Heliyon 10 (2024) e24804

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Prognostic significance of pan-immune-inflammation value (PIV) in nasopharyngeal carcinoma patients

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ARTICLE INFO

Keywords:
Pan-immune-inflammation value
Nasopharyngeal carcinoma
Prognosis
Nomogram

ABSTRACT

Background: Blood-based immune-inflammation indexes have been widely used to predict survival in a variety of cancers. In this research, we seeked to evaluate a novel immune-inflammation marker, named the pan-immune-inflammation value (PIV), in patients with nasopharyngeal carcinoma (NPC) undergoing definitive radiotherapy.

Methods: A group of 377 patients with NPC was retrospectived analyzed. Clinical data and laboratory data were collected. Receiver operating characteristic (ROC) curve analysis was performed in order to determine the optimal PIV cut-off value. Survival curves were estimated by Kaplan-Meier method, and prognostic variables were identified using a Cox regression model. Additionally, we developed a nomogram and assessed its acuracy using the concordance index (C-index) and a calibration curve.

Results: The optimal PIV cut-off value was 146.24 according to ROC analysis. High PIV was related to poorer Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ($p = 0.017$), more advanced T ($p < 0.001$) and clinical stages ($p = 0.024$). In univariate analysis, older Age, poorer ECOG PS, higher Epstein–Barr virus DNA (EBV-DNA), advanced T, N and clinical stage, and higher PIV levels were related to patients' poorer overall survival (OS). Poorer ECOG PS, higher EBV-DNA, later T stage, later clinical stage, and higher PIV were associated with patients' poorer progression free survival (PFS). Male sex and later T stage were associated with patients' poorer locoregional recurrence free survival (LRRFS). Poorer ECOG PS, higher EBV-DNA, later T stage, later clinical stage, and higher PIV were associated with patients' poorer distant metastasis free survival (DMFS). Multivariate analysis demonstrated that PIV was an independent prognostic index for OS (HR 2.231, 95 % CI 1.241–4.011, $P = 0.007$), PFS (HR 1.664, 95 % CI 1.003–2.760, $P = 0.049$), and DMFS(HR 2.081, 95 % CI 1.071–4.044, $P = 0.031$). Nomogram C-indexes for the nomogram of OS were 0.684, and PFS were 0.62, respectively. Survival predictions and actual survival were consistent according to the calibration curve.

Conclusions: Pre-treatment PIV is a promising biomarker for predicting survival in patients with NPC.

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https://doi.org/10.1016/j.heliyon.2024.e24804
Received 29 October 2023; Received in revised form 13 January 2024; Accepted 15 January 2024
Available online 19 January 2024

1. Introduction

Nasopharyngeal carcinoma (NPC), a type of squamous cell cancer, exhibits a distinct geographical prevalence, with over three-quarters of cases occurring predominantly in Southern and Southeast Asia [1]. Most patients with NPC (75.4 %) are diagnosed with locally advanced disease [2], and the standard treatment regimen at this stage is concurrent chemoradiotherapy (CCRT) [3]. Although 15%–30 % of patients with locally advanced NPC will relapse or develop metastases [4], there is no standardized prognostic predictor for these patients. Prognostic biomarkers are urgently needed to help optimize treatment.

Research is increasingly highlighting the association between systemic inflammation and carcinogenesis and cancer prognosis [5]. Complete blood cell counts are research hotspots since they can reveal the underlying inflammation. Studies indicate that ratios such as neutrophil-to-lymphocyte ratio (NLR) platelet-to-lymphocyte ratio (PLR), have been identified as significant prognostic indicators in a vartiety of cancer types [6–8]. The pan-immune-inflammatory value (PIV) is a novel biomarker of systemic inflammation, formulated using complete blood counts. Research indicates that PIV serves as an indicator of the balance between the immune response and inflammatory state, and has potential in prognosticating outcomes in cancer patients. PIV is reported to be a valuable prognostic predictor for lung cancer [9], melanoma [10], and breast cancer [11], etc. However, research on the prognstic significance of PIV in cases of locally advanced NPC remains sparse.

Inflammation is an important component of tumor microenvironment (TME), and the changes in inflammatory cells may affect tumor development. Given that the PIV mirrors the immune and inflamatory conditions within a tumor, it holds potential as a prognositic indicator in NPC. To explore this potential, we carried out a retrospective investigation into PIV's prognostic relevance in NPC patients. Additionally, we developed a nomogram to aid in predicting outcomes for these patients based on PIV values.

