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Original Article

The Clinicopathological Significance and Bioinformatic Characterization of TFRC1 in Oral Squamous Cell Carcinoma

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) shows marked biological variability between patients. Transferrin receptor 1 (TFRC1) regulates cellular iron acquisition and may support tumour growth; however, its significance in OSCC has not been clearly defined. This study examined TFRC1 protein expression in OSCC tissue in relation to clinicopathological features and used TCGA-HNSC data to assess its transcript levels and, on an exploratory basis, its association with survival.

Methods: This retrospective cross-sectional and bioinformatic study of OSCC biopsies, with TCGA-HNSC validation, was conducted at Ziauddin University, Karachi (June 2025–June 2026). Immunohistochemistry (IHC) for TFRC1 was performed on 146 OSCC biopsies, and staining status was compared across clinicopathological parameters. TCGA-HNSC transcript expression and prognostic significance were evaluated using UALCAN and Kaplan–Meier analysis, respectively.

Results: TFRC1 expression was positive in 110/146 (75.3%) OSCC cases and significantly associated with histological differentiation (Chi-square test, $p = 0.04$), but not with gender ($p = 0.07$), anatomical site ($p = 0.41$), or age ($p = 0.91$). TCGA-HNSC analysis showed significantly higher TFRC1 transcript expression in primary tumours than normal tissues ($p < 1 \times 10^{-12}$), with an increasing trend across tumour grades, although not all pairwise comparisons were significant. Kaplan–Meier analysis showed no significant association with overall survival in the overall cohort ($p = 0.47$) or grade-stratified analysis ($p = 0.15$).

Conclusion: TFRC1 was frequently expressed in OSCC and significantly associated with histological differentiation. In TCGA-HNSC, TFRC1 mRNA levels were higher in tumour than in normal tissue. Taken together, these results indicate dysregulated iron homeostasis in OSCC and support further evaluation of TFRC1 as a candidate biomarker.

Keywords: *Immunohistochemistry; Neoplasm Grading; Squamous Cell Carcinoma of Head and Neck; Tumor Biomarkers; Transferrin Receptor*

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) constitutes a substantial proportion of head and neck cancers and continues to cause considerable morbidity and mortality, notwithstanding improvements in surgical and adjuvant treatment[1]. Identification of biologically meaningful and reproducible tissue biomarkers remains an important goal for refining prognostication and understanding tumour biology in OSCC[2].

OSCC represents a significant public health concern in Pakistan, where oral cancer is among the most frequently diagnosed malignancies. The disease demonstrates considerable geographical variation, with a particularly high burden reported in Karachi. The Dow Cancer Registry recorded 4,400 lip and oral cavity cancers between 2010 and 2019, representing 19.2% of all cancers in the registry. Men accounted for 67.8% of these cases and women for 32.1%, and squamous cell carcinoma comprised 97.7% of them[3].

The high prevalence of OSCC in Pakistan is strongly associated with widespread consumption of carcinogenic substances, particularly smokeless tobacco, gutka, naswar, betel quid and areca nut[4]. These habits contribute to malignant transformation of the oral epithelium. The buccal mucosa and tongue are among the commonly affected anatomical sites[5]. Furthermore, inadequate awareness, low socioeconomic status and delayed diagnosis contribute to disease progression and poor clinical outcomes[6]. Despite its considerable burden, limited population-based epidemiological data highlight the need for further research into the molecular mechanisms, diagnostic biomarkers and prognostic indicators of OSCC in the Pakistani population[7].

