Keywords: MUC20, SPRR1B, Oral Squamous Cell Carcinoma, Oral Potentially Malignant Disorders, Immunohistochemistry, Biomarker.

Introduction

The concept of oral lesions with malignant potential has evolved, with the World Health Organization recommending the term oral potentially malignant disorders (OPMDs) to denote lesions with a risk of malignant transformation without certainty [1,4]. OPMDs such as leukoplakia, oral lichen planus (OLP), and oral submucous fibrosis (OSMF) are associated with an increased risk of progression to oral squamous cell carcinoma (OSCC) [4].

OSCC is one of the most common malignancies worldwide, particularly in South-Central Asia, with significant incidence and mortality in India [2,5]. Despite therapeutic advancements, survival rates remain largely unchanged due to late diagnosis and tumor heterogeneity [5].

The progression from OPMDs to OSCC involves complex molecular alterations. Although biomarkers such as p53, Ki-67, and EGFR have been studied, more reliable markers are needed for early detection and prognostic evaluation.

MUC20 and SPRR1B are emerging biomarkers with potential roles in carcinogenesis. MUC20, a mucin glycoprotein, is implicated in tumor progression, invasion, and metastasis across multiple cancers (Chen et al., 2013; Xiao et al., 2013; Wang et al., 2015; Chen et al., 2018) [2,41]. SPRR1B is involved in epithelial differentiation and stress response, showing variable expression in different malignancies (Fujimoto et al., 1997; Michifuri et al., 2013) [2].

This study aims to evaluate the immunoexpression of MUC20 and SPRR1B in OSCC, OPMDs, and normal oral mucosa, and to correlate their expression with clinicopathological parameters.

Materials and Methods

This prospective comparative study was conducted in the Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, King George's Medical University (KGMU), Lucknow, after obtaining ethical approval (Ref. no. XXI-PGTSC-IIA/P75). Formalin-fixed paraffin-embedded (FFPE) tissue samples of oral squamous cell carcinoma (OSCC), oral potentially malignant disorders (OPMDs), and normal oral mucosa were included.

A total of 108 cases were studied, divided into three groups: Group I – OSCC (n = 36), Group II – OPMDs including oral submucous fibrosis (OSMF), oral epithelial dysplasia (OED), and oral lichen planus (OLP) (n = 36), and Group III – normal oral mucosa (n = 36). Inclusion criteria comprised histopathologically confirmed cases of OSCC and OPMDs, surgical resection specimens with complete clinicopathological data, and consented patients of all ages and sexes. Exclusion criteria included cases with prior treatment (radiation, chemotherapy, anti-inflammatory drugs, or vitamin creams), systemic conditions such as autoimmune or hepatic diseases, pregnancy, and unwilling participants.

Sections of 3.5 µm thickness were obtained from FFPE blocks using a rotary microtome (Leica RM2265). Routine hematoxylin and eosin (H&E) staining was performed, and histological grading of OSCC was assessed using Broder's classification. For immunohistochemistry (IHC), primary antibodies

against MUC20 (Elabscience Bionovation Inc.) and SPRR1B (Thermofisher, Invitrogen) were used, along with a poly- HRP anti-rabbit IgG secondary antibody (Biogenex), diaminobenzidine (DAB) chromogen, and Mayer's hematoxylin.

Sections were deparaffinized in xylene and rehydrated through graded alcohols. Antigen retrieval was performed in citrate buffer (pH 6.0) using a pressure cooker. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide, followed by incubation with goat serum to reduce background staining. Slides were incubated with primary antibodies (MUC20 and SPRR1B) at 37°C for 2 hours and overnight at 4°C. After PBS washes, sections were treated with HRP-conjugated secondary antibody for 30 minutes, visualized using DAB, counterstained with hematoxylin, dehydrated, cleared, and mounted. Positive control slides were included in each run.

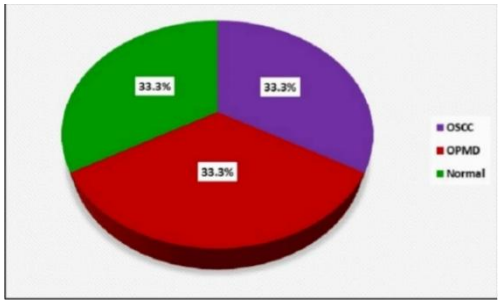
Stained slides were observed under a Carl Zeiss Axioscope A1 microscope with an AxioCam ICc5 camera. MUC20 and SPRR1B expression was evaluated based on cytoplasmic and/or membranous brown staining. Five random high-power fields (×40) were analyzed by two blinded observers. Immunoreactivity was scored semi- quantitatively using Itoh et al.'s method: negative (<5%, score 1), mildly positive (5–50%, score 2), and strongly positive (>50%, score 3).

Data were analyzed using SPSS version 23 (IBM Inc.). Descriptive statistics were expressed as frequencies and percentages. ANOVA was applied to compare mean differences, and Chi-square test was used for categorical variables. A p-value < 0.05 was considered statistically significant.

OBSERVATION AND RESULTS

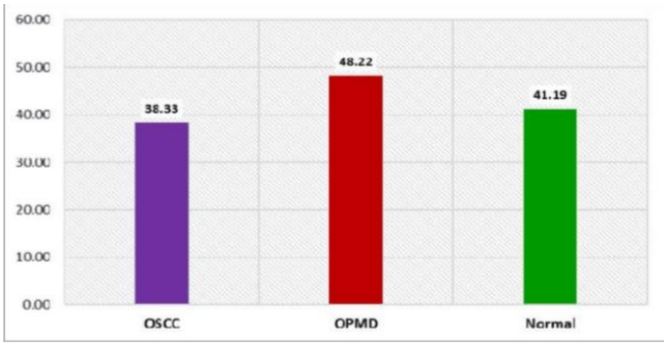
MUC20 and SPRR1B expression progressively increases from normal oral mucosa to OPMDs and OSCC, correlating with histopathological grade and dysplasia severity, highlighting their potential as biomarkers for oral carcinogenesis and disease progression**.**

The study population was evenly distributed across the three groups, with each group comprising 36 individuals, accounting for 33.3% of the total sample. These groups included Oral Squamous Cell Carcinoma (OSCC), Oral Potentially Malignant Disorders (OPMD), and Normal controls, ensuring balanced representation for comparative analysis as shown in Graph 1.

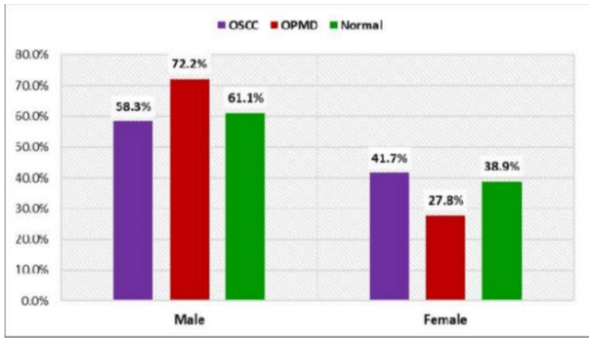


Graph 1: Distribution of Study Subjects According to Study Groups

The mean age of participants varied significantly across the three groups. The mean age in the OSCC group was 38.33 ± 12.78 years, while in the OPMD group, it was notably higher at 48.22 ± 8.74 years. The Normal group had a mean age of 41.19 ± 8.39 years. Statistical analysis using ANOVA revealed a significant difference in age distribution among the groups ($F = 9.02$, $p < 0.001$), indicating that age may be a relevant factor in the comparative evaluation of these groups as shown in Graph 2.