2. Methods and materials

2.1. Patients

A cohort of 377 patients with NPC was retrospectively analyzed. All patients were diagnosed at the Second Xiangya Hospital, Central South University, between July 2014 and December 2019. The patients in our study were identified as having NPC, their disease staging was determined based on the criteria set forth in the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System, specially tailored for nasopharyngeal carcinoma. Patients who have historys of autoimmune diseases, chronic inflammatory diseases, or acute infectious diseases, were excluded. This study adhered to the ethical standards of the 1975 Declaration of Helsinki, as revised in 2008, and received approval from the Second Xiangya Hospital at Central South University. This compliance underscores the study's commitment to ethical research practices.

2.2. Data collection

We meticulously gathered clinical, pathological, and laboratory data from hospital records. This included each patients' age, Eastern Cooperative Oncology Group performance status (ECOG PS) score, sex, T and N stages, overall clinical stage, height, weight, treatment approach, and pre-treatment counts of neutrophils, lymphocytes, platelets, and monocytes, and EBV-DNA levels. For calculating the PIV, we used the formula: PIV= (neutrophil count $\times$ platelet count $\times$ monocyte count)/lymphocyte count [12].

2.3. RT procedure

All participants in the study underwent intensity-modulated radio-therapy (IMRT). The definition of gross and clinical tumor volume adhered to specific guidelines [13]. Radiation doses were tailored as follows: 70Gy for the primary tumor, 60Gy for planning target volume (PTV) 1, and 54Gy for PTV2. Patients received a daily radiation dose ranging from 1.82 to 2.12Gy daily, five days a week. Depending on the tumor stage and patient tolerance, targeted therapy (such as nimotuzumab) and concurrent chemotherapy regimen (using cisplatin or nedaplatin) were performed.

2.4. Follow-up

All patients have been follow-up until April 30, 2023. Overall survival (OS) was defined from the date of diagnosis to their last follow-up date or death from any cause. Progression free survival (PFS) was determined based on the date of diagnosis up to the occurrence of disease progression or death.

2.5. Statistical analysis

SPSS (version 22.0) and R software (version 4.1.3) were used for data analysis. The optimal PIV cut-off value was determined via ROC curves. Chi-square tests were utilized to examine the correlation between PIV and clinicopathological characteristics. Kaplan–Meier method was used to estimate survival curves. A Cox regression model was used for multivariate analysis. P-value less than 0.05 was considered statistical significance. Additionally, a nomogram was developed to illustrate the predictive power of the index for OS and PFS.

3. Results

3.1. Patient characteristics

All the 377 patients' characteristics are presented in Table 1. The median age was 49 years (range from 16 to 83 years). Among these patients, a majority of 266 (70.6 %) were male, ECOG PS scores of 229 (60.7 %) patients were 0. 6.4 % of patients were underweight. 165 patients (43.8 %) were presented with EBV-DNA more than 400 copies/ml. 47 patients (12.4 %) had stage I-II disease, 236 (62.6 %) had stage III, and 94 (24.9 %) had stage IVa. A total of 121 patients (32.1 %) received CCRT, 87 (23.1 %) received radiotherapy concurrent with nimotuzumab, and the remainder received radiotherapy alone. Over a median follow-up time of 55.5 months (range from 8.8 to 112.9 months), 32 (8.5 %) patients had a recurrence, 61 (16.2 %) developed metastasis, and 78 (20.7 %) died.

Table 1
The baseline clinico-pathological characteristics of NPC patients (n = 377).

Characteristics	Number (%)
Age	
Median	49
Range	16–83
Gender	
Male	266 (70.6 %)
Female	111 (29.4 %)
ECOG PS	
0	229 (60.7 %)
1	142 (37.7 %)
2	6 (1.6 %)
T stage	
1	47 (12.5 %)
2	149 (39.5 %)
3	124 (32.9 %)
4	57 (15.1 %)
N stage	
0	25 (6.6 %)
1	60 (15.9 %)
2	251 (66.6 %)
3	41 (10.9 %)
Clinical stage	
I	2 (0.5 %)
II	45 (11.9 %)
III	236 (62.6 %)
IVa	94 (24.9 %)
BMI(kg/m^2)	
< 18.5	24 (6.4 %)
18.5–24.0	191 (50.6 %)
> 24.0	162 (43.0 %)
Mean ± SD	23.43 ± 3.30
EBV-DNA (copy/ml)	
< 400	212 (56.2 %)
≥400	165 (43.8 %)
Treatment	
CCRT	121 (32.1 %)
RT + nimotuzumab	87 (23.1 %)
RT	169 (44.8 %)
Relapse	
Yes	32 (8.5 %)
No	345 (91.5 %)
Metastasis	
Yes	61 (16.2 %)
No	316 (83.8 %)
Death	
Yes	78 (20.7 %)
No	299 (79.3 %)

