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Research article

Development and validation of a prognostic nomogram incorporating neutrophil-to-albumin ratio for predicting overall survival in patients with nasopharyngeal carcinoma undergoing concurrent chemoradiotherapy

Xin Hua [a,2], Meng-Di Wang [a,2], Wei-Qiong Ni [a,2], Zhi-Qing Long [b], Si-Fen Wang [b], Fang-Fang Duan [b], Chao Zhang [b], Xin Huang [b], Fei Xu [a], Wen Xia [b,1], Jia-Yi Chen [a,1], Yun-Sheng Gao [a,*,1]

[a] Department of Radiation Oncology, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China
[b] Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China

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ABSTRACT

Background: Recent research suggests that the emerging neutrophil-albumin ratio (NAR) has a significant correlation with the survival outcomes across a range of tumors, yet its predictive significance for nasopharyngeal carcinoma (NPC) remains insufficiently investigated. This study aimed to evaluate the relationship between the neutrophil-to-albumin ratio (NAR) and overall survival (OS) in patients with NPC, as well as to develop a corresponding prognostic model.

Methods: This retrospective analysis included 861 NPC patients treated with concurrent chemoradiotherapy (CCRT), who were randomly divided into a training group (n = 605) and a validation group (n = 256). To identify factors associated with OS and construct a prognostic nomogram, both univariate and multivariate Cox regression analyses were performed. The nomogram's prognostic accuracy was evaluated and independently validated.

Results: The NAR score successfully segregated NPC patients into two categories with significantly different OS (HR = 0.536; 95 % CI: 0.296–0.972, P = 0.040). Through multivariate analysis, factors such as age, T stage, N stage, and NAR score were identified as independent predictors of OS, leading to the creation of a prognostic nomogram. This nomogram demonstrated superior predictive capability for OS [C-index = 0.702 (95 % CI: 0.636–0.768)], surpassing that of the conventional staging system [C-index = 0.651 (95 % CI: 0.549–0.752)]. The findings underwent internal validation within an independent cohort.

Conclusions: The NAR, an emergent biomarker combining nutritional and inflammatory status, offers a practical, low-cost, and non-invasive prognostic measure for NPC patients treated with CCRT. Additionally, the prognostic nomogram derived from NAR surpasses traditional staging systems in predictive accuracy.

* Corresponding author. Department of Radiation Oncology, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, Shanghai, China.
E-mail address: gys11856@rjh.com.cn (Y.-S. Gao).
[1] Wen Xia, Jia-Yi Chen, and Yun-Sheng Gao contributed equally to this work as senior authors.
[2] Xin Hua, Meng-Di Wang, and Wei-Qiong Ni contributed equally to this article as first authors.

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1. Introduction

Nasopharyngeal carcinoma (NPC) arises from the epithelial lining of the nasopharynx and is a significant type of head and neck cancer. Although fewer than one in 100,000 people globally are diagnosed with NPC each year, almost half of all cases are detected in China, driven by regional environmental factors, genetic predispositions, and viral infections, notably the Epstein-Barr virus (EBV) [1–4]. Projections indicate that the incidence of NPC in China will continue to increase from 2020 to 2049 [5]. Due to the complex anatomical structure and non-specific clinical presentations, many patients are diagnosed at locally advanced stages and often receive intensity-modulated radiation therapy (IMRT) in conjunction with chemotherapy, primarily based on cisplatin [6,7]. Unfortunately, 10–20 % of affected individuals still experience local recurrence and distant metastasis, with those affected facing a dire prognosis—a median overall survival of merely 20 months [8,9]. This situation underscores the critical need for identifying reliable prognostic factors to enhance treatment strategies and improve patient outcomes.

The current clinical tools for assessing the prognosis of NPC patients and guiding treatment decisions are still based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system. However, this system exhibits significant limitations, such as overlooking clinical, molecular, and histopathological factors related to NPC, the similar survival outcomes for patients classified within T2 and T3 stages, and a lack of risk stratification ability for patients with de novo metastatic NPC [10–12]. Consequently, an increasing number of researchers are focusing on integrating non-anatomical prognostic factors, such as clinical and biomarkers, with the traditional TNM staging to improve risk stratification.

