

Prognostic and Clinicopathological Significance of Mucin 1 and Mucin 4 Expression in Oral Squamous Cell Carcinoma: A Systematic Review

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Abstract

Mucin 1 (MUC1) and mucin 4 (MUC4) are transmembrane mucins implicated in epithelial differentiation, cell signaling, tumor progression, and metastatic behavior. Their expression in oral squamous cell carcinoma (OSCC) has been investigated as a potential indicator of clinicopathological characteristics and prognosis. However, the reported findings remain inconsistent. This systematic review evaluated the clinicopathological and prognostic significance of MUC1 and MUC4 expression in OSCC patients. A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, and Google Scholar from database inception to May 31, 2026. Human studies evaluating MUC1 and/or MUC4 expression in histopathologically confirmed OSCC were eligible. Data regarding study characteristics, immunohistochemical methods, expression patterns, clinicopathological associations, co-expression, and prognostic outcomes were extracted and synthesized. Two reviewers independently assessed the methodological quality of the included observational studies using the Newcastle-Ottawa Scale, which evaluates selection, comparability, and outcome/exposure ascertainment. Thirteen studies, involving different populations and methodological approaches, were included. MUC1 expression is generally higher in OSCC than in the normal oral mucosa and is associated in several studies with nodal involvement, advanced stage, vascular invasion, and tumor progression. MUC4 expression was similarly associated with tumor stage, nodal status, and invasive characteristics in larger cohorts, although smaller studies have frequently reported greater expression in well-differentiated tumors. Concurrent MUC1/MUC4 expression has been observed in several studies and is associated with adverse clinicopathological features and poor survival in the largest prognostic cohort. However, substantial heterogeneity in antibody clones, staining thresholds, scoring systems, study populations, and outcome definitions, together with overlap among prognostic cohorts and limited direct comparisons, and the absence of quantitative synthesis, limits the interpretation of the findings. Overall, MUC1 and MUC4 show potential as adjunctive biomarkers in OSCC; however, their independent prognostic value and clinical utility require validation in standardized, adequately powered, multicenter studies.

Categories: Pathology, Dentistry

Keywords: biomarkers, mucins, prognosis, squamous cell carcinoma, tumor

Introduction And Background

Oral squamous cell carcinoma (OSCC) is the predominant malignancy of the oral cavity and is associated with substantial morbidity and mortality, despite advances in diagnosis and treatment [1]. Prognosis is influenced by conventional clinicopathological characteristics, including tumor size, lymph node involvement, tumor stage, histological differentiation, and patterns of local invasion [2]. However, considerable variations in clinical outcomes can occur among patients with similar clinicopathological features, highlighting the need for reliable molecular markers that can improve prognostic stratification and identify patients at greater risk of disease progression or recurrence [3].

Mucins are high-molecular-weight glycoproteins that contribute to epithelial barrier function, cell adhesion, signaling, and interactions between tumor cells and their surrounding microenvironment [4]. Mucin 1 (MUC1) and mucin 4 (MUC4) are transmembrane mucins that have been investigated in several epithelial malignancies because of their involvement in tumor-associated cellular processes [5]. Aberrant expression of these mucins has also been documented in OSCC. Individual expression of MUC1 and MUC4 has been associated with aggressive clinicopathological characteristics and adverse survival outcomes in patients with OSCC [6,7]. For example, MUC4 expression has been associated with a higher primary tumor (T) classification, lymph node metastasis, advanced tumor stage, diffuse invasion, recurrence, and poorer overall and disease-free survival [8].

Although the individual prognostic relevance of these mucins has been investigated, their combined expression may provide additional prognostic information because MUC1 and MUC4 participate in related

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but distinct tumor-associated mechanisms [6]. A study of 206 patients with OSCC specifically demonstrated that MUC1/MUC4 double-positive tumors were associated with tumor size, lymph node metastasis, advanced stage, diffuse invasion, vascular invasion, regional recurrence, and poorer overall and disease-free survival [7]. Subsequent immunohistochemical studies have further examined MUC1 and MUC4 co-expression in oral leukoplakia and OSCC, although these studies differed in sample size, design, assessment methods, and outcomes [6,9]. Therefore, this systematic review aimed to critically synthesize the available evidence on the prognostic and clinicopathological significance of MUC1 and MUC4 co-expression in OSCC, with particular emphasis on tumor aggressiveness, lymph node metastasis, recurrence, overall survival, and disease-free survival.

Review

Methods

Study Design and Eligibility Criteria

This systematic review was conducted and reported in accordance with the PRISMA 2020 guidelines [10]. Eligibility criteria were formulated according to the Population, Prognostic Factor, and Outcomes (PFO) framework [11]. The population comprised human patients with histopathologically confirmed OSCC. The prognostic factors of interest were MUC1 and/or MUC4 expression, primarily assessed by immunohistochemistry. Studies evaluating either marker individually or both markers simultaneously, including co-expression patterns, were eligible. Outcomes were prespecified within two domains: prognostic outcomes, including overall survival, disease-free survival, recurrence, and cancer-related mortality; and clinicopathological indicators of tumor aggressiveness, including lymph node metastasis, tumor stage, tumor size, histological differentiation, local invasion, and vascular or perineural involvement. Eligible study designs included original human observational studies, including retrospective and prospective cohort studies and cross-sectional clinicopathological studies.

