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Diagnostic Potential Of Salivary Interleukins In Oscc: A Comprehensive Review

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Abstract:
Salivary interleukins (ILs), particularly IL-6, IL-8, and tumour necrosis factor-α (TNF-α), are emerging as promising biomarkers for the early detection and prognosis of oral squamous cell carcinoma (OSCC). Elevated levels of these cytokines in patients with OSCC reflect the pro-inflammatory microenvironment associated with tumour initiation and progression. This narrative review synthesised data from peer-reviewed studies published between 2010 and 2023, identified through systematic searches of PubMed, Scopus, and Web of Science databases. Studies were selected based on relevance to salivary biomarkers in OSCC, and data were extracted and analysed to evaluate diagnostic potential. Findings reveal significantly higher salivary IL-6, IL-8, and TNF-α levels in OSCC patients compared to healthy controls and individuals with oral potentially malignant disorders (OPMDs). These cytokines hold promise as non-invasive diagnostic tools in routine clinical settings. However, multicentre studies are needed to standardise protocols and validate clinical utility, potentially transforming OSCC detection and patient management.

Keywords: *Salivary biomarkers, Interleukins, Oral squamous cell carcinoma, Early detection, Cytokines, Tumour necrosis factor-α, IL-6, IL-8*

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I. Introduction:

Oral cancer is a globally prevalent malignancy, with over 389,846 new cases and 188,438 deaths in 2022, of which over 90% are oral squamous cell carcinoma (OSCC)[1,2]. While OSCC accounts for 4% of cancers in Western countries, its prevalence has risen to nearly 40% in India and Southeast Asia[3].

The timing of diagnosis significantly impacts OSCC outcomes[4]. According to the United States (U.S.)-based Surveillance, Epidemiology, and End Results (SEER) Program, the five-year relative survival rate is approximately 87.5% when detected locally, declining to 69.5% with regional lymph node involvement and 37.8% with distant metastasis[5].

In Western populations, OSCC is linked to smoking, alcohol use, and specific human papillomavirus (HPV) strains, though HPV's role in non-oropharyngeal cancers remains uncertain[6].

The pathogenesis of OSCC involves genetic and epigenetic changes disrupting protein expression and signalling pathways[7]. These alterations range from single-nucleotide mutations to chromosomal deletions, frequently inactivating tumour suppressor genes[8].

In a seminal analysis of head and neck cancer, Leemans et al. identified five cellular processes driving OSCC: cell cycle regulation, growth signalling, survival mechanisms, WNT signalling, and epigenetic modifications[9].

The diagnosis of OSCC typically begins with a clinical inspection, biopsy, and histopathological analysis. Techniques like vital staining and autofluorescence imaging aid in identifying dysplastic and cancerous tissues, enhancing biopsy accuracy[10]. Radiographic modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), are invaluable for evaluating adjacent structures, including muscles, bones, and lymph nodes[11].

Oral potentially malignant disorders (OPMDs), such as leukoplakia, erythroplakia, lichen planus, and oral submucous fibrosis, precede most OSCC cases[12,13].

However, subtle lesions frequently evade detection during visual inspections, delaying diagnosis to advanced stages and worsening survival rates. This diagnostic challenge has driven research into identifying accessible biomarkers for early detection.

Salivary Biomarkers for OSCC

'Liquid biopsy' has recently emerged as a non-invasive method for identifying diagnostic biomarkers in OSCC, with saliva offering advantages such as proximity to cancer cells, ease of collection, and cost-effectiveness[14–17]. Advances in molecular research have facilitated the identification of a range of potential salivary biomarkers reflecting proteomic, metabolic, genomic, and epigenetic alterations associated with OSCC, thereby enabling early disease detection[18,19].

Although standardised protocols are under development, 'salivary liquid biopsy' shows promise for diagnosis, prognosis, and patient monitoring[20,21].

Cytokines in Cancer

Among salivary protein biomarkers, cytokines have been extensively investigated for their critical role in the tumour microenvironment (TME), including tumour initiation, progression, invasion, and metastasis[22].

