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HPV status in patients with nasopharyngeal carcinoma in the United States: A SEER database study

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ABSTRACT

Purpose: To investigate the etiologic and prognostic role of Human Papilloma Virus (HPV) in Nasopharyngeal Carcinoma (NPC).

Materials and methods: Patients diagnosed with NPC were identified with the Surveillance, Epidemiology, and End Results (SEER) database. Logistic regression was used to investigate the effect of clinicopathologic predictors on HPV positivity in NPC. Survival analyses were performed with Kaplan-Meier curves and Cox regression models.

Results: 180/517 patients (34.8%) with known HPV testing were positive for HPV-associated NPC. East Asians and individuals over 25 were less likely to have HPV-associated NPC, while controlling for AJCC-7 stage and AJCC-7 M stage. According to the survival analysis, cause-specific survival (CSS) did not differ significantly by HPV status throughout the study period, but did differ significantly by HPV ethnicity group.

Conclusions: The clinical implications of HPV in NPC are further elucidated but require more investigation.

Level of evidence: IV.

1. Introduction

Viral carcinogenesis is an important concept in head and neck oncology. Epstein-Barr virus (EBV), a member of the gamma herpesvirus family, is strongly associated with the undifferentiated nonkeratinizing subtype of endemic nasopharyngeal carcinoma [1]. In the clinical setting, this etiologic understanding has resulted in the use of plasma EBV DNA for screening high risk populations, providing prognostic information, assessing response to treatment, and monitoring for recurrence [2]. Experimental treatments are also being used to treat advanced disease, including therapeutic EBV vaccines.

Human Papilloma Virus (HPV), a sexually transmitted DNA virus, has changed the landscape of oropharyngeal cancer. HPV-associated oropharyngeal squamous cell cancer (ORSCC) has unique molecular pathogenesis and clinical behavior; this disease entity presents in younger patients without traditional risk factors and confers a better prognosis and response to treatment [3,4]. This has resulted in fundamental changes in clinical practice, including a separate staging system in the 8th edition of AJCC, a surge of deintensification clinical trials [5], and most recently, an expansion in the indications for the HPV vaccine.

The role of HPV in other cancers of the head and neck is not well established. Emerging evidence suggests that HPV may play a role in the pathogenesis and prognosis of nasopharyngeal carcinoma.

Biologically, HPV may have tropism for the lymphoepithelial-rich regions of the nasopharynx similar to the tonsil and base of tongue [6]. Vertical transmission and orogenital sex have been proposed as methods for acquiring HPV-associated NPC [7,8]. However, the etiologic and prognostic significance of HPV in both endemic and nonendemic NPC is unclear as most of the literature involves single institution studies with small patient cohorts. A recent study utilized the National Cancer Database (NCDB) to overcome the limitations of small patient numbers [9]; Verma et al. concluded that HPV did not predict survival in NPC. Further, in a recently published systematic review and meta-analysis, a definitive conclusion could not be drawn regarding the prognostic significance of HPV in NPC [10]. To further investigate the role of HPV in cancers of the nasopharynx, we conducted a retrospective cohort study using the Surveillance, Epidemiology and End Results (SEER) database, which collects data on cancer cases from

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various locations and sources across the United States.

2. Methods

2.1. Study design and data source

A retrospective cohort study was conducted with SEER Database (November 2017 Submission). Funded since 1973, the SEER program is supported by the Surveillance Research Program (SRP) in the National Cancer Institute's (NCI) Division of Cancer Control and Population Sciences (DCCPS). It collects and publishes data on cancer incidence and survival from population-based cancer registries covering approximately 34% of the U.S. population. Data is collected from 19 U.S. geographic areas that are representative of the demographics of the entire U.S. population. Approval by the Northwell IRB was not obtained since the data was de-identified and approved for collection. SEER ∗ Stat was used to access the data.

2.2. Patient and variable selection

Eligible patients diagnosed with nasopharyngeal cancer between 2013 and 2015 were identified using the International Classification of Diseases for Oncology Third Edition (ICD-O-3) topography codes for site of origin and (110, 111, 112, 113, 118, 119) and histologic type (8070, 8071, 8072, 8073, 8020, 8021, 8082). Inclusion criteria included histologically-confirmed NPC; patients with cancers of other head neck subsites and those missing follow-up data were excluded from the analysis. Variables extracted included age, gender, year of diagnosis, race, state, AJCC-7 stage, AJCC-7 T stage, AJCC-7 N stage, AJCC-7 M stage, tumor size, HPV status, survival months, SEER cause-specific death classification, sequence of primary disease, ethnicity, marital status, income level, and education level. Of note, EBV status, HPV subtype, and method of HPV detection were unavailable in the SEER database.