In recent years, the intrinsic connection between nutrition, inflammation, and tumors has been increasingly elucidated [13–16]. Due to the accessibility of serum biomarkers, various peripheral blood parameters related to nutrition and inflammation, including the neutrophil-to-lymphocyte ratio (NLR) [17], lymphocyte-C-reactive protein ratio (LCR) [18], systemic immune-inflammation index (SII) [19], prognostic nutritional index (PNI) [20,21], have been extensively employed to predict survival outcomes in NPC. High neutrophil counts combined with low serum albumin levels are closely linked to poor prognoses in several malignancies [22–26]. Therefore, the Neutrophil-to-Albumin ratio (NAR), which combines the benefits of both neutrophils and albumin, presents an advantageous, cost-effective, and non-invasive systemic marker indicative of nutritional and inflammatory status. It has been utilized as a prognostic indicator for various cancers, including colorectal cancer [27], cervical cancer [28], lung cancer [29], gastrointestinal stromal tumor (GIST) [30], and pancreatic cancer [31]. However, research regarding the pre-treatment NAR's relationship with prognosis in NPC patients is still limited, necessitating further exploration to clarify its significance. In this study, we aim to explore the prognostic value of pre-treatment NAR in NPC patients undergoing concurrent chemoradiotherapy (CCRT) and to develop a risk model for the individualized prediction of survival outcomes.

2. Methods

2.1. Patients

This retrospective analysis included a series of newly diagnosed non-metastatic NPC patients who underwent platinum-based CCRT at the Sun Yat-sen University Cancer Center from January 2010 to December 2014. The criteria for inclusion in this study were as follows: (i) histologically and radiographically verified treatment-naïve non-metastatic NPC; (ii) completion of pretreatment assessments, which included peripheral blood analysis and EBV DNA testing; (iii) receipt of radical intensity-modulated radiotherapy in combination with either weekly or triweekly platinum-based concurrent chemotherapy; and (iv) no presence of chronic inflammatory diseases. The patients' stages were updated according to the 8th edition of the AJCC TNM classification system. Participants in the study were randomly divided into training and validation cohorts at a 7:3 ratio. Ethical approval (Number: B2023-537-01, Approved date: 2023-10-16) for this retrospective study was granted by the Research Ethics Committee at Sun Yat-sen University Cancer Center, with informed consent being waived due to the retrospective design of the study.

2.2. Data collection and follow-up

Initial laboratory data were gathered within one week following diagnosis, while clinicopathological information was extracted from the patients' medical records. The plasma levels of EBV-DNA (copies/ml) were determined using real-time quantitative polymerase chain reaction [32]. Body Mass Index (BMI) was determined by dividing the weight in kilograms (kg) by the square of height in meters (m^2), categorizing patients into different weight groups: BMI $\geq$24, BMI 24–28 or BMI $>$ 28. The approach to treatment and follow-up was aligned with previously outlined guidelines [32]. Overall survival (OS) was identified as the interval from diagnosis to either the date of death or the most recent follow-up.

2.3. Statistical analysis

Sample size calculations were not conducted initially due to insufficient evidence for constructing prognostic models. Nevertheless, with 861 participants enrolled and 83 events documented in this study, the research achieved more than 10 events per variable in the multivariate analyses, indicating sufficient evaluative power [33]. In the R software, we set a random seed number to ensure reproducibility of the results. Each patient's unique ID was used as a factor vector parameter. The "createDataPartition" function from the "caret" package was employed to randomly divide the patients into training and validation sets. The ideal cutoff value was established through maximally selected rank statistics, utilizing survival status as the endpoint, by employing the "maxstat" package

[34]. Kaplan-Meier curves were generated and assessed through log-rank tests for comparisons. Schoenfeld residuals were used to evaluate the proportional hazards assumption. Univariate and multivariate Cox regression analyses utilized the Cox proportional hazards model, incorporating variables with P values < 0.05 from univariate analysis into the multivariate model. Nomograms were created based on multivariate analysis outcomes for visual interpretation of survival probabilities. The models' discriminative performance was evaluated using Harrell's concordance index (C-index) and time-dependent receiver operating characteristic (tROC) analysis. Calibration curves, area under the curve (AUC) derived from tROC analysis, and decision curve analysis (DCA) [35] were used to assess the clinical utility of the prognostic model. Statistical significance was determined using a two-tailed P value of <0.05, with analyses conducted using R software, version 4.2.1.

3. Results

3.1. Patient characteristics

In this investigation, 861 patients diagnosed with NPC and who received platinum-based CCRT were included. These individuals were subsequently randomly divided into two cohorts for the study: a training cohort, consisting of 605 patients, and a validation cohort, comprising 256 patients, following a distribution ratio of 7:3. Table 1 presents the baseline clinicopathological characteristics of both the training and validation cohorts, demonstrating comparability across the cohorts. Within the training cohort, 302 patients (49.9 %) and in the validation group, 121 patients (47.3 %) were aged over 45 years. Moreover, males comprised 454 (75.0 %) of the training cohort and 186 (72.7 %) of the validation group, respectively. The majority of the patients included in this study were histologically confirmed to be of the WHO III type. Additionally, 198 (32.7 %) patients in the training cohort and 81 (31.6 %) patients in the validation cohort exhibited an EBV-DNA level of $\geq$4000 copies/ml. Subsequently, based on the NAR cutoff value of 1.41, identified through maximally selected rank statistics (Figure S1), patients within the training cohort were classified into either the high-NAR group (NAR $\geq$1.41, n = 85) or the low-NAR group (NAR $<$1.41, n = 520). Employing this identical cutoff of 1.41, the validation cohort was similarly divided, with 26 patients falling into the high-NAR category (NAR $\geq$1.41) and 230 into the low-NAR category

Table 1
Patient demographics and clinical characteristics between the training and validation cohorts.

