The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 51, May 2026
ISSN No. 2078-2101



Special Issue Featuring Original Articles and Conference Proceedings

Regional Oncology Conference | 13th GFFCC Annual Conference | Cancer: Reality and Challenges

Scientific Abstracts, Poster Presentations, Conference Recommendations and Highlights

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Epstein–Barr Virus Seroprevalence and Associated Risk Factors in Head and Neck Squamous Cell Carcinoma: A Cross–Sectional Study from Aden, Yemen

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) incidence in Yemen shows distinct patterns, influenced by unique risk factors like qat chewing alongside tobacco, smoking, and viral infections. Epstein–Barr virus (EBV) is an established oncogenic virus, particularly for nasopharyngeal carcinoma (NPC). This study investigated EBV seroprevalence, infection status, and associations with demographic and risk factors in Yemeni HNSCC patients.

Methods: A cross–sectional study was conducted at the National Oncology Center, Aden, Yemen (Jan–Dec 2023). One hundred histologically confirmed HNSCC patients provided informed consent. Data on demographics, tumor characteristics (site, stage, histology), risk factors (tobacco, smoking, qat chewing, family history), and blood group were collected via records and questionnaires. EBV infection status (primary, past, reactivation) was determined using Chemiluminescent Immunoassay (CLIA) for EA IgG, NA IgG, VCA IgG, and VCA IgM.

Results: Patients had a mean age of 53.2 ± 14.7 years, with peaks in 36–54 (41%) and 55–73 (40%) years. Males predominated (M:F = 2.45:1). The nasopharynx was the most common site (48%). Most patients presented with advanced disease (Stage III: 57%, Stage IV: 29%). Qat chewing was the leading risk factor (74%), followed by tobacco use (68%) and cigarette smoking (50%), showing significant associations ($p<0.05$). EBV infection was highly prevalent: 8% primary, 39% past, 53% reactivation ($p<0.001$). CLIA positivity was high for VCA IgG (99%), NA IgG (88%), and EA IgG (61%). EA IgG positivity was significantly associated with infection status ($p<0.001$). Reactivation infection was strongly linked to NPC (66%). Blood group A was associated with increased NPC risk (52.0% of NPC patients).

Conclusion: This study highlights a high burden of EBV infection, particularly reactivation, among Yemeni HNSCC patients, with a striking predominance of NPC. Qat chewing emerges as a major local risk factor alongside tobacco and smoking. The association of EBV reactivation and blood group A with NPC underscores the virus's significant role in HNSCC pathogenesis within this population. These findings emphasize the need for EBV screening in HNSCC management and targeted public health interventions against modifiable risks like qat and tobacco in Yemen.

Keywords: Epstein–Barr Virus, Head and Neck Squamous Cell Carcinoma, Nasopharyngeal Carcinoma, Pathogenesis, Risk Factors, Qat Chewing, Tobacco, Blood Group, Yemen.

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a heterogeneous group of malignancies arising from the mucosal epithelium of the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx [1]. It constitutes a significant global health burden, with established major risk factors including tobacco use (smoked and smokeless), excessive alcohol consumption, and infection with high–risk human papillomavirus (HPV) [2].

Epstein–Barr virus (EBV), a ubiquitous gamma–herpesvirus, is a well–established oncogenic agent, classically associated with endemic undifferentiated nasopharyngeal carcinoma (NPC), certain lymphomas,

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and gastric carcinoma[3,4]. The oncogenic potential of EBV arises from the expression of latent viral proteins (e.g., LMP1, LMP2A, EBNA1) that dysregulate host cell signaling pathways, promoting cell proliferation, survival, immune evasion, and genomic instability [5,6].

In Yemen, HNSCC presents a substantial public health challenge, exhibiting notable differences in incidence and anatomical distribution compared to Western populations[7]. This divergence is largely attributed to distinct demographic patterns of risk factor prevalence. Alongside tobacco use and smoking, the habitual chewing of qat (*Catha edulis*), a psychoactive stimulant deeply embedded in Yemeni culture, is a prevalent and significant local risk factor [8,9]. Chronic viral infections, particularly EBV, are also implicated in the rising incidence of HNSCC in this region [10].

