Survivin in the malignant transformation of Oral Potentially Malignant Disorders to Oral Squamous Cell Carcinoma: A Systematic Review

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Abstract

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, contributing 80% of the malignancies in the head and neck region. Survivin **(an** anti-apoptotic protein) has been recently identified as a promising diagnostic and therapeutic target in various types of cancer. This systematic review was aimed at identifying the correlation between the expression levels of survivin and their role in the progression of OSCC. Using a search strategy, articles were searched in the databases up to August 2023, fulfilling the inclusion and exclusion criteria. Articles were collected from online databases: PubMed, Scopus, Web of Science, and the Cochrane Library. Based on the search, about 754 articles were found and retrieved from databases. The titles and abstracts of articles (n = 453) were reviewed, and 421 studies were eliminated. Six studies were included in this systematic review that correlate the expression of survivin with the progression of OPMDs and OSCC. All the studies included in this review were based on immunohistochemical analysis and showed significant upregulation of survivin expression in OSCC, particularly in the suprabasal and superficial thirds of the epithelium. Several molecular markers, such as survivin, may be needed to clarify malignant transformation, hence warranting more research in this area. Based on the findings of this analysis, survivin has been suggested as a possible biomarker that might be used for the early detection of the malignant transition of OPMDs to OSCC.

Keywords: Survivin, Mouth Neoplasms, Carcinoma, Squamous Cell, Precancerous Conditions, Biomarkers, Tumor

Introduction

Oral squamous cell carcinoma (OSCC) is the most common cancer seen in the head and neck region and is characterized by many risk factors, including tobacco chewing, smoking, and alcohol drinking. (1,2) Oral potentially malignant diseases (OPMDs) refer to oral mucosal

conditions that have a statistically significant propensity for malignant transformation into OSCC. The most common OPMDs are oral submucous fibrosis (OSMF), oral leukoplakia (OL), and oral lichen planus (OLP) (3). The development of OSCC is a complex and dynamic phenomenon characterized by the suppression of tumor suppressor genes and the activation of proto-oncogenes and oncogenes. The dysregulation of genes involved in the cell cycle and apoptosis has been shown to have a significant role in the development of cancer (4,5)

Several molecular biomarkers have been studied that aid in early diagnosis, prognosis, prediction of disease progression, therapeutic monitoring, etc. Survivin is an anti-apoptotic protein family encoded by the baculoviral inverted repeat C5 gene(6,7). The expression levels of survivin in normal tissues are mild, and strong survivin expression is largely observed in cancers, and the expression levels in potentially malignant disorders are still unclear(8,9). According to Hanahan et al., the evasion of apoptosis, an important hallmark of cancer, is found to be regulated by survivin in both intrinsic and extrinsic apoptotic pathways(10). A systematic review and meta-analysis by Zhou et al suggested that survivin is a poor prognostic biomarker in patients with HNSCC and a potential therapeutic target for HNSCC.(11,12).

Survivin is triggered upon contact with various proteins, resulting in cellular stress that interferes with autophagy.(13,14,15). Survivin plays a crucial role in angiogenesis and regulates the cell cycle at G2/M phase. The lacuna in the literature is the limited data on survivin as a biomarker in the malignant transformation of OPMD to OSCC. The malignant transformation rates from the highest to the lowest were OSMF>erythroplakia>OLP>OL (16). Although several studies have revealed the correlation between survivin and OSCC, the results still remain controversial due to the variance in sample size, study design, analysis used, and disease progression(17,18). It is important to clarify the diagnostic potential and disease progression role of survivin in OSCC based on case-control studies and cohort studies. This systematic review aims to address this gap by investigating the correlation between survivin expression levels and the malignant transformation of OPMDs to OSCC. By synthesizing existing evidence, this review seeks to elucidate survivin's significance in oral cancer development and its potential implications for clinical practice and research in the field.

