

Gender-Specific Survival of Nasopharyngeal Carcinoma in Endemic and Non-Endemic Areas Based on the US SEER Database and a Chinese Single-Institutional Registry

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Purpose: To investigate the prognostic implications of gender in nasopharyngeal carcinoma (NPC) utilizing data from two independent cohorts: the Xiamen (XM)-NPC cohort (an endemic area in China) and the United States Surveillance, Epidemiology, and End Results (SEER)-NPC cohort (a non-endemic area).

Methods: We included patients diagnosed with NPC from both the XM-NPC and SEER-NPC cohorts. Statistical analysis involved the chi-square test, Kaplan-Meier method, and multivariate Cox regression analyses.

Results: The study identified 728 patients in the XM-NPC cohort and 2237 in the SEER cohort. In the XM-NPC cohort, 515 (70.7%) were male and 213 (29.3%) were female. In the SEER-NPC cohort, 1597 (71.4%) were male and 640 (28.6%) were female. The male-to-female ratio peaked at ≤ 25 years (2.33) and 46–55 years (2.79) in the XM-NPC cohort, and at ≤ 25 years (2.07) and 56–65 years (3.24) in the SEER-NPC cohort. The lowest ratios were observed among patients aged 26–35 years in both cohorts (XM-NPC: 1.64; SEER-NPC: 1.38). In the XM-NPC cohort, females had significantly better overall survival ($P=0.022$) and distant metastasis-free survival ($P=0.038$) compared to males. Similarly, in the SEER-NPC cohort, gender was found to be an independent prognostic factor for overall survival, with females showing better outcomes ($P=0.038$). Consistent trends were observed in patients aged >45 years in both cohorts, while survival outcomes were comparable between genders in patients aged ≤ 45 years.

Conclusion: Gender independently influences survival outcomes of NPC in both endemic and non-endemic areas.

Keywords: nasopharyngeal carcinoma, gender, SEER, Chinese, outcome

Introduction

Nasopharyngeal cancer (NPC) is an epithelial carcinoma originating from the mucosal lining of the nasopharynx and is characterized by a distinct geographical distribution.¹ In non-endemic regions such as the United States (US), NPC is considered a rare malignancy with an age-standardized incidence rate of less than 1 case per 100,000 people, contrasting sharply with endemic areas of southern China where rates can reach 20–30 cases per 100,000.² Major etiological factors include Epstein-Barr virus (EBV) infection, tobacco use, alcohol consumption, dietary nitrite/nitrosamine exposure, and occupational hazards.³ Despite advancements, NPC remains a significant public health concern, exhibiting marked disparities in incidence and mortality between genders.^{4,5} According to GLOBOCAN 2022 data, NPC incidence in Chinese endemic areas is 2.6 times higher in males than females, with a corresponding 3.2 times higher mortality rate among males.⁶ Similarly, US statistics reflect a 2.5 times higher incidence and 3.2 times higher mortality in males compared to females.⁶ These discrepancies suggest a potential survival advantage for females in both endemic and non-endemic regions.

Histological subtype, clinical stage, and treatment regimen significantly influence NPC prognosis.⁷ Studies on esophageal and laryngeal cancers have noted a survival advantage for females, possibly due to differential environmental exposures such as alcohol and tobacco, as well as hormonal influences.^{8,9} In NPC, studies from non-endemic regions report conflicting findings regarding gender-related survival disparities compared to endemic areas.^{10–12} The independent prognostic impact of gender remains unclear, potentially influenced by regional variations and database limitations. In this study, we utilized data from endemic regions in China to investigate the influence of gender on the survival outcomes of NPC patients, complemented by validation from the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods

Patients

Our study included patients from two distinct cohorts. The first cohort consisted of patients from the First Affiliated Hospital of Xiamen University (XM-NPC cohort), diagnosed with NPC between January 2015 and December 2021, with stage I–IVA disease according to the 8th edition of the American Joint Committee on Cancer (AJCC) NPC staging system, and treated with intensity-modulated radiation therapy (IMRT). The second cohort comprised patients from the US SEER database (SEER-NPC cohort),¹³ diagnosed with NPC between 2010 and 2017, with stage I–IVB disease according to the 7th edition of the AJCC NPC staging system, and treated with external radiation. Patients were categorized based on WHO subtypes I (ICD-O-3 codes 8070, 8071), II (ICD-O-3 codes 8072, 8073), and III (ICD-O-3 codes 8020, 8021, 8082, 8083) of NPC. Exclusion criteria included metastatic disease without pathology confirmation, unknown tumor (T) or nodal (N) stages, and non-external radiation treatment. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Xiamen University (No. 2023KY107).

Variables

In the XM-NPC cohort, patient characteristics such as age, gender, smoking history, drinking history, histological subtype, clinical stage, T stage, N stage, and treatment modality (radiotherapy and/or chemotherapy) were analyzed. In the SEER-NPC cohort, we mainly extracted age, gender, race, histological subtype, clinical stage, T stage, N stage, and treatment modality (radiotherapy and/or chemotherapy). Ever smokers included both current and former smokers, defined respectively as those who have smoked within the last year or those who have abstained from smoking for at least one year. Since approximately 90% of women experience menopause between 45 and 55 years of age, patients were further stratified into ≤ 45 years (premenopausal stage) and >45 years (menopausal and postmenopausal stage).¹⁴

Treatment

In our institution, IMRT doses for primary nasopharyngeal tumors, cervical metastatic lymph nodes, high-risk, and low-risk clinical target volumes were 70 grey (Gy)/32–33 fractions (f), 66–70Gy/32–33f, 62Gy/32–33f, and 56Gy/32–33f, respectively. Stage-based treatment guidelines included IMRT for stage I, platinum-based concurrent chemoradiotherapy (CCRT) for stage II, and induction chemotherapy (IC) + platinum-based CCRT for stage III–IVA. Since SEER did not record the radiotherapy technique, dose, chemotherapy regimen, cycle, and dose of patients in detail, the radiotherapy and chemotherapy information of patients were only recorded.

Survival Outcomes

Survival endpoints in the XM-NPC cohort included local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS). LRFS was defined as the time interval between diagnosis of NPC and local or regional recurrence or both. DMFS was defined as the time interval between diagnosis of NPC and distant recurrence. DFS was defined as the time interval between diagnosis of NPC and disease failure or death from any cause. OS was defined as the time interval between diagnosis of NPC and death from any cause or the last follow-up. Since there were no records of recurrence and metastasis in the SEER database, the study endpoints in the SEER-NPC cohort included NPC-specific survival (NPCSS) and OS. NPCSS was defined as the time interval between diagnosis of NPC and death from NPC or the last follow-up.

Statistical Analysis

The chi-square test or Fisher's exact test was used to compare gender differences in patient characteristics. Survival rates were estimated using the Kaplan-Meier method, and the Log rank test was used to compare the differences. Multivariate Cox proportional hazard regression analyses were conducted to identify independent prognostic factors related to survival outcomes. The proportional hazards test was employed to verify the assumptions of the Cox proportional hazard regression. All statistical analyses were performed using the SPSS statistical software package (version 26.0; IBM Corporation, Armonk, NY, USA). Statistical significance was defined as a P-value of less than 0.05.

Results

Patient Characteristics

In the XM-NPC cohort, 728 patients were included, with a median age at diagnosis of 50 years (range, 18–88 years). Of these, 515 patients (70.7%) were male, with a mean age of 50.5 years, and 213 patients (29.3%) were female, with a mean age of 49.3 years. The male-to-female ratio was 2.42:1. There were 249 patients in the ≤ 45 years group (male-to-female ratio 2.11 to 1) and 479 patients in the >45 years group (male-to-female 2.60 to 1). Male patients were more likely to smoke (63.3% vs 1.4%, $P<0.001$) and consume alcohol (41.0% vs 2.8%, $P<0.001$) compared to female patients. There were 9 (1.2%) in stage I, 86 (11.8%) in stage II, 345 (47.4%) in stage III, and 288 (39.6%) in stage IVA. Among male patients, 89.3% ($n=460$) were stage III–IVA disease, compared to 81.2% ($n=173$) of female patients ($P=0.013$). No significant differences were observed in age, histological subtype, T stage, N stage, or treatment modality (Table 1).

