Pan-immune-inflammation value as a novel prognostic biomarker in nasopharyngeal carcinoma

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Abstract. The pan-immune-inflammation-value (PIV) is a comprehensive biomarker that integrates different peripheral blood cell subsets. The present study aimed to evaluate the prognostic ability of PIV in patients with nasopharyngeal carcinoma (NPC) undergoing chemoradiotherapy. PIV was assessed using the following equation: (Neutrophil count x platelet count x monocyte count)/lymphocyte count. The Kaplan-Meier method and Cox hazards regression models were used for survival analyses. The optimal cut-off values for PIV and systemic immune-inflammation index (SII) were determined using receiver operating characteristic analysis to be 428.0 and 1032.7, respectively. A total of 319 patients were recruited. Patients with a low baseline PIV (≤428.0) accounted for 69.9% (n=223) and patients with a high baseline PIV (>428.0) accounted for 30.1% (n=96). Compared with patients with low PIV, patients with a high PIV had significantly worse 5-year progression-free survival [PFS; 66.8 vs. 77.1%; hazard ratio (HR), 1.97; 95% confidence interval (CI), 1.22-3.23); P=0.005] and 5-year overall survival (OS; 68.7 vs. 86.9%, HR, 2.71; 95% CI, 1.45-5.03; P=0.001). PIV was also a significant independent prognostic indicator for OS (HR, 2.19; 95% CI, 1.16-4.12; P=0.016) and PFS (HR, 1.86; 95% CI, 1.14-3.04; P=0.013) and outperformed the SII in multivariate analysis. In conclusion, the PIV was a powerful predictor of survival outcomes and outperformed the SII in patients with NPC treated with chemoradiotherapy. Prospective validation of the PIV should be performed to better stratify radical treatment of patients with NPC.

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Abbreviations: NPC, nasopharyngeal carcinoma; IIB, immune-inflammatory biomarker; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune-inflammation value; CRC, colorectal cancer; IC, induction chemotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; EBV, Epstein-Barr virus; ROC, receiver operating characteristic; SIRI, systemic inflammation response index

Key words: NPC, Pan-immune-inflammation value, IIB, prognosis, survival outcome

Introduction

Nasopharyngeal carcinoma (NPC), which originates from the nasopharyngeal mucosal lining, is endemic to Southeast Asia, North Africa and South China, and more than 70% of new cases are in east and southeast Asia (1,2). Due to improvement of radiotherapy techniques, development of drugs and the accuracy of cancer staging systems, the survival of patients with NPC has notably improved, and the 5-year overall survival rate of early nasopharyngeal carcinoma is 86.6 to 93.2% (3). However, certain patients still experience treatment failure and 11-36% of patients with NPC develop distant metastasis (2). Therefore, it is key to elucidate novel biomarkers to better stratify prognosis and predict treatment outcomes in NPC.

To date, most biomarkers studied have been associated with tumors, whereas less attention has been paid to host-associated factors, such as serum alpha-fetoprotein in Hepatocellular carcinoma (4), carbohydrate antigen 125 in ovarian cancer (5). However, certain blood-derived and easily obtained immune-inflammatory biomarkers (IIBs) have been studied in patients with malignancy, including NPC (6-14). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and neutrophil platelet and monocyte counts have prognostic relevance in NPC (6-14). Furthermore, high NLR may be used to predict positive immune response to radiotherapy in patients with NPC (15). However, the low discriminative ability of these single biomarkers limits their clinical application. Considering the interaction between immunity, inflammation, and cancer, which depends on complicated networks, more stable and robust prognostic power may be achieved using composite biomarkers that encompass diverse immune-inflammatory populations and reflect the overall inflammatory state. Notably, systemic immune-inflammation

index (SII), which includes neutrophil, lymphocyte and platelet counts, but excludes monocytes, has been applied to stratify the prognosis of patients with NPC (8,10,12,16,17). Furthermore, pan-immune-inflammation value (PIV), a novel biomarker encompassing subsets of peripheral blood immune cells (neutrophils platelets, monocytes and lymphocytes) has the potential to reflect immunity and systemic inflammation in a patient (18-27). Based on previous studies and meta-analyses, the PIV has been identified as a strong prognostic indicator of outcomes in patients with advanced cancer treated with surgery, cytotoxic chemotherapy, immunotherapy and targeted therapy, such as in breast, esophageal and colorectal cancer (CRC) and metastatic melanoma (18-27). To the best of our knowledge, however, the role of the PIV in NPC has not been studied.

