

Prognosis Impact of Betel Nut on Oral Squamous Cell Carcinoma: A Population-Based Study

Tianyi Zhang ¹⁻³, Xin Hu ¹⁻³, LiuJun Zeng ¹⁻³, Shiyong Huang ^{4,*}, Tong Su ^{1-3,*}

¹Department of Oral and Maxillofacial Surgery, Center of Stomatology, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, People's Republic of China; ²Research Center of Oral and Maxillofacial Tumor, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, People's Republic of China; ³National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Changsha, Hunan, 410008, People's Republic of China; ⁴Xiangya Stomatological Hospital, Central South University, Changsha, Hunan, 410008, People's Republic of China

*These authors contributed equally to this work

Correspondence: Tong Su, Department of Oral and Maxillofacial Surgery, Center of Stomatology, Xiangya Hospital, Central South University, No. 87 Xiangya Road, Changsha, Hunan, 410008, People's Republic of China, Email sutong@csu.edu.cn; Shiyong Huang, Xiangya Stomatological Hospital, Central South University, No. 72 Xiangya Road, Changsha, Hunan, 410008, People's Republic of China, Email sisibyme@qq.com

Purpose: The prognostic impact of betel nut on oral squamous cell carcinoma (OSCC) remains controversial. This study aimed to determine whether betel nut chewing is an independent prognostic factor in patients treated with standardized surgery.

Methods: This retrospective population-based cohort study enrolled 1113 patients with primary OSCC, including 922 betel nut chewers and 191 non-chewers. All patients underwent standardized surgical treatment. The prognostic impact of betel nut chewing was evaluated by returning to all patients and comparing the disease-free survival times between the two groups. The Chi-square test was used to explore the clinical characteristics associated with betel nut chewing. Kaplan-Meier survival analysis, univariable Cox regression, and multivariable Cox regression analyses were used to investigate the prognostic impact of betel nut.

Results: No significant difference was observed in the disease-free survival time between chewers and non-chewers in either the overall group or subgroup analyses. Univariable Cox regression analysis indicated that betel nut use was not a prognostic factor. After adjusting for potential confounders, multivariable Cox regression confirmed that cervical lymph node metastasis, clinical stage, and pathological grade were independent risk factors for prognosis, whereas betel nut use had no significant impact on prognosis.

Conclusion: These findings suggest that the prognosis of OSCC is dictated by the biological stage of the tumor rather than betel nut use. This allows clinicians to develop more objective, precise treatment plans for OSCC patients.

Plain Language Summary: Betel nut chewing is a major cause of oral cancer; however, its prognostic impact of betel nut on oral cancer remains unclear. This study aimed to verify whether betel nut chewing is an independent prognostic factor in patients undergoing standardized surgery.

Our study included 1113 patients diagnosed with oral cancer between 2018 and 2022. All patients received standard surgical treatment and regular follow-up visits. We then compared the disease-free survival times of those who chewed betel nut with those who did not.

We found that betel nut has no impact on prognosis of oral cancer. Instead, the most important prognostic factors remain cervical lymph node metastasis, clinical stage, and pathological grade.

These results suggest a “dual role” of betel nut: it is a dangerous trigger of oral cancer, but it has no impact on the prognosis of oral cancer. Rather than focusing on a history of betel nut use, clinicians should pay more attention to the specific stage of the tumor to create more objective and precise treatment plans.

Keywords: oral squamous cell carcinoma, betel nut, prognosis



Introduction

In many regions across South and Southeast Asia, betel nut use has overtaken other risk factors to become the predominant cause of oral squamous cell carcinoma (OSCC).^{1–3} As the leading consumer of betel nut, India has reported the highest incidence of OSCC in the world.⁴ Similarly, betel nut chewing in Hunan, China, has resulted in a significant rise in OSCC cases.^{5,6}

The carcinogenic role of betel nut in oral cancer has been fully confirmed,⁷ but its impact on tumor progression remains unclear and controversial. Recently, several studies have reported that betel nut plays a negative role in OSCC prognosis, increasing the risk of local recurrence.^{8–12} However, this recurrence may originate from the second primary cancer caused by betel nut chewing. Moreover, a study from India suggests that betel nut is beneficial for OSCC prognosis.¹³ This prognostic uncertainty indicates that betel nut may possess a “dual role”: it is a pathogenic factor of OSCC rather than a prognostic factor. Importantly, previous studies were often limited by small sample sizes and heterogeneous cohorts. This heterogeneity arose because patients were frequently recruited from multiple regions or hospitals, received varying treatment regimens, and were subjected to inconsistent follow-up quality. These factors may have caused inconsistencies in previous research findings and diminished their reliability. Therefore, a study with standardized and uniform follow-up is essential to clarify the relationship between betel nut use and OSCC prognosis.