Characteristic	Total (n = 861)	Training cohort (n = 605)	Validation cohort (n = 256)	P
Age				0.524
< 45 years	438 (50.9 %)	303 (50.1 %)	135 (52.7 %)	
≥45 years	423 (49.1 %)	302 (49.9 %)	121 (47.3 %)	
Gender				0.518
Male	640 (74.3 %)	454 (75.0 %)	186 (72.7 %)	
Female	221 (25.7 %)	151 (25.0 %)	70 (27.3 %)	
Histological type				0.068
WHO I/II	13 (1.51 %)	6 (1.0 %)	7 (2.7 %)	
WHO III	848 (98.5 %)	599 (99.0 %)	249 (97.3 %)	
HGB				0.531
< 113 g/L	27 (3.1 %)	19 (3.1 %)	8 (3.1 %)	
113–151 g/L	548 (63.6 %)	378 (62.5 %)	170 (66.4 %)	
≥151 g/L	286 (33.2 %)	208 (34.4 %)	78 (30.5 %)	
LDH				0.292
≥245 U/L	51 (5.9 %)	32 (5.3 %)	19 (7.4 %)	
< 245 U/L	810 (94.1 %)	573 (94.7 %)	237 (92.6 %)	
T stage				0.348
T1	42 (4.9 %)	32 (5.3 %)	10 (3.9 %)	
T2	165 (19.2 %)	122 (20.2 %)	43 (16.8 %)	
T3	524 (60.9 %)	366 (60.5 %)	158 (61.7 %)	
T4	130 (15.1 %)	85 (14.0 %)	45 (17.6 %)	
N stage				0.073
N0	81 (9.41 %)	49 (8.1 %)	32 (12.5 %)	
N1	465 (54.0 %)	321 (53.1 %)	144 (56.2 %)	
N2	271 (31.5 %)	203 (33.6 %)	68 (26.6 %)	
N3	44 (5.1 %)	32 (5.3 %)	12 (4.7 %)	
BMI				0.073
≤24 kg/m^2	519 (60.3 %)	360 (59.5 %)	159 (62.1 %)	
24–28 kg/m^2	294 (34.1 %)	217 (35.9 %)	77 (30.1 %)	
≥28 kg/m^2	48 (5.57 %)	28 (4.63 %)	20 (7.81 %)	
EBV-DNA				0.817
< 4000 copy/ml	582 (67.6 %)	407 (67.3 %)	175 (68.4 %)	
≥4000 copy/ml	279 (32.4 %)	198 (32.7 %)	81 (31.6 %)	
NAR				0.148
< 1.41	750 (87.1 %)	520 (86.0 %)	230 (89.8 %)	
≥1.41	111 (12.9 %)	85 (14.0 %)	26 (10.2 %)	

Abbreviations: WHO = World Health Organization; HGB = hemoglobin; LDH = serum lactate dehydrogenase levels; BMI = body mass index; EBV-DNA = Epstein-Barr virus DNA; NAR = neutrophil-albumin ratio.

(NAR <1.41).

3.2. Prognostic value of NAR score for OS in NPC

For the whole cohort, the median duration of follow-up was 63.0 months, with an interquartile range (IQR) from 49.3 to 62.1 months, while the median OS spanned 62.7 months (IQR: 46.4–74.7 months). In the whole cohort, a total of 83 death events were documented, comprising 62 within the training group and 21 among the validation group members. The OS rates at the 1-, 3-, and 5-year intervals for the whole cohort were reported as 97.9 %, 94.1 %, and 90.0 % respectively. Specifically, the training cohort noted 1-, 3-, and 5-year OS rates of 97.5 %, 93.3 %, and 89.1 %, respectively, while the validation cohort recorded OS rates of 98.4 %, 95.4 %, and 91.4 % at these same time points, respectively. No significant difference in OS was observed between the training and validation cohorts (Figure S2, P = 0.299, HR = 0.769; 95 % CI: 0.469–1.262). Kaplan-Meier survival curves indicated that, in both the training and validation cohorts, patients within the low-NAR value experienced markedly improved survival compared to those categorized within the high-NAR value (Fig. 1A, HR = 0.536; 95 % CI: 0.296–0.972, P = 0.040; Fig. 1B, HR = 0.326; 95 % CI: 0.119–0.890, P = 0.029).

