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ORIGINAL RESEARCH

The Naples Prognostic Score Exerts a Significant Impact on the Prognosis of Patients Diagnosed with External Auditory Canal Carcinoma After Surgery

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Background: External auditory canal carcinoma (EACC) is a rare malignant tumor. This study aimed to investigate the influence of the comprehensive index of nutrition- Naples prognostic score (NPS) on the prognosis of EACC patients with surgical resection.

Methods: A total of 73 EACC patients with surgical resection were selected from two tertiary medical institutions, and were diagnosed between Sep 2008 and Aug 2019. The univariate and multivariate Cox regression analyses were used to identify the independent prognostic factors for disease-free survival (DFS) and overall survival (OS) for postoperative EACC patients. The prognosis for postoperative EACC patients with varying NPS were displayed by Kaplan-Meier plots.

Results: The 3- and 5-year survival rate for EACC patients with surgical resection were 72.6%, 32.9% for DFS, and 76.7%, 52.1% for OS, respectively. The multivariate Cox regression analysis revealed that advanced Pittsburgh stage, perineural invasion, vascular invasion, and higher NPS were identified as independent prognostic factors for DFS. Additionally, advanced Pittsburgh stage, vascular invasion, an ACCI score of 6 or higher, and higher NPS were found to be independent predictors for OS.

Conclusion: NPS serves as a crucial predictor of postoperative outcomes in patients with EACC, with higher levels indicating poorer disease-free and overall survival. Additionally, factors such as Pittsburgh stage, perineural and vascular invasion, and ACCI are also significant prognostic indicators.

Keywords: external auditory canal carcinoma, Naples prognostic score, prognosis, disease-free survival, overall survival

Introduction

External auditory canal carcinoma (EACC) is a rare tumor in head and neck malignancies, representing approximately 0.2% of these malignancies.[1,2] The pathological types of EACC include squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, basal cell carcinoma, and mucoepidermoid carcinoma, among others.[3,4] Squamous cell carcinoma is the most prevalent type, accounting for about 80% of all EACC cases.[5] Common clinical symptoms of EACC include ear pain (otalgia), ear discharge (otorrhea), bleeding, neck masses, facial numbness, headaches, tinnitus (ringing in the ears), a feeling of fullness in the ear, and hearing loss. Otalgia is often the initial symptom reported by patients.[6] Most EACC patients are diagnosed at an advanced stage, with studies indicating that the time from the onset of initial symptoms to clinical diagnosis ranges from 12.4 months to 3.9 years. Approximately two-thirds of EACC patients present in the T3 or T4 stages during their first visit.[7,8] This condition can easily be misdiagnosed or overlooked due to the unique anatomical structures of the external auditory canal, leading to delays in treatment and decreased survival rates.[2] Therefore, it is crucial to identify more effective predictors that can accurately forecast the prognosis for EACC patients, which would benefit both patients and clinicians.

Previously, the Pittsburgh staging system was widely used to guide treatment strategies and predict prognosis in patients with EACC.[1] However, this traditional staging system did not account for many important predictors, such as

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pathological type, treatment method, age, gender, nerve invasion, and nutrition-inflammation-related factors. Research has shown that nutrition-related factors significantly affect the prognosis of patients with head and neck cancer.[9,10] For instance, Chen et al[11] found that malnutrition is linked to poor outcomes in these patients, and appropriate nutritional supplementation can enhance anticancer immunity and improve prognosis. Besides, numerous studies indicate that immune-inflammation-related factors are crucial prognostic indicators in various cancers.[12–16] Among the nutrition-inflammation-related factors, the Naples Prognostic Score (NPS) has emerged as a recent topic of interest. NPS was first introduced in 2017 by Gennaro Galizia and his research team,[17] and since then, its association with prognosis has been validated across various malignancies.[18–21] However, the association between NPS and the prognosis of EACC patients remains uncertain. The objective of our study was to conduct a retrospective analysis to further investigate this association.