This study aimed to provide a more precise and reliable assessment of the association between betel nut chewing and OSCC prognosis by examining a homogeneous patient cohort with standardized follow-up and to provide a reference for clinical practice. This will help comprehensively evaluate the role of betel nut throughout the entire disease course, from carcinogenesis to prognosis, and provide more targeted treatment strategies and prognostic management plans for patients with OSCC.

Materials and Methods

Study Design and Ethical Approval

This was a retrospective, population-based cohort study. All patients were divided into two groups based on their betel nut chewing history: the chewing group (n = 922) and the none chewing group (n = 191). We investigated the prognostic impact of betel nut chewing on OSCC by comparing the survival outcomes between the two groups.

This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was independently reviewed and approved by the Ethics Committee of Xiangya Hospital, Central South University (NO. 202212302). As this was a retrospective observational study, the requirement for informed consent was waived by the Ethics Committee of Xiangya Hospital, Central South University. All patient data were anonymized and de-identified prior to analysis to protect patient privacy and confidentiality.

Patients

We extracted 1169 OSCC patients from 2018 to 2022, and 56 (5%) patients were excluded due to loss to follow up. All patients received standardized surgical treatment, including enlarged excision of the primary tumor combined with modified radical neck dissection or selective lymph node dissection. For patients with T1 stage disease and no evidence of lymph node metastases on preoperative imaging, an enlarged excision alone was performed. The decision regarding adjuvant therapy was based on individual postoperative pathological findings. The inclusion criteria were as follows: (a) All patients were first diagnosed with OSCC. (b) All patients had the pathological diagnosis to confirm the diagnosis was correct. (c) The age and gender of patients were unlimited. (d) All patients had no other malignant tumor disease. Patients with other malignant tumors, those who did not undergo standard treatment, and those for whom survival information was unavailable were excluded. We categorized OSCC patients based on their clinical staging and histological grading, adhering to the standards outlined in the 8th edition of the Union for International Cancer Control (UICC) guidelines.

Return Visit and Outcomes

All patients were followed up through multiple channels, including telephone consultations and outpatient visits. Recurrence status was strictly determined by CT, MRI, or pathological verification. The composite endpoint comprised

local recurrence, neck metastases, and distant metastasis. The disease-free survival time was quantified in months, spanning from the cessation of treatment to the timing of the specified outcome events.

Statistical Analysis

Chi-square tests were used to analyze the relationship between categorical variables and betel nut chewing. Survival analysis was performed using the survival package in R software (version 4.2.2). Survival curves were estimated by the Kaplan-Meier method and compared using the Log rank test. The results were visualized using the survminer package. Next, univariable and multivariable Cox proportional hazards regression analyses were performed using the coxph function in the survival package. Variables with $P < 0.05$ in the univariable analysis were included in the multivariable Cox regression model. Finally, we tested the proportional hazards assumption based on Schoenfeld residuals and confirmed the Cox model's validity. $P < 0.05$ was considered to indicate significant differences.

Results

Patients' Clinic Characteristics

Of the 1113 OSCC patients, 922 had experience of chewing betel nut, 957 had the experience of tobacco use, and 796 had the experience of alcohol use. The proportion of male, tobacco use, and alcohol use in the chewing betel nut group was significantly higher than the none chewing betel nut group. The tongue was the most common site of tumor occurrence in both groups, followed by the buccal mucosa. Interestingly, the proportion of buccal mucosa cancer was significantly higher in the betel nut chewing group. Moreover, the OSCC relapse rate of patients in the two groups was not different, and the proportion of age, T stage, cervical lymph node metastasis, clinical grade, and pathologic differentiation was also not different (Table 1).

Table 1 Clinical Characteristics of Oral Cancer Patient in This Study

Group		Number (%)		
		Chewing Betel Nut, n = 922(83)	None Chewing Betel Nut, n = 191(17)	P-value
Gender	Male	884(96)	142(74)	<0.001
	Female	38(4)	49(26)	
Age	Age ≤ 60	773(84)	159(83)	0.830
	Age > 60	149(16)	32(17)	
Tobacco Use	Ever	843(91)	114(60)	<0.001
	Never	79(9)	77(40)	
Alcohol Use	Ever	711(77)	85(45)	<0.001
	Never	211(23)	106(55)	
Relapse	Yes	346(38)	68(36)	0.680
	No	576(62)	123(64)	
Location	Tongue	526(57)	127(66)	<0.001
	Buccal	313(34)	34(18)	
	Gingiva	68(7)	19(10)	
T stage	Mouth floor	15(2)	11(6)	0.705
	T1+T2	339(37)	73(38)	
	T3+T4	583(63)	118(62)	
Cervical lymph node metastasis	Yes	594(66)	113(61)	0.203
	No	303(34)	72(39)	
Clinical stage	I+II	648(70)	135(59)	0.926
	III+IV	464(30)	98(41)	
Pathological grade	Well	594(64)	117(61)	0.320
	Moderate	299(32)	64(34)	
	Poor	29(4)	10(5)	

