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Original Article

Exploring gender-specific prognostic factors and survival outcomes in oral squamous cell carcinoma: Insights from a Taiwanese cohort

Hui-Hsin Ko [a,b,c,d†], Fang-Yu Wu [d,e†], Hsiang-Fong Kao [f,g,h], Wender Lin [i], Ya-Syuan Chen [i*], Shih-Jung Cheng [a,c,d,j**]

[a] Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan
[b] National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan
[c] School of Dentistry, National Taiwan University, Taipei, Taiwan
[d] Department of Dentistry, National Taiwan University Hospital, College of Medicine, Taipei, Taiwan
[e] Department of Dentistry, National Taiwan University Hospital, Jinshan Branch, New Taipei, Taiwan
[f] Institute of Oncology, National Taiwan University, Taipei, Taiwan
[g] Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan
[h] Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan
[i] Department of Health Care Administration, Chang Jung Christian University, Tainan, Taiwan
[j] Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, Taipei, Taiwan

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KEYWORDS
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Prognosis;
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Female;
Woman

Abstract *Background:* /purpose: Oral squamous cell carcinoma (OSCC) is a prevalent malignancy in Taiwan, with sex-specific variations in risk factors, clinical presentation, and prognosis. This study aimed to evaluate the clinicopathological characteristics and survival outcomes of a larger cohort of male and female OSCC patients treated at National Taiwan University Hospital (NTUH) between 2012 and 2022.
Materials and methods: A retrospective review of 240 de-identified, sex- and age-matched OSCC patients was conducted, analyzing clinicopathological characteristics, lifestyle habits (alcohol, betel quid, smoking), and survival outcomes.
Results: Gender differences were observed in tumor location, with males more likely to have buccal mucosa cancer and females more frequently diagnosed with tongue cancer. Survival analysis showed no significant sex differences in overall survival (OS), but oral habits, oral

* Corresponding author. Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, No. 1, Chang-Te Street, Taipei 10048, Taiwan.
** Corresponding author. Department of Health Care Administration, Chang Jung Christian University, No. 1, Chang Jung Road, Gueiren District, Tainan City, 71101, Taiwan.
E-mail addresses: aprilchen@mail.cjcu.edu.tw (Y.-S. Chen), sjcheng56@ntu.edu.tw (S.-J. Cheng).
† These two authors contributed equally to this study.

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ulcer, xerostomia and menopause significantly influenced female prognosis. Multivariate analysis identified age, tumor location, and oral habits as independent factors affecting survival. *Conclusion:* Sex-specific factors, including age, lifestyle, and oral health conditions, contribute to OSCC prognosis. Tailored therapeutic strategies are necessary to address these gender-based disparities and improve survival outcomes for all OSCC patients.

Introduction

Oral squamous cell carcinoma (OSCC) is a major cause of cancer-related morbidity and mortality worldwide,[1] with a significant gender disparity in incidence and prognosis. Traditionally, OSCC has been more common in men due to higher rates of tobacco use, alcohol consumption, and betel quid (BQ) chewing, which are well-established risk factors. However, the increasing incidence of OSCC in women, particularly with tongue cancer, has raised concerns about the distinct biological and clinical behavior of the disease between genders.[2,3] Research into these sex-specific differences is crucial for understanding the underlying mechanisms and improving treatment outcomes.[4]

Oral cancer in Taiwan is strongly influenced by lifestyle factors such as alcohol consumption, betel quid (BQ) chewing, and cigarette smoking, with the combination of these behaviors raising the risk of the disease by as much as 123 times.[5] BQ's active compound, arecoline, and the carcinogenic substances in cigarette, such as nicotine, play a significant role in this elevated risk. In particular, alcohol consumption has been identified as a major contributor to the increased risk of oral cancer in women.[6–9] This increased risk is mainly attributed to women's relatively lower alcohol metabolism rates, which can lead to higher blood alcohol concentrations and, in turn, elevated acetaldehyde levels in oral tissues.[10] The accumulation of acetaldehyde accelerates epithelial atrophy, facilitates the entry of carcinogens into cells, and causes DNA mutations, while simultaneously impairing DNA repair mechanisms.[11] Moreover, gender-specific hormonal differences further exacerbate this effect, making women more vulnerable to the carcinogenic impacts of alcohol.[12–15] As alcohol consumption continues to rise among women in East Asia, this trend is of increasing concern, as it may lead to a significant rise in the incidence of oral cancer among women in the region.

Hormonal shifts during menopause significantly affect women's oral health, leading to atrophic changes in the oral mucosa, making it thinner and more susceptible to infections and oral ulcers.[16] Additionally, stress, particularly when chronic, has been identified as a potential trigger for oral cancer, as it can cause endocrine disturbances and weaken the immune system, creating a more favorable environment for cancer development.[17,18] Furthermore, where diabetes is prevalent among older adults, this condition is also linked to a higher risk of developing oral and oropharyngeal squamous cell carcinoma (OSCC, OPSCC).[19] Beyond these factors, microbial infections, including hyperplastic candidiasis, and human papillomavirus (HPV) are significant contributors to OSCC. These infections can promote carcinogenesis by causing genetic mutations and interfering with tumor suppressor genes, thus exacerbating the risk of cancer.[20–23]

In recent years, the incidence of oral squamous cell carcinoma (OSCC) has been rising among both men and women, though the male-to-female ratio remains notably high. Despite this, women with OSCC often face a poorer prognosis, particularly in cases of tongue cancer, which is more prevalent among females. Our previous study aimed to investigate the sex-specific differences in the prognostic factors and genomic variations in OSCC. Using data from surgical cohort patients treated at National Taiwan University Hospital between 2013 and 2018, the study explored the clinicopathological characteristics, risk factors such as alcohol use, betel quid (BQ) chewing, and smoking habits, and tumor microenvironment (TME) variations.[4] It is critical to understand these sex differences, as they may significantly affect disease progression, treatment response, and overall survival.

This study aimed to evaluate the clinicopathological characteristics and survival outcomes of a larger cohort of male and female OSCC patients treated at National Taiwan University Hospital (NTUH) between 2012 and 2022. We hypothesize that sex-specific factors, including age, tumor location, lifestyle habits, and medical conditions like xerostomia and menopause, significantly influence the prognosis and survival of OSCC patients. By analyzing 240 de-identified, sex- and age-matched patients, we hope to gain insights into the distinct factors that influence OSCC outcomes in men and women, ultimately improving the clinical management of the disease.

