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Research Article

THE TRIPLE BURDEN OF QAT, SHAMMAH, AND SMOKING IN ORAL CANCER PATIENTS FROM HODEIDAH, YEMEN, 2025

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Abstract

Oral cancer poses a significant public health challenge in Yemen, further exacerbated by common cultural practices (qat chewing, shammah use, and tobacco smoking). This study aimed to (1) establish age-adjusted incidence rate (AAIR) of oral cancer, (2)characterize multi-carcinogen exposure patterns ("triple burden") and (3)identify structural management shortcomings in Hodeidah Governorate, Yemen. A retrospective cross-sectional analysis was conducted on consecutive cases of oral cancases registered at the National Cancer Center, Al-Thawara General Hospital in Hodeidah during 2025. To calculate AAIR per 100,000 person-years, we utilized the weights from the WHO World Standard Population. Significance was set at $p<0.05$. The cohort included 46 females (63.9%) and 26 males (36.1%)(mean age 60.6±14.6 years). Notably, 90.3% were residing in rural areas. Crude incidence rate was 2.04 per 100,000 (95% CI: 1.60-2.57); AAIR) was 5.65 (95% CI: 4.42-7.12), with female predominance (6.71 vs. 4.58 per 100,000). Common subsites were oral cavity Not Otherwise Specified (54.2%) and tongue (31.9%). Exposures were notably prevalent: qat (81.9%), shammah (76.4%), and smoking at (50.0%).Qat chewing was significantly more frequent among males (96.2% vs. 73.9%; p=0.033). The "triple burden" was observed in (44.4%) of cases. Median symptom-to-diagnosis delay was 45 days; with a shorter presentation-to-diagnosis delay of just 6.5 days; however, rural cases of gingival or jaw lesions showed the longest delay (21 days). All patients underwent chemotherapy exclusively; none received surgery or radiotherapy during their treatment course. A multivariable analysis did not identify any significant predictors for either triple burden or diagnostic delay, suggesting community-level cultural factors drive these trends. Age-adjusted burden of oral cancer is almost three times higher than crude estimates. The significant prevalence of the"triple burden", combined with patient-level diagnostic delays in rural areas, highlights the urgent need for integrated cessation programs and enhanced early detection efforts. Additionally, the lack of surgical and radiotherapeutic options reflectscritical infrastructure gaps that call for immediate humanitarian iintervention.

Keywords: Epidemiology, Smokeless Tobacco, Diagnostic Delay, Cancer Registry, Rural, Oral Squamous Cell Carcinoma.

INTRODUCTION

Malignant neoplasms affecting the lip and oral cavity represent a considerable global health challenge. In 2021, an estimated 421,577 new cases were reported worldwide, with an Age-Adjusted Incidence Rate (AAIR) of 4.88 per 100,000 individuals [1]. Over 90% of these cases are histopathologically categorized as oral squamous cell carcinomas (OSCC), characterized by aggressive local invasion and poor prognosis upon diagnosis at advanced stages [2]. In the southern Arabian Peninsula, specifically in the coastal Tihama plains of Yemen, the epidemiology of oral cavity squamous cell carcinoma presents a distinctive and growing pattern [3]. This localized increase in incidence can largely be attributed to the prevalent use of highly carcinogenic cultural stimulants: qat (Catha edulis), shammah (traditional smokeless tobacco), and combustible tobacco products [4,5]. Habitual chewing of qat leaves releases psychoactive alkaloids along with cytotoxic tannins and residues from agricultural pesticides, all of which inflict mechanical and chemical trauma on the mucosal lining [6]. Shammah, a mixture comprising powdered tobacco, slaked lime, ash, and oils, is placed directly within the buccal or labial sulcus; its high alkalinity allows for rapid transmucosal absorption of nicotine while simultaneously exposing the epithelium to elevated levels of tobacco-specific N-nitrosamines (TSNAs) [7]. Research has indicated that shammah harbors notably higher bacterial loads compared to other smokeless tobacco options, featuring genes responsible for cadmium/zinc and nickel transport systems enriched in high-carcinogenicity products [8]. The combined effects of these substances yield a synergistic multi-carcinogen impact that accelerates malignant transformation [9]. When used alongside combustible tobacco products, they create what this study refers to as the "triple burden": simultaneous exposure to three predominant oral carcinogens and co-carcinogens. Assessing the genuine public health impact of oral cancer in Yemen involves navigating a demographic paradox. Countries like Yemen have a markedly youth-skewed population distribution, with over 60% under the age of 25 [10]. Given that epithelial carcinomas typically take decades to develop through cumulative exposure, a Crude Incidence Rate tends to obscure actual risk levels, misleadingly portraying a common disease as rare because of the large population of younger individuals who have yet to reach oncogenic risk age [11]. Thus, it becomes essential to calculate the AAIR using World Health Organization (WHO) standards to mitigate age-related confounding effects and facilitate accurate epidemiological comparisons [12]. Previous studies in Yemen have documented a significant prevalence of oral cancer. For instance, Halboub et al. noted that oral cancer represented 4.0% of all registered cancer cases between 2007 and 2008,

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with the tongue being particularly affected (53.6%) and 71.5% of patients diagnosed at more advanced stages [13]. A case-control study conducted in Aden revealed that shammah usage was a considerable risk factor for OSCC, with odds ratios (OR)of 12.6 for ex-users and 39 for current users [14]. A systematic review assessing cultural practices related to oral cancer risk identified both shammah (pooled OR 3.9,95% confidence interval (CI) 2.5–6.2) and qat chewing (pooled OR 2.7, 95% CI 1.9–3.8) as significant contributors to increased risk levels. Notably, regions with high shammah consumption exhibited female-to-male incidence ratios nearing parity [15]. Nonetheless, a recent meta-analysis found no substantial link between qat chewing and OSCC (OR 1.18, 95% CI 0.40–3.48), although it did highlight a notable association with oral white lesions (OR 17.89, 95% CI 4.99–64.21) [16], suggesting that qat might function more as a co-carcinogen or promoter rather than being classified as a direct carcinogen.