2.3. Statistical analysis

A chi-square test was used to determine if there was association between clinicopathologic characteristics and HPV status. Univariable and multivariable logistic regression models were used to evaluate the relationship between HPV status and clinicopathologic factors. Univariable logistic regression was used to screen out variables, and we selected those with overall p-values < 0.15 as candidate variables for the next step. A final multivariable model was constructed with a stepwise method by Akaike Information Criterion (AIC). The Kaplan-Meier (KM) curve was used to estimate CSS, defined as the time from diagnosis to death from NPC. Patients who did not experience the event of interest (death) were censored. Log-rank and Wilcoxon tests were used to find survival differences between the KM curves. Additionally, Cox proportional hazards (CPH) model was used to estimate the hazard ratio (HR) for the identified variables; both univariable and multivariable analyses were performed for CSS. Univariable analysis was used to screen out variables, and we selected variables with overall p-values < 0.15. With these candidate variables, we utilized a stepwise method by AIC to construct a final multivariable model. Of note, the 517 patients with known HPV status were included in the logistic regression and Kaplan-Meier survival analyses. However, in the Cox regression survival analysis, 1527 patients with known survival months and censoring information were included. For both final multivariable logistic regression model and final multivariable CPH model, p-values < 0.05 were considered statistically significant for binary variables, whereas p-values $< 0.05/K$ were considered statistically significant for categorical variables with K pairwise comparisons due to the Bonferroni correction to account for multiple testing. All statistical analyses were performed using R version 3.5.1.

Table 1
Clinical features and characteristics of the study population stratified by HPV status.

Variable	Full sample (N = 517) No. (%)	HPV+ (N = 180) No. (%)	HPV– (N = 337) No. (%)	p-Value
Gender				0.741
Male	368 (71.2%)	126 (70%)	242 (71.8%)	
Female	149 (28.8%)	54 (30%)	95 (28.2%)	
Age				0.001*
0–24	19 (3.7%)	12 (6.7%)	7 (2.1%)	
25–49	138 (26.7%)	39 (21.7%)	99 (29.4%)	
50–74	323 (62.5%)	123 (68.3%)	200 (59.3%)	
75+	37 (7.2%)	6 (3.3%)	31 (9.2%)	
Marital status[a]				0.695
Single	118 (26.5%)	42 (28.4%)	76 (25.6%)	
Married	298 (70.0%)	98 (66.2%)	200 (67.3%)	
Others[b]	29 (6.5%)	8 (5.4%)	21 (7.1%)	
Ethnicity				< 0.001*
White	263 (50.9%)	113 (62.8%)	150 (44.5%)	
East Asians[c]	98 (19.0%)	21 (11.7%)	77 (22.8%)	
Others[d]	156 (30.2%)	46 (25.6%)	110 (32.6%)	
Histologic type				0.339
Keratinizing[e]	204 (39.5%)	78 (43.3%)	126 (37.4%)	
Diff/nonkera[f]	162 (31.3%)	58 (32.2%)	104 (30.9%)	
Undiff/nonkera[g]	51 (9.9%)	14 (7.8%)	37 (11.0%)	
Others[h]	100 (19.3%)	30 (16.7%)	70 (20.8%)	
AJCC-7 Stage[i]				0.127
I	42 (8.1%)	10 (5.6%)	32 (9.5%)	
II	95 (18.4%)	38 (21.1%)	57 (17.0%)	
III	155 (30.0%)	53 (29.4%)	102 (30.4%)	
IV[j]	204 (39.5%)	68 (37.8%)	136 (40.5%)	
Unknown	20 (3.9%)	11 (6.1%)	9 (2.7%)	
AJCC-7 T stage[k]				0.298
Early stage[l]	261 (53.3%)	83 (49.7%)	178 (55.1%)	
Advanced stage[m]	229 (46.7%)	84 (50.3%)	145 (44.9%)	
AJCC-7 N stage[n]				1
N = 0	116 (22.9%)	40 (22.6%)	76 (23%)	
N > 0	391 (77.1%)	137 (77.4%)	254 (77%)	
AJCC-7 M Stage[o]				0.047*
M0	468 (90.7%)	170 (94.4%)	298 (88.7%)	
M1	48 (9.3%)	10 (5.6%)	38 (11.3%)	
Sequence number				0.428
One primary only	441 (85.3%)	150 (83.3)	291 (86.4%)	
Others[p]	76 (14.7%)	30 (16.7)	46 (13.6%)	

Abbreviations: Diff/nonkera = differentiated/nonkeratinizing; undiff/nonkera = undifferentiated/nonkeratinizing.

