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# Therapeutic Insights: HER1–Driven Immune Modulation in Pathological Progression and Disease Management of Oral Cavity Carcinomas

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## ABSTRACT

**Background:** Oral cavity carcinoma (OCC) is a virulent malignancy associated with a poor prognosis, typically presenting under immune evasion and further progression. The Human Epidermal Growth Factor Receptor 1 (HER1/EGFR) is involved in the progression of tumours and immune suppression in solid tumours. The objective of this study was to assess the HER1 expression and its correlations with tumour-infiltrating lymphocytes ($CD8^+$, $FOXP3^+$) and immunosuppressive cytokines (IL-6, TGF-beta) in OCC.

**Methods:** This case-control study was conducted between January and June of 2025 at an oncology department. 150 OCC tissue samples were histologically confirmed, and 50 non-malignant controls were analysed. Immunohistochemistry (IHC) was performed to identify HER1, CD8+, and FOXP3+ markers, whereas IL-6 and TGF-beta were measured by RT-qPCR. Tumours were stratified by HER1 positivity, and statistical tests were conducted using SPSS 26.0. t-Test and chi-square tests were utilized, and the significance level was set at $p < 0.05$.

**Results:** Its overexpression was observed in 123 (82%) of OCC tumours ($p < 0.001$) and strongly correlated with low $CD8^+$, high $FOXP3^+$, regulatory T cells, and high IL-6 and TGF-β concentrations ($p < 0.001$). In HER1-positive samples, the strongest immune suppression was observed in the case of advanced-stage tumours.

**Conclusion:** In addition to being a growth-stimulatory oncogene, HER1 plays a central role in immune dysregulation in OCC. The results support HER1-directed treatments as a strategic resource to reverse immune escape and manage OCC patients.

**Keywords:** Carcinoma, Squamous Cell, Mouth Neoplasms, ErbB Receptors, Tumor Microenvironment, CD8-Positive T-Lymphocytes

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## INTRODUCTION

Oral cavity carcinomas (OCCs) represent a highly aggressive group of head and neck malignancies, with more than 300,000 new cases and nearly 177,000 deaths worldwide each year [1]. Although surgical resection, chemoradiation, and diagnostic imaging have improved, the five-year survival rate of OCCs remains below 60%, especially in low-resource areas where late presentation is prevalent [2]. One of the most well-characterized molecular aberrancies constituting OCC tumor progression is the overexpression of human epidermal growth factor receptor 1 (HER1/EGFR), which occurs in up to 80% of OCC tumors [3].

The hyperactivation of HER1 stimulates the growth of tumors, invasion, and resistance to therapy [4]. HER1 also interferes with immune pathways by inhibiting antitumor T-cell responses and increasing infiltration of regulatory T-cells (Tregs) [5]. Recent data demonstrate that HER1-positive OCCs have attenuated $CD8^+$ T cell infiltration and increased $FOXP3^+$ Tregs, supporting an immunosuppressive phenotype [6]. At the same time, HER1-mediated tumors exhibit elevated levels of IL-6, TGF beta, and cytokine production that have been demonstrated to compromise the activity of cytotoxic T-cells and promote immune tolerance [7].

Transcriptomic profiling has linked HER1-mediated activation of STAT3 and macrophage polarization as important contributors to immune evasion [8]. The preclinical evidence indicates that EGFR inhibition boosts infiltration of tumors with $CD8^+$ T-cells, reduces $FOXP3^+$ Tregs, and improves the tumor response [9]. Nevertheless, OCCs have a limited response to immune checkpoint inhibitors, which may be explained by continued suppression by HER1 [10]. A better understanding of the immunological role of HER1 may optimize therapeutic outcomes.

The objective of this study was to determine the HER1 expression levels and associations with $CD8^+$ and $FOXP3^+$ TIL infiltrates in OCC tissues. This study also assessed the IL-6 and TGF-6 levels in correlation with HER1 status. Moreover, this study aimed to infer the relationship between HER1, clinical stage, and tumor differentiation to inform targeted immunotherapy.