Interleukins (ILs) such as IL-8, IL-6, and tumour necrosis factor-α (TNF-α) are noteworthy, being significantly elevated in the saliva of patients with OSCC compared to healthy controls. IL-8, produced by neutrophils and macrophages, is instrumental in angiogenesis, tumour survival, and migration by activating pathways such as nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), and mitogen-activated protein kinase (MAPK). Similarly, IL-6, elevated in both saliva and serum, promotes cancer cell proliferation through the Janus kinase (JAK)/STAT pathway. Salivary levels of IL-8 and IL-6 correlate with OSCC severity, underscoring their diagnostic and prognostic potential[23].

The TME includes cancer, stromal, and diverse immune cells, differing from normal tissue[24,25]. Immune components include innate immune cells (such as macrophages, neutrophils, mast cells, dendritic cells, and natural killer [NK] cells) and adaptive immune cells (T and B lymphocytes), linking inflammation, immunity, and cancer progression.

Inflammation within the TME, mediated by interactions among stromal and cancer cells, is a critical factor in OSCC progression. This inflammatory milieu stimulates the release of cytokines, growth factors, pro-angiogenic agents, and extracellular matrix remodelling enzymes by cancer and stromal cells, thereby facilitating tumour growth and metastasis[26].

Cytokines are low-molecular-weight proteins secreted by immune and stromal cells that govern cell growth, survival, migration, and immune responses. These proteins exhibit dual roles; they bolster anti-tumour immunity during acute inflammation and contribute to tumour development under chronic inflammatory conditions[22].

Pro-inflammatory cytokines, including IL-1, IL-6, IL-8, interferon-gamma (IFN-γ), and TNF-α, promote OSCC progression by driving cell proliferation, epithelial-mesenchymal transition, and angiogenesis. Conversely, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 suppress inflammation and immune responses; however, they inadvertently allow cancer cells to evade immune surveillance. The imbalance between these cytokine groups underscores the link between chronic inflammation and OSCC development[22,27–29].

Pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α are implicated in OSCC pathogenesis[28] through the activation of signalling pathways like NF-κB, STAT, and MAPK/Extracellular Signal-Regulated Kinase (ERK), which support tumour cell survival and proliferation[30].The ratio of pro-inflammatory to anti-inflammatory cytokines in saliva may be a more reliable indicator of OSCC than individual cytokine levels alone, highlighting the need for composite biomarker panels[29].

Goertzen et al. outlined mechanisms by which TNF-α facilitates OSCC invasion. They demonstrated that TNF-α creates a feedback loop with neutrophils[31], promoting gene expression changes associated with invasive behaviour. However, OSCC-derived cytokines activate the surrounding neutrophils, sustaining the inflammation-cancer interaction. Notably, IL-8, an inflammatory cytokine overexpressed in OSCC, and matrix metallopeptidase 9 (MMP9) are involved in extracellular matrix degradation and tumour invasion. This finding further underscores the potential of salivary cytokine analysis in early detection, with abnormal cytokine levels offering insight into the presence and progression of OSCC.

This review synthesised data from peer-reviewed studies (2010–2023) on salivary biomarkers for OSCC. Studies were identified via systematic searches in PubMed, Scopus, and Web of Science using predefined keywords (such as “salivary biomarkers,” “cytokines,” “IL-6,” “IL-8,” “OSCC”) and refined by language (English) and relevance. Inclusion criteria targeted observational studies (cross-sectional or

longitudinal) involving OSCC, OPMD, or healthy controls with quantitative salivary biomarker data. Data were extracted from full-text articles, focusing on study design, biomarker levels, and diagnostic metrics to highlight common trends and insights into cytokine expression across different OSCC stages. Ethical adherence was verified to ensure reliability and clinical relevance.

Reviewed studies

The analysed studies were categorised into three groups based on their research design: Group I (n = 6) comprised cross-sectional studies that investigated differences in salivary cytokine levels between patients with OSCC and healthy controls; Group II (n = 10) included cross-sectional studies that examined salivary cytokine levels in patients with OSCC and controls, and correlations with histological grades or clinical stages of OSCC; and Group III (n = 3) consisted of longitudinal studies that assessed changes in salivary cytokine levels before and after tumour resection. Eleven studies from Groups I and II included participants with OPMD. Detailed study characteristics and cytokine level comparisons are summarised in **Tables 1, 2, and 3**.