3.3. Univariate and multivariate cox regression analyses of OS in NPC

Univariate and multivariate Cox regression analyses were performed in both the training and validation cohorts**.** Within the training cohort, factors that satisfied the predetermined significance level (P < 0.05) in the univariate Cox model, such as age, T stage, N stage, EBV-DNA status, and NAR score, were included in the multivariate Cox regression analysis. An evaluation for multicollinearity was executed through the calculation of variance inflation factors (VIFs) for the aforementioned variables (with all VIFs <10), revealing the absence of significant multicollinearity. Based on the proportional hazards' diagnostic plots (Figure S3), the multivariable model met the proportional hazards assumption. The results of the multivariate model indicated that, with the exception of EBV-DNA status (P = 0.284), age (P = 0.029), N stage (P < 0.05), T stage (P < 0.05), and the NAR score (P = 0.003) were independently associated with OS in NPC patients undergoing CCRT (Table 2).

3.4. Development of a novel prognostic model based on NAR

Utilizing the four independent prognostic factors identified within the aforementioned Cox multivariate regression model, a novel and pragmatic nomogram has been developed to facilitate the intuitive assessment of 1-year, 3-year, and 5-year OS probabilities among NPC patients (Fig. 2). Clinicians are able to assess prognostic risk associated with individual patients using this nomogram prior to CCRT initiation. The nomogram allows point assignment for each factor based on patient characteristics. As illustrated in Fig. 2, patients aged ≥45 years receive higher points in the "Age" category. The "T stage" row assigns more points to higher stages (T4, T3, T2) compared to lower stages (T1). In a similar vein, the "N stage" row allocates more points to advanced stages (N3, N2, N1) in contrast to lower stages (N0), while the "NAR group" row awards higher points to increased NAR values. By totaling all points, clinicians can estimate the predicted OS rates. For instance, a 40-year-old patient classified as T2 and N2 with an NAR score exceeding 1.41 would achieve a total score of 15.1, correlating with estimated 1-year, 3-year, and 5-year OS probabilities of 97 %, 92 %, and 85 %,

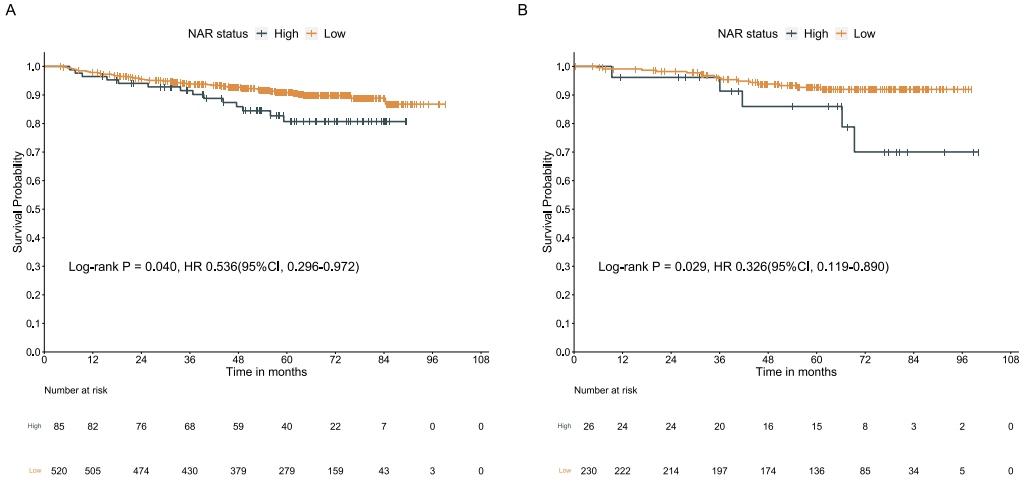

Fig. 1. Survival curves obtained with Kaplan-Meier analysis between different NAR Groups (the HRs reported were unadjusted). A: Survival curves in the training cohort. B: Survival curves in the validation cohort.
AbbreviationsNAR = neutrophil-albumin ratio; HR = hazard ratios; CI = confidence interval.

Table 2
Univariate and multivariate Cox regression analyses of overall survival.

