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Prognostic Value of the Pretreatment Global Immune–Nutrition–Inflammation Index in Nasopharyngeal Carcinoma: A Multicenter Retrospective Cohort Study

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Abstract

Background and Objectives: Nasopharyngeal carcinoma (NPC) exhibits substantial biological heterogeneity that is not fully captured by TNM staging. We investigated the prognostic significance of the pretreatment Global Immune–Nutrition–Inflammation Index (GINI) in NPC. *Materials and Methods*: This multicenter retrospective cohort study included 96 patients with pathologically confirmed NPC who were treated between 2015 and 2024. GINI was calculated using neutrophil, lymphocyte, monocyte, and platelet counts, along with serum C-reactive protein and albumin levels. The optimal cutoff was identified by receiver operating characteristic analysis. Survival outcomes were assessed with Kaplan–Meier and multivariable Cox regression analyses. *Results*: The optimal GINI cutoff was 3403 (AUC: 0.726, $p < 0.001$), which showed a numerically higher AUC than the neutrophil-to-lymphocyte ratio (NLR; AUC: 0.674, $p = 0.003$). High GINI was associated with advanced stage ($p = 0.008$), shorter overall survival (OS) (23 vs. 95 months, $p < 0.001$), and shorter disease-free survival (DFS) (16 vs. 95 months, $p < 0.001$). In multivariable analysis, high GINI remained significantly associated with poorer OS and DFS. *Conclusions*: Pretreatment GINI was strongly associated with survival in patients with NPC and may serve as a useful adjunctive prognostic marker. Further prospective studies and external validation are required before its incorporation into clinical risk-stratification strategies.

Keywords: nasopharyngeal carcinoma; inflammation; nutritional status; prognosis; biomarkers; tumor

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1. Introduction

Nasopharyngeal carcinoma (NPC) is distinct from other head and neck cancers. It differs in aetiology, biological behaviour, and epidemiological distribution [1]. NPC is rare globally but endemic to Southern China, Southeast Asia, and North Africa [2,3]. Genetic susceptibility, dietary factors (especially the consumption of salted fish during childhood), environmental exposures, and Epstein–Barr virus (EBV) infection are key

etiological factors. In contrast, human papillomavirus (HPV) plays a comparatively limited role. NPC occurs more frequently in men and most commonly presents between ages 40 and 60 [2,4]. Patients commonly present with cervical lymphadenopathy secondary to nodal metastasis. Additional symptoms include nasal obstruction, epistaxis, purulent nasal discharge, and otologic manifestations such as unilateral aural fullness, tinnitus, and conductive hearing loss (commonly due to Eustachian tube dysfunction). These symptoms are nonspecific, so diagnosis is often delayed until advanced stages [1,3,4].

Radiotherapy is the standard treatment for early NPC, while more advanced cases receive concurrent platinum-based chemoradiotherapy. In recurrent or metastatic cases, treatments such as gemcitabine–cisplatin combined with immune checkpoint inhibitors have led to improved survival [3,4]. However, survival rates remain variable even within the same tumor–node–metastasis (TNM) stage, highlighting the limitations of anatomical staging alone and the need for accessible, cost-effective biomarkers to guide personalized treatment [5]. In this context, systemic inflammation, the immune response, and nutrition are known to alter the tumor microenvironment and influence cancer outcomes. The Global Immune–Nutrition–Inflammation Index (GINI), which integrates markers of inflammation, immunity, and nutrition, emerges as a promising prognostic tool that may complement TNM staging [5–8].

The GINI is designed to capture the patient's systemic status by combining markers such as C-reactive protein (CRP) and albumin with blood cell counts (neutrophils, monocytes, platelets, and lymphocytes) [6,8]. Originally described by Topkan et al. in stage IIIC non-small cell lung cancer, the GINI has subsequently been associated with survival outcomes across various solid malignancies [6,7,9,10]. In NPC, GINI has been shown to predict radiotherapy-induced trismus [8]. Despite these findings, its role in predicting survival or mortality in NPC remains unexamined. Therefore, this study aimed to evaluate the association between pretreatment GINI levels and both overall survival (OS) and disease-free survival (DFS) in patients with NPC, and to determine the independent prognostic value of GINI. We hypothesized that elevated pretreatment GINI levels would independently predict poorer OS and DFS in patients with NPC.

2. Materials and Methods

2.1. Study Design and Patient Population

This retrospective multicenter cohort study included patients with pathologically confirmed NPC. Patients were diagnosed, treated, or followed at two tertiary hospitals between 1 January 2015 and 31 December 2024. All consecutive patients meeting the predefined eligibility criteria during the study period were included. Given the retrospective cohort design, no a priori sample-size calculation was performed.

2.2. Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they were aged 18 years or older, had histopathologically confirmed NPC, and were treated or followed at a participating centre. Exclusion criteria consisted of a secondary head and neck cancer, incomplete baseline or follow-up clinical data, loss to follow-up, or a blood transfusion within the past 4 months. Additionally, patients with chronic immune or inflammatory diseases, acute infections, or recent use of immunomodulating drugs were excluded. Pretreatment laboratory parameters—including complete blood count (CBC), uric acid, lactate dehydrogenase (LDH, U/L), albumin, and CRP (mg/L)—were required to be drawn within 7–10 days before the initiation of treatment.