A total of 2237 patients were included in the SEER-NPC cohort, with a median age at diagnosis of 55.2 years (range, 18–92 years). Of these, 1597 (71.4%) were male, with a mean age of 55.3 years (range, 18–91 years), and 640 (28.6%) were female, with a mean age of 54.2 years (range, 18–92 years). The male-to-female ratio was 2.50:1. There were 522 patients in the ≤ 45 years group (male-to-female ratio 1.87 to 1) and 1715 patients in the >45 years group (male-to-female ratio 2.74 to 1). A majority of patients ($n=1131$) were aged over 55 years. Males were more frequently diagnosed and tended to be older than females ($P=0.001$). Stage distribution was 8.8% in stage I, 22.1% in stage II, 33.9% in stage III, and 35.2% in stage IV. Among male patients, 69.2% ($n=1105$) were stage III–IVB, compared to 69.1% ($n=442$) of female patients ($P=0.038$). No significant differences were found in race, pathological subtype, T stage, N stage, or treatment modality (Table 2).

Table 1 Patient Characteristics of the XM-NPC Cohort

Variables	N (%)	Male (%)	Female (%)	P
Age (years)				
≤ 45	249 (34.2)	169 (32.8)	80 (37.6)	0.220
>45	479 (65.8)	346 (67.2)	133 (62.4)	
Smoking history				
Never	399 (54.8)	189 (36.7)	210 (98.6)	<0.001
Ever	329 (45.2)	326 (63.3)	3 (1.4)	
Alcoholic history				
No	511 (70.2)	304 (59.0)	207 (97.2)	<0.001
Yes	217 (29.8)	211 (41.0)	6 (2.8)	
Histology				
WHO I	2 (0.2)	2 (0.4)	0 (0)	0.184
WHO II	94 (13.0)	73 (14.2)	21 (9.9)	
WHO III	632 (86.8)	440 (85.4)	192 (90.1)	
Clinical Stage				
I	9 (1.2)	7 (1.4)	2 (0.9)	0.013
II	86 (11.8)	48 (9.3)	38 (17.8)	
III	345 (47.4)	249 (48.3)	96 (45.1)	
IVA	288 (39.6)	211 (41.0)	77 (36.2)	

(Continued)

Table 1 (Continued).

Variables	N (%)	Male (%)	Female (%)	P
T stage				
T1	103 (14.1)	70 (13.6)	33 (15.5)	0.120
T2	164 (22.5)	109 (21.2)	55 (25.8)	
T3	314 (43.1)	221 (42.9)	93 (43.7)	
T4	147 (20.2)	115 (22.3)	32 (15.0)	
N stage				
N0	43 (5.9)	30 (5.8)	13 (6.1)	0.427
N1	237 (32.6)	161 (31.3)	76 (35.7)	
N2	283 (38.8)	210 (40.8)	73 (34.3)	
N3	165 (22.7)	114 (22.1)	51 (23.9)	
Chemotherapy				
No	93 (12.8)	71 (13.8)	22 (10.3)	0.204
Yes	635 (87.2)	444 (86.2)	191 (89.7)	

Abbreviations: WHO, World Health Organization; T, tumor; N, nodal.

Table 2 Patient Characteristics of the SEER-NPC Cohort

Variables	N (%)	Male (%)	Female (%)	P
Age (years)				
≤45	522 (23.3)	340 (21.2)	182 (28.4)	<0.001
>45	1715 (76.7)	1257 (78.8)	458 (71.6)	
Race				
White	1049 (46.9)	752 (47.1)	297 (46.4)	0.822
Black	265 (11.8)	194 (12.2)	71 (11.1)	
Chinese	591 (26.4)	419 (26.2)	172 (26.9)	
Other	332 (14.8)	232 (14.5)	100 (15.6)	
Histology				
WHO I	903 (40.4)	636 (39.8)	267 (41.7)	0.700
WHO II	839 (37.5)	605 (37.9)	234 (36.6)	
WHO III	495 (22.1)	356 (22.3)	139 (21.7)	
Clinical stage				
I	197 (8.8)	144 (9.0)	53 (8.2)	0.038
II	493 (22.1)	348 (21.8)	145 (22.7)	
III	759 (33.9)	517 (32.4)	242 (37.8)	
IVA	788 (35.2)	588 (36.8)	200 (31.3)	
T stage				
T1	756 (33.8)	539 (33.8)	217 (33.9)	0.118
T2	469 (21.0)	330 (20.7)	139 (21.7)	
T3	450 (20.1)	307 (19.1)	143 (22.3)	
T4	562 (25.1)	421 (26.4)	141 (22.1)	
N stage				
N0	522 (23.3)	369 (23.1)	153 (23.9)	0.460
N1	710 (31.7)	515 (32.2)	195 (30.5)	
N2	741 (33.1)	517 (32.4)	224 (35.0)	
N3	264 (11.8)	196 (12.3)	68 (10.6)	
Chemotherapy				
No	246 (11.0)	174 (10.9)	72 (11.3)	0.809
Yes	1991 (89.0)	1423 (89.1)	568 (88.7)	

Abbreviations: WHO, World Health Organization; T, tumor; N, nodal.

Gender Group Based on Age Analysis

In the XM-NPC cohort, both male and female patient numbers peaked in the 46–55 age group, followed by a decline with increasing age. The number of female patients under 45 years (premenopausal stage) generally remained lower compared to those aged 46–55 years (menopausal stage) (Figure 1A). The male-to-female patient ratio across all age groups ranged from 1.64 to 2.79, with an overall ratio of 2.42. The male-to-female ratio showed peaks at ≤ 25 years and 46–55 years, with the lowest ratio (1.64) observed among patients aged 26–35 years. (Figure 2A).

In the SEER-NPC cohort, a similar gender-specific age distribution was observed. The number of male patients peaked in the 55–65 age group. The number of female NPC diagnoses stabilized after the age of 46–55, with 154, 148, and 156 cases in the 46–55, 56–65, and ≥ 66 age groups, respectively (Figure 1B). The male-to-female ratio also showed peaks at ≤ 25 years and 56–65 years, with the lowest ratio (1.38) among patients aged 26–35 years (Figure 2B).

Survival Analysis

In the XM-NPC cohort, patients were followed up for a median of 36.2 months (range, 0–88.8). The 5-year rates of LRFS, DMFS, DFS, and OS rate were 88.6%, 84.4%, 76.7%, and 82.6%, respectively. Male patients had worse OS (79.1% vs 91.3%, $P=0.004$) (Figure 3A) and DMFS (82.3% vs 89.3%, $P=0.024$) (Figure 3D) compared to female patients, with a borderline effect on DFS (75.1% vs 80.6%, $P=0.069$) (Figure 3B). No significant difference was observed in LRFS (88.2% vs 89.6%, $P=0.663$) (Figure 3C). In survival analysis by age group, male patients in the