Analysis of reviewed studies

The reviewed studies consistently demonstrated that salivary cytokine levels, particularly IL-6, IL-8, and TNF-α, were substantially elevated in patients with OSCC compared to healthy individuals. Among the 19 studies analysed, 18 reported elevated salivary cytokine concentrations in patients with OSCC, with the remaining one focused on intra-patient comparisons (pre- vs post-operative) without including healthy controls[32].

Three studies[29,33,34] highlighted a progressive rise in salivary cytokine levels, such as IL-6, IL-8, and IL-1RA, corresponding to histological grades from well-differentiated to poorly differentiated OSCC, indicating a strong association with tumour severity and invasiveness. Similarly, patients with early-stage OSCC (stage I/II or T1/T2) exhibited elevated cytokine levels, including IL-6, IL-8, IL-1β, TNF-α, IFN-γ, macrophage inflammatory protein-1β (MIP-1β), and growth regulated oncogene (GRO), suggesting their utility in distinguishing early-stage OSCC from healthy conditions[28,35,36].

Longitudinal studies observed a marked postoperative reduction in cytokine levels, such as IL-6, IL-8, IL-1β, IL-17, vascular endothelial growth factor (VEGF), MIP-1β, and Interferon Gamma-Induced Protein 10 (IP-10)[32], underscoring their relevance for monitoring treatment response. Furthermore, IL-6, IL-8, and TNF-α levels were consistently higher in patients with OSCC than in individuals with OPMDs or healthy controls[33,34,36,37].

II. Discussion

Oral carcinogenesis is driven by inflammatory processes and immune responses, with IL-6, IL-8, and TNF-α playing critical roles in the TME and promoting cancer progression[38]. Although serum cytokine levels in OSCC remain insufficiently studied, significantly elevated levels of IL-6, IL-8, and soluble IL-2 receptor (IL-2R) are identified in patients with OSCC compared to healthy controls and individuals with OPMDs. These findings support the feasibility of salivary cytokines as reliable diagnostic biomarkers for OSCC.

Singh et al. found salivary IL-1β, IL-8, and Lectin, Galactoside-Binding, Soluble, 3 Binding Protein (LGALS3BP) effective in distinguishing OSCC cases from controls and OPMD. IL-1β showed significant elevation in patients with OSCC compared to controls; however, its ability to distinguish OPMD from controls was limited. However, IL-8 demonstrated marked elevation in OSCC cases compared to controls, with a moderate increase observed in patients with OPMD. Meanwhile, LGALS3BP was notably elevated in both OSCC (particularly in early stages, $P = 0.0008$) and high-risk OPMD cases ($P = 0.0001$)[39].

Vala et al. reported significantly higher mean salivary IL-1 levels in patients with OSCC than in healthy controls, averaging 132.7 pg/mL versus 48.9 pg/mL in controls. Furthermore, salivary IL-1 levels were elevated in patients with advanced-stage OSCC (167.5 pg/mL) compared to those with early-stage OSCC (117.3 pg/mL)[40]. These findings highlight IL-1 as a biomarker for assessing disease severity and aggressiveness.

Supporting this, Piyarathne et al. reported significantly elevated salivary levels of IL-1β, IL-6, and IL-8 in patients with OSCC compared to oral epithelial dysplasia (OED) and control groups. Among these, IL-8 demonstrated exceptionally high levels in OSCC cases (394.3 pg/mL) versus controls (47.3 pg/mL), with $P< 0.0001$, indicating strong discriminatory power for OSCC diagnosis. Receiver operating characteristic (ROC) analysis revealed that IL-8 achieved the highest area under the curve (AUC = 0.978), highlighting its exceptional potential as a robust screening marker for OSCC in high-risk populations[41].

Rani et al. corroborated these findings by observing elevated salivary IL-6 levels in patients with OSCC compared to controls and OPMD groups. The mean optical density (OD) of IL-6 was 0.79 ± 0.09 in patients with OSCC against 0.13 ± 0.01 in controls ($P< 0.001$). Post-hoc Tukey analysis confirmed significantly

higher IL-6 levels in OSCC compared to OPMD, emphasising its diagnostic utility in distinguishing OSCC from premalignant and non-cancerous inflammatory conditions[42].

