ImmunoTargets and Therapy

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ORIGINAL RESEARCH

# Prognostic Significance of Circulating Immune Subset Counts in Nasopharyngeal Carcinoma

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**Purpose:** This study aimed to assess the prognostic value of circulating immune cells in newly diagnosed, non-metastatic nasopharyngeal carcinoma (NPC) and to develop a nomogram combining immune cell counts with clinical characteristics.

**Methods:** In this retrospective study, patients with non-metastatic NPC treated between January 2015 and December 2018 were included. Circulating immune cell subtypes were measured using cellular immunochip technology. Survival outcomes were assessed using Kaplan–Meier analysis, and independent prognostic factors were identified through multivariate analysis (MVA). A prognostic nomogram was constructed and evaluated using Harrell's concordance index (C-index).

**Results:** A total of 459 patients were included, with a median follow-up of 62 months. Optimal cutoff values for CD4+ T cells (420 cells/μL), CD8+ T cells (430 cells/μL), CD3+ T cells (1100 cells/μL), and CD4/CD8 ratio (1.00) were determined using X-tile. Higher levels of CD4+ T cells (78.6% vs 64.2%, $p < 0.001$), CD8+ T cells (77.5% vs 71.4%, $p = 0.113$), CD3+ T cells (83.1% vs 70.0%, $p = 0.003$), and CD4/CD8 ratio (77.6% vs 60.0%, $p = 0.001$) were associated with better 5-year progression-free survival. MVA confirmed high CD4/CD8 ratio and CD3+ T cell count as independent prognostic factors. The nomogram combining CD3+ T cells, CD4/CD8 ratio, and N classification showed superior prognostic accuracy compared with the clinical model alone (C-index: 0.686 vs 0.648, $p < 0.001$).

**Conclusion:** Circulating immune cells, particularly CD3+ T cells and CD4/CD8 ratio, are significant prognostic indicators in NPC. The proposed nomogram may help predict disease progression and support individualized treatment planning.

**Keywords:** immune cells, nasopharyngeal carcinoma, nomogram, progression-free survival

## Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the nasopharyngeal mucosal epithelium, with a high incidence in South China and Southeast Asia.[1] Due to its unique anatomical location and high sensitivity to radiation, radiotherapy is the main treatment modality for NPC.[2] Advances in radiotherapy techniques and combined chemotherapy have made non-metastatic NPC a potentially curable disease, with a 5-year overall survival (OS) rate of about 80%.[3] However, 20−30% of patients experience distant metastasis or locoregional recurrence, which are the main causes of treatment failure.[4]

The current treatment strategy for NPC is primarily guided by the 8th edition of the American Joint Committee on Cancer/ International Union Against Cancer (AJCC/UICC) TNM staging system. Although the TNM system is widely used to assess metastasis risk, there is significant heterogeneity in recurrence, metastasis, and mortality risk among patients within the same stage.[5] Therefore, identifying reliable prognostic factors to complement the TNM staging system is essential for predicting the risk of metastasis and recurrence in patients with NPC. Researchers have explored various

Received: 15 January 2025
Accepted: 3 June 2025
Published: 17 June 2025

approaches, including radiomics,[6] proteomics,[7] and transcriptomics;[8] however, their clinical application is limited by high complexity and costs. While Epstein–Barr virus (EBV) DNA serves as a valuable prognostic marker for NPC, its widespread use is restricted due to inconsistencies in sample handling and testing protocols across laboratories.[9–11]

The tumor microenvironment and immune system are increasingly recognized as crucial factors involved in cancer progression.[12] Recent studies suggest that the number and proportion of circulating lymphocyte subsets, such as CD4+, CD8+, and CD3+ T cells, can serve as prognostic markers in various cancers.[13,14] For instance, high pre-treatment CD4+ T cells counts have been associated with improved OS and progression-free survival (PFS) in multiple myeloma and prostate cancer.[15–17] Although several studies have evaluated the prognostic value of circulating lymphocyte subsets in NPC,[18–20] their results are inconsistent, partly due to variations in immunophenotyping methods and antibody use.

Therefore, this study aimed to explore the prognostic value of the number and ratio of circulating lymphocyte subsets in NPC and construct a prognostic nomogram based on circulating immune cells and clinical characteristics.

# Methods

## Patients

This study retrospectively included patients with NPC admitted to Jiangxi Provincial Cancer Hospital between January 2015 and December 2018. The inclusion criteria were: patients pathologically diagnosed with NPC without distant metastasis, treated with intensity-modulated radiotherapy (IMRT); Kanefsky Performance Status ≥70; and detection of circulating lymphocyte subsets before treatment. The exclusion criteria included synchronous malignancies, incomplete clinical data, immune system diseases, or recent use of drugs affecting immune function. Patients were re-staged according to the 8th edition of the AJCC TNM staging system. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Jiangxi Cancer Hospital (Approval No. 2024ky161). Written informed consent was obtained from all participants for the use of clinical data and residual pathological tissues prior to study initiation. All patient data were anonymized to ensure privacy and confidentiality.