The present study aimed to assess the prognostic ability of the PIV as a novel biomarker, including all immune-inflammatory populations from peripheral blood in non-metastatic NPC.

Materials and methods

Study population. The electronic records of patients with biopsy-proven, non-metastatic NPC admitted to Panyu Central Hospital (Guangzhou, China) between January 2014 and December 2019 were reviewed. All patients detected Epstein-Barr virus (EBV)-encoded RNA (EBER) *in situ* hybridization. A thorough review of the medical records of the patients was performed. The following data were extracted from the medical records of the participants: Age, sex, histological type, smoking status, baseline hematological profile and imaging data. Factors known to affect routine blood tests were also reviewed, including evidence of bacterial infection or abscess, acute or chronic inflammation, current use of corticosteroids and coexisting hematological malignancy (7). Furthermore, the clinical features of the patients (for example, fever, rash and arthritis), past medical history (for example, coexisting hematological malignancy and current use of corticosteroids) and the results of blood and stool tests, urinalysis, chest X-ray or computed tomography, especially when leukocytes were above the normal range requiring ruled out for infections, hormone use, were reviewed (7). Patients who underwent incomplete treatment, patients who were aged <18 year, had a history of malignancies at other sites, hematological disease, incomplete data were excluded. Finally, 319 patients with pathologically confirmed nasopharyngeal carcinoma, no metastasis, and completion of standard treatment were included in the present study. The absolute counts of neutrophils, lymphocytes, monocytes and platelets were used to estimate PIV and SII.

All patients were re-staged based on the eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control Staging System for NPC (28). The therapeutic strategy for all patients was determined according to guidelines of the National Comprehensive Cancer Network (29) and the Karnofsky performance status score (30). All patients were treated by definitive intensity modulated radiation therapy, with or without chemotherapy (2). The total radiation doses were 66-70 Gy to the primary tumor, 60-66 Gy to the involved cervical lymph nodes and ≥54 Gy to potential sites of local infiltration and bilateral cervical lymphatics as 30-33 fractions (2). Induction chemotherapy (IC) was used to treat 280 (87%) patients. IC regimens included docetaxel + cisplatin (TP; 75 mg/m^2 docetaxel on days 1 and 75 mg/m^2 cisplatin on day 1) or gemcitabine + cisplatin (GP; 1,000 mg/m^2 gemcitabine on days 1 and 8, and 80 mg/m^2 cisplatin on day 1) for 2-3 courses. Among patients who received IC, 80.4% (225/280) received TP and 19.6% (55/280) received GP.

Statistical analysis. To represent the weight of the mutual effect between inflammatory pro-tumor populations (neutrophils, monocytes and platelets) and anticancer immune populations (lymphocytes), PIV was measured using the following equation: (Neutrophil count x platelet count x monocyte count)/lymphocyte count (18-27). SII, which was regarded as an outperforming inflammatory biomarker, was measured using the following equation: (Neutrophil count x platelet count)/lymphocyte count (8,10,12,16,17). The optimal cut-offs for PIV and SII were determined using receiver operating characteristic (ROC) analysis, as in previous studies (8,10,12,16,19,20,25).

Overall survival (OS) was defined as time from treatment initiation to last follow-up and/or death; progression-free survival (PFS) was defined as time from treatment initiation to disease progression and/or death.

