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Pretreatment systemic immune-inflammation index predicts survival for non-metastatic nasopharyngeal carcinoma: two independent institutional studies

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ABSTRACT

Objective: This study aimed to evaluate the prognostic value of the pretreatment systemic immune-inflammation index (SII) in non-metastatic nasopharyngeal carcinoma (NPC).

Methods: We retrospectively analyzed the data of 839 patients with non-metastatic NPC recruited from two independent institutions. The training-set cohort and the external validation-set cohort was comprised of 459 and 380 patients from each institution, respectively. The optimal cut-off value of SII was determined, and a prognostic risk stratification model was developed based on the training cohort and further assessed in the validation cohort. The propensity score matching (PSM) method was applied to minimize the confounding effects of unbalanced covariables.

Results: The optimal cut-off value of the SII in the training cohort was 686, which was confirmed using the validation cohort. Multivariate analysis showed that both before and after PSM, SII values > 686 were independently associated with worse progression-free survival (PFS) ratio in both cohorts (before PSM, $P = 0.008$ and $P = 0.008$; after PSM, $P = 0.008$ and $P = 0.007$, respectively). Based on the analysis of independent prognostic factors of SII and N stage, we developed a categorical risk stratification model, which achieved significant discrimination among risk indexes associated with PFS and distant metastasis-free survival (DMFS) in the training cohort. There was no significant difference in PFS between RT alone and combined therapies within the low- and intermediate-risk groups (5-year PFS, 77.5% vs. 75.3%, $P = 0.275$). Patients in the high-risk group who received concurrent chemoradiotherapy experienced superior PFS compared with those who received other therapies (5-year PFS, 64.9% vs. 40.3%, $P = 0.003$).

Conclusion: Pretreatment SII predicts PFS of patients with non-metastatic NPC. Prognostic risk stratification incorporating SII is instructive for selecting individualized treatment.

1. Introduction

Nasopharyngeal carcinoma (NPC) is the most prevalent head and neck malignancy in China. NPC has a high incidence in South China and is associated with Epstein–Barr virus (EBV) infection.[1,2] Compared with typical head and neck squamous cell carcinoma (HNSCC), NPC exhibits unique clinical behavior, greater sensitivity to chemotherapy and radiotherapy, and a more favorable prognosis. Although the local-regional control of NPC has significantly improved through the administration of intensity-modulated radiation therapy (IMRT) and chemotherapy,[3-5] disease failure occurs in 3%–27% of patients, with distant metastasis as the predominant pattern of failure.[6-8] Therefore, it is important to identify prognostic factors and stratify risk groups to implement risk-adapted therapy for patients. Besides the classical TNM stage, numerous studies

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have investigated the prognostic factors of NPC in the IMRT era, and several encouraging prognostic indicators have been reported, such as EBV-DNA, lactate dehydrogenase (LDH), and the nutritional index.[9-12]

Inflammation and immune activity are critically important because they influence oncogenesis and tumor progression. For example, inflammation predisposes to the development of cancer, promotes all stages of tumorigenesis, and drives tumor metastasis.[13] Moreover, circulating platelets mediate immunity and inflammation by interacting with tumor cells, immune cells, and the vessel wall. High platelet counts are significantly associated with decreased survival of patients with diverse malignancies.[14-16] Furthermore, neutrophils in the peripheral blood circulation facilitate metastasis by inducing cancer cells to adhere to endothelial cells at extravasation sites.[17] Lymphocytes are required for cell-mediated inflammatory responses.[18]

These mechanisms are utilized to develop inflammation- and immune-based score indicators that predict the survival of patients with NPC.[19-22] These indicators include the combination of platelet counts and the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), NLR, and the lymphocyte-to-monocyte ratio (LMR). Furthermore, the systemic immune-inflammation index (SII = platelet count × neutrophils/lymphocytes) effectively predicts survival of patients with cancers such as hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), and esophageal squamous cell carcinoma (ESCC).[23-26] In the setting of NPC, two studies have evaluated the prognostic value of SII.[27-28] However, due to their relatively small sample sizes and lack of external validation, the clinical significance of these studies was limited and debatable.

In the current study, we aimed to: (1) determine whether SII was associated with outcomes of non-metastatic NPC based on a retrospective cohort and an independent validation cohort and (2) establish and validate an immune index-based prognostic risk stratification model for non-metastatic NPC patients.

2. Materials and methods

2.1. Patients and data collection

Non-metastatic NPC patients who received IMRT-based therapy between January 2013 and October 2015 at Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College were retrospectively selected as training cohort. The inclusion criteria were as follows: age ≥ 18 years, Karnofsky Performance Status (KPS) ≥ 60, histologically confirmed keratinized carcinoma or nonkeratinized carcinoma, stages I–IVB, according to the 7th edition of the American Joint Committee on Cancer (AJCC) of the TNM cancer staging system,[29] IMRT-based treatment, complete blood count records within 30 days before initial treatment, and complete follow-up information. Exclusion criteria were as follows: (1) if the patients had distant metastasis at diagnosis, (2) had diseases of the immune system, disorders of the hematopoietic system, or treatment with immunosuppressive drugs. Patients, disease, treatment, and follow-up data were collected for analysis. SII was defined as SII = P × N/L, where P, N, and L represent peripheral blood platelet, neutrophil, and lymphocytes counts before treatment, respectively.[23] The local institutional ethics review boards approved this study.