Methods

This systematic review followed the 2020 standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search Strategy

Using a search strategy, the authors undertook a systematic literature search in PubMed, Scopus, Web of Science, and the Cochrane Library. A manual search was further done by the authors to retrieve the additional studies assessing the correlation of survivin in OPMDs and OSCC up to August 2023. The retrieval strategy included: (survivin) and (malignant transformation or carcinogenesis or tumorogenesis) and (head and neck or laryngeal or tonsil or oropharyngeal or oral oropharynx or nasopharyngeal) and (oral potentially malignant disorders or oral leukoplakia or oral lichen planus or oral submucous fibrosis) and (squamous

cell cancer or carcinoma). Furthermore, the reference lists of retrieved articles for additional articles were also manually searched.

Eligibility for studies

Inclusion criteria

Diagnostic studies that evaluated the expression and correlation between survivin expression in patients diagnosed with OPMDs and OSCC prior to any intervention such as surgery, drug treatment/chemotherapy, or radiotherapy were included.

Exclusion criteria

In-vitro and animal studies, literature and systematic reviews, meeting abstracts, animal studies, pilot studies, case reports, and case series were excluded.

Screening and Selection

Two reviewers, conducted a thorough examination of the titles and abstracts of all the publications in order to determine their eligibility. Following the exclusion of papers that were ineligible for the systematic review, the whole texts of publications meeting the inclusion criteria were obtained and subjected to analysis. Additional research was sought by making cross-references to the aforementioned papers.

Data extraction

ReVMan 5.4.1 (Cochrane, London, England) and EndNote Software were used for deduplication of the documents, those papers that were found to be repeated were eliminated. Finally, a comprehensive compilation of full-text articles was accomplished, followed by the finalization of the articles and subsequent execution of the data extraction process. The data extraction process involved obtaining information on the author, year of study, samples, specimen, type, and amount of survivin expression, as well as the method used for detection or estimation. The data were gathered independently from each of the qualifying studies. The data were extracted and stored in a pre-existing Microsoft Excel file (Microsoft, Washington, USA) to facilitate further evaluation of the research quality and synthesis of the data.

Data analysis

For the purpose of summary synthesis, the studies were grouped based on OPMDs and OSCC. There were variations in specimen type and analysis used for survivin expression. Hence, descriptive analysis was performed, and the findings were presented as the mean (SD/SE/95% confidence interval).

Risk of bias

Two reviewers, conducted a thorough examination of all the included publications in duplicate. Their examination focused on identifying study design elements and assessing internal validity issues. The assessment of bias was conducted by assigning a categorization of low, high, or unsure to each study that was included in the analysis. The overall quality of each study was assessed by analyzing the six kinds of bias. A rating of 3, 1, or 0 denoted a low, uncertain, or strong propensity for bias, correspondingly. The risk of bias was evaluated using the nonrandomized study method, ReVMan 5.4.1 (Cochrane, London, England).

Results

Study Selection

The search strategy identified a total of 759 articles from other sources that were initially identified by using the search strategy in the electronic databases. Following that, the articles were screened for duplicates and were removed (n = 453). The articles were screened for titles (n = 453) and abstracts (n = 134); after screening, n = 421 articles were excluded, including in vitro studies, reviews, and other articles. Full-text articles were assessed for eligibility (n = 29), among which n = 23 articles were excluded due to incomplete and irrelevant data. Finally, six articles were eligible for qualitative analysis. The eligibility of each article was determined based on the title, abstract, and full text reading. The study selection and screening processes are provided in the PRISMA flow diagram (Figure 1).