Materials and methods

Patients and ethical considerations

We retrospectively reviewed the medical records of oral cancer patients from National Taiwan University Hospital (NTUH). This study was approved by the Research Ethics Committee of NTUH (NTUH-REC No. 202305050RINC). The independent cohort comprised 240 de-identified, sex- and age-matched OSCC patients, drawn from the Integrated Medical Data Center (IMDC) of NTUH between 2012 and 2022.

The analysis encompassed patients who met specific inclusion criteria: a diagnosis of OSCC, surgical resection, and a complete histopathological evaluation. Exclusion was applied to those with distant organ metastasis, as these

individuals faced surgical contraindications and lacked available surgical specimens. Key patient data collected for this study included sex, age at diagnosis, pathological stage, histopathological grade, and lifestyle factors such as alcohol consumption, betel quid chewing, and cigarette smoking. Additionally, the following critical events were tracked: date of tumor recurrence, last follow-up, and survival status. Information regarding diabetes mellitus, menopause, oral ulceration, and xerostomia was also extracted from patient medical records using ICD codes.

Characteristics of patient cohort

Table 1 provides a detailed correlation of clinicopathological parameters for 240 oral squamous cell carcinoma (OSCC) patients, divided by gender. The table includes several factors, such as patient age, cancer location, tumor status (T status), nodal status (N status), clinical staging, histology, and the presence of oral habits like alcohol consumption, betel quid chewing, and cigarette smoking. It also lists other medical conditions like xerostomia, oral ulcers, diabetes mellitus, menopause, and stress. Statistical significance is highlighted by *P*-values for various characteristics. For instance, significant gender differences were observed in cancer location, with more females presenting tumors on the tongue and more males in the buccal mucosa. Alcohol, betel quid, and cigarette smoking habits also showed marked gender differences, with males generally exhibiting higher rates of these behaviors. These correlations serve as a foundation for understanding the potential risk factors and prognosis in OSCC patients (Table 1).

Definition of oral habits

Regular alcohol consumption was characterized by individuals who drank alcoholic beverages more than once a week for a minimum of one year. Those who chewed betel quid (BQ) were considered regular users if they consumed one or more pieces daily for at least a year. Regular cigarette smokers were defined as individuals who smoked 10 or more cigarettes each day for a minimum of one year. The term "alcohol-betel-cigarette" (ABC) was coined to categorize individuals with a history of all alcohol use, BQ chewing, and cigarette smoking.

Statistical analysis

To evaluate differences in clinicopathological characteristics across groups, statistical comparisons were performed using the Student t-test, analysis of variance (ANOVA), or chi-square test. Survival analysis was conducted using the Kaplan—Meier product-limit method, where overall survival (OS) was defined as the duration from cancer diagnosis to death or the last follow-up. Differences in cumulative survival between groups were tested with the log-rank test, and the analysis was carried out using GraphPad Prism 6.0 (GraphPad Software, Boston, MA, USA). A *P*-value of less than 0.05 was considered indicative of statistical significance.

Table 1 Correlation of clinicopathological parameters for 240 OSCCs.

	Male n = 120	Female n = 120	*P*-value
Patient age (years)			
≤55 (n = 64)	32	32	1.000
>55 (n = 176)	88	88	
Cancer location			
Tongue (n = 86)	29	57	**< 0.0001**
Tongue base (n = 2)	0	2	
Floor of mouth (n = 2)	1	1	
Buccal mucosa (n = 72)	56	16	
Gingiva (n = 34)	29	37	
Palate (n = 9)	4	5	
Lip (n = 5)	1	4	
T Status			
T1 (n = 75)	33	42	0.345
T2 (n = 74)	39	34	
T3 (n = 12)	7	5	
T4a (n = 60)	28	32	
T4b (n = 10)	8	2	
Unknown (n = 10)	5	5	
N status			
N0 (n = 175)	93	82	0.874
N1 (n = 13)	7	6	
N2 (n = 30)	13	17	
N3 (n = 9)	4	5	
Unknown (n = 13)	7	6	
Clinical staging			
Stage 1 (n = 84)	42	42	0.999
Stage 2 (n = 39)	19	20	
Stage 3 (n = 17)	8	9	
Stage 4a (n = 80)	40	40	
Stage 4b (n = 10)	5	5	
Unknown (n = 10)	5	5	
Loco-regional recurrence			
Without (n = 158)	80	78	0.831
With (n = 79)	39	40	
Unknown (n = 3)	1	2	
Histology of OSCC			
Well-differentiated (n = 95)	48	47	0.318
Moderately differentiated (n = 88)	48	40	
Poorly differentiated (n = 14)	4	10	
Unknown (n = 43)	20	23	
Oral habits alcohol consumption			
Without (n = 215)	49	106	**< 0.0001**
With (n = 85)	71	14	
Betel quid chewing			
Without (n = 129)	23	106	**< 0.0001**
With (n = 111)	97	14	
Cigarette smoking			
Without (n = 121)	20	101	**< 0.0001**
With (n = 119)	100	19	
Xerostomia			
Without (n = 225)	117	108	**0.016**
With (n = 15)	3	12	
Oral ulcer			

Table 1 (*continued*)

	Male n = 120	Female n = 120	*P*-value
Without (n = 219)	110	109	0.819
With (n = 21)	10	11	
DM			
Without (n = 216)	107	109	0.667
With (n = 24)	13	11	
Menopause			
Without (n = 24)		24	
With (n = 90)		90	
Unknown (n = 6)		6	
Stress			
Without (n = 223)	111	112	0.801
With (n = 17)	9	8	

DM: *Diabetes* mellitus.

Results

Patients' characteristics

In the NTUH database cohort, 240 patients were enrolled between 2012 and 2022, with a median follow-up of 28 months. Similar to our previous report,[4] no significant differences were observed between men and women for age, tumor size, regional lymph node metastasis, TNM staging, or histopathological differentiation. The most common primary tumor site in males was also the buccal mucosa (56/120, 46.7 %), whereas that in females was the tongue (57/120, 47.5 %). Xerostomia was more prevalent in females ($P = 0.016$). In this cohort, males and females also differed significantly in alcohol consumption, BQ chewing, and smoking habits ($P < 0.0001$). These findings underscore the importance of sex-specific analyses and consideration of oral habits in the treatment and prognosis of oral cancer (Table 1).

Survival analysis

Subgroup survival analysis

We compared survival outcomes between females and males. We selected 240 patients from the NTUH database cohort for analysis including 120 males and 120 females.

Sex and age

Of 240 oral cancer patients who underwent extensive tumor resection and subsequent treatment, 58 % of the males survived and 50 % of the female patients survived.