ECOG PS Eastern Cooperative Oncology Group Performance Status, *BMI* Body Mass Index, *SD* Standard Deviation, *CCRT* concurrent chemo-radiotherapy, *RT* radiotherapy.

3.2. PIV cut-off and association with clinicopathological characteristics

In the study, ROC analysis with OS as the endpoint indicated that the optimal PIV cut-off value was 146.24 (Fig. S1). Based on this, patients were categorized into low- and high-PIV groups. The association between PIV levels and patients' characteristics was detailed in Table 2. Notably, a higher PIV was linked to poorer ECOG PS score ($p = 0.017$) and more advanced T ($p < 0.001$) and clinical stages ($p = 0.024$). However, PIV did not showed a significant association with factors like age, sex, BMI, EBV-DNA levels, N stage, or the type of treatment received (all $p > 0.05$).

3.3. Prognostic value of PIV

The Kaplan-Meier analysis in the study revealed several factors significantly associated with patient outcomes. Specially, variables like age ($p = 0.035$), EBV-DNA ($P = 0.011$), ECOG PS ($p < 0.001$), T stage ($p = 0.003$), N stage ($p = 0.038$), clinical stage ($p = 0.040$), and PIV($p = 0.001$) were linked to OS. (Table 3, Fig. 1A). Additionally, EBV-DNA ($p = 0.001$), ECOG PS($p < 0.001$), T stage ($p = 0.001$), clinical stage ($p = 0.030$), and PIV($P = 0.005$) were correlated with patients' PFS(Table 3, Fig. 1B). The analysis also identified connections between sex ($p = 0.023$), T stage ($p = 0.008$) and LRRFS. (Table 3, Fig. 1C), as well as between EBV-DNA ($p < 0.001$), ECOG PS($p < 0.001$), T stage ($p = 0.009$), clinical stage ($p = 0.009$), PIV($P = 0.004$) and DMFS(Table 3, Fig. 1D).

According to univariate analysis, variables significantly correlated with patients' prognosis were included in multivariate analysis. Cox regression analysis showed that ECOG PS ($p = 0.026$), N stage ($p = 0.039$), and PIV($p = 0.007$) were significant independent predictors for OS. ECOG PS ($p = 0.019$), EBV-DNA ($p = 0.007$), and PIV ($p = 0.049$) were significant independent predictors for PFS. Only T stage ($p = 0.011$) was an significant independent predictor for LRRFS. ECOG PS ($p = 0.013$), EBV-DNA ($p = 0.003$), and PIV ($p = 0.031$) were significant independent predictors for DMFS(Table 4).

3.4. Prognostic nomogram construction

The independent prognostic factors identified from multivariate analysis were utilized to develop a nomogram for predicting 3, 5, and 7 OS(Fig. 2). The nomogram's accuracy, measured by the C-index, was 0.684 for OS. Additionally, the AUCs values for 3, 5, and 7 years OS preditions were retrospectively 0.718, 0.682, and 0.679 (Fig. 3). Calibration curves demonstrated good consistence between the nomogram's predicted OS and the actual observed values for these time frames (Fig. 4).

Table 2
The clinico-pathological characteristics of 377 patients with NPC.

Variables	Low PIV(%)	High PIV (%)	P Value
Age			
≤60	112 (86.8 %)	215 (86.7 %)	0.972
> 60	17 (13.2 %)	33 (13.3 %)	
Gender			
Male	83 (64.3 %)	183 (73.8 %)	0.056
Female	46 (35.7 %)	65 (26.2 %)	
ECOG PS			
0	91 (70.5 %)	138 (55.6 %)	**0.017**
1	37 (28.7 %)	105 (42.4 %)	
2	1 (0.8 %)	5 (2.0 %)	
BMI			
< 18.5	10 (7.8 %)	14 (5.6 %)	0.545
18.5–24	61 (47.2 %)	130 (52.4 %)	
≥24	58 (45.0 %)	104 (41.9 %)	
EBV-DNA			
< 400	78 (60.5 %)	134 (54.0 %)	0.274
≥400	51 (39.5 %)	114 (46.0 %)	
T stage			
1-2	86 (66.7 %)	110 (44.4 %)	**< 0.001**
3-4	43 (33.3 %)	138 (55.6 %)	
N stage			
0-1	31 (24.0 %)	54 (21.8 %)	0.697
2-3	98 (76.0 %)	194 (78.2 %)	
Clinical stage			
I-III	106 (82.2 %)	177 (71.4 %)	**0.024**
IVa	23 (17.8 %)	71 (28.6 %)	
Treatment			
CCRT	43 (33.3 %)	78 (31.5 %)	0.728
Non-CCRT	86 (66.7 %)	170 (68.5 %)	

