EJMI

DOI: 10.14744/ejmi.2023.30252
EJMI 2023;7(3):290–295

Research Article

Relationship of the Hemoglobin/Red Cell Distribution Width Ratio and Inflammatory Biomarkers with Prognosis in Nasopharyngeal Cancer

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Abstract

Objectives: To investigate the ability of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin/red cell distribution width (Hg/RDW) ratio to predict overall survival and progression-free survival in patients with locally advanced nasopharyngeal cancer who received definitive chemoradiotherapy.

Methods: In this retrospective study, the pre-chemoradiotherapy hemogram values and progression and mortality status of 90 patients with nasopharyngeal cancer who received locally advanced definitive chemoradiotherapy were recorded.

Results: The mean overall survival of the patients was 87.1±9.6 months, and their mean progression-free survival was 21.2±2.6 months. The best diagnostic performance for the prediction of mortality and progression belonged to Hg/RDW (area under the curve (AUC): 93.5%, sensitivity: 97.5%, and specificity: 83.67%) and PLR (AUC: 92.1%, sensitivity: 91.3%, and specificity: 88.64%), respectively. When the patients were evaluated in two groups according to the low and high levels of parameters based on their cut-off values determined for the prediction of mortality, the mean survival times were found to be low in those with high NLR and PLR values, as well as in those with low Hg/RDW values.

Conclusion: Nasopharyngeal cancer is mostly diagnosed at locally advanced stage and has a poor prognosis. It is important to predict prognosis in these patients. In this study, among the biomarkers associated with systemic inflammation, Hg/RDW had the best diagnostic test performance in predicting mortality and PLR progression. Inflammatory biomarkers and the Hg/RDW ratio reflecting hypoxia may be useful in prognostic patient follow-up.

Keywords: Hemoglobin/red cell distribution width ratio, nasopharyngeal cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Cite This Article: *Yetisir AE, Buyuksimsek M, Ogul A, Cil T, Bozkurt Duman B. Relationship of the Hemoglobin/Red Cell Distribution Width Ratio and Inflammatory Biomarkers with Prognosis in Nasopharyngeal Cancer. EJMI 2023;7(3):290–295.*

The incidence of nasopharyngeal carcinoma (NPC) originating from the nasopharyngeal epithelial tissue shows distinct geographical variations. NPC is rare, with an incidence of 0.5 to 2 cases per 100.000 in the USA and Western Europe. In contrast, it is endemic in Hong-Kong and Southern China, where its annual incidence can reach 25 cases per 100.000.[1] The absence of symptoms in the early period due to its localization causes NPC to be diagnosed at a locally advanced stage in 70% of cases, leading to a poor prognosis.[2] Definitive chemoradiotherapy is applied for the treatment of locally advanced NPC.[3] The plasma Epstein-Barr virus titer is a well-known independent prognostic factor for NPC. In addition, a family history, blood group A, diabetes mellitus, an age older than 65 years, and a decreased albumin-to-globulin ratio have been associated with a poor prognosis. Identification of

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Submitted Date: May 29, 2023 **Accepted Date:** August 01, 2023 **Available Online Date:** September 19, 2023

new prognostic factors is essential to predict the clinical course of NPC. Inflammatory response is involved in different processes of cancer, such as initiation, prognosis, and metastasis. High neutrophils and platelets are associated with a poor prognosis, while a high lymphocyte count has the opposite effect. Therefore, parameters such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which evaluate the status of neutrophils, platelets, and lymphocytes, have been investigated as possible prognostic markers in many malignancies, including NPC.[2, 4] A low hemoglobin (Hg) level causes tumor hypoxia, as a result of which tumor angiogenesis and aggressiveness increase. Red cell distribution width (RDW), one of the hemogram parameters, is also used as a prognostic marker. Hemoglobin and RDW values are affected by many factors, including malignancy. The hemoglobin/RDW (Hg/RDW) ratio is used to reduce this effect. In addition to NLR and PLR, the hemoglobin/RDW ratio has also been evaluated in pancreatic cancer, head and neck cancer, lung cancer, and bladder cancer [5, 6]; however, there is no study in the literature investigating this ratio in NPC.