Independent samples t, $\chi 2$ and Kruskal-Wallis H tests were used to assess continuous and categorical variables. Kaplan-Meier analysis was used for survival analyses and the log-rank test was used for comparison of survival times between prognostic subgroups. Multivariate analyses were performed using Cox regression analyses to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed using IBM SPSS3 version 22.0 (IBM Corp.) and SigmaPlot 14.0 (Systat Software, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics according to PIV. A total of 319 patients were included in the present analysis. All patients were immunohistochemically confirmed as Epstein-Barr virus (EBV)-encoded RNA+. Among them, 213 (66.7%) patients were tested for EBV DNA and only 73 (34.6%) were positive. Table I and Fig. 1 present the values of the area under the curve, sensitivity and specificity generated using ROC analysis. The optimal cut-off values for the PIV and SII using ROC analysis were 428.0 and 1032.7, respectively.

Overall, 96 patients (30.1%) had high PIV (>428.0) and 223 patients (69.9%) had a low PIV (≤428.0) (Table II). A high PIV was significantly associated with more advanced T stage and a higher SII and notably associated with NPC with a more advanced N stage compared with low PIV. Moreover, patients with high PIV were significantly more likely to receive IC compared with those with low PIV.

Outcomes. The median follow-up time was 40.4 months (range, 5.75-98.79 months). Median OS and PFS were not reached. The 5-year OS and PFS values were 81.3 and 74.0% (Fig. 2), respectively. Patients with high PIV had a worse PFS

Table I. Receiver operating characteristic curve analyses for overall survival.

Curve	Cut-off value	AUC	95% CI	P-value	Sensitivity, %	Specificity, %
SII	1,032.7	0.576	0.473-0.679	0.120	40.0	80.3
PIV	428.0	0.615	0.510-0.720	0.018	52.5	73.1

AUC, area under the curve; CI, confidence interval; SII, systemic immune-inflammation index; PIV, pan-immune-inflammation value.

Table II. Baseline characteristics in low and high PIV groups.

Characteristic	Low PIV (n=223)	High PIV (n=96)	P-value
Median age (range), years	52.0 (23-80)	53.5 (19-78)	0.730
Sex			0.136
Male	151	73	
Female	72	23	
Smoking status			0.032
Yes	43	29	
No	180	67	
T stage			0.001
T1	39	8	
T2	57	15	
T3	86	36	
T4	41	37	
N stage			0.059
N0	14	8	
N1	102	38	
N2	77	26	
N3	30	24	
Induction chemotherapy			0.004
Yes	188	92	
No	35	4	
Chemotherapy regimen			0.208
GP	33	22	
TP	155	70	
SII			<0.001
Low	209	39	
High	14	57	

PIV, pan-immune-inflammation value; GP, gemcitabine + cisplatin; TP, docetaxel + cisplatin; SII, systemic immune-inflammation index.

(5-year PFS, 66.8 vs. 77.1%; HR, 1.97; 95% CI, 1.22-3.23) and a worse OS (5-year OS, 68.7 vs. 86.9%; HR, 2.71; 95% CI, 1.45-5.03) in comparison with patients with low PIV (Fig. 3).

In the univariate analysis (Table III), advanced T and N stage and high SII and PIV were significantly associated with a poor OS. Advanced N stage and high SII and PIV were significantly associated with a poor PFS.

In the multivariate Cox regression analyses (Table IV), advanced N stage (HR, 2.05; 95% CI, 1.39-3.02) and high PIV (HR, 2.19; 95% CI, 1.16-4.12) were significant independent predictors for OS. Similar results were observed for PFS, with advanced N stage (HR, 1.54; 95% CI, 1.15-2.05) and high PIV (HR, 1.86; 95% CI, 1.14-3.04) significant independent predictors for PFS. The blood-based inflammation marker SII was not significant in the multivariate analysis of OS and PFS.

Discussion

The present study demonstrated that PIV, as a novel biomarker, was an independent predictor for poor OS and PFS in patients with non-metastatic NPC and outperformed the SII, another blood-derived inflammation marker.

Inflammation is relevant in cancer: An inflammatory microenvironment is a key constituent of the tumor

Table III. Univariate cox regression analyses for OS and PFS in patients with nasopharyngeal carcinoma.