ECOG PS Eastern Cooperative Oncology Group Performance Status, *BMI* Body Mass Index, *CCRT* concurrent chemo-radiotherapy.

Table 3
Univariate analysis of potential factors associated with OS, PFS, LRRFS, and DMFS.

Variables	OS			PFS			LRRFS			DMFS		
	Case	5y-(%)	P	Case	5y-(%)	P	Case	5y-(%)	P	Case	5y-(%)	P
Age												
≤ 60	327	81.8	**0.035**	327	76.2	0.054	327	89.4	0.923	327	84.3	0.073
> 60	50	73.6		50	64.3		50	90.7		50	72.5	
Gender												
Male	266	78.4	0.065	266	71.9	0.112	266	86.6	**0.023**	266	82.6	0.854
Female	111	85.8		111	80.7		111	96.1		111	83.2	
ECOG PS												
0	229	85.5	**< 0.001**	229	80.5	**< 0.001**	229	90.9	0.095	229	88.5	**< 0.001**
1-2	148	73.3		148	65.4		148	87.2		148	73.9	
BMI												
< 18.5	24	79.2	0.664	24	79.2	0.392	24	95.2	0.509	24	83.1	0.328
18.5–24.0	191	79.1		191	72.0		191	88.0		191	80.3	
> 24.0	162	82.9		162	77.3		162	90.8		162	85.7	
EBV-DNA												
< 400	212	86.1	**0.011**	212	79.9	**0.001**	212	91.1	0.180	212	88.2	**< 0.001**
≥400	165	73.9		165	67.8		165	84.0		165	75.8	
T stage												
1-2	196	85.4	**0.003**	196	81.6	**0.001**	196	93.5	**0.008**	196	87.9	**0.009**
3-4	181	75.6		181	67.1		181	85.1		181	77.2	
N stage												
0-1	85	91.4	**0.038**	85	82.8	0.054	85	95.1	0.121	85	87.0	0.170
2-3	292	77.6		292	72.2		292	87.8		292	81.5	
Clinical stage												
I-III	283	83.2	**0.040**	283	76.9	**0.030**	283	90.2	0.280	283	85.6	**0.009**
IVa	94	73.1		94	67.8		94	87.6		94	74.5	
Treatment												
CCRT	121	83.6	0.571	121	79.0	0.370	121	93.0	0.548	121	84.9	0.402
nonCCRT	256	79.3		256	72.5		256	87.8		256	81.9	
PIV												
Low	129	90.0	**0.001**	129	82.7	**0.005**	129	91.2	0.322	129	90.7	**0.004**
High	248	75.9		248	70.5		248	88.7		248	78.7	

OS overall survival, *PFS* progression free survival, *LRRFS* local regional recurrence free survival, *DMFS* distant metastasis free survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *BMI* Body Mass Index, *CCRT* concurrent chemo-radiotherapy, *PIV* pan-immune-inflammation value.

4. Discussion

In this study, the prognostic value of pretreatment PIV in NPC patients undergoing definitive radiotherapy was investigated for the first time. Findings revealed that PIV serves as an independent prognostic index of OS, PFS and DMFS. A nomogram incorporating PIV and other clinical parameters was created, exhibiting strong predictive performance and accuracy, as evidenced by its C-index value and calibration curve. This suggests that PIV could be a valuable blood-based immune-inflammation biomarker for forecasting NPC patient prognosis.