An independent validation set, including data for 380 patients with non-metastatic NPC who received IMRT-based therapy at Sun Yat-Sen University Cancer Center, was identified using the same inclusion and exclusion criteria as those of the training population.

2.2. Treatment and follow-up

Patients with stage-I NPC in the training cohort received radiotherapy (RT) alone. Patients with stage-II NPC generally underwent RT alone or concurrent chemotherapy. Patients with stages III–IVB NPC underwent concurrent chemoradiotherapy (CCRT), with or without induction chemotherapy (IC), or adjuvant chemotherapy (AC). The following radiation doses were administered: 69.96 Gy to 73.92 Gy, to the planning volume of the gross tumor or positive lymph node; 60.06 Gy to the high-risk areas, and 50.96 Gy to the low- and intermediate-risk areas. The regimens of induction or adjuvant chemotherapy included docetaxel with cisplatin (TP) and TP plus 5-fluorouracil (TPF). Concurrent chemotherapy was cisplatin alone every 3 weeks for 2–3 cycles during radiotherapy. The first follow-up evaluation was generally conducted 1 month after treatment, subsequently every 3 months within the first 2 years, every 6 months for the third to fifth years, and once annually thereafter. Supplementary Fig. 1 presents the treatment and follow-up diagram.

2.3. Ethics statement

The study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the institutional ethics committees of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College and Sun Yat-sen University Cancer Center. All procedures in this study were conducted in accordance with ethical principles.

2.4. Endpoints and statistical analyses

Clinical outcomes of this study included overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS). OS was defined as the interval between the first day of treatment and death from any cause or last follow-up. PFS was defined as the interval between the first day of treatment and relapse or death from any cause. LRFS and DMFS were defined as the intervals from the commencement of treatment to the first occurrence of locoregional recurrence and distant metastasis, respectively. The last follow-up date was August 31, 2019.

The Kaplan–Meier method and log-rank test were used to estimate survival and compare the differences between survival curves. Continuous variables are presented by median (range) values, which were compared using the Student *t*-test or analysis of variance (ANOVA) applied to normally distributed data. Categorical variables were tested using Pearson's chi-square test or Fisher's exact test. The Cox proportional hazards regression model was employed to identify factors significantly associated with survival variables and to determine hazard ratios (HRs) with the 95% confidence interval (95% CI). Only variables with $P < 0.15$ in univariate analysis were eligible for further multivariate analysis. Receiver operating characteristic (ROC) curve analysis was employed to define the optimal cut-off point of the SII for predicting PFS. To minimize the influence of confounding factors on prognosis, propensity score matching (PSM) was performed to balance the baseline data of the two centers. Statistical analyses were performed by using statistical software, SPSS version 22.0 (IBM Corp., Armonk, NY) as well as the Survival, Survminer, and Forest plot packages in R, version 3.6.3 (http://www.r-project.org/). Two-sided $P < 0.05$ indicates a significant difference.

3. Results

3.1. Patient characteristics and identification of the optimal cut-off of the SII

The training and validation cohorts included 459 and 380 patients, respectively. Table 1 summarizes the general characteristics of these cohorts. For both settings, most patients were male and nonsmokers with pathologically confirmed nonkeratinized carcinoma, good performance status, and stages III–IVB disease.

The median value of SII in the training cohort was 512 (range, 93–3823). ROC curve analysis yielded the optimal cut-off value of 686 for predicting PFS. Accordingly, the cohort was stratified into high SII (SII > 686, SII-H) and low SII (SII ≤ 686, SII-L) groups. Compared with the

Table 1
Baseline characteristics of patients in the training and validation cohort.

Characteristics	Training cohort N (%)	Validation cohort N (%)	*P*-value
Age (mean ± SD)	47.5 ± 11.6	45.3 ± 10.1	0.541
Sex			0.058
Male	348 (75.8)	266 (70.0)	
Female	111 (24.2)	114 (30.0)	
Smoking history			< 0.001
Yes (current or ex-smoker)	223 (48.6)	123 (32.4)	
No	236 (51.4)	257 (67.6)	
KPS			0.001
< 80	11 (2.4)	-	
≥ 80	448 (97.6)	380 (100)	
Histological type			< 0.001
WHO I	5 (1.1)	-	
WHO II	196 (42.7)	12 (3.2)	
WHO III	258 (56.2)	368 (96.8)	
T stage			0.194
T1-T2	119 (25.9)	83 (21.8)	
T3-T4	340 (74.1)	297 (78.2)	
N stage			0.007
N0-N1	214 (46.6)	215 (56.6)	
N2-N3	145 (53.4)	165 (43.4)	
Overall stage			0.649
I-II	50 (10.9)	37 (9.7)	
III-IVB	409 (89.1)	343 (90.3)	
Treatment modalities			< 0.001
RT	151 (32.9)	-	
CCRT±AC	230 (50.1)	380 (100)	
IC+CCRT/RT±AC	78 (17.0)	-	
SII			0.415
≤686	317 (69.1)	252 (66.3)	
>686	142 (30.9)	128 (33.7)	

Abbreviations: AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; KPS, Karnofsky Performance Status; RT, radiation therapy; SII, systematic immune-inflammation index; WHO I, keratinizing carcinoma; WHO II, non-keratinizing differentiated carcinoma; WHO III, non-keratinizing undifferentiated carcinoma.