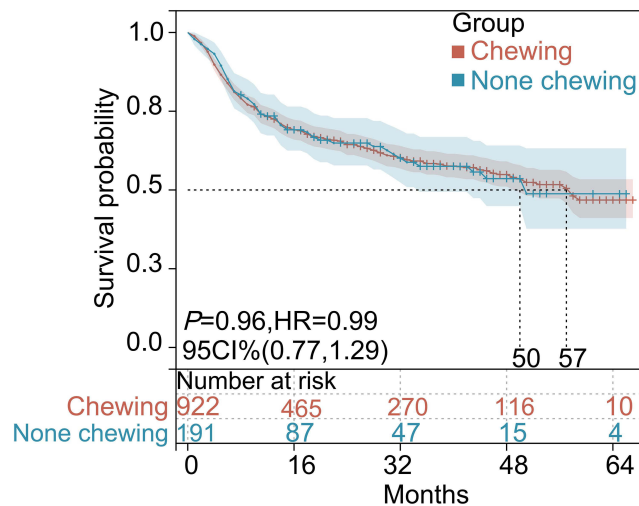


Figure 1 Overall Kaplan-Meier survival curve. There is no significant difference in survival curve between processed betel nut and none chewing processed betel nut groups.

Kaplan-Meier Survival Analysis

To further investigate the impact of betel nut on the prognosis of OSCC patients, we used the Kaplan-Meier survival analysis to compare the 5-year disease-free survival times of the two groups (Figure 1). The median time of return visit was 57 months for the betel nut chewer and 50 months for none betel nut chewer; the average survival time was 50 months for the betel nut chewer and 51 months for none betel nut chewer. Finally, we found that there was no significant difference in prognosis between the two groups (HR = 0.99, 95% CI [0.77–1.29], $P = 0.96$).

To determine whether betel nut affects the prognosis of specific patients with OSCC, all patients were grouped according to clinical related factors, including age, gender, tobacco use, alcohol use, and tumor location. We then compared the 5-year disease-free survival time of each subgroup according to chewing betel nut and found no prognostic difference in each subgroup (Figure 2).

Next, we further grouped all patients based on pathological factors, including T stage, cervical lymph node metastasis, clinical grade, and tumor differentiation grade. Similarly, we found that the 5-year disease-free survival time was also not different in each subgroup (Figure 3).

Univariable Cox Regression Analysis and Multivariable Cox Regression Analysis

To investigate the risk factors associated with the prognosis of oral cancer, we used univariable Cox regression analysis to explore the prognostic factors for OSCC. We found that age (HR = 0.98, 95% CI [0.97–0.99], $P < 0.01$), T stage (HR = 1.5, 95% CI [1.3–1.7], $P < 0.01$), cervical lymph node metastasis (HR = 1.8, 95% CI [1.6–2.1], $P < 0.01$), clinical stage (HR = 1.5, 95% CI [1.4–1.6], $P < 0.01$), and pathological grade (HR = 1.4, 95% CI [1.2–1.6], $P < 0.01$) were the potential prognostic factors. In contrast, betel nut use was not a prognostic factor (HR = 1, 95% CI [0.78–1.3], $P = 0.961$).

To eliminate the interference of other factors on prognosis, we used multivariable Cox regression analysis to correct these factors. We finally found that betel nut still did not affect the prognosis of OSCC patients even after correcting the prognostic impact of other factors (HR = 1, 95% CI [0.78–1.4], $P = 0.626$). In addition, age and T stage were excluded as independent risk factors. Cervical lymph node metastasis (HR = 1.5, 95% CI [1.2–1.9], $P < 0.01$), clinical stage (HR = 1.2, 95% CI [1.1–1.4], $P = 0.002$), and pathological grade (HR = 1.3, 95% CI [1.1–1.6], $P = 0.001$) were considered independent risk factors for prognosis in OSCC (Figure 4).