Characteristic	Univariate analysis	P	Multivariate analysis	P
	Hazard ratio (95%CI)		Hazard ratio (95%CI)	
Age				
≥45 years	1		1	
< 45 years	0.646 (0.418–0.999)	0.049	0.613 (0.395–0.952)	0.029
Gender				
Male	1			
Female	0.737 (0.432–1.257)	0.262		
Histological type				
WHO I/II	1			
WHO III	2.409 (0.760–7.634)	0.135		
HGB				
< 113 g/L	1			
113–151 g/L	2.300 (0.317–16.680)	0.410		
≥151 g/L	3.403 (0.467–24.820)	0.227		
LDH				
≥245 U/L	1			
< 245 U/L	0.723 (0.315–1.660)	0.444		
T stage				
T1	1		1	
T2	3.192 (0.415–24.550)	0.265	3.018 (0.392–23.262)	0.289
T3	4.065 (0.561–29.440)	0.165	3.908 (0.538–28.402)	0.178
T4	7.761 (1.044–57.710)	0.045	7.699 (1.030–57.582)	0.047
N stage				
N0	1		1	
N1	1.601 (0.569–4.505)	0.373	1.864 (0.659–5.272)	0.241
N2	2.889 (1.027–8.130)	0.044	3.414 (1.198–9.729)	0.022
N3	4.671 (1.438–15.171)	0.010	5.138 (1.541–17.130)	0.008
BMI				
≤24 kg/m^2	1			
24–28 kg/m^2	0.798 (0.497–1.283)	0.352		
≥28 kg/m^2	0.795 (0.288–2.195)	0.658		
EBV-DNA				
< 4000 copy/mL	1		1	
≥4000 copy/mL	1.651 (1.068–2.554)	0.024	1.201 (0.762–1.891)	0.284
NAR				
≥1.41	1		1	
< 1.41	0.536 (0.296–0.972)	0.040	0.456 (0.272–0.763)	0.003

Abbreviations: Hazard ratios estimated by Cox proportional hazards regression. All statistical tests were two-sided. Abbreviations: WHO = World Health Organization; HGB = hemoglobin; LDH = serum lactate dehydrogenase levels; BMI = body mass index; EBV-DNA = Epstein-Barr virus DNA; NAR = neutrophil-albumin ratio.

respectively.

3.5. Assessment of predictive performance of the prognostic model

The prognostic model displayed excellent discriminative performance, achieving a C-index of 0.771 (95 % CI: 0.672–0.871) in the training group and 0.702 (95 % CI: 0.636–0.768) in the validation group. Comparatively, the traditional staging system showed lower C-index values of 0.651 (95 % CI: 0.549–0.752) and 0.652 (95 % CI: 0.465–0.838) for the training and validation cohorts, respectively. In a calibration plot, the x-axis usually denotes the predicted probabilities, whereas the y-axis represents the observed proportion of positive outcomes. Ideally, when the calibration curve's predicted incidence aligns closely with the observed incidence, the plot should follow the Y = X line, forming a 45-degree diagonal. Our calibration plot nearly coincides with the Y = X line, demonstrating good model calibration. There is a strong concordance in the 1-, 3-, and 5-year overall survival rates between the training cohort (Fig. 3A) and the validation cohort (Fig. 3B). The model's predictive accuracy for OSwas evaluated using time-dependent ROC curves, where a higher AUC value reflects better predictive performance, enabling patients to benefit from more accurate predictions. The findings indicate that this model surpasses the conventional TNM staging system in both the training set (Fig. 3C) and the validation set (Fig. 3D). DCA illustrates net benefit across threshold probabilities, with the x-axis representing threshold probabilities and the y-axis showing net benefit. The DCA curves for 1-year, 3-year, and 5-year OS clearly reveal that the proposed model achieves a significantly higher net benefit than the traditional staging system in both the training cohort (Fig. 3E) and the validation cohort (Fig. 3F). These findings emphasize the enhanced clinical applicability of the novel nomogram model in accurately forecasting individual survival outcomes when contrasted with the traditional staging system.

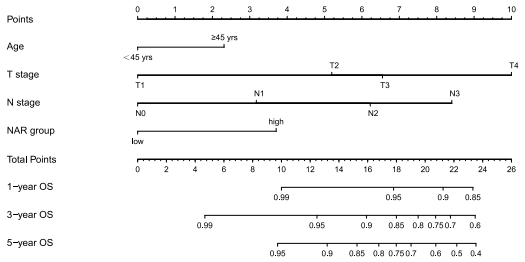

Fig. 2. Nomogram of the current prognostic model for individualized survival predictions. The nomogram enables clinicians to assign points to each factor based on the patient's individual characteristics. For instance, the top row labeled "Age" assigns higher points to patients aged ≥45 years compared to those aged <45 years. Similarly, the row labeled "T stage" assigns more points to higher stages (T4, T3, and T2) compared to lower stages (T1). The third row labeled "N stage" assigns more points to higher stages (N3, N2, and N1) compared to lower stages (N0). The fourth row labeled "NAR group" assigns higher points to higher NAR values compared to lower NAR values. By summing the total points for all factors, clinicians can use the bottom row labeled "Total Points" to determine the predicted OS rate. This nomogram provides estimates for 1-year, 3-year, and 5-year OS rates. Clinicians can draw a line from the Total Points axis to the corresponding survival probability axis, providing a visual representation of the patient's expected survival chances.
AbbreviationsOS = overall survival; NAR = neutrophil-albumin ratio.