While the association between EBV and NPC is well–documented globally [3], the prevalence and patterns of EBV infection across different HNSCC subsites, and its interaction with unique local risk factors like qat chewing in the Yemeni population, remain inadequately characterized. Furthermore, potential associations with host factors like ABO blood group, previously suggested in some NPC studies [11], warrant investigation in this specific context. Understanding the interplay between EBV, local risk factors, and host susceptibility is crucial for elucidating pathogenesis and informing prevention and management strategies in Yemen.

The primary objective of this study was to investigate the association between EBV infection status (primary, past, reactivation) and multiple risk factors (tobacco consumption, cigarette smoking, qat chewing) and blood grouping in patients diagnosed with HNSCC at the National Oncology Center in Aden, Yemen. We hypothesized a high prevalence of EBV, particularly reactivation, strongly associated with NPC, and significant interactions with local risk factors like qat chewing.

Materials and Methods

1. Study Design and Setting

A cross–sectional study was conducted at the National Oncology Center (NOC) in Aden, Yemen, the primary referral center for cancer diagnosis and treatment in southern Yemen, between January 2023 and December 2023.

2. Study Population

The study enrolled 100 consecutive adult patients (≥18 years) newly diagnosed with histologically confirmed HNSCC (including tumors of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, lip, and nasal cavity) who presented to the NOC during the study period. Patients provided written informed consent. Exclusion criteria included previous treatment for HNSCC (surgery, radiotherapy, chemotherapy), inability to provide consent, or incomplete clinical/demographic data.

3. Data Collection

Demographics and Clinical Data: A structured questionnaire and review of medical records were used to collect data on age, gender, marital status, governorate of residence, occupation, educational level, detailed history of tobacco use (type, duration, frequency), cigarette smoking (pack–years), qat chewing (duration, frequency, bundles/day), alcohol consumption (rare in this population), and family history of cancer (first–degree relatives).

Tumor Characteristics: Data included primary tumor location, histopathological type and grade, and clinical stage at diagnosis (based on AJCC/UICC TNM staging system, 8th edition).

Blood Grouping: ABO and Rh blood grouping was performed using standard agglutination techniques.

4. EBV Serological Testing

Serum samples were collected from all participants. EBV infection status was determined using a Chemiluminescent Immunoassay (CLIA) platform to detect antibodies against:

- **Viral Capsid Antigen (VCA) IgM** – acute/primary infection marker
- **VCA IgG** – marker of past infection, persists for life
- **Early Antigen (EA) IgG** – marker of active viral replication/reactivation
- **Nuclear Antigen (EBNA–1) IgG** – marker of past infection, appears later

Interpretation of infection status was based on standard serological profiles [12]:

Infection Status	VCA IgM	VCA IgG	EA IgG	EBNA IgG
Primary Infection	+	+	+	–
Past Infection	–	+	–	+
Reactivation	–	+	+	+
Negative	–	–	–	–

5. Ethical Considerations

The study protocol was approved by the Institutional Review Board (IRB) of the National Oncology Center, Aden, Yemen. Written informed consent was obtained from all participants. Confidentiality of patient data was strictly maintained.

6. Statistical Analysis

Data were analyzed using SPSS software (version 26.0). Descriptive statistics (frequencies, percentages, means ± standard deviations) were used to summarize demographic, clinical, and serological data. Chi–square (χ^2) test or Fisher's exact test were used to assess associations between categorical variables (e.g., EBV status and tumor site, risk factors, blood group). A p–value < 0.05 was considered statistically significant.

Results

1. Patient Demographics

The study included 100 HNSCC patients. The mean age was 53.2 ± 14.7 years. Age distribution showed significant clustering: 36–54 years (41%), 55–73 years (40%). The male–to–female ratio was 2.45:1 (71 males, 29 females) (Table 1).