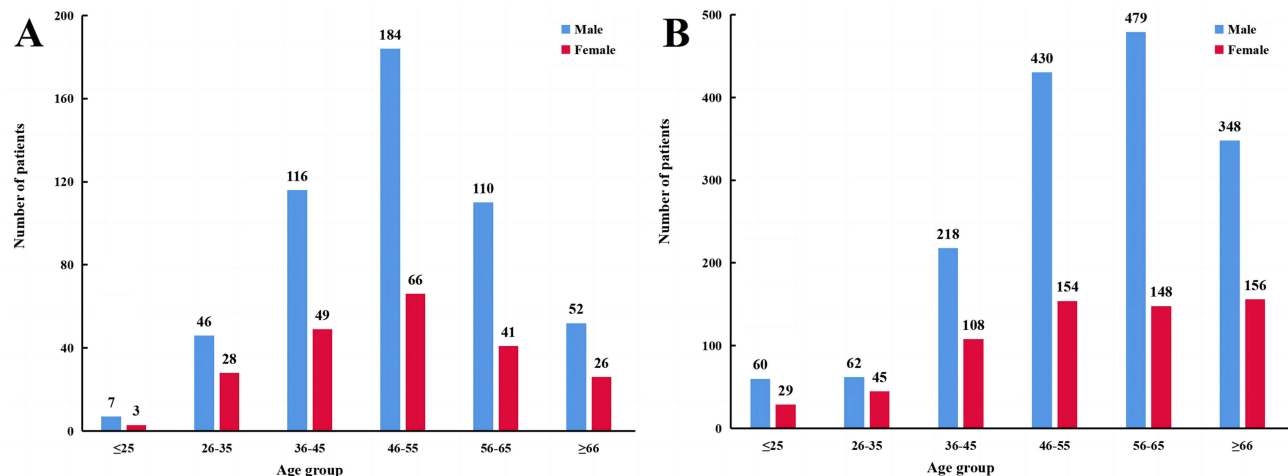


Figure 1 The number of male and female patients in each age group in the XM-NPC cohort and SEER-NPC cohort (A) XM-NPC cohort; (B) SEER-NPC cohort.

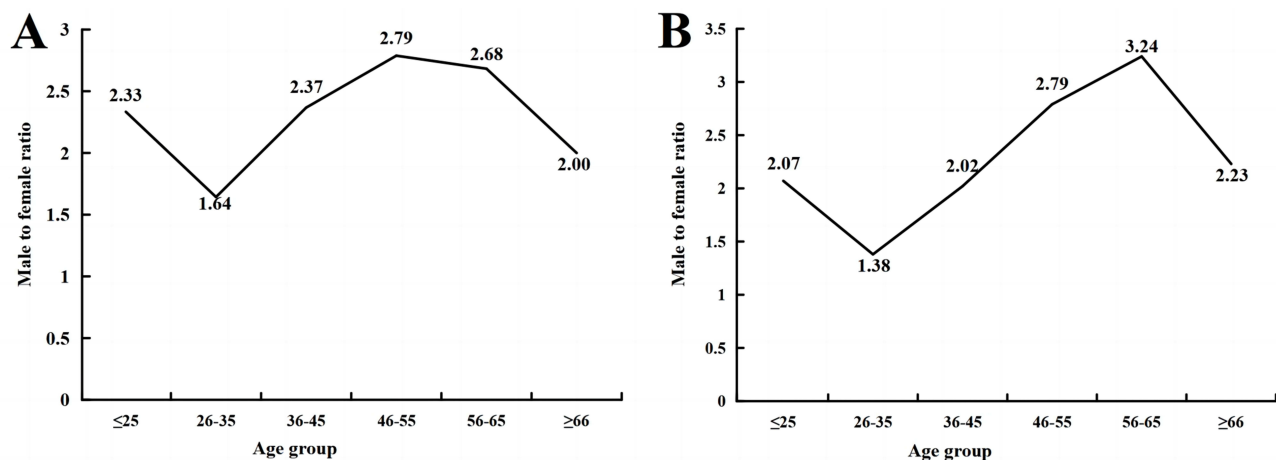


Figure 2 The ratio of male to female patients in each age group in the XM-NPC cohort and SEER-NPC cohort (A) XM-NPC cohort; (B) SEER-NPC cohort.

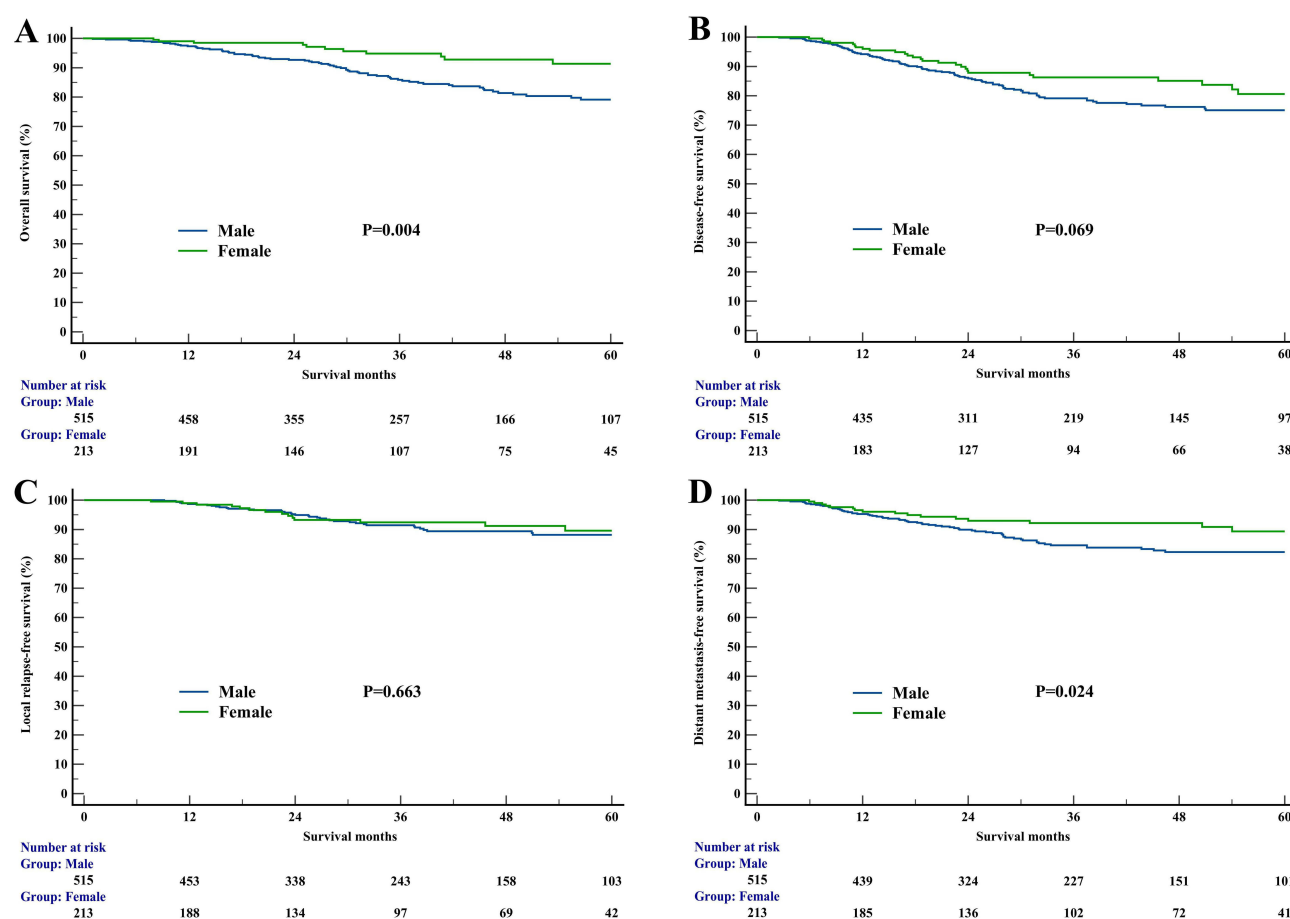


Figure 3 Survival curves comparing male and female patients in the XM-NPC cohort (A) overall survival; (B) disease-free survival; (C) locoregional relapse-free survival; (D) distant metastasis-free survival).