Discussion

Currently, some studies indicate that betel nut can promote the occurrence of OSCC through TP53 mutations, hypoxic microenvironment, and epithelial mesenchymal transition,^{14–16} however, the impact of betel nut on OSCC prognosis remains unclear. To solve this problem, we retrospectively reviewed 1133 OSCC patients. We first observed that the

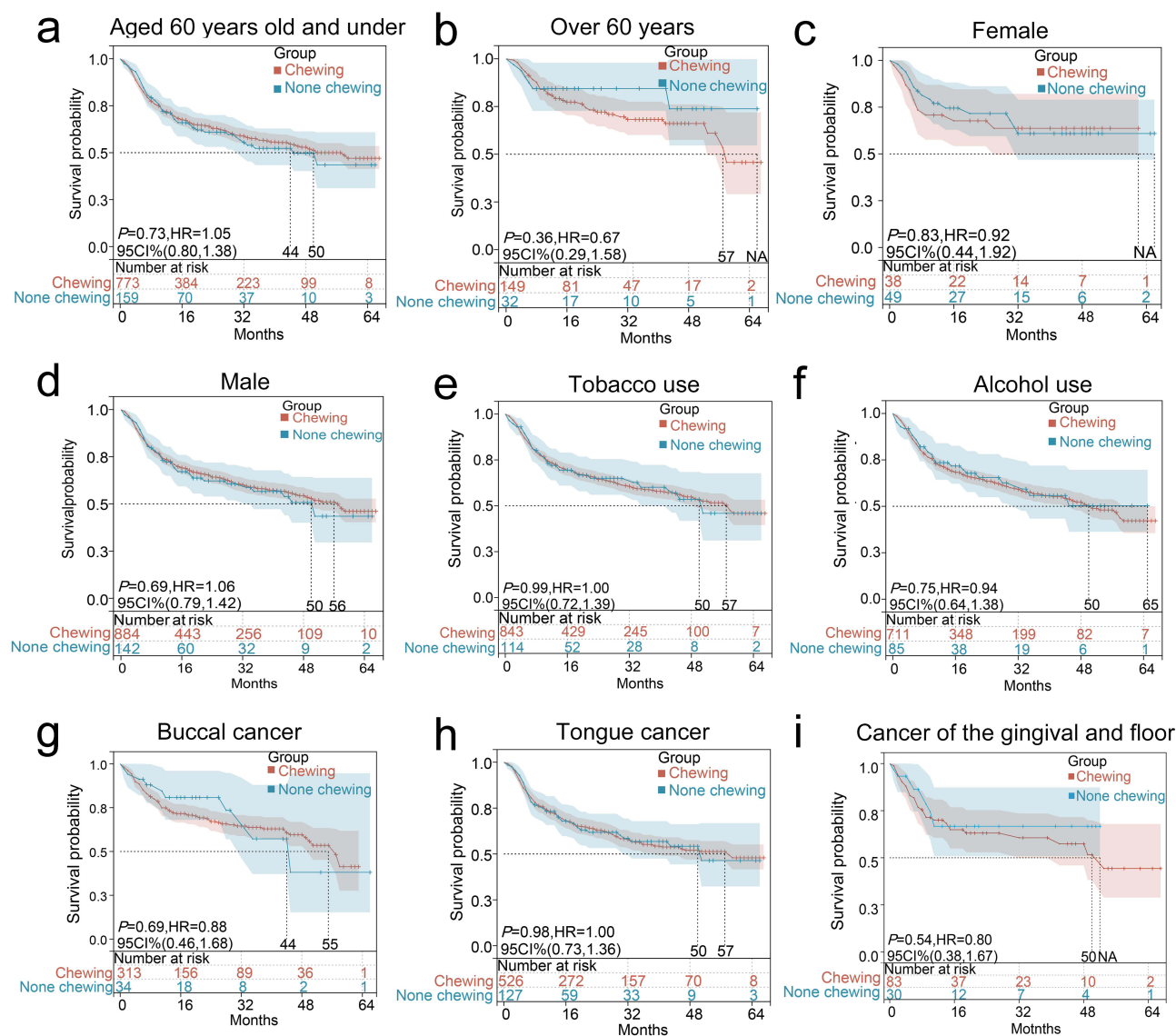


Figure 2 Subgroup survival curves of clinical related factors. There is no significant difference in survival curves between chewing processed betel nut and none chewing processed betel nut groups in the age (a and b), gender (c and d), tobacco use (e), alcohol use (f) and tumor location (g–i) subgroups.
Abbreviation: NA, Not Applicable.