Search Strategy and Study Selection

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, and Google Scholar from database inception to May 31, 2026. The search strategy combined controlled vocabulary and free-text terms related to MUC1, MUC4, OSCC, prognosis, survival, recurrence, and clinicopathological characteristics (Table 1).

Database	Search date	Complete search strategy
PubMed/MEDLINE	May 31, 2026	((("Mucin-1"[MeSH Terms] OR MUC1[Title/Abstract] OR "mucin 1"[Title/Abstract] OR "mucin-1" [Title/Abstract] OR episialin[Title/Abstract]) OR ("Mucin-4"[MeSH Terms] OR MUC4[Title/Abstract] OR "mucin 4"[Title/Abstract] OR "mucin-4"[Title/Abstract])) AND ("Mouth Neoplasms"[MeSH Terms] OR "Carcinoma, Squamous Cell"[MeSH Terms] OR "oral squamous cell carcinoma"[Title/Abstract] OR "oral cancer"[Title/Abstract] OR "oral carcinoma"[Title/Abstract] OR OSCC[Title/Abstract]) AND (prognosis[Title/Abstract] OR prognostic[Title/Abstract] OR survival[Title/Abstract] OR recurrence[Title/Abstract] OR "lymph node metastasis"[Title/Abstract] OR clinicopathological[Title/Abstract] OR differentiation[Title/Abstract] OR invasion[Title/Abstract] OR stage[Title/Abstract])
Scopus	May 31, 2026	TITLE-ABS-KEY ((MUC1 OR "mucin 1" OR "mucin-1" OR episialin OR MUC4 OR "mucin 4" OR "mucin-4") AND ("oral squamous cell carcinoma" OR "oral cancer" OR "oral carcinoma" OR OSCC) AND (prognosis OR prognostic OR survival OR recurrence OR "lymph node metastasis" OR clinicopathological OR differentiation OR invasion OR stage))
Web of Science Core Collection	May 31, 2026	TS=((MUC1 OR "mucin 1" OR "mucin-1" OR episialin OR MUC4 OR "mucin 4" OR "mucin-4") AND ("oral squamous cell carcinoma" OR "oral cancer" OR "oral carcinoma" OR OSCC) AND (prognosis OR prognostic OR survival OR recurrence OR "lymph node metastasis" OR clinicopathological OR differentiation OR invasion OR stage))
Embase	May 31, 2026	('mucin 1'/exp OR MUC1:ti,ab OR 'mucin 1':ti,ab OR 'mucin-1':ti,ab OR episialin:ti,ab OR 'mucin 4'/exp OR MUC4:ti,ab OR 'mucin 4':ti,ab OR 'mucin-4':ti,ab) AND ('mouth cancer'/exp OR 'oral squamous cell carcinoma':ti,ab OR 'oral cancer':ti,ab OR 'oral carcinoma':ti,ab OR OSCC:ti,ab) AND (prognosis:ti,ab OR prognostic:ti,ab OR survival:ti,ab OR recurrence:ti,ab OR 'lymph node metastasis':ti,ab OR clinicopathological:ti,ab OR differentiation:ti,ab OR invasion:ti,ab OR stage:ti,ab)
Google Scholar	May 31, 2026	"MUC1" OR "mucin 1" OR "mucin-1" OR "MUC4" OR "mucin 4" OR "mucin-4" "oral squamous cell carcinoma" OR "oral cancer" prognosis OR survival OR recurrence OR "lymph node metastasis"

TABLE 1: Database-specific search strategies and search dates.

The strategy was adapted according to the indexing system and the search syntax for each database. The reference lists of the included studies and relevant reviews were manually screened to identify additional eligible articles. The retrieved records were imported into reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts, followed by a full-text assessment of potentially eligible articles. Disagreements were resolved through discussion and consensus with the involvement of a third reviewer, when required. The study selection process was documented using the PRISMA flow diagram (Figure 1).