A clinico-epidemiological study from the National Cancer Center in Aden (2020-2024) reported that oral cancer accounted for only 113 cases (1.4%) among all registered cancers; squamous cell carcinoma was most common (67.9%), with the tongue identified as the most affected site (46.2%) [17]. Low public awareness about oral cancer persists in Yemen; research indicates that merely 24.1% and 21.4% of individuals correctly identified red and white lesions as early indicators of oral cancer respectively [18]. Additionally, a multi-country study encompassing 30 Middle Eastern and North African countries found that only 37.2% of participants exhibited sufficient knowledge regarding risk factors associated with oral cancer [19]. Dental students in Yemen also demonstrate significant gaps in their understanding; a multi-institution study revealed that only about 21% felt confident about their knowledge concerning oral cancer [20]. A separate survey involving 247 Yemeni dental students showed that an alarming proportion (84.2%) could not accurately identify risk factors related to oral cancer while another similar percentage (84.8%) failed to recognize its clinical symptoms [21]. These educational shortcomings likely contribute to missed opportunities for early detection within clinical practice.

Diagnostic delays continue to pose critical challenges affecting OSCC outcomes around the world. A scoping review examining diagnostic delays in OSCC indicated total delays ranging from approximately 45 days to 6 months; unfortunately, most patients receive diagnoses at later stages (72.8%) [22]. The review emphasized how patient-related factors (including lack of awareness and fear regarding diagnosis)significantly exacerbate these delays, while professional setbacks stem from insufficient training and ineffective referral processes [22]. A cross-sectional study involving 226 OSCC patients recorded an average diagnostic delay lasting 55.2 days. Notably, 61.9% experienced delays exceeding 40 days, older age groups alongside lower education levels and income were significantly correlated with prolonged delays [23]. Another analysis reported that diagnostic delays exceeding 90 days were linked with larger tumor sizes and more advanced disease stages at presentation [24]. This study aims to address existing gaps by (1) establishing age-adjusted incidence rates of oral cancer in Hodeidah Governorate, Yemen, (2) characterizing patterns of multi-carcinogen exposure "triple burden," and (3) identifying deficiencies in structural management.

MATERIALS AND METHODS

Study Design and Setting

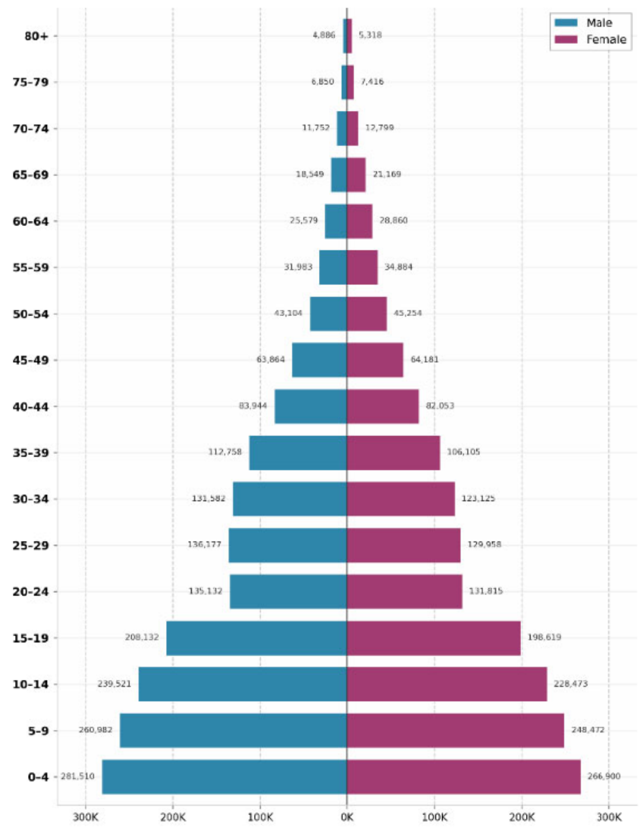
This is a retrospective, cross-sectional analysis utilizing data sourced from the National Cancer Registry at the Cancer Treatment Center within Al-Thawara General Hospital in Hodeidah, Yemen. This facility is the main tertiary oncology referral center for Hodeidah and adjacent rural governorates in the coastal Tihama area. The study period was January 1, 2025, to December 31, 2025. The final cohort was confined to the 72 cases that demonstrated verified residency in the Hodeidah Governorate.

Geographic Stratification and Population Denominators

To discern residential trends, the cohort was categorized into two separate demographic strata according to administrative boundaries:

1. **Urban Districts** (n=7): Encompassing the heavily populated metropolitan area of Hodeidah city, which includes Al-Hawak, Al-Mina, and Al-Hali.
2. **Rural Districts** (n=65): Including all other peripheral agricultural, coastal, and mountainous districts within the governorate.

Denominator data for rate calculations were drawn from the official population estimates for 2025 published by the Central Statistical Office of Yemen for Hodeidah Governorate (N=3,531,706; Males=1,796,523; Females=1,735,183) [10] (Figure 1).



Source: Projected population data, 2025 | Total Population: 3,531,706

Figure 1. Population Pyramid of Hodeidah Governorate, Yemen, 2025

Incidence Rate Calculations and Age-Adjustment

The Crude Incidence Rate was determined by dividing new oral cancer cases by the projected population figure, represented per 100,000 person-years. The AAIR was calculated using the direct standardization method against the WHO World Standard Population weights [12] employing the following formula:

$$\mathbf{AAIR = \Sigma (R\_i \times w\_i) / \Sigma w\_i}$$

where R_i denotes the age-specific crude incidence rate within age stratum i, while w_i signifies the standard population weight attributed by the WHO reference standard.

