# Deciphering prognostic value of OSCC modulators like pre-treatment hemoglobin in Saudi patients via survival analysis and regression model

Syed Hammad Ahsan[a,e], Aseel khalaf[b,e], Abdulsalam Aljabab[c], Saad Hajeri[d], Azeem Hussain Soomro, Bushra Jabeen[a], Hezekiah A. Mosadomi[e], Tariq Ahmad Wani[c], Fahad Murdhi AlEnazi[f,e], Salik Rasool[a]

a) Dow University of Health Sciences
b) Sharjah University
c) King Fahad medical city
d) King Faisal medical city
e) Riyadh Elm University
f) Prince Mohammed Bin Abdulaziz Hospital

## ABSRACT

### Background

OSCC (oral squamous cell carcinoma) constitutes 90% of oral malignancies. It has a multifactorial etiology, however, many cases remain idiopathic. We aimed to assess the impact of sociodemographic, clinicopathological, histopathological and therapeutic parameters on the survival time and final outcome of Saudi OSCC patients.

### Methods

Analytical observational study comprising 145 OSCC patients treated at King Fahad Medical City (KFMC) from 2005 to 2014. Chi square test, kaplan-meier survival analysis and multiple logistic regression analysis were performed.

### Results

Chi-square revealed statistically significant association of final outcome with gender, age, tumor size (T), T4 tumor, lymph node status (N), pre-treatment hemoglobin, and cause of death. Logistic regression analysis revealed that

death increased with increase in pre-treatment anemia, T2 tumor and N2 status. Survival analysis showed a statistically significant relationship of survival time with tumor size, T4 tumor, N status, treatment complications and recurrence.

Conclusion

In OSCC patients, death, as a final outcome, exponentially increased with increase in pre-treatment anemia, tumor size and N status. Lack of association with histological grading vindicates the global need for a better grading system.

KEYWORDS

mouth neoplasms; survival; hemoglobins; oropharyngeal neoplasms; saudi arabia

## INTRODUCTION

Oral squamous cell carcinoma (OSCC), termed oral cancer, is the 16th most common cancer worldwide [1-3]. OSCC has a dispirited 5-year survival rate of 50-70% globally [4 - 8]. Tobacco, alcohol, and human papilloma virus (in case of oropharynx) are considered as main etiological factors [1, 9], although many patients develop OSCC in the absence of this etiology [8], indicating the role of incognito factors [2].

Many cancer patients are anemic [3]. Anemia fosters the development of malignancy, as tissue hypoxia increases the resilience of cancer cells against oncotherapy [10]. Recently, pre-treatment anemia was reported as a strong prognostic indicator for cervical cancer [11], oral cancer [2], and also gastric cancer patients undergoing immunotherapy [12].

As multiple factors modulate the progression of OSCC [13], our aim was to comprehensively assess the effect of sociodemographic, clinicopathological, histopathological and therapeutic factors on the survival time and final outcome of OSCC patients.

Our objectives were to:

- Extract OSCC patients data via database software (Cortex and HIM) of King Fahad Medical City (KFMC) and Saudi Cancer Registry

- Decipher the impact of individual independent variable on the survival time and final outcome of these patients
- Determine the impact of more than one variable on the final outcome of these patients by generating a regression model

## MATERIALS AND METHOD

This was an analytical observational study entailing a non-probability purposive sampling technique. The study subjects were patients treated for OSCC at KFMC from 2005 to 2014. With a Riyadh population of 6,218,322, 9.82/100,000 prevalence of OSCC in Jazan (highest in KSA), we derived a study population of 610. Based on it, 95% confidence level, and confidence interval of 5, we calculated a sample size of 236 [14 – 16]. Our original sample size was 420, but after excluding other head and neck malignancies (n=275) except OSCC, our final sample size was 145.

Inclusion criteria: Clinically and histologically diagnosed OSCC patients with complete record and on a minimum 12 month follow up period

Exclusion criteria: 1. Patients with previous or synchronous malignancies 2. Patients details lost to follow up

Ethical approval (reference number: 016-020) was provided by KFMC RC-IRF committee. The research members, who were trained via workshop on how to operate database software Cortex and HIM, extracted retrospective online data of patients. In addition to that, all patients were contacted via structured telephonic interview (Arabic), to ensure acquisition of updated information regarding their vitality status (alive / dead).