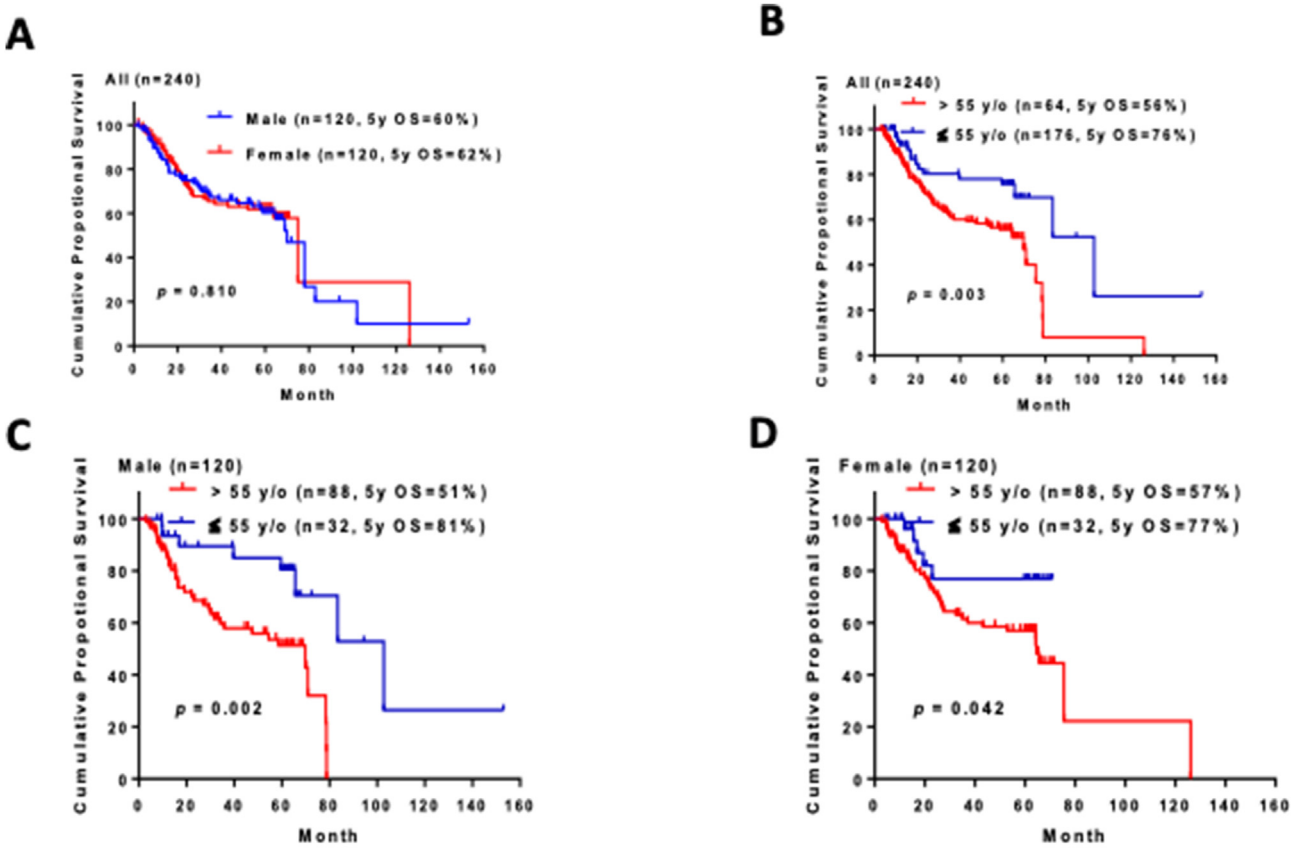

Figure 1 Five-year overall survival analysis of oral cancer patients based on sex and age.
(A) The 5-year overall survival (OS) rate for males was 60 %, whereas that for females was 62 %, with no significant difference between sexes ($P = 0.810$) (left graph). (B) However, comparing 5-year OS rates based on age, patients older than 55 years had a lower 5-year OS rate compared to those aged 55 years or younger (56 % vs. 76 %, $P = 0.003$) (right graph). (C, D) Both sexes aged >55 years had significantly lower 5-year OS rates compared to their younger counterparts aged ≤55 years ($P = 0.002$; $P = 0.042$).

Kaplan—Meier survival curves showed no significant difference in the 5-year OS rates between sexes (60 % for males vs. 62 % for females, $P = 0.810$, Fig. 1A). However, patients older than 55 had lower 5-year OS rates compared to those aged 55 or younger (56 % vs. 76 %, $P = 0.003$, Fig. 1B). Males and females older than 55 exhibited significantly lower 5-year OS rates compared to those aged 55 or younger ($P = 0.002$ for males; $P = 0.042$ for females, Fig. 1C and D).

Oral habits

Five-year OS rates revealed no significant difference between females without alcohol, BQ, or cigarette habits and males (60 % vs. 80 %, $P = 0.454$, Fig. 2A). Similarly, females with any of these habits showed no significant difference in survival compared to males (50 % vs. 60 %, $P = 0.407$, Fig. 2B). However, females with one or more of these habits had significantly lower 5-year OS rates compared to females without such habits (50 % vs. 80 %, $P = 0.029$, Fig. 2C). Furthermore, female oral cancer patients who consumed alcohol had significantly lower 5-year OS rates compared to those who did not (50 % vs. 64 %, $P = 0.045$, Fig. 3A) and compared to females with no habits at all (50 % vs. 80 %, $P = 0.029$, Fig. 3B).

Female tongue cancer and oral habits

Among female tongue cancer patients without oral habits, survival was significantly shorter compared to males (51 % vs. 60 %, $P = 0.041$, Fig. 4A), and compared to all females without any habits (44 % vs. 20 %, $P = 0.005$, Fig. 4B).

Oral ulcer and xerostomia

This study also assessed the effect of environmental factors (e.g., oral ulcers, xerostomia (dry mouth)) on the survival of oral cancer patients. In males, 5-year OS did not differ significantly for those with and without oral ulcers (65 % vs.