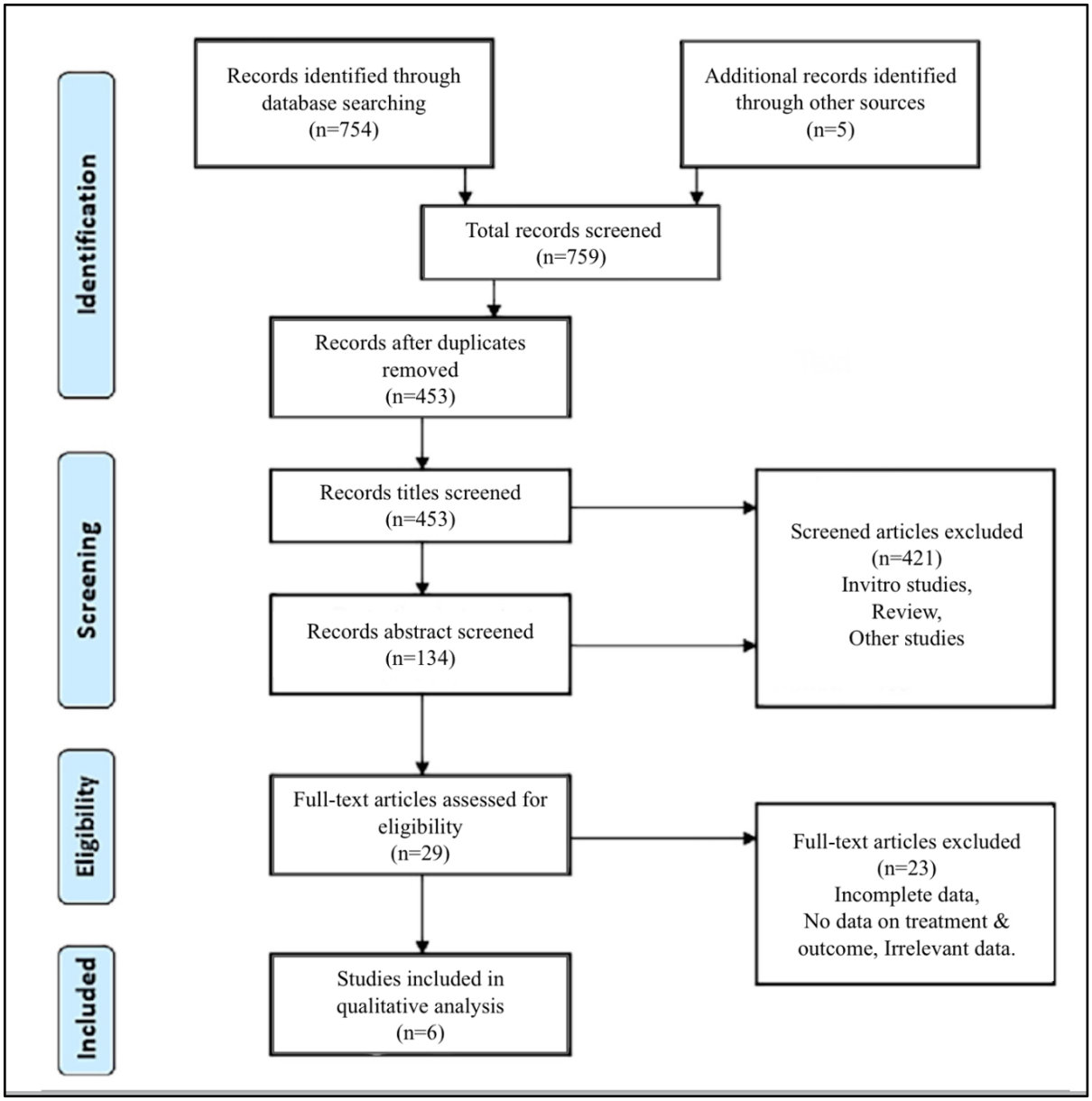

Figure 1: PRISMA 2020 flow diagram showing included studies

Characteristics of included studies

The present systematic review was reported according to PRISMA 2020 guidelines for systematic reviews. The data from all studies included in the systematic review are summarized. The characteristic data of the included studies are presented in Table 1. A case-control study with a cross-sectional study design of a pooled sample size of n = 400, among which OSCC (n = 105); OL (n = 45); OLP (n = 125); OSMF (n = 25); OED (n = 15); and normal mucosa (n = 85). As most of the included studies did not provide values for the level of expression of survivin, a meta-analysis was not performed.