>45 years group had significantly worse survival than female patients in 5-year OS (74.7% vs 92.5%, $P=0.003$) (Figure 4A), DFS (73.0% vs 79.7%, $P=0.029$) (Figure 4B), and DMFS (78.5% vs 88.8%, $P=0.007$) (Figure 4D), with no significant differences in 5-year LRFS (88.5% vs 88.5%, $P=0.866$) (Figure 4C). However, similar survival outcomes were observed between male and female patients in the ≤ 45 years group.

In the SEER-NPC cohort, patients were followed for a median of 57.0 months (range, 0–131.0). The 5-year OS and NPCSS rates were 66.2% and 79.9%, respectively. Male patients had worse OS than female patients (65.0% vs 69.3%, $P=0.004$) (Figure 5A), while NPCSS had no significant difference (79.6% vs 80.8%, $P=0.289$) (Figure 5B). In the >45 years group, male patients had significantly worse 5-year OS (61.1% vs 64.1%, $P=0.044$) than female patients (Figure 6A), with no significant differences in 5-year NPCSS (77.9% vs 77.9%, $P=0.598$) (Figure 6B). No significant differences were observed in the ≤ 45 years group.

Prognostic Analysis

We performed the prognostic analyses to examine the effect of gender on survival outcomes in both the XM-NPC cohort and the SEER cohort using the multivariate Cox proportional hazard regression analyses. All variables in the multivariate Cox regression analyses met the proportional hazards assumption, with hazard ratio [HR] values remaining consistent over time. These assumptions were not violated in the OS and NPCSS analyses for the SEER-NPC cohort, nor in the OS, DFS, LRFS, and DMFS analyses for the XM-NPC cohort.

In the XM-NPC cohort, females were independently associated with better OS (HR 0.498, 95% confidence interval [CI] 0.275–0.903, $P=0.022$) and DMFS (HR 0.559, 95% CI 0.323–0.968, $P=0.038$) compared to males. However, no significant differences were found between males and females in DFS (HR 0.764, 95% CI 0.495–1.179, $P=0.224$) and

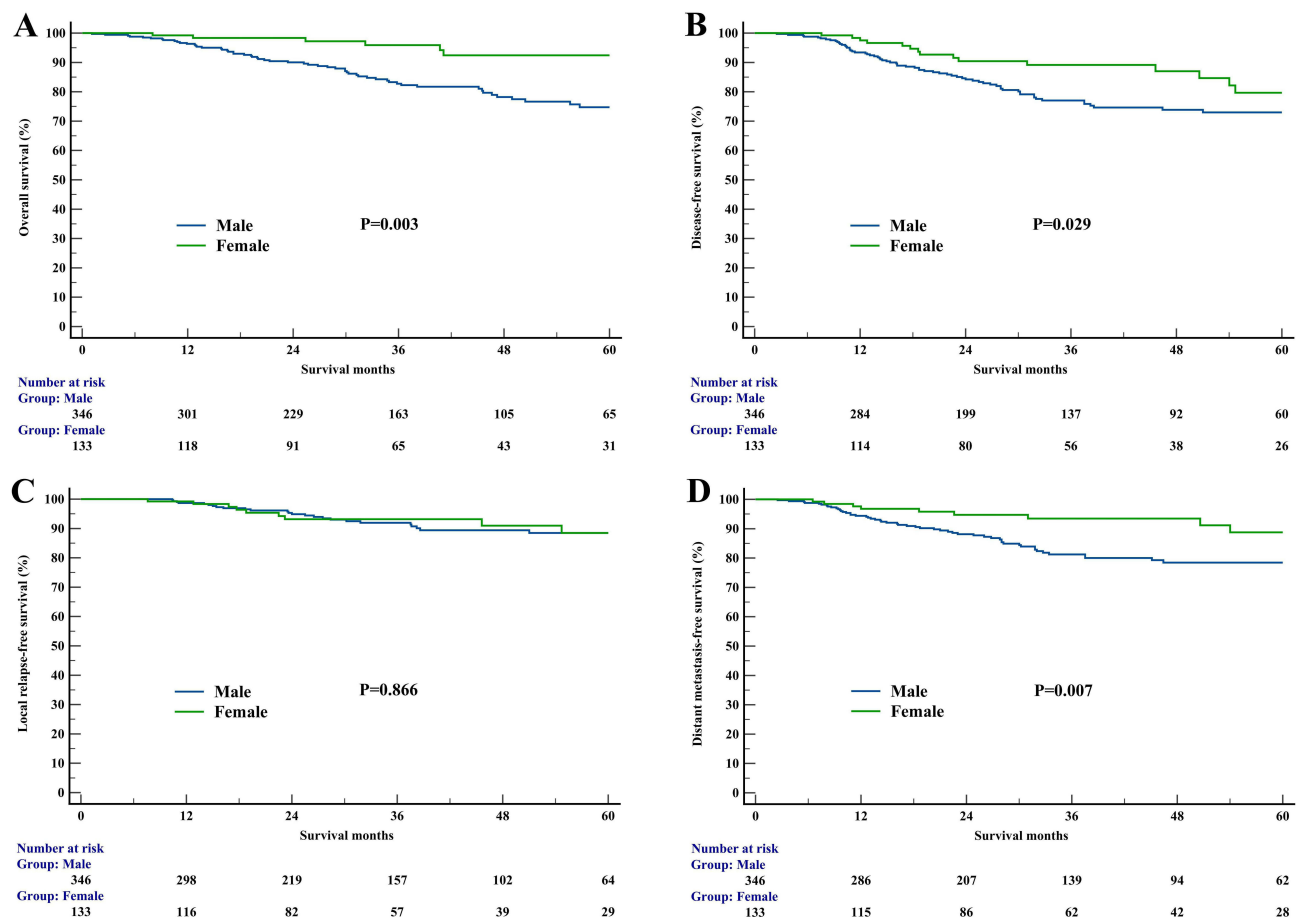


Figure 4 Survival curves comparing male and female patients in the XM-NPC cohort in >45 years group (A) overall survival; (B) disease-free survival; (C) locoregional relapse-free survival; (D) distant metastasis-free survival).

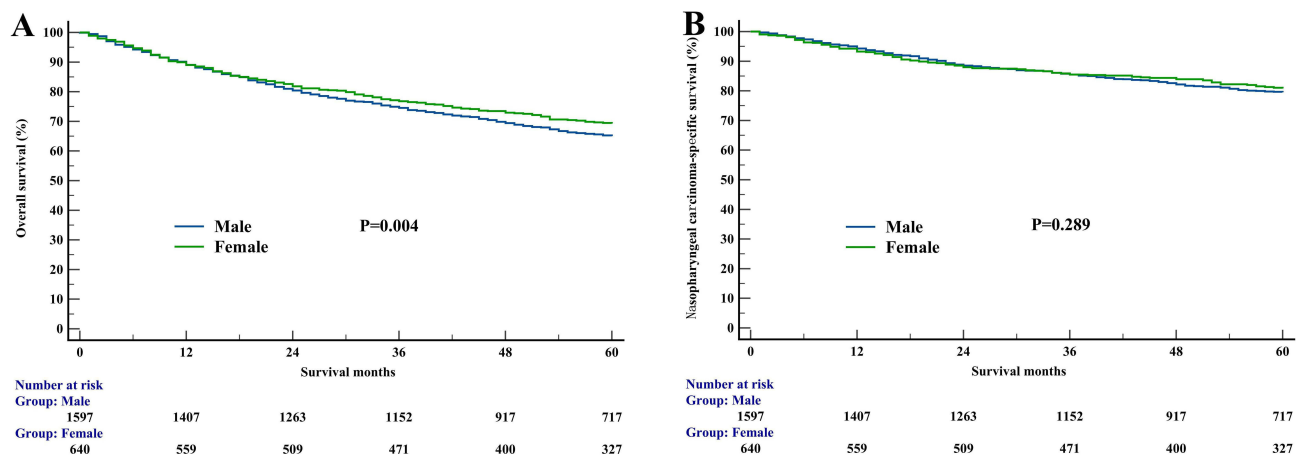


Figure 5 Survival curves comparing male and female patients in the SEER-NPC cohort (A, overall survival; B, nasopharyngeal carcinoma-specific survival).