A, OS

Factor	HR (95% CI)	P-value
Age	1.02 (0.99-1.05)	0.209
Sex (Female vs. male)	0.67 (0.32-1.40)	0.284
Smoking (Yes vs. no)	1.80 (0.93-3.50)	0.082
T stage (T3-4 vs. T1-2)	1.42 (1.01-2.01)	0.044
N stage (N2-3 vs. N0-1)	2.17 (1.46-3.23)	<0.001
Induction chemotherapy (Yes vs. no)	7.10 (0.97-51.7)	0.053
SII (high vs. low)	2.23 (1.19-4.21)	0.013
PIV (high vs. low)	2.71 (1.45-5.03)	0.002

B, PFS

Factor	HR (95% CI)	P-value
Age	1.01 (0.98-1.03)	0.535
Sex (Male vs. female)	1.08 (0.64-1.08)	0.775
Smoking (Yes vs. no)	1.37 (0.79-2.35)	0.259
T stage (T3-4 vs. T1-2)	1.18 (0.92-1.52)	0.198
N stage (N2-3 vs. N0-1)	1.59 (1.19-2.13)	0.002
Induction chemotherapy (Yes vs. no)	1.70 (0.73-3.93)	0.217
SII (high vs. low)	1.82 (1.09-3.03)	0.022
PIV (high vs. low)	1.97 (1.22-3.23)	0.006

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; SII, systemic immune-inflammation index; PIV, pan-immune-inflammation value.

Table IV. Multivariate cox regression analyses for OS and PFS in patients with nasopharyngeal carcinoma.

A, OS

Factor	HR (95% CI)	P-value
N stage (N2-3 vs. N0-1)	2.05 (1.39-3.02)	<0.001
PIV (high vs. low)	2.19 (1.16-4.12)	0.016

B, PFS

Factor	HR (95% CI)	P-value
N stage (N2-3 vs. N0-1)	1.54 (1.15-2.05)	0.003
PIV (high vs. low)	1.86 (1.14-3.04)	0.013

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PIV, pan-immune-inflammation value.

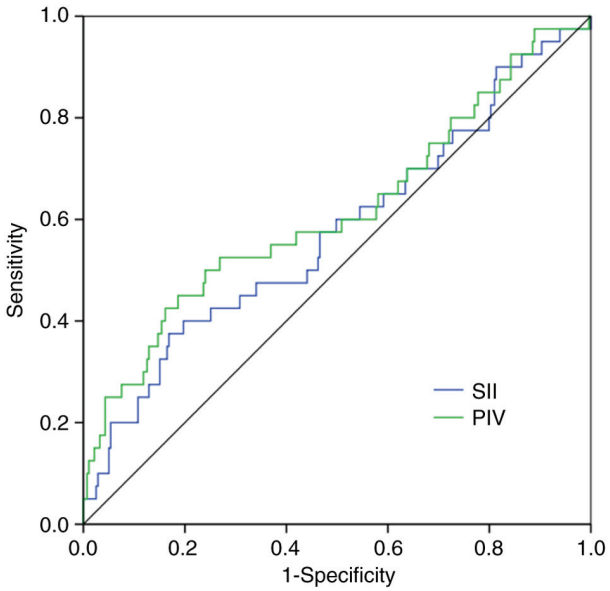

Figure 1. Receiver operating characteristic curves showing optimal cut-off values for PIV and SII. PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.

microenvironment. Chronic inflammation caused by sustained infection or ongoing exposure to non-infectious factors, such as smoke, asbestos or silica, may eventually lead to carcinogenesis (31-33).