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Iron is indispensable for DNA replication, mitochondrial respiration and the activity of numerous enzymes[8,9]. Dietary iron is absorbed mainly in the duodenum and upper jejunum, circulates bound to transferrin, and is stored in the liver, spleen and bone marrow as ferritin and hemosiderin. Systemic iron balance is maintained by hepcidin, a hepatic hormone that restricts both intestinal absorption and the release of iron from body stores. Tumour cells frequently reprogramme these pathways, altering the acquisition, retention, use and efflux of iron to sustain continued proliferation[10,11]. Dysregulation of iron homeostasis can also influence oxidative stress, redox balance, and cell survival, thereby contributing to malignant progression[12,13]. Increasing evidence has therefore established iron metabolism as an important component of cancer biology and has highlighted iron-regulatory proteins as potential biomarkers and therapeutic targets across different malignancies[14]. Transferrin receptor 1 (TFRC1) is the principal pathway for cellular internalisation of transferrin-bound iron and is overexpressed in a number of solid tumours[15] and has been proposed as both a proliferation-associated marker and a potential therapeutic target[2].

Structurally, TFRC1 is a type II membrane glycoprotein expressed on the cell surface as two identical subunits linked by disulfide bonds. Each subunit consists of a short N-terminal cytoplasmic tail, a single membrane-spanning segment and a large extracellular C-terminal region that binds transferrin[16]. The cytoplasmic domain contains a conserved tyrosine-based internalisation motif that facilitates clathrin-mediated endocytosis of the transferrin–TFRC1 complex[17]. Within the acidic endosome, iron dissociates from transferrin, and the receptor is returned to the plasma membrane for further rounds of binding[16].

While TFRC1 has been examined in a range of malignancies[18,19], direct clinicopathological characterisation in OSCC, combined with independent transcriptomic and prognostic validation using large public datasets, remains limited. Combining an in-house immunohistochemical cohort with an independent, much larger validation dataset allows a more complete picture: whether a locally observed protein-level association is reproducible at the transcript level in an independent population, and whether it carries prognostic weight.

The present study therefore aimed to: (1) characterise TFRC1 protein expression by immunohistochemistry in a cohort of 146 OSCC biopsies, and its association with clinicopathological parameters; (2) validate TFRC1 transcript-level expression using the independent TCGA-HNSC cohort via UALCAN, including expression across histological grade; (3) examine whether TFRC1 expression relates to overall survival using Kaplan–Meier analysis; and (4) explore the protein–protein interaction network of TFRC1 using STRING.

METHODOLOGY

Study Design and Setting

This retrospective cross-sectional study used 146 archived formalin-fixed, paraffin-embedded (FFPE) OSCC biopsies retrieved from the Histopathology Laboratory, Ziauddin University, Karachi, from June 2025 to June 2026.

Sample Size and Sampling Technique

The required sample (n = 146) was estimated in OpenEpi from a reported prevalence of 10.58%, 95% confidence and the chosen margin of error[3]. Cases were selected by non-probability convenience sampling.

Selection Criteria

Inclusion Criteria:

Histologically confirmed primary OSCC with adequate FFPE tissue and sufficient tumour tissue for IHC.

Exclusion Criteria:

Inadequate or poor-quality tissue, recurrent tumours, previously treated cases, and specimens without sufficient viable tumour.

Immunohistochemistry

Immunohistochemical staining for TFRC1 was performed using a TFRC1 mouse monoclonal antibody (clone ZM52; 1:100; Zeta Corporation, USA). Antigen unmasking was achieved by microwave heat-induced epitope retrieval (HIER).

Each run included appendix tissue as the positive control and lipoma tissue as the negative control. Slides were graded with the immunoreactive score (IRS): staining intensity (0–3) multiplied by the proportion of stained tumour cells (0–3), yielding a total score ranging from 0 to 9. Based on the scoring distribution in this cohort, cases with an IRS of 0 were classified as negative, whereas cases with an IRS ≥1 were classified as positive.

Staining was evaluated independently by two experienced pathologists using this predefined scoring system. No discrepancies were observed between their assessments; therefore, inter-observer reliability analysis was

not considered necessary, and the final interpretation was based on the concordant assessments of both observers.