Systemic inflammation has long been accepted as a hallmark of cancer, and is considered to be closely associated with oncogenesis, cancer progression, and prognosis of cancer patients [14]. Uncontrolled systemic inflammation modulates the TME by secreting pro-inflammatory cytokines and angiogenesis factors, leading to immune exhaustion and evasion [15–17]. Cell components of peripheral blood, including lymphocytes, neutrophils and platelets, are important mediators of host anti-tumor immunity, and can reflect the systemic and TME immune-inflammation status. Circulating and infiltrating lymphocytes are major mediators of the anti-tumor adaptive immune response [18]. Neutrophils could promote tumor progression via multiple mechanisms, including the enhancement of cell proliferation, angiogenesis, and epithelial-mesenchymal transition [19]. Moreover, tumor-associated neutrophils (TANs) can impair $CD8^+$ T cell anti-tumor activity [20]. Monocytes, the source of tumor associated macrophages, drive immunosuppression in the TME, which impairs immunity and promotes tumor progression [21]. Platelets may coat the circulating tumor cells, allowing them to evade immune attack, and activated platelets release cytokines that support tumor development [21]. Since all pro-inflammatory cells in the blood count are included in PIV calculation, there is a strong biological rationale for PIV as a biomarker.

The utility of blood-cell-based biomarkers for prognostic prediction has been intensely investigated over the past decades. Previous studies have demonstrated that lymphocyte [22], neutrophil [23], monocyte [24], and platelet counts [25], each predict survival in various cancers. However, due to the complexity of the immune system, other parameters combining different blood cell populations have been explored to more accurately predict outcomes for patients with cancer. PLR, NLR, systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) are the most comprehensively studied biomarkers, and mounting evidence has demonstrated their prognostic significance in cancer patients [26–29]. However, since PLR, NLR, SII and SIRI are each composed of two or three peripheral blood cell components, they cannot fully represent immune status. PIV is a novel index that reflects immune-inflammation status more comprehensively because it includes four cell components. Giovanni Fucà et al. first reported in

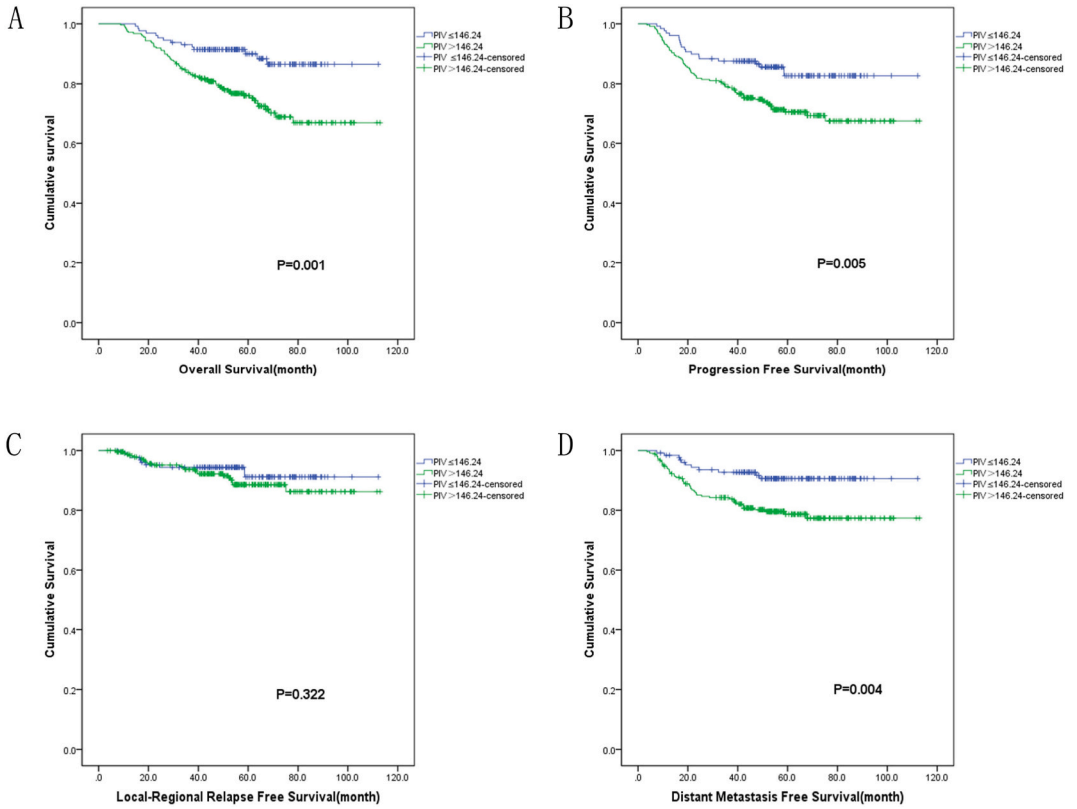

Fig. 1. Prognostic value of PIV in NPC patients. (A) Survival curves for OS, (B) Survival curves for PFS, (C) Survival curves for LRRFS, (D) Survival curves for DMFS.