Summary of Findings

Table 1: Table represents the data of the included studies. NM- Normal Mucosa, OL- Oral Leukoplakia, OLP- Oral Lichen Planus, OSMF- Oral Submucous Fibrosis, OSCC- Oral Submucous Fibrosis

Author and Year	Groups and Sample size	Total Sample size	Method	Results	Interpretation
Suganya et al 2016 (16)	NM (n=10); OLP (n=50); OSCC (n=10)	n=70	Immunohistochemistry	OSCC: Mean positivity in superficial layer: 167.8, OLP: Mean positivity in basal layer: 102.9, NM: Mean positivity in basal layer: 2.25	Statistically significant expression among groups

Angelin et al 2020 (6)	NM (n=20); OL (n=20); OLP (n=20); OSCC (n=20)	n=80	Immunohistochemistry	OSCC: Expression in superficial layer: 80%, OL: Expression in basal layer: 70%, OLP: Expression in basal layer: 45%, NM: Expression in basal layer: 35%	Significant higher expression in OSCC.
Sakthivel et al 2020 (17)	OSCC (n=10); OL (n=10); OLP (n=10); OSMF (n=10); NM (n=10)	n=50	Immunohistochemistry	OSCC: Expression in superficial layer: 70%, OL: Expression in basal layer: 50%, OSMF: Expression in basal layer: 20%, OLP: Expression in basal layer: 10%, NM: Negative staining	Significant difference among groups (p=0.034)

Rajanna et al 2020 (19)	OL (n=15); OLP (n=15); OSMF (n=15); NM (n=15)	n=60	Immunohistochemistry	OLP: Higher expression in basal layer compared to OL and OSMF	Significant difference between groups
Lingam et al 2021(20)	NM (n=20); OSCC (n=20); OLP (n=30)	n=70	Immunohistochemistry	NM: Basal layer staining - weak to moderate, OLP: Basal layer staining - moderate to strong, OSCC: Superficial layer staining - strong	Statistically significant difference among groups
Himanta et al 2022 (24)	NM (n=10); OED (n=15); OSCC - WDSCC (n=15); MDSCC (n=15); PDSCC (n=15)	n=70	Immunohistochemistry	Higher expression in MDSCC followed by PDSCC and WDSCC.	Statistically significant difference between normal and study groups

All the studies included in this review were based on immunohistochemical analysis. 100% of the studies showed significant upregulation of survivin in OSCC, followed by OPMDs (OL, OLP, and OSMF), and minimal expression was found in normal mucosa. Survivin expression in the normal mucosa was predominantly evident in the basal and suprabasal layers, and cases with OSCC showed strong expression in the superficial and suprabasal layers. Cases with OPMD showed varied expression, predominantly in OL with dysplasia, which showed strong, intense expression when compared to OL with no epithelial dysplasia. Nuclear positivity was evident in most of the cases of OLP when compared to those of OL and OSMF.

The risk of bias was assessed using ReVMan 5.4.1 (Cochrane, London, England) for diagnostic studies. The most prevalent source of bias observed throughout the research was the use of a reference standard and index test (Figure 2). The majority of the research exhibited a moderate to high risk of bias, whereas two studies showed a low likelihood of bias (Figure 3). In Risk of Bias analysis, it was found that four studies exhibited a high risk of bias, whereas two studies had an uncertain to low risk of bias.