2.3. Data Collection and Variables

Patient data were extracted from electronic medical records. The main variables were age, sex, performance status, BMI, comorbidities, smoking history, tumor features, pretreatment plasma EBV DNA level, treatment, response, disease progression, and survival. Pretreatment blood tests included neutrophil, lymphocyte, platelet, and monocyte counts, as well as albumin and CRP (mg/L) levels. EBV positivity was determined based on pretreatment plasma EBV DNA testing, rather than tissue-based methods such as EBER in situ hybridization.

2.4. Treatment Details and Response Assessment

All patients were staged using the American Joint Committee on Cancer 8th edition. ^{18}F-FDG PET/CT and nasopharyngeal/cervical contrast-enhanced MRI were performed before treatment. Histological grading was based on the original pathology reports. Treatment was administered according to disease stage and contemporary institutional practice. Patients received definitive radiotherapy alone, concurrent chemoradiotherapy (CCRT), or induction chemotherapy with cisplatin–gemcitabine or cisplatin–5-fluorouracil followed by CCRT. Across all CCRT regimens, cisplatin was the preferred platinum agent, with carboplatin reserved for patients with contraindications to cisplatin. Patients were generally followed every 3 months with imaging and lab tests. Disease-free survival was defined as the time from completion of primary treatment to recurrence, progression, or death from any cause; patients without an event were censored at the date of last follow-up. Overall survival was measured from diagnosis to death or last follow-up. OS was the primary outcome. DFS was a secondary outcome. The study aimed to determine whether pretreatment GINI was associated with OS and DFS and whether it independently predicted survival. ROC curve analysis was used to identify a clinically relevant cutoff and assess GINI's ability to identify high-risk patients.

2.5. Immune–Inflammatory and Nutritional Indices

The following indices were calculated using standard formulas:

GINI = (neutrophil [10^9/L] × platelet [10^9/L] × monocyte [10^9/L] × C-reactive protein [mg/L])/(lymphocyte [10^9/L] × albumin [g/dL]) [6]. Here, neutrophils, monocytes, lymphocytes, and platelets are blood cell types; CRP reflects inflammation; and albumin reflects nutritional status. NLR denotes the neutrophil-to-lymphocyte ratio, which compares two types of white blood cells to indicate inflammation. Patient selection, exclusion process, and final cohort formation are summarized in Figure 1.

2.6. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed continuous variables are presented as mean ± SD. Non-normally distributed data are reported as median (range). The prognostic performance of GINI and NLR was studied using receiver operating characteristic (ROC) curve analysis. Optimal cut-off values for GINI and NLR were chosen by maximizing the Youden index. Groups were then compared with respect to DFS and OS. Associations between GINI and clinicopathological or biochemical variables were tested using the Pearson chi-square test or Fisher's exact test. Survival outcomes were estimated using the Kaplan–Meier method, and comparisons were made using the log-rank test. Variables significant in univariate analysis were included in multivariate Cox models to identify independent predictors of survival. All tests were two-sided. p-values less than 0.05 were considered significant.

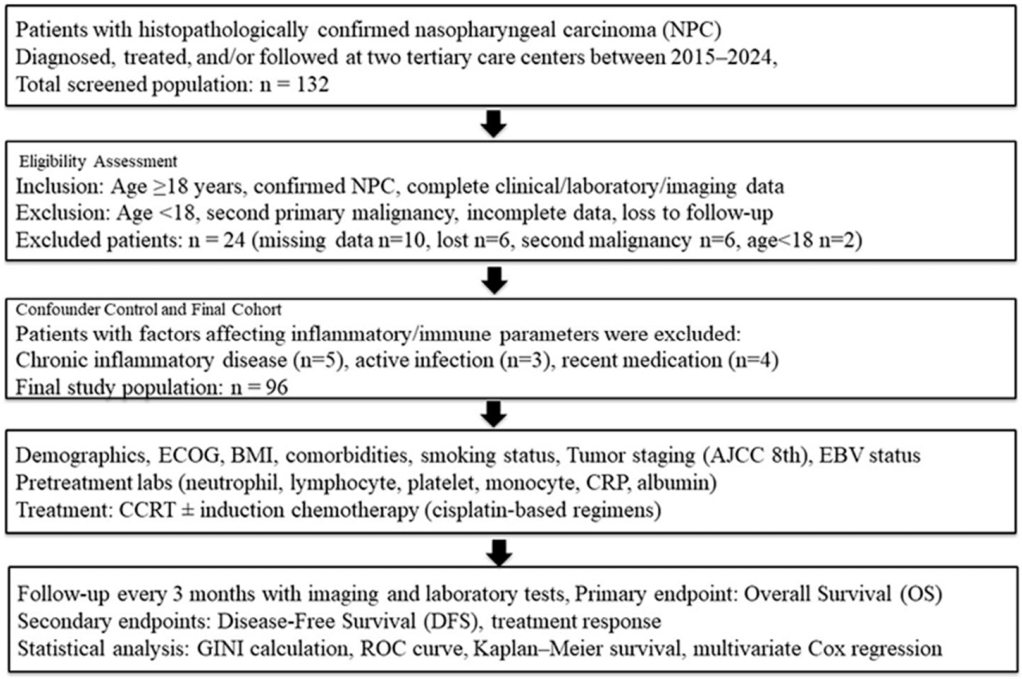


Figure 1. Flow diagram of the study design and patient selection process. ECOG: Eastern Cooperative Oncology Group; BMI: body mass index; AJCC: American Joint Committee on Cancer; EBV: Epstein–Barr virus; CRP: C-reactive protein; CCRT: concurrent chemoradiotherapy; GINI: Global Immune–Nutrition–Inflammation Index; ROC: receiver operating characteristic.