## METHODS

This case-control study was conducted over 6 months (September–December 2024) to determine the expression of HER1 and its relationship with the infiltration of immune cells, including $CD8^+$, $FOXP3^+$, and cytokines (IL-6, TGF beta) in OCC, in PU affiliated tertiary care settings mainly Federal PGMI Lahore, at the Department of Pathology and Oncology (Ref: 1449-06SZH). Consecutive non-probability sampling was employed to identify the eligible patients in the archived histopathology database. Block Formalin-fixed, paraffin-embedded (FFPE) tissue samples were obtained from a series of 150 histologically verified OCC patients who underwent surgical excision. Samples were obtained after informed consent. The sample size included 150 OCC patients and 50 age-matched individuals without OCC. It was determined by OpenEPI version 3.0.0 (released 2013,

Atlanta, GA, USA) based on an assumed HER1 positivity rate of 70%, with a 95% confidence level, and an 80% margin of error [11].

The inclusion criteria for the samples were primary, untreated OCC, aged 18 to 75 years, and adequate formalin-fixed, paraffin-embedded (FFPE) tissue. Exclusion criteria included prior radiotherapy or chemotherapy, recurrent tumors, immunosuppression, or coexisting malignancies. The study sample was divided into two groups: HER1-positive (123 patients) and HER1-negative (27 patients) based on the immunohistochemical score. The natural levels of the expression were measured; no intervention was implemented. The expressions of HER1, $CD8^+$, and $FOXP3^+$ were determined by immunohistochemistry (IHC), and IL-6 and TGF β were measured using real-time quantitative polymerase chain reaction (q-PCR). The intensity and percentage positivity of HER1 were semi-quantitatively graded.

SPSS version 26.0 (released 2019, IBM Corp., Armonk, NY) was used for data analysis. Categorical variables were analyzed with chi-square tests, and continuous variables were examined by t-tests. A statistically significant p-value was $<0.05$.

## RESULTS

In this study, 150 patients with OCC and 50 controls participated to determine the expression levels of HER1 in immune modulation. 123 (82%) of tumors overexpressed HER1, which was linked to the reduced $CD8^+$ T-cell infiltrates, increased $FOXP3^+$ Tregs, and elevated IL-6 and TGF-beta. The HER1-positive cases were more advanced-stage. These findings suggest that HER1 supports immune suppression and tumorigenicity.

**Table 1: Baseline Demographic and Clinical Characteristics**

| Characteristic | OCC Group (n = 150) | Control Group (n = 50) | Statistical Test | Test Value | P-Value |
|---|---|---|---|---|---|
| Age (mean ± SD, years) | 58.3 ± 11.2 | 56.9 ± 10.7 | Independent t-test | t = 0.81 | 0.42 |
| Gender (Male%) | 95 (63.3%) | 32 (64%) | Chi-square test | $\chi^2$ = 0.02 | 0.88 |
| Smoking History (%) | 84 (56.0%) | 18 (36.0%) | Chi-square test | $\chi^2$ = 6.40 | 0.01 |
| Alcohol Consumption (%) | 39 (26.0%) | 10 (20.0%) | Chi-square test | $\chi^2$ = 0.74 | 0.39 |
| HPV-Positive Cases (%) | 27 (18.0%) | 4 (8.0%) | Chi-square test | $\chi^2$ = 3.21 | 0.07 |
| Tumor Stage (III–IV, %) | 92 (61.3%) | N/A | Descriptive | N/A | N/A |
| Histologic Grade (Mod–Poor) | 88 (58.7%) | N/A | Descriptive | N/A | N/A |

*n = Number of Participants, HPV = Human Papilloma Virus, SD = Standard Deviation, % = Percentage, * = Significance at p-value <0.05*

**Table 1** illustrates the baseline demographic and clinical characteristics of the study participants. OCC and control groups were age- and sex-matched ($p > 0.05$). Smoking was significantly higher in the OCC patients (84 (56.0 %) vs. 18 (36.0%), $p = 0.01$). In OCCs, 92 (61.3%) were stage III–IV; 88 (58.7%) were moderate to poorly differentiated, implying that groups are comparable.