Table 4
Multi-variable Cox regression analyses for OS, PFS, LRRFS, and DMFS.

Variables	OS		PFS		LRRFS		DMFS	
	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P
Age								
≤60	ref	0.088						
> 60	1.643 (0.930–2.905)							
ECOG PS								
0	ref	**0.026**	ref	**0.019**			ref	**0.013**
1-2	1.756 (1.070–2.881)		1.718 (1.092–2.701)				2.042 (1.159–3.596)	
EBV-DNA								
< 400	ref	0.075	ref	**0.007**			ref	**0.003**
≥400	1.519 (0.959–2.408)		1.803 (1.175–2.768)				2.229 (1.302–3.814)	
T stage								
1-2	ref	0.390	ref	0.174	ref	**0.011**	ref	0.645
3-4	1.257 (0.746–2.117)		1.394 (0.863–2.250)		2.637 (1.248–5.569)		1.149 (0.636–2.077)	
N stage								
0-1	ref	**0.039**						
2-3	1.974 (1.036–3.762)							
Clinical stage							ref	0.438
I-III	ref	0.596	ref	0.799			1.247 (0.714–2.179)	
IVa	1.147 (0.691–1.904)		1.063 (0.665–1.699)					
PIV								
Low	ref	**0.007**	ref	**0.049**			ref	**0.031**
High	2.231 (1.241–4.011)		1.664 (1.003–2.760)				2.081 (1.071–4.044)	

OS overall survival, *PFS* progression free survival, *LRRFS* local regional recurrence free survival, *DMFS* distant metastasis free survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *PIV* pan-immune-inflammation value.

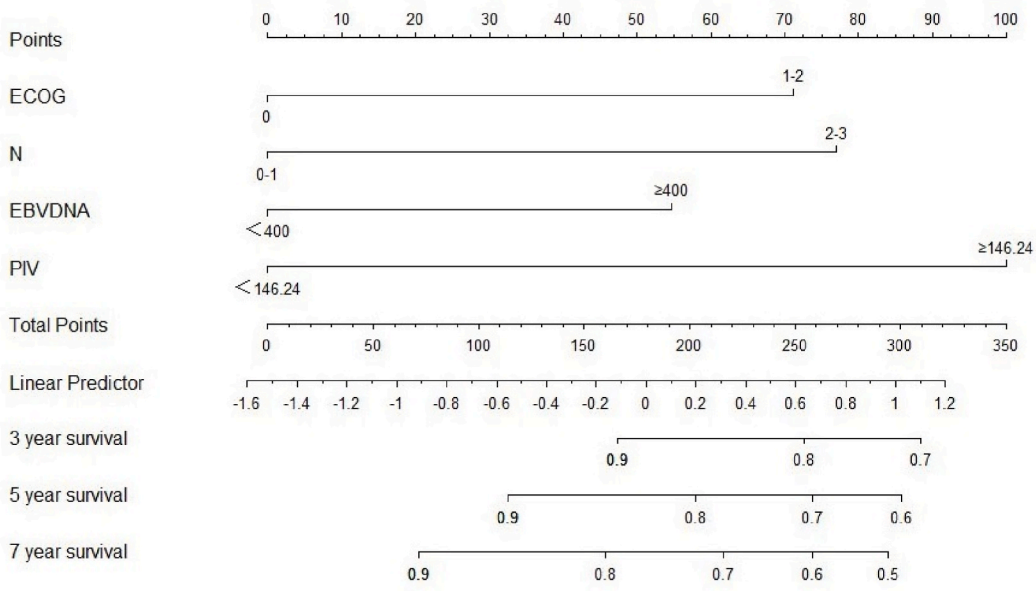

Fig. 2. Nomogram for OS predicting at 3,5, and 7 years.