Materials and Methods

Data Collection

A total of 73 resectable EACC patients were collected from the Affiliated Cancer Hospital of Zhengzhou University and the First Affiliated Hospital of Xinxiang Medical University diagnosed between Sep 2008 and Aug 2019. This study was retrospective, with OS and PFS as study endpoints. The inclusion criteria were as follows: (1) pathology confirmed; (2) age ≥ 18 years old. Patients were excluded if they met any of the following criteria: (1) absence of radical surgery; (2) multiple primary tumors; (3) distant metastasis at the time of initial diagnosis; (4) ECOG PS score ≥ 3; (5) stage was unknown; (6) incomplete clinical data; (7) lack of follow-up information; (8) death within 30 days. Figure 1 is a detailed flow chart. All patients provided written informed consent. The study strictly adhered to the principles delineated in the Declaration of Helsinki. Approval for ethical considerations was acquired from an established ethics committee, with a designated ethical committee approval number assigned as EC-024-499.

The radical surgery type including lateral temporal bone resection (LTBR) or subtotal temporal bone resection (STBR), total parotidectomy (TP) or superficial parotidectomy (SP), and superior cervical lymph node dissection (SCLND). There was a controversy in treatment choice for some patients, who will receive radiotherapy or chemotherapy at the recommendation of a multidisciplinary consultation team at the respective hospital. The radiotherapy techniques employed included conformal radiotherapy (CRT), intensity-modulated radiotherapy (IMRT), and volumetric-modulated arc therapy (VMAT), which was administered once a day at 2.0–2.18 Gy per fraction, up to 60.0–66.0 Gy in

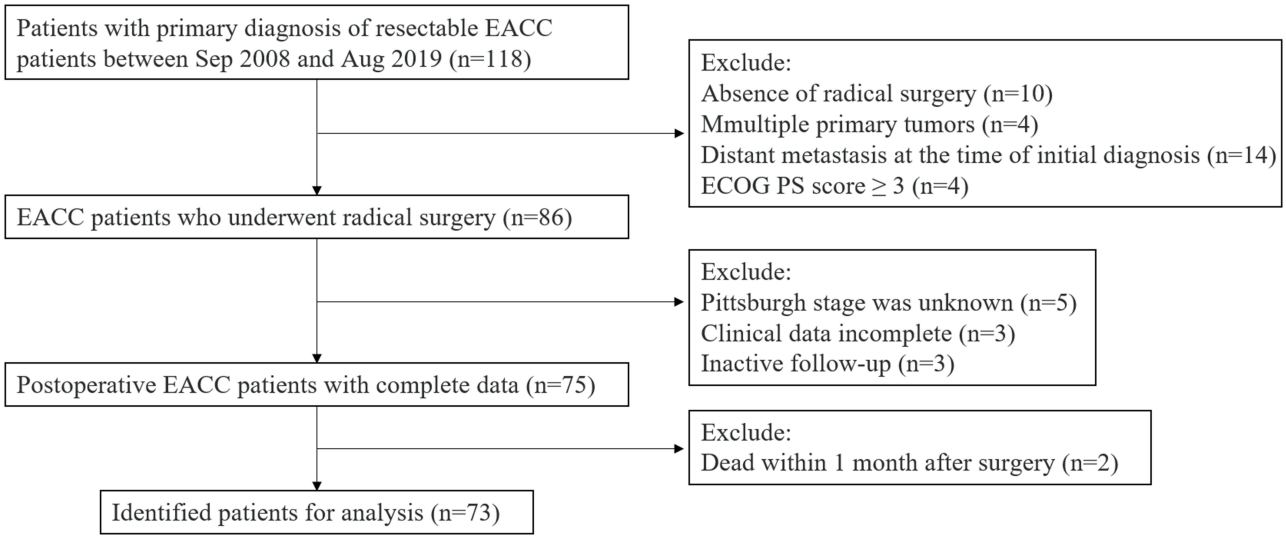

Figure 1 The flow chart of the study.
Abbreviations: EACC, external auditory canal carcinoma; ECOG, eastern cooperative oncology group; PS, performance status.

total, once a day, 5 times a week. A combination of paclitaxel and cisplatin was applied to patients if concurrent chemotherapy was advised.

