



CD 57 EXPRESSION IN ORAL SQUAMOUS CELL CARCINOMA: A CLINICOPATHOLOGICAL AND PROGNOSTIC INSIGHT

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ABSTRACT

Background: Tumor microenvironment (TME) plays a critical role in tumor progression, via tumor-infiltrating immune cells. The role of CD57⁺ cells within the TME has been investigated in oral squamous cell carcinomas as a prognostic biomarker. The present study was done to evaluate the immunohistochemical expression of CD57 in oral squamous cell carcinoma and its correlation with histological grade and clinicopathological parameters.

Methods: A hospital-based descriptive study was conducted on 75 cases of OSCC received at a tertiary teaching hospital in western Uttar Pradesh. The expression of CD57 was assessed using immunohistochemistry and correlated with various clinicopathological parameters.

Results: The age of patients ranged from 30 to 80 years with a mean age of 51.44 ± 11.64 years. Males predominated (85.3%; male-to-female ratio 5.8:1). Buccal mucosa was the most common site (41.3%). Histologically, moderately differentiated tumours constituted the majority (53.3%), followed by well differentiated (34.7%) and poorly differentiated (12.0%). Overall, CD57 positivity was observed in 86.67% of cases. A statistically significant association was found between CD57 expression and histological grade ($\chi^2 = 17.30$, $df = 6$, $p = 0.0083$). The mean CD57 positivity score was significantly higher in well differentiated tumours (7.83 ± 2.74) compared to moderately differentiated (5.10 ± 2.46) and poorly differentiated tumours (1.98 ± 1.38) ($p < 0.001$).

Conclusion: CD57 expression demonstrates a significant inverse correlation with histological grade in OSCC. These findings supported the potential role of CD57 as a biomarker for tumour differentiation status and possibly patient prognosis in OSCC.

KEYWORDS: CD57, Histological Grading, Immunohistochemistry, Natural Killer Cells, Oral Squamous Cell Carcinoma.

Introduction

Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of all oral malignancies and represents a major global health burden, with an estimated 377,713 new cases reported worldwide in 2020[1]. India bears a disproportionately high share of this burden, contributing

nearly one-third of global cases and ranking OSCC among the most common cancers in the country[2,3]. The five-year survival rate remains below 50%, largely due to late-stage presentation, locoregional recurrence, and cervical lymph node metastasis[4,5].

Current prognostic assessment in OSCC relies primarily

on TNM staging and histological grading, which reflect anatomical extent and morphological differentiation[6,7]. Tumor microenvironment (TME) plays a critical role in tumor progression, with tumor-infiltrating immune cells acting as key determinants of disease behavior[8,9]. Among these, natural killer (NK) cells are essential components of innate immunity capable of recognizing and eliminating transformed cells without prior sensitization[10,11]. NK cells can target tumor cells with downregulated MHC class I expression, a common immune evasion strategy, and exert cytotoxic effects through perforin–granzyme pathways, death receptor interactions, and antibody-dependent cellular cytotoxicity[11-14].

The density and functional status of tumor-infiltrating NK cells may serve as important indicators of tumor–immune interactions and disease prognosis[15,16].

CD57 is a marker of terminally differentiated NK cells and cytotoxic T lymphocytes[17,18]. Although CD57 expression is associated with reduced proliferative capacity, CD57+ NK cells exhibit enhanced cytotoxic activity with increased perforin and granzyme expression, representing a highly effective effector population[17,19].

In OSCC, preliminary studies have reported that higher CD57+ tumor-infiltrating cell density correlates with improved survival outcomes[20-22]. Inconsistent findings regarding the association of CD57 expression with tumor progression necessitate further investigation[23,24].

The present study was undertaken to evaluate CD57 expression in OSCC using immunohistochemistry and to correlate its expression with histological grade.

Material and Methods

The present study had been performed in the tertiary teaching hospital in western Uttar Pradesh, after getting the proper ethical approval from the Institutional Ethical Committee. This was a hospital record-based descriptive study for 18 months, including 75 cases of histologically diagnosed OSCC. Both retrospective and prospective samples were examined.

Inclusion Criteria

Squamous cell carcinoma was identified in oral lesion specimens that underwent radical total surgical resection, excisional biopsies, or incisional biopsies.

Exclusion Criteria

Tissues lacking viable or representative material.