**Table 2: HER1 Expression and Immune Marker Profile in OCC**

| Parameter | OCC Group (n = 150) | Control Group (n = 50) | Statistical Test | Test Value | P-value |
|---|---|---|---|---|---|
| **HER1 Overexpression (positive cases)** | **123 (82.0%)** | **6 (12.0%)** | **Chi-square test** | **$\chi^2$ = 94.5** | **<0.001** |
| **$CD8^+$ T-cell infiltration (low density)** | **97 (64.7%)** | **9 (18.0%)** | **Chi-square test** | **$\chi^2$ = 39.8** | **<0.001** |
| **$FOXP3^+$ Tregs (high density)** | **88 (58.7%)** | **6 (12.0%)** | **Chi-square test** | **$\chi^2$ = 37.9** | **<0.001** |
| **IL-6 (mean ± SD, pg/mL)** | **42.5 ± 9.8** | **18.4 ± 6.3** | **Independent t-test** | **t = 17.6** | **<0.001** |
| **TGF-β (mean ± SD, pg/mL)** | **37.1 ± 10.6** | **15.2 ± 5.9** | **Independent t-test** | **t = 15.9** | **<0.001** |

*n = Number of Participants, HER1 = Human Epidermal Growth Factor Receptor 1, IL = Interleukin, FOXP3 = Forehead box protein P3, TGF = Transforming Growth Factor Beta, SD = Standard Deviation, % = Percentage, * = Significance at p-value <0.05*

**Table 2** indicates the HER1 expression and immune marker profile in OCC patients and controls. Overexpression of HER1 was present in 123 (82%) of OCC vs. 6 (12%) controls ($p < 0.001$). OCC cases showed less infiltration by $CD8^+$ T lymphocytes (97 (64.7%)), increased $FOXP3^+$ Tregs (88 (58.7%)), and high IL-6 and TGF-β ($p < 0.001$), suggesting that HER1 is associated with immunosuppression in OCC.

**Table 3: Association of HER1 Overexpression with Immune and Clinical Parameters in OCC Patients**

| Parameter | HER1-Positive Group (n = 123) | HER1-Negative Group (n = 27) | Statistical Test | Test Value | p-value |
|---|---|---|---|---|---|
| $CD8^+$ T-cell infiltration low (n/%) | 88 (71.5%) | 9 (33.3%) | Chi-square | $\chi^2$ = 17.98 | <0.001 |
| $FOXP3^+$ Tregs high (n/%) | 80 (65.0%) | 8 (29.6%) | Chi-square | $\chi^2$ = 13.61 | <0.001 |
| IL-6 (Mean ± SD, pg/mL) | 45.1 ± 8.7 | 29.4 ± 6.5 | Independent t-test | t = 8.61 | <0.001 |
| TGF-β (Mean ± SD, pg/mL) | 38.7 ± 9.5 | 25.3 ± 6.1 | Independent t-test | t = 7.34 | <0.001 |
| Advanced tumor stage (III–IV) (n/%) | 82 (66.7%) | 10 (37.0%) | Chi-square | $\chi^2$ = 8.74 | 0.003 |

*n = Number of Participants, HER1 = Human Epidermal Growth Factor Receptor 1, IL = Interleukin, FOXP3 = Forehead box protein P3, TGF = Transforming Growth Factor Beta, SD = Standard Deviation, % = Percentage, * = Significance at p-value <0.05*

Association of HER1 overexpression with immune and clinical parameters is presented in **Table 3**. $CD8^+$ (88 (71.5%)) and $FOXP3^+$ (80 (65.0%)) had reduced infiltration in HER1-positive tumors, which were linked to elevated IL-6 and TGF-beta ($P < 0.001$). Disease was more prevalent at advanced stages (82 (66.7%) vs. 10 (37.0%), $p = 0.003$). These findings suggest that HER1 is a marker of immune-evasive OCC and can be used to guide therapy.