Clinicopathological Correlation and Statistical Analysis

TFRC1 status (positive or negative) was compared with age, gender, anatomical site and histological grade. Data were analysed in IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). As age was not normally distributed, the Mann–Whitney U test was used to compare it between TFRC1-positive and TFRC1-negative cases. The relationship between TFRC1 status and histological grade was tested with Pearson's Chi-square test, while Fisher's exact test was used for anatomical site because several expected cell counts were small. A p-value of ≤0.05 was taken as the threshold for statistical significance.

External Validation Using TCGA-HNSC

To evaluate TFRC1 transcript levels in an independent public dataset, the head and neck squamous cell carcinoma cohort of The Cancer Genome Atlas (TCGA-HNSC) was queried through UALCAN, a web-based portal for cancer transcriptomic data[20,21]. The analysis included 520 primary tumour samples and 44 normal tissue samples. Data were accessed on 25 July 2026. TCGA-HNSC pools squamous carcinomas from several head and neck subsites, so these analyses were treated as an external HNSC-level evaluation rather than OSCC-specific validation. TFRC1 transcript expression was compared between normal and primary tumour tissues and was further analysed according to histological grade (Grades 1 to 4). Expression values were reported in transcripts per million (TPM). Statistical comparisons between groups were performed using the statistical testing implemented by UALCAN, with an unpaired two-sample t-test used for the relevant group comparisons.

Survival Analysis

The Kaplan–Meier module of UALCAN was used to determine whether TFRC1 transcript levels carried prognostic information. Patients above the 75th percentile of TFRC1 expression formed the high-expression group, and the remaining patients formed the low/medium-expression group. The log-rank test compared overall survival between these groups, first in the whole TCGA-HNSC cohort and then within each tumour grade. A two-sided $p < 0.05$ indicated statistical significance.

Protein–Protein Interaction Analysis

Functional partners of TFRC1 were identified in STRING (version 12.0), retaining interactions with a combined score of at least 0.400 (medium confidence).

Ethical Consideration

The Ethical Review Committee (ERC) of Ziauddin University approved the study (ERC No. 10350525AHPAT). As only archived material was used, the committee waived the need for informed consent.

RESULTS

Demographic and clinicopathological features of the 146 OSCC cases are given in Table 1. Patients had a median age of 37 years (IQR = 7; range 23–73), and the majority were male (123, 84.2%), with 23 females (15.8%). Regarding histological differentiation, 86 cases (58.9%) were moderately differentiated, 53 (36.3%) were well differentiated, and 7 (4.8%) were poorly differentiated. The buccal mucosa was the predominant tumour site (110, 75.3%), followed by the tongue (29, 19.9%). TFRC1 immunoreactivity was detected in 110 of the 146 OSCC cases (75.3%), while 36 cases (24.7%) were classified as TFRC1-negative (Table 1).

Analysis of the UALCAN TCGA-HNSC dataset demonstrated significantly higher TFRC1 transcript expression in primary tumour tissues compared with normal tissues. The analysis included 520 primary tumour samples and 44 normal tissue samples. Median TFRC1 expression was approximately 60 transcripts per million (TPM) in primary tumours compared with approximately 25 TPM in normal tissues; this difference was highly significant ($p < 1 \times 10^{-12}$) (Figure 1A).

Table 1. Characteristics of the OSCC Cohort (n = 146)

Variable	Category	n (%)
Age (years)	Median (IQR)	37 (7)
Gender	Male	123 (84.2)
	Female	23 (15.8)
Anatomical site	Buccal mucosa	110 (75.3)
	Tongue	29 (19.9)
	Palate	3 (2.1)
	Upper lip	2 (1.4)
	Maxilla	1 (0.7)
	Floor of mouth	1 (0.7)
Histological grade	Well differentiated	53 (36.3)
	Moderately differentiated	86 (58.9)
	Poorly differentiated	7 (4.8)
TFRC1 expression	Positive	110 (75.3)
	Negative	36 (24.7)

Values are presented as n (%) unless stated otherwise. IQR: interquartile range.

