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Epstein Barr Virus Positivity and Behavioral Patterns in Nasopharyngeal Cancer Patients Presenting in Oncology Ward at JPMC, Karachi

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ABSTRACT

Immunohistochemistry tests for the presence of the Epstein-Barr virus latent membrane protein (EBV-LMP), which can be used to diagnose non-Hodgkin's lymphoma. Tumors expressing high amounts of latent membrane protein 1(LMP-1) provide more evidence that EBV is an etiologic agent in the development of non-Hodgkin lymphoma. **Objective:** To investigate the association between Epstein-Barr Virus infection and Nasopharyngeal Cancers within a cohort of 131 patients. **Methods:** A prospective, observational approach was employed, gathering demographic data, addiction profiles, clinical stages, histopathological types, and Epstein-Barr Virus status through patient interviews and medical records review. Polymerase chain reaction assisted in the detection of the Epstein Barr Virus in paraffin-embedded tissue slices that had been treated with formalin. **Results:** Among the participants, 92 (70.2%) tested positive for Epstein-Barr Virus infection. Notably, 49.6% of Epstein-Barr Virus-positive individuals were active smokers, and 64.9% were treatment-naive. Epstein-Barr Virus positivity was prevalent in stage II (40.5%) and stage III (35.1%) nasopharyngeal cancer patients. **Conclusions:** It was concluded that understanding the role of the Epstein-Barr Virus and associated risk factors in nasopharyngeal cancer development is crucial for targeted interventions and preventive measures. Further research could enhance our understanding of Epstein-Barr Virus-associated cancers and inform prospective intervention methods.

INTRODUCTION

Twenty percent of all malignancies in humans, or around 2 million cases annually, have an infectious origin [1]. More and more, research into the connection between infections and cancer is illuminating potential therapeutic and preventative measures by revealing the processes that drive the oncogenic process. Being the first human tumor virus to be identified, the Epstein-Barr virus (EBV) has provided valuable information on the development of cancer and the course of chronic herpesvirus infection [2, 3]. Despite being uncommon internationally, Nasopharyngeal Cancers (NPC) is a hotspot in southern China and Southeast Asia. The male infection rate can exceed 25 cases per 100,000 in many southern Chinese cities, including Zhong Shan City, Zhuhai, and Jiangmen. There may be a mix of genetic predisposition and environmental variables that make people living in these regions more prone to developing non-small cell lung cancer (NPC) [4, 5]. Type I keratinizing squamous cell carcinoma and types II and III non-keratinizing epithelial cell carcinoma are the two main histological forms of NPC recognized by the World Health Organization (WHO) based on the light-microscopically seen tumor cell characteristics. Subtypes of non-keratinizing carcinoma include type II differentiated non-keratinizing carcinoma & type III undifferentiated carcinoma; tumors of types II and III are more likely to be EBV positive [6, 7]. While unique

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keratinizing NPC (type I) accounts for fewer than 20% of all NPC cases worldwide and is relatively rare in southern China, EBV has been linked to the more distinct WHO type I NPC, particularly in regions where undifferentiated NPC is widespread [7, 8]. It is common to associate EBV infection with NPC in regions where the virus is common, such as Southern China and Southeast Asia. The prognostic value and prevalence of EBV and HPVs in NPC tumors identified in Finland were investigated in research by Ruuskanen et al., [9]. Although 93 out of 150 NPC patients tested positive for EBV and 21 out of 150 patients tested positive for HPV, the study found that none of these patients had coinfections. When tested for both viruses, 36 tumors (or 24% of the total) came out negative. The percentage of patients with disease-specific survival after 5 years was 69% for those whose cancers tested positive for EBV, 63% for those who tested positive for HPV, and 39% for those who tested positive for both. Individuals diagnosed with cancer who tested positive for both HPV and EBV had a better chance of overall survival in a multivariable-adjusted study than those whose tumors tested negative for both viruses [9]. Therefore, it is essential to determine whether the patient with NPC has EBV infection or not. This could potentially change the outcome of the disease. However, very little literature is currently available from Pakistan, thus the present study was undertaken to highlight the burden of EBV associated with NPC in a tertiary care hospital.

This study aims to evaluate EBV infection in patients with nasopharyngeal carcinoma (NPC) in a tertiary care center in Karachi, Pakistan.