3. Results

Ninety-six patients were included in this study. The median age was 52 years. Patients aged ≥50 years constituted 63.5% of the cohort. Most patients were men (75.0%) and 85.4% had no comorbidities. Tobacco use was found in 18.8% of patients, while alcohol use was reported in 3.1%. For EBV status, 54.2% of patients were EBV-positive, and 30.2% were EBV-negative. Data were unavailable for 15.6% of cases. For performance status, 90.6% had ECOG-PS 0–1. Pathological features showed that 75.0% of tumors were grade 3. According to cT staging, 35.4% were T1–T2 and 64.6% were T3–T4. Nodal involvement (N1–N3) was present in 82 patients (85.4%), whereas 14 patients (14.6%) had N0 disease. Clinically, 79.2% of patients had advanced-stage (III–IV) disease; 20.8% had early-stage (I–II) disease. For treatment, 12.5% received radiotherapy, 43.8% underwent CCRT, and 43.8% received induction chemotherapy (IC) followed by CCRT (Table 1).

Table 1. Baseline demographic, clinical, and pathological characteristics of the study cohort.

Variable	Category	n	%
Age	<50 years	35	36.5
	≥50 years	61	63.5
Sex	Male	72	75.0
	Female	24	25.0
Comorbidity	None	82	85.4
	Present	14	14.6
Smoking	No	78	81.3
	Yes	18	18.8
Alcohol consumption	No	93	96.9
	Yes	3	3.1
Pretreatment plasma EBV DNA, n (%)	Negative	29	30.2
	Positive	52	54.2
	Unknown	15	15.6

Table 1. *Cont.*

Variable	Category	n	%
ECOG performance status	0–1	87	90.6
	≥2	9	9.4
Tumor grade	Grade 2	24	25.0
	Grade 3	72	75.0
cT stage	T1–T2	34	35.4
	T3–T4	62	64.6
Nodal stage	N0	14	14.6
	N1	26	27.1
	N2	34	35.4
	N3	22	22.9
Clinical stage	I–II	20	20.8
	III–IV	76	79.2
Radiotherapy		12	12.5
Concurrent Chemoradiotherapy (CCRT)		42	43.8
Induction Chemotherapy+CCRT		42	43.8

ROC curve analysis showed that GINI had higher discriminative ability (AUC = 0.726; 95% CI: 0.623–0.828; $p < 0.001$) than NLR (AUC = 0.674; 95% CI: 0.567–0.781; $p = 0.003$). The optimal cut-off values from the Youden index were 3403 for GINI and 3.13 for NLR (Table 2, Figure 2).

Table 2. ROC curve analysis for GINI and NLR.

Test Variable	AUC	Std. Error	*p*-Value	95% CI (Lower–Upper)	Sensitivity (%)	Specificity (%)	Optimal Cut-off
GINI	0.726	0.052	<0.001	0.623–0.828	54	91.3	3403
NLR	0.674	0.055	0.003	0.567–0.781	62	65.2	3.13