LRFS (HR 0.985, 95% CI 0.467–2.080, $P=0.969$). Furthermore, patients in the >45 years group showed significantly better OS (HR 1.878, 95% CI 1.121–3.147, $P=0.017$) and DMFS (HR 1.881, 95% CI 1.144–3.092, $P=0.013$). Clinical stage, T stage, N stage, and treatment mode were also identified as independent prognostic factors affecting patient survival outcomes (Table 3). Sensitivity analysis indicated that gender remained an independent prognostic factor for OS

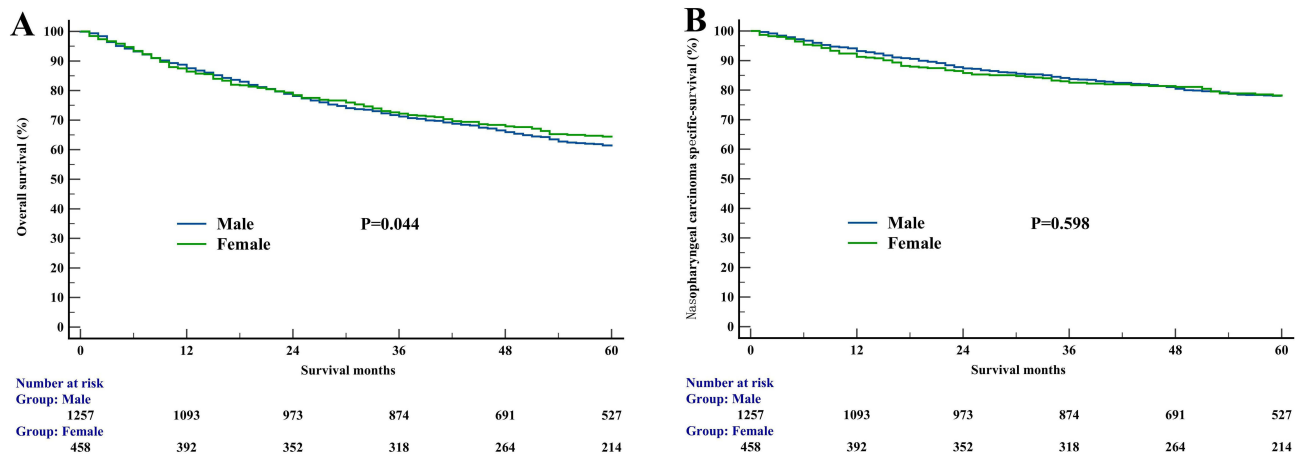


Figure 6 Survival curves comparing male and female patients in the SEER-NPC cohort in ≤45 years group (A, overall survival; B, nasopharyngeal carcinoma-specific survival).

(HR 0.348, 95% CI 0.151–0.804, $P=0.013$), DFS (HR 0.407, 95% CI 0.215–0.769, $P=0.006$) and DMFS (HR 0.333, 95% CI 0.148–0.749, $P=0.008$) in the >45 years group within the XM-NPC cohort (Table 4).

In the SEER-NPC cohort, gender was also identified as an independent prognostic factor for OS, with females exhibiting better survival outcomes (HR 0.848, 95% CI 0.725–0.991, $P=0.038$). However, no significant difference was observed between males and females in NPCSS (HR 0.935, 95% CI 0.755–1.158, $P=0.537$). Patients in the >45 years group were significantly associated with worse OS (HR 2.178, 95% CI 1.778–2.667, $P<0.001$) and NPCSS (HR 1.693, 95% CI 1.312–2.183, $P<0.001$). In addition, clinical stage, pathological subtype, N stage, and treatment mode were also independent prognostic factors affecting patient survival (Table 5). Additionally, gender remained an independent

Table 3 Multivariate Analysis of Prognostic Factors Related to Survival Outcomes in the XM-NPC Cohort

Variables	OS			DFS			LRFS			DMFS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age (years)												
≤45	1			1			1			1		
>45	1.878	1.121–3.147	0.017	1.282	0.868–1.894	0.212	0.960	0.534–1.724	0.891	1.881	1.144–3.092	0.013
Gender												
Male	1			1			1			1		
Female	0.498	0.275–0.903	0.022	0.764	0.495–1.179	0.224	0.985	0.467–2.080	0.969	0.559	0.323–0.968	0.038
Smoking history												
Never	1			1			1			1		
Ever	1.321	0.786–2.220	0.293	1.018	0.633–1.636	0.942	0.912	0.527–1.581	0.744	1.041	0.615–1.761	0.881
Alcoholic history												
No	1			1			1			1		
Yes	0.778	0.460–1.314	0.347	1.039	0.690–1.564	0.855	1.144	0.584–2.240	0.695	0.963	0.572–1.619	0.886
Histology												
WHO I + II	1			1			1			1		
WHO III	0.646	0.375–1.114	0.116	0.495	0.317–0.773	0.002	0.595	0.305–1.159	0.127	0.544	0.318–0.931	0.026
Clinical stage												
I	1			1			1			1		
II	0.145	0.009–2.366	0.175	0.316	0.024–4.130	0.379	0.158	0.009–2.663	0.201	0.055	0.002–1.325	0.074
III	0.243	0.017–3.432	0.295	0.944	0.082–10.843	0.963	1.232	0.153–9.926	0.845	0.105	0.005–2.182	0.146
IVA	0.147	0.010–2.257	0.169	0.282	0.022–3.569	0.328	1.413	0.179–11.153	0.743	0.024	0.001–0.545	0.019
T stage												
T1	1			1			1			1		
T2	0.773	0.290–2.057	0.606	1.412	0.627–3.180	0.405	0.764	0.249–2.346	0.638	3.685	1.091–12.441	0.036
T3	1.692	0.745–3.840	0.209	1.850	0.859–3.984	0.116	1.072	0.393–2.928	0.892	3.882	1.177–12.812	0.026
T4	3.108	1.349–7.163	0.008	4.670	1.854–11.766	0.001	1.263	0.292–5.742	0.755	11.035	2.984–40.812	<0.001

(Continued)

Table 3 (Continued).

Variables	OS			DFS			LRFS			DMFS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
N stage												
N0	1			1			1			1		
N1	1.446	0.424–4.931	0.556	1.521	0.461–5.018	0.492	1.116	0.253–4.923	0.885	2.538	0.336–19.189	0.367
N2	1.471	0.437–4.944	0.533	1.405	0.430–4.583	0.573	0.722	0.167–3.125	0.663	3.198	0.430–23.792	0.256
N3	2.962	0.890–9.860	0.077	8.599	2.281–32.415	0.001	1.609	0.313–7.456	0.557	28.398	3.371–239.252	0.002
Chemotherapy												
No	1			1			1			1		
Yes	0.359	0.224–0.577	<0.001	0.600	0.366–0.983	0.042	0.442	0.220–0.888	0.022	0.638	0.358–1.136	0.127

Abbreviations: WHO, World Health Organization; T, tumor; N, nodal; OS, overall survival; DFS, disease-free survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; CI, confidence interval.

prognostic factor for OS in the > 45 years age group within the SEER-NPC cohort (HR 0.836, 95% CI 0.705–0.991, P=0.039) (Table 4).

Discussion

In this study, we utilized two independent cohorts to examine the impact of gender on the survival of NPC. Our findings indicated that female patients generally experience better survival outcomes compared to males in both endemic and non-endemic regions, particularly among those aged >45 years.