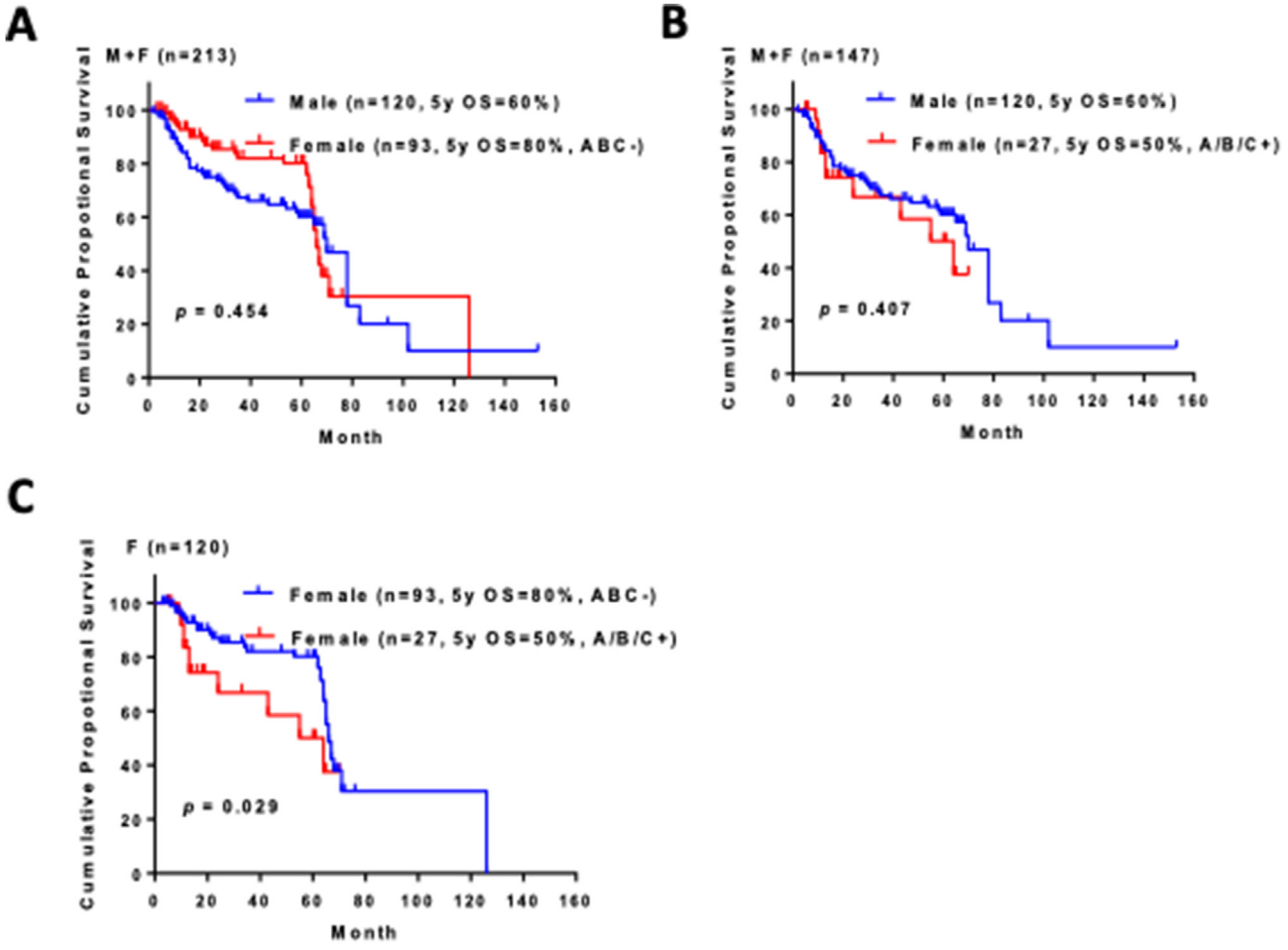

Figure 2 Five-year OS analysis of female oral cancer patients with and without cigarette, alcohol, and betel quid habits compared to all male patients.
(A) Comparison of 5-year OS rates between ABC- females and all male patients revealed no significant difference ($P = 0.454$) (upper left panel). (B) Comparing females with alcohol, betel quid, or cigarette habits (A/B/C+) to all male patients revealed no significant difference in 5-year OS rates ($P = 0.407$) (upper right panel). (C) However, comparing females with any alcohol, betel quid, or cigarette habits (A/B/C+) to those without these habits (ABC-) revealed significantly shorter 5-year OS rates in the former group ($P = 0.029$) (lower left panel) (*A/B/C+: with one or more oral habits; *ABC-: without any one of oral habits).

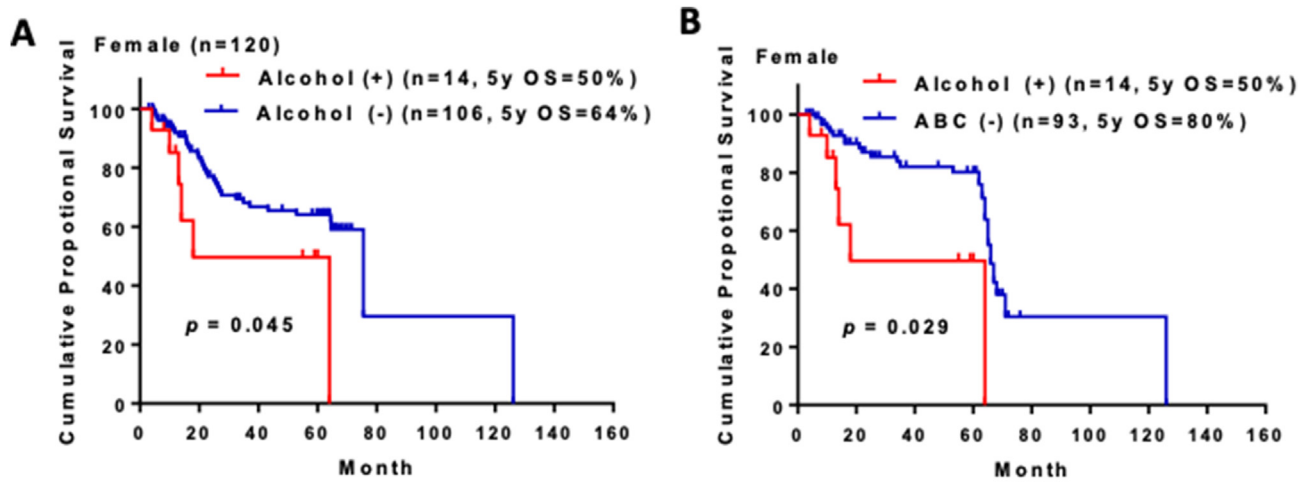

Figure 3 Five-year OS analysis of female oral cancer patients with and without alcohol consumption habits.
(A) Female oral cancer patients who consumed alcohol had significantly lower 5-year OS rates compared to those without alcohol consumption habits (50 % vs. 64 %, $P = 0.045$, left panel). (B) and compared to females without alcohol-betel-cigarette habits (ABC-) (50 % vs. 80 %, $P = 0.029$, right panel (*ABC-: without any one of oral habits).

