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Evaluation of survival rate in patients with tongue squamous cell carcinoma: a retrospective single-center study

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Abstract

Background The tongue squamous cell carcinoma (TSCC) is a highly prevalent form of oral squamous cell carcinoma with poor prognosis and aggressive behavior. The present study aimed to evaluate the association between tumor grade, clinical stage, and survival outcomes in patients with TSCC..

Methodology Patients with a history of having TSCC, complete clinical and demographic data (age and gender), and a through clinical and histopathological follow-up period of six months were included. The overall survival (OS) and disease-free survival (DFS) of the participants were determined.Histopathological grade was assessed as a secondary objective. Kaplan–Meier survival analysis was performed, and data analysis was conducted using the Kaplan-Meier method, log-rank test and a multivariable Cox regression model.

Results A total number of 162 patients were included with the mean age of 59.6 ± 15.7 years. The majority of the patients (53.1%) were women. Most patients were classified as Grade I (37.7%) and Stage I (46.3%). The local recurrence and metastasis rates were 12.3% and 4.3%, respectively. The median OS and DFS of the patients included 46 ± 7.8 months and 36 ± 5.7 months, respectively. Five-year OS and DFS rates of 41.5% and 36%. No significant correlation was found between OS and DFS with patients' gender or histological grade. However, OS and DFS were inversely related to the clinical stage and age, showing statistical significance ($P < 0.05$). Additionally, OS was significantly influenced by tumor size, lymph node involvement, and metastasis ($P < 0.05$). Factors such as tumor size, lymph node involvement, clinical stage, and patient age significantly impacted OS ($P < 0.05$). In contrast, lymph node involvement, clinical stage, and patient age were significantly associated with DFS ($P < 0.05$).

Conclusion Clinical factors including tumor size, lymph node involvement, clinical stage, and patient age were associated with OS. All these variables were also associated with DFS, except for tumor size. The histopathological grade was not influential on OS or DFS.

Keywords Clinical staging, Pathological grading, Squamous cell carcinoma, Survival, Tongue

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Introduction

Each year, over 500,000 new cases of head and neck squamous cell carcinoma are diagnosed, with oral squamous cell carcinoma (OSCC) showing a consistent increase over the past decade [1]. The global incidence of oral cancer is estimated to surpass 300,000 cases annually, resulting in approximately 145,000 deaths. OSCC is responsible for 90% of these cases [2]. The number of new cancer cases in Iran is predicted to increase from 112,000 recorded cancer cases in 2016 to 160,000 new cases in 2025. This represents an increase of 42.6%, of which 13.9% and 28.7% were attributed to changes in risk and population structure, respectively [3].

Despite advancements in diagnostic and therapeutic approaches, overall survival (OS) and disease-free survival (DFS) rates remain stagnant at 50–60%, underscoring the need for improved prognostic models [4, 5]. The TNM staging system has long been a reliable tool for clinicians in predicting patient outcomes and guiding management decisions in OSCC cases. Tumors classified as T1 and T2 carry a 10% and 30% risk, respectively, of metastasizing to cervical lymph nodes, whereas T3 and T4 tumors have a substantially higher risk [6, 7]. Cervical lymph node involvement remains the most critical prognostic factor in OSCC, directly influencing recurrence and survival outcomes [8, 9]. However, the effectiveness of OSCC treatment in clinical settings can sometimes fall short of expectations. Numerous studies have shown that even early-stage tumors can result in fatal outcomes [10–12]. While factors such as vascular invasion, perineural invasion, extracapsular spread, and positive surgical margins have been recognized as prognostic indicators [13, 14], the impact of tumor location, histologic grade, and molecular markers remains inconsistent across studies [15].

Among OSCC subtypes, tongue squamous cell carcinoma (TSCC) is one of the most prevalent and aggressive forms, accounting for 17.8% of all OSCC cases [16]. It is associated with high rates of metastasis, increased recurrence risk, and poorer prognosis compared to other OSCC subsites [17]. Notably, DFS for TSCC declines sharply, from 90% in T1 cases to 72.9% in T2 cases, indicating a more aggressive clinical course even in early-stage disease [18]. Genetic alterations associated with TSCC involve progressive changes in DNA methylation, overexpression of carcinoembryonic antigen, histone modifications, and altered expression levels of microRNAs (miRNAs). As a result, these epigenetic changes—including DNA fragments found in saliva, immune-related gene transcripts, the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio, and microRNA expression—show promise as biomarkers for the early detection and prognosis of the disease [16]. Additionally, TSCC demonstrates resistance to chemotherapy in some cases, further complicating treatment outcomes [19]. Moreover, early-stage TSCC generally has worse overall survival compared to other early T-stage head and neck cancers [20]. Despite being a major OSCC subtype, TSCC exhibits unique clinical and molecular characteristics that contribute to worse survival outcomes, even in early-stage cases. TSCC may be difficult to cure due to uncertainty about which histopathologic features are relevant for risk-stratifying patients and predicting recurrence. While studies have investigated general OSCC prognostic factors, limited research has focused specifically on the impact of histopathologic grade and clinical parameters in TSCC prognosis. Therefore, this study aims to fill this gap by evaluating the association between tumor grade, clinical stage, and survival outcomes in TSCC patients. Understanding these relationships is crucial for refining prognostic models and improving treatment strategies tailored to TSCC patients.