proportions of smoking and alcohol consumption were significantly higher in the betel nut chewing group. This behavioral pattern is typically associated with lower educational attainment or specific occupational environments, which represents a high-risk context for OSCC.^{17,18} Next, the proportion of buccal cancer was significantly increased in chewers, which may be attributable to the buccal mucosa being the most susceptible site to mechanical and chemical injury during betel nut chewing.¹⁹ Furthermore, we found that the HR for age was less than 1 in the univariable model. We speculate that this may be due to the fact that tumor in young patients exhibit stronger invasiveness, and these patients may have a poorer prognosis. More importantly, the risk ratio was extremely close to 1, with 95% confidence intervals around 1. This small change, even if statistically significant, may not have a clinically meaningful protective effect.

Next, Kaplan-Meier analysis revealed no significant prognostic difference between chewers and non-chewers in the overall group or subgroups. Consistently, betel nut use was not considered a prognostic factor in either the univariable or multivariable Cox regression analyses. Notably, cervical lymph node metastasis, clinical stage, and pathological grade

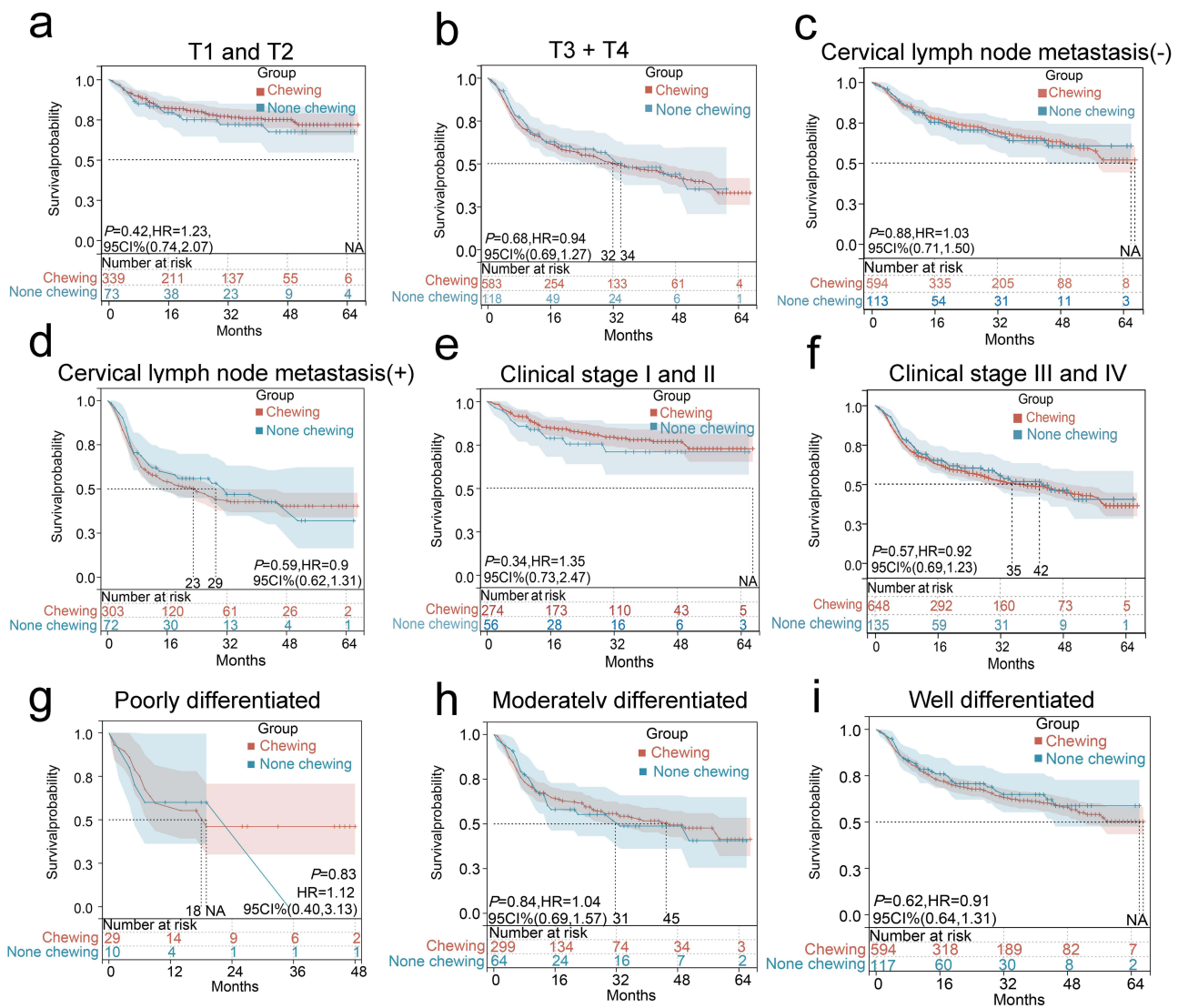


Figure 3 Subgroup survival curves of pathological related factors. There is no significant difference in survival curves between chewing processed betel nut and none chewing processed betel nut groups in the T stage (a and b), N stage (c and d), clinical grade (e and f), and tumor differentiation grade (g-i) subgroups. **Abbreviation:** NA, Not Applicable.