4. Discussion

To the best of our knowledge, this is the first detailed study to explore the prognostic value of the tumor-related inflammatory nutritional marker, NAR, in a substantial cohort of NPC patients treated with CCRT. Derived from the neutrophil count and serum albumin level, the NAR encapsulates both systemic inflammatory status and nutritional status, thereby potentially offering additional insights into tumor outcomes. A higher pre-treatment level of NAR has been identified as being associated with poorer prognosis. Multivariate Cox regression analysis identified age, T stage, N stage, and NAR as independent prognostic factors for survival in NPC patients. This facilitated the creation of a novel and user-friendly nomogram model incorporating NAR. Compared to the traditional TNM staging system, this new prognostic model significantly improves survival prediction accuracy for NPC patients undergoing CCRT, thereby supporting more effective risk stratification and personalized treatment planning for this diverse patient group. Furthermore, these results were successfully replicated in another internally validated cohort.

Undoubtedly, despite significant advancements in radiotherapy techniques and pharmacological treatments, the challenge of achieving a prudent balance between tumor control and minimizing treatment-related toxicity remains prevalent in the clinical management of NPC. This challenge is partly due to the fact that NPC represents a group of cancers characterized by anatomical and biological diversity, with significant prognostic heterogeneity [36–38]. Although treatments can lead to considerable late toxicities, recurrent disease is often challenging to manage, leading to poor survival outcomes and functional impairments. Therefore, achieving effective tumor control and aiming for a cure at the time of initial diagnosis are of utmost importance. Consequently, there is an urgent demand for the discovery of reliable biomarkers to enhance disease risk stratification, facilitating the personalization of treatment plans by strategically adding or reducing therapeutic interventions [39]. With the aid of genomics, transcriptomics, and proteomics technologies, a substantial number of biomarkers associated with the prognosis of NPC have been identified. Nevertheless, the clinical application of these discoveries remains pending, primarily due to small sample sizes and a lack of replication studies. In gene expression profiling, significant challenges include managing small-sized tumors and ensuring high tumor purity. Tissue specimens from nasopharyngeal biopsies are often limited in size. Moreover, NPC tumor purity is compromised by a complex mixture of immune cells, stromal components, and cancerous epithelial cells, undermining genomic analysis accuracy. Additionally, sample fixation and paraffin embedding usually worsen RNA degradation. Thus, while advancing technologies is essential to overcome these obstacles, it will also significantly increase the cost of delivering personalized patient care [12,40,41]. Obviously, the peripheral blood inflammatory-nutritional biomarker NAR investigated in this study has distinct advantages over others, such as being readily accessible, cost-effective, highly reproducible, and easily generalizable.

The prognostic significance of the NAR has been extensively corroborated across various malignancies, establishing its association with long-term survival outcomes. Xie et al. demonstrated that increased preoperative NAR levels act as an independent predictor of postoperative complications in patients with colorectal cancer and are significantly correlated with both progression-free survival (PFS) and OS [27]. Li et al., in a retrospective study involving 229 patients who underwent radical gastrectomy for GIST, observed that elevated postoperative NAR levels were associated with reduced recurrence-free survival (RFS) [30]. Tingle, Samuel J., and colleagues identified NAR as an effective predictor of OS in individuals with unresectable stage III to IV pancreatic ductal adenocarcinoma [31]. Yu et al., in an analysis of 622 patients who underwent surgical treatment for oral squamous cell carcinoma, concluded that elevated preoperative NAR is an independent negative prognostic indicator for OS, cancer-specific survival, and RFS [42]. Consistent with observations of NAR in other types of tumors, our study demonstrates that elevated pre-treatment NAR levels act as an independent prognostic factor for OSin NPC patients receiving concurrent CCRT. A nomogram model based on NAR can directly aid clinicians in