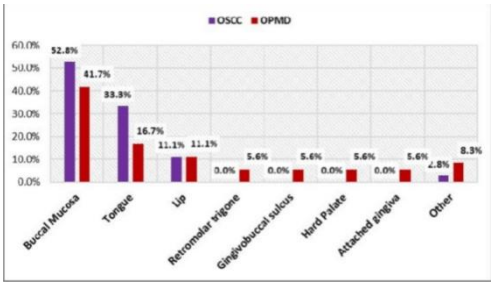
Graph 2: Age-wise distribution of subjects



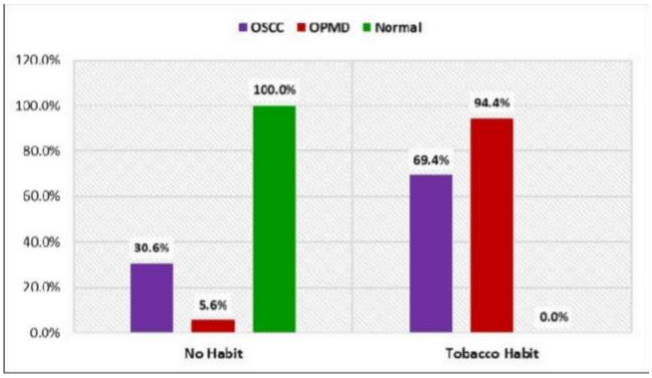
Graph3.indicates that the gender distribution among the groups was not statistically significant.

Graph 3: Gender-wise distribution of study population

The buccal mucosa was the most commonly involved site in both groups, observed in 52.8% of OSCC cases and 41.7% of OPMD cases.. The differences in site distribution between the groups were not statistically significant ($\chi^2 = 11.47$, $p = 0.119$) as shown in graph 4.



Graph 4. Sitewise distribution

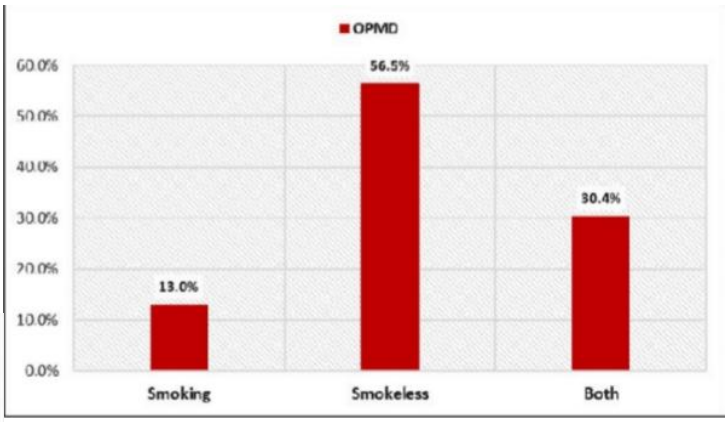


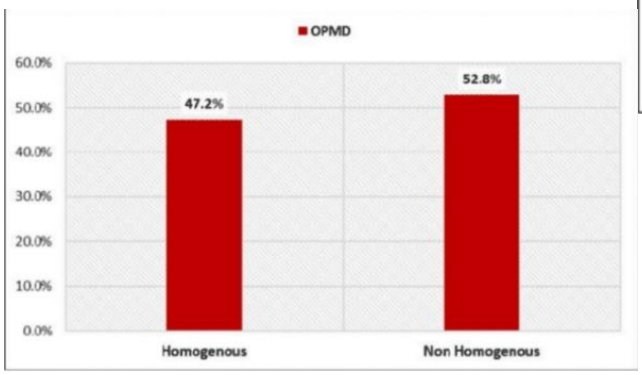
Graph 5: Habit wise distribution of study

The difference in the prevalence of tobacco habits across the three groups was statistically significant ($\chi^2 = 69.60$, $p < 0.001$), highlighting a strong association between tobacco use and the presence of oral lesions as shown in graph 5

The most common type of tobacco habit was smokeless tobacco, reported by 56.5% of the participants. These findings suggest a higher prevalence of smokeless tobacco use among OPMD cases as shown in graph 6

Graph 6: Distribution of OPMD Cases according to Tobacco Consumption Type





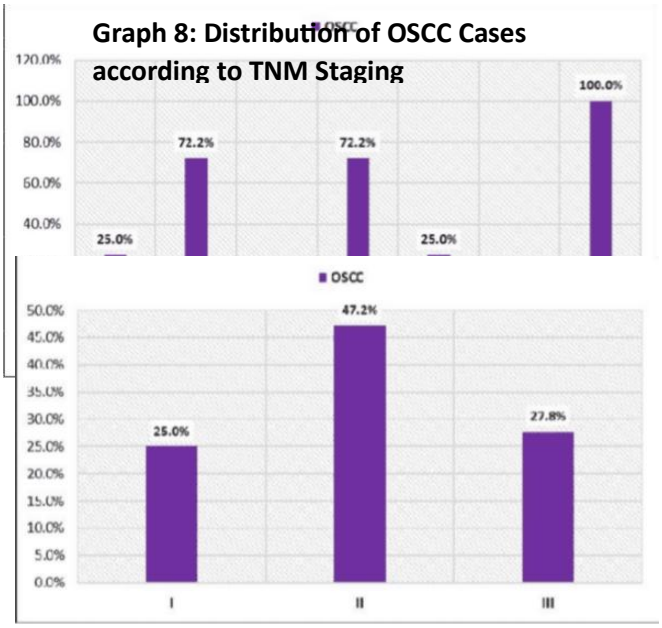
clinical presentation

In the OPMD group, 47.2% presented with a homogenous lesion pattern, while a slightly higher proportion, 52.8%, exhibited a non-homogenous presentation as shown in graph 7.

Graph 7: OPMDs study cases according to

T2 lesions were the most common, observed in 72.2% of patients, followed by T1 in 25.0%, and T3 in 2.8%. Regarding the nodal (N) status, 72.2% had no nodal involvement (N0), while 25.0% had N1, and 2.8% had N2 involvement. All patients (100.0%) were classified as M0, indicating no distant metastasis as shown in graph 8.

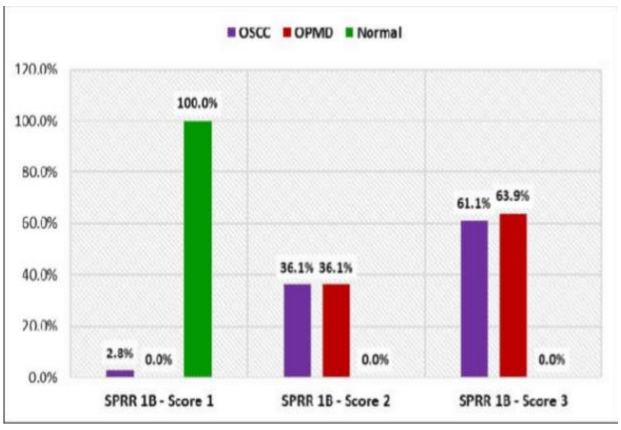
Graph 8: Distribution of OSCC Cases according to TNM Staging

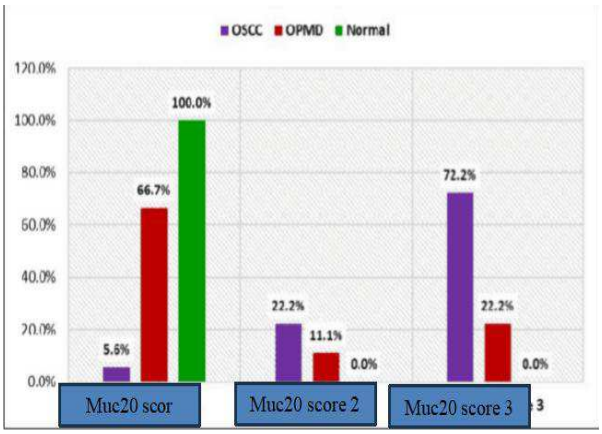


In cases of Oral Squamous Cell Carcinoma (OSCC), the clinical staging revealed that Stage II was the most prevalent, observed in 47.2% of patients, followed by Stage III in 27.8%, and Stage I in 25.0% of the cases. As shown in graph 9.