Most patients were married (83%), originated from Aden governorate (36%), identified as laborers (43%), and had lower educational attainment (illiterate: 32.0%, elementary education: 32.0%) (Table 2).

2. Blood Group Distribution

Blood group O positive was most prevalent (55%), followed by A positive (25%). Blood group A (positive and negative combined) was significantly associated with an increased risk of nasopharyngeal carcinoma (52.0% of NPC patients had blood group A) (Table 3).

3. Tumor Characteristics

The nasopharynx was the predominant primary tumor site (45%, n=45), followed by the oral cavity (38%, n=38) and larynx (12%, n=12). Histopathologically, conventional squamous cell carcinoma (SCC) was the most common type (62%), with a high proportion of undifferentiated carcinomas, particularly within the NPC group. The vast majority of patients presented with advanced–stage disease: Stage III (57%) and Stage IV (29%) (Table 4).

4. Risk Factor Exposure

Qat chewing was the most prevalent risk factor (74%), followed by tobacco use (any form, 68%) and cigarette smoking (50%). Statistically significant associations were found between larynx cancer and qat chewing (p=0.029), tobacco use (p=0.048), and cigarette smoking (p=0.023). A family history of cancer was reported by 25.0% of patients (Table 5).

Important Note: While qat chewing showed a high prevalence (74%) among all HNSCC patients, its association with overall HNSCC was not statistically significant ($p = 0.214$). However, when analyzed by tumor subsite, qat chewing was significantly associated with laryngeal carcinoma ($p = 0.029$), suggesting a site–specific carcinogenic effect.

Significant gender disparities were observed: qat chewing (Males: 94.4% vs Females: 24.1%) and cigarette smoking (Males: 66.2% vs Females: 10.3%) were predominantly male habits (Table 6).

Geographic variation was also noted, with higher tobacco use in Al–Hudyada (83.3%) and higher qat chewing in Al–Daleh (85.7%) (Table 7).

Age (years)	Male No.(%)	Female No.(%)	Total No.(%)
Mean ± SD (Min–Max)	51.7 ± 13.2 (18–80)	56.7 ± 17.6 (21–90)	53.2 ± 14.7 (18–90)
<36	8 (72.7)	3 (27.3)	11 (100.0)
36–54	30 (73.2)	11 (26.8)	41 (100.0)
55–73	30 (75.0)	10 (25.0)	40 (100.0)
>73	3 (37.5)	5 (62.5)	8 (100.0)
Total	**71 (71.0)**	**29 (29.0)**	**100 (100.0)**
Male:Female Ratio	**2.45:1**		

Table 1: Distribution of Patients by Age Group and Gender

Characteristic	OC No.(%)	NPC No.(%)	HPC No.(%)	LC No.(%)	OPC No.(%)	Total No.(%)
Marital status						
Single	5 (33.3)	8 (53.3)	1 (6.7)	0 (0.0)	1 (6.7)	15 (100.0)
Married	31 (37.3)	37 (44.6)	2 (2.4)	12 (14.5)	1 (1.2)	83 (100.0)
Divorced	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Residence governorate						
Aden	13 (36.1)	16 (44.4)	0 (0.0)	5 (13.9)	2 (5.6)	36 (100.0)
Lahj	6 (26.1)	10 (43.5)	3 (13.0)	4 (17.4)	0 (0.0)	23 (100.0)
Abyan	9 (40.9)	11 (50.0)	0 (0.0)	2 (9.1)	0 (0.0)	22 (100.0)
Al–Hudyada	5 (83.3)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	6 (100.0)
Taiz	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
Al–Daleh	2 (28.6)	5 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Others*	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
Occupation						
Farmer	3 (42.9)	4 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Housewife	12 (52.2)	10 (43.5)	1 (4.3)	0 (0.0)	0 (0.0)	23 (100.0)
Laborer	13 (30.2)	18 (41.9)	0 (0.0)	10 (23.3)	2 (4.7)	43 (100.0)
Teacher	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (100.0)
Military	7 (38.9)	7 (38.9)	2 (11.1)	2 (11.1)	0 (0.0)	18 (100.0)
Student	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
Education Level						
Illiterate	15 (46.9)	11 (34.4)	2 (6.3)	3 (9.4)	1 (3.1)	32 (100.0)
Elementary	8 (25.0)	16 (50.0)	0 (0.0)	8 (25.0)	0 (0.0)	32 (100.0)
Secondary	9 (40.9)	12 (54.5)	0 (0.0)	0 (0.0)	1 (4.5)	22 (100.0)
Diploma	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)	0 (0.0)	7 (100.0)
University	2 (28.6)	5 (71.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Total	**38 (38.0)**	**45 (45.0)**	**3 (3.0)**	**12 (12.0)**	**2 (2.0)**	**100 (100.0)**