Inferential Statistical Analysis

Data analysis was carried out using IBM SPSS Statistics (Version 26.0). To assess distributional normality for continuous metrics (age and timelines), we utilized the Shapiro-Wilk test. Given that timeline data exhibited considerable right-skewness and deviated from a Gaussian distribution pattern, non-parametric tests were employed: Mann-Whitney U test for comparisons between two independent groups and the Kruskal-Wallis test for evaluations across multiple categories. Continuous data conforming to normal distributions were reported as means ± standard deviations. Categorical variables were compared using Pearson's Chi-square (χ^2) test or Fisher's Exact test (when expected cell counts <5). The threshold for statistical significance was set at a two-tailed alpha level of $p < 0.05$.

Multivariable Analysis

In order to determine the independent predictors of the "triple burden" which consists of simultaneous qat, shammah, and tobacco use, as well as diagnostic delay, we carried out multivariable regression analyses. For binary outcomes such as the presence of the triple burden and a delay exceeding 30 days from symptom onset, we employed binary logistic regression with a backward stepwise selection method (entry criterion $p<0.10$ and removal criterion $p>0.15$). The independent variables taken into account included sex, age (measured continuously), residence type (urban or rural), cancer subsite categorized appropriately, the presence of comorbidities, and family history related to cancer. When addressing continuous outcomes, specifically the log-transformed delay from symptom onset to confirmation, we utilized linear regression featuring the same set of predictors. The delay data underwent log transformation to approximate a normal distribution (Shapiro-Wilk post-transformation yielded p=0.089).

To manage multiple comparisons effectively, we applied the Bonferroni correction for each analysis, setting an adjusted $\alpha = 0.05/k$, where k represents the number of predictors included in the model. Each multivariable model was scrutinized for multicollinearity by examining variance inflation factors (VIF) and for goodness-of-fit through the Hosmer-Leme show test in logistic regression or residual analysis in linear regression models (with all predictors showing VIF < 2.0). The fit of the models was further assessed using Nagelkerke R^2 for logistic models and adjusted R^2 for those that were linear. The findings are presented with adjusted odds ratios (aOR) or β coefficients alongside 95% CI, including both unadjusted and Bonferroni-adjusted p-values.

Ethical Considerations

This investigation utilized retrospectively extracted anonymized data from the cancer registry. Authorization to access registry logs of the National Cancer Registry in Hodeidah was granted by Al-Thawara General Hospital administration. All data extractions were conducted anonymously; personal identifiers such as names, specific addresses, and registry numbers were removed and securely stored on password-protected electronic drives to ensure strict confidentiality regarding patient information. Informed consent was deemed unnecessary due to the retrospective nature of the data collection and its anonymous character that precluded direct contact with patients.

RESULTS

Crude and Age-Adjusted Incidence Rates

In Hodeidah, the crude incidence rate of oral cavity cancer was 2.04 cases per 100,000 person-years (95% CI: 1.60-2.57). Notably, females experienced a higher rate of 2.65 per 100,000 (95% CI: 1.96-3.51), compared to males, who had a rate of 1.45 per 100,000 (95% CI: 0.96-2.10). After direct standardization using the WHO World Standard Population weights, the AAIR was found to be 5.65 cases per 100,000 person-years (95% CI: 4.42-7.12). There was a significant difference observed between the sexes, as females had a higher AAIR than males: 6.71 (95% CI: 5.02-8.78) versus 4.58 (95% CI: 3.12-6.45) per 100,000 person-years (Table 1).

Urban-Rural and Socio-Demographic Profiles

Among the 72 resident cases, there were 46 females, accounting for 63.9%, and 26 males, representing 36.1%, with a female-to-male ratio of 1.8:1. The mean age at diagnosis was recorded at 60.6 ± 14.6 years, (median: 63.0 years; IQR: 50.0-72.0; range: 25-85 years). The majority of patients 90.3% (n=65), resided in rural districts, whereas only a minority, comprising 9.7% (n=7), resided in urban settings. Most patients were married (86.1%, n=62) followed by widowed/divorced (9.7%, n=7) and single (4.2%, n=3) (Table 2).

Anatomical Subsite Distribution

Oral Cavity Squamous Cell Carcinoma Not Otherwise Specified (NOS) emerged as the predominant type, representing 54.2% of the cases (n=39). This was followed by primary tongue cancer at 31.9% (n=23), cancer of the gingival/alveolar ridge/jaw at 6.9% (n=5), nasal/adjacent extension at 5.6% (n=4), and lip cancer at 1.4% (n=1). The analysis did not indicate any significant differences in the distribution of anatomical subsites when comparing urban and rural populations (Fisher's Exact p=0.812). A gender-based analysis revealed no significant disparities in subsite distribution, except for the 'other adjacent subsites' (p=0.018). However, it is important to interpret this finding with caution due to the implications of multiple comparisons (Table 3).

Carcinogenic Exposures and the "Triple Burden"

The overall prevalence of exposure to the three carcinogenic substances was high: qat (81.9%, n=59; 95% CI: 71.1-89.3%), shammah use (76.4%, n=55; 95% CI: 65.0-85.1%), and active tobacco smoking (50.0%, n=36; 95% CI: 38.2-61.8%).