When stratified according to histological grade, the analysis included 62 Grade 1, 303 Grade 2, 125 Grade 3, and 7 Grade 4 tumour samples. TFRC1 expression showed an overall upward pattern across tumour grades, with median expression increasing from approximately 38 TPM in Grade 1 to approximately 62 TPM in Grade 2, approximately 61 TPM in Grade 3, and approximately 110 TPM in Grade 4 tumours (Figure 1B). Compared with normal tissue, TFRC1 expression was significantly higher in Grade 1 ($p = 3.56 \times 10^{-5}$), Grade 2 ($p < 1 \times 10^{-12}$), and Grade 3 tumours ($p = 2.85 \times 10^{-12}$), whereas the difference for Grade 4 was not statistically significant ($p = 0.093$). Among tumour grades, Grade 1 differed significantly from Grade 2 ($p = 3.15 \times 10^{-7}$) and Grade 3 ($p = 5.57 \times 10^{-4}$), while differences between Grades 2 and 3, and comparisons involving Grade 4, did not reach statistical significance.

These data indicate elevated TFRC1 transcript expression in HNSC. However, because TCGA-HNSC includes multiple anatomical subsites, the results should not be interpreted as OSCC-specific validation.

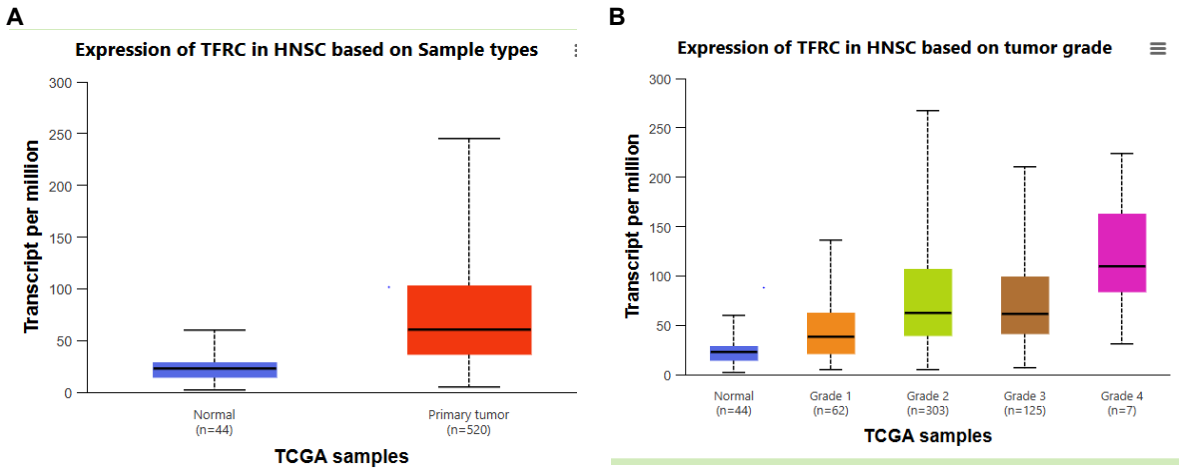


Figure 1. TFRC1 transcript expression in the TCGA-HNSC cohort (UALCAN). (A) Normal versus primary HNSC tumours. (B) Expression according to tumour grade

In HNSC, overall survival did not differ significantly by TFRC1 expression level (high expression, n = 130, vs. low/medium expression, n = 389; p = 0.47) (Figure 2A). When stratified jointly by TFRC1 expression level and tumour grade, the difference in survival across the eight resulting subgroups was also not significant (p = 0.15) (Figure 2B), although the individual grade-stratified subgroups were small (ranging from n = 3 to n = 220), limiting the power of this stratified comparison.