## Detection of Circulating Lymphocytes

Circulating immune cell subsets were detected using cellular immunochip technology, employing antigen-antibody reactions on CD3, CD4, and CD8 antibody-coated slides, which have been previously. This method has demonstrated high concordance with flow cytometry, with previously published study reporting correlation coefficients greater than 0.99.[21] Specific antigen-expressing cells in peripheral blood samples were fixed on slides through antigen-antibody binding. Peroxidase staining was used to distinguish CD4 cells from monocytes, which express low levels of CD4 and contain myeloperoxidase (MPO), resulting in black-gray particles in the cells. In contrast, CD3, CD4, and CD8 lymphocytes do not contain MPO and, therefore, do not show these particles, enabling automated counting of the cells through a microscope. Fasting venous blood (1–2 mL) was collected from each subject and transferred into an EDTA anticoagulation tube. A volume of 20–380 μL phosphate-buffered saline (PBS) was added and mixed thoroughly. Subsequently, 5 μL of the diluted blood sample was applied to the CD3+, CD4+, and CD8+ antibody-coated regions on the slide. The slides were placed horizontally in a humid chamber and incubated for 40 minutes. Following incubation, CD3+, CD4+, and CD8+ T cells were automatically counted using a BM2000 biological microscope. Absolute cell counts per microliter were calculated based on the dilution factor. All procedures were performed in strict accordance with the manufacturer's instructions. Results were available within 2 hours of specimen processing.

## Treatments

All patients received IMRT with or without chemotherapy. Detailed IMRT planning and dose prescription have been previously published.[22] Patients with stage II–IVa disease received platinum-based chemotherapy unless contraindicated, with the regimen and schedule determined by the attending physician. Common regimens included gemcitabine plus platinum, docetaxel with platinum, and platinum plus 5-fluorouracil. Concurrent chemotherapy consisted of cisplatin (80–100 mg/m²) or other platinum agents on days 1 and 22 of radiotherapy.

## Follow-Up

Patients were followed every 3 months for the first 2 years, every 6 months from 2 to 5 years, and annually thereafter. Follow-up included physical exams, plasma EBV-DNA levels, nasopharyngoscopy, chest and abdominal CT, whole-body bone scans, and nasopharyngeal cytology biopsy if treatment failure was suspected.

## Statistical Analysis

The primary endpoint was PFS, defined as the time from diagnosis to progress or death. Secondary endpoints included OS, distant metastasis-free survival (DMFS), and locoregional relapse-free survival (RFS). Basic clinical features were compared using *t*-test, Kruskal−Wallis, chi-square, or Fisher's tests. Survival rates were analyzed with Kaplan−Meier survival curves and Log rank tests. Univariate and multivariate analyses (MVA) were conducted using the Cox proportional hazards model to estimate mortality risk. Harrell's C-index and time-dependent receiver operating characteristic curves were used to compare the predictive accuracy of nomograms for PFS, OS, and DMFS. A two-sided P-value <0.05 was considered statistically significant. Analyses were performed using R (version 3.6.1) and SPSS (version 26.0, IBM Corp, Armonk, NY).

# Results

## Patient Characteristics

Based on the inclusion and exclusion criteria, 459 patients were enrolled in this study, and Patient enrollment flow chart is shown in Figure S1. The median follow-up was 62 months (range: 52−76), and a total of 85 (18.5%) patients had distant metastases, 77 (16.8%) died, 33 (7.2%) had relapses, and 128 (27.9%) had disease progression. The 5-year PFS, OS, DMFS, and RFS were 73.1%, 85.7%, 81.5%, and 92.9%, respectively. Clinical characteristics of the cohort are shown in Table 1.

**Table 1** Clinical Characteristic of the Cohort

| Characteristic | N (%) |
|---|---|
| **Sex** | |
| Male | 339 (73.9%) |
| Female | 120 (26.1%) |
| **Age** (years) | |
| <60 | 339 (73.9%) |
| ≥60 | 120 (26.1%) |
| **EBV-DNA** (Copies/mL) | |
| Low | 315 (68.6%) |
| High | 136 (29.6%) |
| Unknown | 8 (1.8%) |
| **T categories** | |
| T1 | 22 (4.8%) |
| T2 | 51 (11.1%) |
| T3 | 211 (46%) |
| T4 | 175 (38.1%) |
| **N categories** | |
| N0 | 58 (12.6%) |
| N1 | 162 (35.3%) |
| N2 | 170 (37%) |
| N3 | 69 (15.1%) |

(*Continued*)


https://doi.org/10.2147/ITT.S516853

**Table 1** (Continued).

| Characteristic | N (%) |
|---|---|
| **Clinical stage** | |
| I | 1 (0.2%) |
| II | 23 (5%) |
| III | 210 (45.8%) |
| IV | 225 (49%) |
| **Treatment** | |
| IC+CCRT±AC | 149 (32.5%) |
| IC+RT±AC | 39 (8.5%) |
| CCRT± AC | 221 (48.1%) |
| RT alone | 50 (10.9%) |