* p values < 0.05 were considered statistically significant.

[a] Data on 72 patients was missing.

[b] Others include divorced, separated, unmarried, domestic partner, and widowed.

[c] East Asian includes Chinese, Japanese, Korean (1988+), and Vietnamese (1988+).

[d] Others include American Indian/Alaska Native, Asian Indian (2010+), Asian Indian or Pakistani-NOS (1988+), Black, Fiji Islander (1991+), Filipino, Guamanian-NOS (1991+), Hawaiian, Hmong (1988+), Kampuchean (1988+), Laotian (1988+), Micronesian-NOS (1991+), Other, Other Asian (1991+), Pacific Islander-NOS (1991+), Pakistani (2010+), Polynesian-NOS (1991+), Samoan (1991+), Thai (1994+), and Tongan (1991+).

[e] Keratinizing squamous cell carcinoma includes 8070 and 8071.

[f] Differentiated non-keratinizing carcinoma includes 8072 and 8073.

[g] Undifferentiated non-keratinizing carcinoma includes 8020, 8021, 8082.

[h] Others include 8000, 8010, 8032, 8041, 8046, 8051, 8074, 8075, 8083, 8090, 8121, 8123, 8140, 8200, 8240, 8246, 8260, 8310, 8430, 8480, 8525, 8560, 8562, 8800, 8801, 8802, 8805, 8890, 8900, 8910, 8920, 8941, 8982, 9364, 9370, 9371, and 9500.

[i] Data on 1 patient was missing.

[j] IV includes IVA, IVB, IVC, and IV NOS (Not Otherwise Specified).

[k] Data on 27 patients were missing; T0 and TX were considered missing.

[l] Early stage includes T1 and T2.

[m] Advanced stage includes T3, T4, T4a, and T4b.

[n] Data on 10 patients was missing; NX was considered missing.

[o] Data on 1 patient was missing.

[p] Others include 1st of 2 or more primaries, 2nd of 2 or more primaries, 3rd of 3 or more primaries, and 4th of 4 or more primaries.

Table 2
Univariable logistic regression for prediction of HPV positivity in NPC.

Variable	OR (95% CI)	*p*-Value
Gender		
Female	1(−)	Reference
Male	1.21 (0.91–1.61)	0.665
Age[a]		0.001*
0–24	1(−)	Reference
25–49	0.23 (0.08–0.61)	0.004
50–74	0.36 (0.13–0.92)	0.036
75+	0.11 (0.03–0.39)	0.0008
Marital status[a]		0.691
Single	1(−)	Reference
Married	0.89 (0.57–1.39)	0.599
Others	0.69 (0.27–1.64)	0.416
Ethnicity[a]		< 0.001*
White	1(−)	Reference
East Asian	0.36 (0.21–0.61)	0.0002
Others	0.56 (0.36–0.84)	0.006
Histology[a]		0.331
Keratinizing	1(−)	Reference
Diff/nonkera	0.90 (0.59–1.38)	0.632
Undiff/nonkera	0.61 (0.30–1.18)	0.154
Other	0.69 (0.41–1.15)	0.16
AJCC-7 stage[a]		0.131*
I	1(−)	Reference
II	2.13 (0.96–5.04)	0.07
III	1.66 (0.78–3.80)	0.204
IV	1.60 0.77–3.61)	0.23
Unknown	3.91 (1.28–12.55)	0.018
AJCC-7 T stage		
Early stage	1(−)	Reference
Advanced stage	1.24 (0.85–1.81)	0.256
AJCC-7 N stage		
N = 0	1(−)	Reference
N > 0	1.02 (0.67–1.59)	0.912
AJCC-7 M stage		
M = 0	1(−)	Reference
M = 1	0.46 (0.21–0.91)	0.036*
Sequence number		
One primary only	1(−)	Reference
Others	1.27 (0.76–2.08)	0.357

Abbreviations: OR = odds ratio; 95% CI = 95% confidence interval; diff/nonkera = differentiated/nonkeratinizing; undiff/nonkera = undifferentiated/nonkeratinizing.

* *p* values < 0.15 were considered as candidate variables for multivariable analysis.

[a] Overall *p*-value obtained from log likelihood test (LRT) for variables with > 2 categories.