Further analysis of IL-6 levels across histopathological differentiation grades in OSCC revealed a progressive increase, with poorly differentiated OSCC exhibiting the highest IL-6 OD values (0.89 ± 0.08). These findings align with prior studies, suggesting that elevated IL-6 levels may indicate OSCC presence and correlate with disease progression and severity[42].

In the study by Khyani et al., salivary levels of IL-6 and IL-8 were considerably elevated in OSCC cases compared to both OPMD and control groups. IL-6 levels in OSCC were substantially higher than controls, while IL-8 showed even greater significance between OSCC and controls. Furthermore, post-hoc comparisons revealed that IL-8 levels were significantly higher in patients with OSCC than those with OPMD, reinforcing IL-8's role as a robust inflammatory marker. These findings support its utility as a potential biomarker for OSCC and high-risk OPMD cases[43].

Oshin et al. provided additional insights, reporting elevated IL-6 levels in both saliva and serum of patients with OSCC compared to leukoplakia and control groups. The mean salivary IL-6 levels were 93.6 pg/mL for OSCC, significantly higher than those in the leukoplakia (21.04 pg/mL) and control groups (6.91 pg/mL). Similarly, mean serum IL-6 levels were substantially increased in patients with OSCC (61.23 pg/mL) compared to leukoplakia (19.07 pg/mL) and controls (3.1 pg/mL)[44].

Further analysis by Oshin et al. revealed an increasing trend in IL-6 levels across OSCC differentiation grades, with poorly differentiated cases exhibiting the highest IL-6 concentrations in both saliva (175 pg/mL) and serum (94.12 pg/mL)[44]. These findings underscore the role of IL-6 as a potential prognostic biomarker, with elevated IL-6 levels linked to more aggressive disease stages.

Furthermore, IL-1β and IL-8 were elevated in patients who experienced recurrence after surgery. In contrast, patients without recurrence had relatively lower levels of these cytokines, indicating their potential role as recurrence indicators. Conversely, LGALS3BP demonstrated lower levels in recurrent cases and higher levels in non-recurrent cases post-operatively, suggesting its potential as a biomarker for monitoring recovery and post-operative stability in patients with OSCC[39].

A study by Hema et al. longitudinally assessed IL-6 levels in OSCC cases over a year following chemotherapy and radiotherapy. Pre-treatment IL-6 levels (mean = 4794.6 nM) were significantly elevated but declined markedly after treatment (mean = 1954.23 nM) and normalised by the six-month follow-up. Repeated measures analysis of variance (ANOVA) revealed significant changes in IL-6 levels across treatment stages ($P<$ 0.0001), emphasising its value as a prognostic marker in OSCC management[45].Moreover, longitudinal analyses have revealed that post-operative declines in IL-6 and IL-8 levels correlate with improved prognosis, while persistent elevations may indicate an increased risk of recurrence[46].

The reviewed studies consistently adhered to ethical protocols, standardised saliva collection methods, and robust cytokine analysis techniques, ensuring reliability. Most studies utilised unstimulated saliva through passive drool, followed by centrifugation at 4°C to remove debris before freezing samples at -80°C. However, only a few studies employed protease inhibitors to maintain cytokine stability[29,36,47]. For quantification, enzyme-linked immunosorbent assay (ELISA) was the most commonly used technique, while some studies employed multiplex bead-based immunoassays to evaluate multiple cytokines concurrently[28,29,32,35].

Recognising the influence of dental and periodontal health on cytokine levels, many studies controlled these factors by excluding participants with periodontitis or matching controls based on periodontal status. To ensure methodological rigour, some studies excluded individuals with significant comorbidities or confounding lifestyle factors such as alcohol and tobacco use—both of which are prevalent among patients with OSCC and vary geographically.The potential role of salivary cytokines in differentiating OSCC from other chronic inflammatory oral diseases, such as periodontitis, remains underexplored and warrants further investigation to avoid confounding diagnostic interpretations[36].

