Prognostic analysis of peripheral blood inflammatory markers in 99 nasopharyngeal carcinoma patients with recurrence and metastasis

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Abstract
Objective: Nasopharyngeal carcinoma (NPC) is a common malignant tumor in China; furthermore, >80% of cases worldwide occur in South China. This study analyzed the use of peripheral blood inflammatory markers as prognostic factors in patients with local recurrence and distant metastasis after radiochemotherapy for NPC.

Methods: A retrospective analysis was carried out on the prognosis of 99 NPC patients with pathological and imaging diagnosis after radiochemotherapy at The First Affiliated Hospital of Nanchang University between 2010 and 2018. The Kaplan–Meier method was used to calculate survival rates, log-rank tests were used for univariate prognostic analysis, and a Cox regression model was used for multivariate prognostic analysis.

Results: Univariate analysis showed that treatment plan ($\chi^2 = 8.895, P = 0.003$), primary platelet count ($\chi^2 = 3.92, P = 0.048$), and primary lactate dehydrogenase level (LDH; $\chi^2 = 22.138, P < 0.001$) were positively correlated with survival time. Multivariable analysis showed that treatment plan (hazard ratio 2.103, 95% confidence interval 1.276 to –3.469, $P = 0.004$) and LDH (hazard ratio 2.711, 95% confidence interval 1.714–4.289, $P < 0.001$) were independent risk factors for NPC.

Conclusions: Treatment plan, primary platelet count, and primary LDH were positively correlated with survival time. Treatment plan and primary LDH level were independent risk factors for patients with recurrent or metastatic nasopharyngeal carcinoma.

KEYWORDS
metastatic, nasopharyngeal carcinoma, prognosis, recurrent

1 INTRODUCTION

Head and neck cancer (HNC) is the most common malignant tumor worldwide, ranking fifth among cancer types, with approximately 600 000 new cases and nearly 300 000 deaths annually. Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in HNC, with a large regional distribution; the latest epidemiological results show that 80% of NPC occurs in South China. The 5-year recurrence rate of NPC patients after chemoradiotherapy is nearly 15%, and the median overall survival time of patients with local recurrence or distant metastasis is just 20 months. In recent years, studies have shown the key role of systemic inflammatory response (SIR) in promoting microvessel regeneration, tumor metastasis, and tumor cell proliferation, in addition to promoting tumor cell differentiation and inhibiting host immune cell activity. Inflammatory factors in the blood, such as lymphocytes, neutrophils, monocytes, and platelets, show changes in cancer. The combinations of these inflammatory factors, such as platelet-to-lymphocyte ratio (PLR) and...
neutrophil-to-lymphocyte ratio (NLR), are also considered prognostic factors for cancers, such as breast, lung, nasopharyngeal, and gastrointestinal and colon cancer. However, the effect of inflammatory markers on the prognosis of recurrent NPC is rarely reported. Therefore, the present study collected laboratory data on peripheral blood inflammation indicators before initial NPC treatment to observe the prognostic risk factors affecting local recurrence and distant metastasis, and carried out survival analysis to provide a basis for guiding clinical treatment.

2 | METHODS

2.1 | Patient selection and general information

The present retrospective study selected patients with NPC treated at the First Affiliated Hospital of Nanchang University, Nanchang, China, between January 2010 and June 2018. The patients were diagnosed by pathology and imaging, and were evaluated for tumor recurrence or distant metastasis after chemoradiotherapy. A total of 99 NPC patients met the inclusion and exclusion criteria, including 75 men and 24 women aged 22–72 years, with a median age of 48.5 years. Based on the 2003 World Health Organization histological classification of NPC, the present study included 99 cases of non-keratinizing squamous cell carcinoma, of which 88 were differentiated and 11 were undifferentiated. Before treatment, magnetic resonance imaging, thoracoabdominal computed tomography, and bone scan were used to determine the extent of nasopharyngeal tumor infiltration and distant metastasis. After treatment, imaging examinations and clinical symptoms were used to evaluate tumor progression. This study was approved by the institutional review board at the First Affiliated Hospital of Nanchang University, and all the patients provided voluntary informed consent to participate in the study.