White blood cell counts reflect the overall and/or local inflammatory status (34) and each type of white blood cells serves a unique role. Firstly, neutrophils serve a primary role in regulating inflammation and cancer and they actively promote progression and metastasis (35). Secondly, peripheral monocyte count is associated with the density of the M2 phenotype of tumor-associated macrophages (36,37), which derive from circulating monocytes within the tumor microenvironment and promote metastasis and immunosuppression (38,39). A high absolute monocyte count predicts low survival rate for patients with cancer (37). Thirdly, platelets promote tumor cell proliferation and survival through via mechanisms, such as aggregation with tumor cells, thereby protecting them from host immune surveillance through physical shielding and induction of 'platelet mimicry'. This provides an immunosuppressive tumor microenvironment, which is a key source of TGF-β, a key cytokine for immunosuppression in the tumor microenvironment, and facilitates vascular evasion (40,41). High platelet count is associated with unfavorable outcomes in several kinds of cancer such as lung cancer, colon cancer, breast and prostate cancer (42). However, lymphocytes have notable positive effects in tumor-associated immunology. High lymphocyte levels are associated with an improved prognosis in numerous types of tumor, exerting a strong anti-tumor immune function to suppress tumor development (43). Leukocytes serve a role in the development and outcomes of cancer.

Previous studies have analyzed the association between each type of leukocyte (lymphocytes, neutrophils, platelets and monocytes) and clinical results and have constructed computational models (nomograms or scores) driven by statistical methods (6-14). To avoid fragmenting systemic inflammation

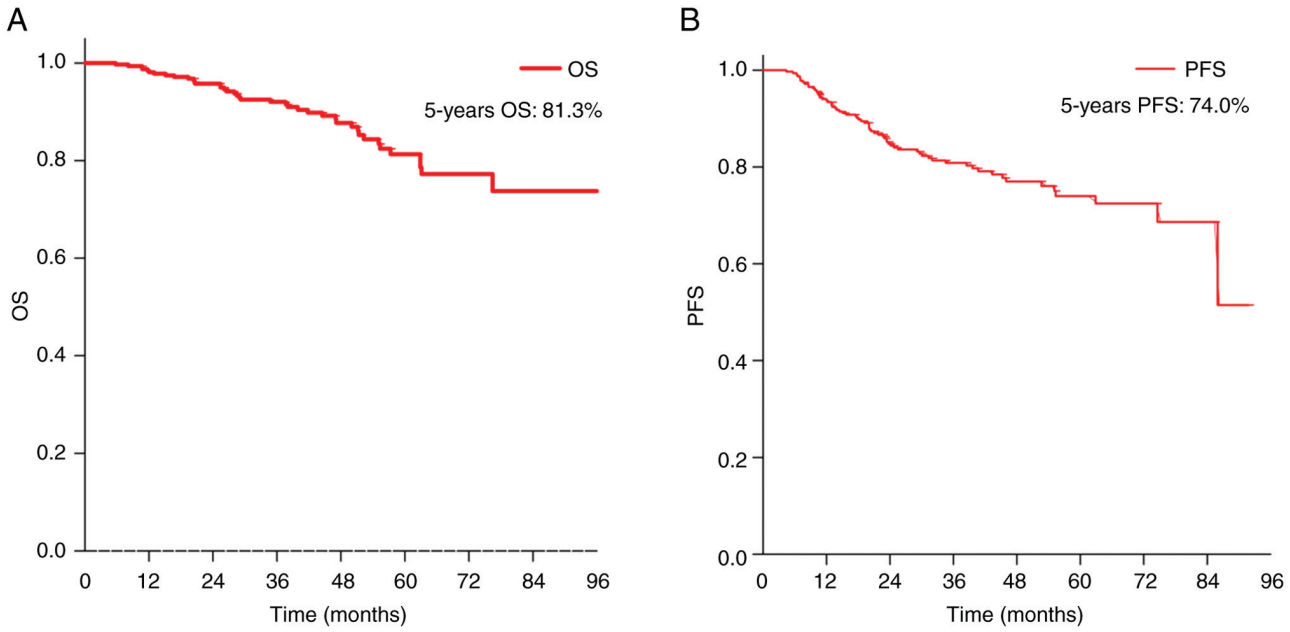

Figure 2. Kaplan-Meier survival curves for OS (A) and PFS (B) in the overall population. OS, overall survival; PFS, progression-free survival.