Gender differences were significantly associated with age at diagnosis and clinical stage, with males typically being diagnosed at an older age and more advanced stage. Studies from endemic and non-endemic areas demonstrated a gradual increase in NPC incidence in both males and females before the age of 60. Notably, NPC incidence among males over 39 years old was significantly higher than that among females (P<0.05). The male-to-female incidence ratio

Table 4 Sensitivity Analysis of Gender-Related to Survival Outcomes in the XM-NPC Cohort and SEER-NPC Cohort

Variables	HR	95% CI	P
XM-NPC cohort			
≤45 years (Female vs Male)			
OS	0.785	0.283–2.180	0.642
DFS	0.999	0.342–2.900	0.995
LRFS	0.751	0.266–2.124	0.589
DMFS	0.779	0.281–2.164	0.632
>45 years (Female vs Male)			
OS	0.348	0.151–0.804	0.013
DFS	0.407	0.215–0.769	0.006
LRFS	0.843	0.335–2.121	0.717
DMFS	0.333	0.148–0.749	0.008
SEER-NPC cohort			
≤45 years (Female vs Male)			
OS	0.857	0.572–1.285	0.455
NPCSS	0.872	0.529–1.438	0.592
>45 years (Female vs Male)			
OS	0.836	0.705–0.991	0.039
NPCSS	0.941	0.741–1.195	0.617

Abbreviations: OS, overall survival; DFS, disease-free survival; LRFS, locoregional relapse-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; CI, confidence interval; NPC, nasopharyngeal cancer; NPCSS, nasopharyngeal cancer-specific survival; XM, Xiamen; SEER, Surveillance, Epidemiology, and End Results.

Table 5 Multivariate Analysis of Prognostic Factors Related to OS and NPCSS in the SEER-NPC Cohort

Variables	OS			NPCSS		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
≤45	1			1		
>45	2.178	1.778–2.667	<0.001	1.693	1.312–2.183	<0.001
Gender						
Male	1			1		
Female	0.848	0.725–0.991	0.038	0.935	0.755–1.158	0.537
Race						
White	1			1		
Black	1.119	0.914–1.369	0.275	1.135	0.847–1.521	0.396
Chinese	0.640	0.504–0.812	<0.001	0.945	0.696–1.283	0.718
Other	0.797	0.670–0.949	0.011	1.006	0.793–1.277	0.961
Histology						
WHO I	1			1		
WHO II	0.653	0.560–0.761	<0.001	0.734	0.597–0.903	0.003
WHO III	0.484	0.393–0.596	<0.001	0.414	0.308–0.558	<0.001
Clinical stage						
I	1			1		
II	1.233	0.855–1.779	0.262	1.304	0.767–2.219	0.327
III	1.386	0.937–2.050	0.103	1.700	1.000–2.892	0.050
IVA	1.794	1.085–2.965	0.023	2.511	1.456–4.331	<0.001
T stage						
T1	1			1		
T2	1.171	0.958–1.430	0.123	1.189	0.874–1.616	0.270
T3	1.505	1.239–1.826	<0.001	1.567	1.132–2.169	0.007
T4	1.836	1.536–2.195	<0.001	1.331	0.940–1.885	0.108
N stage						
N0	1			1		
N1	0.854	0.713–1.025	0.090	0.815	0.609–1.092	0.170
N2	0.887	0.739–1.066	0.201	0.744	0.547–1.012	0.060
N3	1.247	0.995–1.562	0.055	1.057	0.638–1.752	0.829
Chemotherapy						
No	1			1		
Yes	0.662	0.525–0.834	<0.001	0.626	0.446–0.879	0.007

Abbreviations: WHO, World Health Organization; T, tumor; N, nodal; NPCSS, nasopharyngeal carcinoma-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

peaked between ages 55–60, with males showing an earlier peak in age-specific incidence.^{2,15,16} These findings align with our observations. Moreover, across both cohorts, the male-to-female ratio varied notably across different age groups. Understanding these gender-specific and age-related patterns in NPC is crucial for tailored clinical management and further research. The observed differences in gender distribution and age at diagnosis underscore the potential influence of hormonal factors and environmental exposures prevalent in endemic versus non-endemic regions. Future studies should comprehensively explore these factors to elucidate their role in NPC pathogenesis and treatment outcomes.

The etiology of NPC shows gender disparities that are not fully understood and may stem from several factors. The higher burden of NPC in males is primarily attributed to increased exposure and accumulation of risk factors, with smoking being a major contributor. A clear dose-response relationship has been observed between the volume of smoking, cumulative tobacco consumption, and the risk of NPC as well as its mortality rates.¹⁷ Furthermore, other risk factors such as alcohol consumption, occupational exposure to carcinogens, and dietary habits further heighten the risk of NPC in males.¹⁸ EBV infection is implicated in NPC development and progression; however, no significant

gender-based differences have been observed in EBV infection rates among patients.^{1,19,20} The relatively high burden of NPC in endemic areas is primarily due to the prevalence of EBV infection. There is also a rising incidence of EBV-related NPC in non-endemic regions.^{21,22} Genetic factors, such as carriers of the VEGF-2578 C allele, significantly increase NPC susceptibility, particularly among male patients.²³ The presence of EBV-encoded RNA is associated with improved survival outcomes in endemic areas.²⁴

Due to the occult nature of NPC, a substantial proportion (70–80%) of patients are diagnosed at advanced stages (III–IV), emphasizing the critical importance of early screening in high-risk populations.²⁵ Current methods employing dual antibody detection for Epstein-Barr virus capsid antigen-IgA and nuclear antigen 1-IgA in endemic areas have shown promising results.²⁶ Monitoring plasma EBV DNA alongside serological antibodies serves as a complementary approach for NPC screening.²⁷ Therefore, Prioritizing avoidance of NPC-specific risk exposures and enhancing early screening efforts among key populations may help mitigate this gender disparity.

We found that gender was an independent prognostic factor affecting the survival of patients. The survival risk increases with age, with females showing better survival outcomes than males. These results were consistent across subgroup analyses, with survival curves consistently lower in male patients than in female patients. Additionally, male patients experienced a shorter interval before treatment failure, suggesting biological differences in tumor behavior between genders. A large-scale study from endemic areas, incorporating variables such as common lifestyle behaviors and diagnoses into propensity score models, indicated that age and clinical stage alone did not fully explain survival differences between male and female patients. The study suggested that underlying biological characteristics in females may directly and significantly influence outcomes.²⁸ Estrogen and estrogen receptors (ERs) are key biological characteristics linked to sex, demonstrating related differences.²⁹ Estrogen signaling can accelerate tumor development, while ERs have been found to exert anticancer effects and inhibit tumor progression.³⁰ The estrogen receptor inhibitor NAG7 inhibits ER- α function, promoting NPC invasion and development by upregulating the JNK2/AP-1/MMP1 pathway.³¹ Estrogen levels gradually decline from premenopausal to menopausal ages, with only 5% of females entering menopause after age 55.³² Tissue expression of ERs also decreases with age.³³ Therefore, we believe that the survival advantage in females likely involves protective mechanisms mediated by ER-related pathways in NPC risk, particularly as female age increases. These findings align with our study outcomes, confirming gender as an independent prognostic risk factor. Combining data from endemic areas in China with the SEER database enhanced the reliability and comprehensiveness of our findings.

From an epidemiological perspective, smoking and alcohol consumption are well-established risk factors for NPC, with these behaviors being more prevalent among males than females.^{17,18} This disparity in lifestyle habits may partially explain the poorer prognosis observed in male NPC patients. Smoking negatively impacts both local and systemic immune responses and increases the risk of viral infections, potentially exacerbating cancer progression.³⁴ Similarly, alcohol consumption can damage multiple organ systems and compromise survival through immunosuppression and the accumulation of carcinogenic metabolites.³⁵ Therefore, it is crucial to consider and adjust for the effects of smoking and alcohol consumption when analyzing the impact of gender on NPC survival. Future research should incorporate detailed data on the lifestyle habits of patients to provide a more nuanced understanding of the interplay between lifestyle factors and gender in influencing NPC prognosis.