2.2 | Main grouping criteria

The inclusion criteria for NPC were as follows: (i) before initial treatment, patients with NPC did not receive any antineoplastic treatment and had no distant metastasis; (ii) patients were free from infection and use of drugs affecting the hematopoietic function of bone marrow before treatment and with no hematological diseases; (iii) the induced chemotherapy regimens routinely used docetaxel or paclitaxel liposomes combined with platinum regimens for chemotherapy and administration of radical radiotherapy, with a continuous treatment period without interruption; (iv) NPC was confirmed by pathology, with magnetic resonance imaging staging, and with exclusion of distant metastasis by thoracoabdominal computed tomography and bone scans; and (v) regular follow up after treatment to evaluate the therapeutic effect. The exclusion criteria were as follows: (i) patients with previous blood system diseases, infection before treatment, or antibiotic use; (ii) distant metastasis identified before the initial treatment; and (iii) poor treatment compliance and treatment interruption.

2.3 | Therapeutic methods

Among 99 patients with NPC, 27 received three-dimensional conformal radiotherapy, and 72 received intensity-modulated radiation therapy with radiotherapy doses of 66–72 Gy. A total of 91 patients were administered chemotherapy comprising cisplatin (Qilu Pharmaceutical Corporation, Jinan, China; batch number H37021358, 80 mg/m², intravenous drip on day 1–3, 3 weeks per cycle) for 1–4 cycles before radiotherapy, combined with docetaxel (Jiangxi Hengrui Pharmaceutical Corporation, Nanchang, China; batch number H20020543, 20 mg/branch, 75 mg/m², intravenous drip on day 1–d3, 3 weeks per cycle) or paclitaxel liposome (Nanjing Greenleaf Cisco Pharmaceutical Corporation, Nanjing, China; batch number H20030357, 30 mg/branch, 175 mg/m², intravenous drip on day 1, 3 weeks per cycle) as the main regimen. During chemoradiotherapy, cisplatin was administered for one or two cycles, with dosage reduction according to adverse reactions during radiotherapy. A total of 25 patients received radical radiotherapy after induction chemotherapy, whereas 67 patients received concurrent chemoradiotherapy after induction chemotherapy and seven patients received concurrent radiotherapy or concurrent chemoradiotherapy combined with adjuvant therapy.

2.4 | Follow up

The follow-up methods included telephone conversations, short message, outpatient follow up, and regular review. The follow-up schedule was the first month after the end of the treatment, once every 3 months for 2 years, once every 6 months for 2–5 years, and once every year beyond 5 years. Each follow-up examination included measurement of blood biochemical indicators, Epstein–Barr virus antibody titers, nasopharyngeal magnetic resonance imaging, thoracoabdominal computed tomography, whole-body bone scan, and so on. Disease progression was assessed by imaging or nasopharyngoscopy. The time of initial treatment and disease progression were recorded to calculate the progression-free survival (PFS). The survival time was calculated from the end of treatment, and the follow-up time was reviewed 1 month after the end of treatment. The follow-up period was 1–194 months; for a median period of 20 months, the follow-up rate was 100%.

2.5 | Selection of prognostic factors

According to the literature and the analysis of relevant clinical data, the possible factors related to the prognosis of NPC included sex, age, clinical stage, cervical lymph node metastasis, mode of radiotherapy and chemotherapy, leukocyte count, neutrophil count, lymphocyte count, hemoglobin level, lactate dehydrogenase level, PLR, NLR, and so on. The related inflammatory markers were measured within 1 week before the NPC diagnosis and were divided into two groups according to the median values. This information was collected through a unified questionnaire, a unified standard, and a unified method.
TABLE 1  Univariate analysis of progression-free survival according to clinical features