Biomarkers calculated using a complete blood count analysis reflect systemic inflammation status and have prognostic and predictive value in malignancies. They are easily accessible and inexpensive parameters. In the current study, we aimed to investigate the ability of NLR, PLR, and Hg/RDW to predict overall survival (OS) and progression-free survival (PFS) in patients with NPC who received locally advanced definitive chemoradiotherapy. This study is novel in terms of evaluating the Hg/RDW ratio together with NLR and PLR in NPC.

Methods

In this retrospective study, the data of 215 patients diagnosed with NPC between 2013 and 2023 were screened in Adana City Education and Research Hospital, Medical Oncology Clinic, and 90 patients who met the study criteria were included in the sample. All patients had received 70 Gray (Gy) to the primary tumor plus the involved lymph nodes, as well as 59.4 Gy and 54 Gy to the intermediate- and low-risk neck regions, concurrently with one to three cycles of cisplatin.

Age; gender; pathological subtype; stage at diagnosis; dates of diagnosis, progression, and mortality; neutrophil, platelet, lymphocyte, hemoglobin, and RDW values; and OS and PFS times were recorded for all the patients included in the study. Staging was performed according to the American Joint Committee on Cancer guidelines.

NLR was calculated by dividing the neutrophil count by the lymphocyte count; PLR by dividing the platelet count by the lymphocyte count; and Hg/RDW by dividing the Hg count by RDW.

Inclusion Criteria

1. Pathological NPC diagnosis
2. Availability of complete blood count analysis before chemoradiotherapy
3. Having had definitive chemoradiotherapy
4. Stage 2, 3, or 4a

Exclusion Criteria

1. Secondary malignancy
2. Rheumatological, immunological, or infectious diseases that could affect inflammation markers
3. Use of drugs that can affect inflammatory markers
4. Stage 1 or 4b

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v. 25.0 package program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). The Shapiro-Wilk test was used to determine whether the parameters showed a normal distribution. The sensitivity and specificity values of NLR, PLR, and Hg/RDW were calculated based on the mortality and recurrence variables, and the cut-off values of these parameters were determined by examining the area under the receiver operating characteristic (ROC) curve. The Kaplan-Meier and log-rank tests were used for survival analyses. The statistical significance level was taken as 0.05 in all tests.

The study was approved by the local ethics committee of Adana City Education and Research Hospital (approval number: 2498, date:19.04.2023).

Results

Of the 90 patients who received locally advanced definitive chemoradiotherapy, 77.8% were male. The mean age of the patients was 48.6±14.2 years. Among the histological subtypes, type 3 was the most common at a rate of 77.8%, while 78.9% of the cases were stage 3 at the time of diagnosis. The progression and mortality status and hemogram parameters of the patients are presented in Table 1.

The mean OS time of the patients was 87.1±9.6 months, and their mean PFS time was 21.2±2.6 months (Table 2).

Table 1. Characteristics of the patients with NPC

	n	%
Gender		
Male	70	77.8
Female	20	22.2
Histological subtype		
1	10	11.1
2	10	11.1
3	70	77.8
Stage		
2	13	14.4
3	71	78.9
4a	6	6.7
Progression	46	51.1
Mortality	41	45.6
	Mean±SD	**Median (min-max)**
Age	48.6±14.2	49 (18-84)
Neutrophil	4.50±1.6	4.45 (2.1-9.2)
Lymphocyte	1.85±0.6	1.9 (0.77-3.8)
Platelet	292.3±70.6	281.5 (156-459)
Hg	13.4±1.3	13.25 (10.2-16.1)
RDW	14.3±1.2	14.15 (11.9-17.8)
NLR	2.88±1.9	2.02 (1-11.5)
PLR	183.7±102.2	152.0 (54.47-518.18)
Hg/RDW	0.94±0.1	0.94 (0.59-1.24)

NPC: nasopharyngeal carcinoma; SD: standard deviation; RDW: red cell distribution width; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Hg: hemoglobin.

Table 2. Overall survival and progression-free survival of the patients

	Estimate	SE	95% CI	
			Lower	Upper
Overall survival (months)	87.1	9.6	68.3	106.0
Progression-free survival (months)	21.2	2.6	16.1	26.4

Kaplan-Meier test; CI: confidence interval; SE: standard error.