Table 1. Crude and Age-Adjusted Incidence Rates of Oral Cavity Cancer, Hodeidah, Yemen, 2025

Rate Matrix Metric	Female	Male	Total Governorate
Crude Incidence Rate	2.65 (95% CI: 1.96-3.51)	1.45 (95% CI: 0.96-2.10)	2.04 (95% CI: 1.60-2.57)
AAIR*	6.71 (95% CI: 5.02-8.78)	4.58 (95% CI: 3.12-6.45)	5.65 (95% CI: 4.42-7.12)

*Age-Adjusted Incidence Rate (AAIR) calculated using direct standardization against World Health Organization (WHO) World Standard Population weights. Rates are expressed per 100,000 person-years. CI, Confidence Interval;

Table 2. Sociodemographic Characteristics of Oral Cancer Patients, Hodeidah, Yemen, 2025 (n=72)

Chrematistic	Female (n=46)	Male (n=26)	Total (n=72)	p-value*
Geographic Zone				**1.000**
Urban	4 (57.1%)	3 (42.9%)	7 (9.7%)	
Rural	42 (64.6%)	23 (35.4%)	65 (90.3%)	
Age (Years)				**0.612****
Mean ± SD	59.9 ± 14.5	61.7 ± 14.8	60.6 ± 14.6	
Median (IQR)	62.0 (50.0-71.0)	65.0 (46.0-73.0)	63.0 (50.0-72.0)	
Age Group				**0.812**
19-49 Years	9 (60.0%)	6 (40.0%)	15 (20.8%)	
50-65 Ears	22 (71.0%)	9 (29.0%)	31 (43.1%)	
>65 Years	15 (57.7%)	11 (42.3%)	26 (36.1%)	
Marital Status				**0.612**
Married	39 (62.9%)	23 (37.1%)	62 (86.1%)	
Widowed/Divorced	5 (71.4%)	2 (28.6%)	7 (9.7%)	
Single	2 (66.7%)	1 (33.3%)	3 (4.2%)	

*Fisher's Exact test; **Mann-Whitney U test.Data are presented as n (%) unless otherwise specified.. IQR, Interquartile Range; SD, Standard Deviation.

Table 3. Anatomical Subsite Distribution of Oral Cavity Cancer by Sex, Hodeidah, Yemen, 2025 (n=72)

Anatomical Subsite	Female (n=46)	Male (n=26)	Total (n=72)	p-value*
Oral Cavity Not Otherwise Specified	28 (60.9%)	11 (42.3%)	39 (54.2%)	0.132
Primary Tongue Cancer	15 (32.6%)	8 (30.8%)	23 (31.9%)	1.000
Gingival/Alveolar Ridge/Jaw	2 (4.3%)	3 (11.5%)	5 (6.9%)	0.348
Lip Cancer	1 (2.2%)	0 (0.0%)	1 (1.4%)	1.000
Other Adjacent Subsites	0 (0.0%)	4 (15.4%)	4 (5.6%)	0.018**

*Fisher's Exact test comparing female vs. male distribution; **Considered non-significant after Bonferroni correction (adjusted α = 0.01 for 5 comparisons). Data are presented as n (%).

Table 4 Carcinogenic Exposure and "Triple Burden" Profiles Among Oral Cancer Patients, Hodeidah, Yemen, 2025 (n=72)

Exposure Category	Female (n=46)	Male (n=26)	Total (n=72)	p-value*
Standalone Substance Exposure				
Qat Chewing	34 (73.9%)	25 (96.2%)	59 (81.9%)	0.033
Shammah Use	35 (76.1%)	20 (76.9%)	55 (76.4%)	1.000
Tobacco Smoking	23 (50.0%)	13 (50.0%)	36 (50.0%)	1.000
Carcinogen Compound Profiles				
Triple Burden	20 (43.5%)	12 (46.2%)	32 (44.4%)	1.000
Dual Exposure	14 (30.4%)	7 (26.9%)	21 (29.2%)	0.281
Single Exposure	7 (15.2%)	5 (19.2%)	12 (16.7%)	1.000
No Exposure	5 (10.9%)	2 (7.7%)	7 (9.7%)	0.237

*Fisher's Exact test comparing female vs. male distribution. Data are presented as n (%). Bold values indicate statistical significance ($p<0.05$). Triple Burden defined as simultaneous use of qat, shammah, and tobacco.

When examining single-substance habits stratified by sex, a statistically significant difference emerged in qat chewing, which was found to be more common among males compared to females (96.2% vs. 73.9%; $\chi^2=4.56$, p=0.033). On the other hand, shammah use (76.9% in males vs. 76.1% in females; p=1.000) and active tobacco smoking (50.0% for both genders; p=1.000) exhibited a uniform distribution across sexes.

The analysis of combined risk behaviors revealed that the 'triple burden' the (simultaneous use of qat, shammah, and smoking) was identified in 44.4% (n=32; 95% CI: 33.1-56.2%) of patients surveyed. Dual-substance exposure was found in 29.2% (n=21; 95% CI: 19.6-40.9%) of patients, while single exposure accounted for 16.7% (n=12; 95% CI: 9.4-27.1%), and no exposure was recorded in 9.7% (n=7; 95% CI: 4.5-18.6%). The distribution of the triple burden was comparable between sexes, with 43.5% of females and 46.2% of males affected (p=1.000). The comprehensive risk factor matrix is displayed in Table 4.

Clinical Characteristics, and Treatment Patterns by Sex

Table 5 presents the clinical characteristics including comorbidities, family history, and treatment patterns observed among oral cancer patients in the study. All patients (100%, n=72; 95% CI: 95.0-100.0%) underwent systemic chemotherapy, with none undergoing surgical resection aimed at curative intent or radiotherapy administered.

Diagnostic Delays:

In this study, we examined two distinct intervals of diagnostic delay (Table 6):

(I) Delay from Symptom Onset to Confirmation: The median duration from the onset of initial symptoms to histopathological confirmation was found to be 45 days (IQR: 17-155 days; mean: 129.4 ± 182.3 days; range: 1-938 days).

