


The value of hemoglobin-to-red blood cell distribution width ratio (Hb/RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) for the diagnosis of nasopharyngeal cancer

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Abstract

The clinical significance of hemoglobin-to-red blood cell distribution width (Hb/RDW) for the diagnosis of nasopharyngeal cancer (NPC) has not been reported yet. This study aimed to evaluate the value of preoperative Hb/RDW, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) for the diagnosis of NPC.

A total of 180 NPC patients (NPC group) and 149 healthy subjects (control group) were recruited to assess the value of Hb/RDW, NLR, and PLR for the diagnosis of NPC.

It was noted that NLR and PLR were significantly higher in the NPC group than those in the control group ($P < .001$); however, Hb/RDW was lower in the NPC group compared with that in the control group ($P < .001$). NLR was also remarkably different between patients of stage I+II and those of stage III+IV ($P = .043$), and that was different in patients with lymph node metastases or not ($P = .030$). Besides, PLR was significantly different in patients with serosal invasion or not ($P = .031$). In receiver operating characteristic curve, compared with Hb/RDW alone (sensitivity, 66.67%; specificity, 85.23%), the sensitivity (67.78%, 72.78%) and specificity (89.62%, 90.6%) of Hb/RDW with NLR and PLR were both increased. Furthermore, Hb/RDW combined with NLR area under the ROC (AUC), 0.824; 95% confidence interval (CI): 0.779–0.864, $P = .0080$ or PLR (AUC: 0.851, 95% CI: 0.808–0.888, $P = .0002$) had a greater AUC value for the diagnosis of NPC compared with Hb/RDW alone (AUC: 0.781, 95% CI: 0.732–0.824).

Hb/RDW can be used as a valuable indicator for auxiliary diagnosis of NPC. Preoperative Hb/RDW combined with NLR or PLR is of great significance in the auxiliary diagnosis and pathological staging of NPC.

Abbreviations: 95% CI = 95% confidence interval, AUC = area under the receiver operating characteristic (ROC) curve, Hb/RDW = hemoglobin/red cell distribution width (Hb/RDW), NLR = neutrophil-to-lymphocyte, NPC = nasopharyngeal cancer, PLR = platelet-to-lymphocyte ratio.

Keywords: hemoglobin-to-red blood cell distribution width, nasopharyngeal cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

1. Introduction

Nasopharyngeal cancer (NPC) is a common malignant tumor of the nasopharynx in southern China and Southeast Asia. Its

incidence ranks the first in head and neck cancer, especially in Guangdong, with the incidence of 20 to 30 patients per 100,000 people.^[1–4] NPC is highly metastatic and invasive, while it is sensitive to both chemotherapy and radiotherapy. In

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ZL and XZ contributed equally to this work.

The study was approved by the Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences. All the participants gave written informed consent.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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China, about 60,600 new cases are annually diagnosed as NPC, of which 34,100 patients with NPC pass away.^[5] Due to the clinical heterogeneity of NPC, early diagnosis of NPC is a main challenge in the majority of patients. Although new methods for early diagnosis of NPC have been presented, the majority of cases are diagnosed at late stage. Symptoms of NPC are gradually worsen, and about one-fifth of the patients may develop local recurrence or distant metastasis.^[6] Therefore, searching for more credible indicators has become a hot spot in clinical diagnosis of NPC. In recent years, a significant progress has been made in the study of hematological markers for prognosis of different tumors.^[7,8] The hematological indices have been widely used as indicators for prognosis, which are highly reproducible and cost-effective for clinical use.^[9,10] This study aimed to investigate the clinical significance of hemoglobin-to-red cell distribution width ratio (Hb/RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in the diagnosis of NPC. It is noteworthy that we, for the first time, used the above-mentioned indicators for the diagnosis of NPC.