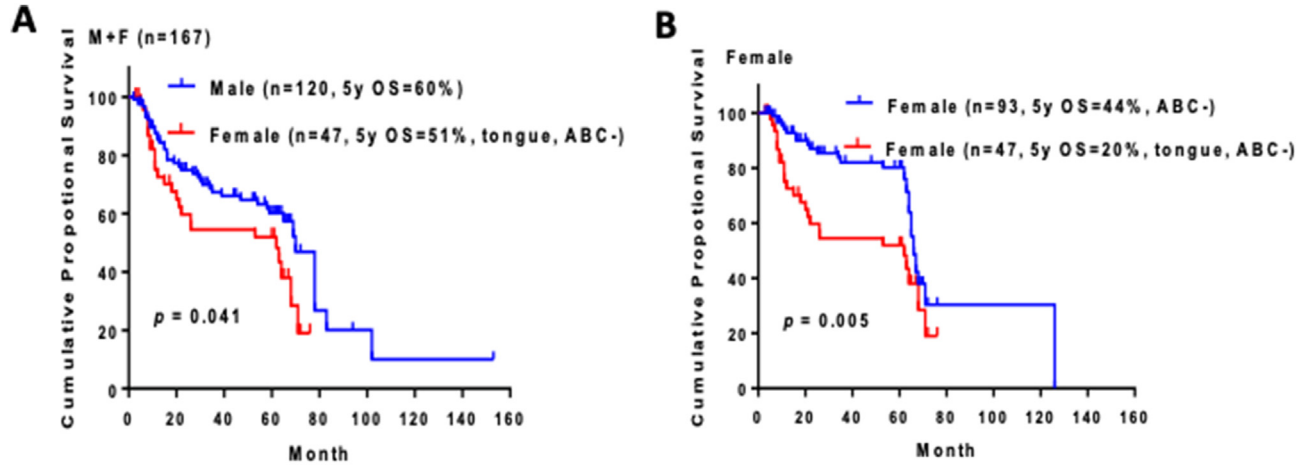

Figure 4 Five-year OS analysis of female tongue cancer patients without alcohol, betel quid, or cigarette habits.
(A) Female tongue cancer patients without oral habits had significantly shorter OS times compared to males (51 % vs. 60 %, $P = 0.041$). (B) For female tongue cancer patients without oral habits, the 5-year OS rate was significantly lower than all female cancers without oral habits (44 % vs. 20 %, $P = 0.005$) (*ABC-: without any one of oral habits)).

60 %, $P = 0.715$, Fig. 5A). However, in females, those with oral ulcers had significantly lower 5-year OS rates than those without (45 % vs. 63 %, $P = 0.022$, Fig. 5B).

For xerostomia, 5-year OS did not differ significantly in males and females, although a trend was observed toward shorter survival in females with xerostomia (47 % vs. 63 %, $P = 0.087$, Fig. 6A and B).

Menopause and diabetes

Postmenopausal women, categorized as those older than 55, based on medical records, had significantly lower 5-year OS rates compared to premenopausal women younger than 50 (60 % vs. 78 %, $P = 0.047$, Fig. 7). However, 5-year OS rates did not differ significantly for patients with and without diabetes (71 % vs. 60 %, $P = 0.449$, Fig. 8A). Among males, the difference in survival rates was similarly nonsignificant (49 % vs. 61 %, $P = 0.571$, Fig. 8B). In females, however, a trend was observed toward shorter survival in those with diabetes (45 % vs. 62 %, $P = 0.058$, Fig. 8C). Hence, both menopause and diabetes may strongly affect prognosis in women.

Risk factor analysis

Multivariate analyses using Cox proportional hazard regression in the NTUH database cohort of females, age >55, tongue cancer, alcohol consumption, xerostomia, and oral ulcers were identified as independent factors affecting OS ($P < 0.05$, Table 2). By contrast, in the NTUH database cohort of males, age >55, buccal cancer, BQ chewing, cigarette smoking, and all ABC habits were identified as independent factors affecting OS ($P < 0.05$, Table 3).

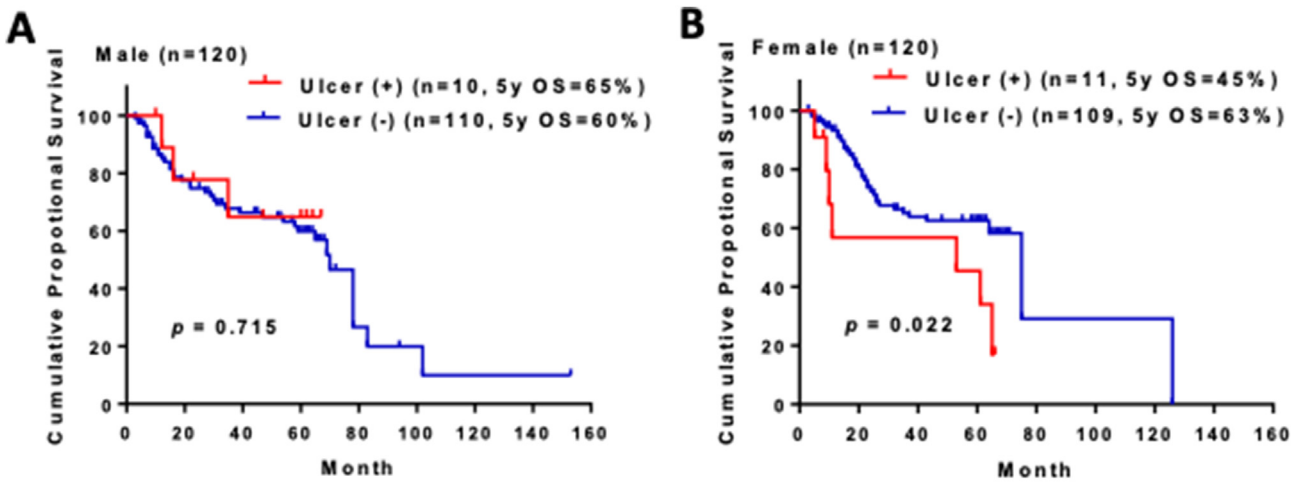

Figure 5 Five-year OS analysis of male and female oral cancer patients with and without oral ulcers
(A) Comparison of 5-year OS rates for male oral cancer patients with and without oral ulcers revealed no significant difference (65 % vs. 60 %, $P = 0.715$) (left panel) (B) For female oral cancer patients, those with oral ulcers had significantly lower 5-year OS rates compared to those without oral ulcers (45 % vs. 63 %, $P = 0.022$) (right panel).