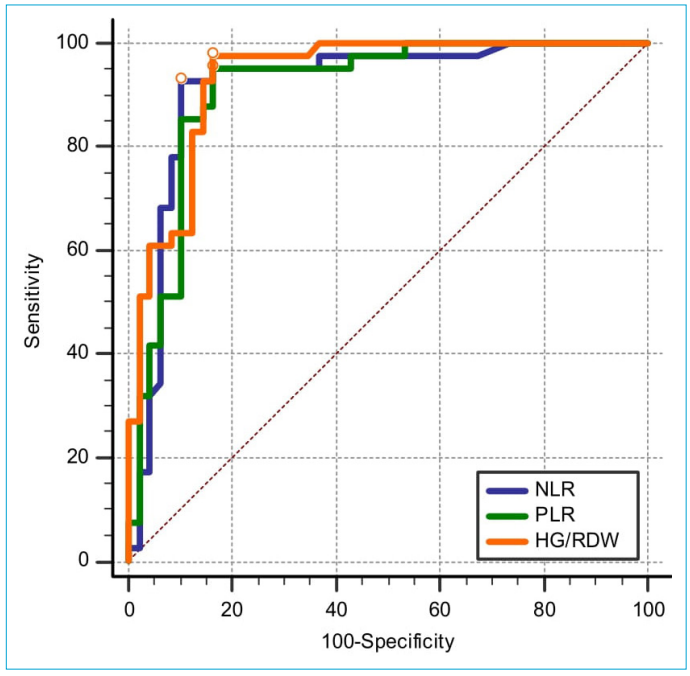

Figure 1. Receiver operating characteristic curves of NLR, PLR, and Hg/RDW in the prediction of mortality.

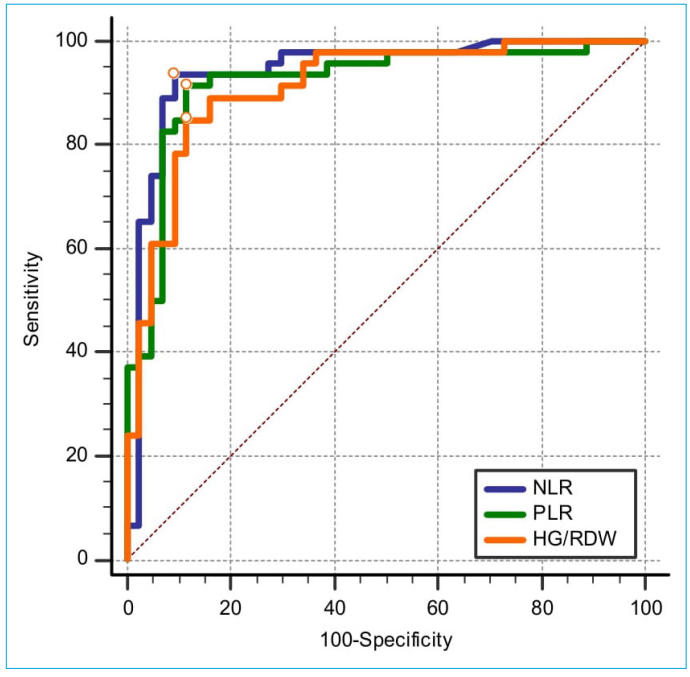

Figure 2. Receiver operating characteristic curves of NLR, PLR, and Hg/RDW in the prediction of progression.

The results of the ROC curve diagnostic test of the NLR, PLR, and Hg/RDW values in the prediction of mortality are shown in Figure 1 and Table 3. Accordingly, Hg/RDW had the best diagnostic test performance in predicting mortality, with an area under the curve (AUC) value of 93.5%, a sensitivity of 97.5%, and a specificity of 83.67%.

Figure 2 and Table 4 show the diagnostic test performance of NLR, PLR, and Hg/RDW in the prediction of progression according to the ROC curve analysis. According to the results, the best performance belonged to PLR, with an AUC value of 92.1%, a sensitivity of 91.3%, and a specificity of 88.64% in the prediction of progression.