were considered independent prognostic factors that are already recognized as risk factors for OSCC. This finding validates the robustness and reliability of our study.

Although previous research has suggested that betel nut may cause the poorer prognosis, we speculate that this may be due to heterogeneity in the patients and treatment protocols.^{8,12} In studies with non-homogeneous treatment, betel nut chewers might receive different treatment due to socioeconomic factors or delayed care-seeking. The observed poorer prognosis might be partly attributable to treatment differences rather than the biological role of betel nut itself. In addition, previous studies may have mistakenly regarded second primary cancer as local recurrence, which is not representative. Our homogeneity study effectively controlled for this confounding factor. Finally, the difference in the results may also be attributable to differences in betel nut. In the Taiwanese province of China and Malaysia, fresh betel nut is usually chewed with betel leaves and mixed with shellfish powder.^{20,21} However, in mainland China, betel nut is processed from fresh betel nut and reduces the content of carcinogens, such as alkaloids, which may lead to lower harmonies on OSCC prognosis.

Alternatively, research on betel nut leading to a better prognosis requires careful explanation.¹³ This discovery may not be due to the protective biological role of betel nut. In contrast, this outcome may be caused by oral submucosal

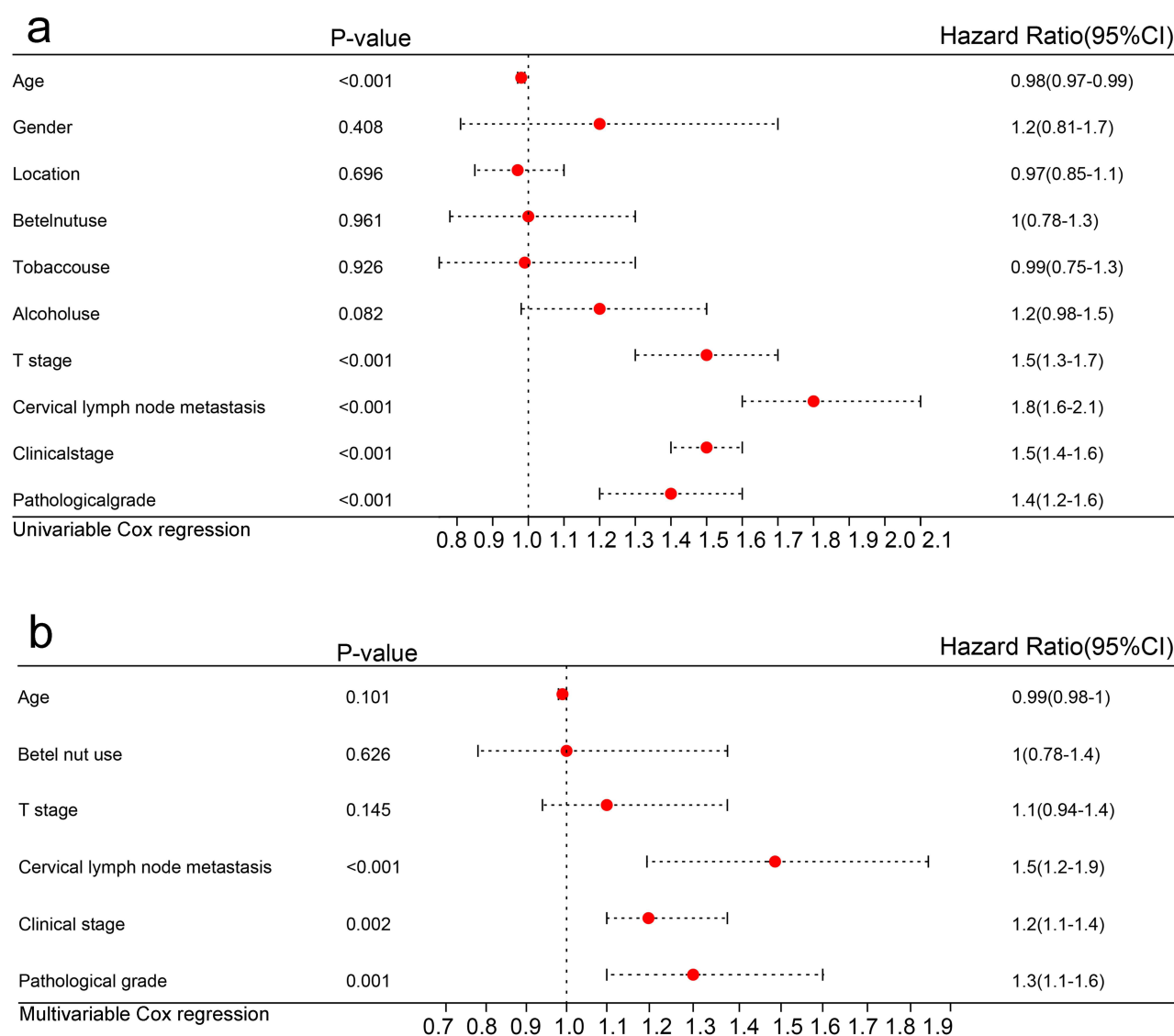


Figure 4 Forest map of univariable Cox regression and multivariable Cox regression analysis. (a), Univariable Cox regression suggested that age, alcohol use, T stage, N stage, clinical stage, and pathological grade were the potential prognostic factors for OSCC. (b), Multivariable Cox regression analysis suggested that N stage, clinical stage, and pathological grade were the independent prognostic factors for OSCC.

fibrosis resulting from chewing betel nut. The characteristics of oral submucosal fibrosis are collagen deposition and reduced blood vessels, which may limit the early infiltration and metastasis of tumors. Unlike previous studies that indirectly inferred betel nut exposure through oral submucosal fibrosis, our study directly collected information on patients' betel nut chewing history, which allowed us to avoid potential bias.

In summary, our findings provide a clearer “dual-role” picture of betel nut: it is the main cause of OSCC, but its role on tumor progression is limited. Cancer progression is a complex biological process, and carcinogens may not be the main driving factors. In contrast, the pathological features of tumors, such as lymph node metastasis, clinical stage, and pathological grade, are prognostic factors that can truly reflect the biological invasiveness of tumors. Our findings allow clinicians to develop more objective and precise treatment plans.