## Dynamic Changes in the Number of Immune Cells During Treatment

There were no statistically significant differences in the number of CD4+, CD8+, and CD3+ T cells and CD4/CD8 ratio after two cycles of induction chemotherapy (IC) compared with those before treatment (all P > 0.05, Figure 1A–D). The number of CD4+, CD8+, and CD3+ T cells and CD4/CD8 ratio at the end of radiotherapy were significantly lower than those before treatment (all P < 0.001, Figure 1A–D). However, the number of CD4+, CD8+, and CD3+ T cells and CD4/CD8 ratio increased at 2−3 months post radiotherapy (all P < 0.001, Figure 1A–D) but still did not reach the pre-treatment levels (all P < 0.001, Figure 1A–D).

Similar results were found in paired samples of circulating lymphocyte subsets before treatment, after two cycles of IC, at the end of radiotherapy, and 2−3 months after the end of radiotherapy. The number of CD4+, CD8+, and CD3+ T cells and CD4/CD8 ratio decreased significantly after two cycles of IC compared with those before treatment (all $P > 0.05$, Figure S2A–D). At the end of radiotherapy, the number of CD4+, CD8+, and CD3+ T cells and CD4/CD8 ratio were significantly lower than those before treatment (all $P < 0.001$, Figure S2A–D). The number and ratio of circulating immune cells were significantly higher at 2−3 months after radiotherapy than those at the end of radiotherapy but still lower than the pre-treatment levels (all $P < 0.001$, Figure S2A–D).

## Correlation Between Circulating Immune Cells and Clinical Characteristics of Patients

By analyzing the differences in circulating lymphocytes among patients with different clinical characteristics, we found that the number of CD4+ ($P<0.001$, Figure 1E), CD8+ ($P = 0.014$, Figure 1F), and CD3+ T cells ($P < 0.001$, Figure 1G) were significantly higher in female patients than those in males. However, there was no significant difference in the CD4/CD8 ratio in patients of different sexes ($P = 0.197$, Figure 1H).

In this study, there were no significant differences in the pre-treatment circulating lymphocyte subtypes in different age groups, T classification, N classification, and clinical stages (all $P > 0.05$, Figure S3A–L, Figure 1M-P). Circulating CD4+ ($P = 0.002$, Figure 1I) and CD3+ T cells ($P = 0.023$, Figure 1K) in patients with high levels of EBV DNA were significantly lower than those in patients with low levels of EBV DNA before treatment, while there were no significant differences in CD8+ T cells ($P = 0.234$, Figure 1J) and CD4/CD8 ratio ($P = 0.094$, Figure 1L) between the two groups.

## Prognostic Value of Circulating Immune Cells Before NPC Treatment

We took PFS as the endpoint and used X-tile analysis to find the cutoff value. The optimal cutoff values for CD4+, CD8+, and CD3+ T cells and the CD4+/CD8+ ratio before treatment were 420/mL, 430/mL, 1100/mL, and 1.00, respectively, using X-tile. Kaplan−Meier survival analysis showed that the 5-year PFS of patients with high CD4+ T cells before treatment was significantly better than those with low CD4+ T cells (78.6% vs 64.2%, $P < 0.001$) (Figure 2A). Similar significant results were also found for CD3+ T cells and CD4/CD8 ratio: 5-year PFS (83.1% vs 70.0%, $P=0.003$ and 77.6% vs 60.0%, $P = 0.001$, respectively) (Figure 2C and D). There was no significant difference in 5-year PFS (77.5% vs 71.4%, $P = 0.113$) between patients with high and low circulating CD8+ T cells (Figure 2B).

