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ORIGINAL RESEARCH

The Prognostic Value of Serum Sialic Acid in Patients with Nasopharyngeal Carcinoma: A Propensity Score Matching Study

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Purpose: Elevated serum sialic acid (SA) is one of the indicators of poor prognosis in various malignant tumors. This study intends to determine the relationship between serum SA levels and survival prognosis in nasopharyngeal carcinoma (NPC).

Patients and Methods: From 2014 to 2016, NPC patients with no distance metastasis undergoing intensity-modulated radiotherapy (IMRT) were retrospectively analyzed. The serum SA levels before initial treatment were measured, and an optimal cut-off level was determined by X-tile software. A propensity score matching (PSM) technique was applied to reduce intergroup differences between the low serum SA level group and the high serum SA level group. Chi-square tests were utilized for comparing intergroup differences, Kaplan-Meier approach was utilized for plotting survival curves, and univariate and multivariate Cox proportional hazards regression models were employed for analyzing prognostic factors.

Results: Overall, 293 NPC patients with no distance metastasis were included. The optimal cut-off level of serum SA was 65.10 mg/dl. The baseline levels after PSM were more balanced compared to those before PSM. Survival analysis showed that the locoregional relapse-free survival (LRRFS, p=0.010), distant metastasis–free survival (DMFS, p=0.014), progression-free survival (PFS, p=0.009), and overall survival (OS, p=0.015) survival curves of the low serum SA level group and high serum SA level group were statistically significant differences. Univariate analysis showed that American Joint Committee on Cancer (AJCC) stage, T stage, N stage, neoadjuvant chemotherapy (NC), and serum SA expression level were factors influencing the prognosis of NPC patients. Multivariate analysis showed that high serum SA expression level was related to worse PFS and OS in NPC patients with no distance metastasis.

Conclusion: High serum SA level (SA > 65.10 mg/dl) before treatment is associated to poor survival outcomes in NPC and is an independent adverse prognostic factor in NPC patients with no distance metastasis.

Keywords: serum sialic acid, nasopharyngeal carcinoma, prognosis, propensity score matching

Introduction

Nasopharyngeal carcinoma (NPC) is highly prevalent in Southern China, Southeast Asia, and North Africa.[1] However, the exact causes of NPC remain unclear, although several factors have been implicated, including genetic susceptibility, Epstein-Barr virus (EBV) infection, smoking, and consumption of preserved foods such as salted fish.[2,3] Studies have shown that 95% of non-keratinizing NPC cases are associated with EBV infection.[2–4] The chromosome loci 6p21, 5p15, and 16p13 have been identified as the major susceptible gene sites for NPC.[5,6] The primary treatment modalities for NPC are radiation therapy and chemotherapy. Over the past 2 decades, significant advancements have been made in radiation therapy techniques, particularly with the shift from two-dimensional to three-dimensional conformal radiation therapy and IMRT. These advancements have greatly enhanced the precision and accuracy of radiation beams, leading to improved local control rates.[7] Additionally, the use of neoadjuvant chemotherapy has shown promising results in

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improving prognosis, where neoadjuvant chemotherapy achieves early eradication of subclinical lesions, reduces tumor burden, and enhances sensitivity to subsequent radiation therapy.[8] However, despite standard treatment protocols, approximately 20% of NPC cases still experience treatment failure, characterized by local recurrence and/or distant metastasis. Adverse prognostic factors for NPC include advanced tumor stage, incomplete decline in EBV viral load after treatment, malnutrition, elevated lactate dehydrogenase (LDH) levels, lymph node necrosis, and a high proportion of inflammatory markers.[9–12] Clinicians rely on adverse prognostic factors to develop individualized treatment plans and follow-up strategies for NPC patients. Consequently, there is a need to research and identify early prognostic factors for predicting treatment failure in NPC.

Studies have shown that elevated serum sialic acid (SA) levels indicate increased severity of precancerous oral lesions and unfavorable pathological features in oral cancer.[13] In gynecological malignancies, including ovarian, endometrial, and cervical cancers, increased SA expression has been associated with more advanced disease stages and poorer prognosis.[14] Furthermore, higher serum SA levels have been linked to poorer survival in G3 gastric neuroendocrine neoplasms.[15] Currently, there is no existing research investigating the relationship between SA prior to treatment and the prognosis of NPC. More studies are demanded to better understand the relationship between the two.