Methods and materials

The protocol for this cross-sectional study was received approval from the Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.DENTISTRY.REC.1400.045). Patient files of individuals diagnosed with OSCC who were referred to Omid Hospital in Mashhad, Iran, between 2005 and 2020 were reviewed. The inclusion criteria were having a history of TSCC, complete clinical and demographic data, a through clinical and histopathological follow-up period of six months, and the availability of sufficient tissue samples embedded in paraffin blocks. The patient files of those who passed away due to causes other than TSCC, such as accidents, COVID-19, heart attacks, etc., were excluded. Ultimately, 162 patients with focus on complete OS and DFS data were included in the study.

Demographic data, including age and gender, along with the clinical stage of the disease, were recorded for each patient. OS and DFS of the participants were determined. OS was defined as the period from disease diagnosis until death and DFS was defined as the time from surgical tumor removal to disease recurrence. The histopathological grade of tumor was also assessed as a secondary objective.

Statistical analysis

Data were analyzed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). The relationship between OS, DFS, and clinical parameters, including stage, grade, and lymph node involvement, was assessed using log rank analysis. Kaplan–Meier survival analysis was employed to compute three-year and five-year OS and DFS. A multivariable Cox regression model was also used to evaluate the associations between clinicopathologic parameters and

Table 1 Clinical and pathological characteristics of the disease

Parameter	Sub-group	*N* (%)
T	1	72 (44.4)
	2	62 (38.3)
	3	21 (13)
	4	7 (4.3)
N	0	124 (77.5)
	1	21 (13.1)
	2	15 (9.3)
M	0	137 (95.8)
	1	6 (4.2)
Stage	1	61 (37.7)
	2	48 (29.6)
	3	33 (20.4)
	4	20 (12.3)
Grade	1	75 (46.3)
	2	71 (43.8)
	3	16 (9.9)

OS and DFS outcomes. The significance level was set at 0.05.

Results

Characteristics of the study sample

The mean age of the patients in the study was 59.6 ± 15.7 years, with an age range of 22 to 91 years. The majority of the patients (53.1%) were women. At the time of the study, 54.3% of the patients were still alive. A significant majority of the lesions, 93.2%, were located on the tongue, and due to the low prevalence of OSCC on the floor of the mouth, this site was excluded from further analysis.

Table 1 details the characteristics of the disease, including stage, grade, and presence of metastasis. Most patients were classified as Grade I (37.7%) and Stage I (46.3%). The local recurrence and metastasis rates were 12.3% and 4.3%, respectively.

Univariate analysis of demographic and clinical parameters and histopathological grade

The median follow-up period for the study was 18.5 months. The median OS and DFS were 46 ± 7.8 months and 36 ± 5.7 months, respectively (Fig. 1). The 6-months OS and DFS rates were 98.7 ± 0.9 and 96.2 ± 1.5 respectively.

As shown in Table 2, there was no significant relationship between the patients' gender and survival (Fig. 2A). However, age was significantly associated with both OS and DFS. Specifically, the median OS for patients younger than 60 years was 117 months, compared to 24 months for those older than 60 years, indicating a strong association between age and OS and DFS ($P < 0.001$) (Fig. 2B).

The T parameter was also significantly associated with both OS and DFS ($P < 0.001$) (Fig. 3A). Similarly, the N parameter showed a significant relationship with OS ($P = 0.021$) and DFS ($p = 0.003$) (Fig. 3B). While the M parameter did not significantly affect OS, it was significantly related to DFS ($P = 0.009$) (Fig. 3C). The pathological grade of the lesion did not significantly impact survival (Fig. 4A); however, the clinical stage parameter was significantly associated with both OS and DFS ($P < 0.001$) (Fig. 4B).