Variables Collection

The study encompassed a total of 15 variables, including age, gender, Pittsburgh stage, histology, eastern cooperative oncology group (ECOG), performance status (PS) score, smoking status, perineural invasion vascular invasion surgical margin, age-adjusted Charlson comorbidity index (ACCI), NPS, adjuvant chemotherapy, adjuvant radiotherapy, DFS, and OS. The disease-free survival (DFS) overall survival (OS) were the endpoints in this study.

Calculation

NPS was calculated from the results of blood tests performed before surgery. The patients met the following four criteria: serum albumin ≥ 4mg/dL, total cholesterol > 180 mg/dL, NLR ≤ 2.96, and LMR > 4.44. The scores of the above four cases were summed to obtain NPS. The NPS ranged from 0 to 4 points. The calculation and grouping methods of NPS are shown in detail in Figure 2.[17] The calculation procedure for ACCI is summarized in Table S1.

Statistical Analysis

All statistical analyses were performed by SPSS (version 20.0) and R (version 4.22) software. $P < 0.05$ was considered statistically significant. Univariate Cox regression analysis was employed to identify potential predictors of DFS and OS in patients with EACC. The findings were incorporated into a multivariate Cox regression analysis to identify independent factors impacting the prognosis of EACC patients. We further plotted Kaplan-Meier curves to illustrate the disparities in DFS and OS among patients with varying NPS.

Results

Clinical Characteristics

The clinical characteristics of selected patients with EACC who underwent radical resection are listed in Table 1. The median age of the patients was 64 years, with a range from 29 to 90 years. The majority of patients were male, accounting for approximately 62.2% of the study cohort.

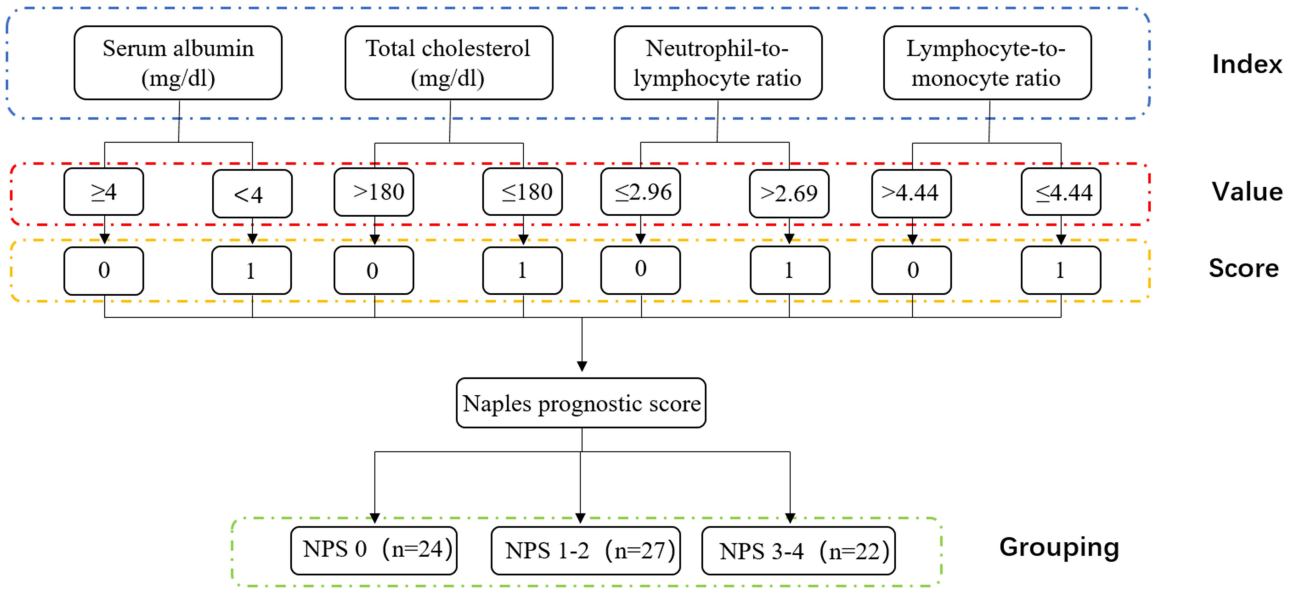

Figure 2 The calculation method of the Naples prognostic score.
Abbreviation: NPS, Naples prognostic score.