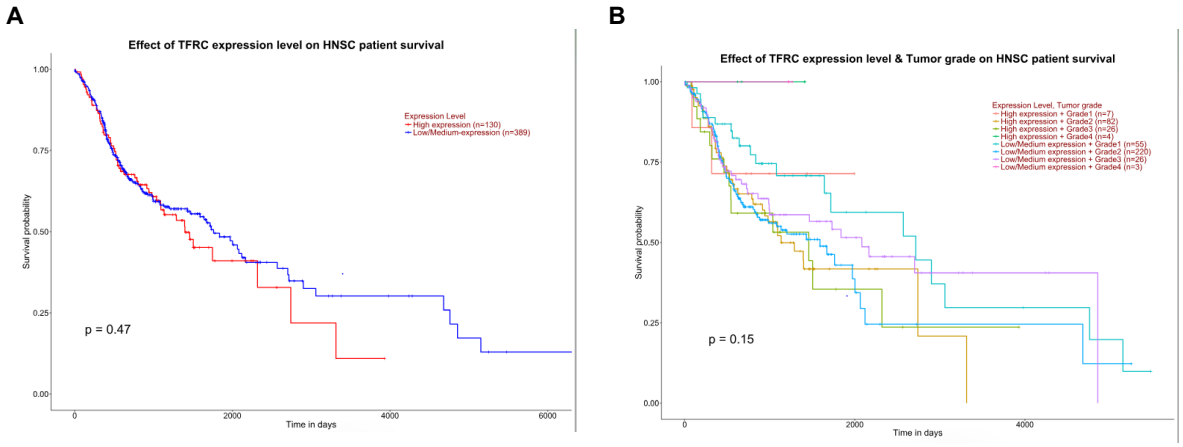


Figure 2. Overall survival of TCGA-HNSC patients on Kaplan–Meier analysis. (A) Grouped by TFRC1 expression level (p = 0.47). (B) Grouped by both TFRC1 expression level and tumour grade (p = 0.15)

The STRING protein–protein interaction network identified ten high-confidence functional partners of TFRC1, including TF (0.999), HFE (0.999), B2M (0.998), FTH1 (0.995), HJV (0.994), HSPA8 (0.969), SLC11A2/DMT1 (0.960), IREB2 (0.959), SLC40A1/Ferroportin (0.936), and RAB5A (0.934) (Table 2; Figure 3).

Table 2. Top Ten Predicted Functional Partners of TFRC1 (STRING v12.0, confidence ≥0.400)

Partner	STRING Score	Functional Role
TF (Transferrin)	0.999	Iron-carrying ligand bound and internalised by TFRC1
HFE	0.999	Competes with transferrin for TFRC1 binding; modulates iron uptake
B2M	0.998	Forms complex with HFE at the cell surface
FTH1 (Ferritin heavy chain)	0.995	Intracellular iron storage
HJV (Hemojuvelin)	0.994	BMP co-receptor regulating hepcidin and systemic iron homeostasis
HSPA8	0.969	Molecular chaperone involved in TFRC1 trafficking/folding
SLC11A2 (DMT1)	0.960	Transports iron out of the endosome into the cytoplasm after TFRC1-mediated uptake
IREB2	0.959	Post-transcriptionally regulates TFRC1 mRNA stability via iron-responsive elements
SLC40A1 (Ferroportin)	0.936	Cellular iron exporter; functionally opposes the import role of TFRC1
RAB5A	0.934	Regulates endosomal trafficking/fusion required for TFRC1-mediated endocytosis

STRING: Search Tool for the Retrieval of Interacting Genes/Proteins; scores are combined interaction confidence scores.

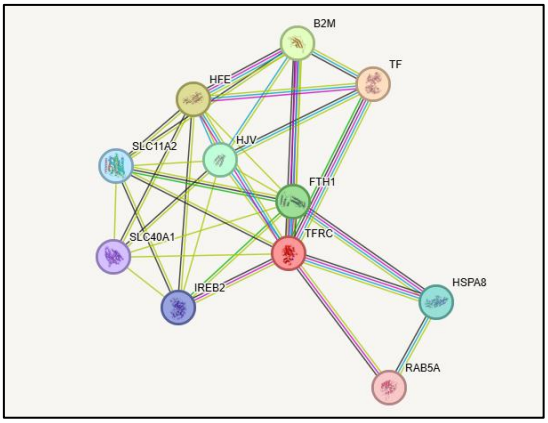


Figure 3. Predicted interaction partners of TFRC1 in STRING (protein–protein interaction network)