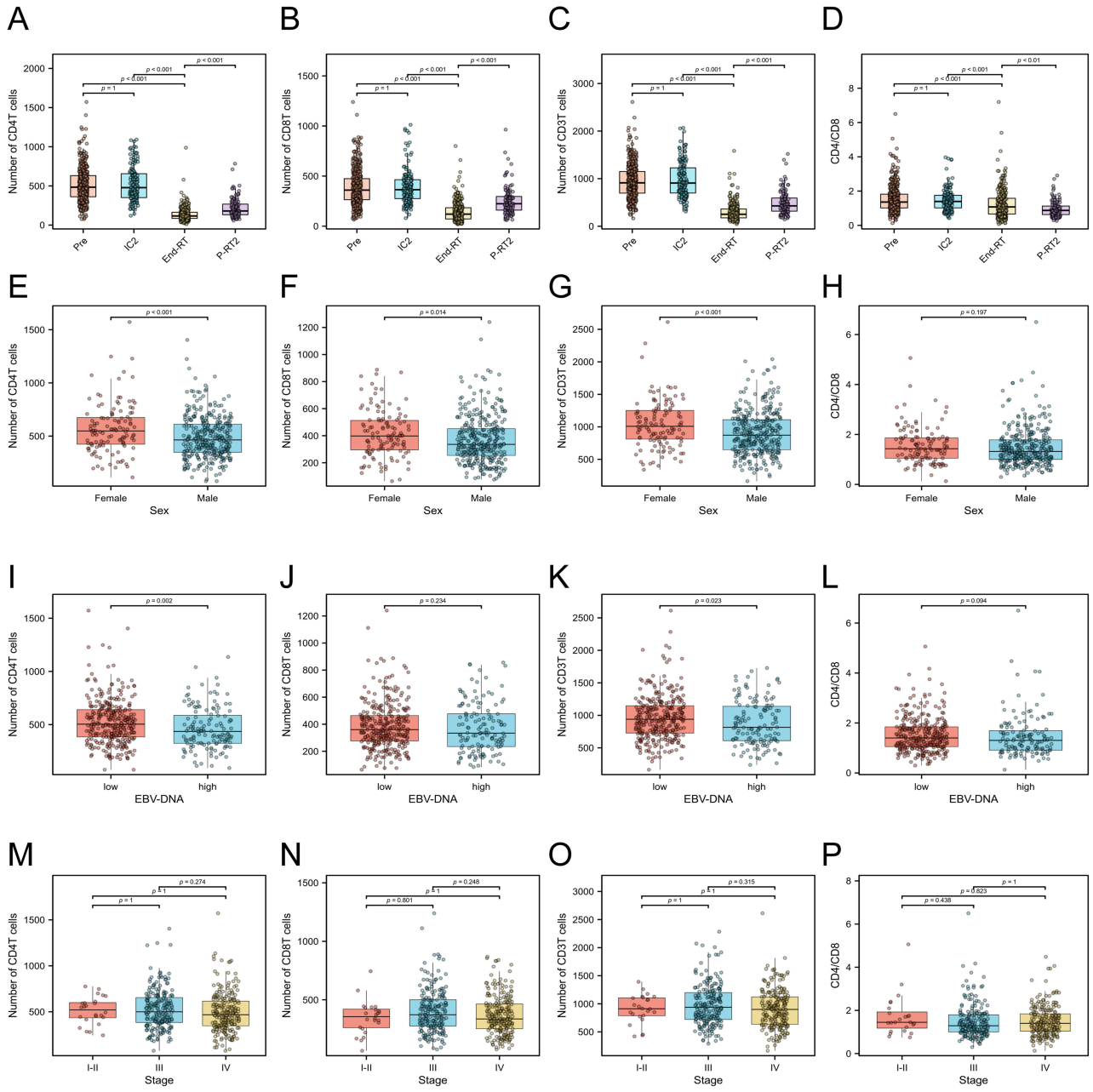


**Figure 1** Dynamic changes in the number of immune cells during treatment and correlation between circulating immune cells and clinical characteristics of patients. (**A**) Number of CD4+ T cells, (**B**) Number of CD8+ T cells, (**C**) Number of CD3+ T cells, (**D**) CD4/CD8 ratio, (**E**–**H**) Sex, (**I**–**L**) EBV-DNA, (**M**–**P**) Stage.
**Abbreviations**: pre, before treatment; IC2, after two cycles of induction chemotherapy; End-RT, at the end of radiotherapy, P-RT2, 2–3 months post radiotherapy; EBV-DNA, Epstein–Barr virus deoxyribonucleic acid (low: ≤1250 copy/mL; high: >1250 copy/mL).

Considering the significant correlation between CD3, CD8, and CD4+ cells, MVA was performed using the backward regression method. After adjusting for age, sex, T classification, N classification, concurrent chemoradiotherapy, and EBV DNA, the MVA showed that the number of high CD3+ T cells (hazard ratio [HR] = 0.45, 95% confidence interval [CI]: 0.27−0.73, $P = 0.002$) and CD4/CD8 ratio (HR = 0.55, 95% CI: 0.37−0.82, $P = 0.002$) were independent prognostic factors for PFS. Although EBV DNA (HR = 1.76, 95% CI: 1.23−2.51, $P = 0.002$) was a potential prognostic factor for NPC in univariate analysis, consistent with previously widely confirmed prognostic factors, plasma EBV DNA (HR = 1.33, 95% CI: 0.91−1.94, $P = 0.137$) was not an independent prognostic factor for PFS in MVA that included circulating immune cells (Table 2).