SII-L group, the SII-H group was significantly associated with a higher proportion of stages T3–4 ($P = 0.011$) and stages III-IV disease burdens ($P = 0.029$). Table 2 shows the detailed baseline characteristics of the two SII groups in the training cohort.

3.2. Correlation between SII and survival indexes of the training cohort

The median follow-up of the training cohort was 52.9 (range, 1.4–78.6) months. The 5-year OS, PFS, LRFS, and DMFS rates were 79.6%, 71.8%, 84.6%, and 78.6%, respectively. Univariate analyses of OS, PFS, DMFS, and LRFS indexes are shown in Supplementary Table 1. Significantly worse OS (HR = 1.54, 95% CI: 1.01–2.34, $P = 0.043$; 5-year rates, 71.8% vs. 83.3%); PFS (HR = 1.62, 95% CI: 1.14–2.30, $P = 0.007$; 5-year rates, 62.2% vs. 76.1%), and DMFS (HR = 1.61, 95% CI: 1.07–2.42, $P = 0.022$; 5-year rates, 71.3% vs. 81.8%) were experienced by the SII-H group (Fig. 1A–C). No statistically significant difference was found in LRFS between the two groups (HR = 1.43, 95% CI: 0.88–2.32, $P = 0.15$; 5-year rates, 79.6% vs. 86.8%) (Fig. 1D). Subgroup analysis for patients with stages III–IVB revealed that patients with SII > 686 were significantly associated with worse PFS (5-year PFS: 61.9% vs. 75.5%, $P = 0.019$).

3.3. Multivariate analysis based on the training cohort

Multivariate Cox regression analysis revealed that SII-H (HR = 1.61, 95% CI: 1.13–2.29, $P = 0.008$) and stages N2–3 (HR = 1.57, 95% CI: 1.09–2.27, $P = 0.017$) were independently associated with worse PFS (Fig. 2A). Accordingly, T stage (HR = 1.70; 95% CI: 1.00-2.88; $P = 0.049$) and N stage (HR = 2.30; 95% CI: 1.47-3.5; $P < 0.001$) were demonstrated to be independent prognostic indicators for DMFS (Fig. 2B). With respect to OS, only N 2-3 stage (HR = 1.60; 95% CI: 1.04-2.46; $P = 0.034$) were identified as significant determinants for OS (Supplementary Fig. 2).

Table 2
General characteristics of patients in the training and validation cohorts stratified by SII before and after PSM.

Characteristics	Training cohort		*P*	After PSM		*P*	Validation cohort		*P*	After PSM		*P*
	SII-L (*n* = 317)	SII-H (*n* = 142)		SII-L (*n* = 138)	SII-H (*n* = 138)		SII-L (*n* = 252)	SII-H (*n* = 128)		SII-L (*n* = 128)	SII-H (*n* = 128)	
Age			0.074			0.323			0.056			1.000
≤ 48	159 (50.2)	84 (59.2)		89 (64.5)	80 (58.0)		152 (60.3)	90 (70.3)		90 (70.3)	(70.3)	
> 48	158 (49.8)	158 (49.8)		49 (35.5)	58 (42.0)		100 (39.7)	38 (29.7)		38 (29.7)	38 (29.7)	
Sex			0.182			0.506			0.042			0.897
Male	246 (77.6)	102 (71.8)		96 (69.6)	101 (73.2)		185 (73.4)	81 (63.3)		82 (64.1)	81 (63.3)	
Female	71 (22.4)	40 (28.2)		42 (30.4)	37 (26.8)		67 (26.6)	47 (36.7)		46 (35.9)	47 (36.7)	
Smoking history			0.226			0.330			0.085			
No	157 (49.5)	79 (55.6)		83 (60.1)	75 (54.3)		163 (64.7)	94 (73.4)		93 (72.7)	94 (73.4)	0.888
Yes	160 (50.5)	63 (44.4)		55 (39.3)	63 (45.7)		89 (35.3)	34 (26.6)		35 (27.3)	34 (26.6)	
KPS			0.086			0.180						
< 80	5 (1.6)	6 (4.2)		17 (12.4)	25 (18.2)							
≥ 80	312 (98.4)	72 (95.8)		120 (87.6)	112 (81.8)		252 (100)	128 (100)		128 (100)	128 (100)	
Histological type			0.199[a]			0.167[a]			0.776			0.734
WHO I	4 (1.3)	1 (0.7)		1 (0.7)	1 (0.7)							
WHO II	127 (40.1)	69 (48.6)		52 (37.7)	66 (47.8)		7 (2.8)	5 (3.9)		4 (3.1)	5 (3.9)	
WHO III	186 (58.6)	73 (50.7)		85 (61.6)	71 (51.4)		245 (97.2)	123 (96.1)		124 (96.9)	123 (96.1)	
T stage			0.011			0.180			0.019			0.257
T1/T2	98 (29.3)	26 (18.3)		17 (12.3)	25 (18.1)		64 (25.4)	19 (14.8)		13 (10.2)	19 (14.8)	
T3/T4	224 (70.7)	116 (81.7)		121 (87.7)	113 (81.9)		188 (74.6)	109 (85.2)		115 (89.8)	109 (85.2)	
N stage			0.285			0.216			0.756			0.260
N0/N1	155 (48.9)	59 (42.8)		78 (56.5)	59 (42.8)		144 (57.1)	71 (55.5)		80 (62.5)	71 (55.5)	
N2/N3	162 (51.1)	79 (57.2)		60 (43.5)	79 (57.2)		108 (42.9)	57 (44.5)		48 (37.5)	57 (44.5)	
Overall stage			0.029			0.276			0.045			0.328
I-II	40 (12.6)	10 (7.0)		14 (10.1)	9 (6.5)		30 (11.9)	7 (5.5)		11 (8.6)	7 (5.5)	
III-IVB	277 (87.4)	132 (93.0)		124 (89.8)	129 (93.5)		222 (88.1)	121 (94.5)		117 (91.4)	121 (94.5)	