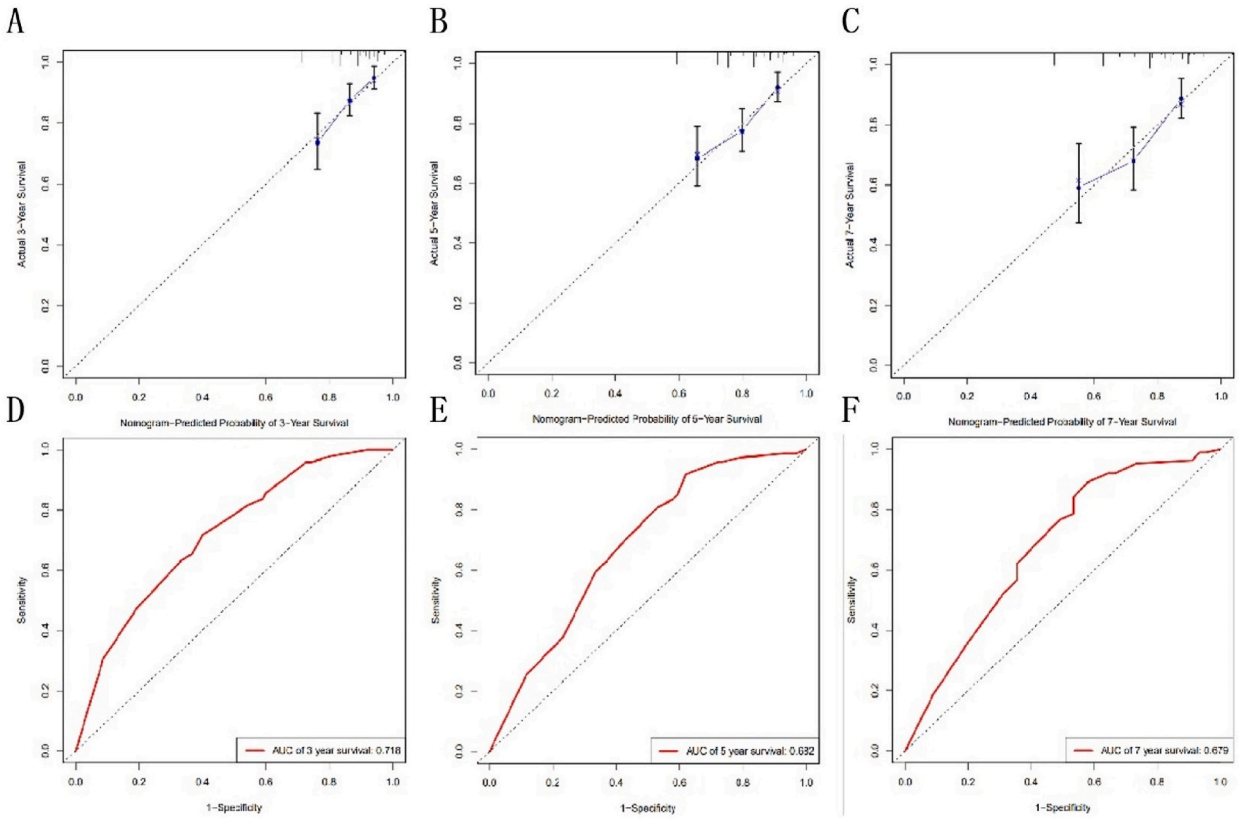

Fig. 3. The nomogram-predicted probablity of 3 years OS (A), 5 years OS (B), 7 years OS (C). The AUCs for 3 years OS(D), 5 years OS (E), 7 years OS (F).