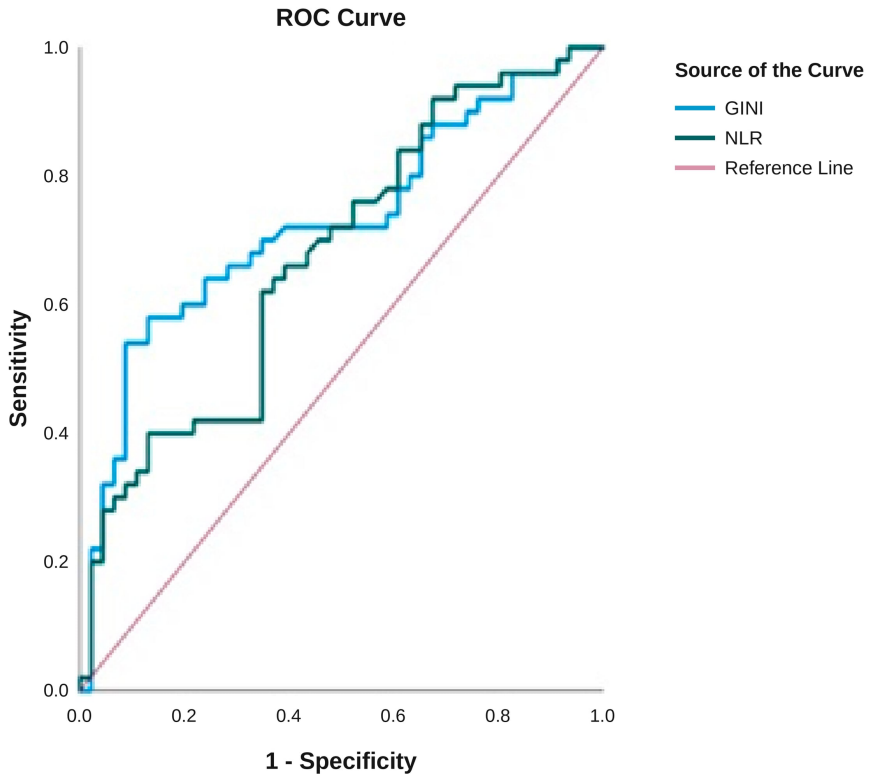


Figure 2. Receiver operating characteristic (ROC) curves of the Global Immune–Nutrition–Inflammation Index (GINI) and neutrophil-to-lymphocyte ratio (NLR) for predicting overall survival in the study cohort.

Based on the optimal cut-off value of 3403, 53.1% of the patients had low GINI values (≤3403), while 46.9% had elevated GINI levels (>3403). Using a cut-off value of 3.13, 59.4% of patients were classified as having a low NLR, and 40.6% as having an elevated NLR. Patients in the high-GINI group (>3403) were significantly older (77.8% were ≥50 years of age; $p = 0.006$). Patients in the high-GINI group were more likely to have advanced clinical-stage disease than those in the low-GINI group (93.3% vs. 66.7%, $p = 0.008$). Additionally, nodal stage distribution differed significantly between the GINI groups ($p = 0.016$). Although the sex distribution trended towards a higher proportion of females in the high-GINI group (33.3% vs. 17.6%; $p = 0.062$), this difference did not reach statistical significance. Similarly, comorbidities, ECOG performance status, histological grade, cT stage, EBV positivity, and treatment modalities (radiotherapy or chemotherapy) demonstrated no statistically significant differences between the low- and high-GINI groups (Table 3).

Table 3. Comparison of clinicopathological parameters according to the Global Immune–Nutrition–Inflammation Index (GINI) groups.

		GINI				
		Low ≤ 3403	**%**	**High > 3403**	**%**	***p***
Age	<50	25	49.0	10	22.2	0.006
	≥50	26	51.0	35	77.8	
Sex	Male	42	82.4	30	66.7	0.062
	Female	9	17.6	15	33.3	
Comorbidity	No	42	82.4	40	88.9	0.271
	Yes	9	17.6	5	11.1	
Smoking	No	41	80.4	37	82.2	0.514
	Yes	10	19.6	8	17.8	
Alcohol	No	50	98.0	43	95.6	0.413
	Yes	1	2.0	2	4.4	
ECOG PS	0–1	48	94.1	39	86.7	0.185
	≥2	3	5.9	6	13.3	
Pretreatment plasma EBV DNA, n (%)	Negative	17	33.3	12	26.7	0.430
	Positive	27	52.9	25	55.6	
	Unknown	7	13.7	8	17.8	
Histologic Grade	Grade 2	11	21.6	13	28.9	0.277
	Grade 3	40	78.4	32	71.1	
cT stage	1–2	18	35.3	16	35.6	0.98
	3–4	33	64.8	29	64.5	
Nodal stage	N0	12	23.5	2	4.4	0.016
	N1	16	31.4	10	22.2	
	N2	15	29.4	19	42.2	
	N3	8	15.7	14	31.1	
Clinical stage	Stage 1–2	17	33.3	3	6.7	0.008
	Stage 3–4	40	66.7	36	93.3	
Radiotherapy		6	11.8	6	13.3	
Concurrent Chemoradiotherapy (CCRT)		22	43.1	20	44.4	
Induction Chemotherapy + CCRT		23	45.1	19	42.2	0.88
NLR	≤3.13	39	76.5	18	40.0	<0.001
	>3.13	12	23.5	27	60.0	

Importantly, a strong and significant correlation was observed between the GINI and NLR, another widely used inflammatory index. As expected given their shared neutrophil and lymphocyte components, elevated GINI was associated with elevated NLR ($p < 0.001$).

During the study period, 50 patients (52.1%) died. The median follow-up among surviving patients was 75.0 months (range, 15–97 months), while the median OS was 77 months (95% CI: 47.2–106.8).The median OS was 87 months in patients with an NLR ≤ 3.13 (95% CI, 70.3–103.6), whereas it decreased to 44 months in patients with an NLR > 3.13 (95% CI, 12.5–75.4). Similarly, the median OS was 95 months in patients with GINI ≤ 3403 (95% CI,

85.1–104.9), whereas in the high-GINI (> 3403) group, it was 23 months (95% CI, 15.3–30.7) (Figure 3).