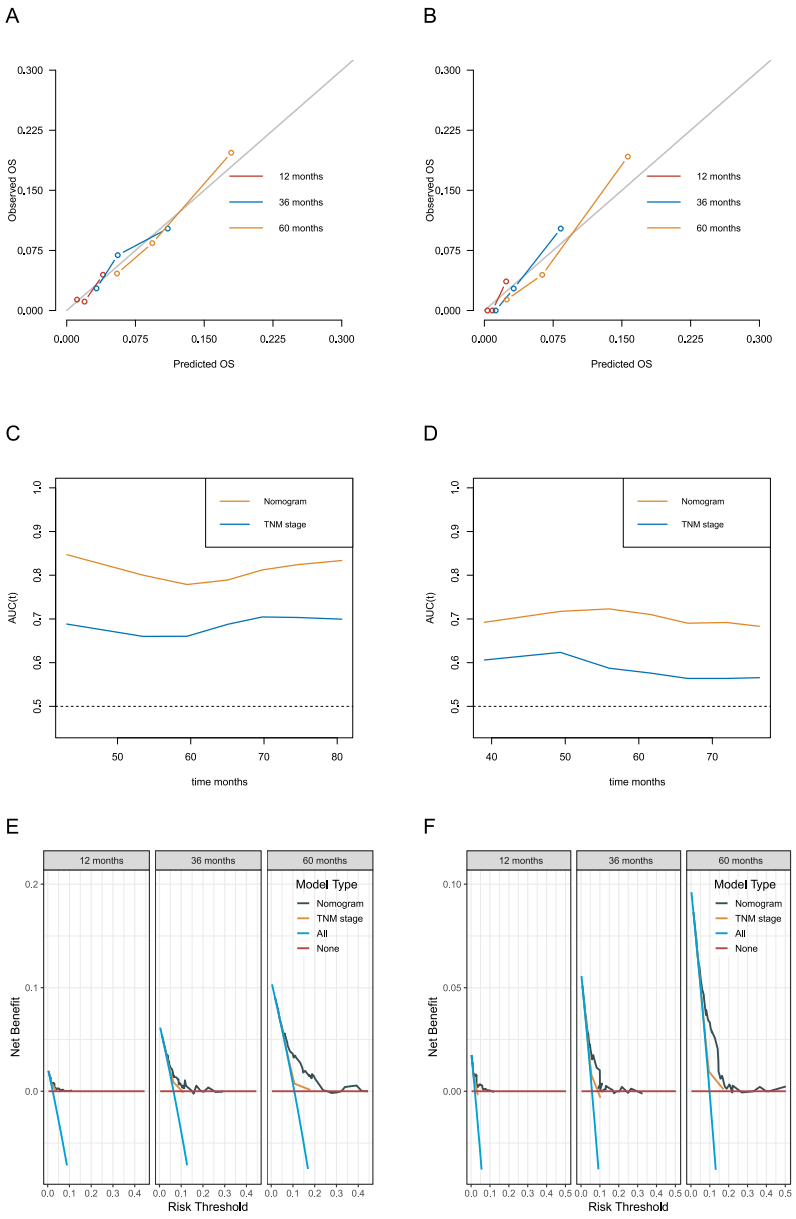

Fig. 3. Assessment of predictive performance of the prognostic model. (A) Calibration plot of the nomogram model at 1-, 3-, and 5-year in the training cohort. Calibration plot, the x-axis typically represents the predicted probabilities, while the y-axis shows the actual fraction of positive cases. Ideally, the plot should show a straight line at a 45-degree angle, indicating perfect calibration where the observed outcomes match the predicted probabilities perfectly. Our calibration plot nearly coincides with the Y = X line, demonstrating good model calibration. (B) Calibration plot of the nomogram model at 1-, 3-, and 5-year in the validation cohort. Calibration plot, the x-axis typically represents the predicted probabilities, while the y-axis shows the actual fraction of positive cases. Ideally, the plot should show a straight line at a 45-degree angle, indicating perfect calibration where the observed outcomes match the predicted probabilities perfectly. Our calibration plot nearly coincides with the Y = X line, demonstrating good model calibration. (C) Time-independent ROC curves compared the predictive accuracy of the current model and the traditional TNM stage in the training cohort.(D) Time-independent ROC curves compared the predictive accuracy of the current model and the traditional TNM stage in the validation cohort. (E) DCA curves compared the net benefit rate of the current model and the traditional TNM stage in the training cohort. The DCA curve is a graphical representation where the x-axis displays the range of threshold probabilities and the y-axis shows the net benefit. The DCA curves based on 1-year, 3-year, and 5-year overall survival benefits clearly demonstrate that the proposed model provides a significantly higher net benefit compared to the traditional staging system in the training set. (F) DCA curves compared the net benefit rate of the current model and the traditional TNM stage in the validation cohort. The DCA curve is a graphical representation where the x-axis displays the range of threshold probabilities and the y-axis shows the net benefit. The DCA curves based on 1-year, 3-year, and 5-year overall survival benefits clearly demonstrate that the proposed model provides a significantly higher net benefit compared to the traditional staging system in the validation

set.
Abbreviations: OS = overall survival; AUC = area under curve; TNM = tumor-node-metastasis.

quantifying the prognostic risks for NPC patients, thus facilitating the development of appropriate personalized treatment plans.