Tissue biopsies/specimens of patients with oral squamous cell carcinoma were taken, followed by their fixation in 10% buffered formalin, embedding in paraffin, and processing by a semi-automated tissue processor and sectioned at 3 - 4µm. H&E (haematoxylin and eosin) staining steps were followed.

IHC staining was done according to the manufacturer's

guidelines including incubation with CD57 (BIO SB Tinto CD 57 Mouse Monoclonal antibody (Mmab) clones, followed by secondary antibody, Super enhancer, PolymerHRP reagent and DAB chromogen were applied to the sections one after the other for specific time periods[25].

The sections were first analyzed for the expression of CD-57 at low power (10×). Selected fields were then used for the assessment of the CD-57 positive cells. In each slide, 500 cells were counted in five different fields (high power field) using a magnification of 40× and if the cytoplasm of the cell was stained with CD-57 regardless of the intensity of the stain, then it was included in the counting[25].

Interpretation of CD57 Staining (adapted from Kumar et al., 2023)

When distinct brown staining was confined to the cytoplasm of the cell, CD-57 expression was considered positive.²⁵ Scoring System for CD57 Expression (Klein et al. Scoring System)[26]:

The area of labelled cells was graded as:

- Grade 0- When none of the areas expressed CD57
- Grade 1- When <30% of the area expressed CD57
- Grade 2- When 30% to 60% of the area expressed CD57
- Grade 3- When >60% of the area expressed CD57

The intensity of expressed cells was graded as:

- Grade 0- No reaction
- Grade 1- Weak intensity
- Grade 2- Mild intensity
- Grade 3- Strong intensity

Final Score Calculation: Final Score = A + B (Area Grade + Intensity Grade)

- 0–1 = Negative; 1–2= Mild; >2–4= Moderate; >4–6= Severe

Observer Variation Control: Evaluation was performed independently by two observers who were blinded to the clinical outcome.

Statistical Analysis

Statistical analysis was performed using SPSS; the Chi-square test, Fisher's exact test, one-way ANOVA, and Kruskal–Walli's test was applied as appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

The present study included 75 cases of oral squamous cell carcinoma (OSCC). The age of patients ranged from 30 to 80 years. Majority of the subjects belonged to 40-49 years age group (41.3%) followed by 50-59 years (22.7), 60-69 years (20.0%), 30-39 years (8.0%) and above 70 years (8.0%). The mean age of presentation was 51.44 ± 11.64 years, indicating that OSCC predominantly affects middle-aged individuals in the fourth and fifth decades of life (Figure 1).

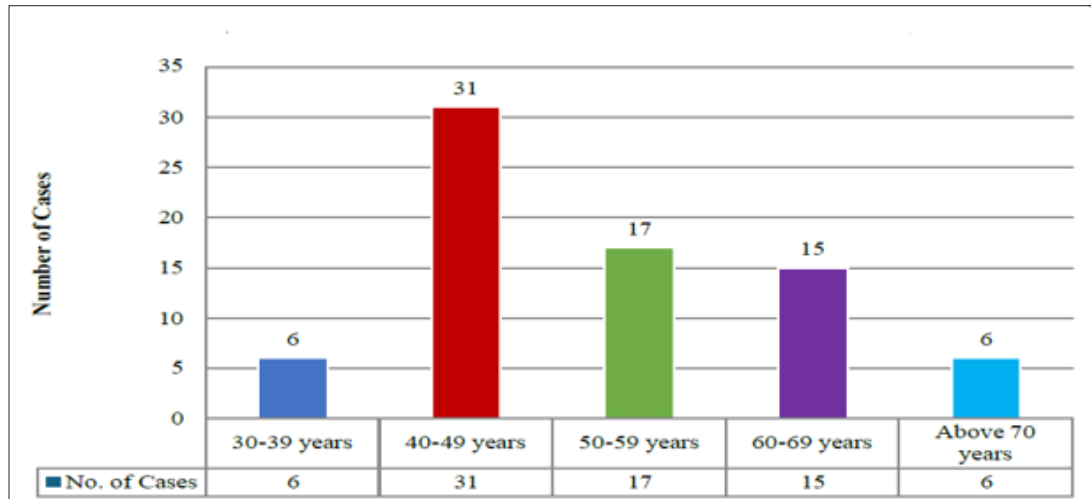


Figure 1. Age-wise distribution of OSCC Cases)

Out of 75 cases of OSCC, 64 cases (85.3%) were male and 11 cases (14.7%) were female, with a male to female ratio of 5.8:1. This marked male predominance is consistent with the higher prevalence of tobacco and betel quid chewing habits among males in this region, which are well-established risk factors for oral cancer.