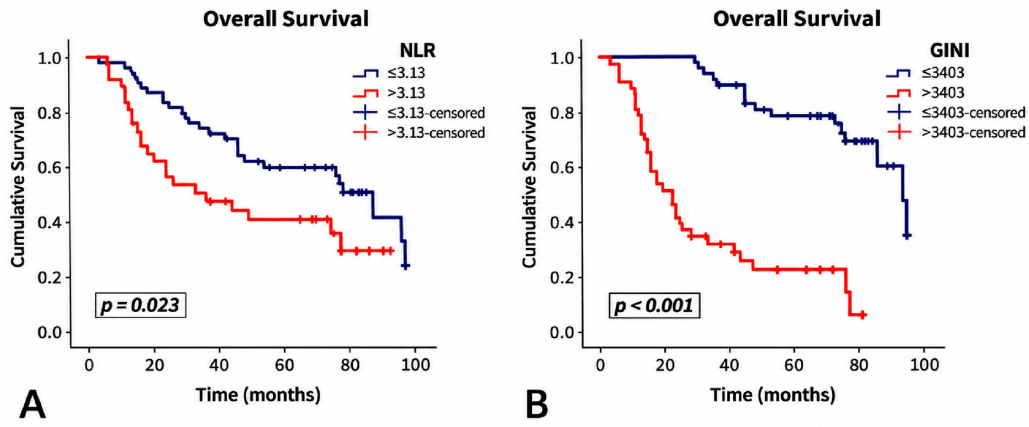


Figure 3. Kaplan–Meier overall survival curves stratified according to (**A**) neutrophil-to-lymphocyte ratio (NLR) and (**B**) Global Immune–Nutrition–Inflammation Index (GINI).

During the follow-up period, 71 patients (74.0%) experienced a DFS event. The median DFS was 57 months (95% CI: 33.0–81.1). The median DFS was 77 months in patients with an NLR ≤ 3.13 (95% CI: 50.2–103.7), whereas in those with an NLR > 3.13, it decreased to 34 months (95% CI: 20.5–47.4; $p = 0.036$). Likewise, the median DFS in patients with a GINI ≤ 3403 was 95 months (95% CI: 77.2–112.7), while in the high-GINI (>3403) group, it was 16 months (95% CI: 8.19–23.8; $p < 0.001$) (Figure 4).

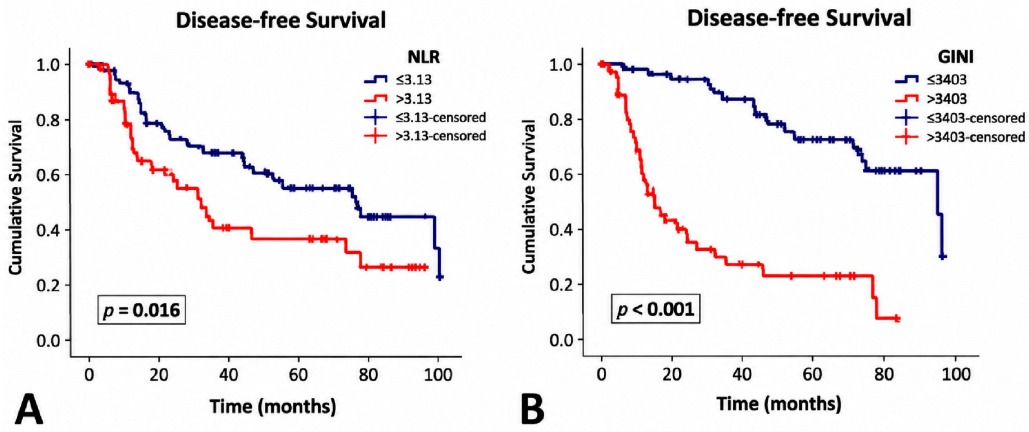


Figure 4. Kaplan–Meier disease-free survival curves stratified according to (**A**) neutrophil-to-lymphocyte ratio (NLR) and (**B**) Global Immune–Nutrition–Inflammation Index (GINI).

In univariable Cox regression analysis, age, tumor grade, NLR, and GINI were significantly associated with OS. Tumor grade was also significantly associated with OS (HR = 0.454; 95% CI: 0.249–0.828; $p = 0.010$). For DFS, age, smoking status, tumor grade, NLR, and GINI were significant variables. Tumor grade (HR = 0.476; 95% CI: 0.261–0.866; $p = 0.015$) was significantly associated with DFS. Because the hazard ratios for tumor grade were below 1, the direction of these associations should be interpreted with respect to the reference categories used in the Cox model. Patients with elevated GINI levels showed a nearly six-fold increase in the risk of a DFS event (recurrence, progression, or death) (HR = 5.790; 95% CI: 3.040–11.027; $p < 0.001$) (Table 4).

Table 4. Univariable Cox proportional hazards models for overall survival (OS) and disease-free survival (DFS).