The molecular mechanisms linking NAR status to tumor prognosis are not yet fully understood. However, scientific hypotheses may be proposed based on the role of neutrophil and serum albumin within the tumor context, utilizing their physiological and pathological functions as a basis. Neutrophils, derived from the venous sinuses of the bone marrow, are the predominant inflammatory cells in the circulatory system. Under the influence of cytokines and inflammatory mediators such as IL-1, IL-6, and S100A8/A9 proteins, neutrophils are recruited and activated. They engage in direct interactions with tumor cells at localized sites, facilitating an environment conducive to tumor cell proliferation. Moreover, activated neutrophils secrete neutrophil extracellular traps (NETs), which serve to ensnare circulating tumor cells and may reactivate dormant tumor cells, potentially precipitating tumor relapse. Therefore, an increase in peripheral blood neutrophil count correlates with adverse prognostic outcomes [43–45]. Albumin (ALB), produced by hepatocytes, is the most abundant protein in human serum and serves as a marker of both nutritional status and, to some extent, systemic inflammation. In cancer patients, systemic inflammatory responses lead to the significant release of cytokines like IL-6 and TNF. These not only inhibit the biosynthesis of serum albumin but also increase the permeability of capillaries, facilitating the easier transcapillary migration of albumin. Such mechanisms adversely affect the albumin-mediated anti-tumor immune responses. Additionally, tumor cells may capture plasma albumin as a nutritional source for their growth [25,46–49]. Consequently, low levels of ALB are considered indicative of poor nutritional status and a higher risk of disease progression. This has been validated as a prognostic indicator of unfavorable outcomes in multiple cancers, such as breast, lung, gastric, and head and neck cancers [24,25,50,51]. In conclusion, an elevated NAR in patients with NPC is indicative of compromised nutritional status, augmented systemic inflammation, and reduced capacity for anti-tumor immunity, correlating with negative survival prognoses.

This cohort study also has some limitations that warrant special attention. Firstly, as a single-center retrospective investigation, it may possess inherent selection bias and lacks external validation. Consequently, multi-center prospective studies that incorporate diverse populations are essential for strengthening the reliability of our findings. Secondly, the focus on patients undergoing comprehensive assessments may mean that the final cohort does not represent all cancer patients in our institution. Although strict inclusion and exclusion criteria were enforced, the serum biomarker NAR might still be influenced by various clinical factors, hence necessitating caution in results interpretation. Lastly, this research emphasizes a representative cohort undergoing CCRT in endemic regions for NPC; therefore, these findings may not be directly relevant to populations in non-endemic areas. Further verification through large-scale studies from other centers is critical to confirming the robustness of our findings. Furthermore, unlike prior studies [52–54], this research did not identify pre-treatment EBV DNA levels as an independent prognostic factor for overall survival in NPC patients undergoing CCRT. This discrepancy may be attributed to variables such as sample size, the laboratory techniques used for EBV DNA detection, and the established threshold values. Acknowledging these limitations, we plan to design larger prospective cohort studies in the future, aiming to validate the reliability of these findings through dynamic analysis of diverse population data.

5. Conclusions

In conclusion, this study confirms the designation of NAR as an innovative, easy-to-obtain, cost-effective, and minimally invasive indicator for forecasting prognosis among NPC patients undergoing CCRT. Furthermore, prognostic models driven by NAR have displayed greater predictive accuracy in comparison to conventional staging methods. By employing the NAR-based scoring system, oncologists can improve the precision of survival outcome predictions, thereby facilitating the formulation of optimal management strategies for NPC patients before and following CCRT.

CRediT authorship contribution statement

Xin Hua: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Meng-Di Wang:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Wei-Qiong Ni:** Writing – original draft. **Zhi-Qing Long:** Investigation, Formal analysis. **Si-Fen Wang:** Project administration, Methodology. **Fang-Fang Duan:** Software, Resources. **Chao Zhang:** Validation, Software. **Xin Huang:** Validation, Supervision. **Fei Xu:** Software, Formal analysis. **Wen Xia:** Writing – review & editing, Conceptualization. **Jia-Yi Chen:** Writing – review & editing, Conceptualization. **Yun-Sheng Gao:** Writing – review & editing, Conceptualization.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval (Number: B2023-537-01 and Approved date: 2023-10-16) for this retrospective study was obtained from the Research Ethics Committee at Sun Yat-sen University Cancer Center, with informed consent waived due to the study's retrospective nature.

Availability of data and materials

The data related to this study has not been deposited in a public repository. However, the data and code are available upon request from the corresponding author.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations:

NPC	Nasopharyngeal Carcinoma
EBV	Epstein-Barr Virus
IMRT	Intensity-Modulated Radiation Therapy
TNM	Tumor-Node-Metastasis
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control
CCRT	Concurrent Chemoradiotherapy
NLR	Neutrophil-to-Lymphocyte Ratio
LCR	Lymphocyte-C-reactive Protein Ratio
SII	Systemic Immune-Inflammation Index
PNI	Prognostic Nutritional Index
BMI	Body Mass Index
OS	Overall Survival
IQR	Interquartile Range
VIF	Variance Inflation Factor
PFS	Progression-Free Survival
GIST	Gastrointestinal Stromal Tumor
RFS	Recurrence-Free Survival
NETs	Neutrophil Extracellular Traps
IL	Interleukin
TNF	Tumor Necrosis Factor
ALB	Serum Albumin
DCA	Decision Curve Analysis

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