Comparisons between OSCC, OPMD, and healthy groups reveal that salivary cytokine levels effectively differentiate these conditions, with OPMD cytokine levels typically falling between those of patients with OSCC and healthy controls. This gradient supports the diagnostic utility of these biomarkers. Studies employing ROC analysis confirm the diagnostic accuracy of selected cytokines such as IL-6, IL-8, and TNF-α, with AUC values ranging from 0.70 to 0.99, indicating robust discriminatory power[28,33,34,47,48,49].

In the study by Singh et al., IL-1β and IL-8 exhibited robust predictive power for late-stage OSCC, achieving AUC values of 0.9017 and 0.7619, respectively, particularly in distinguishing stages III and IV OSCC from controls. LGALS3BP emerged as a critical marker for early-stage OSCC (P = 0.0008) and high-risk OPMD (P = 0.001), showing intense discrimination from controls, underscoring its relevance in early disease detection[39].

A combination of multiple cytokine biomarkers consistently demonstrated superior predictive power over individual markers. A diagnostic model incorporating six cytokines achieved higher AUC values for OSCC detection while integrating proteomic and transcriptomic data further improved discrimination,

accounting for risk factors such as tobacco use[28,50,51].Furthermore, recent research highlights the potential of integrating salivary cytokines with molecular signatures such as microRNAs (miRNAs) to improve diagnostic accuracy, reducing false positives and negatives in OSCC detection[47].

Limitations of existing literature

While salivary cytokines have shown promise in OSCC diagnosis, their utility should be compared with other biomarker modalities, such as serum markers, tissue biopsies, and imaging techniques. Serum biomarkers, including circulating tumor DNA (ctDNA) and exosomal RNA, have demonstrated high specificity in OSCC detection, but their invasive collection methods limit routine use[52]. Similarly, tissue biopsies remain the gold standard but are invasive and impractical for frequent monitoring. Imaging techniques like PET-CT and MRI offer structural insights but lack molecular specificity. In this context, salivary cytokines offer a unique advantage due to their non-invasive collection and potential for real-time monitoring, but further research is needed to establish their diagnostic superiority[53].

Despite these promising findings, inter-individual variability in cytokine levels poses challenges for developing standardised salivary screening tests. Group III studies suggest longitudinal monitoring could mitigate these variations, enhancing reliability. To improve accuracy, future research should focus on multicentre cohorts with a broader spectrum of disease stages and refined quantitation methods, such as normalising cytokine levels to salivary protein content.Moreover, geographic and ethnic variations in cytokine expression patterns suggest the necessity for population-specific validation studies before implementing salivary cytokine-based diagnostics in routine clinical practice[51].

A major challenge in implementing salivary cytokines as clinical biomarkers is the lack of standardization in sample collection, processing, and analysis. Variability in cytokine concentrations can arise due to differences in saliva collection techniques, patient hydration levels, and diurnal fluctuations[54]. Moreover, inconsistencies in assay methodologies, including ELISA and multiplex bead-based assays, pose reproducibility concerns. Establishing universally accepted cut-off values and integrating machine learning algorithms for data normalization could enhance diagnostic reliability[55].

Despite the promise of salivary cytokines in OSCC detection, several limitations need to be addressed. One significant issue is the overlap in cytokine expression profiles between OSCC and other inflammatory conditions, such as periodontitis and autoimmune disorders, which could lead to false positives[56]. Additionally, inter-individual variability in cytokine levels necessitates personalized reference ranges rather than fixed diagnostic thresholds. Future research should focus on large-scale, multicenter validation studies to confirm the diagnostic reliability of salivary cytokines across diverse populations. Furthermore, the integration of artificial intelligence (AI)-driven data analytics could refine biomarker interpretation, improving predictive accuracy[57].

Ultimately, a point-of-care salivary screening test leveraging selected cytokine biomarkers holds promise for earlier OSCC detection, enabling timely diagnosis and improved patient outcomes in dental and primary care settings.

III. Conclusion

This review highlights salivary ILs, particularly IL-6, IL-8, and TNF-α, as biomarkers for OSCC diagnosis and prognosis. Elevated cytokine levels reflect their role in tumour progression and the pro-inflammatory microenvironment. While significant strides have been made in understanding the diagnostic utility of these biomarkers, further multicentre studies with standardised protocols are essential to validate their clinical applicability. Such efforts could pave the way for a reliable, non-invasive, and cost-effective salivary diagnostic tool for OSCC, ultimately contributing to better patient outcomes through earlier diagnosis and treatment. Salivary cytokine analysis could revolutionise OSCC management by enabling targeted screening, risk stratification, and disease monitoring.