The most common site of involvement was buccal mucosa (42.6%) followed by tongue (33.3%), gingiva (8.0%), palate (4.0%), lip (4.0%), floor of mouth (2.7%), retromolar trigone (2.7%) and angle of mouth (2.7%) (Table 1).

Table 1: Site-Wise Distribution, type of growth and histological grading of OSCC Cases (n=75)

Parameters	No. of Cases	Percentage
Anatomical Site		
Buccal Mucosa	32	42.6%
Tongue	25	33.3%
Gingiva	6	8.0%
Hard Palate	3	4.0%
Lip	3	4.0%
Floor of Mouth	2	2.7%
Retromolar Trigone	2	2.7%
Angle of Mouth	2	2.7%
Type of Growth		
Ultero-proliferative	29	38.7%
Ultero-infiltrative	22	29.3%
Ulcerative	24	32.0%
Histological Grade		
Well Differentiated (WD)	26	34.7%
Moderately Differentiated (MD)	40	53.3%
Poorly Differentiated (PD)	9	12.0%
Total Cases	75	100.0%

Out of 75 cases, 52 (69.3%) were tobacco users and 23 (30.7%) were non-tobacco users. Among the 52 tobacco users, 11 (21.2%) were only smokers, 19 (36.5%) were only tobacco chewers, and 22 (42.3%) had the habit of both smoking and tobacco chewing. This data highlights the significant role of tobacco in all forms as a major etiological factor in the development of OSCC in this population.

Based on gross appearance, the majority of cases (38.7%) showed ultero-proliferative type of growth, followed by ulcerative type in 24 cases (32.0%), and ultero-infiltrative pattern in 22 cases (29.3%). (Table 1)

Histological grading was performed using Broder's grading system. Maximum number of cases i.e., 40 cases (53.3%) were moderately differentiated (Grade II), followed by 26 cases (34.7%) of well differentiated (Grade I), and 9 cases (12.0%) of poorly differentiated (Grade III). The predominance of moderately differentiated tumors is consistent with the typical distribution pattern observed in OSCC cases (Table 1).

CD57 Immunohistochemical Analysis

In our study we found that CD57 expression decreases with increasing grade of malignancy, suggesting an inverse relationship between CD57 expression and tumor aggressiveness. The association between CD57 expression and histological grade was found to be statistically significant ($p = 0.0083$).

Well differentiated tumors showed higher CD57 expression with 34.62% cases showing severe expression, while poorly differentiated tumors predominantly showed negative (33.33%) and mild (55.56%) expression. Low positive (Mild) expression was predominant in poorly differentiated tumors (55.56%). This pattern further supports the inverse correlation between CD57 expression and tumor differentiation.

Table 2: Association of CD57 Expression with Histological Grade (n=75)

Histological Grade	Negative (0)	Mild (1-2)	Moderate (3-4)	Severe (5-6)	Total
Well Differentiated (n=26)	2 (7.69%)	4 (15.38%)	11 (42.31%)	9 (34.62%)	26
Moderately Differentiated (n=40)	5 (12.50%)	11 (27.50%)	20 (50.00%)	4 (10.00%)	40
Poorly Differentiated (n=9)	3 (33.33%)	5 (55.56%)	1 (11.11%)	0 (0.00%)	9
Total	10 (13.33%)	20 (26.67%)	32 (42.67%)	13 (17.33%)	75
<i>Chi-square test: $\chi^2 = 17.30$, $df = 6$, $p\text{-value} = 0.0083$ (Statistically Significant)</i>					

Table 3: CD57 Positive vs Negative Expression by Histological Grade (n=75)

Histological Grade	CD57 Positive n (%)	CD57 Negative n (%)	Total
Well Differentiated (n=26)	24 (92.31%)	2 (7.69%)	26
Moderately Differentiated (n=40)	35 (87.50%)	5 (12.50%)	40
Poorly Differentiated (n=9)	6 (66.67%)	3 (33.33%)	9
Total	65 (86.67%)	10 (13.33%)	75
<i>Chi-square test: $\chi^2 = 3.86$, $df = 2$, $p\text{-value} = 0.1455$ (Not Statistically Significant)</i>			

Overall, CD57 positivity was observed in 65 cases (86.67%) while 10 cases (13.33%) were negative. The positivity rate was highest in well differentiated tumors (92.31%) followed by moderately differentiated (87.50%) and poorly differentiated (66.67%). Although there was a trend showing decreasing CD57 positivity with increasing tumor grade, this association did not reach statistical significance ($p = 0.1455$), possibly due to the high overall positivity rate across all grades.