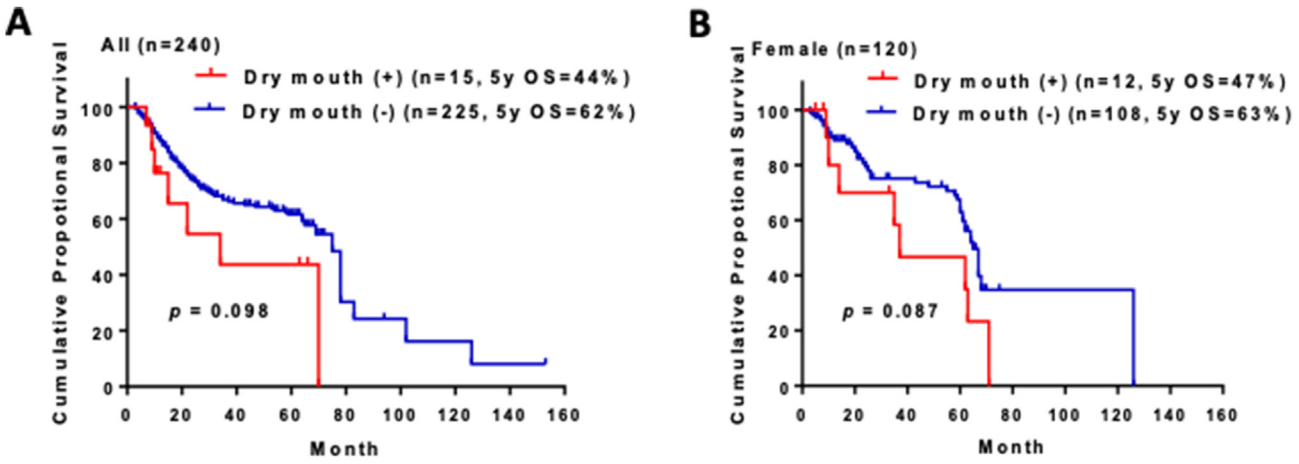

Figure 6 Five-year OS analysis of oral cancer patients with and without xerostomia symptoms.
(A) Comparison of 5-year OS rates for oral cancer patients with and without xerostomia symptoms revealed no significant difference (44 % vs. 62 %, $P = 0.098$) (left panel). (B) For female oral cancer patients, the difference in 5-year OS rates between those with and without xerostomia symptoms was nonsignificant, but a trend was observed toward shorter OS for those with xerostomia symptoms (47 % vs. 63 %, $P = 0.087$) (right panel).

Discussion

The independent cohort for this study included 240 sex- and age-matched OSCC patients, de-identified and sourced from the Integrated Medical Data Center (IMDC) of National Taiwan University Hospital (NTUH) between 2012 and 2022. The IMDC consolidates a wide range of patient data from over 600,000 individuals and approximately 3 million visits annually across multiple affiliated hospitals. The database integrates electronic health records (EHR) covering diagnoses, prescriptions, laboratory results, imaging studies, and clinical exams, all anonymized and stored in a central research database. This facilitates advanced medical research and the use of artificial intelligence to enhance patient care. The NTUH-iMD system ensures data quality through regular validation checks, addressing discrepancies from data transmission and coding errors. It allows real-time access to integrated data with minimal delays, promoting efficient research and hypothesis testing. Through strict data governance, the IMDC supports predictive model development and aids clinical decision-making, ultimately improving healthcare delivery.[24,25]

This study examined the differences in epidemiological trends, clinical features, and survival outcomes between Taiwanese women and men with oral cancer. It found that women were more likely to develop cancer on the tongue, while men had a higher incidence in the buccal mucosa. The findings are consistent with other reports.[2,3,26] Key prognostic factors for women included being over 55 years of age, having tongue cancer, alcohol use, oral ulcers,

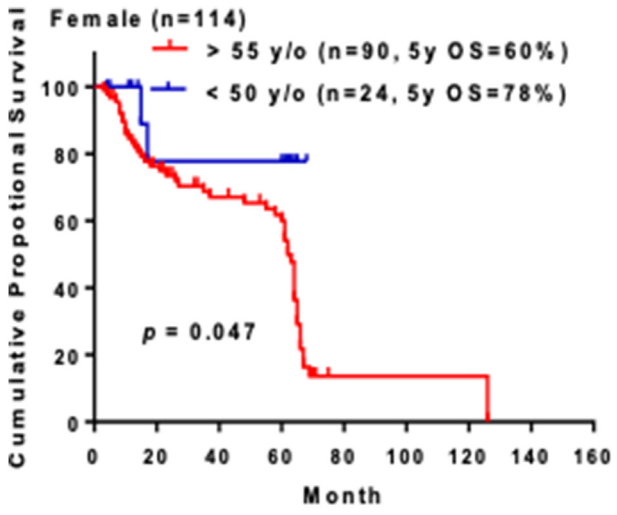

Figure 7 Five-year OS analysis of female oral cancer patients with and without menopause.
Postmenopausal women aged >55 years had significantly lower 5-year OS rates compared to premenopausal women aged <50 years (60 % vs. 78 %, $P = 0.047$).

xerostomia, and menopause. In contrast, for men, significant factors included being over 55, buccal cancer, betel quid (BQ) chewing, smoking, and the combined use of alcohol, BQ, and cigarettes (ABC habits). Although diabetes mellitus showed a marginal influence on five-year overall survival in women, it may emerge as a significant prognostic factor. These findings highlight important gender-based differences in age, cancer sites, oral risk factors, oral health conditions, and associated comorbidities, suggesting the need for tailored approaches in diagnosis and treatment.