[a] Fisher exact test.

Abbreviations: KPS, Karnofsky Performance Status; PSM, propensity score matching; SII, systematic immune-inflammation index; SII-H, high SII; SII-L, low SII; WHO I, keratinizing carcinoma; WHO II, non-keratinizing differentiated carcinoma; WHO III, non-keratinizing undifferentiated carcinoma.

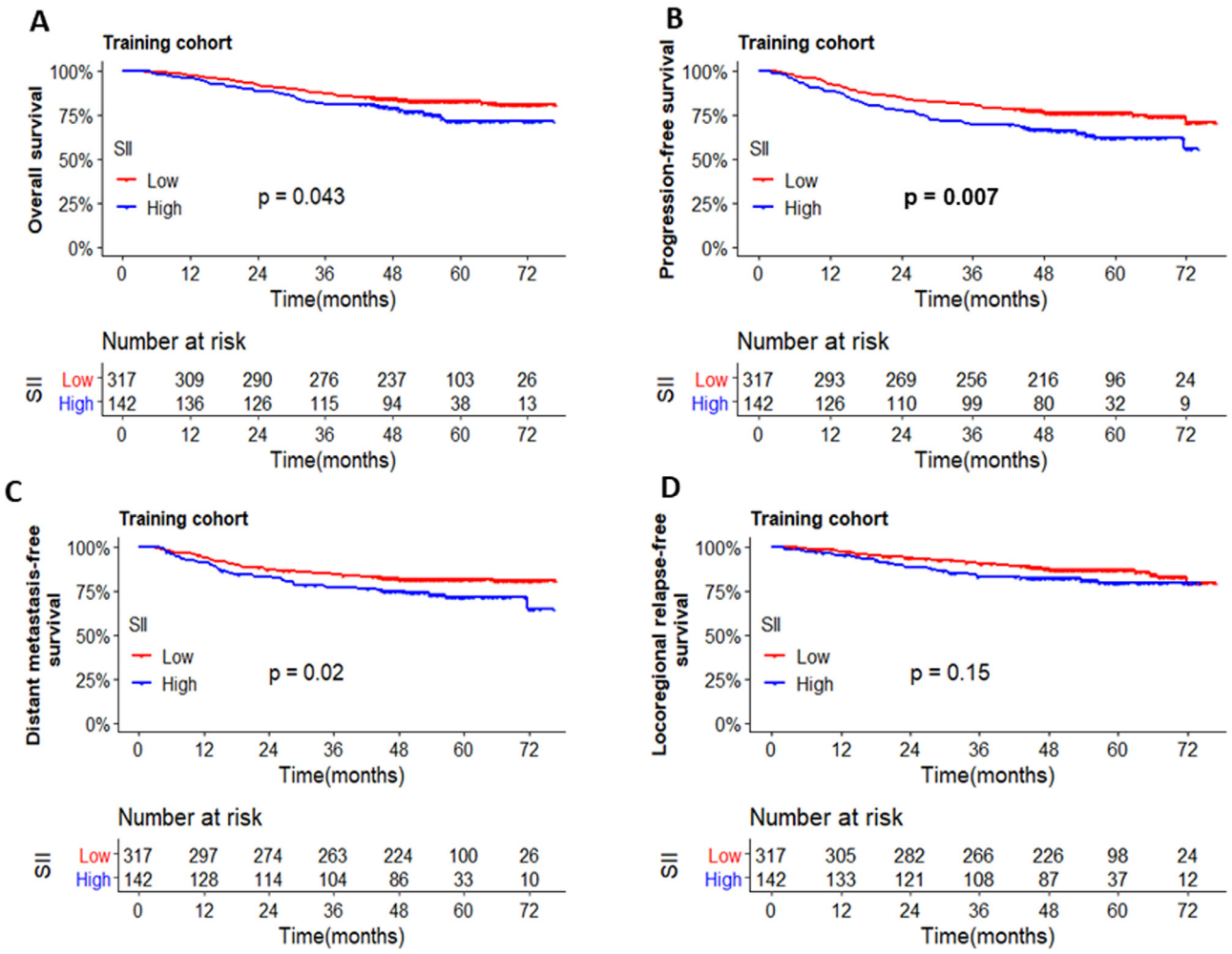

Fig. 1. Kaplan–Meier survival curves for overall survival (A), progression-free survival (B), distant metastasis-free survival (C), and locoregional relapse-free survival (D) in the training cohort between the SII-L group and SII-H group. SII, systemic immune-inflammation index; SII-H, high SII; SII-L, low SII.