METHODS

A cross-sectional, observational study was conducted after receiving approval from the Institutional Review Board (IRB Ref No. F.2-81/2022-DENL/116/JPMC) of Jinnah Postgraduate Medical Center, Karachi, Pakistan from the period 1st August 2023 to 30th June 2024. The research was carried out at the Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan, within six months of obtaining IRB approval. The sampling technique was non-probability purposive. We estimated the sample size using a prevalence of 18% of Epstein-Barr Virus, a margin of error of 10%, and a confidence interval of 95% [10]. The formula was used: $n=Z^2P(1-P)/d^2$, where n=Sample size, Z=Z statistic for a level of confidence (1.96 for 95% confidence level), P=Expected prevalence or proportion, and d=Precision. Patients aged 18 years or older and those diagnosed with nasopharyngeal carcinoma on histopathology were included. All samples were checked for EBV status on histopathology. Adults who did not consent and cases where EBV status was not mentioned in histopathology were excluded. To collect data, all eligible participants were given both verbal and written informed consent. Patients were enrolled based on these criteria. Data regarding the patient's socio-economic and demographic (SED) factors, along with other clinical variables were recorded in a predefined pro forma including gender, residence (rural/urban), education level, employment status, income level (low, medium, and high), spouse's occupation, ethnicity (Pashtun, Sindhi, Punjabi), marital status (married, single, divorced, or widowed), parity and gravidity, and age (below 50 years vs. 50 and above), menopausal status (pre, peri, and post-menopausal), symptoms with duration in months, stage at diagnosis (TNM), and grade. EBV viral load was also determined, maintaining patient anonymity throughout the process. As per the instructions provided by the manufacturer, the QIAamp® DNA FFPE Tissue kit was used to extract EBV DNA from tissue blocks (QIAGEN, Hilden, Germany, cat # 56404). After DNA was extracted, it was eluted in a final volume of 50 µL and its concentration was measured with a Nano-Drop spectrometer (Nano-Drop™ 2000/2000c Spectrophotometers). 131 NPC patients' EBV status (positive or negative) was determined from diagnostic laboratory pathology findings. The findings of variables as mentioned above were entered in predesigned proforma. The Statistical Package for the Social Sciences (IBM, IL, version 23.0) was used to analyze the data. All continuous variables, including age at presentation, mean duration of disease, viral loads, etc., were presented as mean and standard deviation. The frequency distribution for categorical variables like the presence of EBV infection and stage, gender etc. were calculated. Vaccination status was also determined among all cases by using the chi-square test. After post-stratification, the impact of sociodemographic parameters on EBV positivity and the stage of nasopharyngeal carcinoma was determined using the Chi-square test. Statistical significance was defined at a p-value<0.05.

RESULTS

The study included 131 participants, with a mean age of 41.82 years. Demographics comprised 61.8% male and 38.2% female participants. Ethnically, 46.6% were Urdu-speaking, and common comorbidities were diabetes mellitus (25.2%) and hypertension (29.0%). Residentially, 59.5% were urban. Socioeconomic status distribution was 42.0% lower, 43.5% middle, and 14.5% upper. Educational background included 45.8% illiterate and 43.5% with matriculation (Table 1).

Table 1: Demographic Characteristics of Study Participants (n=131)

Variables	Mean ± SD	95% C. I
Age in Years	41.82 ± 14.33	39.35-44.30
Age Group		
18-40 Years	58 (44.3)	

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>40 Years	73 (55.7)
Gender	
Male	81 (61.8)
Female	50 (38.2)
Ethnicity	
Urdu	61 (46.6)
Sindhi	38 (29.0)
Punjabi	13 (9.9)
Push toons	8 (6.1)
Balochi	11 (8.4)
Comorbidities	
Diabetes Mellitus	33 (25.2)
Hypertension	38 (29.0)
Ischemic Heart Disease	16 (12.2)
Residential Status	
Urban	78 (59.5)
Rural	53 (40.5)
Socioeconomic Status	
Lower	55 (42.0)
Middle	57 (43.5)
Upper	19 (14.5)
Educational Status	
Illiterate	60 (45.8)
Matric	57 (43.5)
Postgraduate	3 (2.3)
Professional	11 (8.4)

The addiction profile of the participants revealed that 31.3% used Betel Nut, 13.7% used Gutka, 32.1% used Pan, and 3.1% used Naswar. Physical activity was categorized into house chores, inactive lifestyle, regular exercise, and exercise once a week. House chores showed (45) EBV-positive and (13) EBV-negative cases, while an inactive lifestyle had (31) EBV-positive and (15) EBV-negative cases. Regular exercise revealed (3) EBV-positive and (1) EBV-negative cases, and exercise once a week had (13) EBV-positive and (10) EBV-negative cases (Figure 1).