Table 3
Multivariable logistic regression for prediction of HPV positivity in NPC.

Variable	OR (95% CI)	*p*-Value
Age		
0–24	1(−)	Reference
Age 25–49	0.20 (0.06–0.55)	0.002*
Age 50–74	0.26 (0.09–0.71)	0.01*
Age 75+	0.08 (0.02–0.28)	< 0.001*
Ethnicity		
White	1(−)	Reference
East Asian ethnicity	0.36 (0.20–0.63)	< 0.001*
Other ethnicity	0.52 (0.33–0.80)	0.004*
AJCC-7 stage		
I	1(−)	Reference
II	2.33 (1.02–5.67)	0.051
III	1.68 (0.77–3.95)	0.21
IV	1.91 (0.87–4.48)	0.119
Unknown	4.58 (1.43–14.38)	0.011*
AJCC-7 M stage		
M = 0	1(−)	Reference
M = 1	0.47 (0.20–1.00)	0.061

Abbreviations: OR = odds ratio; 95% CI = 95% confidence interval.

* *p* values < 0.05 are considered statistically significant for binary variables, whereas *p* values < 0.05/K are considered statistically significant for categorical variables with K pairwise comparisons.

3. Results

3.1. Cohort characteristics

Of 1762 patients with NPC, 517 had known HPV testing. In this cohort, 180 patients (34.8%) had HPV-Positive NPC and 337 patients (65.2%) had HPV-negative NPC. There were 368 males (71.2%) and 149 females (28.8%). Age frequencies were 19 (3.7%) for 0–24, 138 (26.7%) for 25–49, 323 (62.5%) for 50–74, and 37 (7.2%) for over 75 years. Most of the cohort was married (70.0%), while half of the cohort was Caucasian (50.9%). Histology frequencies were 204 (39.5%) for keratinizing, 162 (31.3%) for differentiated non-keratinizing, 51 (9.9%) for undifferentiated non-keratinizing, and 100 (19.3%) for others. Most of the patients had either stage III or IV disease (69.5%), with nodal involvement (77.1%), and no distant metastases (90.7%). Most patients had one primary only (85.3%). The characteristics of the cohort stratified by HPV status are further detailed in Table 1.

3.2. Predictors of HPV positivity

Four of ten potential variables were selected as candidate from univariable logistic regression (Table 2): age, ethnicity, AJCC-7 stage, and AJCC-7 M stage. All four variables remained in the final multivariable model after stepwise selection by AIC (Table 3). The odd ratios (ORs) of age were all lower than 1, indicating that individuals older than 25 years were less likely to have HPV-associated NPC than those under 25 years (OR [25–49 years] = 0.20, 95% CI 0.06–0.55, $p < 0.01$; OR [50–74 years] = 0.26, 95% CI 0.09–0.71, $p = 0.01$; OR [75+ years] = 0.08, 95% CI 0.02–0.28, $p < 0.01$). Furthermore, East Asians were less likely than Caucasians to have HPV-associated NPC (OR = 0.36, 95% CI 0.20–0.63, $p < 0.01$). Other ethnicities were less likely to HPV positive as well (OR = 0.52, 95% CI 0.33–0.80, $p < 0.01$). The ORs of AJCC-7 stage were all > 1, which indicates that individuals with higher AJCC-7 stage, including II, III, and IV stages, were more likely to have HPV-associated NPC than those with stage I (OR [II] = 2.33, 95% CI 1.02–5.67, $p = 0.05$; OR [III] = 1.68, 95% CI 0.77–3.95, $p = 0.21$; OR [IV] = 1.91, 95% CI 0.87–4.48, $p = 0.12$). Individuals with unknown AJCC-7 stage were highly likely to have HPV-associated NPC (OR = 4.58, 95% CI 1.43–15.38, $p = 0.01$). Finally, the presence of metastatic disease decreased the odds of HPV-associated NPC (OR = 0.47, 95% CI 0.20–1.00, $p = 0.06$).

3.3. Survival analysis (CSS)

The median survival time was inestimable given the number of excess censored observations. A Kaplan-Meier curve was constructed, and the log rank and Wilcoxon tests showed no significant difference in CSS between patients with HPV-associated and HPV-unassociated NPC ($p = 0.75$, $p = 0.80$, Fig. 1). A second Kaplan-Meier curve was constructed, and the log rank and Wilcoxon tests showed a significant difference in CSS between HPV ethnicity groups ($p = 0.01$, $p = 0.01$, Fig. 2). We can observe that HPV positivity was associated with worse CSS in Caucasians and better CSS in East Asians over the study period. Survival analysis was also performed with univariable and multivariable Cox regression models.