When the patients were evaluated in two groups according to the low and high levels of parameters based on the cut-off values determined for the prediction of mortality, the mean survival times were found to be low in those with

Table 3. Diagnostic test performance of NLR, PLR, and Hg/RDW in predicting mortality

	NLR	PLR	Hg/RDW
AUC (95% CI) (%)	0.916 (0.838-0.94)	0.911 (0.833-0.961)	0.935 (0.862-0.976)
Cut-off	>2.19	>140	< 0.95
Sensitivity (95% CI) (%)	92.68 (80.1-98.5)	95.12 (83.5-99.4)	97.56 (871-99.9)
Specificity (95% CI) (%)	89.8 (77.8-96.6)	83.67 (70.3-92.7)	83.67 (70.3-92.7)
PPV (95% CI) (%)	88.4 (76.7-94.6)	83 (72-90.2)	83.3 (72.6-90.4)
NPV (95% CI) (%)	93.6 (83.1-97.8)	95.3 (84.1-98.8)	97.6 (85.5-99.7)
p	<0.001*	<0.001*	<0.001*

*p < 0.001, receiver operating characteristic curve analysis; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Hg: hemoglobin; RDW: red cell distribution width; AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

Table 4. Diagnostic test performance of NLR, PLR, and Hg/RDW in predicting progression

	NLR	PLR	Hg/RDW
AUC (95% CI) (%)	0.914 (0.871-0.980)	0.921 (0.845-0.967)	0.913 (80.35-0.962)
Cut-off	>1.94	>140	<0.92
Sensitivity (95% CI) (%)	93.48 (82.1-98.6)	91.3 (79.2-97.6)	84.78 (71.1-93.7)
Specificity (95% CI) (%)	90.91 (78.3-97.5)	88.64 (75.4-96.2)	88.64 (75.4-96.2)
PPV (95% CI) (%)	91.5 (80.8-96.5)	89.4 (78.6-95.1)	88.6 (77.2-94.7)
NPV (95% CI) (%)	93 (81.6-97.6)	90.7 (79.2-96.2)	84.8 (73.6-91.7)
p	<0.001*	<0.001*	<0.001*

*p < 0.001, receiver operating characteristic curve analysis; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Hg: hemoglobin; RDW: red cell distribution width; AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

high NLR and PLR values, as well as in those with low Hg/RDW values (p<0.001 for all) (Table 5).

Discussion

NPC is rare except in endemic areas. It is important for clinicians to predict the course of the disease since it is usually diagnosed at an advanced stage. In this study, we investigated the ability of biomarkers obtained from a complete blood count analysis, namely NLR, PLR, and Hg/RDW, to predict the PFS and OS of patients with NPC.

Table 5. Relationship between the mean survival times and investigated parameters grouped according to cut-off values

	Estimate	SE	95% CI		p
			Lower	Upper	
NLR					
Low	154.3	11.8	131.2	177.4	<0.001*
High	27.7	2.7	22.5	32.9	
PLR					
Low	157.6	11.6	134.9	180.2	<0.001*
High	28.6	2.7	23.2	33.9	
Hg/RDW					
Low	29.3	2.9	23.5	35.2	<0.001*
High	159.6	11.1	137.8	181.4	

*p < 0.001, Kaplan-Meier analysis and log-rank test; SE: standard error; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Hg: hemoglobin; RDW: red cell distribution width.

The incidence of NPC is higher in men, being two or three times higher than in women in most populations.[7] Consistent with the literature, 77.8% of our patients were male. In almost all NPC cases seen in high-incidence areas, the histological subtype is undifferentiated non-keratinized subtype (type 3), and the remainder are differentiated non-keratinized subtype (type 2), while in low-incidence areas, a significant percentage of patients with NPC have keratinized squamous cell subtype (type 1) disease.[8] In our study, when histological subtypes were examined, type 3 was the most common with a percentage of 77.8%, similar to the rates reported in high-incidence areas, while types 1 and 2 were observed equally at a rate of 11.1%. In low-risk populations, two peaks are observed in the young adult period and in the age range of 65-79 years, while in high-risk areas, it has a single peak in the age range of 45-49.[8] The mean age of our patients was 48.6 years, similar to the mean age observed in high-risk areas.