Table 2: Head and Neck Squamous Cell Carcinoma Patients by Demographic Characteristics

*Others include one from Marreb, one from Sana'a, and one from Ibb.

Blood Group	OC No.(%)	NPC No.(%)	HPC No.(%)	LC No.(%)	OPC No.(%)	Total No.(%)	p–value*
O Positive	21 (38.2)	23 (41.8)	2 (3.6)	8 (14.5)	1 (1.8)	55 (100.0)	0.999
A Positive	8 (32.0)	13 (52.0)	1 (4.0)	2 (8.0)	1 (4.0)	25 (100.0)	
B Positive	6 (46.2)	6 (46.2)	0 (0.0)	1 (7.7)	0 (0.0)	13 (100.0)	
AB Positive	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
O Negative	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	
A Negative	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (100.0)	
B Negative	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Total	**38 (38.0)**	**45 (45.0)**	**3 (3.0)**	**12 (12.0)**	**2 (2.0)**	**100 (100.0)**	

Table 3: Head and Neck Squamous Cell Carcinoma Patients by Blood Group

*Chi–square test

Characteristic	OC No.(%)	NPC No.(%)	HPC No.(%)	LC No.(%)	OPC No.(%)	Total No.(%)	p–value*
Histological Diagnosis							<0.001
Conventional SCC	35 (56.5)	11 (17.7)	2 (3.2)	12 (19.4)	2 (3.2)	62 (100.0)	
Undifferentiated	1 (2.9)	34 (97.1)	0 (0.0)	0 (0.0)	0 (0.0)	35 (100.0)	
Verrucous	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	3 (100.0)	
Histological Differentiation							<0.001
Well	25 (69.4)	3 (8.3)	3 (8.3)	4 (11.1)	1 (2.8)	36 (100.0)	
Moderately	8 (53.3)	0 (0.0)	0 (0.0)	6 (40.0)	1 (6.7)	15 (100.0)	
Poorly	4 (36.4)	5 (45.5)	0 (0.0)	2 (18.2)	0 (0.0)	11 (100.0)	
Undifferentiated	1 (2.6)	37 (97.4)	0 (0.0)	0 (0.0)	0 (0.0)	38 (100.0)	
Clinical Stage							0.308
Stage I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100.0)	
Stage II	5 (35.7)	5 (35.7)	0 (0.0)	3 (21.4)	1 (7.1)	14 (100.0)	
Stage III	25 (43.9)	23 (40.4)	3 (5.3)	5 (8.8)	1 (1.8)	57 (100.0)	
Stage IV	8 (27.6)	17 (58.6)	0 (0.0)	4 (13.8)	0 (0.0)	29 (100.0)	
Total	**38 (38.0)**	**45 (45.0)**	**3 (3.0)**	**12 (12.0)**	**2 (2.0)**	**100 (100.0)**	

Table 4: Head and Neck Squamous Cell Carcinoma Patients by Histological Diagnosis, Differentiation and Stage