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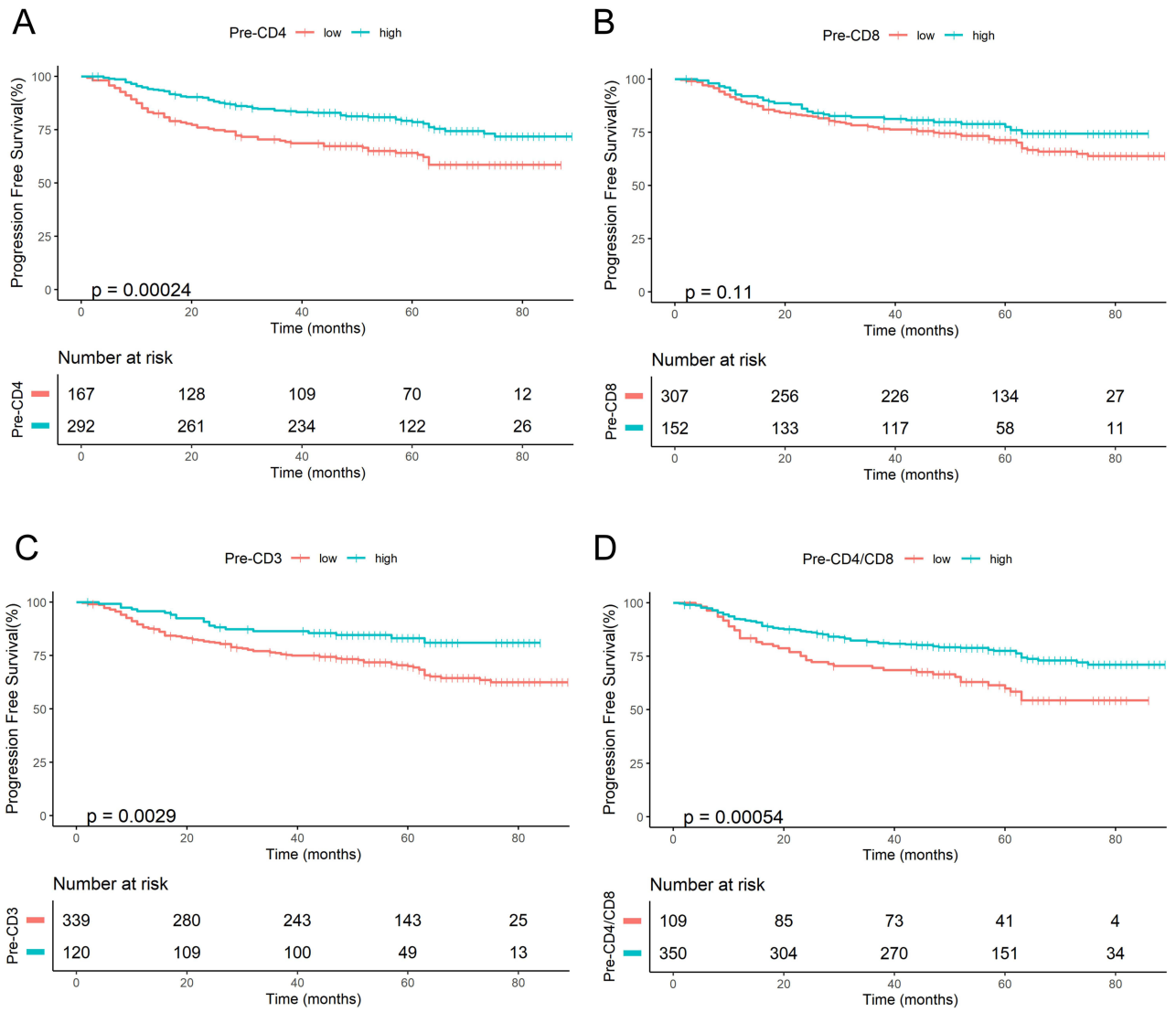


**Figure 2** Kaplan–Meier curves for progression-free survival (PFS) stratified by the number of immune cells. (**A**) Number of CD4+ T cells before treatment, (**B**) Number of CD8+ T cells before treatment, (**C**) Number of CD3+ T cells before treatment, (**D**) CD4/CD8 ratio before treatment.

## Evaluating the Prognostic Performance of the Constructed Nomogram

The nomogram (Nomogram A, Figure 3A) was constructed using the factors with statistical significance in the MVA results (CD3 + T cell count, CD4/CD8 ratio, and N category). According to the nomogram score, the patients were classified into low risk (score: 0−120), intermediate risk (score: 120−166.5), and high risk (score: 166.5−240). As the risk increased, the 5-year PFS (85.9 vs 68.7 vs 42.0%, $P < 0.001$), 5-year OS (93.3 vs 82.8 vs 68.7%, $P < 0.001$), and 5-year DMFS (91.2 vs 76.2 vs 61.1%, $P < 0.001$) decreased significantly in the three groups (Figure 3A–E).

To further confirm the prognostic performance of the nomogram with circulating immune cells (Nomogram A, Figure 3A), we constructed a nomogram without circulating immune cells (Nomogram B, Figure S4A), which included the N category, Age, and EBV DNA. The patients were divided into 3 groups (low, medium and high groups) according to the nomogram scores, and survival analysis was performed (Figure S4B–E). The prognostic performance of nomogram A was significantly better than nomogram B regarding PFS (area under the curve [AUC]: 0.690 vs 0.648, $P < 0.001$, Figure 4A; C-index: 0.686 vs 0.648, $P < 0.001$, Figure 4B).