Eight of eleven potential candidate variables, including HPV status, were selected from univariable analysis (Table 4): age, marital status, ethnicity, histologic type, AJCC-7 stage, AJCC-7 T stage, AJCC-7 M stage, and sequence number. All of these variables except marital status and AJCC-7 stage were included in the final model after stepwise selection by AIC. Of note, HPV status was not significantly associated with

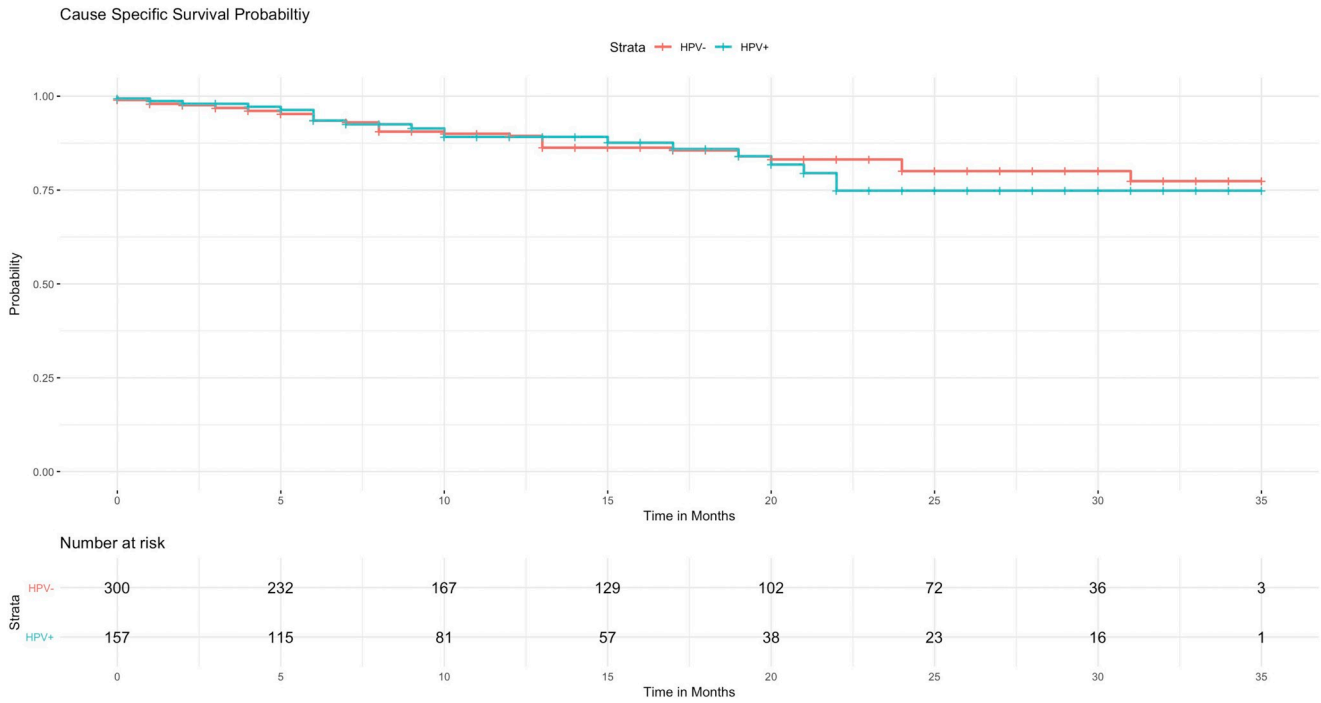

Fig. 1. Kaplan-Meier curves of cause-specific survival (CSS) stratified by HPV status. The difference in survival between groups was not significant ($p = 0.75$).