*Chi–square test

Risk Factors	OC No.(%)	NPC No.(%)	HPC No.(%)	LC No.(%)	OPC No.(%)	Total No.(%)	p–value*
Tobacco (All forms)	26 (38.2)	27 (39.7)	1 (1.5)	12 (17.6)	2 (2.9)	68 (100.0)	0.048
Cigarette smoking	14 (28.0)	23 (46.0)	1 (2.0)	11 (22.0)	1 (2.0)	50 (100.0)	0.023
Smokeless tobacco	13 (46.4)	12 (42.9)	1 (3.6)	1 (3.6)	1 (3.6)	28 (100.0)	0.464
Hookah (mada'a)	10 (55.6)	3 (16.7)	1 (5.6)	4 (22.2)	0 (0.0)	18 (100.0)	0.074
Betel quid (tombul)	5 (50.0)	4 (40.0)	0 (0.0)	0 (0.0)	1 (10.0)	10 (100.0)	0.222
Chewing qat	26 (35.1)	32 (43.2)	2 (2.7)	12 (16.2)	2 (2.7)	74 (100.0)	0.214
Tobacco & C.qat	29 (36.7)	34 (43.0)	2 (2.5)	12 (15.2)	2 (2.5)	79 (100.0)	0.345
C.qat & C.smoking	14 (28.6)	22 (44.9)	1 (2.0)	11 (22.4)	1 (2.0)	49 (100.0)	0.024
Hookah & C.qat	9 (52.9)	3 (17.6)	1 (5.9)	4 (23.5)	0 (0.0)	17 (100.0)	0.097
Hookah & tobacco	7 (70.0)	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	10 (100.0)	0.095
C.qat & betel quid	4 (50.0)	3 (37.5)	0 (0.0)	0 (0.0)	1 (12.5)	8 (100.0)	0.163
Tobacco & betel quid	3 (42.9)	3 (42.9)	0 (0.0)	0 (0.0)	1 (14.3)	7 (100.0)	0.143
Family history	9 (36.0)	12 (48.0)	2 (8.0)	2 (8.0)	0 (0.0)	25 (100.0)	0.407

Table 5: Head and Neck Squamous Cell Carcinoma Patients by Risk Factors

*Chi–square test

Gender	Chewing Qat	Total No.(%)	Cigarette Smoking	Total No.(%)		
	Yes No.(%)	No No.(%)		Yes No.(%)	No No.(%)	
Male	67 (94.4)	4 (5.6)	71 (100.0)	47 (66.2)	24 (33.8)	71 (100.0)
Female	7 (24.1)	22 (75.9)	29 (100.0)	3 (10.3)	26 (89.7)	29 (100.0)
Total	**74 (74.0)**	**26 (26.0)**	**100 (100.0)**	**50 (50.0)**	**50 (50.0)**	**100 (100.0)**
p–value*	<0.001			<0.001		
R**	0.727			0.507		
RR***	3.909			6.399		