Table 5. Clinical Characteristics and Treatment Modalities Among Oral Cancer Patients by Sex, Hodeidah, Yemen, 2025 (n=72)

Exposure Category	Female (n=46)	Male (n=26)	Total (n=72)	p-value*
Comorbidities				**0.767**
Any Comorbidity	8 (17.4%)	6 (23.1%)	14 (19.4%)	
Diabetes Mellitus	4 (8.7%)	3 (11.5%)	7 (9.7%)	
Hypertension	2 (4.3%)	2 (7.7%)	4 (5.6%)	
Heart Disease	1 (2.2%)	2 (7.7%)	3 (4.2%)	
Thyroid Disease	1 (2.2%)	0 (0.0%)	1 (1.4%)	
Family History of Cancer				**1.000**
Positive Family History	6 (13.0%)	4 (15.4%)	10 (13.9%)	
Treatment Modality				
Chemotherapy Alone	46 (100%)	26 (100%)	72 (100%)	---
Surgical Resection	0 (0%)	0 (0%)	0 (0%)	
Radiotherapy	0 (0%)	0 (0%)	0 (0%)	

*Fisher's Exact test comparing female vs. male distribution. Data are presented as n (%). ---: Statistical test not applicable (no variation in treatment modality)

Table 6. Diagnostic Delay by Subsite and Sex Among Oral Cancer Patients, Hodeidah, Yemen, 2025 (n=72)

Exposure Category	Female (n=46)	Male (n=26)	Total (n=72)	p-value*
Delay from Symptoms to Confirmation (Days)				**0.252***
Mean (±SD)	118.1 ± 167.7	149.4 ± 209.9	129.4 ± 182.3	
Median (IQR)	38.5 (17-155)	55.0 (18-195)	45.0 (17-155)	
Range	1 - 679	2 – 938	1 – 938	
Delay from Healthcare Presentation to Confirmation (Days)				**0.192***
Mean (±SD)	14.1 ± 18.5	8.1 ± 10.6	11.9 ± 15.8	
Median (IQR)	6.5 (1-16)	2.0 (1-15)	6.5 (1-16)	
Range	1 - 83	1 – 42	1 – 83	
Delay Category (Symptoms to Confirmation)				
0-30 days	7 (26.9%)	13 (28.3%)	20 (27.8%)	
31-60 days	6 (23.1%)	12 (26.1%)	18 (25.0%)	
61-90 days	2 (7.7%)	6 (13.0%)	8 (11.1%)	
91-180 days	3 (11.5%)	8 (17.4%)	11 (15.3%)	
181-365 days	4 (15.4%)	3 (6.5%)	7 (9.7%)	
>365 days	4 (15.4%)	4 (8.7%)	8 (11.1%)	
Subsite-Specific Median Delay (Symptoms to Confirmation)				**---**
Oral Cavity (NOS)	35	84	42	
Tongue Cancer	45	45	45	
Gingival/Jaw Cancer	45	84	45	
Other	55	55	55	
Subsite-Specific Median Delay (Presentation to Confirmation)				**0.043****
Oral Cavity (NOS)	5	5	5	
Tongue Cancer	8	7	7.5	
Gingival/Jaw Cancer	21	21	21	
Lip Cancer	1	-	1	
Other	17	12	17	

*Mann-Whitney U test; **Kruskal-Wallis test; Bold indicates p<0.05. IQR, Interquartile Range; NOS, Not Otherwise Specified; SD, Standard Deviation; ---, Not applicable.

Table 7. Logistic Regression: Predictors of "Triple Burden" Among Oral Cancer Patients (n=72)

Predictor	aOR*	95% CI	p-value	Bonferroni-adjusted p-value**
Sex (Male vs. Female)	1.12	0.42-2.98	0.818	1.000
Age (per 10-year increase)	0.89	0.63-1.26	0.508	1.000
Rural Residence (vs. Urban)	2.34	0.48-11.42	0.292	1.000
Tongue Cancer (vs. Oral NOS)	0.72	0.26-1.98	0.528	1.000
Gingival/Jaw Cancer (vs. Oral NOS)	1.18	0.18-7.62	0.864	1.000
Diagnostic Delay (>45 days)	1.54	0.58-4.08	0.386	1.000

*Adjusted Odds Ratio (aOR) from binary logistic regression with backward stepwise selection.*Bonferroni correction for 6 comparisons: adjusted $\alpha = 0.05/6 = 0.0083$. CI, Confidence Interval; NOS, Not Otherwise Specified. **Model Summary:** Hosmer-Lemeshow goodness-of-fit $\chi^2=5.23$, p=0.733; Nagelkerke $R^2=0.087$

For male patients, the median delay was 55.0 days (IQR: 18-195), while for female patients it was shorter at 38.5 days (IQR: 17-155). Only 27.8% (n=20) of the patients received confirmation within a month after symptom onset, and it is noteworthy that 11.1% (n=8) faced delays exceeding one year. The analysis indicated that there were no significant differences in the delay from symptom onset to confirmation between male and female patients (Mann-Whitney U = 501.5; p = 0.252).

(II) Delay from Healthcare Presentation to Confirmation: The median duration from an initial visit to a healthcare facility until histopathological confirmation was 6.5 days (IQR: 1-16 days; mean: 11.9 ± 15.8 days; range: 1-83 days). For males, the median delay was recorded at 2.0 days (IQR: 1-15), whereas females experienced a median delay of 6.5 days (IQR: 1-16) (U=492.5, p=0.192). A majority of patients (66.7%, n=48) received confirmation within one week of their presentation. No significant sex-based differences were noted (Mann-Whitney U = 492.5; p = 0.192).

Comparison of Delay Intervals: The notable difference between these two measures specifically a median of 45 days from the onset of symptoms as opposed to just 6.5 days from the point of healthcare presentation highlights that most delays in diagnosis are attributable to factors occurring at the patient-level prior to seeking medical attention.