Graph 9: Distribution of study cases according to histopathological diagnosis

The distribution of MUC20 scores among the study groups demonstrated a significant difference (chi-square = 68.07, $p < 0.001$). All normal subjects (100.0%) had a MUC20 score of 1, whereas this score was observed in 66.7% of OPMD cases and only 5.6% of OSCC cases. In contrast, Score 3, indicating the highest level of expression, was most common in OSCC cases (72.2%), followed by 22.2% in OPMD, and was absent in the normal group. Score 2 was found in 22.2% of OSCC and 11.1% of OPMD, with none in normal controls. This pattern suggests a progressive increase in MUC20 expression from normal mucosa to OPMD and OSCC as shown in graph 10. In a similar way SPRR1B score distribution across OSCC, OPMD, and normal groups showed a highly significant difference (chi-square = 103.70, $p < 0.001$). This clear gradation in scores from normal mucosa to premalignant and malignant lesions underscores the potential role of SPRR1B as a biomarker in disease progression as shown in graph 10





and fig 3 and 4.

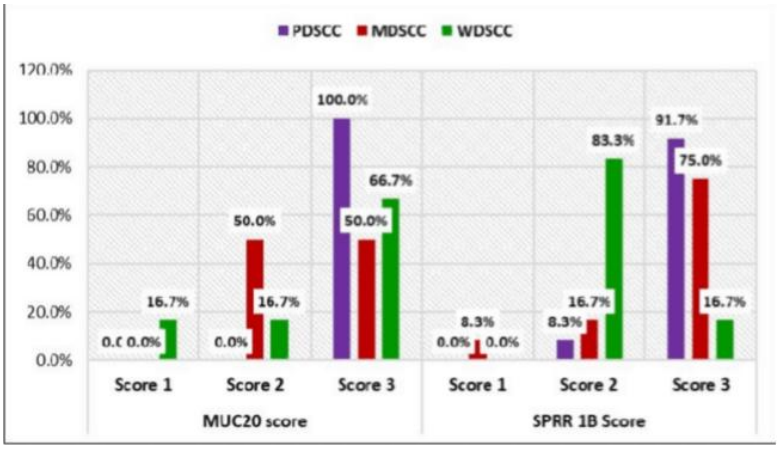
For MUC20 score (chi-square = 13.15, $p = 0.011$), all PDSCC cases (100%) exhibited Score 3, indicating high expression. Among MDSCC, expression was evenly distributed with

Graph 10: Intergroup Comparison of both markers

50.0% showing Score 2 and 50.0% showing Score 3. In WDSCC, the expression was more varied with 16.7% cases showing Score 1, another 16.7% with Score 2, and 66.7% exhibiting Score 3.

For SPRR1B score (chi-square = 19.32, p = 0.001), the majority of PDSCC cases (91.7%) showed Score 3, while 8.3% had Score 2. In MDSCC, 75.0%of cases had Score 3, 16.7% had Score 2, and 8.3% had Score 1. Conversely, in WDSCC, 83.3% of cases showed Score 2 and only 16.7% had Score 3. These findings suggest that higher scores for both MUC20 and SPRR1B are associated with poor differentiation in OSCC, highlighting their potential role in tumor aggressiveness and differentiation status. As shown in graph 11.

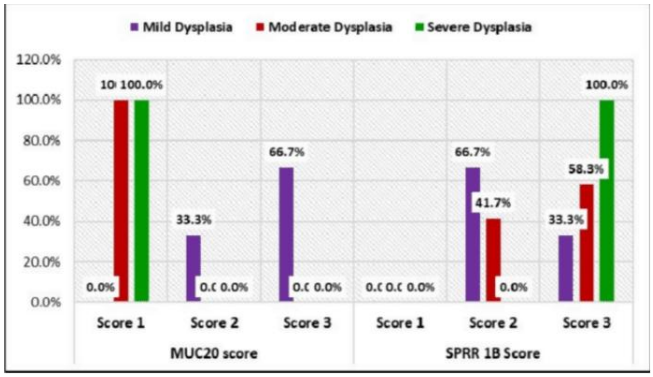
The distribution of gene expression scores (MUC20 and SPRR1B) across various grades of oral potentially malignant disorders (OPMD), including mild, moderate, and severe dysplasia, demonstrated statistically significant differences.



Graph 11: Intergroup Comparison of MUC20 & SPRR 1B Expressions among OSCC group

For MUC20 expression (chi-square = 36.00, p < 0.001), all cases with moderate and severe dysplasia showed Score 1 (100% each), indicating a uniform lower expression in higher grades. In contrast, mild dysplasia cases had a broader distribution, with 66.7% showing Score 3 and 33.3% exhibiting Score 2, suggesting significantly higher expression of MUC20 in mild dysplasia as shown in graph 13.

For SPRR1B score (chi-square = 11.80, p = 0.003), a progressive increase in expression was observed with increasing severity. In severe dysplasia all cases (100%) demonstrated Score 3, indicating the highest expression. In moderate dysplasia, 58.3% had Score 3 and 41.7% had Score 2, while in mild dysplasia, 66.7% showed Score 2 and 33.3% showed Score 3. These results suggest a clear upward trend in SPRR1B expression with increasing dysplasia severity, highlighting its potential as a biomarker for progression risk in OPMD. A shown in graph 12 and fig 1, 2.

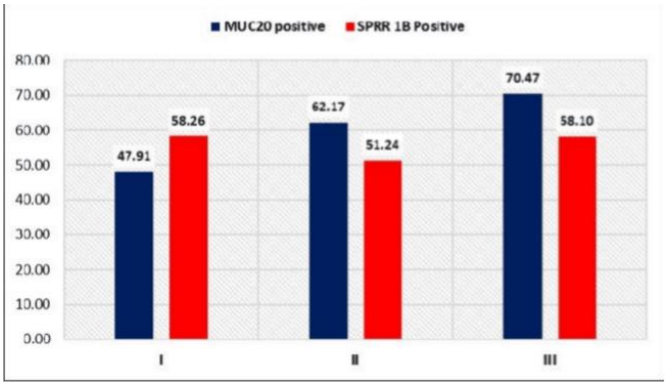


Graph 12 Intergroup Comparison of MUC20 & SPRR 1B Gene Expressions among OPMD groups

In the OSCC group, the mean expression levels of MUC20 and SPRR1B were assessed across different clinical stages (I, II, and III). The mean MUC20 expression increased progressively from 47.91 ± 27.70 in Stage I to 62.17 ± 22.04 in Stage II and 70.47 ± 20.47 in Stage III. However, the difference was not statistically significant as per ANOVA (F = 2.30, p = 0.116). For SPRR1B, the mean expression was 58.26 ± 31.62 in Stage I, 51.24 ± 25.30 in Stage II, and 58.10 ± 33.10 in Stage III, showing minimal variation without statistical significance (F = 0.25, p = 0.778).

These results suggest that there is no significant association between expression levels and OSCC staging.