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Table 1 Baseline Clinical Characteristics of EACC Patients

Characteristics	Subgroups	Number (%)
No. of Patients		73
Age at Diagnosis (years)	≥60	43 (58.8%)
	<60	30 (41.1%)
Gender	Male	45 (61.6%)
	Female	28 (38.4%)
Pittsburgh Stage	I	18 (24.7%)
	II	15 (20.5%)
	III	26 (35.6%)
	IV	14 (19.2%)
Histology	Squamous Cell Carcinoma	45 (61.6%)
	Adenoid Cystic Carcinoma	19 (26.0%)
	Basal Cell Carcinoma	9 (12.3%)
Symptom	Otalgia	65 (89.0%)
	Otorrhea	36 (49.3%)
	Hearing Loss	10 (13.7%)
	Neck Mass	9 (12.3%)
	Facial Numbness	8 (11.0%)
	Headache	3 (4.1%)
Surgery Type	LTBR	27 (37.0%)
	LTBR+SP	22 (30.1%)
	LTBR+SP+SCLND	2 (2.7%)
	STBR	5 (6.8%)
	STBR+SP	4 (5.5%)
	STBR+TP	2 (2.7%)
	STBR+SP+SCLND	9 (12.3%)
	STBR+TP+SCLND	2 (2.7%)
ECOG PS score	0–1	51 (69.9%)
	2	22 (30.1%)
Smoking	No	57 (78.1%)
	Yes	16 (21.9%)
Perineural invasion	No	59 (80.8%)
	Yes	14 (19.2%)
Vascular invasion	No	62 (84.9%)
	Yes	11 (15.1%)
Surgical Margin	≥ 5mm	58 (79.5%)
	< 5mm or Positive	15 (20.5%)
ACCI	2–5	47 (64.4%)
	≥ 6	26 (35.6%)
NPS	0	24 (32.9%)
	1–2	27 (15.6%)
	3–4	22 (30.1%)
Chemotherapy	No	47 (64.4%)
	Yes	26 (35.6%)
Radiotherapy	No	44 (60.3%)
	Yes	29 (39.7%)

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; EACC, external auditory canal carcinoma; ECOG PS, eastern cooperative oncology group performance status; LTBR, lateral temporal bone resection; NPS, Naples prognostic score; SCLND, superior cervical lymph node dissection; SP, superficial parotidectomy; STBR, subtotal temporal bone resection; TP, total parotidectomy.

The most common symptoms reported among EACC patients were otalgia, experienced by 89.0% of patients, and otorrhea, reported by 49.3%. These symptoms often appeared in the early stages of the disease. The major pathological types of EACC included squamous cell carcinoma (61.6%) and adenoid cystic carcinoma (26.0%). According to the EACC Pittsburgh classification, the patients were distributed by stage as follows: stage I (n = 18, 24.7%), stage II (n = 15, 20.5%), stage III (n = 26, 35.6%), and stage IV (n = 14, 19.2%). Perineural invasion was observed in 14 patients (19.2%), while vascular invasion was identified in 11 patients (15.1%). Most of the patients (79.5%) attained safety surgical margins (≥ 5mm) following the surgery.

The primary surgical options for most EACC patients were LTBR alone (37.0%) or combined with SP (30.1%). A total of 26 patients received chemotherapy: 3 underwent neoadjuvant chemotherapy, 4 received adjuvant chemotherapy, and the remaining patients received chemotherapy for sensitization concurrent with radiotherapy. Additionally, 29 patients underwent radiotherapy, with 3 receiving neoadjuvant radiotherapy and 26 receiving adjuvant radiotherapy.