	Univariable for OS			Univariable for DFS		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age	2.064	1.092–3.901	0.026	2.138	1.131–4.042	0.019
Sex	1.505	0.805–2.813	0.200	1.293	0.690–2.421	0.422
Comorbidity	0.736	0.313–1.730	0.482	0.617	0.262–1.453	0.270
EBV	0.875	0.584–1.313	0.520	0.923	0.616–1.381	0.696
ECOG PS	2.242	0.947–5.306	0.066	2.161	0.913–5.110	0.079
Grade	0.454	0.249–0.828	0.010	0.476	0.261–0.866	0.015
cT	0.898	0.515–1.566	0.705	0.849	0.486–1.481	0.564
Nodal stage	1.369	0.773–2.424	0.281	1.413	0.798–2.499	0.235
Stage	1.052	0.598–1.851	0.860	0.990	0.563–1.740	0.971
Treatment	1.748	0.953–3.206	0.071	1.758	0.958–3.229	0.069
NLR	1.906	1.078–3.372	0.027	1.813	1.027–3.203	0.040
GINI	7.332	3.770–14.258	<0.001	5.790	3.040–11.027	<0.001

In multivariable Cox regression analysis, tumor grade and GINI remained significantly associated with OS, whereas age and NLR were not independently significant. Tumor grade (HR = 0.521; 95% CI: 0.278–0.976; $p = 0.042$). Elevated GINI remained a strong independent predictor of poorer OS (HR = 7.092; 95% CI: 3.484–14.438; $p < 0.001$). For DFS, tumor grade, and GINI remained statistically significant, whereas age and NLR did not. Tumor grade (HR = 0.514; 95% CI: 0.275–0.960; $p = 0.037$) and elevated GINI (HR = 5.890; 95% CI: 2.946–11.778; $p < 0.001$) were independently associated with DFS. In conclusion, elevated GINI levels increased the risk of a DFS event (recurrence, progression, or death) by nearly sixfold (Table 5).

Table 5. Multivariable Cox proportional hazards models for overall survival (OS) and disease-free survival (DFS).

	Multivariable for OS			Multivariable for DFS		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age	1.466	0.762–2.822	0.252	1.478	0.761–2.872	0.249
Grade	0.521	0.278–0.976	0.042	0.514	0.275–0.960	0.037
NLR	1.108	0.604–2.032	0.739	1.047	0.568–1.927	0.884
GINI	7.092	3.484–14.438	<0.001	5.890	2.946–11.778	<0.001

To address the potential loss of information associated with dichotomization, GINI was additionally evaluated as a continuous variable in multivariable Cox regression analyses. GINI remained significantly associated with both OS (HR = 1.236, 95% CI: 1.140–1.341, $p < 0.001$) and DFS (HR = 1.210, 95% CI: 1.116–1.312, $p < 0.001$) per 1000-unit increase. These findings were consistent with the categorical analyses, suggesting that the prognostic association of GINI was not solely dependent on the selected cutoff value (Table 6).

Table 6. Multivariable Cox proportional hazards regression analysis of GINI as a continuous variable for overall survival (OS) and disease-free survival (DFS).

	OS HR (95% CI)	***p***	**DFS HR (95% CI)**	***p***
Age	1.394 (0.702–2.769)	0.343	1.484 (0.744–2.961)	0.263
Grade	0.339 (0.179–0.641)	0.001	0.363 (0.192–0.687)	0.002
NLR	0.973 (0.481–1.968)	0.940	0.917 (0.454–1.852)	0.809
GINI (per 1000-unit increase)	1.236 (1.140–1.341)	<0.001	1.210 (1.116–1.312)	<0.001

4. Discussion

Nasopharyngeal carcinoma is biologically distinct from other squamous cell malignancies of the head and neck due to its strong association with EBV, prominent stromal inflammation, and early lymphatic spread [1–3]. Through latent membrane protein 1 (LMP1), EBV constitutively activates the NF-κB pathway, thereby driving the production of proinflammatory cytokines, including IL-6, IL-8, and TNF-α, and establishing a chronic inflammatory microenvironment [1,3]. While increased glycolysis, lactate accumulation, and immunosuppressive cell infiltration drive tumor progression, systemic biochemical alterations manifest concurrently, including elevated CRP, decreased albumin, and lymphocyte suppression [3,11].

The contemporary model of cancer biology reveals that tumor progression is driven not solely by genetic alterations but also by multidimensional processes, including the inflammatory microenvironment, immune evasion, and metabolic reprogramming [5]. This biological framework suggests that anatomical TNM staging alone may be insufficient to fully account for prognosis [4]. Indeed, numerous studies have demonstrated that inflammatory indices derived from peripheral blood parameters correlate with NPC prognosis [6,8–10]. Although meta-analyses have established an association between an elevated NLR and OS, the marked heterogeneity in cut-off values remains a notable limitation, directly limiting clinical generalizability [12,13]. Similarly, various studies have demonstrated significant associations between systemic inflammatory indices, such as the SII and the SIRI, and both overall and progression-free survival in head and neck cancers [14–16].