In a retrospective study evaluating 528 patients with NPC who received radiotherapy, NLR and NLR trend values were calculated before, during, and after radiotherapy, and a lower NLR trend was associated with worse PFS and

three- and five-year OS. According to the multivariate Cox regression analysis, NLR trend independently predicted three- and five-year OS.[9] In a study of 180 patients followed up with NPC in Taiwan, the prognostic effect of NLR was investigated. The cut-off value of NLR was determined to be ≥3.6, and PFS, OS, and disease-specific survival were found to be lower in patients with a high NLR. The authors concluded that a high NLR was an independent prognostic factor.[4] In another study, NLR was correlated with T stage, and NLR ≥2.92 was associated with poor five-year OS in 251 stage 2 NPC cases.[10] In a study in which NLR and PLR calculated from the intensity-adjusted pre-radiotherapy values were evaluated (n=342), the cut-off values of these parameters were found to be 2.65 and 184.91, respectively, and it was determined that the patients with high NLR and PLR had worse OS and PFS compared to those with low values.[2] In a retrospective cohort of non-metastatic NPC cases treated with intensity-module radiotherapy, an NLR greater than 3 was found to be an independent prognostic marker for poor OS.[11] In a study investigating the predictive status of preoperative Hg/RDW, NLR, and PLR for the diagnosis of NPC, 180 patients were included in the NPC group, and 149 healthy subjects were included in the control group. The NPC group was found to have statistically significantly higher NLR and PLR and statistically significantly lower Hg/RDW. The combined evaluation of Hg/RDW with NLR or PLR was found to be more valuable for the diagnosis of NPC than the evaluation of this parameter alone.[12] In another study, a low Hg/RDW ratio was found to be associated with worse event-free survival, but not OS, in patients with head and neck cancer who underwent curative surgery.[13]

In this study, it was determined that the mean OS time of the patients was 87.1±9.6 months, and their mean PFS time was 21.2±2.6 months. The predictive ability of NLR, PLR, and Hg/RDW for mortality and progression was analyzed using the ROC curve diagnostic test. It was found that Hg/RDW had the best diagnostic performance in the prediction of mortality, with the AUC, sensitivity, and specificity values being calculated to be 93.5%, 97.5%, and 83.67%, respectively. For the prediction of progression, the best diagnostic performance was observed in PLR, which had an AUC value of 92.1%, a sensitivity of 91.3%, and a specificity of 88.64%. When the patients were evaluated in two groups according to whether they had low or high values for NLR and PLR, the mean survival time was found to be lower among the patients with high NLR and PLR values and in those with low Hg/RDW values ($p<0.001$ for all).

In this study, the number of patients with different stages and histological subtypes was not sufficient to evaluate the parameters according to subgroups. Therefore, the inability to compare parameters between subgroups and the small sample size are the main limitations of the study.

In conclusion, NPC is diagnosed at a locally advanced stage and has a poor course. Tumor hypoxia and increased inflammation are other factors that worsen the prognosis. In our study, in support of this, the mean survival times were found to be lower in patients with high NLR and PLR and low Hg/RDW values. Hg/RDW and PLR showed the best diagnostic test performance in predicting mortality and progression, respectively. In the clinical setting, evaluation of these parameters in patients with NPC can contribute to the prediction of the course of the disease.

Disclosures

Ethics Committee Approval: The study was approved by the local ethics committee of Adana City Education and Research Hospital (approval number: 2498, date:19.04.2023).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.E.Y., M.B., A.O.; Design – A.E.Y., T.C., B.B.D.; Supervision – T.C., B.B.D.; Materials – A.E.Y., M.B., A.O.; Data collection &/or processing – A.E.Y., M.B., A.O.; Analysis and/or interpretation – A.E.Y., M.B., A.O., T.C. B.B.D.; Literature search – A.E.Y., M.B., A.O., T.C., B.B.D.; Writing – A.E.Y., M.B., A.O.; Critical review – A.E.Y., T.C., B.B.D.

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