Variables: (1) Exposures: Age, gender, tobacco, pre-treatment hemoglobin, tumor location, tumor size, lymph node status, metastasis, histological grade, treatment type, treatment complications, recurrence, cause of death; (2) Outcomes: survival time (months), final outcome defined as event of interest "death" occurring before or till the end of the study); (3) following Bias were minimized by : "Detection bias" and "Loss to follow up bias": incorporating two methods for outcome collection, namely, online database, and a structured telephonic interview. "Sampling bias": Including patients of a Riyadh based hospital only, so that they would represent Riyadh population. "Recall bias": corroborating telephonic Interview with online data of all the patients. "Observer bias": utilizing blinded external researchers for data collection.

SPSS Version 26 was utilized for statistics. Descriptive statistics comprised frequency distribution for qualitative variables and measure of central tendency for quantitative variables. Chi-square test of independence, Kaplan-Meier survival analysis and Multiple logistic regression were utilized for inferential statistics. p < 0.05 was considered as statistically significant.

## RESULTS

Our study comprised 145 patients. The mean time from diagnosis to event (survival time) was 45.5 months (Table 1). Chi-square revealed a statistically significant association of age (X2 6.63, df 1, p 0.01, OR 3.34), gender (X2 6.07, df 1, p 0.01, OR 0.40), T size (X2 14.91, df 3, p < 0.01), T4 sized tumor (X2 7.92, df 1, p 0.005, OR 2.79), N status (X2 17.32, df 3, p 0.001), pre-treatment hemoglobin (X2 7.51, df 2, p 0.02), and cause of death (X2 10.82, df 1, p 0.001, OR 0.20) with final outcome (Table 1). The kaplan-meier survival analysis revealed a statistically significant relationship of T size (Figure 1), T4 sized tumor, N status (Figure 2), and treatment complications (Figure 3) with survival time.

Table 1: Final outcome in association with the studied variables based on univariate analysis

| | | Survived | Died | p value |
|---|---|---|---|---|
| Gender | Female | 38 (58.4) | 27 (41.5) | 0.014 (OR 0.409) |
| | Male | 62 (77.5) | 18 (22.5) | |
| Age (yr) | ≤50 | 34 (85.0) | 6 (15.0) | 0.010 (OR 3.348) |
| | > 50 | 66 (62.8) | 39 (37.1) | |

| | | | | |
|---|---|---|---|---|
| Tobacco Usage | No | 81 (68.0) | 38 (31.9) | 0.617 (OR 0.785) |
| | Yes | 19 (73.0) | 7 (26.9) | |
| Location of primary lesion | Left | 10 (62.5) | 6 (37.5) | 0.592 (OR NA) |
| | Middle/anterior | 1 (100) | 0 (0) | |
| | Right | 8 (57.1) | 6 (42.8) | |
| | Bilateral | 81 (71.0) | 33 (28.9) | |
| T4 tumor | No | 71 (77.1) | 21 (22.8) | 0.005 (OR 2.79) |
| | Yes | 29 (54.7) | 24 (45.2) | |
| T_Size | T1 | 23 (92.0) | 2 (8.0) | 0.002 (OR NA) |
| | T2 | 17 (60.7) | 11 (39.2) | |
| | T3 | 32 (80.0) | 8 (20.0) | |
| | T4 | 28 (53.8) | 24 (46.1) | |
| N_Status | N0 | 44 (88.0) | 6 (12.0) | 0.001 (OR NA) |
| | N1 | 27 (71.0) | 11 (28.9) | |

| | | | | |
|---|---|---|---|---|
| | N2 | 22 (50.0) | 22 (50.0) | |
| | N3 | 7 (53.8) | 6 (46.1) | |
| M_Status | M0 | 95 (69.3) | 42 (30.6) | 0.684 (OR 1.357) |
| | M1 | 5 (62.5) | 3 (37.5) | |
| Histological grading | Moderately differentiated | 55 (64.7) | 30 (35.2) | 0.281 (OR NA) |
| | Poorly differentiated | 8 (61.5) | 5 (38.4) | |
| | Undifferentiated | 3 (100) | 0 (0) | |
| | Well differentiated | 34 (77.2) | 10 (22.7) | |
| Treatment | Not given | 16 (69.5) | 7 (30.4) | 0.946 (OR 1.034) |
| | Given | 84 (68.8) | 38 (31.1) | |
| Treatment Complications | No | 95 (70.3) | 40 (29.6) | 0.179 (OR 2.375) |
| | Yes | 5 (50.0) | 5 (50.0) | |
| Pre-treatment hemoglobin | Normal | 59 (75.6) | 19 (24.3) | 0.023 (OR NA) |
| | Mild anemia | 12 (50.0) | 12 (50.0) | |