Multivariate analysis

As shown in Table 3, the Cox regression model included the variables of T, N, clinical stage, and patient age. For OS, T was significantly associated with survival

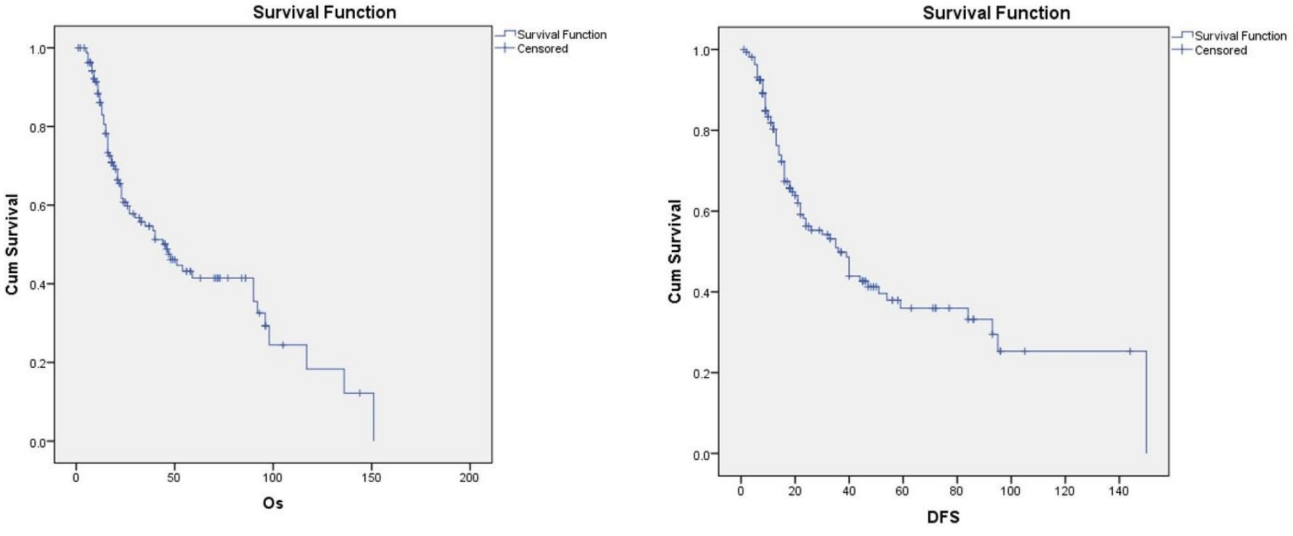

Fig. 1 OS and DFS values of the participants

Table 2 The relationship between the demographic, clinical and pathological and OS and DFS of the patients (Median ± Standard Error)

Parameter	Subgroup	OS	*P*-value	DFS	*P*-value
Gender	Women	59 ± 21.75	0.079	51 ± 9.7	0.146
	Men	27 ± 5.95		24 ± 2.8	
Age	<=60	117 ± 24.45	< 0.001*	-	< 0.001*
	> 60	24 ± 2.31		24 ± 4.15	
T	1, 2	51 ± 8.67	< 0.001*	40 ± 7.5	< 0.001*
	3, 4	15 ± 2.32		12 ± 3.03	
N	0	54 ± 17.59	0.021*	44 ± 10.15	0.003*
	1	19 ± 11.49		16 ± 4.98	
	2	15 ± 3.44		12 ± 2.71	
M	0	46 ± 9.27	0.095	39 ± 7.69	0.009*
	1	16 ± 6.42		11 ± 4.29	
Grade	1	59 ± 19.56	0.232	40 ± 11.76	0.117
	2	40 ± 11.63		33 ± 8.88	
	3	21 ± 4.38		21 ± 8.96	
Stage	1	136 ± 0.0	< 0.001*	59 ± 0.0	< 0.001*
	2	40 ± 11.-3		33 ± 11.03	
	3	40 ± 8.32		35 ± 11.04	
	4	12 ± 2.53		11 ± 1.5	

OS = Overall Survival; DFS = Disease-Free Survival

*Values less than 0.05 represent a significant difference between the OS and DFS of the sub-groups of demographics, clinical, and histopathological parameters according to the log-rank test.