IMRT demonstrates favorable locoregional control in NPC, but a 20–30% incidence of distant progression underscores the need for systemic treatment.³⁶ Our endemic area-based results revealed that male patients over 55 years old were more prone to distant metastases and exhibited lower OS and DFS than female patients. The treatment mode had a significant impact on patient survival, and the addition of chemotherapy had a positive effect on patient survival. With a larger sample size, gender differences might have shown statistical significance across more endpoints. This suggests that sex influences not only survival outcomes but also disease progression rates and treatment responses. Estrogen slows gastrointestinal and gastric emptying rates, leading to slower oral medication absorption in females.³⁷ Higher male metabolic activity results in increased drug clearance and reduced liver bioavailability, whereas females experience longer biological half-lives and higher drug retention in target organs.³⁸ Gender significantly and independently affected paclitaxel distribution and elimination, with women exhibiting lower plasma elimination and longer exposure.³⁹ Chemotherapy dose-response relationships further indicated higher drug response rates correlate positively with extended

survival in females. Insufficient relative dosing may contribute to poorer prognoses in males, potentially increasing differences in treatment efficacy and raising male patients' risk of distant metastasis.^{40,41} Gender differences in response to radiotherapy are evident, likely due to variations in DNA double-strand break recognition and repair abilities and hormone levels.⁴²

According to the World Health Organization, the life expectancy for males and females is 69.8 and 74.2 years, respectively. Women generally have a longer life expectancy than men across all age groups.⁴³ Moreover, elderly male patients often present with more comorbidities and poorer performance status due to advanced age at diagnosis and disease progression. This can result in reduced tolerance and adherence to intensive therapies such as radiation and/or chemotherapy, leading to higher non-tumor-related mortality among older male patients. Therefore, exploring more tailored chemotherapy dosages and radiotherapy regimens based on gender are worthy of further investigation, such as dosing adjusted for fat-free weight and personalized radiotherapy based on radiosensitivity.^{44,45}

Population screening of EBV-DNA has significantly improved the diagnosis of NPC and resulted in a significant decline in NPC mortality among affected patients.⁴⁶ A previous study demonstrated that men aged 55 to 59 years with the highest risk profile exhibited a remarkable 5-year absolute NPC risk of 6.5%.⁴⁷ These findings highlight the importance of incorporating age and risk profiles in addition to gender when assessing NPC prognosis and developing screening programs. However, widespread screening remains unimplemented in regions with high NPC incidence. Expanding the availability of NPC screening and increasing awareness, especially targeting at-risk populations, might mitigate the gender disparities of the disease. Such initiatives may not only facilitate earlier detection but also advance our understanding of NPC epidemiology across various demographic groups.

Our study also encountered several limitations. Firstly, due to its retrospective design, our assessment did not encompass comprehensive patient characteristics. Secondly, the SEER database lacked data on patient recurrence and metastasis, precluding evaluation of gender disparities in these aspects. Additionally, detailed information on chemotherapy protocols, techniques, dosages, treatment completion rates, and sequences of chemotherapy and radiotherapy was insufficient in the SEER database. Finally, it is important to note that the patient cohort may not fully encompass the most current treatment practices for nasopharyngeal carcinoma (NPC), particularly given the advent of immunotherapy in recent years.⁴⁸ Stratified analysis by age groups offers a valuable approach to indirectly elucidate correlations between survival disparities by gender and intrinsic biological factors. Expanding data from endemic regions is likely to yield more robust findings, further validating the influence of gender on NPC survival across both endemic and non-endemic areas. We anticipate that more meaningful insights could emerge with expanded dataset inclusion.

Conclusions

In conclusion, our findings underscore the significant impact of gender, particularly female gender, on survival outcomes among NPC patients compared to males. Gender emerges as an independent prognostic factor for survival outcomes of NPC patients in endemic or non-endemic areas. Future research efforts should focus on deepening our understanding of the intrinsic biological traits of gender-specific influences with age on NPC progression.

Human Rights

This research was conducted on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 [<http://ethics.iit.edu/ecodes/node/3931>].

Data Sharing Statement

The data supporting the findings of the article are available within the article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (No. 2023KY107).

Author Contributions

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

Consent for Publication

Informed consent was obtained from all patients.

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Disclosure

The authors declare no conflict of interest, financial or otherwise.

References

- Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet*. 2019;394(10192):64–80. doi:10.1016/S0140-6736(19)30956-0
- Zhang Y, Rumgay H, Li M, Cao S, Chen W. Nasopharyngeal Cancer Incidence and Mortality in 185 Countries in 2020 and the Projected Burden in 2040: population-Based Global Epidemiological Profiling. *JMIR Public Health Surveill*. 2023; 9:e49968. doi:10.2196/49968
- Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. *Chin J Cancer*. 2011;30(2):114–119. doi:10.5732/cjc.010.10377
- Carioli G, Negri E, Kawakita D, Garavello W, La Vecchia C, Malvezzi M. Global trends in nasopharyngeal cancer mortality since 1970 and predictions for 2020: focus on low-risk areas. *Int J Cancer*. 2017;140(10):2256–2264. doi:10.1002/ijc.30660
- Long Z, Wang W, Liu W, et al. Trend of nasopharyngeal carcinoma mortality and years of life lost in China and its provinces from 2005 to 2020. *Int J Cancer*. 2022;151(5):684–691. doi:10.1002/ijc.33998
- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
- Goshtasbi K, Leirich BM, Birkenbeul JL, Abiri A, Harris JP, Kuan EC. A Comprehensive Analysis of Treatment Management and Survival Outcomes in Nasopharyngeal Carcinoma. *Otolaryngol Head Neck Surg*. 2021;165(1):93–103. doi:10.1177/0194599820973241
- Jackson SS, Marks MA, Katki HA, et al. Sex disparities in the incidence of 21 cancer types: quantification of the contribution of risk factors. *Cancer*. 2022;128(19):3531–3540. doi:10.1002/cncr.34390
- Bohanes P, Yang D, Chhibar RS, et al. Influence of sex on the survival of patients with esophageal cancer. *J Clin Oncol*. 2012;30(18):2265–2272. doi:10.1200/JCO.2011.38.8751
- Sun LM, Li CI, Huang EY, Vaughan TL. Survival differences by race in nasopharyngeal carcinoma. *Am J Epidemiol*. 2007;165(3):271–278. doi:10.1093/aje/kwk008
- Ou SI, Zell JA, Ziogas A, Anton-Culver H. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. *Ann Oncol*. 2007;18(1):29–35. doi:10.1093/annonc/mdl320
- Lu X, Wang FL, Guo X, et al. Favorable prognosis of female patients with nasopharyngeal carcinoma. *Chin J Cancer*. 2013;32(5):283–288. doi:10.5732/cjc.012.10058
- Surveillance E, Results E (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: incidence - SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2020) - Linked To County Attributes - Time Dependent (1990-2020) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022.
- Wang M, Kartsonaki C, Guo Y, et al. Factors related to age at natural menopause in China: results from the China Kadoorie Biobank. *Menopause*. 2021;28(10):1130–1142. doi:10.1097/GME.0000000000001829
- Bai R, Sun J, Xu Y, Sun Z, Zhao X. Incidence and mortality trends of nasopharynx cancer from 1990 to 2019 in China: an age-period-cohort analysis. *BMC Public Health*. 2022;22(1):1351. doi:10.1186/s12889-022-13688-7
- Wei KR, Zheng RS, Zhang SW, Liang ZH, Li ZM, Chen WQ. Nasopharyngeal carcinoma incidence and mortality in China, 2013. *Chin J Cancer*. 2017;36(1):90. doi:10.1186/s40880-017-0257-9
- Long M, Fu Z, Li P, Nie Z. Cigarette smoking and the risk of nasopharyngeal carcinoma: a meta-analysis of epidemiological studies. *BMJ Open*. 2017;7(10):e016582. doi:10.1136/bmjopen-2017-016582
- Jia WH, Qin HD. Non-viral environmental risk factors for nasopharyngeal carcinoma: a systematic review. *Semin Cancer Biol*. 2012;22(2):117–126. doi:10.1016/j.semcancer.2012.01.009
- Cui L, Chen Z, Zeng F, et al. Impact of sex on treatment-related adverse effects and prognosis in nasopharyngeal carcinoma. *BMC Cancer*. 2023;23(1):1146. doi:10.1186/s12885-023-11564-0
- OuYang PY, Zhang LN, Lan XW, et al. The significant survival advantage of female sex in nasopharyngeal carcinoma: a propensity-matched analysis. *Br J Cancer*. 2015;112(9):1554–1561. doi:10.1038/bjc.2015.70