In the OSCC group, the mean expression levels of MUC20 and SPRR1B were compared across different histological grades— WDSCC (well differentiated), MDSCC (moderately differentiated), PDSCC (poorly differentiated), and MUC20 expression was highest in PDSCC (85.19 ± 11.34), followed by WDSCC (50.68 ± 23.40) and MDSCC (46.85 ± 13.48),with the differences being

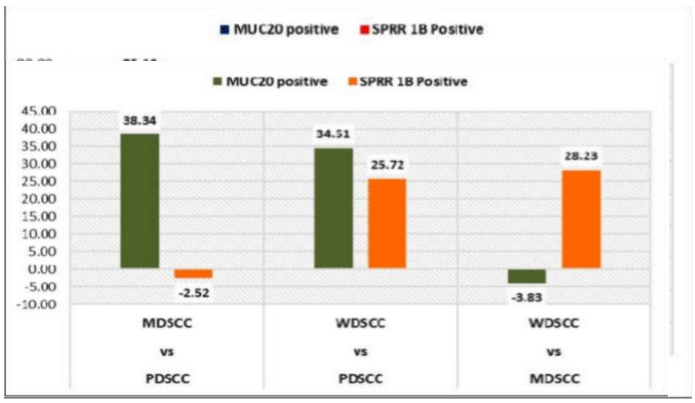


Graph 13: Intergroup Comparison of MUC20 & SPRR 1B Positivity Level among OSCC Stages

statistically significant (ANOVA F = 18.71, p < 0.001). Similarly, SPRR1B expression showed significant variation across the grades, with the highest mean in MDSCC (65.15 ± 33.17), followed by PDSCC (62.63 ± 23.09) and the lowest in WDSCC

(36.92 ± 20.67), also reaching statistical significance (F = 4.27, p = 0.023) as shown in graph 13 and fig 7, 8 ,9.

Graph 14: Post Hoc Comparisons MUC20 & SPRR



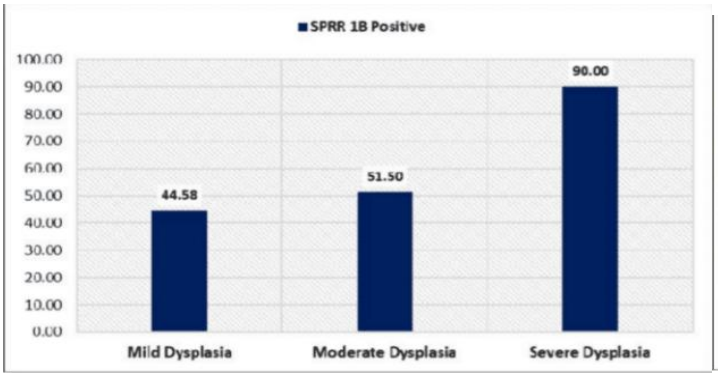
Graph 15: Intergroup Comparison of MUC20 & SPRR 1B Positivity Level among OSCC Groups

Post-hoc comparisons in graph 14 within the OSCC group revealed significant differences in MUC20 expression between PDSCC and MDSCC (mean difference = 38.34, p < 0.001) as well as between PDSCC and WDSCC (mean difference = 34.51, p < 0.001), indicating markedly higher expression in PDSCC. However, the difference between MDSCC and WDSCC was not statistically significant (mean difference = -3.83, p = 0.845).

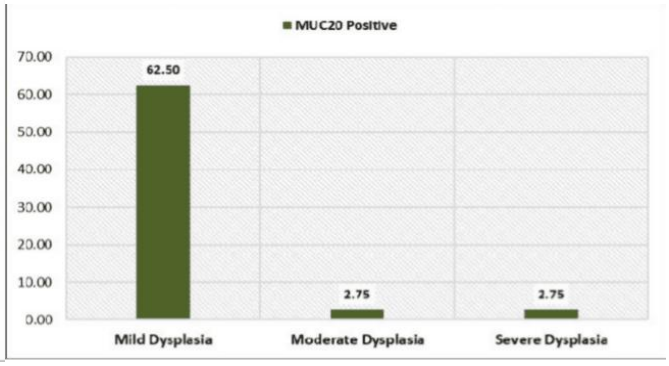
For SPRR1B expression, a significant difference was observed between MDSCC and WDSCC (mean difference = 28.23, p = 0.033),with higher expression in MDSCC. The differences between PDSCC and MDSCC (mean difference = -2.52, p = 0.970) and PDSCC and WDSCC (mean difference = 25.72, p = 0.056) did not reach statistical significance. As shown in graph 15

MUC20 expression was highest in cases with mild dysplasia, with a mean positivity of 62.50 ± 14.85The difference in MUC20 positivity across these groups was highly significant (ANOVA, F = 192.1, p < 0.001) as shown in graph 17 and fig 6.

On the other hand, SPRR1B positivity showed a progressive increase with the severity of dysplasia showing the highest mean value of 90.00 ± 8.53 in severe dysplasia as shown in graph 16. This upward trend in SPRR1B expression among the dysplasia grades was also statistically significant (ANOVA, F = 25.26, p < 0.001).

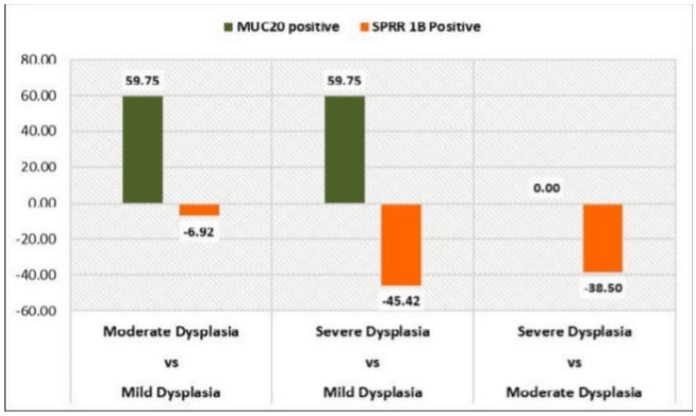


Graph-16Intergroup Comparison of SPRR 1B Positivity Level among OPMD Groups



Graph-17 Intergroup Comparison of MUC20 Positivity Level among OPMD Groups

The mean difference in MUC20 positivity between mild and moderate dysplasia was 59.75 with a p-value of <0.001, and the same significant difference (59.75, p < 0.001) was observed between mild and severe dysplasia. However, there was no difference in MUC20 expression between moderate and severe dysplasia (mean difference = 0.00, p = 1.000).



Graph-18 Post Hoc Paired Comparisons of MUC20 Positivity and SPRR 1B Positivity Level among

In terms of SPRR1B positivity, no significant difference was noted between mild and moderate dysplasia (mean difference = -6.92, p = 0.579). However, a highly significant decrease was found when comparing mild dysplasia with severe dysplasia (mean difference = -45.42, p < 0.001), and similarly, moderate dysplasia showed significantly lower SPRR1B expression than severe dysplasia (mean difference = -38.50, p < 0.001). as shown in graph 18