DISCUSSION

TFRC1 protein was detected in 110 of 146 OSCC cases (75.3%), indicating frequent expression in OSCC. TFRC1 status was significantly associated with histological differentiation (Chi-square test, p = 0.04), whereas age, sex and anatomical site showed no significant relationship with TFRC1 status. These findings suggest a relationship between TFRC1 expression and histopathological characteristics rather than demographic or anatomical variables.

Elevated TFRC1 expression has likewise been described in oral dysplasia and OSCC by earlier investigators. Nagai et al. demonstrated that TFRC1-mediated transferrin uptake contributes to tumour-cell growth and survival[22]. Similarly, Miyamoto et al. reported TFRC1 staining in oral malignant tumours and observed differences according to histological differentiation and proliferative activity[23].

Together with the significant association observed in the present study between TFRC1 status and differentiation, these findings support a relationship between altered iron acquisition and the histopathological phenotype of OSCC. However, the binary assessment used in this study of TFRC1 positivity should not be interpreted as evidence of a progressive increase in expression from well- to poorly differentiated tumours. Recent evidence further indicates that the role of TFRC1 in OSCC may depend on tumour context[24]. Si et al. demonstrated increased TFRC1 expression at the invasive tumour front and showed that the transferrin–TFRC1 axis promotes OSCC proliferation and migration[2]. Their findings also suggested that the prognostic relevance of TFRC1 may vary according to tumour localisation and invasive pattern. This supports the possibility that TFRC1 reflects specific biological features of OSCC rather than functioning as a universal prognostic marker.
The high TFRC1 positivity rate (75.3%) observed in this study may partly reflect the relatively permissive IRS cut-off (IRS ≥1), which classified even weak immunoreactivity as positive. A higher cut-off may have resulted in a lower positivity rate. Furthermore, differences between the local OSCC cohort and the TCGA-HNSC dataset may be attributed to variations in population characteristics, tumour composition, sample processing and analytical methods. The local cohort assessed TFRC1 protein expression by immunohistochemistry, whereas TCGA analysis evaluated transcript-level expression. Therefore, direct comparisons should be interpreted cautiously, as differences in protein and mRNA expression do not necessarily reflect biological inconsistencies.

The UALCAN analysis of TCGA-HNSC data showed higher TFRC1 transcript expression in tumour tissue than in normal tissue. This finding provides independent support for elevated TFRC1 expression in head and neck squamous cancer and is in keeping with the established role of TFRC1 in cellular iron acquisition and tumour biology. However, because TCGA-HNSC includes multiple head and neck anatomical subsites, these findings should be regarded as supportive transcriptomic evidence rather than direct molecular validation of the present OSCC IHC findings.

Importantly, survival analysis in this study was performed using UALCAN TCGA-HNSC data rather than the 146 OSCC specimens examined by IHC. In the HNSC dataset, TFRC1 expression showed no significant relationship with overall survival (p = 0.47). This differs from Arora et al., who reported an association between high TFRC1 expression and poorer survival in an HPV-negative OSCC population[25]. Differences in tumour subsite, HPV status, patient characteristics, expression thresholds, and transcriptomic versus protein-level assessment may contribute to this discrepancy[26-28]. Therefore, the survival analysis should be interpreted as an exploratory analysis of HNSC rather than as evidence regarding survival in the present OSCC cohort.