| | | | | |
|---|---|---|---|---|
| | Severe anemia | 16 (55.1) | 13 (44.8) | |
| Recurrence | No | 92 (69.1) | 41 (30.8) | 0.857 (OR 1.122) |
| | Yes | 8 (66.6) | 4 (33.3) | |
| Cause of death | No | 100 (79.3) | 26 (20.6) | 0.001 (OR 0.20) |
| | Yes (Cancer) | 0 (0) | 19 (100) | |

OR, odd ratio; NA, not available (> 2*2 table)

Figure 1. Survival time in relation to tumor size based on survival analysis

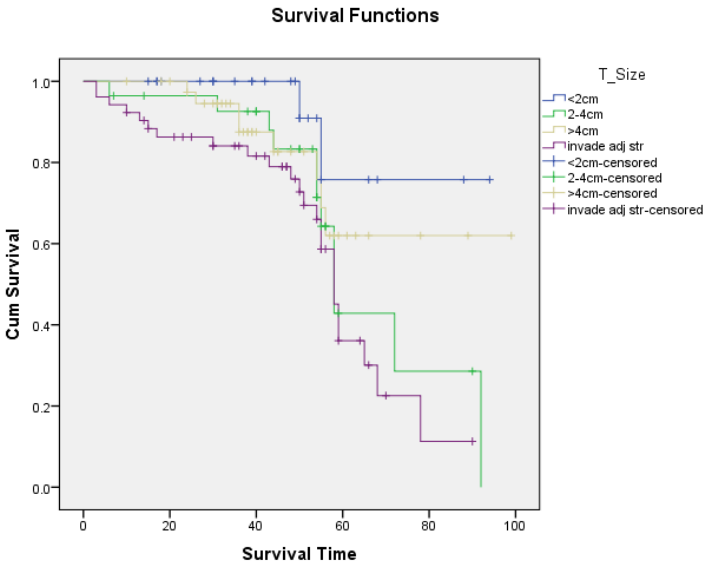



Figure 2. Survival time in relation to lymph node status based on survival analysis

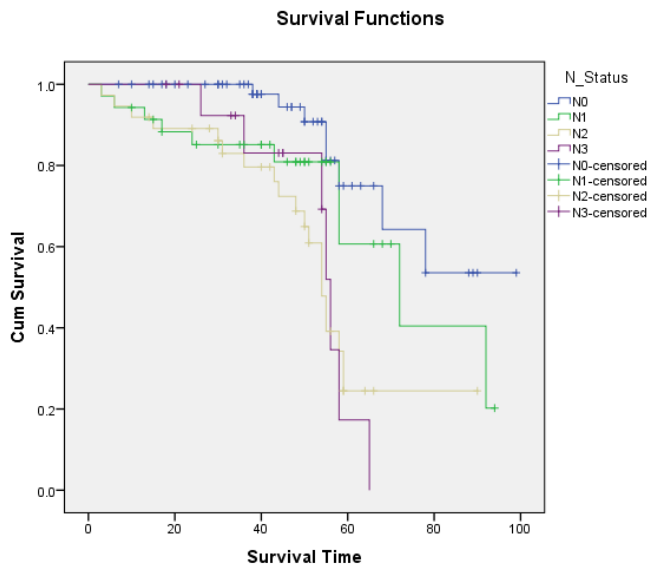
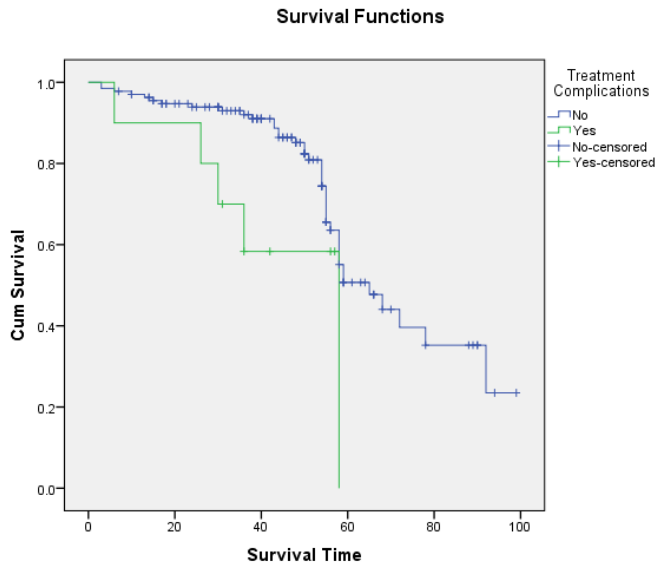