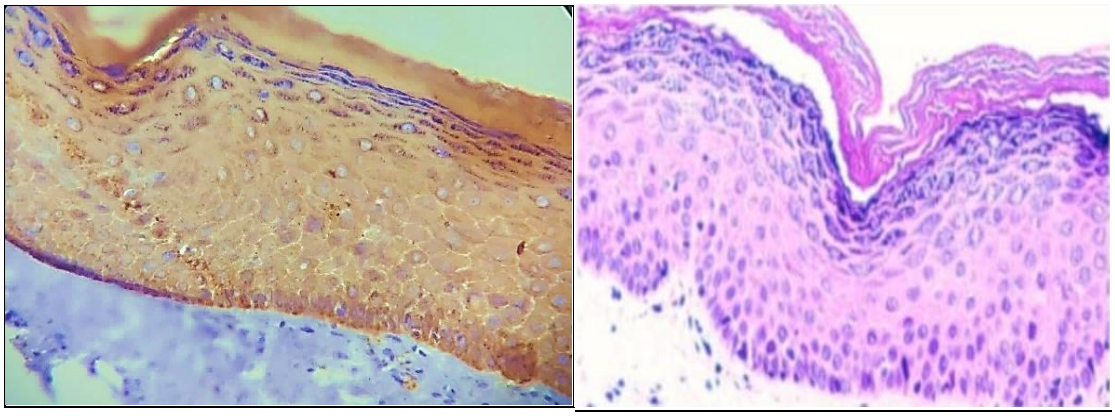


FIG 1. EXPRESSION OF SPRR1B IN MILD DYSPLASIA AT 1OX. MAGNIFICATION

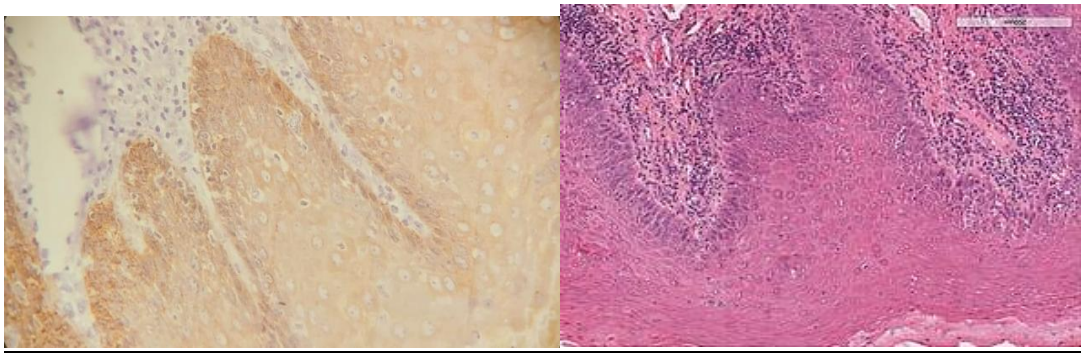


FIG 2.EXPRESSION OF SPRR1B IN SEVERE DYSPLASIA AT 10X. MAGNIFICATION

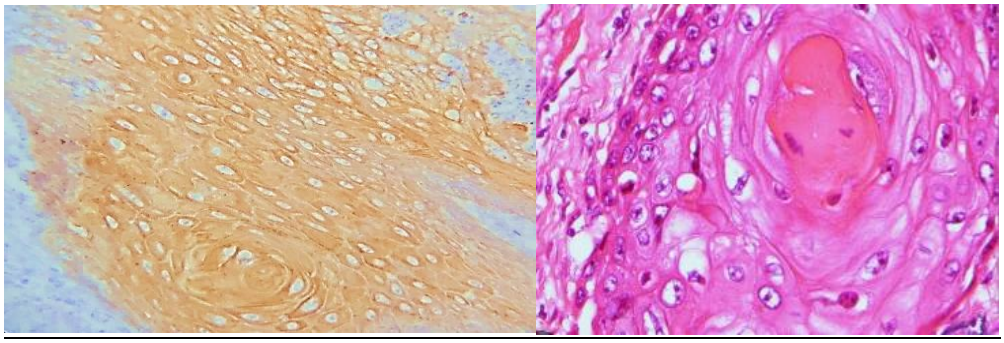


FIG3. EXPRESSION OF SPRR1B IN WDSCC AT 10X. MAGNIFICATION

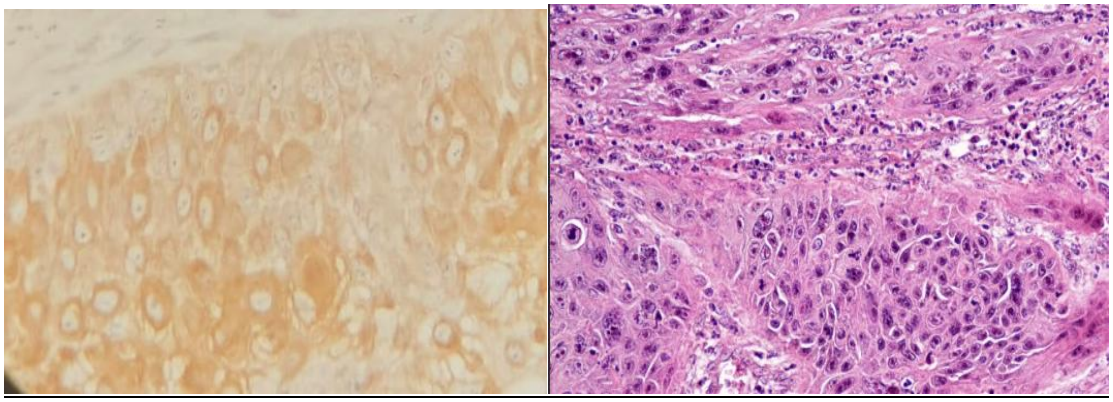


FIG 4. EXPRESSION OF SPRR1B IN MDSCC AT 10X. MAGNIFICATION

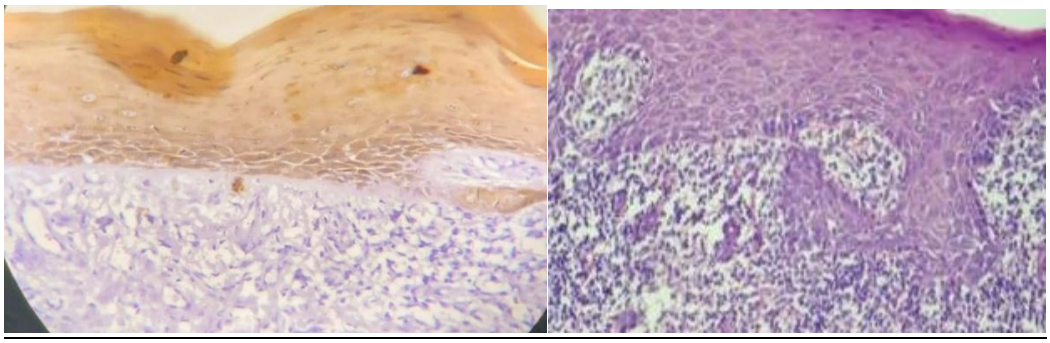


FIG 5. EXPRESSION OF SPRR1B IN ORAL LICHEN PLANUS AT 1OX. MAGNIFICATION

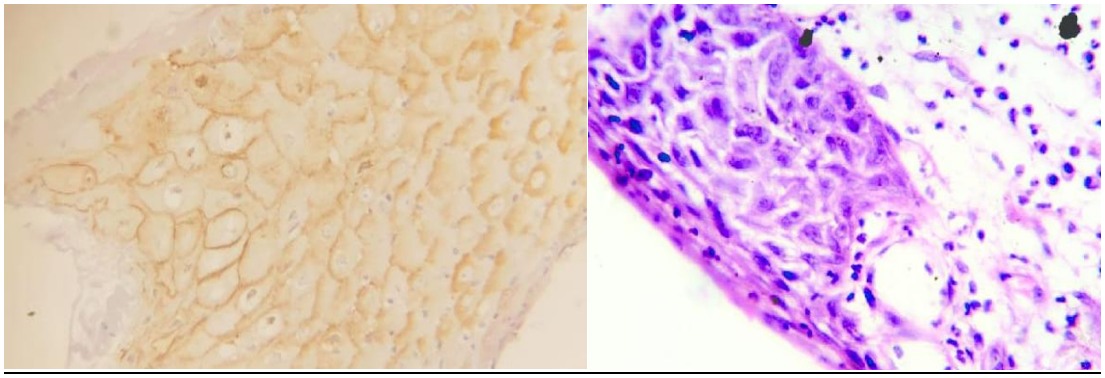


FIG 6. EXPRESSION OF MUC 20 IN MILD DYSPLASIA AT 1OX. MAGNIFICATION

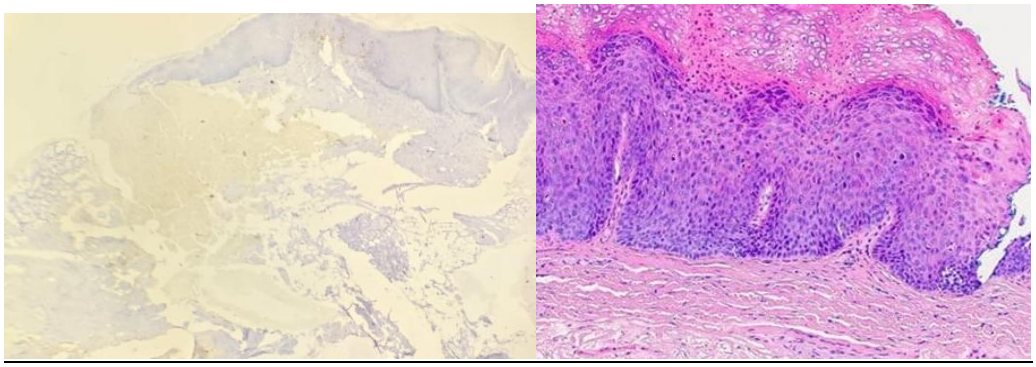


FIG 7. EXPRESSION OF MUC 20 IN SEVERE DYSPLASIA AT 1OX. MAGNIFICATION

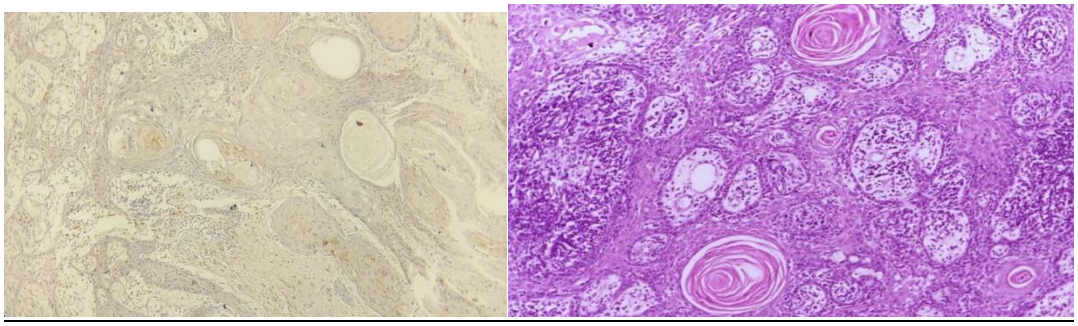


FIG 8. EXPRESSION OF MUC 20 IN WDSCC AT 1OX. MAGNIFICATION

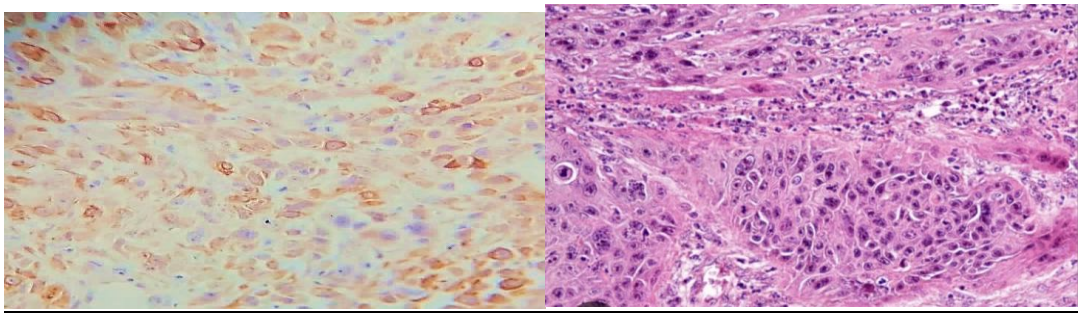


FIG 9. EXPRESSION OF MUC20 IN MDSCC AT10X.MAGNIFICATION

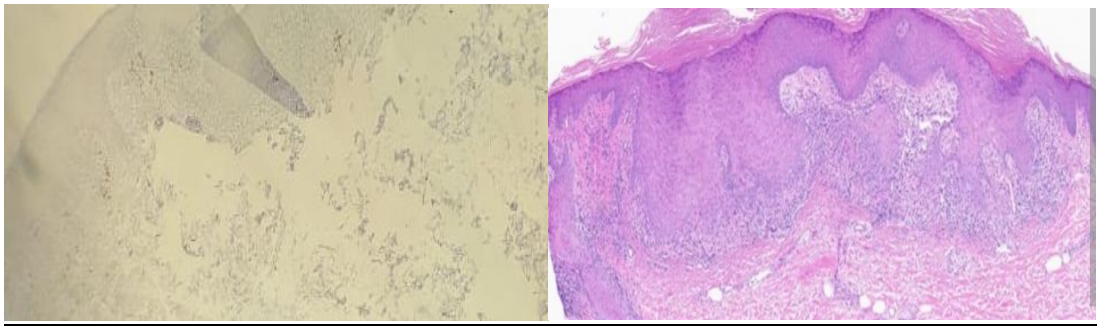


FIG10.EXPRESSION OF MUC20 IN ORAL LICHEN PLANUS AT1OX. MAGNIFICATION

Discussion

Oral cancer is a major global health concern, with over 389,000 new cases and 188,000 deaths annually, and a high burden in India due to tobacco-related habits [49,50]. OSCC constitutes over 90% of oral cancers and is frequently preceded by OPMDs in approximately 80% of cases [51,54]. Early diagnosis is crucial, as initial OPMDs may be reversible with appropriate intervention [55].

In this study, both MUC20 and SPRR1B showed a progressive increase in expression from normal mucosa to OPMDs and OSCC, supporting their role in oral carcinogenesis. MUC20 expression was significantly elevated in OSCC, particularly in poorly differentiated tumors, indicating its association with tumor aggressiveness. Similar findings have been reported in other malignancies, where MUC20 promotes proliferation, invasion, and metastasis (Li et al., 2022; Wang et al., 2019) [2,61].

Interestingly, MUC20 expression was higher in mild dysplasia compared to advanced dysplasia, suggesting a potential role in early dysplastic changes. This pattern indicates a complex role of MUC20 in tumor initiation and progression.