Furthermore, Pan-Immune-Inflammation Value (PIV)-based nomograms have been shown to provide superior prognostic discrimination compared with conventional TNM staging and are emerging as potential biomarkers for immunotherapy response [5,12]. Nevertheless, these indices predominantly reflect the cellular components of inflammation, providing only limited insight into metabolic reserve and nutritional status. Kozan and Haznedar evaluated the impact of the systemic immune-inflammation index (SII) on survival outcomes in patients with NPC, reporting that elevated SII levels were associated with poorer OS. This finding further corroborates that peripheral blood-derived inflammatory indices can effectively reflect prognosis in NPC [17]. However, while the SII predominantly reflects the cellular inflammatory burden, it lacks nutritional and acute-phase parameters. The Prognostic Nutritional Index (PNI) has been reported as a crucial prognostic biomarker reflecting both the inflammatory and nutritional status in NPC [18–20]. Jiang et al. demonstrated that the PNI is an independent prognostic factor for OS in patients with NPC [19]. In a meta-analysis comprising 4511 patients, Tu et al. reported that low PNI levels were significantly associated with poorer OS [20]. Miao et al. analyzed the impact of PNI on survival in patients with NPC treated with intensity-modulated radiotherapy (IMRT) ± chemotherapy, demonstrating that 5-year OS and disease-specific survival (DSS) were significantly lower in patients with PNI ≤ 52 ($p < 0.05$). The finding that the PNI remained an independent prognostic factor in multivariable analysis indicates that nutritional reserve can affect clinical outcomes independently of tumor burden. These findings demonstrate that host nutritional status is not merely a supportive parameter but a determining factor in the tumor–host interaction [18].

In cancer progression, inflammation and malnutrition are mutually reinforcing processes. The chronic inflammatory response accelerates catabolism, suppresses albumin synthesis, and impairs cellular immunity. Accordingly, composite approaches integrating inflammatory and nutritional parameters have been developed. Similarly, scores that integrate albumin, the SII, and the monocyte count, such as the INRS, have been reported as robust, independent predictors of OS [21]. These observations reinforce the need for more integrated biomarker approaches. In this context, the GINI, which incorporates in-

flammatory and nutritional markers such as CRP and albumin alongside hematological parameters, emerges as a more comprehensive index that simultaneously assesses systemic inflammation, immune competence, and metabolic reserve [6,8–10]. The biological rationale for the GINI is consistent with previously validated indices in NPC, such as the NLR, PLR, PNI, and, notably, the PIV [6,8–10,12,13]. Consequently, the GINI may be a promising approach to enhance individualized risk stratification, particularly in patients with NPC diagnosed at an advanced stage and at high risk of post-treatment mortality. Unlike the NLR, which reflects only the inflammatory burden, incorporating albumin into the GINI equation enables simultaneous assessment of the patient's nutritional status and overall condition [6,22,23]. Evidence demonstrating the prognostic significance of the GINI across different malignancies has been well documented [22–25].

In an analysis of patients with RAS wild-type metastatic colorectal cancer using a ROC-derived cut-off value of 2000, Bozkurt et al. reported that an elevated GINI was associated with shorter PFS and OS, and remained an independent prognostic factor in multivariable analysis (HR = 3.25, $p < 0.001$ for OS; HR = 1.79, $p = 0.004$ for PFS). These findings demonstrate that the GINI, which integrates inflammatory markers with nutritional and immune indicators into a single composite framework, can capture clinical heterogeneity beyond what individual inflammatory markers can [25]. The GINI integrates the inflammatory burden driven by neutrophils, monocytes, and platelets; immune competence, reflected by lymphocytes; the acute-phase response, indicated by CRP; and metabolic reserve, represented by albumin, all within a single mathematical equation [6,8–10].

This holistic framework provides a functional snapshot of the systemic tumor–host interaction [26]. It has been reported that the GINI exhibits independent prognostic performance in non-small cell lung cancer, glioblastoma, esophageal cancer, metastatic pancreas and metastatic colorectal cancer [6,7,9,10,22,24,25]. These studies demonstrate that the index exhibits biological consistency across various solid tumors. In the present study, elevated GINI levels were strongly associated with both OS and DFS and remained statistically significant in multivariable analyses. In contrast, the NLR lost statistical significance, suggesting that integrating nutritional and acute-phase parameters with cellular inflammatory indices may provide additional prognostic information. Although the observed hazard ratios were relatively high (HR = 7.092 for OS and HR = 5.89 for DFS), these estimates should be interpreted with caution. The limited sample size and potential residual confounding may have influenced the magnitude of these associations. Therefore, the findings suggest a strong association between elevated GINI and poor survival rather than providing a definitive estimate of its prognostic effect. In contrast to the cut-off value of 2000 reported in metastatic colorectal cancer, the threshold of 3403 in our study may reflect differences in patient populations, tumor biology, laboratory measurement units, and calculation methods; therefore, direct comparison of absolute thresholds should be interpreted with caution [25].

The higher proportion of advanced-stage disease in the high-GINI group suggests that GINI may partly reflect tumor burden, as advanced disease is often associated with increased inflammation and poorer nutritional status. Although GINI remained significantly associated with survival, disease stage was not included in the multivariable models. Therefore, the influence of tumor burden cannot be excluded. Further studies are needed to determine whether GINI provides additional prognostic information beyond disease stage.

This observation suggests that the GINI is a dynamic index requiring cancer-specific validation. In a cohort of 138 patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant immunochemotherapy followed by surgery, Feng et al. demonstrated that pretreatment GINI accurately predicted pathological response (cut-off: 73.47; AUC: 0.912). The relatively low cut-off value may be attributed to variations in GINI calculation methods and differences in the reporting scales of the biochemical parameters.

In multivariable analysis, an elevated GINI level was independently associated with a poor pathological response and shorter OS; furthermore, 3-year OS (87.8% vs. 68.7%) and DFS (82.7% vs. 63.3%) rates were significantly higher in the low-GINI group. These findings support the potential of the GINI as a robust biomarker for predicting both treatment response and long-term prognosis [22].