(HR = 0.378, 95% CI [0.181, 0.790], $P = 0.010$). Nodal involvement at level N [1] was also significantly associated with OS (HR = 0.391, 95% CI [0.163, 0.936], $P = 0.035$), whereas N [2] showed no significant impact. Overall, the N category was significantly associated with OS ($P = 0.015$). Patients in Stage 1 (HR = 0.258, 95% CI [0.100, 0.665], $P = 0.005$), Stage 2 (HR = 0.311, 95% CI [0.131, 0.735], $P = 0.008$), and Stage 3 (HR = 0.152, 95% CI [0.070, 0.326], $P < 0.001$) had significantly better OS compared to the reference category. The overall impact of the disease stage was statistically significant ($P < 0.001$). Additionally, age was a significant prognostic factor for OS (HR = 1.058, 95% CI [1.036, 1.081], $P < 0.001$), indicating that increasing age was associated with poorer survival outcomes.

For DFS, T and nodal involvement (N [1] and N [2]) were not significantly associated with DFS. However, the overall N category was significantly associated with DFS ($P = 0.011$). M value did not show a significant association with DFS. Similar to OS, patients in Stage 1 (HR = 0.150, 95% CI [0.033, 0.672], $P = 0.013$), Stage 2 (HR = 0.167, 95% CI [0.038, 0.728], $P = 0.017$), and Stage 3 (HR = 0.159, 95% CI [0.048, 0.527], $P = 0.003$) had significantly higher DFS compared to the reference category, with an overall significant impact of staging ($P = 0.025$). Moreover, age was a significant predictor of DFS (HR = 1.041, 95% CI [1.021, 1.062], $P < 0.001$), suggesting that older patients had a higher risk of disease recurrence or progression.

Discussion

In this study, the survival rate of 162 patients were analyzed, revealing a median OS of 46 months and a median DFS of 36 months. The 6-months OS and DFS rates were 98.7 ± 0.9 and 96.2 ± 1.5 percentage respectively. Although women had a slightly longer survival duration, the difference was not statistically significant. The histopathologic grade did not correlate with patient survival, but an increase in tumor size was associated with decreased survival. Factors such as age, lymph node involvement, and the clinical stage of the disease showed an inverse relationship with patient survival. While metastasis did not significantly impact OS, it was significantly related to DFS.

As derived from epidemiological studies, identifying factors that affect prognosis and survival in patients with TSCC plays a crucial role in guiding appropriate treatment strategies. In this study, approximately 32.7% of patients were in stages III and IV, indicative of advanced disease. In contrast, studies conducted in countries with lower income or inadequate healthcare services have shown that about 40.4–49.7% of the patients present with stage IV of the disease [21–24]. Factors contributing to delayed diagnosis include insufficient knowledge about oral and dental conditions, high treatment costs, and the lack of prioritization for oral and dental care [25].

In the current study, the majority of patients were women, but there was no significant difference in survival between the genders. Similar epidemiological studies in Nepal [21] and India [22, 23] have reported a higher prevalence of head and neck SCC among men, attributed to factors such as smoking, alcohol consumption, and the chewing of tobacco and betel quid, particularly in Southeast Asian countries. In the study of Karim-Kos et al. [26], the male-to-female ratio for head and neck SCC was approximately 1.5:1 in Northern European countries and as high as 7:1 in Lithuania. However, in more developed countries, where smoking and alcohol use among women are more common, the gender ratio has become more balanced, as seen in the present study. Additionally, this ratio can vary across different geographical locations due to factors like atmospheric conditions and environmental pollution [27]. Consistent with our findings, Aittiwarapoj et al. [28] and Zhang et al. [29] also reported similar prevalence rates of TSCC among men and women.

In this study, the survival rate decreased significantly with increasing age, with the highest prevalence of the disease observed in the fifth decade of life [30]. This fintding aligns with the study by Gajurel et al. [21]. Similarly, studies by Zini et al. [31], Malhotra et al. [22], and Alvez et al. [32] reported the highest prevalence of the disease among individuals aged 55 and above, with survival rates declining as age increased. Aittiwarapoj et al. [28] also observed that the highest prevalence of SCC occurred in