The results showed that 47 out of 73 patients (64.4%) had ACCI scores ranging from 2 to 5, while 26 patients (35.6%) had scores of 6 or higher. Furthermore, the NPS scores indicated that 24 patients (32.9%) had a score of 0, 27 patients (15.6%) scored between 1 and 2, and 22 patients (30.1%) had scores ranging from 3 to 4.

Univariate and Multivariate Analyses in EACC Patients

Based on the results of our study, the 3- and 5-year OS rates were 76.7% and 52.1%, respectively. Moreover, the 3- and 5-year DFS rates significantly decreased to 72.6% and 32.9%, respectively. The findings from the univariate and multivariate analyses of clinicopathologic data in postoperative EACC patients regarding DFS and OS are presented in Tables 2 and 3, respectively. These analyses were performed to identify significant factors associated with survival outcomes.

Table 2 Univariate and Multivariate Analyses of Clinicopathologic Data in Postoperative EACC Patients for DFS

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (years)	1.011 (1.002–1.027)	0.130		
Gender				
Male	Reference			
Female	2.095 (0.846–5.189)	0.102		
Pittsburgh Stage				
I	Reference		Reference	
II	1.048 (0.456–4.809)	0.514	1.245 (0.344–4.449)	0.739
III	2.677 (0.944–6.591)	0.064	2.454 (0.803–7.501)	0.115
IV	3.591 (1.393–8.993)	**0.012**	3.701 (1.283–9.226)	**0.020**
Histology				
Squamous Cell Carcinoma	Reference		Reference	
Adenoid Cystic Carcinoma	1.008 (0.413–2.462)	0.986	1.224 (0.420–3.571)	0.711
Basal Cell Carcinoma	0.289 (0.072–0.933)	**0.039**	0.455 (0.095–2.192)	0.327
ECOG PS score				
0–1	Reference		Reference	
2	2.140 (0.994–4.606)	**0.042**	1.502 (0.644–3.505)	0.347
Smoking				
No	Reference			
Yes	0.931 (0.395–2.197)	0.871		
Perineural invasion				
No	Reference		Reference	
Yes	2.758 (1.202–6.328)	**0.017**	2.633 (1.048–6.612)	**0.039**

(*Continued*)

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Table 2 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		**HR (95% CI)**	
Vascular invasion				
No	Reference		Reference	
Yes	2.702 (1.144–6.383)	**0.023**	2.987 (1.137–7.845)	**0.026**
Surgical Margin				
≥ 5mm	Reference		Reference	
< 5mm	2.915 (1.162–7.311)	**0.023**	1.090 (0.298–3.990)	0.896
ACCI				
2–5	Reference		Reference	
≥ 6	2.776 (1.285–5.995)	**0.009**	1.578 (0.640–3.890)	0.322
NPS				
0	Reference		Reference	
1–2	2.724 (1.006–7.379)	0.049	2.428 (0.845–4.972)	0.099
3–4	3.412 (1.776–9.387)	**0.003**	4.002 (1.751–10.567)	**0.004**
Chemotherapy				
No	Reference			
Yes	0.476 (0.214–1.057)	0.068		
Radiotherapy				
No	Reference			
Yes	0.742 (0.337–1.635)	0.458		

Note: P value in bold means statistically significant.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; CI, confidence interval; DFS, disease-free survival; EACC, external auditory canal carcinoma; ECOG PS, eastern cooperative oncology group performance status; NPS, Naples prognostic score.