21. Hu CY, Wang WM, Chu XH, Ren ZH, Lyu J. Global, regional, and national burden of nasopharyngeal carcinoma from 1990 to 2017-Results from the Global Burden of Disease Study 2017. *Head Neck*. 2020;42(11):3243–3252. doi:10.1002/hed.26378
22. Argirion I, Zarins KR, Ruterbusch JJ, et al. Increasing incidence of Epstein-Barr virus-related nasopharyngeal carcinoma in the United States. *Cancer*. 2020;126(1):121–130. doi:10.1002/cncr.32517
23. Nasr HB, Chahed K, Bouaouina N, Chouchane L. Functional vascular endothelial growth factor -2578 C/A polymorphism in relation to nasopharyngeal carcinoma risk and tumor progression. *Clin Chim Acta*. 2008;395(1–2):124–129. doi:10.1016/j.cca.2008.05.022
24. Shi W, Pataki I, MacMillan C, et al. Molecular pathology parameters in human nasopharyngeal carcinoma. *Cancer*. 2002;94(7):1997–2006. doi:10.1002/cncr.0679
25. Petersson F. Nasopharyngeal carcinoma: a review. *Semin Diagn Pathol*. 2015;32(1):54–73. doi:10.1053/j.semdp.2015.02.021
26. Yu X, Li F, Cheng W, et al. Efficacy of Chemiluminescence Immunoassays on VCA-IgA and EBNA1-IgA Antibodies of Epstein-Barr Virus in Diagnosing Nasopharyngeal Carcinoma. *J Cancer*. 2020;11(24):7176–7183. doi:10.7150/jca.47260
27. Chen WJ, Xu WN, Wang HY, et al. Plasma Epstein-Barr virus DNA and risk of nasopharyngeal carcinoma in a prospective seropositive population. *BMC Cancer*. 2021;21(1):651. doi:10.1186/s12885-021-08408-0
28. Li WZ, Lv SH, Liu GY, Liang H, Xia WX, Xiang YQ. Age-dependent changes of gender disparities in nasopharyngeal carcinoma survival. *Biol Sex Differ*. 2021;12(1):18. doi:10.1186/s13293-021-00361-8
29. Xie SH, Yu IT, Tse LA, Mang OW, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983–2008: suggestion of a potential protective role of oestrogen. *Eur J Cancer*. 2013;49(1):150–155. doi:10.1016/j.ejca.2012.07.004
30. Svoronos N, Perales-Puchalt A, Allegranza MJ, et al. Tumor Cell-Independent Estrogen Signaling Drives Disease Progression through Mobilization of Myeloid-Derived Suppressor Cells. *Cancer Discov*. 2017;7(1):72–85. doi:10.1158/2159-8290.CD-16-0502
31. Huang C, Wu M, Tang Y, et al. NAG7 promotes human nasopharyngeal carcinoma invasion through inhibition of estrogen receptor alpha and up-regulation of JNK2/AP-1/MMP1 pathways. *J Cell Physiol*. 2009;221(2):394–401. doi:10.1002/jcp.21867
32. Nelson HD. Menopause. *Lancet*. 2008;371(9614):760–770. doi:10.1016/S0140-6736(08)60346-3
33. Park YM, Erickson C, Bessesen D, Van Pelt RE, Cox-York K. Age- and menopause-related differences in subcutaneous adipose tissue estrogen receptor mRNA expression. *Steroids*. 2017;121:17–21. doi:10.1016/j.steroids.2017.03.001
34. Saint-André V, Charbit B, Biton A, et al. Milieu Intérieur Consortium. Smoking changes adaptive immunity with persistent effects. *Nature*. 2024;626(8000):827–835. doi:10.1038/s41586-023-06968-8
35. Daré B L, Lagente V, Gicquel T. Ethanol and its metabolites: update on toxicity, benefits, and focus on immunomodulatory effects. *Drug Metab Rev*. 2019;51(4):545–561. doi:10.1080/03602532.2019.1679169
36. Lee AW, Ma BB, Ng WT, Chan AT. Management of Nasopharyngeal Carcinoma: current Practice and Future Perspective. *J Clin Oncol*. 2015;33(29):3356–3364. doi:10.1200/JCO.2015.60.9347
37. Waxman DJ, Holloway MG. Sex differences in the expression of hepatic drug-metabolizing enzymes. *Mol Pharmacol*. 2009;76(2):215–228. doi:10.1124/mol.109.056705
38. Allegra S, Chiara F, De Francia S. Gender Medicine and Pharmacology. *Biomedicines*. 2024;12(2):265. doi:10.3390/biomedicines12020265
39. Joerger M, Huitema AD, van den Bongard DH, Schellens JH, Beijnen JH. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of Paclitaxel in patients with solid tumors. *Clin Cancer Res*. 2006;12(7 Pt 1):2150–2157. doi:10.1158/1078-0432.CCR-05-2069
40. Özdemir BC, Csajka C, Dotto GP, Wagner AD. Sex Differences in Efficacy and Toxicity of Systemic Treatments: an Undervalued Issue in the Era of Precision Oncology. *J Clin Oncol*. 2018;36(26):2680–2683. doi:10.1200/JCO.2018.78.3290
41. Wheatley-Price P, Blackhall F, Lee SM, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol*. 2010;21(10):2023–2028. doi:10.1093/annonc/mdq067
42. De Courcy L, Bezak E, Marcu LG. Gender-dependent radiotherapy: the next step in personalised medicine? *Crit Rev Oncol Hematol*. 2020;147:102881. doi:10.1016/j.critrevonc.2020.102881
43. *World Health Statistics 2019: Monitoring Health for the Sdgs, Sustainable Development Goals*. Geneva: World Health Organization; 2019.
44. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005;44(10):1051–1065. doi:10.2165/00003088-200544100-00004
45. Roberson JD 2nd, Burnett OL 3rd, Robin N. Radiogenomics: towards a personalized radiation oncology. *Curr Opin Pediatr*. 2016;28(6):713–717. doi:10.1097/MOP.0000000000000408
46. Chen WJ, Yu X, Lu YQ, et al. Impact of an Epstein-Barr Virus Serology-Based Screening Program on Nasopharyngeal Carcinoma Mortality: a Cluster-Randomized Controlled Trial. *J Clin Oncol*. 2024;JCO2301296. doi:10.1200/JCO.23.01296
47. Chen GH, Liu Z, Ji MF, et al. Prospective assessment of a nasopharyngeal carcinoma risk score in a population undergoing screening. *Int J Cancer*. 2021;148(10):2398–2406. doi:10.1002/ijc.33424
48. Cai M, Wang Y, Ma H, Yang L, Xu Z. Advances and challenges in immunotherapy for locally advanced nasopharyngeal carcinoma. *Cancer Treat Rev*. 2024;131:102840. doi:10.1016/j.ctrv.2024.102840

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