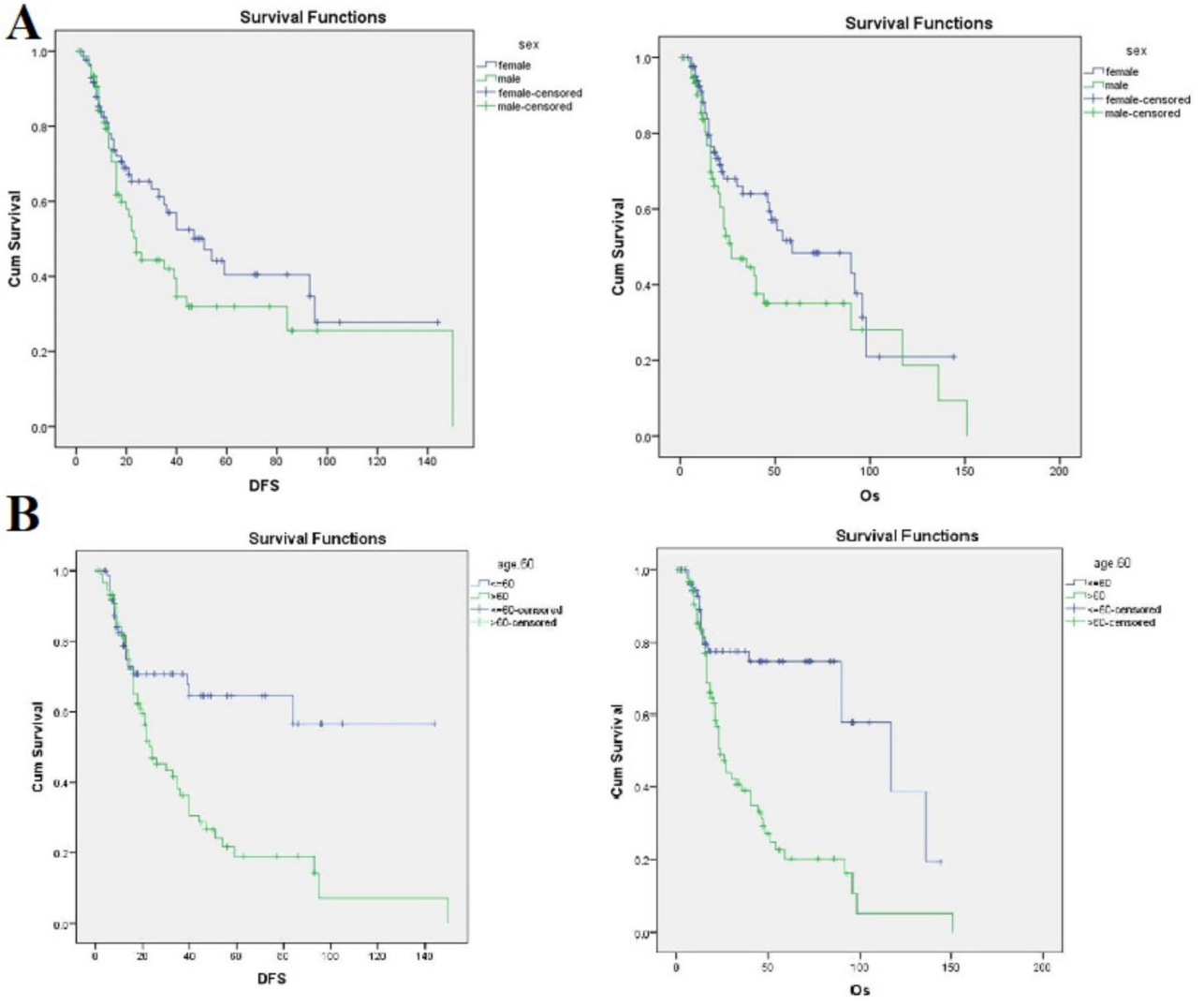

Fig. 2 The effect of (**A**) gender and (**B**) age groups on OS and DFS

the sixth decade of life, with patient survival decreasing with age.

In the present study, the OS and DFS of female patients were higher than those of male patients, though the difference was not statistically significant. Similarly, in the study by Migueláñez-Medrán et al. [33], the recurrence risk was slightly higher in men than in women. However, this difference could be attributed to the smaller sample size in Migueláñez-Medrán et al.'s study (26 participants) and the focus on different types of OSCCs. In contrast, Garavello et al. [34], who studied 213 patients with OSCC of the tongue, found no correlation between gender and patient survival. Similarly, Amaral et al. [35], who investigated OSCC of the floor of the mouth and tongue, reported no relationship between gender and disease survival. Dissanayaka et al. [36] also found no difference in OS between men and women, attributing this to the equal consumption of betel quid by both sexes in Sri Lanka.