Table 3 Univariate and Multivariate Analyses of Clinicopathologic Data in Postoperative EACC Patients for OS

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		**HR (95% CI)**	
Age at diagnosis (years)	1.020 (0.986–1.054)	0.258		
Gender				
Male	Reference			
Female	2.419 (0.906–6.455)	0.078		
Pittsburgh Stage				
I	Reference		Reference	
II	1.886 (0.566–3.800)	0.301	2.151 (0.602–4.690)	0.239
III	3.948 (1.027–6.661)	0.046	3.450 (1.003–6.121)	0.048
IV	4.542 (1.499–9.765)	**0.007**	4.580 (1.015–10.696)	**0.005**
Histology				
Squamous Cell Carcinoma	Reference			
Adenoid Cystic Carcinoma	1.375 (0.545–2.467)	0.500		
Basal Cell Carcinoma	0.308 (0.087–1.088)	0.067		
ECOG PS score				
0–1	Reference		Reference	
2	2.062 (0.920–4.621)	**0.040**	1.974 (0.830–4.693)	0.124
Smoking				
No	Reference			
Yes	0.889 (0.369–2.146)	0.794		

(*Continued*)

Table 3 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Perineural invasion				
No	Reference		Reference	
Yes	2.424 (0.954–6.163)	**0.033**	1.558 (0.439–5.526)	0.492
Vascular invasion				
No	Reference		Reference	
Yes	3.243 (1.319–7.971)	**0.010**	4.580 (1.734–12.069)	**0.002**
Surgical Margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	3.863 (1.706–8.360)	**0.003**	2.240 (0.573–8.755)	0.246
ACCI				
2–5	Reference		Reference	
≥ 6	3.599 (1.401–8.962)	**0.008**	2.778 (1.360–8.890)	**0.010**
NPS				
0	Reference		Reference	
1–2	1.806 (0.707–4.612)	0.216	1.321 (0.500–3.496)	0.574
3–4	3.661 (1.213–11.047)	**0.021**	3.781 (1.178–12.141)	**0.025**
Chemotherapy				
No	Reference			
Yes	0.497 (0.173–0.910)	0.061		
Radiotherapy				
No	Reference			
Yes	0.922 (0.418–2.038)	0.842		

Note: P value in bold means statistically significant.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; CI, confidence interval; EACC, external auditory canal carcinoma; ECOG PS, eastern cooperative oncology group performance status; NPS, Naples prognostic score; OS, overall survival.

In the univariate analysis for DFS, we found that patients with advanced Pittsburgh stage, basal cell carcinoma histology, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 2, perineural invasion, vascular invasion, a surgical margin of less than 5 mm or positive, an ACCI score of 6 or higher, and a higher NPS had poorer disease-free survival. The multivariate analysis further confirmed that advanced Pittsburgh stage, perineural invasion, vascular invasion, and higher NPS were independent prognostic factors for DFS.

Regarding OS, the univariate analysis indicated that patients with advanced Pittsburgh stage, basal cell carcinoma histology, an ECOG PS score of 2, vascular invasion, perineural invasion, a surgical margin of less than 5 mm or positive, and higher NPS exhibited worse overall survival rates. The multivariate analysis established the significance of advanced Pittsburgh stage, vascular invasion, an ACCI score of 6 or higher, and higher NPS as independent predictors for OS. Additionally, Kaplan-Meier curves were used to predict DFS (Figure 3A) and OS (Figure 3B) among patients with different NPS levels.

Discussion

EACC is a rare malignant tumor located in the temporal bone. The Pittsburgh University staging system, revised by Moody et al in 2000, was commonly used in clinical practice.[1] This system was based on CT examinations, intraoperative findings, and postoperative pathological results. However, recent research has identified several nutrition-related factors,[10,22–24] and inflammatory-related factors[25–28] that influence the prognosis of EACC. These factors had not been included in the Pittsburgh staging system. As a result, the current system has some shortcomings in accurately predicting outcomes for EACC patients due to the lack of comprehensive predictors. Therefore, it is crucial to identify more effective predictors and incorporate them into prognosis assessments for patients with EACC.