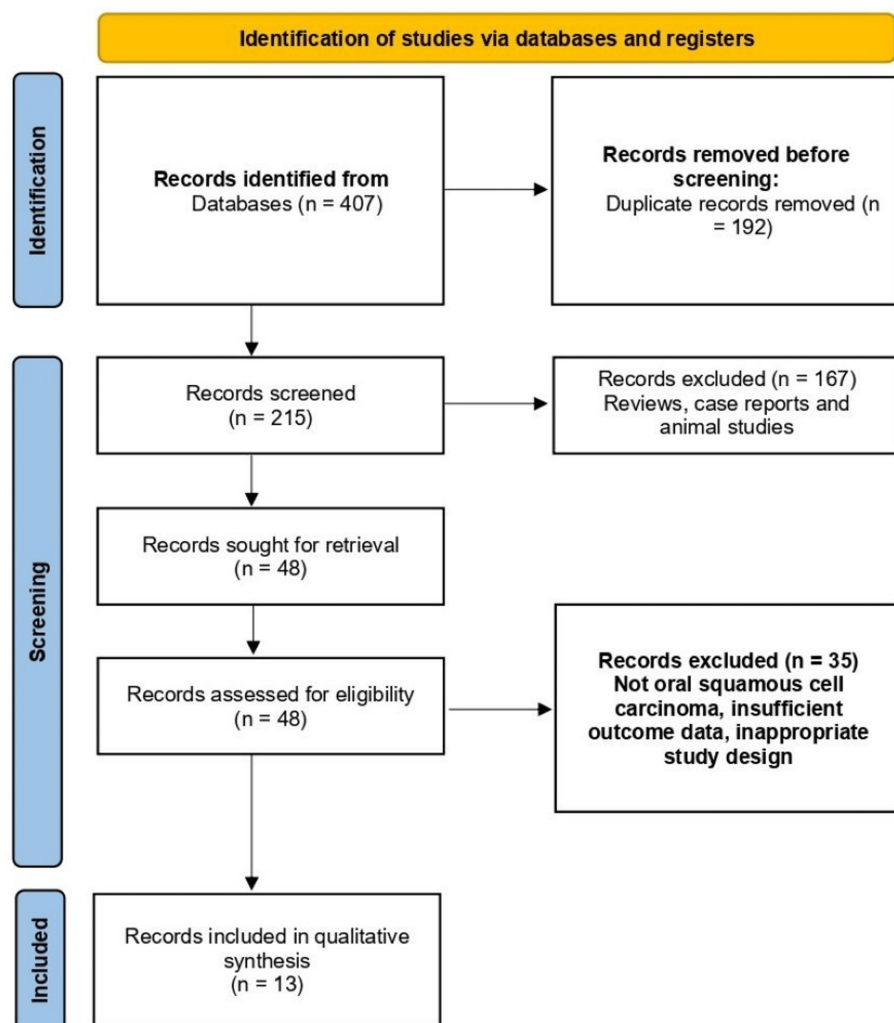


FIGURE 1: PRISMA flowchart.

Flowchart adapted from Page et al. [10] and prepared using Canva (Canva Pty Ltd., Sydney, Australia).

Data Extraction and Risk-of-Bias Assessment

The data were independently extracted by two reviewers (MSM and TP). Extracted information included author and publication year, country, study design, sample size, participant characteristics, tumor site, histopathological characteristics, methods used to assess MUC1 and/or MUC4, antibody characteristics, immunohistochemical scoring criteria, cutoff values, definition of positive or high expression, and, where applicable, definitions of combined or co-expression categories. Information regarding the distribution of mucin expression, follow-up duration, and reported clinicopathological and prognostic outcomes was also extracted. Prognostic data included overall survival, disease-free survival, recurrence, and cancer-related mortality, together with reported effect estimates such as HRs, RRs, risk ratios, and corresponding 95% CIs.

Two reviewers (AA and AK) independently assessed the methodological quality of the included observational studies using the Newcastle-Ottawa Scale (NOS), which evaluates selection, comparability, and outcome/exposure ascertainment [12]. Disagreements were resolved by consensus or consultation with a third reviewer (SK). The assessment comprised three domains: selection (maximum 4 points), comparability (maximum 2 points), and outcome or exposure ascertainment (maximum 3 points), yielding a maximum score of 9 points. Domain-level assessments were considered alongside the methodological limitations of each study when interpreting the overall risk of bias. As the original NOS was developed primarily for cohort and case-control studies, its criteria were adapted where necessary to accommodate differences in study design. Accordingly, assessments of cross-sectional and other studies for which the original criteria were not directly applicable were interpreted as NOS-derived judgments rather than formal applications of the original instrument. The criteria used to assign overall risk categories are reported alongside the risk-of-bias figure.

Data Synthesis

Because the included studies were expected to demonstrate substantial clinical and methodological heterogeneity, a quantitative meta-analysis was not performed. Differences were anticipated in patient characteristics, tumor sites and stages, sample sizes, antibodies and immunohistochemical techniques, staining and scoring systems, cutoff values for mucin positivity, definitions of MUC1 and MUC4 expression or co-expression, follow-up periods, and outcome definitions. In addition, the available studies reported heterogeneous statistical measures and varying levels of adjustment for potential confounders, limiting the validity and clinical interpretability of the pooled estimates. Therefore, the findings were synthesized and organized according to the prognostic and clinicopathological outcomes.

Prognostic findings were summarized according to overall survival, disease-free survival, recurrence, and cancer-related mortality, whereas clinicopathological findings were grouped according to lymph node metastasis, tumor stage, tumor size, histological differentiation, invasion, and other indicators of tumor aggressiveness. MUC1 and MUC4 findings were considered separately, while studies reporting the simultaneous co-expression of both markers were summarized as distinct categories. The direction and consistency of associations across studies were compared, with greater emphasis placed on adjusted estimates and findings from studies with a lower risk of bias. Differences in immunohistochemical methodology, expression thresholds, and study populations were considered when interpreting the consistency of the evidence. We did not obtain pooled effect estimates.

Results

Thirteen studies were included in the qualitative analysis. Studies published between 2000 and 2026 evaluated MUC1 and/or MUC4 expression in OSCC using immunohistochemical methods. The sample sizes ranged from 20 to 206 participants. Considerable variation was observed in antibody clones, staining thresholds, scoring systems, and outcome definitions (Tables [2](#), [3](#)).