SPRR1B expression demonstrated a progressive increase with dysplasia severity and was highly expressed in OSCC, indicating its role in epithelial transformation and disease progression. Previous studies have linked SPRR1B overexpression to enhanced proliferation, epithelial–mesenchymal transition, and poor prognosis (Lee et al., 2014; Zhao et al., 2017; Zhang et al., 2016) [2].

No significant association was observed between marker expression and clinical staging of OSCC, suggesting that these biomarkers are more closely related to histological differentiation rather than tumor stage.

Overall, these findings highlight the potential of MUC20 and SPRR1B as biomarkers for early detection, risk stratification, and prognostic evaluation in oral carcinogenesis.

Conclusion

The present study demonstrates a progressive increase in MUC20 and SPRR1B expression from normal oral mucosa to OPMDs and OSCC, indicating their involvement in oral carcinogenesis. MUC20 expression correlates with tumor differentiation and aggressiveness, while SPRR1B shows a strong association with dysplasia severity and malignant transformation.

These findings suggest that both markers have potential as diagnostic and prognostic biomarkers in oral lesions. However, limitations such as small sample size, cross-sectional design, and lack of functional analysis restrict definitive conclusions. Further large-scale and longitudinal studies are required to validate their clinical utility and underlying molecular mechanisms.

ABBREVIATIONS

MUC20 – Mucin 20

SPRR1B – Small Proline-Rich Protein 1B

OSCC – Oral Squamous Cell Carcinoma

WDSCC – Well-Differentiated Squamous Cell Carcinoma

MDSCC – Moderately Differentiated Squamous Cell Carcinoma

PDSCC – Poorly Differentiated Squamous Cell Carcinoma

OPMDs – Oral Potentially Malignant Disorders

IHC – Immunohistochemistry

OLP – Oral Lichen Planus

OSMF – Oral Submucous Fibrosis

EGFR – Epidermal Growth Factor Receptor

MMPs – Matrix Metalloproteinases

MET – Mesenchymal-Epithelial Transition factor

NOM – Normal Oral Mucosa

GLOBOCAN – Global Cancer Observatory

TANGO – Transport and Golgi Organization Protein

Declarations

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding -NA

Data availability The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical approval: This article does not contain any studies with animals performed by any of the authors.