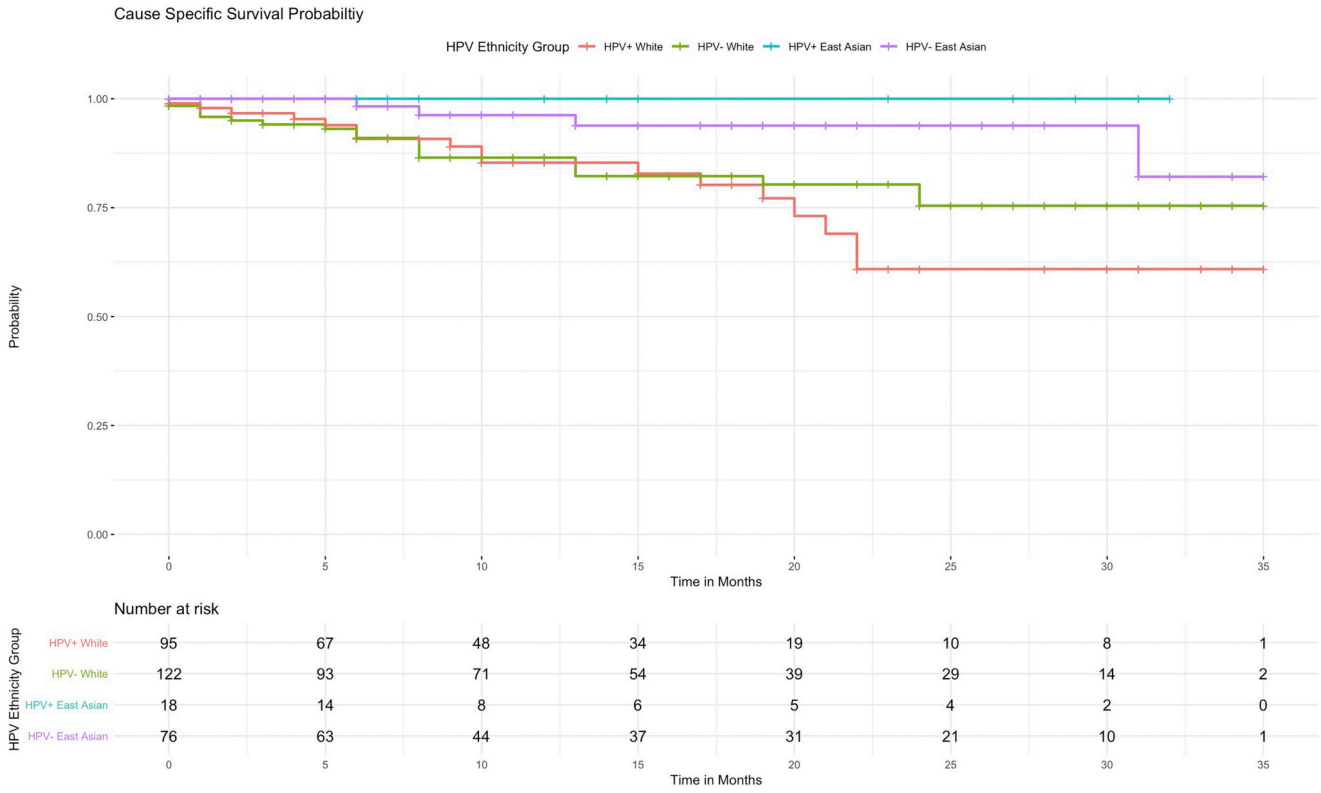

Fig. 2. Kaplan-Meier curves of cause-specific survival (CSS) stratified by HPV ethnicity group. The difference in survival between groups was significant ($p = 0.012$); HPV positivity was associated with better CSS in East Asians and worse CSS in Caucasians. East Asian = Chinese, Japanese, Korean, and Vietnamese.

CSS ($p = 0.76$). In the final multivariable cox regression model (Table 5), the HRs (Hazard Ratios) of age were all > 1. This implies that older patients definitely had higher death rate than those under 25 years (HR [25–49 years] = 2.22, 95% CI 0.53–9.32, $p = 0.28$; HR [50–74 years] = 5.53, 95% CI 1.36–22.44, $p = 0.02$; HR [75+ years] = 11.43, 95% CI 2.67–48.97, $p < 0.01$). The death rate of East Asians was 0.55 times that of Caucasians (HR = 0.55, 95% CI 0.34–0.89, $p = 0.01$), and the death rate between.

Caucasians and other ethnicities was not significantly different ($p = 0.79$). The HRs of histologic type were all lower than 1. In particular, the death rate of the undifferentiated non-keratinizing carcinoma group was 0.29 times that of the keratinizing squamous cell carcinoma

Table 4
Univariable cox regression for cause-specific survival (CSS).