In this study, Grade I prevalence was 46.3%, which aligns with other studies reporting rates between 54.5% and 55.8%, depending on the type of OSCC [37, 38]. However, the percentage reported by Aittiwarapoj et al. [28] in Thailand was much higher at 82.1%, specifically in studies focusing on TSCC. Similar to the present study, Aittiwarapoj et al. did not observe Grade IV cases. The histopathological grade was not related to patient survival or DFS, a finding consistent with studies by Weijers et al. [39] and Sawair et al. [40], which also found no relationship between lesion grade and survival rate. Acharya et al. [41] similarly reported no correlation between lesion grading and patients' invasiveness or treatment prognosis. In Tong et al.'s study [42], histopathological differentiation of the lesion was not associated with two-year survival rates in patients with oral SCC. Acharya

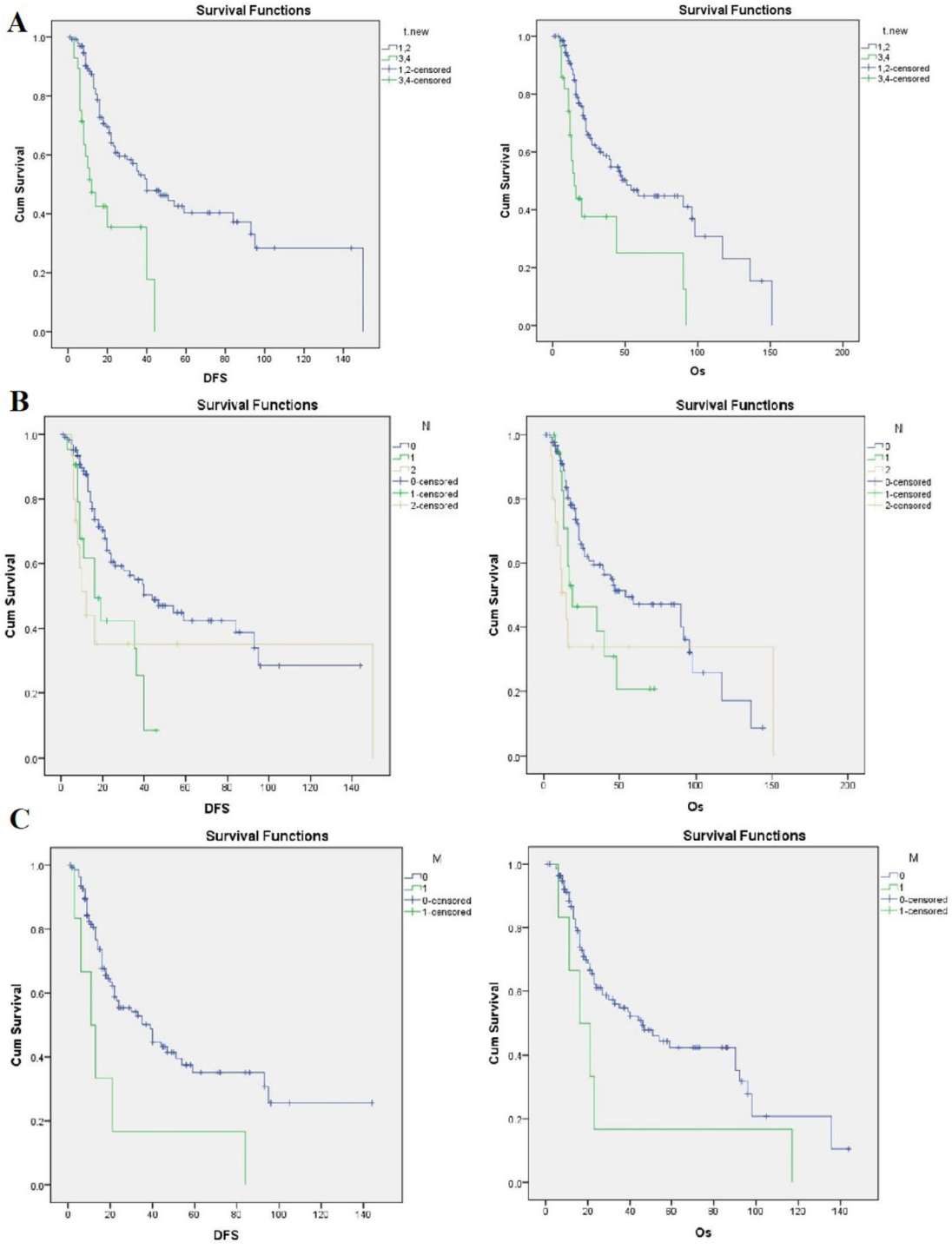

Fig. 3 The effect of (**A**) T, (**B**) N, and (**C**) M on OS and DFS

et al. [43] noted that histopathological grade was more closely related to recurrence rates and lesion invasiveness in younger patients. Dissanayaka et al. [36] observed a significant difference in survival between patients with differentiated and undifferentiated lesions, highlighting the impact of lesion differentiation on patient outcomes.