Figure 3. Survival time in relation to treatment complications based on survival analysis




Multiple logistic regression analysis generated a model in which the final outcome was categorized as a dependent, dichotomous (alive = 0, death = 1), categorical variable. This model was statistically significant ($\chi^2(4)$ = 46.27, df = 13, p = 0.001). It explained 41.7% (Nagelkerke $R^2$) of variance in final outcome and correctly classified 81.4% of cases. Mild anemia was 1.804 times more likely to cause death than normal hemoglobin level. T2

tumor was 5.161 times more likely to cause death than smaller tumor. N2 lymph node was 2.177 times more likely to cause death than N0 lymph node (Table 2).

Table 2: Strength of an association between parameters and final outcome (death) based on multivariate analysis

| Variables | B | Wald $\chi^2$ | P | OR [Exp(B)] | $CI_{95}$ |
|---|---|---|---|---|---|
| Age | -1.971 | 9.587 | 0.002 | 0.139 | 0.040-0.485 |
| Size of primary tumor | 1.641 | 2.157 | 0.142 | 5.161 | 0.577-46.138 |
| T4 tumor | -1.116 | 1.165 | 0.280 | 0.328 | 0.043-2.486 |
| N status | 0.778 | 0.708 | 0.400 | 2.177 | 0.355-13.331 |
| Pre-treatment hemoglobin | 0.590 | 0.708 | 0.400 | 1.804 | 0.456-7.135 |
| Treatment | 0.670 | 0.860 | 0.354 | 1.955 | 0.474-8.058 |
| Recurrence | -0.306 | 0.101 | 0.750 | 0.736 | 0.112-4.843 |

B, intercept; Wald $\chi 2$, wald chi-squared test; p, probability value; OR [Exp(B)], Odd ratio [ exponentiation of the B coefficient]; CI95, 95% confidence interval

## DISCUSSION

This study corroborated OSCC research in Saudi Arabia specifically and Asia generally, as the existing literature lacks large sample studies and models denoting prognosis. The prevalence of males and old age in our study was in agreement with literature [17]. The mean age of our patients was 57 years ($CI^{95}$ 55 – 59). OSCC is ranked 8th most common cancer in men, in contrast to 16th in women, globally [1]. However, the male-to-female ratio and age depends on genetic, social, cultural and geographical variations [1, 18]. We showed a statistically significant association of age (p 0.010) and gender (p 0.014) with final outcome (table 1). Though, there was no significant effect of these parameters on final outcome and survival time in the regression model (table 2) and survival analysis. Our findings are in contradiction with Garzino-Demo P. et al. who observed that older age (> 40 years) had a higher survival rate than younger age (< 40 years) (68% vs 62%) [13]. Our findings are inline with the conventional belief that older age (> 50 years) has a lower survival rate than younger age (< 50 years) (63% vs 85%) [13]

Tobacco is an important risk factor for OSCC [18]. It is consumed in various forms, thus, it has varying effects on different aero-digestive tract tissues. Cigarette smoking has a miniscule effect on the oral cavity [19]. In contrast, pipe smoking is a common cause of OSCC [20]. Though, smokeless tobacco is most commonly associated with OSCC [21]. In our study, 26 (18%) patients had a history of tobacco usage. This might be due to high prevalence of HPV positive oropharyngeal cancers in our sample. There is no concrete evidence of tobacco and betel quid as risk factors of HPV positive oropharyngeal cancer, although HPV 18 and especially HPV 16 are strongly associated with these neoplasms [19].