In this retrospective study, we analyzed the predictive capacity of serum SA in NPC patients with no distance metastasis. PSM was employed to minimize confounding factors, and the association between serum SA levels and survival outcomes, including LRRFS, DMFS, PFS, and OS, was assessed.

Materials and Methods

Patients

Retrospectively, clinical case information of NPC patients with no distance metastasis treated at Hainan General Hospital from 2014 to 2016 was collected. The study included individuals who met the following inclusion criterions: histologically confirmed NPC; AJCC 8th edition staging determining NPC patients with no distance metastasis (Stage I-IVa); serum SA level measured before treatment; Karnofsky score ≥70; exclusion of NPC patients with concomitant diabetes; history of other malignant tumors; systemic infectious diseases, immune disorders, or other conditions that could potentially interfere with SA detection levels.

Detection Method of Serum SA

Prior to any initial treatment, 5 mL of fasting blood was collected from patients. The blood samples underwent centrifugation at a speed of 3500 rpm for 5 minutes in order to obtain serum for analysis. The measurement of serum SA was performed using the N-acetylglucosamine enzymatic assay method with a kit purchased from LEADMAN (Beijing, China). The serum samples were analyzed using an automated biochemical analyzer (ARXHITECT c16000 system, Abbott Laboratories, Tochigi, Japan).

Radiotherapy and Chemotherapy

All NPC patients underwent radiation therapy using IMRT technique. The gross tumor volume (GTV) was delineated based on the MRI findings of the primary nasopharynx tumor and positive neck lymph nodes. The high-risk clinical target volume (CTV1) was defined by a 0.6 cm three-dimensional automatic expansion from the GTV with modifications based on anatomical structures. The low-risk clinical target volume CTV2 was also delineated. The prescription doses were as follows: PGTV: 68–71.04 Gy/30–32 fractions, PGTVnd: 64–68 Gy/30–32 fractions, PTV1: 60–62 Gy/30–32 fractions, PTV2: 54–56 Gy/30–32 fractions. Radiation therapy was delivered 5 times per week. Chemotherapy regimens consisted of platinum-based agents combined with either 5-fluorouracil (5-FU) or taxanes.

Statistical Analysis

The study defined the LRRFS as the duration from histological diagnosis to the occurrence of local-regional (the region of nasopharynx or/and positive neck lymph node) failure, and DMFS as the period from histological diagnosis to the occurrence of distant metastasis. The PFS was calculated as the time from histological diagnosis to either local-regional

failure, distant metastasis, or death from any cause, whichever came first. Lastly, OS was determined as the time from histological diagnosis to death from any cause.

The optimal cutoff value for serum SA level in predicting OS was determined as 65.10 mg/dl by X-tile software, a tool designed by researcher.[16] Based on this cutoff value, all NPC patients were categorized into low SA level group and high SA level group. We utilized Chi-square test and Fisher's exact test to assess and compare the categorical variables in the baseline characteristics.

To reduce confounding factors, PSM was applied to match the low SA level group and high SA level group for NPC based on age, gender, family history of NPC, pathological type, AJCC staging, T staging, N staging, use of neoadjuvant chemotherapy (NC), concurrent chemotherapy (CC), and adjuvant chemotherapy (AC). The propensity scores were analyzed using a multivariable logistic regression model. Then, the low SA level group and high SA level group were matched at a ratio of 4:1 using nearest-neighbor matching with a caliper of 0.2. Survival curves were estimated via the Kaplan-Meier method, and comparisons were performed utilizing the Log rank test. Cox proportional hazards regression analysis was conducted to evaluate the factors influencing patient survival prognosis. A p-value less than 0.05 was deemed statistically significant. The chi-square test, survival analysis, and PSM were performed via SPSS 26.0 software. Survival curves were plotted using GraphPad Prism 9 tool.