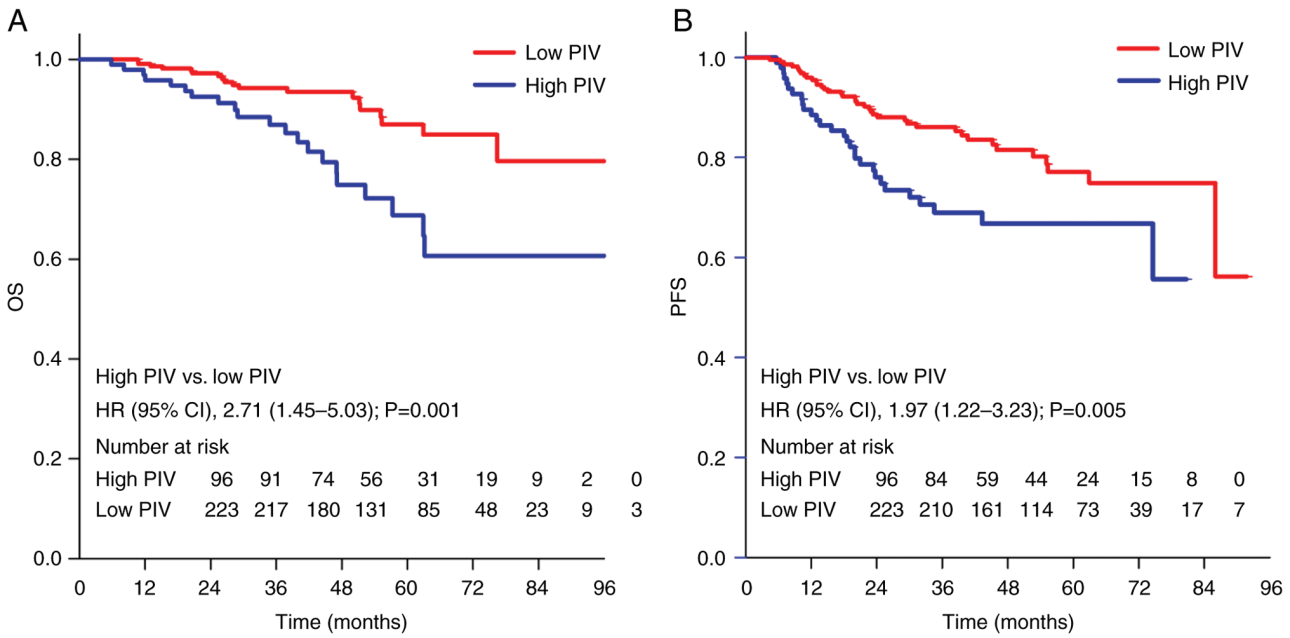

Figure 3. Kaplan-Meier survival curves for OS (A) and PFS (B) in the overall population according to PIV. Patients with high PIV had worse survival outcomes compared with patients with low PIV. OS, overall survival; PFS, progression-free survival; PIV, pan-immune-inflammation value; HR, hazard ratio; CI, confidence interval.

information, SII and systemic inflammation response index (SIRI) have been evaluated (8,10-12,16,17,44,45). SII and SIRI have been assessed as prognostic markers for NPC (8,12,16,17,44,45); prognostic value of SII is superior to that of PLR, NLR and MLR (8). However, two studies reported that SIRI was not an independent risk factor for OS in patients with NPC (10,11). Thus, the role of SIRI requires more investigation. To the best of our knowledge, no studies have comprehensively evaluated the prognosis of lymphocytes, neutrophils, platelets, and monocytes in nasopharyngeal carcinoma.