Study	Country	Design	OSCC, n	Other arms	Marker(s)	Eligible evidence/outcome	Important caveat
Rathee et al. (2021) [6]	India	Cross-sectional IHC	24	Leukoplakia 24; NOM 12	MUC1 + MUC4	Co-expression frequencies; differentiation	No prognostic follow-up
Kamikawa et al. (2015) [7]	Japan	Surgical cohort IHC	206	-	MUC1 + MUC4	Co-expression; OS; DFS; regional recurrence; clinicopathological factors	Primary co-expression prognostic study; overlaps with [8] and [13]
Hamada et al. (2012) [8]	Japan	Surgical cohort	150	-	MUC4	Overall survival; disease-free survival; recurrence; later nodal disease	Overlapping Kagoshima series with [7]
John et al. (2025) [9]	India	Cross-sectional IHC + qRT-PCR	21	OPMD; NOM	MUC1 + MUC4	Clinicopathological/grade patterns	No survival; PBMC qPCR is not tumor-tissue expression
Hamada et al. (2012) [13]	Japan	Surgical cohort	206	-	MUC1 (DF3)	Overall survival; disease-free survival; subsequent lymph node metastasis	Same 206-patient cohort as [7]
Narashiman et al. (2014) [14]	India	Cross-sectional IHC	20	Leukoplakia 15; NOM 5	MUC4	MUC4 expression; grade; normal/leukoplakia comparison	No survival follow-up
Kumar et al. (2016) [15]	India	Cross-sectional IHC	20	PMD 20; NOM 20	MUC1	Mean percentage of positive cells; group comparison	No survival follow-up
Thakur et al. (2018) [16]	India	Cross-sectional IHC	30	NOM 30	MUC1	OSCC versus normal mucosa	26/30 cases were well differentiated; limited grade comparison
Shobhita et al. (2018) [17]	India	Cross-sectional IHC	30	NOM 10	MUC1	OSCC versus normal mucosa; grade-related expression	Direction differed between extent and intensity/IRS
Kohli et al. (2019) [18]	India	Cross-sectional IHC	30	NOM 5	MUC4	MUC4 expression; differentiation trend	No survival follow-up
Nitta et al. (2000) [19]	Japan	Cross-sectional IHC + electron microscopy	77	Dysplasia 36; CIS 12	MUC1	Disease progression; mode of invasion; lymph node metastasis	No survival follow-up
Abidullah et al. (2023) [20]	India	Retrospective IHC	45	OED 45; NOM 10	MUC4	MUC4 expression; OED/OSCC grade	No survival follow-up
Abidullah (2026) [21]	India	Cross-sectional IHC	40	Oral leukoplakia 40	MUC1 + MUC4	Co-expression; high IRS expression	No follow-up; diagnostic logistic ORs are not prognostic

TABLE 2: Characteristics of the included studies.

:- no data available; CIS: carcinoma in situ; DFS: disease-free survival; DN: double-negative; DP: double-positive; IHC: immunohistochemistry; LNM: lymph node metastasis; MUC1: mucin 1; MUC4: mucin 4; NOM: normal oral mucosa; OED: oral epithelial dysplasia; OPMD: oral potentially malignant disorder; OS: overall survival; OSCC: oral squamous cell carcinoma; PMD: potentially malignant disorder; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; SP: single-positive

Study	MUC1 antibody	MUC4 antibody	Positivity threshold	Scoring/assessment	Observers/reliability
Rathee et al. (2021) [6]	Anti-MUC1	Anti-MUC4	>5% cells	Grades I-IV by percentage; DP/SP/DN	Not stated
Kamikawa et al. (2015) [7]	DF3, 1:10	8G7, 1:3000	>5% cells	Binary; DP/SP/DN	Not stated
Hamada et al. (2012) [8]	-	8G7	>5% by ROC	Binary	Not stated
John et al. (2025) [9]	MUC1: clone not standardized in abstract	MUC4: clone not standardized in abstract	Not uniform across grades	Intensity + pattern; qRT-PCR 2-ΔΔCt on PBMCs	Not stated
Hamada et al. (2012) [13]	DF3 (Toray-Fuji)	-	>5% cells	Binary; mean staining 7.7% (range 0-80)	Not stated
Narashiman et al. (2014) [14]	-	BioGenex MUC4	Mild <25%; moderate 25-50%; intense >50%	Percentage of cells + intensity	Two pathologists
Kumar et al. (2016) [15]	Thermo Scientific MUC1, 1:50	-	Continuous mean % per 5 HPF	Mean % positive cells	Two observers
Thakur et al. (2018) [16]	BioGenex rabbit anti-MUC1, 1:50	-	>5%; I <5, II 5-10, III 11-50, IV >50	Percentage + intensity	Two observers
Shobhita et al. (2018) [17]	PathnSitu EP85, 1:100	-	Remmele IRS 0-12	Percentage of cells, intensity, IRS	Two observers
Kohli et al. (2019) [18]	-	MUC4 kit protocol	Same percentage bins as Narashiman et al. [14]	Percentage + intensity; ANOVA	Not stated
Nitta et al. (2000) [19]	MUC1 (DF3 lineage)	-	Membranous versus cytoplasmic pattern	Light microscopy + TEM gold	Not stated
Abidullah et al. (2023) [20]	-	PathnSitu mouse anti-MUC4, 1:50	LI; IRS low/high >3	Labeling index + IRS	Two; r = 0.634
Abidullah (2026) [21]	Anti-MUC1	Anti-MUC4	IRS ≥4 = high	IRS = intensity × extent; any-positivity for co-expression	Not stated

TABLE 3: Immunohistochemical methods and expression assessment.