Results

Patient Characteristics

The X-tile software calculated the cutoff value for serum SA level as 65.10 mg/dl (Figure 1). Using this value as the threshold, patients with a serum SA level equal to or below 65.10 mg/dl were sorted into the low SA level group, while those with a level above 65.10 mg/dl were classified into the high SA level group. The baseline characteristics of the low SA level and high SA level groups are presented in Table 1. The proportion of patients over 45 years old was 62.12%, and the distribution of males and females was 2.37:1. Approximately 8.53% of patients had a family history of nasopharyngeal carcinoma. Almost all patients had non-keratinizing carcinoma (WHO type II), accounting for 97.95% of cases. Moreover, 87.03% patients received a diagnosis of locally advanced NPC (AJCC staging III and IVa). A total of 176 low-level SA patients and 83 high-level SA patients were successfully matched using PSM (Table 1).

PSM and Survival Outcomes

In this study, a cohort of 293 patients was enrolled, and the mean follow-up time was 65.6 months. The OS rates for the 293 patients at 1 year, 3 years, and 5 years were 97.6%, 85.3%, and 79.9%, respectively. The PFS rates at 1, 3, and 5

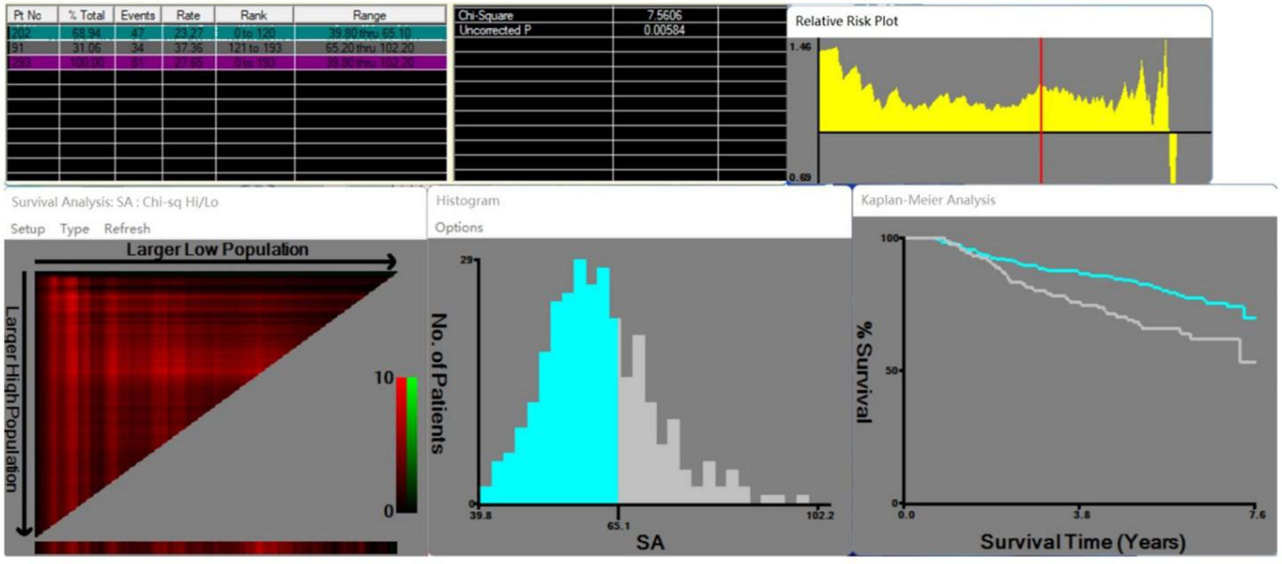

Figure 1 The results of X-tile software analysis showed that the cut-off of SA level was 65.10 mg/dl.

Table 1 Baseline Characteristics of Nasopharyngeal Carcinoma Patients with No Distance Metastasis

Characteristics	Before PSM			After PSM		
	SA≤65.10 mg/dl (n=202)	SA>65.10 mg/dl (n=91)	P value	SA≤65.10 mg/dl (n=176)	SA>65.10 mg/dl (n=83)	P value
Age, years						
≤45	76	35	0.891	66	32	0.870
>45	126	56		110	51	
Gender						
Male	142	64	0.995	126	59	0.933
Female	60	27		50	24	
Family history						
Yes	20	5	0.212	16	5	0.399
No	182	86		160	78	
Pathology						
WHO type I	3	3	0.379	3	1	1.000
WHO type II	199	88		173	83	
AJCC staging						
I	3	0	0.008	1	0	0.290
II	29	6		21	6	
III	106	39		92	39	
IVa	64	46		62	38	
T staging						
T1	21	3	< 0.001	14	3	0.006
T2	97	23		82	23	
T3	54	39		50	37	
T4	30	26		30	20	
N staging						
N0	9	2	0.375	6	2	0.809
N1	56	24		46	23	
N2	100	41		89	38	
N3	37	24		35	20	
Neoadjuvant chemotherapy						
Yes	79	34	0.776	67	30	0.765
No	123	57		109	53	

(*Continued*)

Table 1 (Continued).