Table 8: Linear Regression:Predictors of Diagnostic Delay (Symptom to Confirmation)

Predictor	B*	95% CI	p-value	Bonferroni-adjusted p-value**
Sex (Male vs. Female)	0.29	-0.21 to 0.79	0.258	1.000
Age (per 10-year increase)	-0.05	-0.22 to 0.12	0.558	1.000
Rural Residence (vs. Urban)	0.84	-0.14 to 1.82	0.092	0.552
Triple Burden (vs. No/Dual)	0.36	-0.14 to 0.86	0.156	0.936
Tongue Cancer (vs. Oral NOS)	-0.12	-0.62 to 0.38	0.638	1.000
Gingival/Jaw Cancer (vs. Oral NOS)	0.18	-0.72 to 1.08	0.692	1.000
Comorbidity Present	0.42	-0.18 to 1.02	0.170	1.000

*β Coefficient from linear regression with backward stepwise selection. **Bonferroni correction for 7 comparisons: adjusted $\alpha = 0.05/7 = 0.0071$. CI, Confidence Interval; NOS, Not Otherwise Specified **Model Summary:** Adjusted $R^2 = 0.041$; $F(7, 64) = 1.42$, $p = 0.214$

Table 9: Logistic Regression: Predictors of Delayed Diagnosis (>30 days from Symptom Onset)

Predictor	aOR*	95% CI	p-value	Bonferroni-adjusted p-value**
Sex (Male vs. Female)	1.73	0.58-5.15	0.327	1.000
Age (per 10-year increase)	0.94	0.61-1.45	0.778	1.000
Rural Residence (vs. Urban)	3.92	0.58-26.5	0.160	0.960
Triple Burden	0.82	0.28-2.40	0.717	1.000
Tongue Cancer (vs. Oral NOS)	0.67	0.22-2.04	0.482	1.000
Gingival/Jaw Cancer (vs. Oral NOS)	1.21	0.18-8.28	0.846	1.000

*Adjusted Odds Ratio (aOR) from binary logistic regression with backward stepwise selection. **Bonferroni correction for 6 comparisons: adjusted $\alpha = 0.05/6 = 0.0083$. CI, Confidence Interval; NOS, Not Otherwise Specified.CI, Confidence Interval; NOS, Not Otherwise Specified.
Model Summary: Hosmer-Lemeshow χ^2=5.87, p=0.662; Nagelkerke R^2=0.079.

Subsite-Specific Delays: A detailed analysis based on different cancer subsiteindicated that patients diagnosed with oral cancer NOS experienced a median delay of 42.0 days. In contrast, individuals with tongue cancer experienced a median delay of 45.0 days, which was the same for those with gingival/jaw cancer; other subsites reported median delays reaching up to 55.0 days. Notably, the delays from healthcare presentation to confirmation varied significantly across subsites (Kruskal-Wallis p=0.043). Among these, gingival/jaw lesions had the longest median duration at 21.0 days, while delays for oral cavity NOS at 5.0 days, those for tongue cancer at 7.5 days, lip cancer at just 1.0 day, and other subsites averaged at 17.0 days.

Multivariable Analysis

Factors Associated with the "Triple Burden"

No predictor emerged as significantly related to the triple burden following Bonferroni correction. The model exhibited limited explanatory power, with a Nagelkerke R^2 of 0.087. This indicates that there may be other unmeasured factors that could affect the patterns of combined exposure (Table 7).

Factors Associated with Diagnostic Delay

The predictors analyzed did not significantly elucidate the variation observed in diagnostic delay. The model's low R^2 value suggests that the factors considered only explain 4.1% of the variance in delay durations (Table 8).

Factors Associated with Delayed Diagnosis (>30 Days)

While living in rural areas indicated a tendency for higher odds of experiencing delayed diagnosis (OR 3.92), this finding did not reach statistical significance. After adjusting for multiple comparisons, no predictor was found to be significantly linked with delays exceeding 30 days (see Table 9).

DISCUSSION

This study offers the first age-adjusted incidence rates for oral cavity cancer specifically within the Hodeidah Governorate, revealing an AAIRof 5.65 cases per 100,000 person-years. This age-standardized measure is almost three times higher than the crude rate (2.04 per 100,000), illustrating how Yemen's youth-dominant population pyramid can obscure a significant disease burden among older age groups if only crude metrics are considered [11]. The pronounced female predominance (AAIR: 6.71/100,000 for females compared to 4.58/100,000 for males) and the rural concentration of cases (90.3%) underscore a distinctive epidemiological profile in this area, contrasting with global patterns that generally show higher age-standardized incidence rates among males [1].

The high prevalence of the concurrent "triple burden" configuration (44.4% overall) subjects the oral epithelium to a potent combination of carcinogens and co-carcinogens. The alkaline agents present in shammah modify mucosal permeability, which enhances the absorption of tobacco-specific N-nitrosamines along with cytotoxic residues from chewed qat leaves [7,9]. Prior research found shammah users have increased odds of oral leukoplakia, with a dose-dependent relationship (OR 6.91 for daily applications exceeding 5 minutes) [5].Notably, 46.8% of mucosal burns and 59.2% of oral leukoplakia lesions in shammah users occur on the tongue or floor of the mouth, reinforcing the site-specific carcinogenic effects [5].