2. Patients and methods

2.1. Patients

The medical records of 180 patients (165 (91.67%) were males; mean age, 54.53 ± 11.05 years old), who were pathologically diagnosed as NPC in our hospital between December 2010 and September 2019, were retrospectively reviewed. Exclusion criteria: previous treatment; other malignant tumors; multiple infections; blood disorders; anemia; diabetes mellitus; acute and chronic infectious diseases. Additionally, 149 healthy subjects (139 (93.29%) were male; mean age, 53.65 ± 10.44 years old) were included in control group. The study protocol was approved by the Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences (Nanning, China). All the participants gave written informed consent.

2.2. Methods

Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. Hematology test included measurement of the levels of hemoglobin (Hb), hematocrit, plateletcrit, RDW, neutrophil, lymphocyte, and platelets using the Sysmex XN-9000 hematology analyzer (Sysmex Corp, Kobe, Japan) for 30 minutes after the blood draw was completed. All the patients with NPC were clinically staged in accordance with the 7th edition of the American Joint Committee on Cancer tumor, node, metastasis (TNM) staging manual.

2.3. Statistical analysis

The statistical analysis was undertaken using SPSS19.0 software (IBM, Armonk, NY). The normally distributed data were presented as mean \pm standard deviation, and the categorical data were expressed as percentage. The Tukey test was employed to evaluate the differences between groups. Pearson correlation coefficient was used to analyze the correlation between variables in NPC group. In addition, MedCalc 15.0 software was found to be helpful to calculate sensitivity and specificity, and draw ROC curves. $P < .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients with NPC and healthy controls

In short, 180 patients with NPC (165 (91.67%) males) with a mean age of 54.53 ± 11.05 years old, and 149 healthy controls (139 (93.29%) males) with a mean age of 53.65 ± 10.44 years old were included in this study. There was no marked difference in sex and age between the 2 groups ($P = .581$, $P = .460$, respectively).

Results of analysis of differences in laboratory variables between the NPC group and control group are presented in Table 1, and there were significant differences in Hb, hematocrit, Hb/RDW, plateletcrit, RDW, NLR, and PLR between the 2 groups ($P < .05$). It also was found that NLR and PLR were significantly higher in NPC group than those in control group ($P < .001$, Fig. 1, A and B). However, Hb/RDW was noticeably lower in the NPC group compared with that in the control group ($P < .001$, Fig. 1C).

3.2. NLR and PLR in patients with NPC

The values of NLR and PLR in NPC group are shown in Table 2. It was found that NLR was markedly different between stage I+II and stage III+IV ($P = .043$). In addition, the value of NLR increased from early to late stages ($P = .043$, Fig. 2A), and it was significantly different in patients with lymph node metastases or not ($P = .030$, Fig. 2B). Moreover, PLR was significantly different in patients with serosal invasion or not ($P = .031$, Fig. 2C).

3.3. Correlation analysis of NLR, PLR, and Hb/RDW in patients with NPC

Results of correlation analysis of NLR, PLR, and Hb/RDW in patients with NPC are presented in Table 3. It was noted that Hb/RDW was negatively correlated with NLR and PLR ($P = 0.039$, $r = -0.154$); NLR was positively correlated with TNM stage ($P = .043$, $r = 0.151$), and lymph node metastasis ($P = .030$, $r = 0.162$), and negatively correlated with distant metastasis ($P = .002$, $r = -0.232$). Besides, PLR was positively correlated with serosal invasion ($P = .031$, $r = 0.161$), and negatively correlated with distant metastasis ($P = 0.002$, $r = -0.227$).

Table 1
Comparing demographic and experimental variables between patients with nasopharyngeal cancer and healthy controls.