In our study, the mean primary tumor size was 3.68 cm (SD 2.11). It is posited as a strong prognostic indicator of survival [22]. Goldstein DP. et al. showed survival to be dependent on tumor size via univariate analysis but multivariate analysis revealed contradictory findings [22]. Weckx A. et al. showed a statistically significant association of disease specific survival with tumor size (p 0.001) [24]. In our study, tumor size had a statistically significant association with final outcome (p 0.002) and survival time (logrank 0.022, breslow 0.058, tarone-ware 0.045). patients with T1 tumors survived the longest (mean = 84 months, CI95 74 – 96). Death increased

5.161 times for every unit increase in T2 tumors as compared to smaller tumors (table 2). Similarly, Weckx A. et al., noted a two times increase in hazard ratio of larger tumors as compared to smaller tumors [24].

In our cohort, T4 tumor was most prevalent (n=52) and most commonly associated with death (n=24). Thirteen (9%) T4 tumors extended to larynx, six to base of skull (4%), five to pharynx (3%), and four to base of tongue (3%). There was a statistically significant association between T4 tumor and final outcome (p 0.005). Patients with smaller tumors survived longer (mean = 73 months, CI95 65 – 81) in contrast to T4 tumors (mean = 58 months, CI95 49 - 66). Verily, a statistically significant association was found between T4 tumor and survival time (logrank 0.038, breslow 0.025, tarone-ware 0.030).

Nodal involvement abates survival of cancer patients [5, 22, 24]. In our cohort, ninety five (66%) patients were positive for lymph node involvement on initial diagnosis. We observed a statistically significant association of lymph node involvement (N) with final outcome (p 0.001). Death increased 2.177 times for every one unit increase in N2 as compared to N0 status (table 2). Similarly, Hosni et al., observed a 1.83 times increase in death for every one unit increase in N2 and N3 status as compared to N0 and N1 status in OSCC patients [24].

We observed a gradual decrease in survival time as nodal involvement increased. Patients with N0 status had highest mean survival time (81 months, CI95 71 – 91), followed by N1 (mean = 67, CI95 54 – 80), N2 (mean = 55, CI95 46 – 64) and finally N3 (mean = 53, CI95 46 – 60), indicating a statistically significant association of N status with survival time (log rank 0.001, breslow 0.002, tarone-ware 0.01). Hosni et al., also showed that survival decreased the most in patients with N 2 and N 3 [24]. Are T size and N status correlated with or corroborate each other? Our univariate analysis revealed a statistically significant association between T size and N status (X2 36.706, df 9, p 0.001), whereby lymph nodes were most commonly detected in T4 tumors.

Distant metastasis (M) is considered as a prognostic indicator of OSCC [17]. However, there is inconclusive evidence regarding histological grading as a prognostic indicator [17]. It might be due to utilization of different grading systems by different pathologists, resulting in incongruent prognostic prediction of OSCC [17]. In our study, distant metastasis was found in lungs

(n= 2) and intracranial region (n= 3). Huang et al. showed metastasis in lungs (n=8), T-spine (n=3), liver (n=2) and brain (n=1) [23]. We did not find a statistically significant association of M status (p 0.684) and histological grading (p 0.281) with final outcome of patients. There was no statistical significant relationship of M status (logrank 0.174, breslow 0.273, tarone-ware 0.213) and histological grading (logrank 0.679, breslow 0.760, taarone-ware 0.737) with survival time also. Though a positive but unremarkable association of final outcome (death) was seen with M status (table 2).

Over the years, the mainstay of oncotherapy has not changed; the preferred primary treatment is surgery, either alone or followed by radiotherapy (in conjunction with chemotherapy termed "chemoradiotherapy" or alone) [6]. In our cohort, primary surgery with adjuvant radiotherapy was the most common type of treatment (n=41, 28.3 %), followed by primary surgery and adjuvant chemotherapy and radiotherapy (n=30, 20.7 %), surgery alone (n=18, 12.4 %), radiotherapy alone (n=18, 12.4 %), and chemoradiotherapy (n=9, 6.2%). There was no statistically significant association between type of treatment and final outcome of patients (p 0.946), therefore, the choice of treatment did not affect mortality. A review published in 2023 purported that any form of solitary treatment is ineffective in managing locally advanced OSCC, such lesions should be treated by multimodal therapies [25]. However, the choice of type, number and sequence of treatment(s) depends on TNM stage, recurrence and metastasis of OSCC [26]. Interestingly, a retrospective study conducted in 2016 showed that the 5-year overall survival rate of OSCC patients who had surgery only was around 81.2% [26]. Our regression model revealed that the option of not receiving treatment was 1.955 times more likely to cause death than treatment given (table 2).