Institutional review board statement “This study protocol was submitted to the Institutional Ethical Committee of King George’s Medical University for evaluation and clearance. The ethical clearance number was obtained vide Ref. no. XXI- PGTSC-IIA/P75).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Author Participation

Dr. Payal Panwar contributed to the study conception and design, data collection, analysis, and manuscript drafting.
Dr. Shalini Gupta contributed to study supervision, overall guidance, critical revision of the manuscript, and final approval.

Dr. Priyanka Singh contributed to data analysis and manuscript preparation.
Dr. Uma Shanker Pal contributed to study design, interpretation of data, and manuscript review.
Dr. Vandana Singh contributed to literature review and manuscript editing.
Dr. Sameer Gupta contributed to data collection and manuscript review.
All authors have read and approved the final manuscript.

REFERENCES

1. Oral potentially malignant disorders: risk of progression to malignancy Paul M. Speight BDS, PhD, FDSRCPS, FDSRCS (Eng), FRC Path Syed Ali Khurram BDS, MSc, PhD, MFDSRCS, FDSRCS, FRCPath and Omar Kujan DDS, DipOPath, MSc, PhD
2. Identification of Oral Squamous Cell Carcinoma markers MUC2 and SPRR1B downstream of TANGO Tomonori Sasahira1 · Miyako Kurihara-Shimomura1,2 · Hiroyuki Shimomura1,2 · Anja Katrin Bosserhoff3 Tadaaki Kirita (2021)
3. Kumari, Pratima, Priyanka Debta, and Anshuman Dixit. "Oral Potentially Malignant Disorders: etiology, pathogenesis, and transformation into oral cancer." Frontiers in pharmacology 13 (2022): 825266.
4. Michifuri, Yoshitaka, et al. "Small proline-rich protein-1B is overexpressed in human oral squamous cell cancer stem-like cells and is related to their growth through activation of MAP kinase signal." Biochemical and Biophysical Research Communications 439.1 (2013): 96-102.
5. Neelam g. shah, phd,1 trupti i. trivedi, phd,1 rajen a. tankshali, ms,2jigneshv. goswami, ms,2 dhaval h. jetly, md,3 shilin n. shukla, md,4 pankaj m. shah,md,4 ramtej j. verma, phd prognostic significance of molecular markers in oralsquamous cell carcinoma: a multivariate analysis.
6. Cheng, Hui, et al. "Bladder Cancer Patients with Elevated SPRR1B Expression Experiencing a Poor Prognosis." Archivos Espanoles de Urologia 77.5 (2024): 554-569.
7. Xuanyuan, Xinyang, et al. "SPRR1B+ keratinocytes prime oral mucosa for rapid wound healing via STAT3 activation." Communications Biology 7.1 (2024): 1155.
8. Chaudhary, Raushan Kumar, et al. "Decoding the role of SPRR1A and SPRR1B gene in cancer: A comprehensive review." Gene Reports (2024): 101926.
9. Sasahira, Tomonori, et al. "Searching for new molecular targets for oral squamous cell carcinoma with a view to clinical implementation of precision medicine." Journal of Personalized Medicine 12.3 (2022): 413.
10. Zhang, Zihe, et al. "Identification of small proline-rich protein 1B (SPRR1B) as a prognostically predictive biomarker for lung adenocarcinoma by integrative bioinformatics analysis." Thoracic cancer 12.6 (2021): 796-806

11. Song, Yan, et al. "DGUOK-AS1 promotes cervical squamous cell carcinoma progression by suppressing miR-499a-5p that targets SPRR1B in vitro." Biochemical and Biophysical Research Communications 585 (2021): 177-184

12. Cao, Hao, et al. "High Expression of SPRR1B Indicates Unfavourable Clinical Outcomes in Lung Adenocarcinoma." (2020) of MUC12, MUC16, and MUC20 in patients with active and remission ulcerative colitis." Mediators of Inflammation 2015.1 (2015): 659018.

13. Xiao, Xiuying, et al. "Role of MUC20 overexpression as a predictor of recurrence and poor outcome in colorectal cancer." Journal of translational medicine 11 (2013): 1-12.

14. Higuchi, Toshio, et al. "Molecular cloning, genomic structure, and expression analysis of MUC20, a novel mucin protein, up-regulated in injured kidney." Journal of Biological Chemistry 279.3 (2004): 1968-1979.

15. Strous, Ger J., and Jan Dekker. "Mucin-type glycoproteins." Critical reviews in biochemistry and molecular biology 27.1-2 (1992): 57-92.

16. Higuchi, Toshio, et al. "MUC20 suppresses the hepatocyte growth factor-induced Grb2-Ras pathway by binding to a multifunctional docking site of met." Molecular and cellular biology 24.17 (2004): 7456-7468.

17. Wang, Hui, et al. "The expression and prognostic significance of Mucin 13 and Mucin 20 in oesophageal squamous cell carcinoma." Journal of Cancer Research and Therapeutics 11.Suppl 1 (2015): S74-S79.

18. Cox, Kristin E., et al. "The mucin family of proteins: candidates as potential biomarkers for colon cancer." Cancers 15.5 (2023): 1491.

19. Chen CH et al (2013) MUC20 overexpression predicts poor prognosis and enhances EGF-induced malignant phenotypes via activation of the EGFR-STAT3 pathway in endometrial cancer. Gynecol Oncol 128:560–567. https://doi.org/10.1016/j.ygyno.2012.12.012

20. Chen ST, Kuo TC, Liao YY, Lin MC, Tien YW, Huang MC (2018) Silencing of MUC20 suppresses the malignant character of pancreatic ductal adenocarcinoma cells through inhibition of the HGF/MET pathway. Oncogene 37:6041–6053. https://doi.org/ 10.1038/s41388-018-0403-0

21. Fu, Lingfeng, et al. "Intracellular MUC20 variant 2 maintains mitochondrial calcium homeostasis and enhances drug resistance in gastric cancer." Gastric Cancer 25.3 (2022): 542-557.

22. Jonckheere, Nicolas, and Isabelle Van Seuningen. "Integrative analysis of the cancer genome atlas and cancer cell lines encyclopedia large-scale genomic databases: MUC4/MUC16/MUC20 signature is associated with poor survival in human carcinomas." Journal of translational medicine 16 (2018): 1-22

23. Woodward, Ashley M., and Pablo Argüeso. "Expression analysis of the transmembrane mucin MUC20 in human corneal and conjunctival epithelia." Investigative ophthalmology & visual science 55.10 (2014): 6132-6138.

24. Li, Meng, et al. "Paclitaxel promotes mTOR signaling-mediated apoptosis in esophageal cancer cells by targeting MUC20." Thoracic Cancer 14.31 (2023): 3089-3096.

25. Shimomura, H.; Sasahira, T.; Nakashima, C.; Kurihara-Shimomura, M.; Kirita, T. Non-SMC Condensin I Complex Subunit H (NCAPH) Is Associated with Lymphangiogenesis and Drug Resistance in Oral Squamous Cell Carcinoma. J. Clin. Med. 2020, 9, 72. https://doi.org/10.3390/jcm9010072

26. Yamamoto-Furusho, Jesús K., et al. "Differential expression of MUC12, MUC16, and MUC20 in patients with active and remission ulcerative colitis." Mediators of Inflammation 2015.1 (2015): 659018.

27. Wang, Huihan, et al. "Mucin 20 (MUC20) Modulates Proteasome Assembly Chaperones through the c-MET Pathway and Is a Biomarker of Proteasome Inhibitor Sensitivity in Myeloma." (2014): 274-274.

28. Wang, Xiaobin, et al. "MUC20 regulated by extrachromosomal circular DNA attenuates proteasome inhibitor resistance of multiple myeloma by modulating cuproptosis." Journal of Experimental & Clinical Cancer Research 43.1 (2024): 68

29. Li, Guisen, et al. "Tandem repeats polymorphism of MUC20 is an independent factor for the progression of immunoglobulin A nephropathy." American journal of nephrology 26.1 (2006): 43-49.