Our study confirms that male and female OSCC patients exhibit notable differences in clinicopathological characteristics, with men showing higher rates of alcohol consumption, BQ chewing, and cigarette smoking. These habits have long been identified as major risk factors for OSCC, with their combined use increasing the cancer risk by up to 123-fold.[5] However, despite these behavioral differences, women with OSCC often experience poorer prognoses, particularly in cases of tongue cancer. This finding is consistent with the recent report. The study examines how gender and risk-taking behaviors impact the clinical presentation of oral squamous cell carcinoma (OSCC). It found

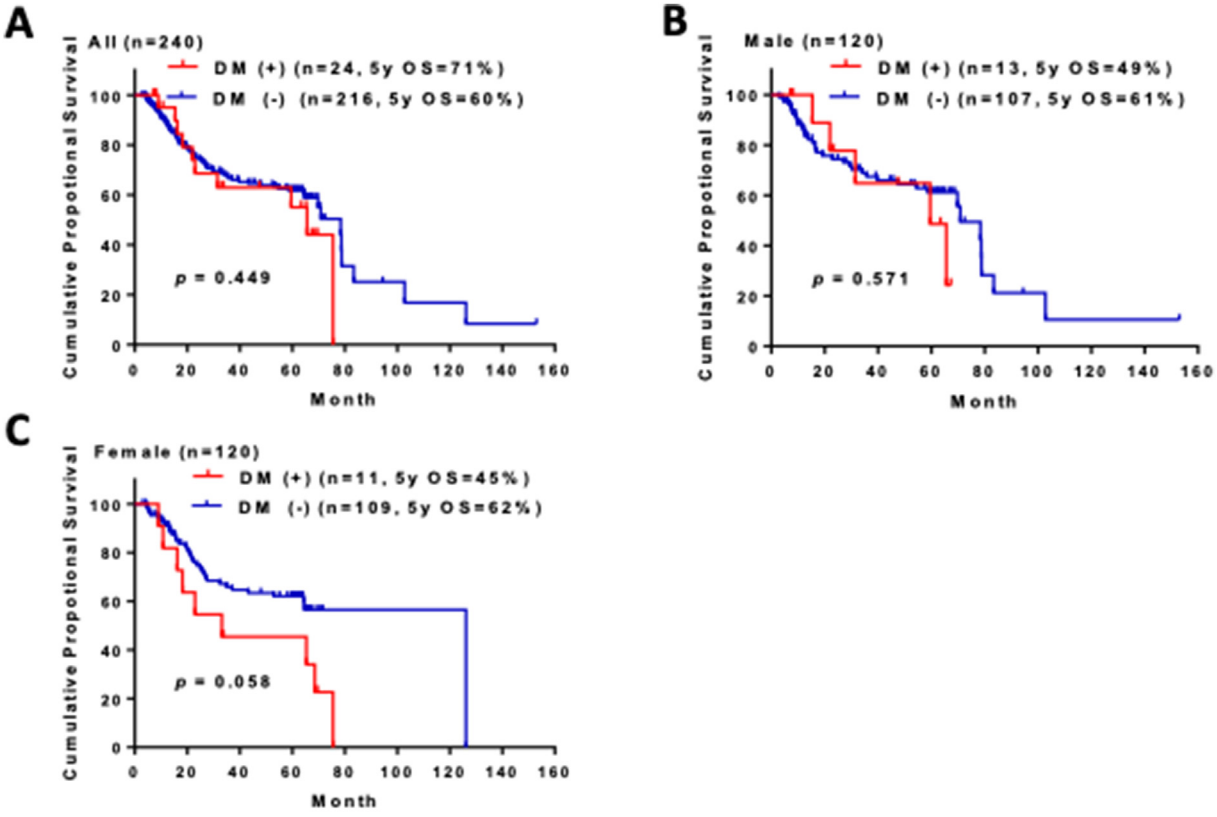

Figure 8 Five-year OS analysis of oral cancer patients with and without diabetes.
(A) Comparison of 5-year OS rates for oral cancer patients with and without diabetes revealed no significant difference (71 % vs. 60 %, $P = 0.449$). (B) Similarly, a comparison of male oral cancer patients with and without diabetes also revealed no significant difference (49 % vs. 61 %, $P = 0.571$). (C) For female oral cancer patients with and without diabetes symptoms, the difference in 5-year OS rates was not statistically significant, but a trend was observed toward shorter OS for those with diabetes (45 % vs. 62 %, $P = 0.058$).

Table 2 Univariate and multivariate survival analyses of clinicopathological parameters of 120 women with OSCCs by Cox proportional hazards regression model.

Factors	Hazard ratio (95 % CI)	*P* -value
Univariate		
Age (<55 vs.≥55)	3.908 (1.557—5.482)	**0.029**
Cancer location (non-tongue vs. tongue)	1.632 (1.045—2.548)	**0.031**
T status (T1, T2 vs. T3, T4)	1.411 (0.860—2.314)	0.173
N Status (N0 vs. N1-3)	0.855 (0.526—1.390)	0.528
Clinical staging (stage I, II vs. stage III, IV)	1.131 (0.725—1.770)	0.578
Alcohol consumption (without vs. with)	2.270 (1.145—4.499)	**0.019**
Betel quid chewing (without vs. with)	1.366 (0.649—2.878)	0.411
Cigarette smoking (without vs. with)	1.361 (0.715—2.000)	0.348
[a]Alcohol-betel-cigarette (without vs. with)	0.626 (0.362—1.084)	0.095
Xerostomia (without vs. with)	12.785 (2.886—56.644)	**0.001**
Oral ulcer (without vs. with)	1.716 (1.287—3.786)	**0.035**
DM (without vs. with)	0.711 (0.362—1.399)	0.324
Menopause (without vs. with)	0.951 (0.579—1.561)	0.843
Multivariate		
Age (<55 vs.≥55)	2.257 (1.033—3.011)	**0.032**
Cancer location (non-tongue vs. tongue)	1.484 (1.176—2.513)	**0.042**
T status (T1, T2 vs. T3, T4)	1.177 (0.665—2.082)	0.576
N Status (N0 vs. N1-3)	0.966 (0.530—1.759)	0.910
Clinical staging (stage I, II vs. stage III, IV)	1.022 (0.574—1.823)	0.940
Alcohol consumption (without vs. with)	2.639 (0.904—7.704)	**0.046**
Betel quid chewing (without vs. with)	0.969 (0.344—2.731)	0.953
Cigarette smoking (without vs. with)	0.832 (0.358—1.933)	0.670
[a]Alcohol-betel-cigarette (without vs. with)	0.743 (0.158—3.480)	0.706
Xerostomia (without vs. with)	9.922 (2.089—47.133)	**0.004**
Oral ulcer (without vs. with)	1.648 (1.247—2.701)	**0.041**
DM (without vs. with)	0.848 (0.412—1.744)	0.654
Menopause (without vs. with)	3.263 (0.408—26.119)	0.265

Without: no history of consuming alcohol, chewing betel quid, or smoking cigarettes.
DM: *Diabetes* mellitus.
[a] With: a history of consuming alcohol, chewing betel quid, and smoking cigarettes together.

that men are more likely to engage in smoking and alcohol use, while women often exhibit minimal risk behaviors. Gender differences in tumor location, staging, and prognosis were observed, particularly with women more prone to tongue cancer. Further research is needed to understand the additional factors influencing OSCC development in women.[26]