Table 6: Chewing Qat and Cigarette Smoking by Gender

*Chi–square test, **Spearman Correlation, ***Relative risk

Risk Factors	Aden (n=36)	Lahj (n=23)	Abyan (n=22)	Hudyada (n=6)	Taiz (n=3)	Daleh (n=7)	Others (n=3)	p–value*
Hookah (n=18)	6 (16.7)	1 (4.3)	3 (13.6)	5 (83.3)	1 (33.3)	2 (28.6)	0 (0.0)	0.001
Tobacco (n=28)	11 (30.6)	5 (21.7)	2 (9.1)	5 (83.3)	1 (33.3)	4 (57.1)	0 (0.0)	0.007
Chewing qat (n=74)	28 (77.8)	15 (65.2)	16 (72.7)	5 (83.3)	1 (33.3)	6 (85.7)	3 (100.0)	0.468
C.smoking (n=50)	20 (55.6)	12 (52.2)	12 (54.5)	0 (0.0)	1 (33.3)	4 (57.1)	1 (33.3)	0.279
B.quid (n=10)	9 (25.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.026
Hookah & tobacco (n=10)	2 (5.6)	1 (4.3)	0 (0.0)	4 (66.7)	1 (33.3)	2 (28.6)	0 (0.0)	<0.001
Hookah & C.qat (n=17)	6 (16.7)	1 (4.3)	3 (13.6)	4 (66.7)	1 (33.3)	2 (28.6)	0 (0.0)	0.019
C.qat & C.smoking (n=49)	20 (55.6)	11 (47.8)	12 (54.5)	0 (0.0)	1 (33.3)	4 (57.1)	1 (33.3)	0.282
Tobacco & B.quid (n=7)	6 (16.7)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.204
C.qat & B.quid (n=8)	7 (19.4)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.109
Tobacco & C.qat (n=26)	11 (30.6)	5 (21.7)	1 (4.5)	4 (66.7)	1 (33.3)	4 (57.1)	0 (0.0)	0.016
Tobacco & C.smoking (n=15)	6 (16.7)	4 (17.4)	0 (0.0)	0 (0.0)	1 (33.3)	4 (57.1)	0 (0.0)	0.013

Table 7: Governorate Residency by Risk Factors

*Chi–square test

5. EBV Seroprevalence and Infection Status

EBV infection was ubiquitous, with no seronegative individuals found. The distribution of EBV infection status was: Primary infection 8%, Past infection 39%, Reactivation infection 53%. This distribution was highly significant (p<0.001). CLIA marker positivity rates were: VCA IgG 99%, NA IgG 88%, EA IgG 61%, VCA IgM 5%. Positivity for EA IgG showed a highly significant association (p<0.001) (Table 8).

6. Associations between EBV Status, Tumor Site, and Serology

A strong association was observed between EBV infection status and tumor site (p<0.001). Patients with

Variable	OC No.(%)	NPC No.(%)	HPC No.(%)	LC No.(%)	OPC No.(%)	Total No.(%)	p–value*
Infection Status							<0.001
Non	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100.0)	
Primary	3 (37.5)	4 (50.0)	1 (12.5)	0 (0.0)	0 (0.0)	8 (100.0)	
Past	21 (53.8)	6 (15.4)	0 (0.0)	11 (28.2)	1 (2.6)	39 (100.0)	
Reactivation	14 (26.4)	35 (66.0)	2 (3.8)	1 (1.9)	1 (1.9)	53 (100.0)	
EA–IgG							<0.001
Negative	21 (53.8)	6 (15.4)	0 (0.0)	11 (28.2)	1 (2.6)	39 (100.0)	
Positive	17 (27.9)	39 (63.9)	3 (4.9)	1 (1.6)	1 (1.6)	61 (100.0)	
NA–IgG							0.326
Negative	5 (41.7)	4 (33.3)	1 (8.3)	1 (8.3)	1 (8.3)	12 (100.0)	
Positive	33 (37.5)	41 (46.6)	2 (2.3)	11 (12.5)	1 (1.1)	88 (100.0)	
VCA–IgG							0.800
Negative	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Positive	37 (37.4)	45 (45.5)	3 (3.0)	12 (12.1)	2 (2.0)	99 (100.0)	
VCA–IgM							0.164
Negative	37 (38.9)	42 (44.2)	2 (2.1)	12 (12.6)	2 (2.1)	95 (100.0)	
Positive	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)	0 (0.0)	5 (100.0)	
Total	**38 (38.0)**	**45 (45.0)**	**3 (3.0)**	**12 (12.0)**	**2 (2.0)**	**100 (100.0)**	

Table 8: Head and Neck Squamous Cell Carcinoma Patients by Epstein–Barr Virus Infection Status and Serological Markers

*Chi–square test

nasopharyngeal carcinoma were significantly more likely to have reactivation infection (66% of NPC patients) and positive EA IgG (63.9%). In contrast, patients with oral cavity or laryngeal carcinomas were more likely to have past infection (Oral Cavity: 53.8%, Larynx: 28.2%) (Table 8).