Characteristics	Before PSM			After PSM		
	SA≤65.10 mg/dl (n=202)	SA>65.10 mg/dl (n=91)	P value	SA≤65.10 mg/dl (n=176)	SA>65.10 mg/dl (n=83)	P value
Concurrent chemotherapy						
Yes	145	78	0.010	128	70	0.040
No	57	13		48	13	
Adjuvant chemotherapy						
Yes	52	27	0.483	46	26	0.384
No	150	64		130	57	

Abbreviations: PSM, propensity score matching; SA, sialic acid; WHO, World Health Organization; AJCC, American Joint Committee on Cancer.

years were 91.4%, 79.6%, and 74.3%, respectively. After PSM, 259 individuals were encompassed in the analysis. The standard mean difference for each categorical variable decreased after PSM matching (Figure 2). After PSM, the high SA level group showed significantly poorer LRRFS (68.0 vs 77.0 months; p = 0.010), DMFS (66.9 vs 76.4 months; p = 0.014), PFS (65.2 vs 75.5 months; p = 0.009), and OS (70.3 vs 77.9 months; p = 0.015) compared to the low SA level group (Figure 3).

Serum SA Was an Independent Prognostic Indicator of NPC Patients with No Distance Metastasis

After PSM, a total of 259 individuals were involved in the analysis, with 176 individuals in the low SA level group and 83 individuals in the high SA level group. Univariate Cox regression analysis indicated that AJCC staging, T staging, N staging, whether to receive neoadjuvant chemotherapy, and SA level were associated with poorer PFS rates (Table 2; p < 0.001, p < 0.001, p < 0.001, p = 0.025, p = 0.010) and poorer OS rates (Table 2; p < 0.001, p < 0.001, p = 0.001, p = 0.035, p = 0.017). Multivariate Cox regression analysis revealed that SA level was identified as an independent predictor for both PFS and OS in NPC patients with no distance metastasis, with hazard ratios of 1.854 (95% CI: 1.154–2.978; p = 0.011) and 1.766 (95% CI: 1.098–2.839; p = 0.019), respectively.

Discussion

The increase in serum SA is not specific to malignant tumors; it can also be observed in the presence of inflammation or diabetes.[17,18] In the present study, we excluded patients with systemic infectious diseases and/or diabetes. We analyzed the prognostic value of serum SA for NPC patients with no distance metastasis (Stage I–IVa, AJCC 8th edition staging). The optimal cutoff value for SA was determined to be 65.10 mg/dl using the X-tile prognostic analysis software. Patients were stratified into high and low serum SA level groups based on this cutoff, and PSM analysis was employed to minimize confounding factors between the two groups. Survival analysis after PSM demonstrated poorer outcomes in the high serum SA level group for LRRFS, DMFS, PFS, and OS. Furthermore, both univariate and multivariate analyses revealed that high SA level was an independent unfavorable prognostic factor for both OS and PFS among NPC patients with no distance metastasis.

The occurrence and development of tumors are closely related to alterations in glucose metabolism, and metabolic reprogramming has been observed in various cancer cells.[19,20] The metabolic reprogramming includes the Warburg effect, SA synthesis metabolism and so on.[21] SA is an important component of cell surface glycoproteins and glycolipids.[22] It participates in the reprogrammed metabolisms of cancer cells, thus affecting cell adhesion, intercellular communication, and contact inhibition.[14,21] Under normal circumstances, the serum SA level remains stable. However, when cells undergo malignant transformation, SA is shed from the cell surface and circulates in the bloodstream as serum