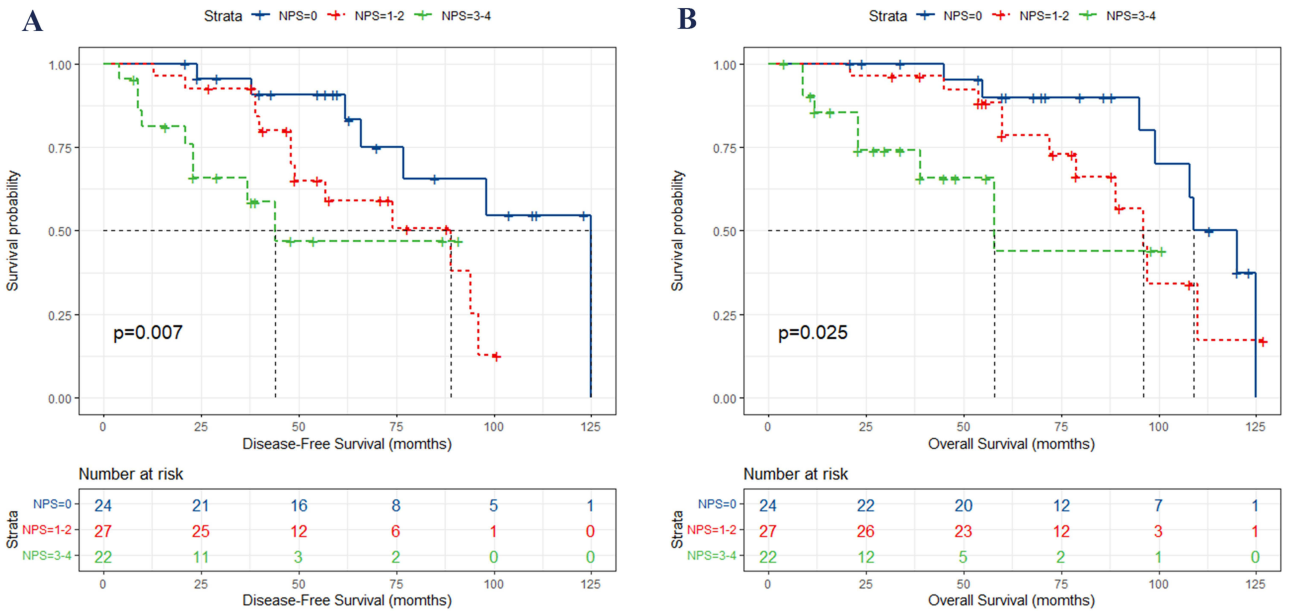

Figure 3 The KM curves to predict DFS (**A**) and OS (**B**) for patients with varying NPS.
Abbreviation: NPS, Naples prognostic score.

The NPS is derived from a panel of inflammatory and nutritional biomarkers, including lymphocyte-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), serum albumin, and total cholesterol (TC).[17] Systemic inflammation shapes the tumor microenvironment, impacting growth, metastasis, immune response, evasion, and drug resistance.[29] Cancer cells release a range of cytokines and chemokines, including IL-6, CCL2, CSF1, and CSF2, affecting vascular permeability, microvascular stability, and lymphangiogenesis. These markers also influence metastasis by affecting cancer cell adhesion. The prognosis of patients with head and neck tumors is influenced by various inflammatory markers, as confirmed by numerous studies.[9,30–32] LMR and NLR were included in NPS as two of these inflammatory markers. Similarly, the influence of nutrition-related markers on cancer patients has been extensively documented. The presence of low serum albumin in patients with head and neck cancer following surgery is indicative of a heightened likelihood of postoperative complications[33] and an unfavorable prognosis.[34] High cholesterol levels can significantly impact the nutritional status and prognosis of cancer patients, potentially enhancing tumor growth and invasion through inflammation and oxidative stress, affecting nutrient absorption and utilization.[35] However, cholesterol is crucial for cell function and immune responses, serving as a precursor for cell membranes and hormone synthesis.[36]

The prognostic significance of NPS has been consistently demonstrated across multiple clinical studies in various malignant tumors. We found that NPS has been identified as a significant prognostic factor in cholangiocarcinoma,[37] ampullary carcinoma,[19] gastric cancer,[38] colorectal cancer,[39] esophageal cancer,[40] upper tract urothelial cancer,[41] pancreatic cancer,[42] endometrial cancer,[43] and hepatocellular carcinoma.[44] However, the relationship between NPS and the prognosis of EACC has not been investigated in any studies yet. Our findings suggest that postoperative EACC patients with a high score of NPS were more likely to have a shorter DFS and OS. This is a very important supplement to previous research.