The debate regarding qat's direct carcinogenic potential remains ongoing. A Yemeni case-control study identified shammah as the only significant risk factor for oral cancer, yielding odds ratios of 12.6 for ex-users and 39 for current users; while qat chewing was not significant after tobacco adjustment [14]. A recent meta-analysis found no significant link between qat and OSCC (OR 1.18, 95% CI 0.40-3.48), but qat was associated with oral white lesions (OR 17.89, 95% CI 4.99-64.21) [16]. This implies that qat may serve more as a co-carcinogen or promoter instead of acting as a direct carcinogen by facilitating the absorption of tobacco carcinogens into the oral mucosa through both mechanical and chemical irritation [6]. A systematic review addressing cultural practices in the Middle East confirmed that smokeless tobacco (shammah: pooled OR 3.9, 95% CI 2.5-6.2) and qat chewing (pooled OR 2.7, 95% CI 1.9-3.8) are significant risk factors for OSCC [15]. The high prevalence of this triple burden among participants emphasizes the necessity to tackle all three exposures concurrently. The observed female-to-male ratio of 1.8:1 (AAIR6.71 vs. 4.58) contrasts with global patterns where males typically have higher rates [1]. This reverse gender gap appears to be deeply embedded within local cultural practices. A systematic review indicated that female-to-male incidence ratios neared parity in regions characterized by high shammah usage, diverging from typical global trends [15]. In Hodeidah, qat chewing is more common among males (96.2%), while shammah (76.1%) and smoking (50%) are also prevalent among females. This sex difference in qat use was statistically significant (p=0.033). This suggests that although males engage universally in qat use, females tend to have more varied profiles concerning multiple carcinogenic exposures.

A key finding is the identification of two distinct intervals contributing to diagnostic delays. The median duration from symptom onset to diagnosis confirmation was 45 days; while the time from healthcare presentation to confirmation was only 6.5 days, indicating a substantial gap of 38.5 days reflecting patient-level delays in seeking care. This finding aligns with the literature. A scoping review found that the total OSCC diagnostic delays ranged from 45 days up to six months with patient-related factors being crucial [22]. Similarly, a cross-sectional study involving 226 OSCC patients reported an average diagnostic delay of 55.2 days with 61.9% who encountered delays extending beyond the threshold of forty days [23]. Furthermore, this same study determined that older individuals (>50 years), those with lower education and income levels were significantly associated with prolonged delays [23].

Patient-level delays in our cohort likely reflect: (1) low awareness regarding early signs indicative of oral cancer a point underscored by findings indicating only about 24.1% of Yemen's populace could correctly identify red lesions while just over one-fifth recognized white lesions as early signals [18], (2) normalization of oral lesions due to chronic usage patterns associated with qat and shammah, (3) psychological barriers such as fear surrounding diagnosis which has been noted previously as an underappreciated obstacle preventing timely care-seeking behavior among OSCC patients [22], (4) financial limitations hindering access to health services,(5) geographic challenges faced particularly by rural residents (90% originating from rural districts), and (6) reliance on traditional remedies prior to engaging formal medical treatment.

After presentation, patients experienced relatively short confirmation delays (median 6.5 days), which suggests that the referral processes and diagnostic pathways implemented at cancer treatment centers operate efficiently overall. Nevertheless, patients specifically those experiencing gingival or jaw lesions experienced longer delays, (median: 21 days from presentation), indicating that diagnostic pathways pertaining specifically to subsites where initial symptoms might mimic benign dental conditions need improvement. Compounding these challenges are knowledge gaps present among practitioners themselves. A multi-institutional study involving nearly 1,000 senior dental students across Yemen found that only 21% felt confident regarding their understanding related to oral cancer while slightly over half felt adequately trained to provide smoking cessation advice effectively [20]. Another survey targeting 247 Yemeni dental students found that 84% failed to recognize key risk factors tied to oral cancer while similar proportions could not identify clinical symptoms associated with it accurately [21]. These educational shortcomings likely translate into lost opportunities concerning early detection since dentists often represent frontline healthcare professionals who first meet individuals displaying signs indicative of oral lesions.

The finding indicating that (90.3%, n=65) of cases arose from rural districts points towards critical geographic inequities affecting health outcomes. Indeed, within rural Hodeidah, early signs related to neoplastic changes are regularly misidentified as minor trauma or infections from chronic usage patterns involving qat chewing which adds further complexity regarding patient-level delays. The limited explanatory power of our multivariable models (Nagelkerke R^2=0.087 for triple burden; adjusted R^2=0.041 for diagnostic delay) suggests that: (1) The concept of triple burden appears to be influenced more by cultural norms at the community level rather than by individual demographic factors. The prevalence rates that are relatively similar across genders (43.5% for females versus 46.2% for males) and the absence of a significant relationship with age or residence suggest that these behaviors are intricately woven into the social fabric of Hodeidah, especially within rural settings.(2) Factors that we were unable to quantify (such as health literacy, fear, financial obstacles, and geographic access) seem to play a pivotal role in determining diagnostic delay. Although the association between rural residence and delayed diagnosis (OR 3.92 for delays exceeding 30 days) was notable, it did not achieve statistical significance, which could be attributable to the limited sample size (n=72). (3) The specific delays observed for gingival/jaw lesions (median wait time of 21.0 days from presentation) may indicate instances of misdiagnosis as dental issues, thereby underscoring the urgent need for enhanced training focused on identifying malignant lesions that may resemble benign conditions.

These insights highlight the necessity for: (1) community-oriented interventions aimed at addressing cultural norms related to substance use; (2) programs designed to improve health literacy regarding the early detection of oral lesions; (3) enhanced training for dental professionals to better identify malignant conditions; and (4) continued research directed at uncovering specific barriers that hinder care-seeking behaviors within this population. This study brings attention to an important therapeutic gap evident amongst participants: it was noted that all patients received systemic chemotherapy alone without any undergoing curative surgical resection or radiotherapy, contradicting established international protocols that recommend surgical resection accompanied by clear margins as the cornerstone of curative treatment strategies aimed toward managing OSCC cases effectively [9].

In Hodeidah, ongoing conflict and economic deterioration have depleted specialized surgical oncology teams and radiotherapy units. This explains why reliance purely upon chemotherapy tends primarily towards palliative measures rather than curative intents, especially concerning advanced stages seen commonly amongst many presenting cases. This likely elucidates elevated mortality-to-incidence ratios commonly associated with oral cancers prevalent throughout Yemen's demographic landscape [25]. Our findings align with the established epidemiological profile of oral cancer in Yemen.