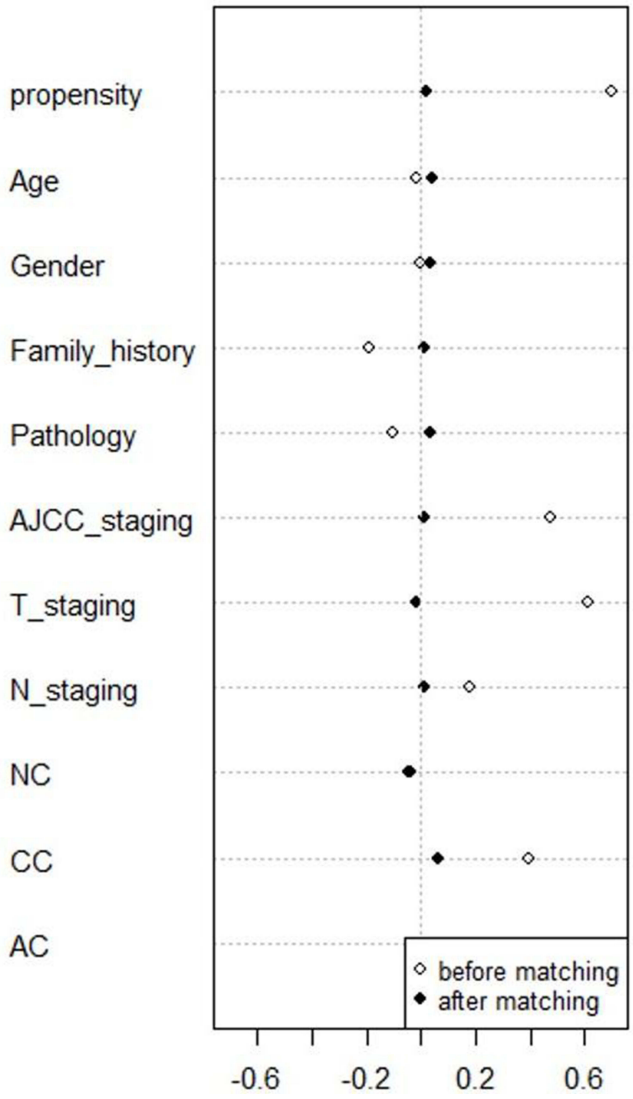

Figure 2 The effect of propensity score matching was evaluated through an analysis using a love plot. White dots indicate the standard mean differences before matching and black dots indicate that after matching.
Abbreviations: NC, neoadjuvant chemotherapy; CC, concurrent chemotherapy; AC, adjuvant chemotherapy.

SA.[23] In malignant tumor cells, there is an increase in SA synthesis metabolism, known as hypersialylation, which promotes tumor progression.[24] SA synthesis incorporates a negatively charged sugar, leading to a buildup of these molecules on cancer cell surfaces. This buildup causes increased repulsion between cells, mechanical stress, compression, and deformation of cell shape, ultimately triggering cell migration.[21] Therefore, the elevation of SA level is closely associated with tumor carcinogenesis and metastasis.

Our study showed that the high SA group had a lower LRRFS, DMFS, PFS, and OS, indicating that increased SA is a poor prognostic factor for tumors, correlating with the clinical activity of the disease, similar to conclusions from studies conducted on many cancer types.[13–15,25,26] Research has also shown that SA levels were higher in the group of patients with metastatic breast cancer compared to those with non-metastatic breast cancer.[27]

Currently, chemoradiotherapy is the preferred treatment modality for NPC. However, existing treatments become less effective when patients experience recurrence or distant metastasis. There is an urgent need to develop new immunotherapies or small molecule targeted drugs for these patients. Antibody-Drug Conjugates (ADCs), which combine small molecule chemotherapy drugs and monoclonal antibody drugs for targeted therapy, provide a new approach for the treatment of recurrent or metastatic NPC.[28] Clinical trials have been initiated in this regard. Serum SA detection

