MOLECULAR SIGNATURES – BIOMARKERS FOR EARLY DETECTION OF OPMDs

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INTRODUCTION: Oral potentially malignant disorders (OPMDs) are conditions comprising of a variety of clinico pathological alterations with variable malignant transformation. Common **OPMDs are leukoplakia, erythroplakia, oral lichen planus, and oral submucus fibrosis**. Oral squamous cell carcinoma (OSCC) is a common type of malignancy mostly preceded by OPMD which may show histopathological changes called oral epithelial dysplasia. When compared to other cancers, OSCC has a low five-year survival rate, which is **roughly 20% when diagnosed at an advanced stage and up to 80% when discovered at an early stage**. Lack of effective screening methods to identify OPMDs developing into malignancy is a major barrier for its early detection. Hence the **need of biomarkers arose,** and the current review looked at the role of **various biomarkers in OPMDs for better screening, diagnosis and prognosis.**

AIM: To review the role of diagnostic and prognostic utility of various biomarkers reported in OPMDs.

MATERIALS AND METHOD- A comprehensive search of online databases including PUBMED, MEDLINE and SCOPUS were conducted to identify studies from published data between January 2013 to December 2022 (last 10 years) using key words **"biomarkers in OPMDs", "salivary biomarkers in OPMDs", "biomarkers of epithelial mesenchymal transition."** Relevant data from 50 articles tabulated based on the type of specimens used.

TISSUE

Author	Group (Sample size)	Biomarkers	Result
Padin-Iruegas E et al, 2022	Leukoplakia, Lichen planus (85)	MLH1, MGMT	MLH1 ↑ in OSCC , MGMT ↑ in OPMD converting into malignancy
Jawahar G et al, 2022	OPMD (30)	E6 oncoprotein, p16 Ink4a	↑ in severe and moderate dysplasia
Soodet A et al, 2022	OPMD (153)	S100A-7	↑ in OSCC as compared to OPMD
de Vicente et al, 2019	OPMD (180)	NANOG	↑ with increasing grades of dysplasia
Sharada et al, 2018	OSFWT (60)	E-cadherin	↓ with progression of disease
Gadbail A R et al, 2018	OPMD (170)	Ki67, CD105, α-SMA	↑ with increasing grade of dysplasia
Habiba U et al, 2017	Leukoplakia (79)	ALDH1, Podoplanin	↑ with OSCC incidence
Surendran S et al, 2017	OPMD (550)	CD44, CD31, CXCR4, SDF1	↑CD44 with increase in grade of dysplasia.
Philipone et al, 2016	Leukoplakia (77)	mi-RNA-208b-3p, 3065-5p	↑ with progression to OSCC
Chattopadhyay et al, 2016	leukoplakia, lichen planus, OSMF (96)	miR7, 31, 133a, 204, 206, 1293	↑ with progression towards cancer
Reyes et al, 2015	Leukoplakia, Erythroplakia (58)	β- catenin	↑ with progression and early malignant transformation to OSCC
Silva et al, 2015	Leukoplakia (49)	β- catenin	expression with mild & moderate dysplasia
Shi et al, 2015	Lichen planus (36)	miR-375	↓with progression from normal to OLP and than to OSCC
Kai-Feng Hung et al, 2015	OPMD (46)	miR-21, miR-31	Both ↑in OPMD, miR-31 ↑ more in malignant transformation
Anura et al, 2014	Epithelial dysplasia, OSFWT (68)	E-cadherin	Potential in assessment of malignant potentiality of OSMF
Silva D F et al, 2014	Leukoplakia (50)	E-cadherin, Twist	Prediction of malignant transformation
kyrodimou et al, 2014	Leukoplakia (75)	desmoglein-3, γ-catenin, E-cadherin, β- catenin	Altered expression & role in malignant transformation
Von zeidler et al, 2014	Leukoplakia (43)	E- cadherin	↓early phenomenon observed in moderate-severe dysplasia
De sarkar et al, 2014	Leukoplakia, lichen planus (96)	has-miR- 1293, 31, 7, 206, 204, 133a	has-miR-31 ↑ in cancer and leukoplakia tissues.
Lameira A G et al, 2014	Leukoplakia (98)	MCM3, Ki67	MCM-3 a better marker than Ki67 for evaluation of dysplastic changes
Rani et al, 2013	Epithelial dysplasia (136)	Laminin- 5	↑in OSCC, confirming its role as a marker of malignant transformation

BLOOD

Author	Groups	Biomarkers	Results
Leiyu Chen et al, 2020	OPMD (197)	SNCG, SCCAg	↑in OSCC as compared to OPMD
Saurabh Juneja et al, 2017	OPMD (50)	nitric oxide, vitamin C	↑ in OSCC whereas vitamin C levels ↓in OSCC
Sun et al, 2016	Leukoplakia (174)	miR-9	miR-9 is a tumor suppressor in OSCC and can serve as a potential therapeutic target to treat malignancy
Dadhich M et al, 2014	OPMD (85)	Sialic acid	↑in OSCC