Table 4: Mean CD57 Positivity by Histological Grade

Histological Grade	N	Mean Positivity	Standard Deviation
Well Differentiated	24	7.83	2.74
Moderately Differentiated	35	6.59	0.72
Poorly Differentiated	6	1.98	1.38
Total CD 57 Positive cases	65	6.62	2.38
<i>One-way ANOVA: $F = 25.48$, $p\text{-value} < 0.001$ (Highly Significant)</i>			

The mean CD57 positivity showed a highly significant difference among the three histological grades ($p < 0.001$). Well differentiated tumors had the highest mean positivity (7.83 ± 2.74), followed by moderately differentiated tumors (6.59 ± 0.72), and poorly differentiated tumors had the lowest mean positivity (1.98 ± 1.38). This quantitative analysis confirms that CD57 expression is significantly higher in well differentiated tumors compared to poorly differentiated ones, suggesting that CD57 may serve as a marker of tumor differentiation and potentially as a prognostic indicator in OSCC.

When CD57 expression was analyzed in relation to sex, no statistically significant association was found ($p = 0.1610$). Although females showed a tendency towards lower CD57 expression compared to males, this difference did not reach statistical significance, suggesting that sex may not be an independent factor influencing CD57 expression in OSCC.

The association between CD57 expression and age group (≤ 50 years vs > 50 years) was not statistically significant ($p = 0.8027$).

Pairwise Comparisons of Cd57 Expression

Table 5: Comparison of CD57 Expression in Well Differentiated and Moderately and Poorly Differentiated OSCC

SCC Differentiation	Negative	Mild	Moderate	Severe	Total	
Comparison of CD57 Expression in Well Differentiated and Moderately Differentiated OSCC						
Well Differentiated	2 (7.7%)	4 (15.4%)	11 (42.3%)	9 (34.6%)	26	Chi-square test: $p\text{-value} = 0.0934$ (Not Statistically Significant)
Moderately Differentiated	5 (12.5%)	11 (27.5%)	20 (50.0%)	4 (10.0%)	40	
Total	7 (10.6%)	15 (22.7%)	31 (47.0%)	13 (19.7%)	66	

Comparison of CD57 Expression in Moderately Differentiated and Poorly Differentiated OSCC						
Moderately Differentiated	5 (12.5%)	11 (27.5%)	20 (50.0%)	4 (10.0%)	40	Chi-square test: p-value = 0.0653 (Not Statistically Significant)
Poorly Differentiated	3 (33.3%)	5 (55.6%)	1 (11.1%)	0 (0.0%)	9	
Total	8 (16.3%)	16 (32.7%)	21 (42.9%)	4 (8.2%)	49	
Comparison of CD57 Expression in Well Differentiated and Poorly Differentiated OSCC						
Well Differentiated	2 (7.7%)	4 (15.4%)	11 (42.3%)	9 (34.6%)	26	Chi-square test: p-value = 0.0065 (Statistically Significant)
Poorly Differentiated	3 (33.3%)	5 (55.6%)	1 (11.1%)	0 (0.0%)	9	
Total	5 (14.3%)	9 (25.7%)	12 (34.3%)	9 (25.7%)	35	