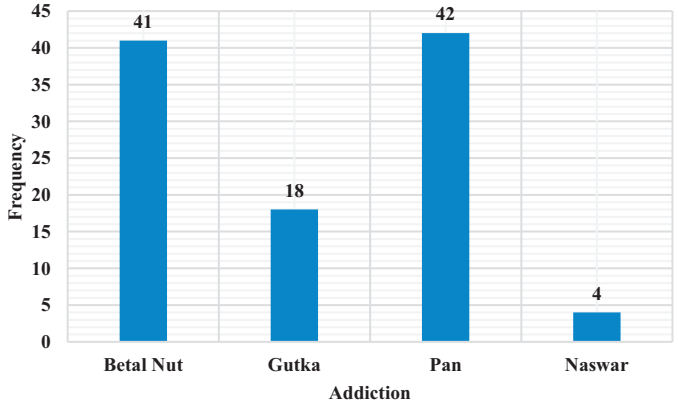

Figure 1: Substance Use among Participants

Physical activity was categorized into house chores, inactive lifestyle, regular exercise, and exercise once a week (Figure 2).

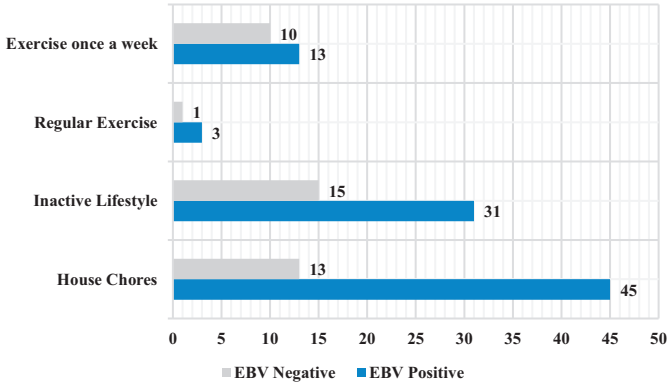

Figure 2: Physical Activity Between EBV Positive & Negative

The relationship between clinical stage, histopathological types according to the WHO classification, and viral status (EBV positive or negative) in 131 patients. Clinical stage distribution includes 5 cases (3.8%) in Stage I, 53 cases (40.5%) in Stage II, 46 cases (35.1%) in Stage III, and 27 cases (20.6%) in Stage IV. Regarding histopathological types, Type I is observed in 62 cases (47.3%), Type II in 14 cases (10.7%), and Type III in 55 cases (42.0%) (Table 2).

Table 2: Relationship Between Clinical Stage and Histological Types According to the WHO Classification and Viral Status (n=131)

Variables	All Patients	EBV Positive (n=92)	EBV Negative (n=39)	p-Value
Clinical Stage				
Stage I, n (%)	5 (3.8)	4 (3.1)	1 (0.8)	<0.001
Stage II, n (%)	53 (40.5)	44 (33.6)	1 (0.8)	
Stage I, n (%)	5 (3.8)	4 (3.1)	1 (0.8)	
Stage III, n (%)	46 (35.1)	33 (25.2)	13 (9.9)	
Histopathological Type				
Type I, n (%)	62 (47.3)	58 (44.3)	4 (3.1)	<0.002
Type II, n (%)	14 (10.7)	11 (8.4)	3 (2.3)	
Type III, n (%)	55 (42.0)	23 (17.6)	32 (24.4)	

EBV (Epstein-Barr virus) and vaccination status against measles and chickenpox in a cohort of 131 patients. Among the vaccinated group (n=57), 39 (29.8%) were EBV-positive, and 18 (13.7%) were EBV-negative. In the non-vaccinated group (n=74), 53 (40.5%) were EBV-positive, and 21 (16.0%) were EBV-negative. The p-value for the comparison is 0.691, indicating no statistically significant difference in EBV status based on vaccination against measles and chickenpox (Table 3).