| Characteristic                | n   | <3 years | 3–5 years | >5 years | $\chi^2$ | P    |
|------------------------------|-----|---------|-----------|----------|---------|------|
| Sex                          |     |         |           |          |         |      |
| Male                         | 75  | 78.7    | 14.9      | 6.7      | 0.321   | 0.571|
| Female                       | 24  | 70.8    | 25        | 4.2      |         |      |
| Age (years)                  |     |         |           |          |         |      |
| ≤50                          | 56  | 78.6    | 21.4      | 0        | 2.79    | 0.095|
| >50                          | 43  | 74.4    | 11.6      | 14       |         |      |
| Cervical lymph nodes         |     |         |           |          |         |      |
| Non-unilateral               | 25  | 56      | 36        | 8        | 3.035   | 0.081|
| Bilateral                    | 74  | 83.8    | 10.8      | 5.4      |         |      |
| N stage                      |     |         |           |          |         |      |
| N0–N1                        | 24  | 58.3    | 33.3      | 8.3      | 2.578   | 0.108|
| N2–N3                        | 75  | 82.7    | 12        | 5.3      |         |      |
| T stage                      |     |         |           |          |         |      |
| T1–T2                        | 62  | 77.4    | 14.5      | 8.1      | 1.057   | 0.304|
| T3–T4                        | 37  | 75.7    | 21.6      | 2.7      |         |      |
| Radiotherapy dose (Gy)       |     |         |           |          |         |      |
| ≤68                          | 75  | 78.7    | 17.3      | 4        | 1.337   | 0.248|
| >68                          | 24  | 70.8    | 16.7      | 12.5     |         |      |
| Treatment plan               |     |         |           |          |         |      |
| Induced + radiotherapy       | 25  | 92      | 8         | 0        | 8.895   | 0.003|
| Induced + chemoradiotherapy  | 67  | 74.6    | 20.9      | 4.5      |         |      |
| WBC (10^9/L)                 |     |         |           |          |         |      |
| ≤6.48                        | 55  | 74.5    | 20        | 5.5      | 0.006   | 0.938|
| >6.48                        | 44  | 79.5    | 13.6      | 6.8      |         |      |
| N (10^9/L)                   |     |         |           |          |         |      |
| ≤4.14                        | 59  | 72.9    | 22        | 5.1      | 0.093   | 0.76 |
| >4.14                        | 40  | 82.5    | 10        | 7.5      |         |      |
| PLT (10^9/L)                 |     |         |           |          |         |      |
| ≤223.25                      | 54  | 70.4    | 20.4      | 3.3      | 3.92    | 0.048|
| >223.25                      | 45  | 84.4    | 13.3      | 2.2      |         |      |
| L (10^9/L)                   |     |         |           |          |         |      |
| ≤1.67                        | 49  | 73.5    | 14.3      | 12.2     | 2.259   | 0.133|
| >1.67                        | 50  | 80      | 20        | 0        |         |      |
| LDH (U/L)                    |     |         |           |          |         |      |
| ≤214.7                       | 55  | 67.3    | 21.8      | 10.9     | 22.138  | 0.000|
| >214.7                       | 44  | 88.6    | 11.4      | 0        |         |      |
| Hb (g/L)                     |     |         |           |          |         |      |
| ≤139.35                      | 52  | 76.9    | 13.5      | 9.6      | 0.199   | 0.656|
| >139.35                      | 47  | 76.6    | 21.3      | 2.1      |         |      |
| PLR                          |     |         |           |          |         |      |
| ≤143.2                       | 61  | 73.8    | 21.3      | 4.9      | 1.183   | 0.277|
| >143.2                       | 38  | 81.6%   | 10.5%     | 7.9%     |         |      |
| NLR                          |     |         |           |          |         |      |
| ≤2.71                        | 62  | 75.8%   | 21%       | 3.2%     | 0.514   | 0.473|
| >2.71                        | 37  | 78.4%   | 10.8%     | 10.8%    |         |      |

Hb, hemoglobin; L, lymphocyte count; LDH, primary lactate dehydrogenase level; N, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; WBC, white blood cells.

2.6 | Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY, USA). The Kaplan–Meier method was used to calculate survival rates, log–rank tests were used for univariate prognostic analysis, and a Cox regression model was used for multivariate prognostic analysis to identify independent prognostic factors. An $\alpha = 0.05$ (bilateral) was considered statistically different.

3 | RESULTS

3.1 | Therapeutic effects

Metastasis occurred in 99 NPC patients after treatment, including lung metastasis in 31 patients, bone metastasis in 24 patients, liver metastasis in 15 patients, local recurrence in 21 patients, more than two distant metastasis sites defined as multiple metastases in seven patients, and buttock metastasis in one patient. The time of initial treatment to the time of local recurrence or distant metastasis (PFS) was <1 year in 32 patients, 1–2 years in 26 patients, 2–3 years in 18 patients, 3–4 years in seven patients, 4–5 years in 10 patients, and >5 years in six patients.

3.2 | Univariate analysis

Table 1 shows the factors included in the univariate analysis, including baseline patient data and levels of related inflammation indicators before initial treatment. Univariate analysis was carried out by log–rank tests. Seven patients received radiotherapy or concurrent chemoradiotherapy combined with adjuvant therapy, with
different dosages of chemotherapeutics before and after radiotherapy. As shown in Figure 1a, the therapeutic regimens were divided into induction plus radiotherapy, and induction plus concurrent chemoradiotherapy groups. The median PFS of the two groups was 13.7 and 23.6 months, respectively. The difference between the two groups was statistically significant ($\chi^2 = 8.895, P = 0.003$). In Figure 1b, the patients were divided into high (>214.7 U/L) and low (<214.7 U/L) primary lactate dehydrogenase (LDH) levels based on median values before initial treatment. The median PFS of the two groups were 11.3 and 26.3 months, respectively. The prognosis of the low LDH group was significantly better than that of the high LDH group ($\chi^2 = 22.138, P < 0.001$). In Figure 1c, primary platelet count (PLT) was divided into low (<223.25 $\times 10^9$/L) and high (>223.25 $\times 10^9$/L) groups, with median PFS of 23.6 and 18 months, respectively. The prognosis of the low PLT group was significantly better than that of the high PLT group ($\chi^2 = 3.92, P = 0.048$).