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Table 1 Evidence from the literature on salivary cytokines as candidate biomarkers for OSCC (Group I).

Ref.	Study groups	Cytokine	OSCC vs. Controls	*P*-Value	OPMD vs. Controls	*P*-Value
Khyani et al.[43]	OSCC: 35, Controls: 35, OPMD: 35[a–d]	IL-6	n.p.		n.p.	
		IL-8	OSCC > Control	<0.0001	OPMD > Control	0.001
Piyarathne et al.[41]	OSCC: 37, Controls: 30, OPMD: 30	IL-8	OSCC > Control	<0.0001	OSCC > OED	<0.0001
		IL-6	OSCC > Control	<0.001	OSCC > OED	<0.001
		IL-1β	OSCC > Control	<0.001	OSCC > OED	<0.01
Rani et al.[42]	OSCC: 15, Controls: 15, OPMD: 15	IL-6	OSCC > Control	<0.001	OSCC > OPMD	<0.001
Hema Shree et al.[45]	OSCC: 60, Controls: 10	Il-6	OSCC > Control	<0.0001	Not available	-

Table 1 Evidence from the literature on salivary cytokines as candidate biomarkers for OSCC (Group I) (contd.).

Gleber-Netto et al.[47]	OSCC: 60, Controls: 60, OPMD: 60	IL-1β	OSCC > Control	=0.01	-	-
			OSCC > OPMD	0.004	-	-
		IL-8	OSCC > Control	<0.0001	-	-
			OSCC > OPMD	<0.0001	-	-
Polz-Dacewicz et al.[58]	OSCC: 78, Controls: 40	IL-10	OSCC > Control	0.00002	-	-
		TNF-α	OSCC > Control	0.00002	-	-
		TGF-β	OSCC > Control	0.00002	-	-
		VEGF	OSCC > Control	0.0000		

Abbreviations: OSCC, oral squamous cell carcinoma; OPMD, oral potentially malignant disorders; n.s., non-significant; n.p., not performed (cytokine level resulted undetectable in most cases of OPMD and controls).
[a]Oral submucous fibrosis, OMSF; [b]Oral lichen planus, OLP; [c]Leukoplakia; [d]Erythroplakia.

Table 2 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group II).

Ref.	Study Groups	Cytokine	OSCC vs. Control/OPMD	*P*-Value	OPMD vs. Control	*P*-Value	Histological Grade/Stage	*P*-Value
Dikova et al.[28]	OSCC: 66, Controls: 25, OPMD:- Leukoplakia: 66	IL-1α	OSCC > Control	n. s.	OPMD > Control	n. s.	T1/T2 stage > Control	n. s.
							OPMD > T1/T2 stage	n. s.
							T1/T2 stage> T3/T4 stage	n. s.
		IL-6	OSCC > Control	≤0.0001	OPMD > Control	0.001	T1/T2 stage > Control	<0.001
							T1/T2 stage > OPMD	<0.001
							T3/T4 stage > T1/T2 stage	0.01
		IL-8	OSCC > Control	≤0.0001	OPMD > Control	0.004	T1/T2 stage > Control	<0.001
							T1/T2 stage > OPMD	0.05
							T3/T4 stage > T1/T2 stage	n. s.

Table 2 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group II) (contd.).

Aziz et al.[29]	OSCC: 30, Controls: 33	IL-10	OSCC > Control	0.004	-	-	WD > Control	0.001
		IL-13	OSCC > Control	0.01	-	-	-	n. s.
		IL-1RA	OSCC > Control	n. s.			PD > MD	0.000
							PD > WD	0.002
							PD > Control	0.000
		IL-4	OSCC > Control	n. s.	-	-	-	-

Table 2 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group II) (contd.).