Variable	HR (95% CI)	*p*-Value
Gender		
Female	1(−)	Reference
Male	1.21 (0.91–1.61)	0.182
Age[a]		< 0.001*
0–24	1(−)	Reference
25–49	0.96 (0.43–2.14)	0.92
50–74	2.10 (0.98–4.47)	0.055
75 +	4.58 (2.04–10.29)	0.0002
Marital status[a]		0.016*
Single	1(−)	Reference
Married	0.79 (0.58–1.08)	0.14
Others	1.60 (0.97–2.66)	0.068
Ethnicity[a]		< 0.001*
White	1(−)	Reference
East Asian	0.44 (0.30–0.65)	< 0.001
Others	0.77 (0.58–1.01)	0.058
Histology[a]		< 0.001*
Keratinizing	1(−)	Reference
Diff/nonkera	0.50 (0.36–0.71)	0.001
Undiff/nonkera	0.24 (0.14–0.41)	< 0.001
Other	0.85 (0.64–1.14)	0.283
AJCC-7 stage[a]		< 0.001*
I	1(−)	Reference
II	1.06 (0.42–2.66)	0.906
III	2.52 (1.09–5.84)	0.031
IV	4.47 (1.98–10.13)	< 0.001
Unknown	4.22 (1.70–10.52)	0.002
AJCC-7 T stage		
Early stage (T1,T2)	1(−)	Reference
Advanced stage (T3,T4)	2.30 (1.74–3.04)	< 0.001*
AJCC-7 N stage		
N = 0	1(−)	Reference
N > 0	1.02 (0.74–1.40)	0.903
AJCC-7 M stage		
M = 0	1(−)	Reference
M = 1	4.33 (3.29–5.70)	< 0.001*
Sequence number		
Other	1(−)	Reference
One primary only	0.50 (0.21–1.22)	0.127*
HPV status		
Negative	1(−)	Reference
Positive	1.09 (0.63–1.89)	0.759

Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval; diff/nonkera = differentiated/nonkeratinizing; undiff/nonkera = undifferentiated/nonkeratinizing.

* *p* values < 0.15 were considered as candidate variables for multivariable analysis.

[a] Overall *p*-value obtained from log likelihood test (LRT) for variables with > 2 categories.

group (HR = 0.29, 95% CI 0.15–0.54, $p < 0.01$). Patients with advanced stage for AJCC-7 T had higher death rate than those with early stage (HR = 1.92, 95% CI 1.40–2.64, $p < 0.01$). The death rate of AJCC-7 M stage of 1 was 5.44 times higher than that of AJCC-7 M stage of 0 (HR = 5.44, 95% CI 3.85–7.70, $p < 0.01$), and the death rate of others for sequence number was 0.37 times that of one primary only (HR = 0.37, 95% CI 0.12–1.16, $p = 0.09$).

4. Discussion

The etiologic role of HPV in NPC is not well established in the United States population. Using the SEER database, we found a detection rate of 35% (180/517). In their study using the NCDB database, Verma et al. reported a detection rate of HPV in NPC of 32% (308/956). Both of these findings suggest that HPV-associated NPC is not uncommon in the United States, which is considered a non-endemic region. Detection rates of HPV is other non-endemic regions have been reported in studies from Ghana [11] (19%, 14/72), the Philippines [12] (0%, 0/56), Turkey [13] (1%, 1/82), Morocco [14] (34%, 24/70), Japan [15] (3%, 2/59), Iran [16] (22%, 9/41), England [17] (16%, 11/67), Finland [18] (14%, 21/150) and eastern Europe [19] (2%, 1/62). In retrospect, the role of HPV in non-endemic NPC is not well established given the small cohorts in the literature. Nevertheless, our results using a national database suggest that HPV-associated NPC is a significant disease entity in the US population.

The role of HPV in NPC is also not well-established in endemic populations. Two studies report a detection rate of 7.7% (102/1328) [20] and 2.9% (2/70) [21] in endemic southern China. On the other hand, Kang et al. found a p16 detection rate of 67.4% (31/46) in southern Korea [22]. Albeit, the detection rate for HPV DNA was only 6.5% (3/46), which the authors attributed to destruction of HPV RNA during sample preparation. Given this controversy, our study used regression analysis to investigate the relationship of ethnicity and HPV positivity and found that HPV was more common in Caucasians than East Asians in the United States. In accordance with this finding, Thavaraj et al. reported in their review that the majority of HPV-positive NPC occurred in white patients in studies from the United States and United Kingdom [23].

In regard to other clinical factors associated with HPV status in NPC, we found that younger age was associated HPV positivity. This finding is in accordance with Verma et al., who found that HPV-associated NPC was more common in younger patients in the NCDB dataset. Other studies from nonendemic populations, including Iran [16] and Morocco [14], did not find an association between HPV status and age. However, these two studies are in agreement with our finding that gender was not associated with HPV status. Of note, histologic subtype was not associated with HPV positivity in our study. Other publications have found a correlation between HPV and specific subtypes of NPC, including World Health Organization (WHO) classification I [24] and II [23]. Therefore, this relationship requires further investigation.