**Table 2** Univariable Analyses and Multivariable Analyses of Circulating Immune Cell Subset and Clinical Characteristic for Progression-Free Survival (PFS)

| Variable | Univariable Analyses | | Multivariable Analyses | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| Age | | | | |
| ≤60 (*ref*) vs >60 | 1.58 (1.09–2.27) | 0.015 | 1.59 (1.08–2.34) | 0.018 |
| EBV-DNA | | | | |
| Low(*ref*) vs High | 1.76 (1.23–2.51) | 0.002 | 1.33 (0.91–1.94) | 0.137 |
| N categories | | | | |
| N0-1 (*ref*) vs.N2-3 | 1.86 (1.30–2.68) | 0.001 | 1.90 (1.30–2.78) | 0.001 |
| CCRT | | | | |
| No (*ref*) vs.Yes | 0.72 (0.48–1.09) | 0.120 | 0.71 (0.46–1.09) | 0.115 |
| CD4 T cell counts | | | | |
| ≤420 (*ref*) vs. >420 | 0.53 (0.37–0.75) | <0.001 | 0.79 (0.52–1.20) | 0.275 |
| CD8 T cell counts | | | | |
| ≤430 (*ref*) vs. >430 | 0.73 (0.49–1.08) | 0.115 | 0.84 (0.51–1.40) | 0.503 |
| CD3 T cell counts | | | | |
| ≤1100 (*ref*) vs. >1100 | 0.49 (0.31–0.80) | 0.004 | 0.45 (0.27–0.73) | 0.002 |
| CD4/CD8 | | | | |
| ≤1.00 (*ref*) vs. >1.00 | 0.53 (0.37–0.77) | 0.001 | 0.55 (0.38–0.80) | 0.002 |

## Discussion

In clinical practice, patients with the same TNM stage often exhibit significant prognostic heterogeneity, underscoring the need to identify and tailor treatment for patients with varying outcomes.[5] This study identified circulating immune cells, particularly CD3+ T cells and the CD4/CD8 ratio, as crucial prognostic factors for assessing the risk of disease progression in nasopharyngeal carcinoma. Additionally, our findings demonstrate that a nomogram incorporating circulating immune cells and clinical characteristics can effectively stratify patients by PFS, OS, and DMFS, enhancing individualized treatment strategies for patients with NPC.

We found that the CD3+ and CD4+ T cell counts were significantly associated with survival outcomes in NPC. This aligns with the findings of Li et al, who reported that higher circulating CD3+ and CD4+ T cell counts predicted better PFS and OS in patients with breast cancer.[23] Similarly, Zhang et al demonstrated that elevated circulating CD4+ lymphocytes before treatment were associated with improved PFS and OS.[24] Our study also identified the CD4/CD8 ratio as an independent prognostic factor for PFS in patients with NPC, with a higher ratio indicating a lower risk of progression, consistent with previous studies on NPC and other cancers.[14,19,25–27]

While several studies have assessed the prognostic value of circulating immune cells in NPC, they primarily focused on the percentages of immune cell subsets rather than absolute counts.[28,29] This limitation stems from using flow cytometry, which measures the proportions of specific immune subsets without providing absolute counts. Our study utilized cellular immunochip technology, which detects absolute counts of circulating lymphocyte subsets and has shown high consistency (correlation coefficients >0.99) with flow cytometry results for CD3+, CD4+, and CD8+ T cells.[21] Additionally, the immunochip method is cost-effective, simple, and suitable for primary and resource-limited healthcare settings.

A critical finding of our study is that CD3+ T cell counts and CD4/CD8 ratio may outperform plasma EBV DNA in predicting PFS for NPC. From the MVA, plasma EBV DNA was an independent prognostic factor only when circulating immune cells were excluded. When immune cells were included, EBV DNA lost its significance as an independent factor. Furthermore, the nomogram based on circulating immune T cells significantly outperformed the nomogram based on EBV DNA. Notably, we found significantly lower CD3+ and CD4+ T cell counts in patients with high EBV DNA levels, with a weak negative correlation between immune cell counts and EBV DNA load (Figure S5). This correlation was not observed with clinical stage, T stage, or N stage. This finding is somewhat surprising, as it has not been