CYTOLOGY

Author	Groups	Biomarkers	Results
Abirami Moorthy et al, 2022	OSMF (49)	EGFR	18 fold ↑ in OSCC & 3 fold ↑in OSMF as compared to normal
Omar kujan et al, 2020	Leukoplakia (72)	MSH-6, MSH-2, MLH-1, PMS-2	↓ with increasing grade of oral epithelial dysplasia
Omar kujan et al, 2019	Leukoplakia (55)	CDK4, CDK6, Notch1	↑ with development OSCC from non- dysplastic epithelium

SALIVA

Author	Groups	Biomarkers	Results
Moorthy A et al, 2022	OSMF (49)	EGFR	18 fold ↑in OSCC & 3 ↑in OSMF
Tu et al, 2022	OPMD (67)	miR-375	↓in OPMD
His- Feng Tu et al, 2021	OPMD (69)	miR-375	↓ in cases with malignant transformation
Meng et al, 2021	Leukoplakia (100)	miR-142	↑ in OPMD
Babiuch, 2020	OED, OLP (45)	IL1α, IL6, IL8	↑ with progression to OSCC
Singh, 2020	OPMD (159)	IL1β, IL8	↑ with progression to OSCC
Menaka TR et al, 2019	OPMD (42)	Alkaline phosphatase	↑in OPMD
Ankita K et al, 2019	leukoplakia, OSMF (60)	Endothelin-1	↑in OSCC followed by OSMF and leukoplakia
Komal Smriti et al, 2019	OPMD (88)	MMP-9	↑OPMD and OSCC(very ↑ in poorly differentiated
Khyani, 2017	OPMD (105)	IL6, IL8	↑OPMD and OSCC
Shahidi et al, 2017	lichen planus (62)	microRNA-320a	Non invasive predictive tool for dysplastic OLP
Gleber-Netto, 2016	OPMD (180)	IL1β, IL8	Potential for early detection of OSCC & OPMD
Panneer, 2015	Leukoplakia (75)	IL6	Proposed for further evaluation to assess its clincal utility
Zahran et al, 2015	OPMD without dysplasia, OPMD with dysplasia (100)	miR-184, 21, 145	miR-21 and 184 ↑in OSCC and 145 lowest in OSCC
Kai-Feng Hung et al, 2015	OPMD (20)	miR-21, miR-31	↑ in OPMD, miR-31 more in malignant transformation
Lisa Cheng, 2014	OLP (101)	IL6, IL8	Useful biomarker for OSCC & not influenced by OLP
Rajkumar, 2014	OPMD (300)	IL8	IL8 in saliva is a better medium for cancer prediction than blood
Momen- Hervai et al, 2014	Leukoplakia (34)	miR-24, miR-27b	↑in OSCC
Dadhich M et al, 2014	OPMD (85)	Sialic acid	↑in OSCC
Juretiŏ, 2013	OPMD (57)	IL6	↑ in OSCC
Punyani, 2013	OPMD (75)	IL8	↑ in OSCC
Yang et al, 2013	Leukoplakia (52)	miR-10b, 145, 99b, 708, 181c	used for monitoring of cancer precursor lesions & early detection of disease progression
R. Cerovic et al, 2013	Lichen planus (19)	TNF-α, IL-6	↑in OSCC

DISCUSSION

- ✓ Tissues, saliva, blood, and cells are all tested for biomarkers. **Saliva is recommended as a useful specimen** for identifying biomarkers associated with diseases due to its noninvasiveness and the presence of a diversity of biomolecules.
- ✓ **Salivary biomarkers**, which bathe the oral cavity, are recommended as **essential diagnostic and screening adjuncts for oral disorders**, particularly OSCC and OPMDs.
- ✓ In our review, miRNAs were detected in tissue, saliva and blood samples, which offers a great advantage over other types. They were found in 14 out of 50 studies.
- ✓ E-cadherin (5/22) & β-catenin (3/22) were found more in tissues and were associated with malignant transformation.
- ✓ IL-6 (6/23), IL-8 (7/23) were seen in majority of studies involving saliva as samples. IL-6 & 8 are involved in pathogenesis and malignant transformation of OPMD and hence are suitable biomarkers in saliva.

CONCLUSION

- ✓ Biomarkers are **critical to identify high-risk people** and tracking the course of OPMDs to malignancy. The **use of biomarkers in clinical practice** has the potential to **improve diagnostic accuracy and treatment approaches**.
- ✓ Further studies are required to identify reliable biomarkers that can help in identification of risk stratification and malignant transformation of OPMDs.

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