30. Patterson, Tricia, et al. "Mechanism of repression of squamous differentiation marker, SPRR1B, in malignant bronchial epithelial cells: role of critical TRE-sites and its transacting factors." Oncogene 20.5 (2001): 634-644.

31. Li, Shimin, et al. "Small proline-rich protein 1B (SPRR1B) is a biomarker for squamous metaplasia in dry eye disease." Investigative ophthalmology & visual science 49.1 (2008): 34-41.

32. Tesfaigzi, Yohannes, Paul S. Wright, and Steven A. Belinsky. "SPRR1B overexpression enhances entry of cells into the G0 phase of the cell cycle." American Journal of Physiology-Lung Cellular and Molecular Physiology 285.4 (2003): L889-L898.

33. Zhang, Chenlu, et al. "Small proline-rich proteins (SPRRs) are epidermally produced antimicrobial proteins that defend the cutaneous barrier by direct bacterial membrane disruption." Elife 11 (2022): e76729.

34. McNamara, N. A. "Small Proline Rich Protein, SPRR1B: A Biomarker for Squamous Metaplasia in Human Patients With Sjögren's Syndrome." Investigative Ophthalmology & Visual Science 47.13 (2006): 5609-5609.

35. Hao, Siyu, et al. "SPRR1B is Related to the Immune Microenvironment and Can Be Used as a Biomarker for the Diagnosis of Psoriasis." International Journal of General Medicine (2024): 401-418.

36. Michifuri, Yoshitaka, et al. "Small proline-rich protein-1B is overexpressed in human oral squamous cell cancer stem-like cells and is related to their growth through activation of MAP kinase signal." Biochemical and Biophysical Research Communications 439.1 (2013): 96-102.

37. Yao, Ling, et al. "Small proline-rich protein 2B Facilitates gastric adenocarcinoma proliferation via MDM2-p53/p21 signaling pathway." OncoTargets and therapy (2021): 1453-1463.

38. Feng, Yan, et al. "Establishment of a prognostic prediction system based on tumor microenvironment of pancreatic cancer." Medicine 101.51 (2022): e32364.

39. Geng, Lou, et al. "Identification of potential key biomarkers and immune infiltration in oral lichen planus." Disease Markers 2022.1 (2022): 7386895.

40. Pillai, J., Chincholkar, T., Dixit, R. et al. A systematic review of proteomic biomarkers in oral squamous cell cancer. World J Surg Onc 19, 315 (2021). https://doi.org/10.1186/s12957-021-02423-y

41. Bhatia, R., Gautam, S.K., Cannon, A. et al. Cancer-associated mucins: role in immune modulation and metastasis. Cancer Metastasis Rev 38, 223–236 (2019). https://doi.org/10.1007/s10555-018-09775-0

42. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338

43. Scully R, Panday A, Elango R, Willis NA. DNA double-strand break repair-pathway choice in somatic mammalian cells. Nat Rev Mol Cell Biol. 2019 Nov;20(11):698-714. doi: 10.1038/s41580-019- 0152-0. Epub 2019 Jul 1. PMID: 31263220; PMCID: PMC7315405.

44. Addissouky, T.A., El Sayed, I.E.T., Ali, M.M.A. et al. Oxidative stress and inflammation: elucidating mechanisms of smoking- attributable pathology for therapeutic targeting. Bull Natl Res Cent 48, 16 (2024). https://doi.org/10.1186/s42269-024-01174-6

45. Menon SS, Guruvayoorappan C, Sakthivel KM, Rasmi RR. Ki-67 protein as a tumour proliferation marker. Clin Chim Acta. 2019 Apr;491:39-45. doi: 10.1016/j.cca.2019.01.011. Epub 2019 Jan 14. PMID: 30653951.

46. Cívico-Ortega JL, González-Ruiz I, Ramos-García P, Cruz- Granados D, Samayoa-Descamps V, González-Moles MÁ. Prognostic and Clinicopathological Significance of Epidermal Growth Factor Receptor (EGFR) Expression in Oral Squamous Cell Carcinoma: Systematic Review and Meta-Analysis. Int J Mol Sci. 2023 Jul 25;24(15):11888. doi: 10.3390/ijms241511888. PMID: 37569265; PMCID: PMC10419199.

47. Silva, Gabriela Vivili Domingues, et al. "Exploring the combination of tumor-stroma ratio, tumor-infiltrating lymphocytes, and tumor budding with WHO histopathological grading on early-stage oral squamous cell carcinoma prognosis." Journal of Oral Pathology & Medicine 52.5 (2023): 402-409.

48. Itoh T, Yonezawa S, Nomoto M, Ueno K, Kim YS, Sato E (1996) Expression of 2011, antigens and Lewis X-related antigens in carcinomas and dysplasia of the pharynx and larynx. Pathol Int 46:646–655

49. Singh, Mayank, et al. "Expression of CD44 and Its Correlation With Clinicopathological Factors in Oral and Oropharyngeal Carcinoma: A Retrospective Immunohistochemical Study." *Cureus* 17.3 (2025).

50. Bray F et al (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74(3):229– 263. https://doi.org/10.3322/caac.21834

51. Gharat SA, Momin M, Bhavsar C (2016) Oral squamous cell carcinoma: current treatment strategies and nanotechnology-based approaches for Prevention and Therapy. Crit Rev Ther Drug Carrier Syst 33(4):363–400.

52. Gigliotti J, Madathil S, Makhoul N (Sep. 2019) Delays in oral cavity cancer. Int J Oral Maxillofac Surg 48(9):1131– 1137. https://doi.org/10.1016/j.ijom.2019.02.015

53. Kowalski LP, de Oliveira MM, Lopez RVM, Silva DRME, Ikeda MK, Curado MP (2020) Survival trends of patients with oral and oropharyngeal cancer treated at a cancer center in São Paulo, Brazil. Clin Sao Paulo Braz 75:e1507. https://doi.org/10.6061/clinics/2020/e1507

54. Sheetal Choudhari, Deepak Kulkarni, Sangeeta Patankar, Supriya Kheur, Sachin Sarode,Linking inflammation and angiogenesis with fibrogenesis: Expression of FXIIIA, MMP-9, and VEGF in oral submucous fibrosis.

55. N. Cirillo Precursor lesions, overdiagnosis, and oral cancer: a critical review Cancers (Basel) (2024)

56. Y.B. Adhane *et al.* Oral submucous fibrosis: histopathological features with pathophysiologic correlations IP J Diagn Pathol Onco(2021)

57. Sneha Masne Deshpande, Sheetal Choudhary, Sangeeta Patankar, Palak Khetan, Girish Sadaphule, Sanpreet Singh Sachdev, Comparative analysis of Ki-67, α-SMA, and MMP-9 expression in oral submucous fibrosis and oral leukoplakia with/without dysplasia: Insights into malignant transformation mechanisms.

58. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer.Oral Oncol. 2009 Apr-May;45(4-5):309-16.doi: 10.1016/j.oraloncology.2008.06.002. Epub 2008 Sep 18. PMID: 18804401.

59. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008 Apr;83(4):489-501. doi: 10.4065/83.4.489. Erratum in: Mayo Clin Proc. 2008 May;83(5):604. PMID: 18380996.

60. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, Rajan B; Trivandrum Oral Cancer Screening Study Group. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. Lancet. 2005 Jun 4- 10;365(9475):1927-33. doi: 10.1016/S0140-6736(05)66658-5. PMID: 15936419.

61. Mucin 20 modulates proteasome capacity through c-Met signalling to increase carfilzomib sensitivity in mantle cell lymphomaXiaobin Wang, Fazal Shirazi, Wei Yan, Xiaoyu Liu, Hua Wang, Robert Z. Orlowski, Huihan Wang

62. Farzana Mahomed, Recent advances in mucin immunohistochemistry in salivary gland tumors and head and neck squamous cell carcinoma.