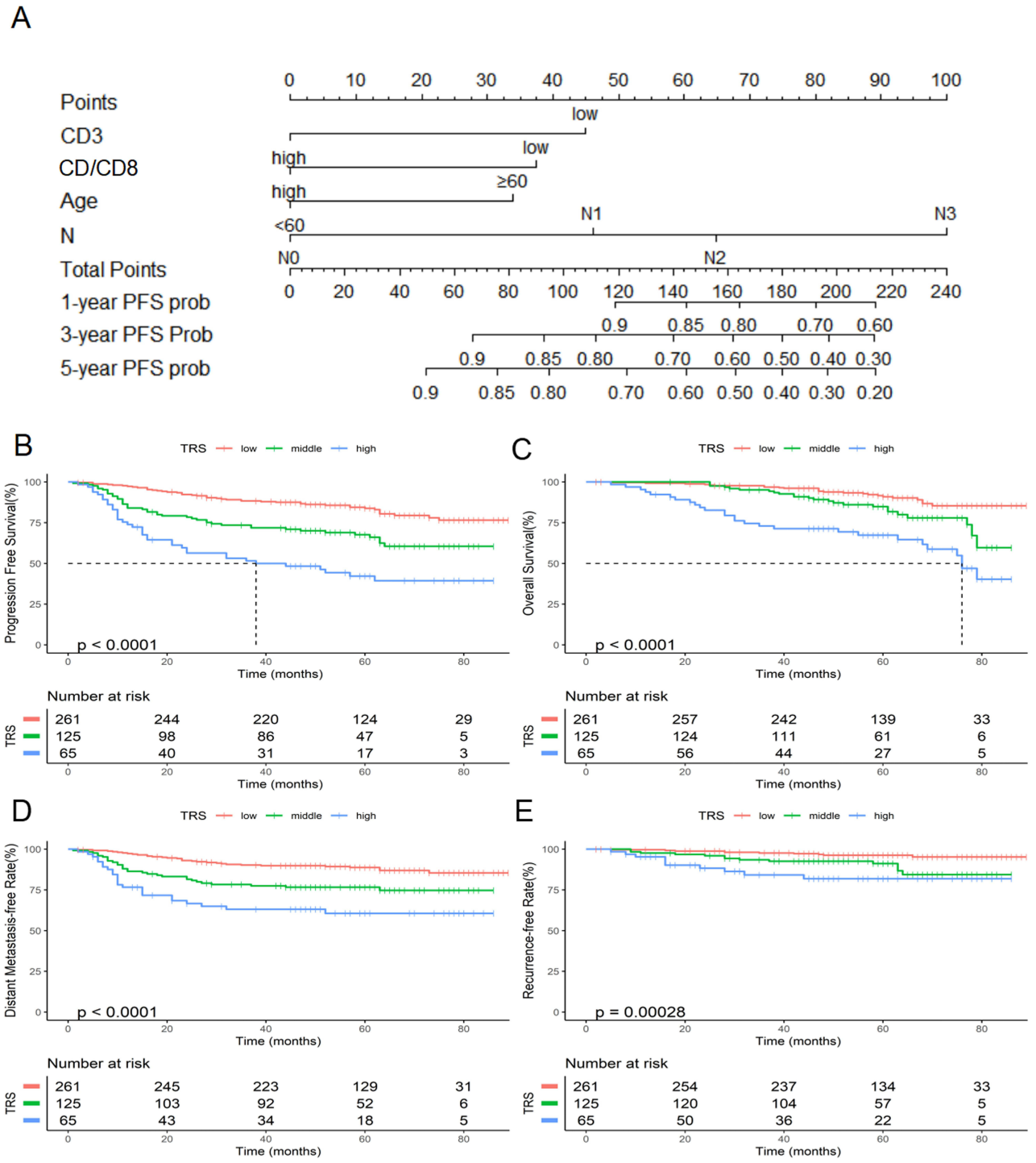


**Figure 3** Nomogram scores based on circulating CD3+ T cell counts and CD4/CD8 ratio, and Kaplan–Meier curves of progression-free survival (PFS), overall survival (OS), and distant metastasis-free survival (DMFS) for three risk groups (low, middle, and high risk) stratified by the total risk score (TRS). (**A**) Nomogram for the 1-, 3- and 5-year PFS in patients with NPC, (**B**) Kaplan–Meier curves of PFS for the three risk groups, (**C**) Kaplan–Meier curves of OS for three risk groups, (**D**) Kaplan–Meier curves of DMFS for the three risk groups, (**E**) Kaplan–Meier curves of relapse-free survival (RFS) for the three risk groups.

previously reported in NPC, indicating that circulating EBV DNA or EBV may be associated with immune escape. Although several studies have analyzed the correlation between circulating immune cell subtypes and clinical characteristics in NPC, previous studies only examined the association between the population of circulating T cell subsets detected by flow cytometry and plasma EBV-DNA load.[30–32] These limitations led to their failure to analyze and discover