However, this study had several limitations inherent to its retrospective design. First, we did not quantify the frequency of betel nut chewing and did not consider the impact of consumption patterns on patients. Second, our study did not consider socioeconomic variables that significantly affect treatment adherence and overall survival rates. Finally, despite attempts to adjust for known confounders, the possibility of residual confounding from unmeasured

factors cannot be excluded. Our findings need to be validated in a large, multicenter, prospective cohort study in the future.

Conclusion

In conclusion, our findings suggest that betel nut use does not independently influence OSCC prognosis in patients undergoing standardized surgical treatment. The clinical treatment decisions and prognostic evaluations should be guided by established tumor pathologic features.

Abbreviations

OSCC, Oral squamous cell carcinoma.

Data Sharing Statement

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

Ethics Approval

This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was independently reviewed and approved by the Ethics Committee of Xiangya Hospital, Central South University (NO. 202212302).

Informed Consent

As this was a retrospective observational study, the requirement for informed consent was waived by the Ethics Committee of Xiangya Hospital, Central South University. All patient data were anonymized and de-identified prior to analysis to protect patient privacy and confidentiality.

Acknowledgments

The study team is grateful to all patients who contributed to this study and the projects that funded this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation [82170973] and Project of National Clinical Medical Research Center for Geriatric Diseases [2021LNJJ08].

Disclosure

The authors declare that they have no competing interests in this work.

References

1. van Dijk BA, Brands MT, Geurts SM, Merx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. *Int J Cancer*. 2016;139(3):574–583. doi:10.1002/ijc.30107
2. Su SY, Chen WT, Chiang CJ, Yang YW, Lee WC. Oral cancer incidence rates from 1997 to 2016 among men in Taiwan: association between birth cohort trends and betel nut consumption. *Oral Oncol*. 2020;107:104798. doi:10.1016/j.oraloncology.2020.104798
3. Warnakulasuriya S, Chen THH. Areca nut and oral cancer: evidence from studies conducted in humans. *J Dent Res*. 2022;101(10):1139–1146. doi:10.1177/00220345221092751