Indicators	Nasopharyngeal cancer	Healthy controls	P
Number	180	149	
Age, yrs	54.53 ± 11.05	53.65 ± 10.44	.460
Sex, male: female	165:15	139:10	.581
Hemoglobin, g/L	133.00 ± 14.95	150.21 ± 6.34	<.001
Hematocrit	0.41 ± 0.04	0.45 ± 0.02	<.001
Plateletcrit	0.23 ± 0.06	0.19 ± 0.03	<.001
RDW, %	0.14 ± 0.02	0.13 ± 0.01	.003
Hb/RDW	977.68 ± 168.79	1121.41 ± 78.68	<.001
NLR	2.99 ± 2.11	1.81 ± 0.83	<.001
PLR	159.54 ± 82.71	98.28 ± 47.78	<.001

Data are expressed as mean \pm standard deviation (SD).

P value was determined by the Turkey test.

Hb/RDW = hemoglobin-to-red cell distribution width ratio (Hb/RDW), NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red blood cell distribution width.

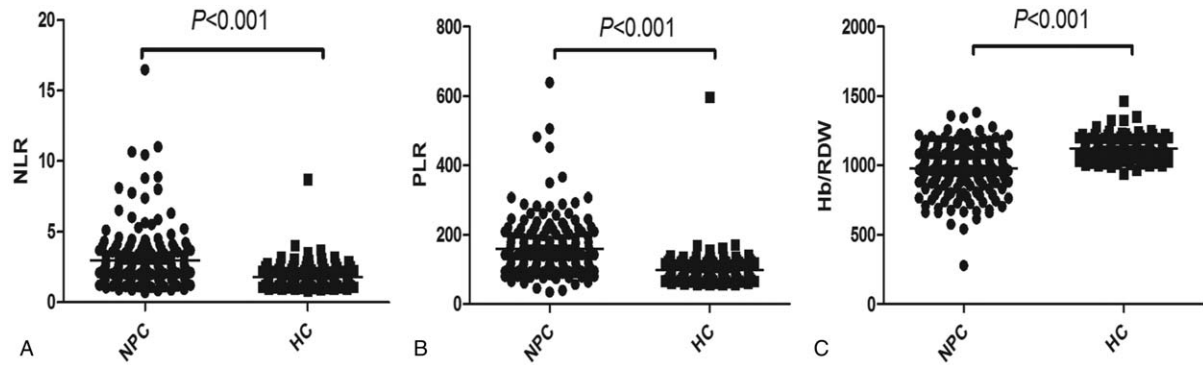


Figure 1. Values of NLR, PLR, and Hb/RDW in the NPC group and HC group. A, NLR in NPC group and HC group. B, PLR in NPC group and HC group. C, Hb/RDW in NPC group and HC group. Hb/RDW = hemoglobin-to-red cell distribution width ratio, HC = healthy controls, NLR = neutrophil-to-lymphocyte ratio, NPC = nasopharyngeal cancer, PLR = platelet-to-lymphocyte ratio.

Table 2
Values of NLR, PLR, and Hb/RDW in 180 patients with nasopharyngeal cancer.

Indicators	N	Hb/RDW	P	NLR	P	PLR	P
Stage							
I+II	84	989.87 ± 166.42	.152	2.67 ± 1.73	.043	147.53 ± 57.28	.424
III+IV	96	967.02 ± 171.00		3.27 ± 2.37		170.05 ± 98.92	
Serosal invasion							
T ₁ +T ₂	56	1004.26 ± 142.69	.182	2.57 ± 1.68	.055	136.68 ± 50.03	.031
T ₃ +T ₄	124	965.68 ± 178.58		3.18 ± 2.26		169.87 ± 92.15	
Lymph node metastasis							
Absence	84	985.20 ± 165.48	.301	2.66 ± 1.74	.030	146.80 ± 57.40	.313
Presence	96	971.11 ± 172.23		3.28 ± 2.36		170.69 ± 98.71	
Distant metastasis							
Absence	171	983.11 ± 166.97	.065	2.98 ± 2.13	.570	158.43 ± 79.29	.745
Presence	9	874.65 ± 180.30		3.25 ± 1.81		180.71 ± 137.72	

P value was analyzed by the Kruskal–Wallis H test or the Wilcoxon rank-sum test. Hb/RDW = hemoglobin-to-red cell distribution width ratio (Hb/RDW), NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

3.4. Diagnostic efficiency of NLR, PLR, and Hb/RDW in NPC group and control group

We used the NLR, PLR, and Hb/RDW values of the 2 groups of NPC and healthy controls to draw the ROC curve and calculate the area under the curve (AUC), sensitivity, specificity, and other parameters to evaluate their significance in the diagnosis of NPC.