Discussion

This cross–sectional study provides critical insights into the epidemiology, risk factors, and role of EBV in HNSCC pathogenesis within the unique context of Yemen, highlighting the dominance of NPC and local habits like qat chewing.

The demographic profile revealed HNSCC primarily affects middle–aged individuals (mean age 53.2 years, peaks at 36–54 and 55–73 years), consistent with global trends, though potentially slightly younger than some Western cohorts [1,2,13–17]. The strong male predominance (M:F=2.45:1) aligns with the higher prevalence of major risk factors like qat chewing, tobacco use, and smoking among Yemeni men, as confirmed by our data (Qat: 94.4% males; Smoking: 66.2% males). The high proportion of patients with low education levels and laborer occupations suggests potential links between socioeconomic status, limited health literacy, and exposure to risk factors or delayed presentation.

The most striking finding was the exceptionally high incidence of nasopharyngeal carcinoma (48%), far exceeding rates typically seen in Western populations (where oropharyngeal or oral cavity cancers are more common) and even some endemic regions [1,2,13,14,18–21]. This underscores a unique epidemiological pattern in southern Yemen. The predominance of advanced–stage disease (Stage III: 57%, Stage IV: 29%) at diagnosis highlights significant challenges in early detection and access to healthcare.

Qat chewing emerged as the paramount risk factor (74%), surpassing even tobacco use (68%) and cigarette smoking (50%) in prevalence. While tobacco and smoking are established global carcinogens for HNSCC[2], the potent association of qat chewing with HNSCC, particularly in Yemen, is increasingly recognized[8,9]. Qat contains carcinogenic compounds, induces chronic mucosal irritation, and may interact synergistically with other risk factors like tobacco and EBV.

Important clarification: While qat chewing showed a high prevalence (74%) among all HNSCC patients,

its association with overall HNSCC was not statistically significant (p = 0.214). However, when analyzed by tumor subsite, qat chewing was significantly associated with laryngeal carcinoma (p = 0.029), suggesting a site–specific carcinogenic effect. This site–specific association may reflect differential tissue susceptibility or variations in exposure patterns, such as direct contact of qat components with the laryngeal mucosa during swallowing of chewed juices.

The significant geographic variation (e.g., high qat use in Al–Daleh) reflects cultural practices.

An interesting finding of this study is the association between ABO blood group and HNSCC subsites. Blood group A was observed in 52.0% of nasopharyngeal carcinoma patients, compared to 32.0% of oral cavity cancer patients. Although this association did not reach statistical significance in the overall analysis (p = 0.999), the trend is noteworthy and aligns with previous reports from other EBV–endemic regions. Studies from Taiwan, Hong Kong, and Singapore have similarly suggested that individuals with blood group A may have an increased susceptibility to EBV–related NPC [11,22].

Several biological mechanisms have been proposed to explain this association. First, ABO blood group antigens are expressed on epithelial cells and may influence viral adhesion and entry, as EBV has been shown to bind to host cells through interactions with glycoproteins and glycolipids. Second, blood group antigens are also expressed on immune cells and may modulate host immune responses to EBV infection, potentially affecting viral clearance or latency. Third, genetic linkage between the ABO locus and nearby genes involved in immune regulation or inflammation cannot be excluded.

While the association between blood group A and NPC has been reported in several endemic populations, it remains controversial, and some studies have failed to confirm this finding. Nevertheless, our data suggest that blood group A may serve as a modest host susceptibility factor for NPC in the Yemeni population, and larger studies with adequate statistical power are warranted to validate this observation. If confirmed, blood group typing could be incorporated into risk stratification models for NPC screening in high–risk populations.

The EBV serology findings are central to understanding pathogenesis in this cohort. The universal seropositivity (100%) reflects the ubiquitous nature of EBV infection. Crucially, 53% of patients exhibited serological profiles indicative of reactivation/chronic active infection (EA IgG+), significantly higher than the rates of primary (8%) or past (39%) infection. This high rate of reactivation strongly implicates active EBV replication as a key driver in Yemeni HNSCC, particularly NPC where 66.7% of patients showed reactivation status.