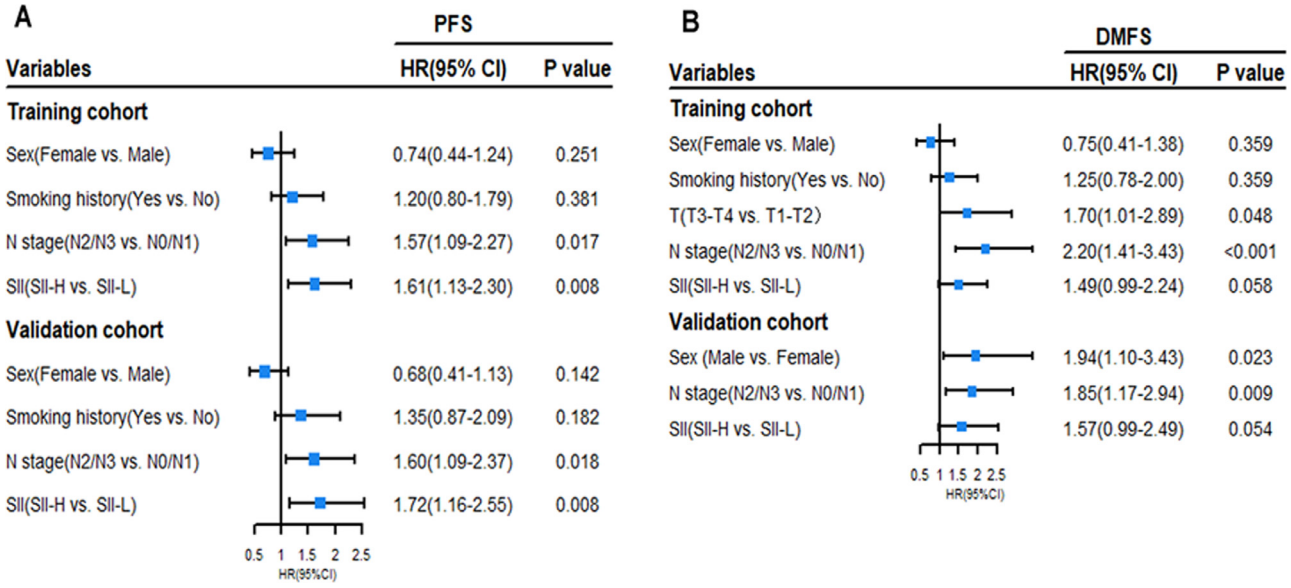

Fig. 2. Forest plots indicate the multivariate Cox regression models-based hazard ratio for PFS (A) and DMFS (B) in the training and validation cohorts. CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; PFS, progression-free survival; SII, systemic immune-inflammation index.