### 3.3 | Multivariate analysis

Univariate analysis showed that treatment plan ($\chi^2 = 8.895, P = 0.003$), primary PLT ($\chi^2 = 3.92, P = 0.048$), and LDH ($\chi^2 = 22.138, P < 0.001$) were positively correlated with survival time. The significant prognostic factors in univariate analysis were included in multivariate Cox analysis. As shown in Table 2, the multivariable factor analysis showed treatment plan (hazard ratio 2.103, 95% confidence interval 1.276–3.469, $P = 0.004$) and LDH (hazard ratio 2.711, 95% confidence interval 1.714–4.289, $P < 0.001$) as independent risk factors for the prognosis of recurrent and metastatic NPC.

### 4 | DISCUSSION

SIR plays an important role in disease occurrence and development by inhibiting apoptosis, and promoting angiogenesis and DNA
Chemoradiotherapy is the main treatment method for NPC, and concurrent chemoradiotherapy plays an important role in the treatment of NPC by improving local control and survival rates. A retrospective study by Palazi et al. showed that improvements in radiotherapy and concurrent chemoradiotherapy could improve the local control and survival rates. Li et al. concluded that chemotherapy was a good prognostic factor for NPC survival without distant metastasis. Lin et al. reported that concurrent chemotherapy could improve local recurrence-free survival and tumor-free survival rates of stage III NPC after radiotherapy. In the present study, seven patients were administered radiotherapy or concurrent chemoradiotherapy combined with adjuvant therapy, with differences in the use and doses of chemotherapeutic drugs before and after radiotherapy; thus, just two groups were compared. The treatment regimens were divided into induction plus radiotherapy and induction plus concurrent chemoradiotherapy groups. The 3-year distant metastasis rates of the two groups were 8% and 25.4%, and the median PFS of the two groups were 13.7 and 23.6 months. The survival curves of the two groups were different, and the difference was statistically significant. The Cox multivariate analysis showed that induction plus radiotherapy was an independent prognostic factor for recurrent and metastatic nasopharyngeal carcinoma. It is concluded that concurrent chemoradiotherapy after induction chemotherapy for NPC is more effective, and can be selected according to the specific conditions and stages of patients, which is consistent with previous studies.

Previous studies have confirmed the important role of LDH in predicting the prognosis of malignant lymphoma, multiple myeloma, and malignant germ cell tumors. Hermes showed worse prognosis after treatment of small-cell lung cancer patients with high serum LDH levels and a significantly higher liver bone metastasis rate of patients with high LDH levels than that of patients with low LDH levels. Wang et al. suggested that LDH combined with PLT and neuron-specific enolase could be used to evaluate the prognosis of extensive small-cell lung cancer. According to the median serum LDH value before initial treatment, the present study divided patients into high and low LDH groups. The 3-year distant metastasis rate and median PFS in the low LDH group were significantly better than those in the high LDH group. The Cox multivariate analysis showed that low LDH was an independent predictor of NPC recurrence and metastasis. Therefore, we preliminarily concluded that serum LDH level had predictive value for NPC prognosis. However, as this was a retrospective study with limited samples and prone to selective bias, future randomized, large-scale, and prospective clinical studies are warranted.

Platelets are multifunctional cells that participate in immune response, inflammation, allergy, tissue regeneration, and lymphangiogenesis. The most well-known role of platelets in non-hemostatic or thrombotic diseases is in cancer growth, invasion, and metastasis. Different types of cancer cells activate platelets, which promote carcinogenic and metastatic activities. The potential antineoplastic effects of antiplatelet therapy were reported in 662 patients with prostate cancer receiving radiotherapy in which the biochemical control rate (prostate-specific antigen level) of patients receiving warfarin, clopidogrel, and/or aspirin antithrombotic therapy was significantly higher than that of patients not receiving antithrombotic therapy. The effect was most prominent in patients with high-risk disease without evidence of metastasis. However, a recent retrospective, observational cohort study of clopidogrel antiplatelet therapy in 41 403 newly diagnosed patients with colorectal, breast, and prostate cancer showed no significant difference in cancer-related mortality among these cancers after adjusting for confounding factors. Therefore, the prognostic effect of platelets on malignant tumors remains unclear. The present study divided patients into high and low groups based on the median PLT before treatment, and observed significantly better survival prognosis in the low PLT group than that in the high PLT group.