The prognostic importance of HPV in NPC is another important clinical question. In our previous meta-analysis, we were unable to draw a definitive conclusion as to the prognostic impact of HPV or p16 expression in NPC (HR = 0.77, 95% CI 0.55–1.09, $p = 0.14$) [10]. However, we demonstrated that when controlling only for large studies, there was a prognostic impact of HPV in NPC (HR = 0.69, 95% CI 0.48–0.98, $p = 0.04$), which might point to a subgroup of HPV-associated NPC patients who might have superior survival outcomes. The results of this present study indicate that HPV status did not affect survival, which is in accordance with Verma et al., who used propensity-matched survival analysis in addition to Kaplan-Meier and Cox regression analysis. Similar to etiology, the prognostic role of HPV varies in studies involving both endemic and non-endemic populations, precluding from definitive conclusion. For example, HPV positivity was not associated with survival in studies from England [17] and Taiwan [25] but correlated with a better prognosis in studies from China [20], Finland [18], Iran [16] and South Korea [22].

Therefore, we accounted for ethnicity in our survival analysis, which revealed that HPV status was associated with a better prognosis in East Asians and a worse prognosis in Caucasians. An interesting case report from Dana-Farber Cancer Institute documented the case of a 56-year-old white male with metastatic HPV-positive NPC that demonstrated an unusual pattern of aggressive hematogenous spread [26], highlighting this potential poor prognosis. While we cannot comment on the prognostic role of HPV in other populations, ethnicity may be an important factor when considering the impact of HPV on survival in the United States.

There are several important limitations of this study. Retrospective bias and the short-follow up time are important considerations. Further, most patients did not have HPV testing in the SEER database, limiting our ability to draw definitive conclusions. The SEER database did not specify the test by which HPV status is determined nor the subtype of HPV detected (low versus high risk). In truth, methods of HPV testing differ across institutions and have specific operating characteristics that need to be considered. The discordance between HPV DNA and P16

Table 5
Multivariable cox regression for cause-specific survival (CSS).

Variable	HR (95% CI)	*p*-Value
Age		
0–24	1(−)	Reference
25–49	2.22 (0.53–9.32)	0.277
50–74	5.53 (1.36–22.44)	0.017
75+	11.43 (2.67–48.97)	0.001*
Ethnicity		
White	1(−)	Reference
East Asian	0.55 (0.34–0.89)	0.015*
Others	1.05 (0.75–1.48)	0.787
Histology		
Keratinizing	1(−)	Reference
Diff/nonkera	0.74 (0.49–1.10)	0.134
Undiff/nonkera	0.29 (0.15–0.54)	< 0.001*
Other	0.74 (0.50–1.08)	0.118
AJCC-7 T stage		
Early stage	1(−)	Reference
Advanced stage	1.92 (1.40–2.64)	< 0.001*
AJCC-7 M stage		
M = 0	1(−)	Reference
M = 1	5.44 (3.85–7.70)	< 0.001*
Sequence number		
One primary only	1(−)	Reference
Others	0.37 (0.12–1.16)	0.087

Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval; diff/nonkera = differentiated/nonkeratinizing; undiff/nonkera = undifferentiated/nonkeratinizing.

* p values < 0.05 are considered statistically significant for binary variables, whereas p values < 0.05/K are considered statistically significant for categorical variables with K pairwise comparisons.

testing in NPC requires further investigation as well. Similar to the limitations in the NCDB study by Verma et al., EBV status is not reported in the SEER database, which precluded from incorporating this important variable in the survival analysis and investigating the rate of coinfection with EBV, another source of controversy in the literature. Moreover, the statistical analysis was limited by small numbers in several categories, such as patients under the age of 25 with HPV-positive NPC [19] and individuals with unknown AJCC stating [20]. Finally, it is possible that oropharyngeal primaries with extension in the nasopharynx were miscoded and used in the analysis.

5. Conclusions

We present one of the largest studies to date that investigates the relationship between HPV and NPC.

HPV status was associated with younger age and white ethnicity in the United States, while controlling for AJCC-7 stage and AJCC-7 M stage. Moreover, our data suggests that HPV status might appear to play different prognostic roles in East Asians and Caucasians. Similar to prior reports, this investigation is limited by its design as a database study. Future research is needed to confirm these findings given the important clinical implications of HPV in oropharyngeal neoplasms.

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Declaration of Competing Interest

No conflicts of interest to declare.

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