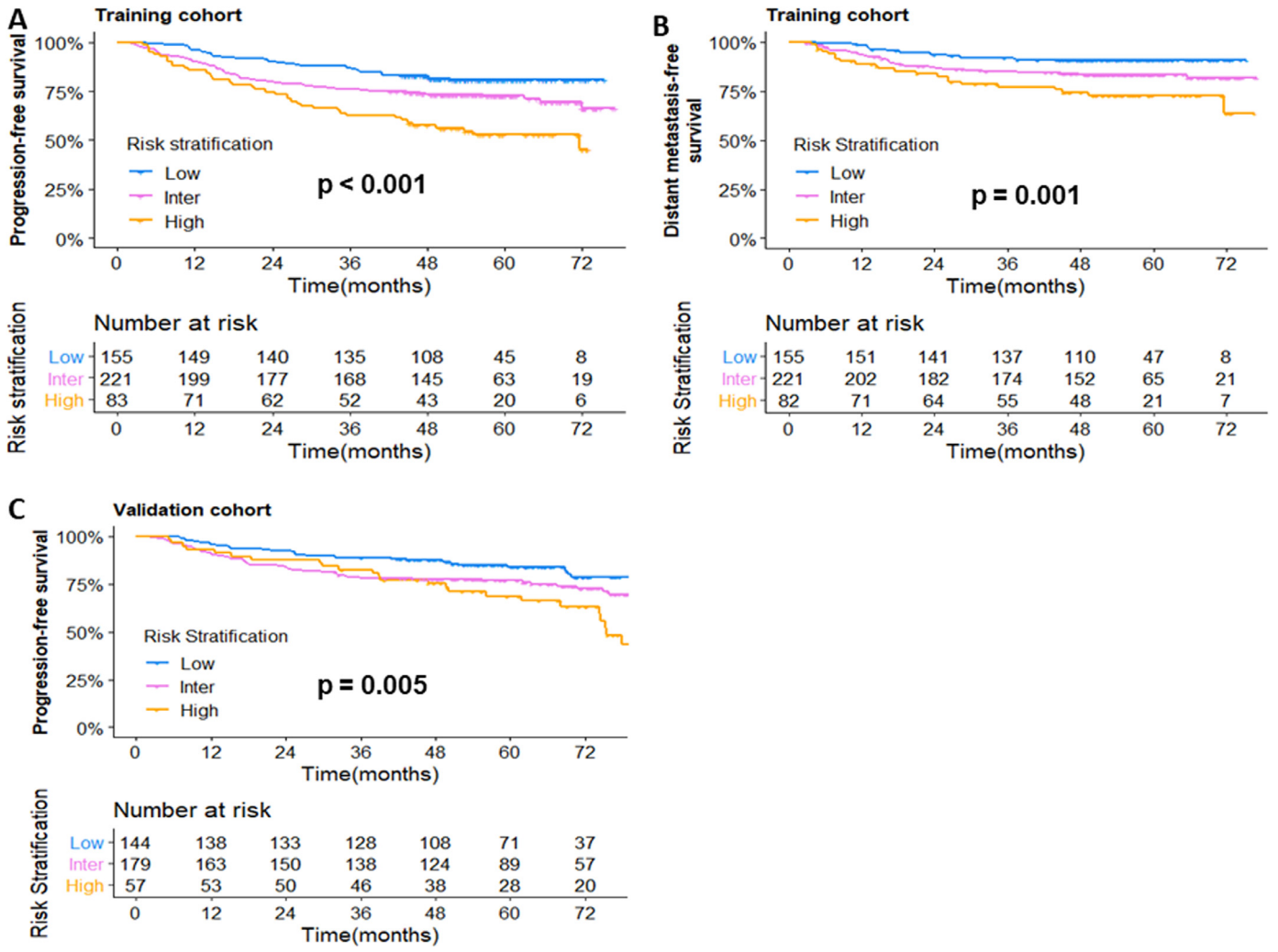

Fig. 3. PFS (A) and DMFS (B) stratified by risk classification (low-, intermediate- and high-risk groups) for all patients in the training cohort, and PFS in the validation cohort (C). DMFS, distant metastasis-free survival; PFS, progression-free survival.

3.4. PSM analysis of the training cohort

Considering the imbalance of T stage and TNM stage between the SII-H and SII-L groups, which may overestimate the prognostic impact of SII, we conducted 1:1 PSM according to sex, age, smoking history, T stage, N stage, TNM stage, KPS, and concurrent chemotherapy. PSM yielded 138 pairs of patients with balanced baseline characteristics (Table 2). Kaplan–Meier analysis of patients after PSM indicated that the SII-H group was still significantly associated with worse OS, PFS, and DMFS ($P = 0.027$, $P < 0.001$, and $P = 0.011$, respectively) (Supplementary Fig. 3A–C). Univariate analyses of OS, PFS, and DMFS conducted after PSM are shown in Supplementary Table 2. Multivariate analyses indicated that a high SII was an independent prognostic factor for inferior PFS (HR = 1.872, 95% CI: 1.11–3.03, $P = 0.018$) (Supplementary Table 3).

3.5. Prognostic risk stratification of the training cohort

According to the independent risk factors (stages N2/N3, SII > 686) for PFS, patients were stratified as low- (0 factor, $n = 155$), intermediate- (1 risk factor, $n = 221$), and high-risk (2 risk factors, $n = 83$) groups. The 5-year PFS rates for three strata were 80.7%, 72.8%, and 53.5%, respectively (intermediate-risk group: HR = 1.603, 95% CI: 1.03–2.49; high-risk group: HR = 2.92, 95% CI: 1.80–4.72, $P < 0.001$) (Fig. 3A). There were significant differences among the three stratified groups associated with DMFS ($P = 0.001$) (Fig. 3B).

In the low- and intermediate-risk groups, patients who received RT alone experienced OS, PFS, and DMFS rates comparable to those who received CCRT or sequential RT and chemotherapy ($P > 0.05$) (Supplementary Fig. 4A–C). In the high-risk groups, patients receiving CCRT experienced longer OS, PFS, and DMFS compared with those receiving RT alone or other therapeutic modalities ($P < 0.05$) (Supplementary Fig. 5A–C).

3.6. External validation

The general characteristics of the validation cohort are listed in Table 1. Similar to the training cohort, SII-H was significantly associated with a higher T stage and a more advanced overall stage in the validation cohort (Table 2). The 5-year OS, PFS, LRFS, and DMFS rates of the entire cohort were 83.3%, 77.2%, 92.5%, and 83.3%, respectively. Kaplan–Meier analysis revealed that the PFS of SII-L groups was significantly longer (5-year PFS 81.0% vs. 71.9%, $P = 0.019$) and that DMFS was marginally longer (5-year DMFS 85.2% vs. 79.5%, $P = 0.089$) (Fig. 4A–B). Furthermore, there was no significant difference between the SII-L and SII-H groups associated with OS (83.8% vs. 80.3%, $P = 0.11$) or LRFS (93.0% vs. 91.7%, $P = 0.48$) (Supplementary Fig, 6A and B). Univariate analyses and multivariate analyses demonstrated that the SII was an independent prognostic factor for PFS, with comparable HR and 95% CI values to those of the training cohort (HR = 1.72, 95% CI: 1.16–2.55, $P = 0.008$; Fig. 2A).