- When comparing CD57 expression between well differentiated and moderately differentiated squamous cell carcinoma, the Chi-square analysis showed no statistically significant difference ($p = 0.0934$). Although well differentiated tumors showed a higher percentage of severe expression (34.6% vs 10.0%) and lower percentage of mild expression (15.4% vs 27.5%) compared to moderately differentiated tumors, this difference did not reach statistical significance. Both grades showed predominant moderate to severe CD57 expression.
- On comparing the immune expression of CD57 between moderately differentiated and poorly differentiated squamous cell carcinoma, the Chi-square analysis showed a Chi-square value of 7.22 with an insignificant p-value of 0.0653. Poorly differentiated tumors showed markedly lower CD57 expression with 33.3% negative and 55.6% mild expression, compared to moderately differentiated tumors which predominantly showed moderate (50.0%) expression. However, this difference approached but did not reach statistical significance.
- On comparing the positive and negative staining of well and poorly differentiated squamous cell carcinoma, the Chi-square analysis showed a Chi-square value of 12.29 with a highly significant p-value of 0.0065. Well differentiated tumors showed predominantly moderate (42.3%) and severe (34.6%) CD57 expression, while poorly differentiated tumors showed predominantly negative (33.3%) and mild (55.6%) expression with no severe expression. This highly significant difference confirms the inverse relationship between CD57 expression and tumor dedifferentiation.

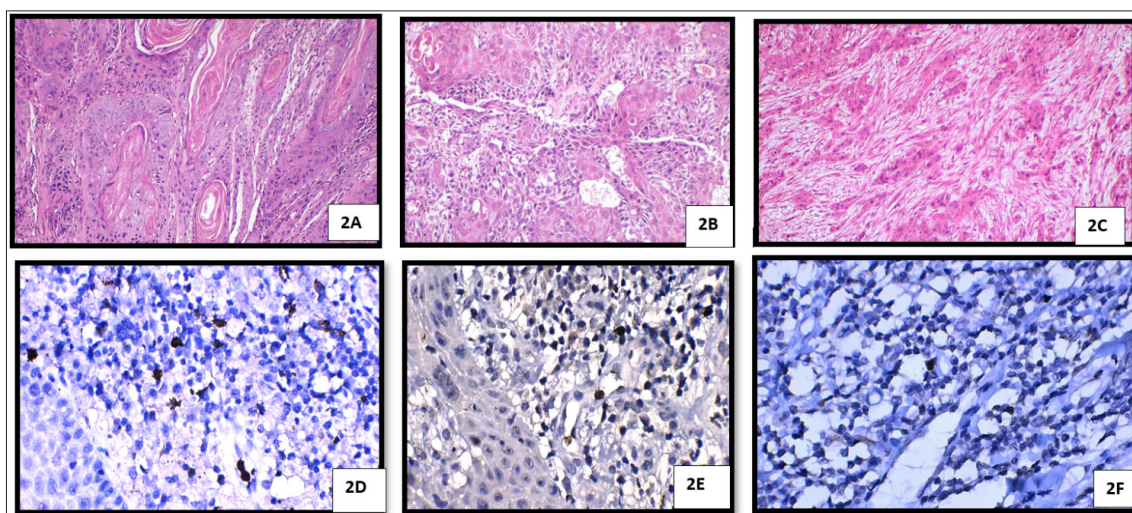


Figure 2.2A Photomicrograph of Well Differentiated Oral Squamous Cell Carcinoma, **2B** Moderately Differentiated Oral Squamous Cell Carcinoma, **2C** Photomicrograph of Poorly Differentiated Oral Squamous Cell Carcinoma (H&E 100x) **2D**-Shows positive CD57 Staining in well differentiated OSCC Cases (severe), **2E** Shows Positive CD57 Staining in Moderately differentiated OSCC Case (Moderate), **2F** Shows positive CD57 Staining in Poorly differentiated OSCC Cases (Negative) (40x)

Discussion

Oral squamous cell carcinoma (OSCC), particularly in India, contributes significantly to global cancer burden and is frequently diagnosed at advanced stages.

In the present study, the age of patients ranged from 30 to 80 years with a mean age of 51.44 ± 11.64 years. The majority of subjects belonged to the 40-49 years age group

(41.3). This indicates that OSCC predominantly affects middle-aged individuals in the fourth and fifth decades of life. These findings are consistent with the epidemiological data reported in Indian studies. Agarwal et al[21], in their study of 100 OSCC cases reported a similar age distribution with peak incidence in the 40-60 years age group. Similarly, Cs et al[27], reported comparable age demographics in their study of 30 OSCC cases examining CD57 expression.