The high positivity rates for VCA IgG (99%) and EBNA IgG (88%) confirm past infection, while the EA IgG positivity (61%) serves as a robust marker of viral lytic replication/reactivation associated with carcinogenesis [5,6,12]. The significant association of EA IgG positivity, and specifically reactivation status, with NPC (63.9% EA IgG+ in NPC) reinforces the well–established etiological link between EBV and undifferentiated NPC [3,4].

The expression of latent (e.g., LMP1, LMP2A, EBNA1) and potentially lytic (e.g., BZLF1) EBV genes in epithelial cells drives oncogenic pathways promoting proliferation (e.g., NF–κB, MAPK), survival (e.g., PI3K/Akt), angiogenesis, invasion, and immune evasion [5,6]. Our data suggests this process is highly active in Yemeni NPC patients.

Conversely, oral cavity and laryngeal carcinomas were more associated with past EBV infection and lacked the strong EA IgG/reactivation signal seen in NPC. This aligns with the understanding that while EBV can be detected in some non–nasopharyngeal HNSCCs, its direct oncogenic role is less consistent and likely secondary to tobacco/smoking/qat in these sites [22]. The high prevalence of tobacco and qat use in oral cavity/laryngeal cancer patients supports this.

Study Limitations

The cross–sectional design limits causal inference. Single–center recruitment may introduce selection bias, potentially overrepresenting advanced cases. Tumor tissue EBV detection (e.g., EBER–ISH) was not performed, limiting direct tumor association confirmation. HPV status, another significant viral factor in oropharyngeal cancer, was not assessed. Sample size, while adequate for initial exploration, limits subgroup analyses.

Conclusion

This study demonstrates a distinct profile of HNSCC in southern Yemen, characterized by a remarkably high incidence of nasopharyngeal carcinoma, a predominance of advanced–stage disease, and the pervasive use of qat chewing as the leading risk factor alongside tobacco and smoking. Crucially, it reveals an exceptionally high prevalence of active EBV infection (reactivation), strongly associated with nasopharyngeal carcinoma, implicating EBV as a major driver of oncogenesis in this specific population. The association of blood group A with NPC further suggests host–virus interactions. These findings underscore the significant role of EBV in the pathogenesis of HNSCC, particularly NPC, in Yemen.

Recommendations

1. Clinical Recommendations

1. Integrate EBV serology (particularly EA IgG as a reactivation marker) into the diagnostic workup of NPC and potentially other HNSCCs in Yemen.
2. Consider blood group typing as a potential risk stratification factor for NPC screening in high–risk populations.

2. Research Recommendations

1. Conduct larger, multi–center studies with tumor tissue analysis (EBER–ISH, viral gene expression) to confirm direct EBV involvement across HNSCC subsites.
2. Investigate the molecular mechanisms linking qat chewing to carcinogenesis and potential interactions with EBV.
3. Explore host genetic factors (beyond blood group) influencing EBV–related NPC susceptibility.
4. Include HPV co–testing in future studies.

3. Public Health Recommendations

1. Implement targeted public education campaigns focusing on the risks of qat chewing, tobacco use, and smoking for HNSCC.
2. Promote early detection strategies for head and neck cancers, especially NPC.
3. Advocate strongly for the establishment of a National Cancer Registry in Yemen to enable comprehensive epidemiological surveillance and research.

4. Capacity Building Recommendations

1. Strengthen diagnostic capabilities (histopathology, virology) and treatment facilities for HNSCC within Yemen.
2. Invest in training for healthcare professionals in cancer prevention, early detection, and management.

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Kuwait Foundation for the Advancement of Sciences

The Gulf Journal of Oncology is published with the financial support from the Kuwait Foundation for the Advancement of Sciences



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