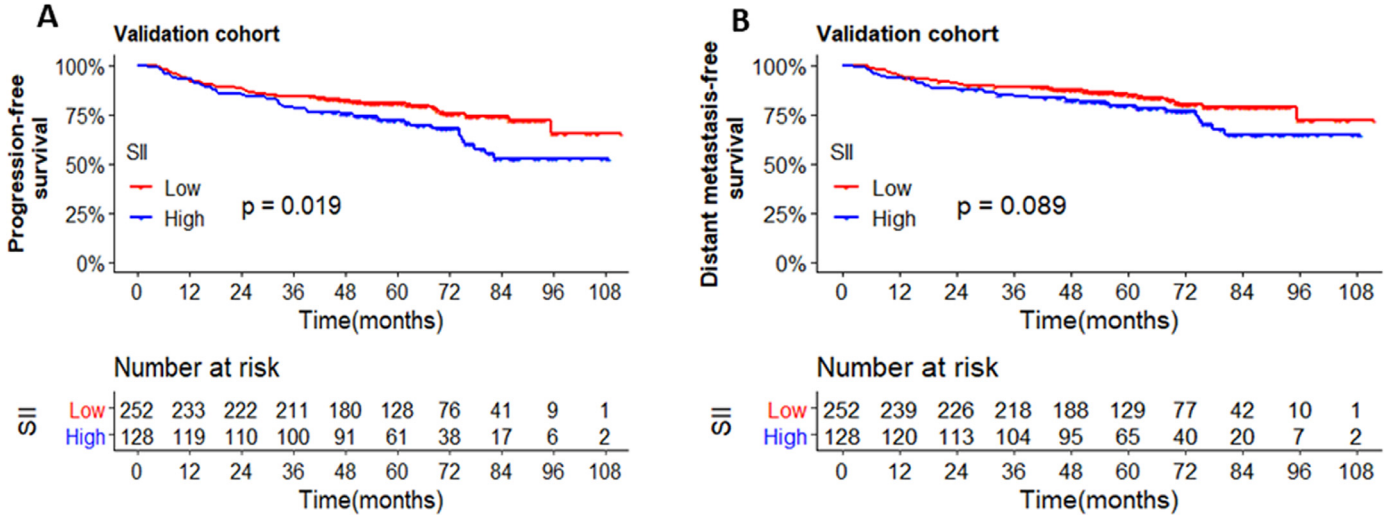

Fig. 4. Kaplan–Meier survival curves for progression-free survival (A), distant metastasis-free survival (B) in the validation cohort between the SII-L group and SII-H group. SII, systemic immune-inflammation index; SII-H, high SII; SII-L, low SII.

PSM was performed to reduce the effects of confounders on survival in the validation cohort. PSM yielded 128 matching pairs of patients (Table 2). Similar to the training cohort, the SII-H subgroup of the validation cohort was significantly associated with shorter OS and PFS (P = 0.009 and 0.002, respectively; Supplementary Fig. 7A and B). Patients in the SII-L group experienced longer DMFS compared with the SII-H group, although the difference was not significant (P = 0.058) (Supplementary Fig. 7C). Moreover, multivariate analyses of the PSM cohorts showed that a high SII was an independent prognostic factor for shorter OS (HR = 1.769, 95% CI: 0.58–1.93, P = 0.041) and PFS (HR = 1.926, 95% CI: 1.20–3.09, P = 0.007) (Supplementary Table 3).

According to the risk stratification of the training cohort, the validation cohort comprised 144 (37.9%), 179 (47.1%), and 57 (15.0%) patients in the low-risk, intermediate-risk, and high-risk groups, respectively. The 5-year PFS differed significantly across risk groups in the validation cohort as follows: 84.9%, 77.6%, and 38.7% for the low-, intermediate- and high-risk groups, respectively (P = 0.005; Fig. 3C).

4. Discussion

In the current study, SII was proved to be a critical determinant of PFS in two independent cohorts of patients with non-metastatic NPC. Furthermore, prognostic risk stratification based on SII and N stage was developed and validated in an external cohort. Patients within various prognostic risk stratification may gain different benefits from current clinical practices. Both inflammatory and immune systems play significant roles in tumorigenesis and metastasis.[13,30] Studies have documented that inflammation predisposes to the development of cancer and promotes all phases of tumorigenesis through complex mechanisms in association with changes in the immune system. Neutrophils are key effectors in innate immunity, representing a significant part of the tumor microenvironment.[17] Furthermore, neutrophils in the tumor microenvironment often play a protumor role through the formation of the neutrophil extracellular trap, the release of reactive oxygen species, which suppress T-cell activation, the secretion of protumor cytokines and chemokines, and the promotion of immune-suppression, thereby promoting tumor growth and the metastatic process.[31-35] Lymphocytes play a pivotal role in the immune response. Cytokines such as IFN-γ and TNF-α released by lymphocytes help control a tumor and are associated with improved prognosis of diverse cancers.[23,36] Accordingly, the prognostic utility of the NLR has been extensively explored for application to multiple cancer types, including NPC.[19-22,37] Furthermore, platelets are active players in tumorigenesis, including tumor growth, tumor-cell extravasation, and metastasis. Platelets infiltrate the tumor microenvironment and directly interact with cancer cells, which are indispensable for successful hematogenous metastatic dissemination.[38-39] As an integrated indicator based on the components of peripheral blood, the SII may function as a more robust predictor of tumor progression. So far, SII had been observed effectively in predicting survival of patients with HCC, NSCLC, and ESCC.[23-26]