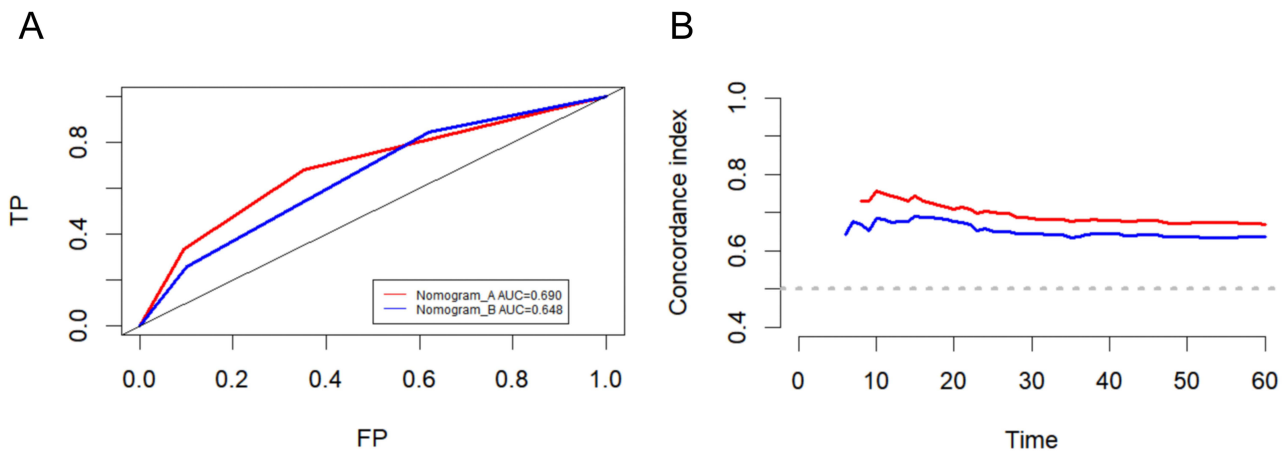


**Figure 4** Comparing the prognostic accuracy of two nomograms. (**A**) Two nomogram models predicted the receiver operating characteristic (ROC) curve of progression-free survival, (**B**) The C-index of two nomogram models to predict progress.

the relationship between absolute counts of circulating T cells and plasma EBV DNA load. This finding needs to be confirmed by larger or prospective studies, and the specific underlying mechanisms require in-depth research.

We observed that pre-treatment CD4+, CD8+, and CD3+ T cell counts were significantly higher in female patients compared to males. This trend is consistent with prior studies, including findings by Chen et al in patients with NPC[8] as well as broader evidence in both disease populations and healthy individuals.[33,34] Several biological mechanisms may underlie this difference. One proposed explanation involves X-linked immune regulatory genes, such as the lymphocyte-specific adaptor protein expressed on the X chromosome, which has been shown to promote T cell proliferation, activation, and survival.[35] In addition, sex hormones such as estrogen have been reported to enhance humoral and cellular immune responses, while androgens may exert immunosuppressive effects.[36–38] These factors may contribute to the generally stronger immune profiles observed in females.

We also observed that radiotherapy significantly reduced circulating immune cell counts, while IC did not cause substantial changes. This finding is consistent with previous studies on NPC, malignant glioma, and pancreatic cancer, which have shown that lymphocytes are highly sensitive to radiation, leading to lymphopenia.[39–41] In contrast, IC reportedly has minimal impact on circulating immune T cell subsets,[42] which is consistent with our findings.

This study had several limitations. First, its retrospective, single-center design, which may have introduced confounding factors and selection bias. Second, the study population was primarily from EBV-endemic areas where EBV-related and non-keratinizing NPC are common, limiting external validation. While our findings suggest a link between circulating EBV DNA and immune escape, the underlying mechanisms remain unclear and require further research. Moreover, this study did not explore the relationship between peripheral immune profiles and the tumor immune microenvironment. The mechanisms underlying the prognostic significance of circulating immune cells remain to be fully elucidated. Future research integrating peripheral immune markers with intratumoral immune signatures and leveraging multi-omics approaches such as transcriptomics and epigenomics may help uncover the biological interactions driving NPC progression and treatment response. Additionally, as this was a retrospective observational study, only a limited number of patients had paired immune cell data at multiple time points, which precluded robust longitudinal analyses. Thus, we were unable to assess the prognostic impact of immune cell recovery dynamics over the course of treatment. Prospective cohort studies are warranted to address this gap, and we anticipate results from our ongoing prospective trial (ClinicalTrials.gov identifier: NCT06762470) will provide further evidence on the longitudinal prognostic value of immune cell dynamics in NPC.

## Conclusions

Our study showed that circulating CD4+ and CD3+ T cell counts and CD4/CD8 ratio are important prognostic factors for NPC. The nomogram constructed based on the number of circulating CD3 cells, CD4/CD8 ratio, and clinical characteristics can more effectively distinguish NPC outcomes with satisfactory accuracy, discriminatory capability, and clinical utility. This model would enable individualized prediction of PFS, OS, and DMFS and guide personalized treatment.


https://doi.org/10.2147/ITT.S516853

## Abbreviations

EBV, Epstein–Barr virus; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival; DMFS, distant metastasis-free survival; RFS, relapse-free survival; IC induction chemotherapy.

## Declaration of Generative AI in Scientific Writing

During the preparation of this work, the authors used generative ChatGPT to assist in the drafting/editing process for language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by the Open Fund for Scientific Research of Jiangxi Cancer Hospital (2021K01, 2021J06, 2021J09, 2021J13), Jiangxi Province Key R&D Program (Key Program) (20232BBG70025), and The "Five-level Progressive" talent cultivation project of Jiangxi Cancer Hospital & Institute (WCDJ2024YQ01), Science and Technology Plan Project of Jiangxi Provincial Health Commission (202510518).

## Disclosure

All authors report no conflicts of interest in this work.

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