According to Halboub et al., oral cancer accounted for 4.0% of all registered cancer cases in Yemen during the years 2007 to 2008, with the tongue being the most frequently affected site (53.6%) and 71.5% of patients diagnosed at advanced stages [13]. A clinico-epidemiological study conducted in Aden from 2020-2024 reported oral cancer as 1.4% of all registered cancers, with OSCC being the most common type (67.9%)and the tongue asthe most frequent site (46.2%) [17]. The consistency observed in female predominance and risk factor patterns across these studies further reinforces the enduring epidemiological profile of oral cancer in Yemen. This study's strengths include: (1) geographic rigor through a systematic verification process regarding residency within Hodeidah; (2) adjustments to population-based rates were made using local denominators alongside WHO standardization; (3) comprehensive risk coding facilitates quantification of the "triple burden"; (4) robust inferential testing was carried out utilizing non-parametric statistical as well as multivariable analysis with Bonferroni correction; and (5) a novel distinction between patient-level and system-level diagnostic delays.

Nevertheless, certain limitations must be recognized. The focus on a single governorate limits the generalizability of findings to other regions of Yemen that may have differing cultural practices and risk factor profiles. Dependence on registry data might have led to an undercounting of cases diagnosed in private facilities or those not referred to tertiary centers. Furthermore, risk factor data largely relied on self-reporting, which could be influenced by recall issues and social desirability bias, possibly leading to an underestimation of actual exposure prevalence. Consistent availability of stage, grade, and detailed histopathological data was lacking, which hinders a thorough assessment of disease severity and prognostic factors. The relatively modest cohort size (n=72) also limited statistical power for conducting subgroup analyses. Due to its cross-sectional design, establishing causal relationships remains impossible. Calculations regarding diagnostic delay depend on patient-reported dates for symptom onset, which are susceptible to recall bias. Additionally, data regarding mortality, survival rates, and HPV status were not accessible. The ongoing conflict within Yemen has disrupted healthcare services along with data collection systems, which may affect registry completeness. Lastly, the absence of a control group constrains our ability to calculate odds ratios or determine population attributable fractions.

CONCLUSION

Oral cavity cancer poses a significant public health challenge in Hodeidah Governorate with an age-adjusted incidence of 5.65 per 100,000 person-years. The disease predominantly affects females and shows a pronounced concentration in rural settings. The burden is further exacerbated by high levels of multi-substance use: 44.4% of patients engage in the simultaneous use of qat, shammah, and smoking, the 'triple burden'. Compounding these issues is a considerable diagnostic delay, with a median of 45 days from the onset of symptoms to diagnosis, primarily due to factors at the patient level. Multivariable analysis suggests that community-level cultural factors, rather than individual demographics, drive exposure patterns and delays. This underscores an urgent need for enhanced community awareness and early detection initiatives. Moreover, reliance on palliative chemotherapy as the sole treatment option without access to curative surgical or radio therapeutic measures highlights a significant deficiency within the regional oncological infrastructure that necessitates immediate humanitarian intervention.

Recommendations

The findings of this study lead to several key recommendations:

For Public Health Authorities and Policymakers:

1. It is essential to implement integrated substance cessation programs that address qat chewing, shammah use, and tobacco smoking concurrently, while tailoring the messaging culturally for rural women. This is particularly important as 76.1% of female patients reported using shammah. Community and religious leaders should be engaged to promote behavior change effectively.
2. There is a pressing need to launch community-based oral cancer awareness campaigns targeting rural populations, highlighting the significance of early detection of non-healing oral ulcers, red and white lesions, and encouraging prompt healthcare-seeking behavior. Only 24.1% of the population can identify red lesions as early signs of oral cancer [18], underscoring the urgency for these campaigns.
3. Mobile health units and community screening programs are needed to reach remote rural districts, where 90.3% of cases originated, thus reducing barriers related to geography and finances for early diagnosis.
4. It is important to enhance the cancer registry system so that it includes standardized data on stage, grade, histopathological subtype, treatment outcomes, and survival rates, which will enable thorough epidemiological monitoring and evaluation of the effectiveness of interventions.

For Healthcare Institutions and Educators:

5. Dental and medical curricula should be revised to include comprehensive oral cancer education on risk factors identification, clinical recognition of early lesions, biopsy techniques, and cessation counseling. The finding that only 21% of senior dental students feel confident in their knowledge about oral cancer [20] indicates that curriculum reform is necessary.
6. Continuing professional development programs aimed at practicing dentists and primary care physicians should be provided regarding oral cancer screening and early detection to address the knowledge gaps identified among dental professionals [20,21].
7. Streamlined referral pathways from primary care facilities to specialized diagnostic centers must be developed, especially for gingival and jaw lesions which have seen the longest delays (median 21.0 days from healthcare presentation).

For International Humanitarian Organizations:

8. The restoration of surgical oncology and radiotherapy services in Hodeidah should be prioritized, as the complete lack of these services (with 100% of patients receiving chemotherapy alone) indicates a significant gap in cancer care.
9. Telemedicine initiatives should be supported to connect rural healthcare providers with oncology specialists for earlier diagnosis and appropriate referrals.

For Future Research:

10. Multicenter studies across various Yemeni governorates are needed to obtain a national perspective on oral cancer epidemiology.
11. Prospective cohort studies should also be carried out to establish causal relationships between specific combinations of risk factors and different cancer subtypes while assessing survival outcomes.
12. Qualitative research should investigate the impact of fear and psychological barriers on diagnostic delay; fear of diagnosis has been recognized as an overlooked factor contributing to delayed presentation in OSCC [22].

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Authors contributions

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All authors have read and approved the final manuscript.

Conflicts of interest

The authors affirm that there are no conflicts of interest to declare.

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Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request, subject to institutional approval and data protection regulations.

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