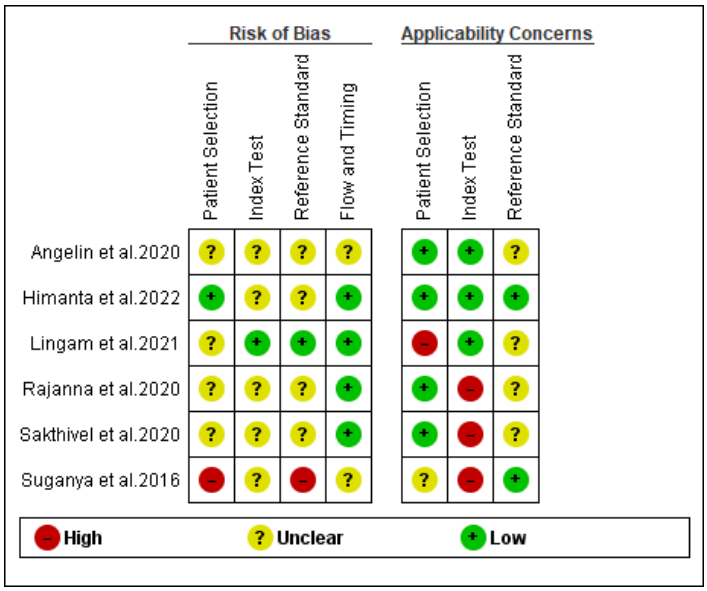

Figure 2: Risk of bias of included studies

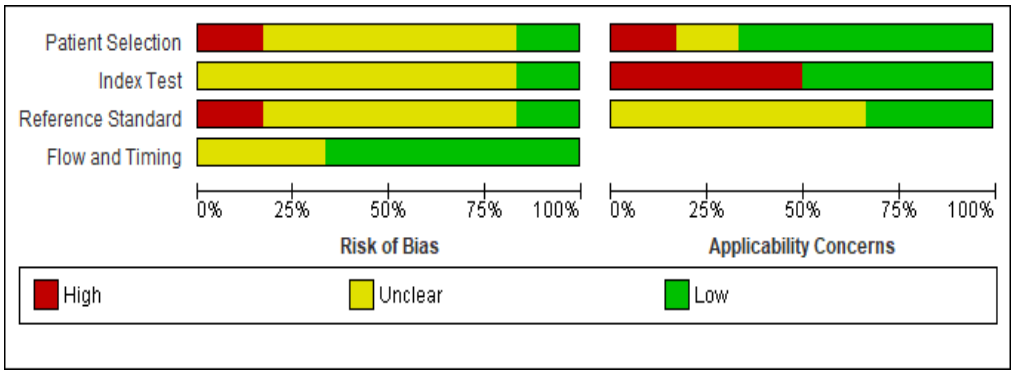

Figure 3: Risk of bias assessment

Discussion

Numerous researchers have examined various molecular markers associated with the development of OSCC. These indicators encompass molecules involved in the control of the cell cycle, programmed cell death, the formation of new blood vessels, the repair of DNA damage, and the breakdown of the extracellular matrix. The early diagnosis might potentially be facilitated by the identification of these molecules through the investigation of DNA, RNA, and protein expression. The techniques most often employed in this field of study include cDNA microarray, polymerase chain reaction, in situ hybridization, immunohistochemistry, enzyme-linked immunosorbent assay, and western blot. Nevertheless, the existing body of information pertaining to molecular markers continues to lack clear findings. Therefore, there

is an ongoing necessity to establish the primary biological indicators for the development and invasiveness of OSCC (19,20,21).

The extant literature has a limited number of studies on the prediction of malignant change from OPMDs to OSCC. However, there have been several studies in the literature that have focused on the diagnostic potential and prognosis, specifically survival outcomes, of OSCC. In a previous systematic review conducted by Zhou et al. to assess the prognostic implications of survivin in head and neck squamous cell carcinoma (HNSCC), The findings of this research indicated a significant correlation between survival and an unfavourable prognosis, as well as reduced overall survival, specifically in cases of OSCC (10). However, contrasting findings from studies suggested a less pronounced correlation between survivin expression and survival outcomes in OSCC, emphasizing the need for further investigation into its prognostic significance.(22,23)

Survivin, an anti-apoptotic protein, is classified as a proto-oncogene that plays a role in the development of cancer by disrupting normal cell growth. The analysis of survivin expression in normal oral mucosa, leukoplakia, and OSCC revealed a statistically significant disparity in the quantity of survivin positive cells ($p < 0.001$). This finding suggests that the upregulation of survivin is linked to unregulated cellular proliferation(24,25). Furthermore, studies examining the molecular mechanisms underlying survivin's role in oral carcinogenesis have identified its interactions with key signaling pathways involved in cell cycle regulation and apoptosis, providing mechanistic insights into its oncogenic properties. Angelin et al. conducted a comparative analysis of survivin expression levels in several oral conditions, including oral squamous cell carcinoma (OSCC), oral leukoplakia, oral lichen planus, and normal mucosa. The study revealed that the expression level of survivin was found to be greater in OSCC (80%) compared to OL (70%), OLP (45%), and NM (35%). The observed differences in the levels of survivin expression across the samples were found to be statistically significant, as shown by a p-value of 0.015 (6). Conversely, a study reported comparable levels of survivin expression between OSCC and oral leukoplakia, challenging the notion of survivin's specificity as a diagnostic marker for OSCC. Lingam et al conducted an investigation to assess the expression of survivin by IHC in a sample of 30 cases of OLP, 20 cases of OSCC, and 20 healthy individuals. The study revealed a statistically significant distinction among the groups, with a p-value of 0.001(20).