Table 3: Comparison Between EBV and Vaccination Status Against Measles & Chicken Box (n=131)

Variables	Vaccinated (n=57)	Non-Vaccinated (n=74)	p-Value
Vaccination Status Against Measles & Chicken Box			
EBV Positive, n (%)	39 (29.8)	53 (40.5)	0.691
EBV Negative, n (%)	18 (13.7)	21 (16.0)	

Applied Chi-Square test, EBV (Epstein Barr Virus)

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The relationship was analyzed between EBV (Epstein-Barr virus) status and numerous risk factors in 131 individuals, including smoking, alcohol intake, family history of cancer, cancer therapy, oral contraception, steroid use, and eating habits. Among the EBV-positive group (n=92), 49.6% were active smokers, 13.0% consumed alcohol, 64.9% were treatment-naive, and 59.5% had a family history of cancer and other factors. In the EBV-negative group (n=39), the corresponding percentages were lower. Each risk factor is given an odds ratio (OR), a 95% confidence interval (CI), and a p-value to indicate the intensity and significance of the association with EBV status (Table 4).

Table 4: EBV, Risk Factor with Smoking, Alcohol, Family History of Cancer, Treatment Uses and Eating Habits (n=131)

Variable	EBV Positive (n=92)	EBV Negative (n=39)	OR	95% CI	p-Value
Smoking Status					
Active Smoker	65 (49.6)	33 (25.2)	0.429	(0.18-1.00)	0.105
Passive Smoker	19 (14.5)	6 (4.6)			
Non-Smoker	8 (6.1)	0 (0.0)			
Alcohol Consumption					
Yes	17 (13.0)	10 (7.6)	0.657	(0.27-1.60)	0.354
No	75 (57.3)	29 (22.1)			
Treatment-Naïve					
Yes	85 (64.9)	33 (25.2)	2.208	(0.69-7.05)	0.173
No	7 (5.3)	6 (4.6)			
Family History of Cancer					
Yes	78 (59.5)	32 (24.4)	1.219	(0.45-3.30)	0.697
No	14 (10.7)	7 (5.3)			
Any Other Cancer					
Yes	3 (2.3)	1 (0.8)	1.281	(0.12-12.71)	0.656
No	89 (67.9)	38 (29.0)			
Oral Contraception					
Yes	14 (10.7)	7 (5.3)	0.821	(0.30-2.22)	0.697
No	78 (59.5)	32 (24.4)			
Uses of Steroids					
Yes	43 (32.8)	22 (16.8)	0.678	(0.31-1.44)	0.311
No	49 (37.4)	17 (13.0)			
Eating Habit (Salt Cured Fish)					
Yes	39 (29.8)	17 (13.0)	0.952	(0.44-2.02)	0.899
No	53 (40.5)	22 (16.8)			
Eating Habit (Salt Cured Meat)					
Yes	42 (32.1)	18 (13.7)	0.980	(0.46-2.07)	0.958
No	50 (38.2)	21 (16.0)			

Applied Chi-Square test, EBV (Epstein Barr Virus), OR (Odd Ratio), CI (Confidence Interval)