The tumor microenvironment (TME), especially immune cell infiltration, plays a pivotal role in tumor progression and prognosis. Among immune cells, CD57-positive natural killer (NK) cells represent terminally differentiated cytotoxic lymphocytes crucial for anti-tumor immunity. In our study, well-differentiated OSCC showed the highest CD57 expression (mean positivity 7.83 ± 2.74), with 76.92% cases demonstrating high positive expression, whereas poorly differentiated tumors exhibited the lowest expression (mean positivity 1.98 ± 1.38), with predominance of negative (33.33%) and low expression (55.56%). Moderately differentiated tumors showed intermediate expression (mean 6.59 ± 0.72). The difference in mean CD57 expression across grades was highly significant ($p < 0.001$). These findings clearly indicate that CD57 expression decreases progressively with increasing tumor grade, reflecting reduced NK cell-mediated immune response in aggressive tumors.

These results are in strong agreement with Cs et al. (2023) [27], who reported a significant decline in CD57-positive NK cell counts from well-differentiated to poorly differentiated OSCC ($p < 0.001$). Similarly, Agarwal et al. (2016) [21], demonstrated that CD57 labeling index was highest in well-differentiated tumors and decreased significantly with increasing grade. Rathpriya et al. (2023) [26], also reported a progressive reduction in CD57 expression with tumor dedifferentiation, along with a strong negative correlation between CD57 and proliferative marker PCNA ($r = -0.82$, $p < 0.001$), indicating that increased tumor aggressiveness is associated with reduced immune infiltration. These findings closely parallel the observations of the present study.

Fang et al. (2017) [22], further supported these findings by demonstrating that higher CD57+ stromal cell density was associated with early-stage disease ($p = 0.016$) and better prognosis. Kumar et al. (2023) [25], reported that CD57 expression was significantly higher in well-differentiated tumors and in patients with better survival outcomes, further validating its prognostic significance. The consistency of these findings across multiple studies strengthens the evidence that CD57 expression is closely linked to tumor differentiation and clinical behaviour.

The inverse relationship between CD57 expression and tumor grade observed in our study can be explained by cancer immunoediting. In well-differentiated tumors, preserved antigenicity allows effective recognition by NK cells, resulting in higher CD57+ infiltration. However, as tumors dedifferentiate, they acquire immune evasion mechanisms such as downregulation of activating ligands, secretion of immunosuppressive cytokines, and metabolic alterations that inhibit NK cell function. Taghavi et al. (2016) [20], demonstrated an inverse correlation between TGF- β expression and CD57+ infiltration ($p = 0.01$), suggesting that immunosuppressive cytokines play a key role in suppressing NK cell activity in aggressive tumors.

An important observation in our study is that although overall CD57 positivity was high (86.67%), the intensity of expression, rather than simple positivity, showed significant correlation with tumor grade. This highlighted the importance of quantitative assessment of CD57 expression. Marques et al. (2024) [28], similarly reported that CD57+ cells was present in most OSCC cases, but their density determines prognostic significance. Fang et al. (2017) [22], also emphasized that quantitative evaluation provides superior predictive accuracy compared to categorical assessment.

The prognostic implications of our findings are supported by existing literature. Troiano et al. (2019) [23], in a meta-analysis, demonstrated that high CD57+ infiltration is significantly associated with improved overall survival (HR 0.35, $p < 0.0001$). Taghavi et al. (2016) [20] reported that patients with high CD57 expression had significantly better survival outcomes compared to those with low expression. These studies support our findings that higher CD57 expression is associated with well-differentiated tumors and likely reflects better prognosis.

Clinically, the findings of our study suggested that CD57 immunohistochemical evaluation can serve as a valuable adjunct to conventional histopathological grading. High CD57 expression indicates effective anti-tumor immune response and favorable prognosis. Patients with low CD57 expression may benefit from aggressive therapy and closer follow-up, while those with higher expression may have better outcomes.

Despite these findings, certain limitations should be considered. The relatively small sample size, particularly for poorly differentiated tumors, may limit statistical power. Additionally, long-term follow-up was not available to directly correlate CD57 expression with survival. However, the strong concordance of our results with multiple previous studies supports the validity of our observations.

Conclusion

This study demonstrated a significant inverse correlation between CD57 expression and histological grade in oral squamous cell carcinoma. Well-differentiated tumors showed higher CD57 positivity, whereas poorly differentiated tumors exhibited markedly reduced expression, with a significant difference between the two groups. These findings support the role of CD57+ NK cells as a potential biomarker for tumor differentiation and prognosis. Larger studies with long-term follow-up are required to validate its clinical utility.

Statements and declarations Conflicts of interest

The authors declare that they do not have conflict of interest.

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