-. no data available; DF3: DF3 epitope of mucin 1; DN: double-negative; DP: double-positive; HPF: high-power field; IRS: immunoreactive score; LI: labeling index; MUC1: mucin 1; MUC4: mucin 4; NR: not reported; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; SP: single-positive; TEM: transmission electron microscopy

MUC1 Expression and Clinicopathological Associations

MUC1 expression has been associated with several adverse clinical features. Nitta et al. [19] reported membranous MUC1 expression in 59.7% of OSCC cases, which was significantly associated with lymph node metastasis, the mode of invasion, and disease progression. Hamada et al. [13] reported that MUC1 expression in 38.8% of 206 patients was significantly associated with nodal involvement, disease stage, diffuse invasion, and vascular invasion. Smaller studies have generally demonstrated greater MUC1 expression in OSCC than in normal oral mucosa, although the direction of the association with histological grade varied across studies (Table 4).

Study	Marker(s)	Expression in OSCC	Differentiation/grade	Clinicopathological association	Interpretation within study
Rathee et al. (2021) [6]	MUC1 + MUC4	MUC1 20/24 (83%); MUC4 22/24 (92%); DP 18/24	DP is frequent in WD and MD.	NOM→leukoplakia→OSCC: p = 0.002 and p < 0.001	Co-expression was frequent in OSCC.
Kamikawa et al. (2015) [7]	MUC1 + MUC4	DP 60/206 (29.1%); SP 55/206 (26.7%); DN 91/206 (44.2%)	Grade is not the principal discriminator.	Size, p = 0.014; N, p = 0.0001; stage, p = 0.006; diffuse invasion, p = 0.028; vascular invasion, p = 0.014	DP associated with adverse clinicopathological features
Hamada et al. (2012) [8]	MUC4	61/150 (40.7%) MUC4+	Grade gradient not reported as a main finding	T, p = 0.0004; N, p = 0.049; stage, p = 0.002; diffuse invasion, p = 0.004	MUC4+ associated with adverse T/N/stage/invasion
John et al. (2025) [9]	MUC1 + MUC4	OSCC is highest among groups; the extraction does not state exact marker-specific OSCC proportions.	MUC1 higher in PD; MUC4 stronger in WD	Group comparison, p < 0.001	No survival follow-up
Hamada et al. (2012) [13]	MUC1 (DF3)	80/206 (38.8%) DF3+	Grade NS (p=0.79)	N, p = 0.002; stage, p = 0.02; diffuse invasion, p = 0.03; vascular invasion, p = 0.01	DF3 positivity tracked nodal/stage/invasion features
Narashiman et al. (2014) [14]	MUC4	14/20 (70%)	WD 9/10; MD 5/10	Group comparison, p = 0.010; LNM NS	MUC4 is more frequent in WD than MD.
Kumar et al. (2016) [15]	MUC1	Mean 44.0% positive cells in OSCC	WD 42% versus PD 47%, NS	Group comparison, p < 0.001	OSCC > PMD > NOM
Thakur et al. (2018) [16]	MUC1	21/30 (70%) versus 0/30 NOM	26/30 were WD; grade and stage not significant	OSCC versus NOM, p < 0.001	Higher MUC1 staining in OSCC than NOM
Shobhita et al. (2018) [17]	MUC1	30/30 OSCC showed some staining.	Extent is highest in PD; intensity/IRS is intermediate and highest in WD.	NOM versus OSCC, p < 0.01	Direction varied by scoring component.
Kohli et al. (2019) [18]	MUC4	21/30 (70%)	WD 8/10; MD 7/10; PD 5/10	Group comparison, p = 0.041	Expression decreased from WD to PD.
Nitta et al. (2000) [19]	MUC1	Membranous staining 59.7%; cytoplasmic-predominant 25/77 (32.5%)	Progression from dysplasia/CIS to OSCC	LNM, p < 0.01; mode of invasion, p < 0.02; membrane pattern and progression, p < 0.01	Membranous and cytoplasmic patterns differed with progression
Abidullah et al. (2023) [20]	MUC4	High IRS, highest in WD and lowest in PD	WD > MD > PD	OSCC grade, p = 0.001; OED grade, p=1.00	Grade association; no survival
Abidullah (2026) [21]	MUC1 + MUC4	High IRS: MUC1 33/40 (82.5%); MUC4 28/40 (70%); any co-expression 36/40 (90%)	Not reported	High MUC1, p < 0.001; co-expression, p = 0.027	No survival follow-up

TABLE 4: MUC1 and MUC4 expression and clinicopathological associations.

LNM: lymph node metastasis; MD: moderately differentiated; MUC1: mucin 1; MUC4: mucin 4; NOM: normal oral mucosa; NR: not reported; NS: not significant; OED: oral epithelial dysplasia; PD: poorly differentiated; PMD: potentially malignant disorder; WD: well differentiated

MUC4 Expression and Clinicopathological Associations

MUC4 expression was detected in 40.7% of the patients in a large cohort, as reported by Hamada et al. [8], and was significantly associated with T classification, nodal status, disease stage, and diffuse invasion. Narashiman et al. [14], Kohli et al. [18], and Abidullah et al. [20] also reported significant differences in

MUC4 expression according to histological characteristics, with higher expression generally observed in well-differentiated tumors in smaller Indian cohorts (Table 3).