Numerous studies have illuminated the role of peripheral blood components in affecting the prognosis of NPC. He et al. found that the pretreatment NLR was significantly related to the poor prognosis of NPC, and a high percentage of lymphocytes was significantly associated with favorable prognosis.[21] Moreover, patients with platelet count>300 $\times$ 10^9/L were reported to have poor prognosis.[15] Lu et al. reported that a relatively high PLR was associated with shorter survival of patients with NPC patients,[19] and SII>403 was associated with shorter OS.[27] Additionally, patients with NPC with a high SII experienced shorter OS, PFS, and DMFS.[28] However, these studies were based on retrospective single-center data and inconsistent cut-off values assigned to blood components, individually or combined. None were validated using an external population.

To the best of our knowledge, the current study is the first to develop and independently validate the prognostic role of the SII combined with risk stratification of patients with non-metastatic NPC. Despite the existence of two previous studies investigating SII in NPC, inconsistent cutoffs of SII (403 vs. 527), relatively small sample size, and lack of external validation have restricted their clinical significance and relevance. Both studies have identified SII by using ROC curve analysis to compare their discrimination ability for OS.[27,28] Given that OS is prone to be confounded by competing risks, we selected tumor progression as the event of interest to determine the optimal cut-off. Here we stratified patients into SII-H and SII-L groups according to the optimal cut-off value of 686. Remarkably, this cutoff has successfully been validated in an external cohort, indicating the validity of this cut-off value for non-epidemic and epidemic settings.

As expected, we found that a high SII before treatment was related to the more advanced T stage and overall stage. The association between the high SII and N stages was insignificant. This trend was similar to two previous studies showing that a high SII was significantly associated with advanced T stage.[27,28] This may be explained by the contribution of platelets to tumor growth through the release of growth factors as well as the ability of neutrophils to promote the growth of tumor cells and tumor-associated stromal cells at primary tumor lesions and metastatic sites.[17,32] Moreover, a larger size tumor is associated

with a higher burden of cancer and extensive inflammation, reflecting the decreased antitumor activity of the host defense that subsequently allows cancer development. In addition, another previous study showed a positive correlation between the SII and circulating tumor cells.[40] All these findings implied the aggressive features of tumors with high SII. Consistent with the theoretical hypothesis, SII was verified to be an independent determinant for PFS in both training and external settings.

A significant strength of the present study is the application of PSM in both training and validation cohorts to minimize the effects of confounders. Considering the imbalance of T and TNM stages between the SII-H and SII-L groups, which may overestimate the prognostic impact of SII, we conducted the PSM analysis to balance other potential prognostic factors between SII-high and SII-low groups. Before and after PSM, survival analyses demonstrated that the SII remained an independent prognostic factor for PFS in both cohorts. In addition, considering that stage I/II patients only account for a small proportion of our study population, we further made a subgroup analysis specifically based on patients with stage III/IV. Again, subgroup analysis for patients with stages III–IVB still demonstrated a significant association of the patients with SII>686 with worse PFS scores.

Furthermore, we established a risk-stratified prognostic index for PFS, which was validated in the external cohort. Optimization of risk stratification is more clinically appropriate for assessing prognosis and guiding individualized therapy. The risk stratification generated in the current study was validated for predicting PFS in the training cohort but not in the validation cohort, possibly because of the single treatment protocol (concurrent chemotherapy) administered to the validation cohort. Furthermore, the association of risk stratification with treatment showed that in the low- and intermediate-risk groups the efficacy of RT alone was comparable to that of combined therapy. In the high-risk group, CCRT alone was superior to RT alone or comprehensive treatment. Therefore, risk stratification was instructive for treatment decision-making, such as reducing the treatment intensity of low- and intermediate-risk patients and improving the efficacy of treating high-risk patients.

There are a few limitations to this study. First, this is a retrospective study, so the results might have been affected by unavoidable bias. Second, promising prognostic biomarkers such as EBV DNA were incomplete in our study and therefore were not included in analysis. Third, all patients in the validation cohort received uniform modality of treatment, and thus they were not fit for validating the instructive value of risk stratification on treatment decision making.

5. Conclusions

This study suggested that pretreatment SII, as a cost-effective, accessible and reproducible blood-based index, was a robust prognostic indicator for non-metastatic NPC. The risk stratification comprising the SII and N stages provided a beneficial tool for caregivers to identify the patients with stratified risk of progression and to make tailored decisions on treatment and surveillance.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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Author contributions

F.Z. performed data analysis and drafted the paper. F.Z., L.L., S.S., X.C., Y.Z. and R.W. performed the investigation, data curation and validation. K.W., Y.Q., Q.C. and L.T. provided the resources and performed the data analysis and validation. X.H., H.M., J.Z. and Q.L. performed the data analysis and validation. J.L., J.X., L.G. and G.X. performed the data visualization and supervision. J.Y. and J.W. supervised and led the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2021.11.008.

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