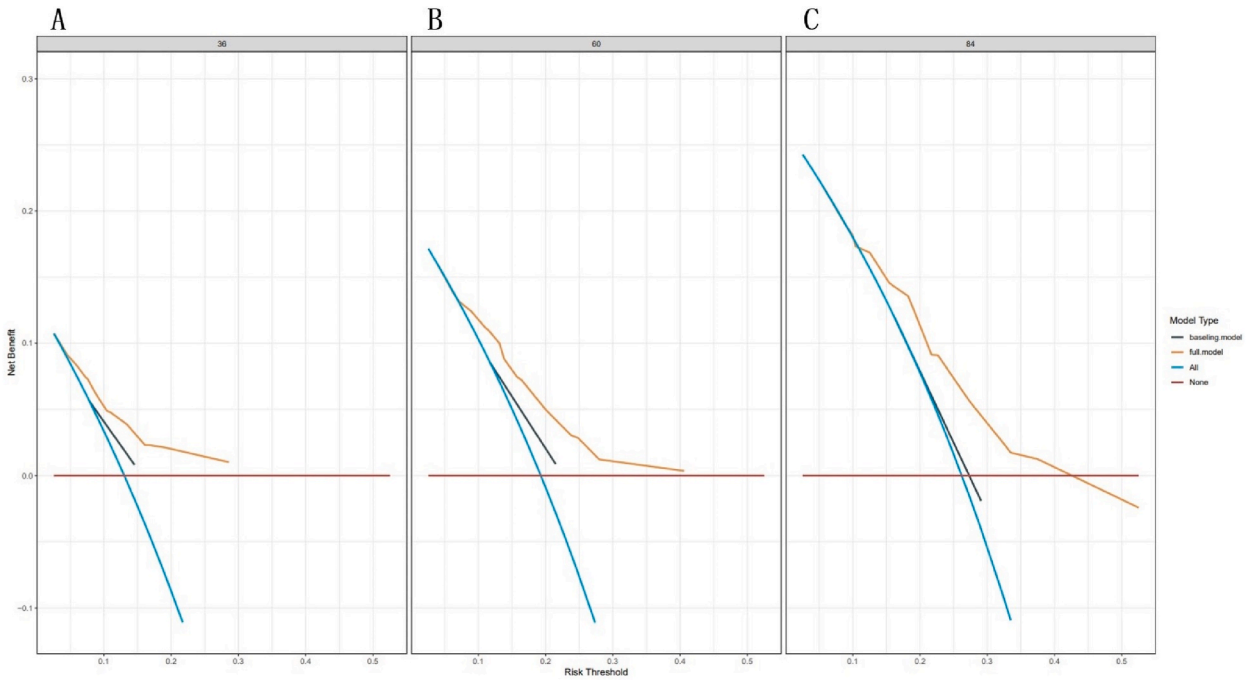

Fig. 4. The calibration curves for 3 years OS (A), 5 years OS (B), 7 years OS (C).

2020 that PIV can act as predictor for OS and PFS in colorectal cancer patients with metastatic disease, patients with high PIV presented with worse OS and PFS [12]. The prognostic role of PIV was subsequently explored in breast cancer [11,30], head and neck squamous cell carcinoma [31], small cell lung cancer [9], pancreatic adenocarcinoma [32], and prostate cancer [33], with high PIV consistently predicting a poorer prognosis. In the present study, we demonstrated that PIV is an independent prognostic index of OS, PFS and DMFS for patients with NPC, which is in agreement with these studies. A nomogram was constructed that confirmed the accuracy of the PIV prediction.

PIV includes all the inflammatory peripheral blood cells and therefore reflects the complex interactions between cancer and host immune-inflammatory responses. It is a strong predictor of cancer survival outcomes, and our research has confirmed PIV as a promising prognostic biomarker in patients with NPC. However, our research has several shortcomings. First, it is a single center retrospective research, which may have introduced bias. Second, the sample size is too small, internal and external validation were not considered. Finally, patients who receive CCRT may have experienced inflammatory adverse reactions such as radiation-induced oral mucositis and mandibular osteoradionecrosis [34], which may have influenced the results. Therefore, a further prospective multicenter study may be needed to further confirm our findings.

5. Conclusions

In summary, this retrospective study concluded that high pre-treatment PIV is an indicator of poorer OS, PFS and DMFS in patients with NPC. The study suggests PIV as a convenient and practical biomarker that could assist in better patient stratification and treatment planning. It also propose that targeting systemic inflammation might be a viable approach to enhance NPC prognosis, a hypothesis that merits further research.

Ethics statement

This research was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (certification for clinical research 2023 [No. 092]). The Ethics Committee waived the requirement of written informed consent since this was a retrospective study.

Funding declaration

This research was sponsored by the Clinical Medical Technology Innovation Guidance Project of Hunan Province (2021SK53515), the Natural Science Foundation of Hunan Province (2021JJ40882, 2022JJ40682), and the National Natural Science Foundation of China (81802476).

Data availability statement

The raw data supporting the conclusions of this article will be made available on request from the authors.

CRediT authorship contribution statement

Na Zhang: Writing – original draft, Methodology, Conceptualization. **Tao Hou:** Methodology, Data curation. **Sujuan Zhang:** Methodology, Data curation. **Jie Ling:** Methodology, Data curation. **Shun Jiang:** Software, Data curation. **Yangchun Xie:** Writing – review & editing, Data curation. **Xianling Liu:** Supervision, Investigation. **Chunhong Hu:** Supervision, Investigation. **Yuhua Feng:** Writing – review & editing, Software, Resources, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24804.

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