MUC1/MUC4 Co-Expression

The co-expression of MUC1 and MUC4 was reported in four studies (Table 5). Kamikawa et al. [7] reported dual positivity in 29.1% of the patients and found significant associations with tumor size, nodal status, stage, diffuse invasion, and vascular invasion. Rathee et al. [6] reported dual positivity in 75% of cases, while Abidullah [21] reported positivity for both markers in 90% of patients. John et al. [9] also evaluated both markers, although formal co-expression frequencies have not yet been reported.

Study	OSCC, n	Co-expression definition	Double-positive	Single-positive	Double-negative	Key co-expression finding
Rathee et al. (2021) [6]	24	Both markers are >5%.	18 (75.0%)	6 (25.0%)	0 (0.0%)	Co-expression is more frequent in OSCC than leukoplakia/NOM; no survival data
Kamikawa et al. (2015) [7]	206	MUC1 and MUC4 are both >5%.	60 (29.1%)	55 (26.7%)	91 (44.2%)	DP associated with tumor size, N, stage, diffuse and vascular invasion; poorest OS/DFS
John et al. (2025) [9]	21	Both markers were evaluated.	NR	NR	NR	No formal DP/SP/DN table; qualitative clinicopathological/grade findings only
Abidullah (2026) [21]	40	Any positivity of both markers; high IRS reported separately	36/40 (90%) any+	NR	NR	Any co-expression is 90% in OSCC versus 65% in leukoplakia (p=0.027); no follow-up

TABLE 5: MUC1/MUC4 co-expression patterns.
Co-expression definitions were not uniform across studies and should not be treated as directly equivalent.
DN: double-negative; DP: double-positive; NR: not reported; OSCC: oral squamous cell carcinoma; SP: single-positive

Prognostic Outcomes

Three reports provided longitudinal prognostic data. Hamada et al. [8] reported significantly poorer overall and disease-free survival among patients with MUC4-positive tumors, together with higher local recurrence and subsequent lymph node metastasis. Similarly, Hamada et al. [13] demonstrated significantly poorer overall and disease-free survival among patients with MUC1-positive tumors, with MUC1 expression being independently associated with these outcomes. Kamikawa et al. [7] found that dual MUC1/MUC4 positivity was associated with poorer overall and disease-free survival and increased regional recurrence. These three reports originated from the same Japanese institutional cohort and, therefore, should not be considered three independent cohorts (Table 6).

Study	Contrast	Population/follow-up	Overall survival	Disease-free survival	Recurrence/late nodal disease	Cohort-overlap note
Kamikawa et al. (2015) [7]	MUC1/MUC4 double-positive versus others	206; surgical cohort	Multivariable p = 0.007; HR 3.60	Multivariable p = 0.0019	Regional recurrence p = 0.0025	Primary co-expression prognostic evidence
Hamada et al. (2012) [8]	MUC4+ versus MUC4-	150; overlapping Kagoshima series	KM p = 0.0001; stepwise p = 0.0015; HR 1.619 (95% CI 1.115-2.409)	KM p < 0.0001	Local recurrence p = 0.017; later LNM p = 0.0001	Use as MUC4-only prognostic evidence only if the MUC4 component of [7] is not analyzed separately.
Hamada et al. (2012) [13]	DF3/MUC1+ versus MUC1-	206; mean follow-up 61 months; same cohort as [7]	KM p = 0.001; multivariable HR 2.09 (95% CI 1.04-4.29), p = 0.04	KM p = 0.0003; multivariable HR 1.71 (95% CI 1.02-2.85), p = 0.04	Subsequent LNM: HR 2.29 (95% CI 1.08-4.93), p = 0.03	Use as MUC1-only prognostic evidence only if the MUC1 component of [7] is not analyzed separately.

TABLE 6: Prognostic outcomes reported in studies with longitudinal follow-up.

The included studies report involve overlapping Kagoshima surgical patients and should not be interpreted as three independent cohorts.

DFS: disease-free survival; KM: Kaplan-Meier; LNM: lymph node metastasis; OS: overall survival

Risk of Bias and Overall Synthesis

The NOS-derived assessment indicated generally more favorable methodological ratings for the larger Japanese prognostic cohorts, whereas smaller cross-sectional studies more frequently presented methodological limitations related to sample size, confounding, and the absence of longitudinal follow-up (Figure 2).

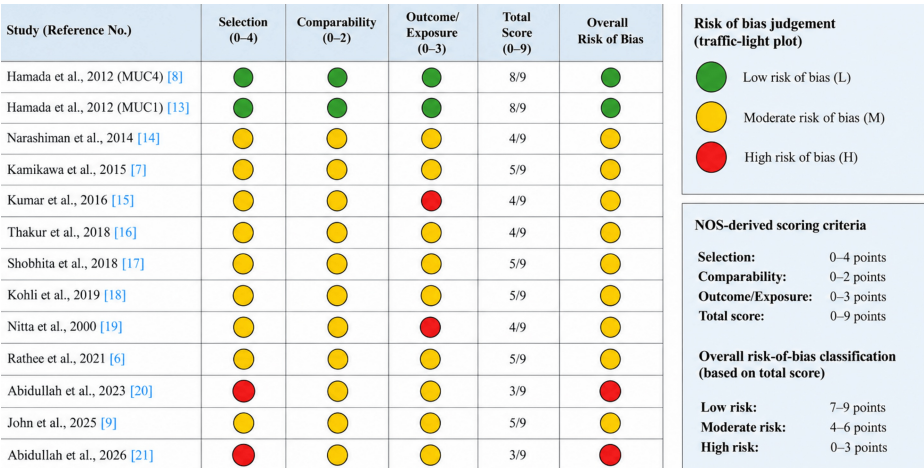


FIGURE 2: Traffic-light representation of methodological quality and risk-of-bias assessments using an NOS-derived framework.