Notably, women with a history of alcohol consumption exhibited significantly lower five-year overall survival (OS) rates compared to their non-drinking counterparts. This finding supports previous research highlighting the increased vulnerability of women to the carcinogenic effects of alcohol.[6,8] This heightened risk in women may be linked to lower alcohol metabolism rates and hormonal factors that increase acetaldehyde concentrations in oral tissues, leading to greater epithelial damage and impaired DNA repair mechanisms.[10,11]

Additionally, our findings reveal that oral health conditions, such as xerostomia and oral ulcers, play a more prominent role in female OSCC prognosis. Women with xerostomia exhibited a trend toward shorter survival times, and those with oral ulcers had significantly lower survival rates compared to men and women without these conditions. These results are consistent with previous studies suggesting that chronic dry mouth and oral ulcers can exacerbate the risk of OSCC by increasing mucosal vulnerability to carcinogens and impairing immune function.[16,17] Interestingly, menopause also emerged as an independent factor affecting the survival of female OSCC patients, with postmenopausal women showing significantly lower OS rates than their premenopausal counterparts. This finding aligns with other research suggesting that hormonal changes during menopause may lead to atrophic changes in the oral mucosa, further complicating oral cancer progression.[16]

Another issue was associated with sugar consumption. The study found a significant association between high sugar-sweetened beverage (SSB) intake and an increased risk of oral cavity cancer (OCC) in women, regardless of smoking or drinking habits. Women consuming 1 or more SSBs daily had a 4.87 times higher risk of OCC compared to those consuming fewer than 1 SSB monthly. The risk was even higher for nonsmokers and light smokers, suggesting the need for further research on dietary impacts,[27] particularly in diabetic prevalent patients among older adults.[19]

Our study also highlights the growing concern of OSCC in female patients, particularly those with tongue cancer. In

Table 3 Univariate and multivariate survival analyses among clinicopathological parameters of 120 men with OSCCs by Cox proportional hazard regression model.

Factors	Hazard ratio (95 % CI)	*P* -value
Univariate		
Age (<55 vs.≥55)	3.809 (1.571–9.233)	**0.003**
Cancer location (non-tongue vs. tongue)	1.448 (0.736–2.852)	0.284
Cancer location (non-buccal vs. buccal)	2.704 (1.377–2.313)	**0.037**
T status (T1, T2 vs. T3, T4)	0.583 (0.322–1.055)	0.075
N Status (N0 vs. N1-3)	0.660 (0.361–1.206)	0.177
Clinical staging (stage I, II vs. stage III, IV)	0.506 (0.268–0.957)	0.036
Alcohol drinking (without vs. with)	1.683 (0.096–3.486)	0.052
Betel quid chewing (without vs. with)	2.473 (2.681–3.186)	**0.026**
Cigarette smoking (without vs. with)	1.901 (1.443–2.836)	**0.035**
*Alcohol-betel-cigarette (without vs. with)	2.697 (2.245–3.984)	**0.028**
Xerostomia (without vs. with)	0.049 (0.01–0.0001)	0.831
Oral ulcer (without vs. with)	0.927 (0.402–2.136)	0.859
DM (without vs. with)	1.315 (0.512–3.376)	0.570
Multivariate		
Age (<55 vs.≥55)	4.215 (1.600–11.105)	**0.004**
Cancer location (non-tongue vs. tongue)	1.475 (0.625–3.479)	0.375
Cancer location (non-buccal vs. buccal)	2.002 (1.439–2.288)	**0.039**
T status (T1, T2 vs. T3, T4)	1.019 (0.430–2.413)	0.966
N Status (N0 vs. N1-3)	0.719 (0.368–1.404)	0.334
Clinical staging (stage I, II vs. stage III, IV)	0.482 (0.177–1.309)	0.152
Alcohol drinking (without vs. with)	1.998 (0.200–19.961)	0.056
Betel quid chewing (without vs. with)	2.172 (1.298–4.601)	**0.037**
Cigarette smoking (without vs. with)	2.784 (1.077–7.945)	**0.039**
[a]Alcohol-betel-cigarette (without vs. with)	3.842 (1.031–22.745)	**0.029**
Xerostomia (without vs. with)	0.001 (0.0001–0.01).	0.986
Oral ulcer (without vs. with)	1.948 (0.653–5.807)	0.232
DM (without vs. with)	1.513 (0.556–4.116)	0.418

Without: no history of consuming alcohol, chewing betel quid, or smoking cigarettes.
DM: *Diabetes* mellitus.
[a] With: a history of consuming alcohol, chewing betel quid, and smoking cigarettes together.

this cohort, female tongue cancer patients without alcohol, betel quid, or cigarette habits had significantly poorer survival rates than their male counterparts, suggesting that other unknown biological or environmental factors may contribute to the increased vulnerability of women to tongue cancer. A reasonable hypothesis is that the breakdown of the body's defense mechanisms has a greater impact than the local oral irritants from smoking, alcohol, and betel nut consumption in men, leading to the lowest five-year survival rate in female tongue cancer patients, even though they do not have the habits of smoking, drinking, or chewing betel quid. These findings warrant further investigation into the molecular mechanisms underpinning these gender disparities, particularly focusing on the tumor microenvironment (TME) and genomic variations, which may differ between sexes and influence disease progression and treatment response.[4]

One limitation of this study is its retrospective design, which relies on existing patient records, potentially introducing biases due to incomplete or inconsistent data. While the IMDC of NTUH offers a large and diverse patient cohort, the data is limited to those who sought treatment at this specific medical system, which may not fully represent the broader Taiwanese population or individuals with less severe cases. Additionally, the study's observational nature restricts the ability to draw causal inferences between risk factors and survival outcomes. Furthermore, the potential influence of unmeasured confounders, such as genetic factors or environmental exposures not captured in the database, could have impacted the findings. Future prospective studies with more comprehensive data collection and molecular analyses are needed to validate these results and further explore the underlying mechanisms of sex-specific differences in OSCC prognosis.

In conclusion, the sex-specific differences observed in this cohort emphasize the need for personalized treatment strategies for OSCC. Understanding the distinct risk factors and biological mechanisms in male and female patients is crucial for improving prognostic models, enhancing treatment efficacy, and ultimately increasing survival rates for all OSCC patients. Future studies should further explore the influence of hormonal factors, lifestyle habits, and TME variations on OSCC prognosis, with a focus on developing gender-specific therapeutic approaches to address these disparities.

Declaration of competing interest

There are no conflicts of interest to declare.

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