The diagnostic efficiency of Hb/RDW combined with NLR or PLR in NPC group is shown in Table 4. The sensitivity (66.67%) of Hb/RDW and the specificity (89.28%) of PLR for the diagnosis of NPC were both the highest. Compared with Hb/RDW alone (sensitivity: 66.67%; specificity: 85.23%), the sensitivity (67.78%, 72.78%) and specificity (89.62%, 90.6%)

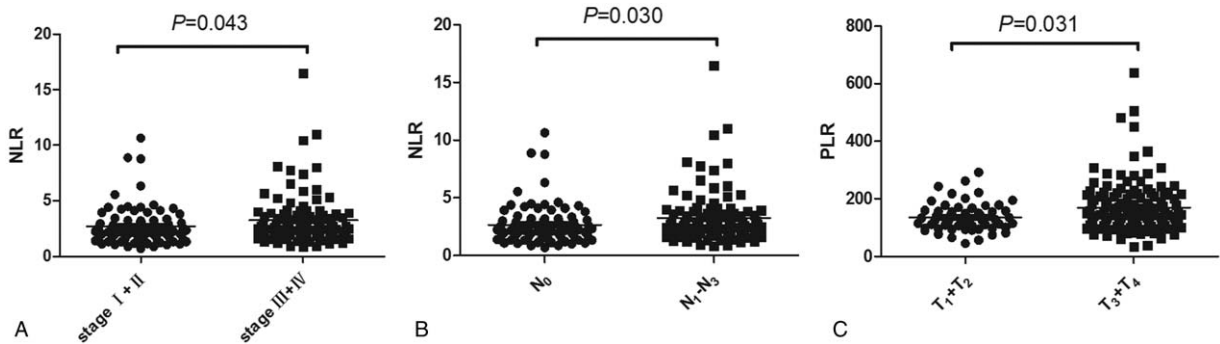


Figure 2. NLR and PLR in patients with nasopharyngeal cancer. A, NLR in different stages. B, NLR in different lymph node metastases. C, PLR in different serosal invasion. NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

Table 3**Correlation analysis of experimental indicators of 180 patients with nasopharyngeal cancer.**

Indicators	Hb/RDW (P/r)	NLR (P/r)	PLR (P/r)
Hb/RDW	*	0.039/−0.154	0.039/−0.154
NLR	0.039/−0.154	*	0.000/0.704
PLR	0.039/−0.154	0.000/0.704	*
Stage	0.152/−0.107	0.043/0.151	0.425/0.060
Serosal invasion	0.184/−0.100	0.055/0.143	0.031/0.161
Lymph node metastasis	0.302/−0.077	0.030/0.162	0.314/0.075
Distant metastasis	0.064/−0.138	0.002/−0.232	0.002/−0.227

P value was calculated by the Pearson or Spearman correlation analysis. The r value indicates the degree of correlation between the two related indicators.

Hb/RDW = hemoglobin-to-red cell distribution width ratio (Hb/RDW), NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

* Indicates that there is no correlation between the 2 indicators.