The domains assessed were selection, comparability, and outcome or exposure ascertainment, together with the overall risk-of-bias judgment. Green indicates low risk, yellow indicates moderate risk, and red indicates high risk. The overall classifications were based on the assessment criteria applied in this review, taking account of domain-level judgments and study-specific methodological limitations. Because the framework was adapted for different observational study designs, the results should be interpreted as NOS-derived assessments rather than formal applications of the original NOS to every included study.

H: high risk; L: low risk; M: moderate risk; NOS, Newcastle-Ottawa Scale

[6-9,13-21]

The principal limitations of this study include small sample sizes, lack of longitudinal follow-up, incomplete

adjustment for confounding factors, and variability in immunohistochemical assessment. Due to the substantial heterogeneity in immunohistochemical methods, expression thresholds, scoring systems, study designs, and outcome definitions, together with potential cohort overlap, the findings were synthesized narratively rather than quantitatively (Table 7).

Evidence domain	Study references	Summary of extracted evidence
MUC1 alone	[13,15-17,19]	MUC1 was associated with disease progression, nodal disease, stage, and invasion in the larger Japanese studies. Smaller Indian studies generally showed greater staining in OSCC than normal mucosa, but the direction of grade-related associations varied across scoring components.
MUC4 alone	[8,14,18,20]	The larger Japanese cohort linked MUC4 positivity with adverse T/N/stage/invasion and survival outcomes. Smaller Indian studies generally showed stronger MUC4 expression in well-differentiated than poorly differentiated tumors.
MUC1 and MUC4 co-expression	[6,7,9,21]	Co-expression was demonstrated across the available studies. Only [7] provided adjusted prognostic evidence specifically for double-positive tumors; the smaller studies mainly addressed expression frequencies and differentiation.
Cohort overlap	[7,8,13]	The three Kagoshima reports involve overlapping surgical patients. They should not be counted as three independent cohorts when describing the evidence base or interpreting prognostic findings.
Overall synthesis	All eligible studies	Differences in antibodies, thresholds, scoring systems, study designs, sample sizes, outcomes, and cohort overlap precluded quantitative pooling. Findings were therefore synthesized narratively without meta-analysis.

TABLE 7: Narrative synthesis by evidence domain.

Because of heterogeneity in antibodies, expression thresholds, scoring systems, study designs, sample sizes, outcome definitions, and cohort overlap, no quantitative meta-analysis was performed.

MUC1: mucin 1; MUC4: mucin 4; OSCC: oral squamous cell carcinoma

Discussion

This systematic review synthesized the available evidence on the clinicopathological and prognostic significance of MUC1 and MUC4 expression in OSCC. Overall, these findings suggest that MUC1 and MUC4 may be biologically relevant markers of the tumor phenotype; however, this interpretation should be considered preliminary because the available evidence is derived largely from individual studies, many of which had small sample sizes, and the three longitudinal prognostic reports were based on overlapping Japanese cohorts rather than independent populations. Accordingly, the clinical interpretation of MUC1 and MUC4 expression remains dependent on the marker assessed, immunohistochemical methodology, and disease context, and their independent prognostic significance requires validation in larger, multicenter studies with non-overlapping populations. MUC1 expression was consistently higher in OSCC than in normal oral mucosa or potentially malignant lesions in several smaller studies, whereas a larger Japanese cohort demonstrated associations with lymph node involvement, advanced stage, diffuse invasion, and vascular invasion [7,8,13,19]. Similarly, MUC4 expression was associated with tumor size, nodal status, stage, and diffuse invasion in a larger cohort. These observations are important because conventional histopathological parameters do not completely capture the biological heterogeneity of OSCC, and molecular markers may provide complementary information regarding tumor behavior.

The association between MUC1 and aggressive diseases is biologically plausible. MUC1 is not simply a structural component of the epithelial surface; its C-terminal subunit participates in intracellular signaling and interacts with receptor tyrosine kinases, β-catenin, and other signaling proteins. These interactions can promote proliferation and survival pathways and interfere with cell-cell adhesion, thereby facilitating malignant progression and invasion [22,23]. Experimental evidence specifically in OSCC has further shown that MUC1 promotes migration and invasion through PI3K-AKT signaling, with MUC1 suppression reducing matrix metalloproteinase activity and malignant cellular behavior [24]. Thus, the associations observed in clinical studies between MUC1 expression and nodal metastasis, vascular invasion, and advanced stage are consistent with the potential role of MUC1 in maintaining an invasive phenotype, rather than representing an isolated immunohistochemical finding.