PIV is proposed as a biomarker based on peripheral blood count, which integrates different peripheral blood immune cell subpopulations (neutrophils, platelets, monocytes and lymphocytes). Considering its potential to mirror comprehensive manifestations of systemic inflammation and immunity, PIV is considered a powerful and robust prognostic indicator of survival in patients with cancer undergoing surgery, cytotoxic chemotherapy, immunotherapy and targeted therapy (18-27). A study reported that baseline PIV is a predictor for a pathological complete response and survival and has greater predictive abilities than NLR, MLR and PLR

in patients with breast cancer receiving neoadjuvant chemotherapy (20). Similar results have been observed in patients with advanced human epidermal growth factor receptor 2+ breast cancer (23). A proposed nomogram incorporating PIV could be a feasible tool for individualized prognostic assessment in patients with breast cancer receiving surgery (18). Furthermore, PIV is a strong prognostic indicator of survival outcomes, outperforming other IIBs, such as NLR and SII, not only in patients with metastatic CRC receiving first-line therapy (24), but also in patients with stage I-III CRC (19). PIV serves a role in patients with advanced cancer receiving immune checkpoint inhibitors (21). Moreover, in patients with metastatic melanoma, high PIV is significantly associated with primary resistance to both targeted therapy [odds ratio (OR), 8.42; 95% CI, 2.50-34.5; P<0.001] and immunotherapy (OR, 3.98; 95% CI, 1.45-12.32; P=0.005). Therefore, PIV may be used to guide the treatment decision process and the development of novel first-line treatment strategies (22). In esophageal cancer, high PIV is significantly associated with low tumor-infiltrating lymphocyte status (P<0.001) and low CD8+ cell count (P=0.011), which may allow response to treatment (25). In addition, high PIV is associated with more advanced AJCC stage and younger age (46). Consistent with the aforementioned studies, the present study demonstrated that patients with high PIV had more advanced T stage and worse survival outcome than those with a low PIV. Moreover, to the best of our knowledge, the present study is the first to report that PIV may be a more reliable predictor of OS and PFS than SII in patients with NPC.

The present study had limitations, including the retrospective nature of the study and the fact that the population was only recruited from a single center in an endemic area. Furthermore, the EBV DNA data were missing in the present study. Although EBV DNA has been established as a robust prognostic marker in NPC for clinical outcomes, there is no internationally recognized EBV DNA standardized testing process and comparatively large interlaboratory variability has been observed, even for the same assay using identical procedures without harmonization (1,2,47,48). In the present study, only 66.7% patients were tested for EBV DNA because some patients refused to have their blood drawn again. Among the tested patients, only 34.6% patients were positive. EBV DNA testing is key but the accuracy of EBV DNA testing needs improvement. NPC and laboratory medicine experts focused on harmonization and validation of the assay, as well as adaptation of new technologies to improve assay quantification, such as next-generation sequencing or digital polymerase chain reaction (1). However, tests for peripheral blood immune cell are mature and robust. Moreover, they are routine, cheap, convenient and stable and thus have good prospects in clinical application (8,10-12,16,17,44,45). To improve detection of EBV DNA, use of regular test markers to predict the survival of patients with NPC should be performed, such as using the PIV, in which a high PIV can predict worse survival and identify patients that might need more intensive treatment. The selection of appropriate patients requires exclusion of other causes of abnormal blood results, such as fever. Although the technology to detect peripheral blood immune cells is mature, the cut-off value for the PIV (high vs. low) was different in the present study and previous studies that the cut-off values raged 285.0 to 513.4 (18-27). In future studies, optimal PIV cut-off for clinical application should be assessed. PIV is not directly measured but calculated by a formula. In the future, PIV results may be obtained directly through blood test instrument, which may require a program to calculate PIV.

In conclusion, the present study demonstrated that baseline PIV had a significant predictive value and outperformed SII in patients with NPC. Therefore, the PIV may be a helpful tool to tailor management of patients with NPC; however, further research is needed to confirm the findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZS,JT, GRZ and XLC contributed to study conception and design. Material preparation, data collection and analysis were performed by ZS, JT, YH, WHZ and QY. The collection of pathological data was performed by QY. ZS wrote the manuscript. ZS and JT confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Panyu Central Hospital (Guangzhou, China; approval no. PYRC-2023-395). The data were anonymous and the requirement for informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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