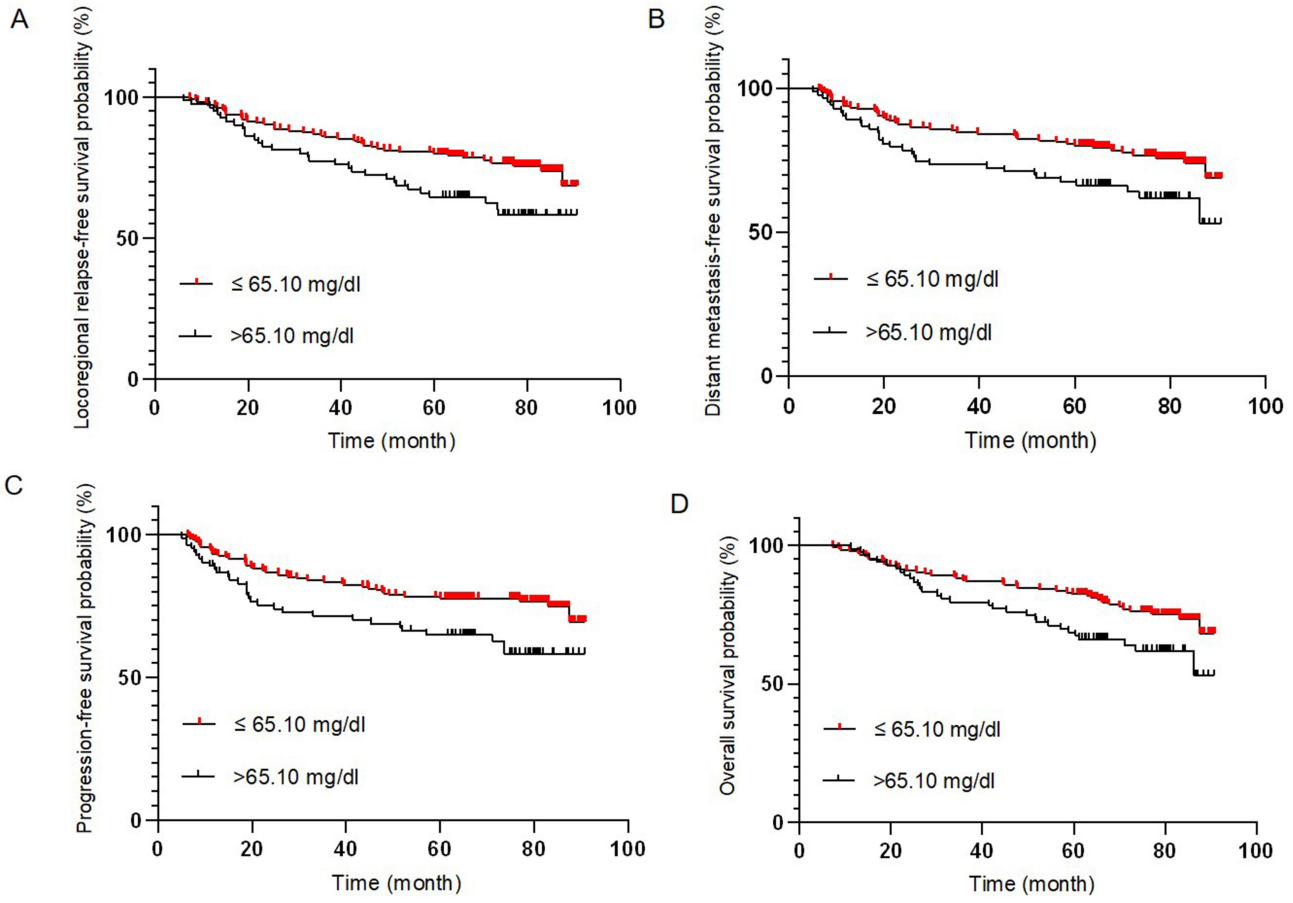

Figure 3 The Kaplan-Meier survival curves of comparing nasopharyngeal carcinoma patients according to the serum sialic acid (SA) levels after propensity score matching. (**A**) Locoregional relapse-free survival (p=0.010); (**B**) Distant metastasis-free survival (p=0.014); (**C**) Progression-free survival (p=0.009); (**D**) Overall survival (p=0.015).

possesses characteristics of safety, low cost, ease of implementation, and easy clinical promotion. As one of the unfavorable prognostic factors for NPC, it provides a promising therapeutic target for the management of this disease. In vivo, the application of a SA mimetic via intratumoral injections effectively inhibits tumor SA expression and

Table 2 Cox Regression Analysis for PFS and OS Outcomes in NPC Patients with No Distance Metastasis After PSM

Variables	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	PValue	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years								
>45 vs ≤45	1.648 (0.992–2.736)	0.054			1.652 (0.995–2.743)	0.052		
Gender								
Female vs Male	0.989 (0.595–1.644)	0.967			1.02 (0.614–1.695)	0.939		
Family history								
Yes vs No	0.586 (0.214–1.608)	0.300			0.571 (0.208–1.564)	0.275		
Pathology								
WHO II vs WHO I	0.597 (0.146–2.435)	0.472			0.519 (0.127–2.117)	0.360		

(*Continued*)

Table 2 (Continued).