4. Du M, Nair R, Jamieson L, Liu Z, Bi P. Incidence trends of lip, oral cavity, and pharyngeal cancers: global burden of disease 1990-2017. *J Dent Res.* 2020;99(2):143–151. doi:10.1177/0022034519894963
5. Yang J, Wan SQ, Huang L, et al. Analysis of hospitalization costs and length of stay for oral cancer patients undergoing surgery: evidence from Hunan, China. *Oral Oncol.* 2021;119:105363. doi:10.1016/j.oraloncology.2021.105363
6. Hunan Daily. Please attention, the cancer registration annual report of Hunan Province in 2022 has been published. Available from: <https://m.voc.com.cn/xhn/news/202302/16041023.html>. Accessed February 2, 2023.
7. Singh AG, Chaturvedi P. Areca nut and oral cancer. *Oral Dis.* 2025;31(5):1467–1472. doi:10.1111/odi.14943
8. Liao CT, Kang CJ, Chang JT, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. *Oral Oncol.* 2007;43(8):811–819. doi:10.1016/j.oraloncology.2006.10.003
9. Liao CT, Chang JT, Wang HM, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. *Ann Surg Oncol.* 2008;15(3):915–922. doi:10.1245/s10434-007-9761-5
10. Yang WF, Qin N, Song X, et al. Genomic signature of mismatch repair deficiency in areca nut-related oral cancer. *J Dent Res.* 2020;99(11):1252–1261. doi:10.1177/0022034520930641
11. Yang J, Wang ZY, Huang L, et al. Do betel quid and areca nut chewing deteriorate prognosis of oral cancer? A systematic review, meta-analysis, and research agenda. *Oral Dis.* 2021;27(6):1366–1375. doi:10.1111/odi.13456
12. Mroueh R, Nevala A, Haapaniemi A, Pitkaniemi J, Salo T, Makiitie AA. Risk of second primary cancer in oral squamous cell carcinoma. *Head Neck.* 2020;42(8):1848–1858. doi:10.1002/hed.26107
13. Gadbaill AR, Chaudhary M, Gawande M, et al. Oral squamous cell carcinoma in the background of oral submucous fibrosis is a distinct clinicopathological entity with better prognosis. *J Oral Pathol Med.* 2017;46(6):448–453. doi:10.1111/jop.12553
14. Chang LY, Wan HC, Lai YL, Chou IC, Chen YT, Hung SL. Areca nut extracts increased the expression of cyclooxygenase-2, prostaglandinE2 and interleukin-1alpha in human immune cells via oxidative stress. *Arch Oral Biol.* 2013;58(10):1523–1531. doi:10.1016/j.archoralbio.2013.05.006
15. Zhang TY, Xiong HF, Zeng LJ, Yang ZM, Hu X, Su T. The key target and role of betel nut in oral squamous cell carcinoma. *Bmc Oral Health.* 2025;25(1):1212. doi:10.1186/s12903-025-06558-2
16. Senevirathna K, Pradeep R, Jayasinghe YA, et al. Carcinogenic effects of areca nut and its metabolites: a review of the experimental evidence. *Clin Pract.* 2023;13(2):326–346. doi:10.3390/clinpract13020030
17. Lin HJ, Wang XL, Tian MY, Li XL, Tan HZ. Betel quid chewing and oral potential malignant disorders and the impact of smoking and drinking: a meta-analysis. *World J Clin Cases.* 2022;10(10):3131–3142. doi:10.12998/wjcc.v10.i10.3131
18. Su MJ, Ho CH, Yeh CC. Association of alcohol consumption, betel nut chewing, and cigarette smoking with mortality in patients with head and neck cancer among the Taiwanese population: a nationwide population-based cohort study. *Cancer Epidemiol.* 2024;89:102526. doi:10.1016/j.canep.2024.102526
19. Lee KW, Chin CT. The effects of betel-nut chewing on the buccal mucosa: a histological study. *Br J Cancer.* 1970;24(3):433–441. doi:10.1038/bjc.1970.51
20. Tsai MH, Li TC, Li CI, et al. Development and preliminary validation of a mandarin Chinese language questionnaire measuring betel quid dependency among adults in Taiwan. *Psychiatry Res.* 2019;271:153–160. doi:10.1016/j.psychres.2018.11.027
21. Lee CH, Ko AM, Warnakulasuriya S, et al. Population burden of betel quid abuse and its relation to oral premalignant disorders in South, Southeast, and East Asia: an Asian Betel-quid Consortium Study. *Am J Public Health.* 2012;102(3):e17–24. doi:10.2105/AJPH.2011.300521

International Journal of General Medicine

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-general-medicine-journal>

Dovepress
Taylor & Francis Group