Table 4**Diagnostic efficiency of NLR, PLR, and Hb/RDW in patients with nasopharyngeal cancer and healthy controls.**

Indicators	Younder index	Sensitivity	Specificity	AUC	95% CI
NLR	0.3975	60.56	79.19	0.734	0.683–0.781
PLR	0.5016	58.89	89.28	0.809	0.763–0.850
Hb/RDW	0.5190	66.67	85.23	0.781	0.732–0.824
NLR+Hb/RDW	0.5704	67.78	89.26	0.824	0.779–0.864
PLR+Hb/RDW	0.6338	72.78	90.60	0.851	0.808–0.888

AUC = area under the receiver operating characteristic (ROC) curve, 95% CI = 95% confidence interval, Hb/RDW = hemoglobin-to-red cell distribution width ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

of Hb/RDW combined with NLR and PLR, which were used for the diagnosis of NPC, respectively, were separately increased. In other words, compared with the Hb/RDW indicator alone, the true positive rate and true negative rate of Hb/RDW combined with NLR and PLR used to diagnose NPC increased respectively. Therefore, the probability of missed diagnosis and misdiagnosis

is reduced. Furthermore, Hb/RDW combined with NLR (AUC: 0.824, 95% confidence interval [CI]: 0.779–0.864, $P = .0080$) or PLR (AUC: 0.851, 95% CI: 0.808–0.888, $P = .0002$) had a greater AUC value for the diagnosis of NPC compared with Hb/RDW alone (AUC: 0.781, 95% CI: 0.732–0.824, Fig. 3).

4. Discussion

NPC is a common cancer in southern China, seriously endangering human health. Hence, exploration of further reliable diagnostic indicators is highly significant to improve the diagnosis of NPC. Recent studies demonstrated that chronic inflammation is one of the biological characteristics of tumors, and inflammation is associated with the development of NPC.^[11–13] NLR and PLR were previously found as indicators of inflammation for the diagnosis or prognosis of NPC.^[14] Liao et al^[15] studied the influence of NLR elevation on the prognosis of patients with NPC. Yang et al^[16] found that high levels of PLR were associated with poor prognosis of NPC. The mechanism of NPC influenced by NLR and PLR may be that systemic inflammatory responses stimulate tumor metastasis via promoting angiogenesis and inhibiting apoptosis. Lymphocytes are immune cells found in the blood and lymph tissues, and T and B lymphocytes are the 2 main types. It is well known that tumor-infiltrating lymphocytes in tumors can attack and eradicate tumor cells in the cancer patients. Inflammatory chemokines are mainly produced in nonlymphoid organs and primarily affect cells of the innate immune system, while they may influence different types of effector and memory lymphocytes.^[17] Platelets, as a key source of circulating angiogenesis-related proteins, can regulate tumor cell growth and angiogenesis, thereby accelerating reproduction and metastasis of tumor cells.^[18,19]

In the present study, the values of NLR and PLR in the NPC group were significantly higher than those in the control group.

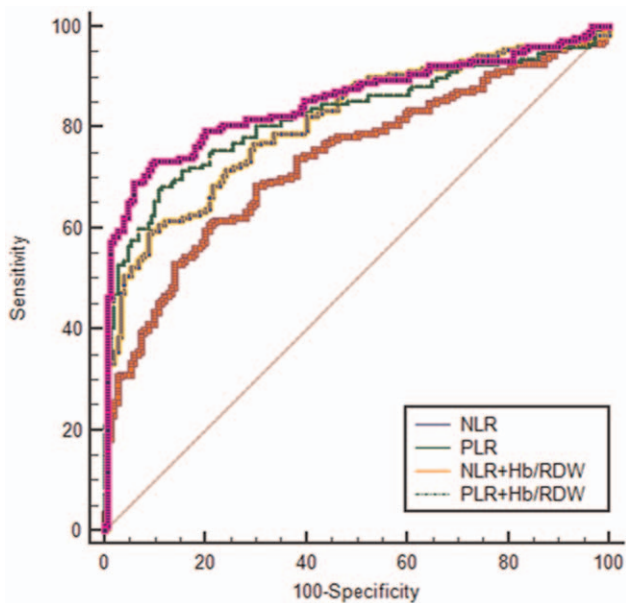


Figure 3. Combination of NLR, PLR, and Hb/RDW for the diagnosis of nasopharyngeal cancer. Hb/RDW = hemoglobin-to-red cell distribution width ratio, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