Variables	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	PValue	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AJCC staging								
IVa vs I/II/III	3.686 (2.28–5.975)	<0.001	1.714 (0.539–5.456)	0.361	3.429 (2.122–5.54)	<0.001	1.535 (0.48–4.906)	0.469
T staging								
T4 vs T1/T2/T3	2.77 (1.713–4.48)	<0.001	1.948 (0.705–5.378)	0.198	2.674 (1.654–4.323)	<0.001	2.065 (0.745–5.725)	0.163
N staging								
N3 vs N0/N1/N2	2.453 (1.51–3.982)	<0.001	1.921 (0.696–5.306)	0.208	2.274 (1.401–3.691)	0.001	1.952 (0.703–5.419)	0.199
Neoadjuvant chemotherapy								
Yes vs No	1.695 (1.07–2.688)	0.025	1.276 (0.792–2.055)	0.316	1.642 (1.035–2.604)	0.035	1.257 (0.78–2.026)	0.348
Concurrent chemotherapy								
Yes vs No	1.643 (0.900–3.002)	0.106			1.584 (0.867–2.896)	0.135		
Adjuvant chemotherapy								
Yes vs No	0.763 (0.438–1.33)	0.340			0.722 (0.415–1.259)	0.251		
SA mg/dl								
>65.10 vs ≤65.10	1.843 (1.157–2.934)	0.010	1.854 (1.154–2.978)	0.011	1.765 (1.108–2.811)	0.017	1.766 (1.098–2.839)	0.019

Abbreviations: NPC, nasopharyngeal carcinoma; PFS, progression-free survival; OS, overall survival; PSM, propensity score matching; HR, hazard ratio.

demonstrates a notable suppression of tumor growth across multiple tumor models.[29] Li et al[30] developed a sialic acid-cholesterol conjugate modified doxorubicin liposome targeting the surface SA of tumor cells through the ligand Siglec-1, which selectively targets and kills immune-suppressive functional cells enriched around the tumor tissue, indirectly exerting anti-tumor effects. Gray et al[31] designed an αHER2 antibody-sialidase conjugate targeting sialoglycans (sialic acid-containing proteins and lipids), which prolonged the survival of mice in a breast cancer model. However, there is limited research on directly targeting SA with ADCs. Therefore, there is a need to confirm the predictive significance of SA and develop SA as a therapeutic target for the treatment of NPC.

This study utilized X-tile, which is a reliable and widely used tool, to obtain the optimal cut-off value.[16] Furthermore, PSM was employed to reduce confounding factors in the comparison group. The conclusions drawn from the analysis might be highly credible. However, there are several limitations in this study. Firstly, this study was a single-institution retrospective study, which may introduce bias and confounding factors. Secondly, although PSM analysis was performed to minimize confounding factors, the absence of EBV DNA viral load and antibody data in certain instances led to their exclusion from the analysis as missing values are not desirable during PSM analysis. Future prospective clinical trials are demanded to validate the prognostic value of serum SA and further explore the underlying mechanisms through basic research.

Conclusion

Our study reveals a compelling association between serum SA expression levels and the survival of NPC patients with no distance metastasis. Serum SA may be involved in the progression and poor prognosis of NPC patients with no distance metastasis. Therefore, serum SA may serve as a useful independent prognostic tumor antigen. Further research on blockade therapies targeting SA is necessary and may improve the survival outcomes of NPC patients.

Data Sharing Statement

All data generated or analyzed during this study can be obtained from the corresponding author.

Ethical Approval and Informed Consent

This study was carried out following the guidelines of the Declaration of Helsinki, and reviewed and approved by the Medical Ethics Committee of Hainan General Hospital. Informed consent was obtained from all individuals involved in the study.

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Disclosure

All authors declare no conflicts of interest in this work.

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