STRING analysis demonstrated strong functional associations of TFRC1 with TF, HFE, FTH1, HJV, SLC11A2/DMT1, IREB2, and SLC40A1, placing TFRC1 within the broader iron-uptake and iron-homeostasis network. This network is biologically coherent and centres on iron uptake, storage, export, and systemic regulation, together with the endosomal trafficking machinery through which TFRC1-mediated endocytosis is executed. TF and HFE represent the immediate ligand/competitor axis governing TFRC1-mediated iron internalisation; FTH1 and SLC40A1 represent the downstream storage and export arms that determine the fate of iron once delivered; HJV links the local function of TFRC1 to systemic iron-hormone (hepcidin) regulation; IREB2 is a direct post-transcriptional regulator of TFRC1 expression itself; and RAB5A and HSPA8 represent the trafficking and chaperone machinery required for receptor-mediated endocytosis to proceed. These associations provide biological context but do not establish OSCC-specific or causal

interactions, as STRING associations are derived from general functional and physical evidence across contexts rather than tissue- or tumour-specific data. The network instead provides mechanistic grounding for why TFRC1 upregulation is plausible in a proliferating, iron-demanding tumour cell population.

Overall, the findings demonstrate frequent TFRC1 protein expression in OSCC and a significant association with histological differentiation. The complementary UALCAN and STRING analyses provide broader transcriptomic and functional context, while the HNSC survival analysis does not establish the prognostic significance of TFRC1 in the present OSCC cohort. Further OSCC-specific studies incorporating quantitative TFRC1 assessment, tumour localisation, molecular characterisation, and clinical follow-up are warranted to clarify its prognostic and therapeutic significance.

Strengths and Limitations

The study integrates immunohistochemical assessment of TFRC1 protein expression with external TCGA-HNSC transcriptomic validation. It also incorporates clinicopathological correlations, survival analysis and STRING-based protein–protein interaction analysis, providing broader insight into the potential role of TFRC1 in OSCC.

This study has several limitations. First, the poorly differentiated subgroup in the IHC cohort was small (n = 7), and the grade-association Chi-square test includes a cell with an expected count below the conventional validity threshold; this finding should be interpreted with caution and ideally confirmed with a larger poorly differentiated subgroup or an exact test suited to this table size. Second, the TCGA-HNSC cohort used for external validation includes head and neck squamous cell carcinomas from multiple subsites (including oropharynx and larynx), not exclusively oral cavity tumours, which may introduce some biological heterogeneity relative to the OSCC-specific study cohort. Third, survival analysis was performed on the TCGA-HNSC cohort rather than on the study patients, because outcome and follow-up information was unavailable for the local cases; the null survival finding therefore reflects the validation cohort and cannot be assumed to generalise to the patients examined by IHC. Fourth, the retrospective design precludes causal inference. Finally, these findings should be considered hypothesis-generating; confirmation is required in larger, prospectively followed OSCC cohorts in which molecular and clinical outcome data are collected together.

CONCLUSION

TFRC1 protein was frequently expressed in OSCC and was significantly associated with histological differentiation in the present IHC cohort. In the TCGA-HNSC dataset, TFRC1 mRNA levels were higher in tumour tissue than in normal tissue and tended to rise with tumour grade, although not all pairwise comparisons were significant, and it was not associated with overall survival. These findings support TFRC1 as a potential marker of tumour differentiation in OSCC rather than a standalone prognostic biomarker. Larger OSCC-specific studies with clinical follow-up, together with functional work, are needed to clarify its biological and prognostic significance.

Author Contributions

AH: Conception and design, data collection, data analysis and interpretation, manuscript writing, critical revision, and final approval
FAB: Conception and design, data collection, critical revision, and final approval
SZA: Conception and design, data collection, data analysis and interpretation, manuscript writing, critical revision, and final approval
UT: Conception and design, data collection, data analysis and interpretation, manuscript writing, critical revision, and final approval

Conflict of interest: The authors declare no conflict of interest.

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Ethical approval: The study was approved by the Ethical Review Committee of Ziauddin University (ERC No. 10350525AHPAT). The requirement for informed consent was waived because of the retrospective design.

Data availability: Data were obtained from archived FFPE tissue blocks and histopathology reports at the Histopathology Laboratory, Ziauddin University. They are not publicly available.

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