## DISCUSSION

This study aimed to explore the immunomodulatory properties of HER1 (EGFR) expression in OCC with a focus on tumor-infiltrating lymphocytes and immunosuppressive cytokines, and its significance in disease development and treatment. The findings that HER1 over-expression is not only a biomarker of tumor growth but also a key contributor to immune evasion in OCC.

Overexpression of HER1 was associated with an immunosuppressive tumor microenvironment (TME), characterized by low levels of $CD8^+$ and high $FOXP3^+$ infiltration, in line with recent findings in head and neck squamous cell carcinoma (HNSCC), in which EGFR activation inhibits antitumor immunity [12,13]. The current study findings of a significant correlation between HER1 and

elevated IL-6 and TGF-β align well with previous reports of HER1-induced regulation of cytokines that promote immune tolerance and metastatic phenotype [14]. These findings align with those that consider EGFR overexpression as a poor-prognosis biomarker, specifically in terms of its effects on immune evasion and cytokine networks [15]. Although previous research mainly focused on the role of EGFR in proliferation and therapeutic resistance, recent discoveries indicated that EGFR is highly important in regulating immune checkpoints and T-cell exclusion [16]. Moreover, HER1 enhances STAT3 and inhibits STAT1 signals, contributing to the macrophage polarity and effect of T-cell activation, which this study demonstrated as increased TGF-β and IL-6 [17].

Unlike in earlier studies, which were inconsistent in their association between EGFR status and immune cell infiltrates, we found a definite and statistically significant trend of immune depression in HER1-positive OCCs [19]. This difference may be attributed to variation in study design, tumor heterogeneity, and analysis. Remarkably, the spatial exclusion of $CD8^+$ T cells in EGFR-high zones was validated in a separate survival study targeting oral squamous cell carcinoma (OSCC), utilizing spatial transcriptomics [20]. The evidence that inhibition of EGFR may reverse immune exclusion by promoting infiltration of $CD8^+$ cells and decreasing the size of Treg in preclinical models is consistent with these findings [21]. Furthermore, EGFR stimulation of IL-6 expression has been found to make tumors resistant to PD-1 inhibition by strengthening immune resistance mechanisms [22]. Therefore, ineffective clinical responses of immune checkpoint inhibitors (ICIs) in OCC may be due to the prevalence of unresolved HER1 signaling [23].

These findings demonstrate the potential of HER1-based treatment as a method of managing tumor development [24]. Anti-HER1, including Cetuximab and new EGFR-TKIs, may work synergistically by reducing immunosuppressive cytokines [25]. Furthermore, combined HER1/IL-6 or TGF-beta has interesting preclinical activity in overcoming immune exclusion and improving sensitivity to ICIs [26,27].

This study had limitations due to its single-center, cross-sectional design, restricting causal inference and generalization. The unavailability of functional immune assays and stratification of confounders, including HPV status, smoking, and genetic changes, might have affected outcomes. Further studies should focus on longitudinal, multicentric studies with immunogenomic profiling and interventional clinical research of HER1 to validate and extend these results.

## CONCLUSION

This study correlated HER1 expression and immunological and clinical characteristics in OCC and established that overexpression of HER1 (EGFR) in OCC was significantly linked to an immunosuppressive tumor

microenvironment. Increased HER1 expression was associated with reduced $CD8^+$ T-cell infiltrates, enrichment of $FOXP3^+$ regulatory T cells, and increased levels of IL-6 and TGF-beta. These results have proven the significance of HER1 in immune evasion and tumor development. These discoveries underscore the advancement of HER1-directed agents to boost immune response and improve patient satisfaction.

## LIST OF ABBREVIATIONS

None

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None

## CONFLICT OF INTEREST

None

## ETHICAL APPROVAL

This case-control study was conducted over 6 months (September–December 2024) in PU affiliated tertiary care settings mainly Federal PGMI Lahore, at the Department of Pathology and Oncology (Ref: 1449-06SZH).

## AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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