DISCUSSION

This prospective, observational study underscores the association between Nasopharyngeal Cancers (NPC) and Epstein-Barr Virus (EBV), revealing that among 131 NPC patients, 92 tested positive for EBV infection. Furthermore, this research sheds light on the addiction profile, elucidating the connection between EBV status and various risk factors. Within the EBV-positive group, 49.6% were active smokers, 13.0% consumed alcohol, 64.9% were treatment-naive, and 59.5% had a family history of cancer, among other factors. A similar study on the aetiology of NPC found that the homogeneous histopathological type of NPC, which is frequent in southern China and Southeast Asia, had the strongest relationship between EBV infection and human tumors [11]. It also states that risk factors for NPC include genetic predisposition, dietary factors (salt-cured meat and fish), and EBV infection. In contrast, our findings showed that salt-cured meat and fish were not related to the development of NPC. Sharif *et al.*, mentioned in their research on Focus on NPC that the WHO classification categorizes NPC into three histopathological types, distinguishing them based on the degree of differentiation. Type I NPC is keratinizing squamous cell carcinoma (SCC), similar to other head and neck malignancies; Type II is differentiated non-keratinizing carcinoma; and Type III is undifferentiated carcinoma [12]. In regions with a high prevalence, such as Southern China, more than 97% of nasopharyngeal carcinoma cases are classified as World Health Organization (WHO) Type III, which represents undifferentiated carcinoma. Conversely, keratinizing squamous cell carcinoma (SCC) is more prevalent in Western countries. There are many other similar studies supporting this evidence [13, 14]. In the local context, a study by Su et al, found non-keratinizing NPC was the most prevalent subtype, constituting 92% (92 cases) while keratinizing squamous cell carcinoma (KSCC) accounted for 8% (8 cases) [15]. However, in our study, most of the patients of NPC were found to have histopathology Type I (n=62) of which 58 patients were EBV-positive. Though an EBV infection may increase the likelihood of developing undifferentiated carcinoma of the n (NPC), it is not a necessary condition for the development of this cancer [16]. In addition to EBV, other variables, such as environmental hazards and genetic predisposition, may combine with EBV to cause NPC. Factors that increase the likelihood of developing Type III nasopharyngeal carcinoma (NPC) include being of Cantonese ethnicity, being male, having Epstein-Barr virus (EBV) infection, having a personal or family history of NPC, eating too much salt-preserved fish, not getting enough fresh produce, smoking, and having specific human leukocyte antigen (HLA) class I alleles [10]. Similarly, in this study, it was observed that 61.8% of male were affected and a positive familial history (OR=1.219) is associated with the development of NPC. In the local context, research conducted on the clinical presentation of NPC at Jinnah Hospital Lahore revealed that 76% of male are affected [17]. Another study by Al-Anazi *et al.*, revealed the link between nasopharyngeal carcinoma (NPC) risk and cigarette smoking which

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appeared more pronounced for non-keratinizing carcinoma compared to keratinizing squamous cell carcinoma (KSCC), while a family history of cancer showed a stronger association with KSCC. The study did not find an association between NPC risk and alcohol consumption. The findings indicate that cigarette smoking and a family history of cancer can both operate as risk factors for NPC aetiology, potentially impacting the risk of different histopathological types of NPC in distinct ways. Internationally, previously reported that 75% and 75.5% of their NPC patients presented with neck mass respectively [18], which is only slightly more than our study whereas one study reported neck swellings in 80.8% of patients which could be due to loco-regional difference in presentation of NPC [19]. Globally, neither type I nor type II has been linked to a specific disease. For example, in Hau et al., a study from China, EBV type I dominated in patients with leukemia as well as those with myelodysplastic syndrome [21]. Likewise, in a study conducted on healthy blood donors from different nationalities in Qatar, EBV genotype I also predominated [20]. It is worth noting in our study that thirteen samples could not be genotyped because the PCR reaction yielded insufficient amplicon. One possible explanation could be the degradation or fragmentation of the viral DNA inside the block, possibly due to a stringent paraffin fixation procedure or long-term storage. Prolonged formalin fixation causes proteins as well as nucleic acid crosslinking. This understanding may contribute to a better comprehension of NPC aetiology overall and within each histologic type, offering insights that could enhance preventive efforts. Further information on the function of EBV and related risk factors in the onset and advancement of NPC is provided by the latest research. To establish a robust correlation between EBV and NPC subtypes across various ethnic groups, as well as to provide novel prospective therapeutic approaches for this EBV-associated malignancy, more study is necessary.

CONCLUSIONS

It was concluded that this study highlighted a significant association between Epstein-Barr Virus (EBV) infection and nasopharyngeal carcinoma (NPC) revealing that 70.2% of NPC patients were EBV-positive. Notably, EBV positivity was linked with higher stages of NPC. These findings highlight the importance of EBV in NPC's aetiology and progression, suggesting that understanding these relationships could lead to more effective screening, prevention, and treatment strategies. Future research should focus on revealing the complex interactions between EBV, genetic predispositions, and environmental factors in NPC development, providing a foundation for innovative therapeutic interventions and improved patient outcomes.

Authors Contribution

Conceptualization: SN
Methodology: SN, ZM, TBK
Formal analysis: MJ, AS, BR, SS
Writing review and editing: SN, GH, MJ, SZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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