TNM is one of the most reliable classifications for OSCC, in which tumor size and lymph node involvement have shown the strongest correlation with disease prognosis. In the present study, tumor size and lymph node involvement were found to have a significant inverse relationship with disease survival, consistent with other studies [36, 44, 45]. Additionally, this study revealed that

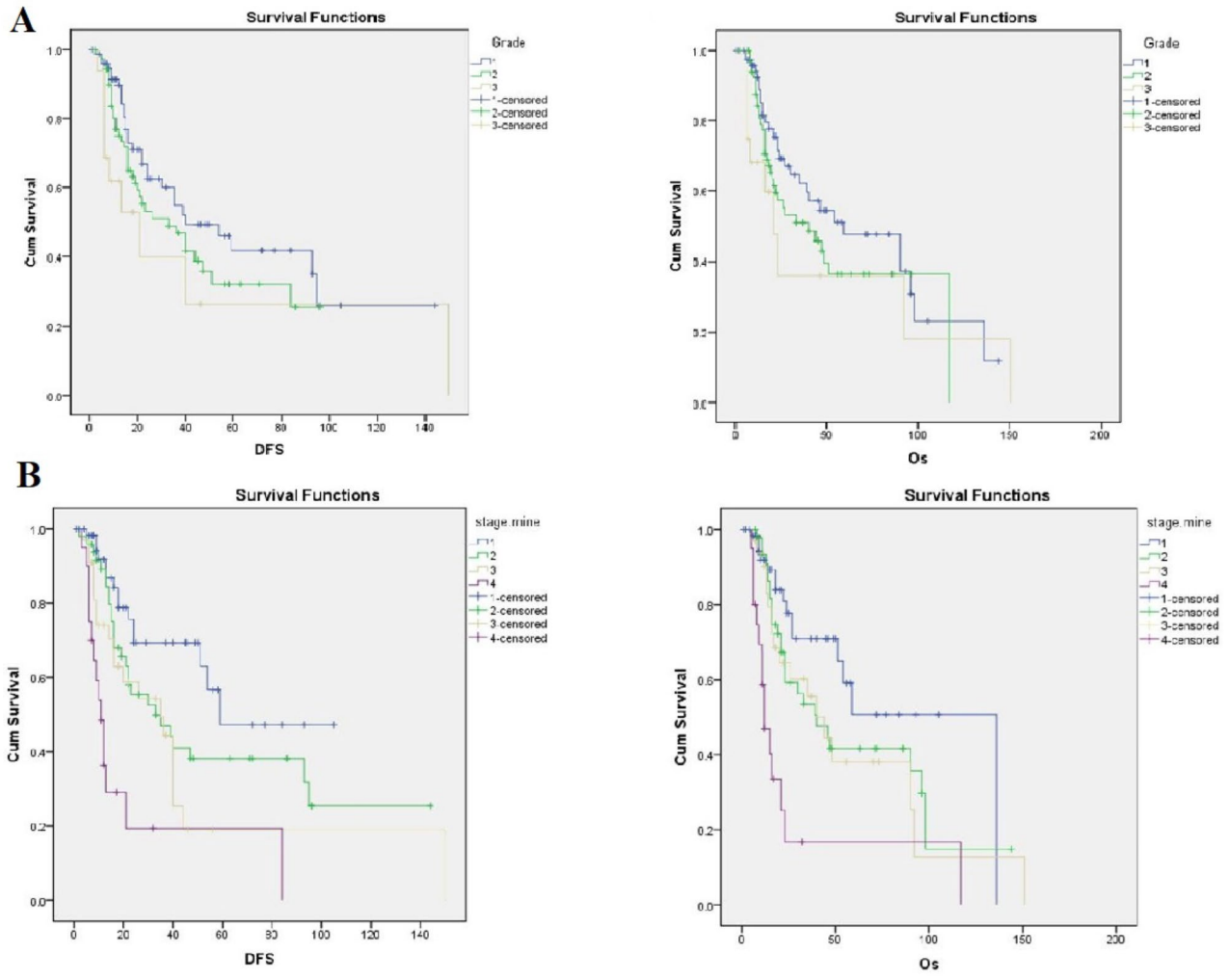

Fig. 4 The effect of (**A**) the pathological grade and (**B**) the clinical stage of the disease on OS and DFS

the clinical stage had a significant inverse relationship with overall survival, while no correlation was observed between histopathological grade and patient survival. In the study by Nobrega et al. [46], patients with lower clinical stages had a better prognosis. Their study identified the absence of lymph node involvement and smaller tumor size as the most critical factors related to disease prognosis. Similarly, Banipal et al. [47], who investigated TSCC, observed that patient survival is more strongly related to the clinical stage than histopathological grade, with better treatment outcomes in patients with lower stages. Zhang et al. [29] also noted that, in addition to smoking and alcohol consumption, the clinical stage is directly related to patient survival. Tong et al. [42] found that the lesion stage in patients with OSCC is more crucial in determining prognosis and two-year survival rates. Ebrahimi et al. [48] emphasized that T and N stages are important factors for predicting prognosis and local recurrence in OSCC patients. Wang et al. [45] also identified tumor differentiation and size as key predictors of disease recurrence following surgery. Dissanayaka et al. [36] demonstrated that the five-year survival rate for OSCC patients in Stages I and II is significantly higher than in Stages III and IV.