The ACCI, a multifaceted metric incorporating comorbidity and age, has been instrumental in prognosticating various cancers.[45–48] Its relationship with EACC remains unexplored. This study introduces the ACCI into the analysis, revealing its pivotal role in predicting survival time, specifically OS, for EACC patients post-surgery. The prognosis of post-operative EACC patients with ACCI ≥6 is relatively unfavorable. This finding underscores the ACCI's potential as a valuable tool in tailoring treatment plans and improving outcomes for patients with EACC.

The presence of vascular invasion in certain head and neck tumors is frequently correlated with an unfavorable prognosis.[49–51] EACC patients with perineural invasion can also lead to shorter survival time, which commonly manifests with facial paralysis or pathological positive.[5,52–55] In our research, we also found that vascular invasion

and perineural invasion were significant predictors for prognosis prediction, which was consistent with previous studies. EACC Patients with vascular or perineural invasion tend to have a worse prognosis no matter whether adjuvant treatment is performed.

At present, surgical resection combined with adjuvant radiotherapy is a standard therapeutic regimen for EACC patients,[6,56–58] especially for advanced EACC patients.[59–61] Additionally, adjuvant chemotherapy was often applied in advanced EACC or metastatic EACC previously.[62] However, in our analysis, neither radiotherapy nor chemotherapy could improve DFS and OS of EACC patients included in the study. This may be attributed to a limited sample size, which hindered precise subgrouping and potentially introduced statistical biases. Further research with a larger sample size and more detailed subgroup analysis is warranted to elucidate the impact of these treatments on DFS and OS in EACC patients.

Although this study had incorporated related clinical factors as many as possible, there are still some inevitable limitations. Firstly, some important clinical factors were not involved due to insufficient clinical data, such as meningeal invasion, temporal bone invasion, and the proportion of positive lymph nodes, which may lead to incomprehensive evaluation of prognosis. Secondly, this is a retrospective study, the number of selected cases was very limited due to the very low morbidity of EACC. The selection bias and systematic error were increased and thus reduced the statistical power. Finally, prospective clinical research for EACC patients should be performed in the future. More reliable and effective clinical factors should be involved to make better individual treatment strategy and achieve better clinical management.

Conclusion

As a novel prognostic indicator, NPS plays a pivotal role in predicting the postoperative prognosis of patients with EACC. Elevated NPS levels are indicative of unfavorable DFS and OS, underscoring its clinical utility in risk stratification. Furthermore, Pittsburgh stage, perineural invasion, vascular invasion, and ACCI also emerge as significant prognostic factors in postoperative EACC patients.

Abbreviations

ACCI, age-adjusted Charlson comorbidity index; CRT, conformal radiotherapy; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EACC, external auditory canal carcinoma; IMRT, intensity-modulated radiotherapy; LMR, lymphocyte-monocyte ratio; LTBR, Lateral temporal bone resection; NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; OS, overall survival; PS, performance status; SCLND, superior cervical lymph node dissection; SP, superficial parotidectomy; STBR, subtotal temporal bone resection; TP, total parotidectomy; VMAT, volumetric-modulated arc therapy.

Data Sharing Statement

The data of this study is available upon request from the correspondence author.

Ethics Approval and Consent to Participate

The study strictly adhered to the principles delineated in the Declaration of Helsinki. It was approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University and the Affiliated Cancer Hospital of Zhengzhou University. Approval for ethical considerations was acquired from an established ethics committee, with a designated ethical committee approval number assigned as EC-024-499. All patients willingly provided written informed consent.

Consent for Publication

All the authors agreed to publish the article.

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All the researchers should be appreciated. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3743049/v1.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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