Regarding the relationship between PLR and NLR before treatment, and the prognosis of solid tumors, Deng et al. reported a worse prognosis of esophageal cancer patients in the high PLR group in a 2017 meta-analysis of 4621 patients in 13 studies. In terms of objective remission rate, high PLR was closely associated with tumor infiltration, lymph node metastasis, tumor size, tumor score, and phase; therefore, PLR is an important prognostic factor of esophageal cancer. However, the results of the present study showed that PLR was not related to the prognosis of NPC, which might be due to the small number of samples.

### Table 2: Multivariate analysis of progression-free survival in 99 patients with recurrent and metastatic nasopharyngeal carcinoma

| Variable                                      | B     | Wald  | P      | HR    | 95% CI Upper limit | Lower limit |
|-----------------------------------------------|-------|-------|--------|-------|--------------------|-------------|
| Treatment plan (induced + radiotherapy vs. induced + chemoradiotherapy) | 0.744 | 8.484 | 0.004 | 2.103 | 1.275              | 3.469       |
| LDH (> 214.7 vs. ≤ 214.7 U/L)                | 0.997 | 18.163| 0.000  | 2.711 | 1.714              | 4.289       |
| PLT (≤ 223.25 vs. > 223.25 x 10^9/L)         | 0.233 | 1.173 | 0.279  | 1.263 | 0.828              | 1.926       |

CI, confidence interval; HR, hazard ratio; LDH, primary lactate dehydrogenase level; PLT, platelet count.
included in this study and its retrospective design. A meta-analysis of NLR-predicting prognostic risk factors for lung cancer by Zhao et al. included 7054 patients in 22 studies. They reported superior PFS and overall survival in the low NLR compared with those in the high NLR group. Therefore, NLR was considered an independent risk factor for NPC. Song et al. evaluated 1990 patients with gastric cancer with a median follow-up period of 37 months. The total survival rate in the high NLR (>2.1) group was significantly lower than that in the low NLR (<2.1) group. There was a significant difference in predicting gastric cancer survival. The present study divided patients into high and low groups based on the median NLR, and observed no significant difference between the two groups. However, the small sample size might have affected these findings.

Previous studies with large numbers of samples have shown the correlation between inflammatory markers and cancer. Inflammatory cells and mediators might produce microenvironments that affect tumor growth, progression, angiogenesis, and metastasis. The present relation between inflammatory markers and cancer. Inflammatory cells have affected these findings. Weiguo Gu et al. included 23 patients in 22 studies. They reported superior PFS for NPC. Song et al. evaluated 1990 patients with gastric cancer with a median follow-up period of 37 months. The total survival rate in the high NLR (≥2.1) group was significantly lower than that in the low NLR (<2.1) group. There was a significant difference in predicting gastric cancer survival. The present study divided patients into high and low groups based on the median NLR, and observed no significant difference between the two groups. However, the small sample size might have affected these findings.

Previous studies with large numbers of samples have shown the correlation between inflammatory markers and cancer. Inflammatory cells and mediators might produce microenvironments that affect tumor growth, progression, angiogenesis, and metastasis. The present study divided levels of related inflammatory markers into high and low groups, and analyzed their univariate and multivariate prognosis. The final results showed no significant difference in predicting the risk of recurrence and metastasis of NPC between NLR, PLR, and neutrophil count. Because the number of patients who might be included was small and selection bias was possible, it was difficult to separate the survival curves of the two groups; therefore, studies with larger sample sizes are required to provide additional evidence for clinical guidance of NPC treatment. The correlation between SIR and various cancers suggests that the treatment of abnormal inflammation might prevent and treat cancer, and is a simple and easy monitoring index to ultimately guide clinical treatment.

CONFLICT OF INTEREST

The authors declare that they have read the article and there are no competing interests.

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How to cite this article: Gu W, Yu F, Mao Q, Qiu F. Prognostic analysis of peripheral blood inflammatory markers in 99 nasopharyngeal carcinoma patients with recurrence and metastasis. Prec Radiat Oncol. 2020;4:18–24. https://doi.org/10.1002/pro6.1084