Pretreatment EBV DNA is an important prognostic marker in NPC. However, EBV DNA data were missing for 15.6% of patients in our study, which may have influenced the results. Although EBV DNA was not included in the multivariable models because it was not significantly associated with survival in univariable analyses, its established prognostic role should be considered. The relatively small sample size and missing data may have limited our ability to detect a significant association. Furthermore, the absence of sensitivity analyses makes it difficult to determine how missing EBV DNA data may have affected our findings. Future studies with larger cohorts and more complete EBV DNA data are needed to confirm whether GINI provides prognostic information independently of EBV DNA. EBV DNA is an important prognostic marker in NPC, reflecting tumor burden and disease activity. Similarly, Filippini et al. highlighted the potential prognostic value of circulating HPV DNA in head and neck cancers. Although these viral markers differ, both highlight the importance of combining molecular biomarkers with clinical factors [27]. Integrating EBV DNA, tumor stage, and GINI may improve prognostic assessment in NPC, although further validation is needed.

Within this framework, our findings suggest that the GINI may represent a robust prognostic biomarker in patients with NPC. ROC curve analysis revealed that the GINI yielded a numerically higher AUC for predicting mortality than the NLR (AUC = 0.726 vs. 0.674), and the optimal cut-off value was 3403. Survival outcomes were markedly poorer in patients with elevated GINI levels. Whereas the median OS was 95 months in the low-GINI group, it decreased to 23 months in the high-GINI group. Likewise, a significantly shorter DFS was observed in the high-GINI group (16 vs. 95 months). The finding that GINI remained an independent prognostic factor for both OS and DFS, while NLR lost statistical significance in multivariable analysis, suggests that a composite index that simultaneously reflects inflammation, the immune response, and nutritional status may possess greater prognostic power. However, given the relatively small cohort and the possibility of model overfitting, the strength of these associations should be interpreted cautiously. Further studies are needed to determine whether the observed effect sizes can be reproduced in independent patient populations.

These findings also support the notion that elevated GINI scores may be associated with increased immune evasion potential and a more aggressive tumor biology. Consequently, beyond merely serving as a prognostic laboratory composite, the GINI may represent a clinically measurable reflection of the systemic tumor–host interaction. Its reliance on routine, cost-effective laboratory parameters may facilitate its evaluation across diverse clinical settings. However, these findings support further evaluation of GINI as an adjunctive prognostic marker rather than its immediate use for treatment selection or surveillance modification. Prospective studies incorporating GINI alongside EBV-DNA kinetics, established clinicopathological factors, and dynamic inflammatory variables are warranted before GINI is integrated into clinical decision-making algorithms. Such integrative models may contribute to biologically driven personalized risk stratification, moving beyond traditional anatomical staging. The strengths of our study include the investigation of a homogeneous NPC cohort, the two-center nature of the data, and the demonstration of GINI's independent prognostic value through multivariate analyses.

5. Limitations

This study should be interpreted in light of several limitations. The retrospective design carries inherent risks of selection bias and residual confounding. Although the inclusion of 96 patients from two tertiary centers constitutes a clinically meaningful cohort for NPC, the sample size reduced the precision of the effect estimates and precluded adequately powered subgroup and validation analyses. GINI was calculated from a single pretreatment blood sample; therefore, the prognostic relevance of longitudinal changes during and after treatment could not be assessed. Nutritional support and corticosteroid use before blood sampling may have affected GINI values by altering albumin levels, inflammatory markers, and blood cell counts. As detailed information on these factors was unavailable, their potential influence on our findings cannot be excluded. Differences in disease stage and treatment modality may also have influenced survival outcomes despite multivariable adjustment. Furthermore, pretreatment plasma EBV DNA data were unavailable for 15.6% of patients, and serial EBV DNA measurements were not evaluated. Importantly, the optimal GINI cutoff value of 3403 was determined using ROC analysis and subsequently evaluated for its prognostic significance within the same patient cohort. This data-driven approach introduces a risk of overfitting and may result in overly optimistic estimates of prognostic performance, potentially limiting the generalizability and reproducibility of the identified threshold. Moreover, the absence of an independent validation cohort prevented assessment of the stability and external validity of this cutoff. Therefore, the proposed GINI threshold should be regarded as exploratory rather than a clinically established cutoff value. Independent external validation in larger, prospective, multicenter cohorts is essential to confirm its prognostic reliability, determine the reproducibility of the optimal threshold, and establish its potential clinical utility before GINI can be incorporated into routine risk-stratification strategies for patients with NPC.

6. Conclusions

In conclusion, pretreatment GINI was strongly associated with OS and DFS in patients with NPC, supporting its potential role as an adjunctive prognostic biomarker reflecting systemic inflammation, immune status, and nutritional reserve. Although these findings suggest that GINI may provide clinically relevant prognostic information, the present results should be considered hypothesis-generating rather than sufficient for immediate clinical implementation. Prospective multicenter studies with external validation and integration of established prognostic factors, including TNM stage and EBV-related parameters, are warranted to clarify the incremental prognostic value of GINI in NPC.

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