Recurrence is associated with high mortality rate in cancer patients [23]. However, cancer patients die due to other co-morbidities also. For instance, in a previous study, many OSCC patients died due to cardiovascular and pulmonary diseases [23]. In our study, twelve (8%) patients had recurrence, while ten (7%) encountered post_treatment complications (table I). Amongst them, 7 had minor morbidity, 2 had major morbidity and 1 died due to complications. There was no statistically significant association between recurrence and final outcome (p 0.857). However, a statistically significant relationship was found between recurrence and survival time (log rank 0.059, breslow 0.012, tarone-ware 0.018). Survival time decreased for patients with recurrence (mean = 45 months, CI95 28 - 62) as compared to those without recurrence (mean = 68, CI95 61 – 74). Similarly, a statistically significant relationship was observed of treatment complications with survival time (log

rank 0.038, breslow 0.014, tarone-ware 0.020). Crosstabulation of recurrence with T size revealed that patients with recurrence either had T3 (n=5) or T4 (n=6) tumors. Although there was no statistically significant association between T size and recurrence (p 0.192).

Based on Hb values defined by World Health Organization, we categorized pre-treatment haemoglobin level of our patients into following groups: "normal" (female Hb≥12.0 g/dl; male Hb≥13.0 g/dl), "mild anemia" (female Hb = 11.0-11.9 g/dl; male Hb = 11.0-12.9 g/dl), and "severe anemia" (female & male Hb<11.0 g/dl) [2]. Thus, 78 (54%) of our patients had normal Hb level, 23 (16%) had mild anemia, and 29 (20%) had severe anemia. Pre-treatment haemoglobin was statistically associated with final outcome (p 0.023). Death increased 1.804 times for every one unit increase in mild anemia (table 2). Our findings are in sync with findings of few previous studies which showed pre-treatment anemia to be a prognostic factor for the survival outcome of cancers [11, 27, 28]. In our study, patients with normal Hb survived longer (mean = 123 months, $CI_{95}$ 92 - 154) when compared to patients with mild anemia (mean = 59, $CI_{95}$ 46 - 71) and severe anemia (mean = 56, $CI_{95}$ 46 - 67). Similarly, in a German study, pre-treatment anemia patients, as compared to non-anemic patients, were associated with a 25% drop of 5-year survival rate from OSCC [2]. Although, in our study, the difference between survival curves of the aforementioned Hb levels was not statistically significant (log rank 0.158, breslow 0.066, tarone-ware 0.114). But since, "survival time" is described as the measure of time from a starting point (diagnosis) to the point where the event of interest (in this case, death) occurs [29], our findings raise the prospect of the varying effect of pre-treatment Hb on the survival outcome during different time intervals. A consistently low Hb level during different time intervals would have a greater impact on the survival outcome as compared to a brief phase of drop in Hb level at one time interval suggesting that the trajectory of Hb level is more important than its level at a single time interval [28]. It's worth noting that correcting the Hb level has been shown to increase the overall survival in cervical cancer patients [11].

The generalizability of this study's results is evident by the fact that this isn't an in-vitro study, in addition to that, there are no threats to the external and ecological validity (study sample didn't have any constraints in relevance to age, gender, residence, ethnicity or any other parameter and the findings are applicable to the entire population).

Limitations: 1) Extraction of data which was not originally meant for research purpose 2) Data of hospitals from which some of the patients were referred was not accessible 3) No data on tumor markers

Future Work: 1) Prospective cohort study deciphering the prognostic significance of genetic / epigenetic markers, depth of invasion, involvement of margins, neuro-invasion and trajectories of Hb on survival outcome of HPV +ve and HPV -ve OSCC patients.

## CONCLUSION

This study identified parameters; namely age, gender, tumor size, lymph node involvement and pre-treatment haemoglobin level, which played a significant role in modulating the final outcome of OSCC patients. These findings were corroborated by a regression model with death of OSCC patients as the outcome variable. In addition to the aforementioned parameters, survival time of OSCC patients was influenced by treatment complications and recurrence. These prognostic indicators should abet clinicians in screening, categorizing and managing future OSCC patients.

## CONFLICT OF INTEREST

'Declarations of interest: none'

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