Previous research has indicated that survivin expression in OLP was observed in 95% of cases, mostly exhibiting moderate intensity. Additionally, survivin expression was predominantly observed in the basal layer of cells, with all cells demonstrating 100% nuclear positivity. Lingam et al (20). demonstrated that a significant proportion of the cases exhibited mild to moderate intensity, with survivin nuclear expression predominantly seen in the basal layer of the epithelium. These findings align with the study conducted by Suganya et al(16). Chaiyarit et al. (25) conducted a study that indicated the predominant expression of survivin in the nucleus in instances of OLP, with about one fourth of the cases showing both nuclear and

cytoplasmic positive (26,27,28). Although the nuclear expression of survivin is considered an adverse prognostic factor in many cancers and OPMDs seen in humans, several authors have suggested that survivin nuclear positivity may serve as a good prognostic marker (20).

While the findings suggest a potential diagnostic utility of survivin expression in distinguishing between normal, premalignant, and malignant oral lesions, the conflicting evidence underscores the complexity of its role and the need for further investigation. Clinically, the identification of reliable biomarkers such as survivin could aid in early detection and risk stratification of OSCC, potentially improving patient outcomes through timely intervention. However, discrepancies in study findings highlight the importance of standardization in methodology and interpretation to ensure reproducibility and clinical applicability. This lack of standardisation prevented us from performing meta-analysis.

In our study, we opted to use immunohistochemistry as the primary methodology for survivin assessment in Oral Potentially Malignant Disorders (OPMDs) and Oral Squamous Cell Carcinoma (OSCC). While techniques like cDNA microarray, polymerase chain reaction (PCR), in situ hybridization, enzyme-linked immunosorbent assay (ELISA), and western blot offer additional insights into survivin expression, they were not included in our research. This decision was influenced by factors such as sample availability, feasibility, and the specific goals of our study. Integrating multiple techniques in future research could provide a more comprehensive understanding of survivin's role in oral carcinogenesis and enhance its clinical relevance as a biomarker for predicting malignant transformation in OPMDs.
The studies included in this analysis exhibit several limitations, such as a small sample size, variability among the participants, and variations in the methodologies employed to measure protein levels and expression. Furthermore, challenges related to standardization of survivin assessment protocols and interpretation criteria have been identified, highlighting the need for consensus guidelines to ensure reproducibility and reliability of results. The present study is subject to several limitations, mostly due to a lack of literature data pertaining to the role of survivin in the malignant transition of OPMDs into OSCC. Additionally, the number of original articles available for review was rather limited. The future prospects of this review encompass the exploration of sequencing studies and markers that have the potential to be utilized in the identification of OSCC. Future research directions should also focus on elucidating the underlying molecular mechanisms driving survivin dysregulation in OSCC progression, potentially identifying novel therapeutic targets for intervention.

Conclusion

Based on the findings, survivin expression appears to be a promising biomarker for detecting Oral Potentially Malignant Disorders (OPMDs) that are at risk of developing invasive carcinoma. However, it is critical to recognize the intricacies of oral carcinogenesis and the limitations of the current study.

While our data shows a significant increase in survivin expression in Oral Squamous Cell Carcinoma (OSCC), we must exercise caution when applying these findings to clinical practice. More research, with bigger patient populations and longer follow-up periods, is needed to determine the precise involvement of survivin in the initiation and progression of oral carcinogenesis.

The recent discovery of molecular markers such as survivin provides insight into the complex pathways behind malignant transformation. Nonetheless, more research and confirmation are required before these findings may be applied in therapeutic settings. Thus, while survivin shows promise as a biomarker, its clinical usefulness for predicting the malignant evolution of OPMDs requires rigorous validation in prospective investigations.

In conclusion, this work emphasizes the significance of continued research efforts to understand the molecular complexities of oral carcinogenesis. Future research should focus on survivin and other molecular markers in a broader framework, to understand their relevance in clinical practice for risk classification and prognosis in patients with OPMDs. By resolving these issues and expanding our understanding of molecular markers, we can pave the road for more effective early diagnosis and intervention options in oral cancer.

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