NLR was found to be negatively correlated with distant metastasis ($P=.002$, $r=-0.232$), while it was positively correlated with lymph node metastasis ($P=.030$, $r=0.162$), and TNM stage ($P=.043$, $r=0.151$), which appeared as an appropriate marker of disease severity, as its value was markedly elevated with worsening of NPC. Additionally, PLR was negatively correlated with distant metastasis ($P=.002$, $r=-0.227$), whereas it was positively correlated with serosal invasion ($P=.031$, $r=0.161$). The above-mentioned results indicated that NLR and PLR are closely associated with the clinicopathological characteristics of NPC patients, demonstrating that these 2 indicators can guide the clinical pathological staging of NPC.

To our knowledge, anemia is a common complication of myelosuppressive chemotherapy that results in a decreased functional capacity and quality of life for cancer patients. Anemia can be caused by blood loss, decreased red blood cell production, and increased red blood cell breakdown. Hb is taken as a diagnostic indicator of anemia, and is used for the prognostic evaluation of lung cancer patients.^[20] However, RDW is an indicator of the type of anemia, which is associated with the aggressiveness of advanced tumors,^[14,21,22] and is used for differential diagnosis of tumors as well.^[23] High values of RDW were correlated with advanced tumor stage and invasiveness in patients with non-small cell lung cancer^[14] and kidney cancer.^[22] It has been reported that low levels of Hb may accelerate tumor angiogenesis by causing hypoxia.^[24–26] Additionally, a low Hb level is a known prognostic marker for patients with oral squamous cell carcinoma.^[27] In recent years, different studies demonstrated that Hb/RDW is associated with survival of patients with advanced non-small cell lung cancer,^[14] and can be used as a marker for prognosis of esophageal cancer as well.^[28] Different studies reported that Hb/RDW presents further reliable information compared separately with Hb and RDW, eliminating potential bias. The results of the present study showed that although there was no correlation between Hb/RDW and TNM stage of NPC, the mean Hb/RDW in the NPC group was significantly lower than that in the control group. Moreover, Hb/RDW was found to be negatively correlated with NLR and PLR ($P=.039$, $r=-0.154$).

According to the results of the ROC curve analysis, Hb/RDW had the highest sensitivity for the diagnosis of NPC, and PLR had the highest specificity for the diagnosis of NPC. Compared with Hb/RDW alone, sensitivity and specificity were increased when Hb/RDW was combined with NLR or PLR for the diagnosis of NPC, respectively. In addition, Hb/RDW combined with NLR or PLR led to a greater AUC for the diagnosis of NPC compared with Hb/RDW alone, demonstrating that Hb/RDW in combination with NLR or PLR can be used for the auxiliary diagnosis of NPC. A combined detection approach improves the specificity and sensitivity, thereby elevating the diagnostic value of NPC. However, further large-scale prospective studies need to be conducted to elucidate the underlying mechanism.

In summary, Hb/RDW combined with NLR or PLR may be associated with a higher sensitivity and specificity for diagnosis of NPC. However, there are a number of deficiencies that need to be elucidated by further conducting large sample studies with longer duration of follow-up. This is the first study that Hb/RDW is used for the diagnosis of NPC, and NLR and PLR combined with Hb/RDW have higher efficiency for the auxiliary diagnosis of NPC.

5. Conclusions

Hb/RDW can be used as a valuable indicator for auxiliary diagnosis of NPC. Preoperative Hb/RDW combined with NLR or PLR is of great significance in the auxiliary diagnosis and pathological staging of NPC.

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Author contributions

LZY and ZX collated study data, assisted with the study data analysis, and wrote the manuscript. LZY, ZX, and LY conceived the idea and designed the study. CYY carried out the statistical analysis and interpreted the results. YYL revised the manuscript. All authors reviewed the manuscript and agreed to submit.

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