Dineshkumar et al.[33]	OSCC: 100, Controls: 100, OPMD:- Leucoplakia: 50, OSMF: 50	IL-6	OSCC > OPMD	<0.01	OPMD > Control	<0.05	PD > MD	<0.05
							PD > WD	<0.01
							MD > WD	<0.05
Rajkumar et al.[34]	OSCC: 100, Controls: 100, OPMD:- Leucoplakia: 50, OSMF: 50	IL-8	OSCC > Control	<0.001	OPMD > Control	<0.05	PD > MD	<0.01
							PD > WD	<0.001
							MD > WD	<0.05
							T1 > OPMD	<0.05
			OSCC > OPMD	<0.01				

Table 2 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group II) (contd.).

Lee et al.[35]*	OSCC: 41, Controls: 24	IL-6	OSCC > Control	<0.001	-	-	stage III/IV > Control	<0.01
							stage I/II > Control	<0.01
		IL-8	OSCC > Control	0.001			stage III/IV > Control	<0.01
							stage I/II > Control	<0.05
		IL-1β	OSCC > Control	0.002			stage III/IV > Control	<0.01
							stage I/II > Control	<0.05
Cheng et al.[36]	OSCC: 18, Controls: 21, OPMD:- OLP: 41	IL-6	OSCC > Control	<0.001	-	-	stage IV > Control	0.002
							stage I > Control	0.001
			OSCC > OPMD	≤0.001				
		IL-8	OSCC > Control	0.014				n. s.
Selvam et al.[37]	OSCC: 25, Controls: 25, OPMD:- Leukoplakia: 25	IL-6	OSCC > Control	<0.001	OPMD > Control	<0.001	stage IV > stage II	0.021
			OSCC > OPMD	<0.001				

Table 2 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group II) (contd.).

Singh et al.[39]	OSCC: 117, Controls: 42, OPMD: 30	IL-1β	OSCC > Control	<0.0001	n.s.	>0.9999	late stage (Stage III-IV)	AUC = 0.9017
		IL-8	OSCC > Control	<0.0001	OPMD > Control	0.251	late stage (Stage III-IV)	AUC = 0.7619
Vala et al.[40]	OSCC: 50, Controls: 50	IL-1	OSCC > Control	<0.001	-	-	Advanced > Early	<0.05
Oshin et al.[44]	OSCC: 15, Controls: 15, OPMD: 15	IL-6	OSCC > Control	<0.001	OPMD > Control	0.05	WD > Control	<0.05

Abbreviations: OSCC, oral squamous cell carcinoma; OPMD, oral potentially malignant disorders; OSMF, oral submucous fibrosis; OLP, oral lichen planus; n. s., non-significant; AUC, area under the curve; Histological grades WD, Well Differentiated; MD, Moderately Differentiated; PD, Poorly Differentiated; Stages I-IV correspond to the four OSCC stage groups; T1-T4 stages correspond to tumour different sizes in Tumour-Node-Metastasis (TNM) staging system.

* This study analysed 14 cytokines; only significant variations are reported here.

Table 3 Evidence from the literature supporting salivary cytokines as OSCC biomarkers (Group III).

Ref.	**Study Groups**	**Cytokine**	**OSCC vs. Control**	***P*-Value**	**Pre/Post-Operative**	***P*-Value**	**24 Months Post-operation**	***P*-Value**
Val et al.[32]*	OSCC: 20	IL-8	-		Pre > Post [b]	0.004	-	-
		IL-6			Pre > Post [b]	0.005	-	-
		IL-1β			Pre > Post [b]	0.049	-	-
		IL-5			Pre < Post [b]	0.048	-	-
Abbas et al.[46]	OSCC: 25, Controls: 25	IL-17	OSCC > Control	<0.001	Pre > Post [a]	<0.001	-	-
Sato et al.[59]	OSCC: 27, Controls: 21	IL-6	-				Immediate Post op. > 24 mos. Post-op.	0.006
							24 mos. Post-op. > Control	n. s.
							Late recurrence† > recurrence (‡)	0.03

Abbreviations: OSCC, oral squamous cell carcinoma; n. s., non-significant; mos., months; Pre: pre-operative; Post/ Post-op.: post-operative; *This study analysed 27 cytokines; only significant variations are reported here; [a,b] Interval between pre- and postoperative salivary collections was 12 days and 2 months for a and b, respectively; †Late locoregional recurrence occurred in the 24–48 months after surgery; ‡Patients without recurrence.