The last follow-up occurred in 2020, coinciding with the onset of the COVID-19 pandemic. During this time, COVID-19 was frequently recorded as the primary cause of death, while other diseases were considered contributory factors. As a result, patient files in which COVID-19 was listed as the primary cause of death were excluded from the study. Additionally, the COVID-19 pandemic likely impacted the study results by hindering follow-ups for OSCC patients, leading to delayed diagnoses and lower survival rates [49]. According to Rochel-Rochel et al. [49], when follow-ups from the pandemic were included in the survival analysis for Colombia and Spain, OS and DFS decreased compared to when only pre-COVID-19 follow-ups were considered. On the other hand, Petti [50] reported that Missing oral and pharyngeal cancer deaths reported in Europe in 2020–2021

Table 3 Variables in the final logistic regression model for OS and DFS

Survival	Parameters	HR	CI 95%	*P* value
OS	T	0.378	[0.181, 0.790	0.010*
	N(1)	0.391	[0.163, 0.936]	0.035*
	N(2)	1.026	[0.404, 2.605]	0.956
	N			0.015*
	Stage 1	0.258	[0.100, 0.665]	0.005*
	Stage 2	0.311	[0.131, 0.735]	0.008*
	Stage 3	0.152	[0.070, 0.326]	< 0.001*
	stage			< 0.001*
	Age	1.058	[1.036, 1.081]	< 0.001*
DFS	T	0.532	[0.229, 1.237]	0.143
	N(1)	0.589	[0.184, 1.889]	0.373
	N(2)	1.827	[0.528, 6.321]	0.341
	N			0.011*
	M	2.314	[0.551, 9.713]	0.252
	Stage 1	0.150	[0.033, 0.672]	0.013*
	Stage 2	0.167	[0.038, 0.728]	0.017*
	Stage 3	0.159	[0.048, 0.527]	0.003*
	Stage			0.025*
	Age	1.041	[1.021, 1.062]	< 0.001*

OS = Overall Survival; DFS = Disease-Free Survival; HR = Hazard Ratio
*Values less than 0.05 were associated with a significant association to the OS and DFS according to the Cox regression.
Reference categories are last one

could be explained by changes in the death certification of oral and pharyngeal cancer patients who developed COVID-19. Therefore, similar to the present study, it was challenging to determine the exact causes of death during the COVID-19 pandemic, which is a limitation of research conducted during this period.

There were limitations associated with the present study. The high number of records with incomplete data led to the exclusion of a considerable portion of them, highlighting the need to encourage electronic record-keeping in hospitals, particularly for patients with cancer. Additionally, patient habits, such as smoking status and alcohol consumption, were not investigated in this study, warranting further research in these areas. Further research is needed to assess the impact of additional clinicopathological variables, such as the depth of invasion, as well as the effects of different treatment modalities and adjuvant therapies on patient survival.

Conclusion

Clinical factors, including tumor size, lymph node involvement, clinical stage, and patient age, were significantly related to OS. Regarding DFS, all these variables were also influential, except for tumor size. Therefore, within the current study's limitations, it can be concluded that clinical and demographic factors, unlike histologic grade, play a crucial role in determining the patient's prognosis.

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Author contributions
N.G, N.S, K.A, and S.SK. conceptualized, supervised, and administered the study. M.H. conducted the formal analysis. K.A, R.B, and M.H. conducted the investigation. M.H. wrote the main manuscript text. H.M, S N.G, N.S, K.A, S.SK., and R.B. reviewed and edited the manuscript. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study adhered to the principles of the Declaration of Helsinki. All methods were conducted in accordance with relevant guidelines and regulations. The experimental protocols were approved by the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.DENTISTRY.REC.1400.045). This study was retrospective and involved the patients' files. Therefore, obtaining informed consent to participate was waived by the ethics committee of Mashhad University of Medical Sciences.

Consent for publication
Obtaining consent for publication did not apply to the current study.

Competing interests
The authors declare no competing interests.

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