MUC4 appears to play a related, but biologically distinct, role. MUC4 contains EGF-like domains capable of interacting with ErbB2/HER2 and can modulate receptor phosphorylation and downstream survival signaling [9,23]. Its large extracellular domain may additionally alter cell-cell and cell-matrix interactions, providing a mechanistic basis for enhanced tumor cell survival and dissemination. Therefore, the association

between MUC4 positivity and adverse T classification, nodal disease, stage, and diffuse invasion reported by Hamada et al. [8] supports the concept that MUC4 may reflect the activation of growth and survival mechanisms accompanying tumor progression. However, smaller Indian studies frequently showed stronger MUC4 staining in well-differentiated tumors than in poorly differentiated tumors [14,18,20]. This apparent discrepancy highlights that MUC4 expression may also reflect epithelial differentiation and tissue phenotype, rather than functioning as a simple monotonic marker of dedifferentiation. Consequently, MUC4 levels should not be interpreted independently of tumor grade and scoring methodology.

An important finding was the potential added value in simultaneously assessing MUC1 and MUC4. Kamikawa et al. [7] demonstrated that double-positive tumors were associated with tumor size, nodal metastasis, advanced stage, diffuse invasion, and vascular invasion, and showed poorer survival outcomes. A combined assessment is biologically reasonable because MUC1 and MUC4 can influence complementary aspects of tumor biology, including receptor signaling, cell adhesion, survival, and interactions with the tumor microenvironment [5,22,23]. Nevertheless, evidence for co-expression remains limited. Rathee et al. [6], John et al. [9], and Abidullah [21] demonstrated frequent simultaneous expression. However, these studies were small and did not provide comparable longitudinal prognostic evidence. Importantly, three Japanese prognostic reports involved overlapping Kagoshima patients [7,8,13]. Therefore, their findings strengthen the consistency of the signal but should not be interpreted as evidence from three independent populations.

From a clinical perspective, MUC1/MUC4 assessment may have potential as an adjunctive biomarker for identifying OSCCs with biological features associated with invasion, nodal dissemination, recurrence, or reduced survival [6,7]. Immunohistochemistry is particularly attractive because it can be performed on routinely available biopsy or resection specimens and is potentially integrated with histopathological assessment [25]. However, the present evidence does not support the replacement of established clinicopathological staging with MUC1 or MUC4 testing. Rather, these markers may eventually contribute to multidimensional risk stratification, along with tumor stage, depth of invasion, nodal status, extranodal extension, and other validated molecular biomarkers. Contemporary OSCC research has increasingly emphasized integrated molecular and clinicopathological models because of the substantial tumor heterogeneity and limitations of individual biomarkers.

Limitations

This study had several limitations. First, substantial methodological heterogeneity existed among the included studies with respect to antibody clones, dilutions, staining thresholds, scoring systems, and definitions of positivity, limiting direct comparisons across studies. Second, most included studies were small, cross-sectional, or retrospective and lacked longitudinal survival follow-up; consequently, prognostic evidence was concentrated in three reports derived from overlapping Japanese cohorts rather than independent populations. Third, differences in tumor grade and population characteristics may partly explain the contrasting directions of grade-related associations observed across studies. Fourth, observer reliability was incompletely reported in several studies. Fifth, substantial heterogeneity in study designs, patient populations, immunohistochemical methods, outcome definitions, and reported statistical measures prevented the planned quantitative synthesis; therefore, the findings were synthesized narratively, and no pooled effect estimates were calculated. Finally, potential publication bias, missed or unpublished studies, and residual confounding cannot be excluded. Although the NOS was used to assess methodological quality, it was originally developed primarily for cohort and case-control studies and was not specifically designed for all study designs included in this review, particularly cross-sectional studies. These limitations should be considered when interpreting the strength and generalizability of the available evidence.

Future Recommendations

Future studies should use large, multicenter prospective cohorts with standardized MUC1 and MUC4 antibodies, validated positivity thresholds, pre-specified scoring systems, and blinded assessments with inter-observer reliability reporting. Studies should distinguish membranous, cytoplasmic, and subcellular staining patterns and evaluate MUC1 and MUC4 simultaneously with established pathological variables and molecular biomarkers. Multivariable models should assess whether individual and combined MUC1/MUC4 expression provides incremental prognostic value beyond TNM stage and established pathological risk factors. Longitudinal studies should additionally evaluate recurrence, disease-specific survival, treatment response, and regional or distant metastasis. Integration with transcriptomic, proteomic, spatial, and liquid biopsy approaches may clarify whether these markers can progress from tissue-associated observations to reproducible biomarkers for risk stratification and treatment selection [26].

Conclusions

MUC1 and MUC4 expression appears to be associated with clinically relevant features of OSCC, including tumor progression, lymph node involvement, invasion, and survival outcomes. Co-expression of MUC1 and MUC4 may provide additional information regarding aggressive tumor behavior. However, these findings should be interpreted with caution because the available evidence is derived largely from individual studies, many with small sample sizes, and the prognostic evidence includes overlapping Japanese cohorts.

Substantial heterogeneity in immunohistochemical methods, scoring systems, study populations, and outcome definitions further limits definitive clinical interpretation. Current evidence therefore supports MUC1 and MUC4 as promising adjunctive biomarkers rather than established independent prognostic tools. Standardized, adequately powered, multicenter prospective studies involving independent populations are required to validate their prognostic and clinical utility.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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