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ORIGINAL ARTICLE

A prognostic parameter in advanced non-small cell lung cancer: the ratio of hemoglobin-to-red cell distribution width

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Abstract

Background This study aims to investigate the prognostic value of the ratio of hemoglobin–RDW (HRR) at diagnosis, in terms of overall survival (OS) and progression-free survival in patients with advanced non-small cell lung cancer (NSCLC).

Methods Patients with metastatic NCCLC who attended two separate medical oncology clinics between April 2013 and December 2017 were retrospectively screened. HRR was calculated as Hgb (g/dL) divided by the RDW (%). Patients were assigned to either the low HRR group or high HRR group.

Results A total of 153 patients were included in the study. The cuff-value for HRR was taken as 0.88. Among the low and high HRR groups, Glasgow prognostic scores (GPS), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and weight loss were statistically significantly different ($p < 0.05$). OS was found to be 5.6 months in the low HRR group and 13.9 months in the high HRR group ($p < 0.001$) while PFS was 5.1 months and 8.6 months in these two groups, respectively ($p < 0.001$). Univariate and multivariate analyses revealed that low HRR was an independent factor, predictive of both OS ($p = 0.03$, Hazard Ratio (HR) = 1.607, 95% CI = 1.041–2.480) and PFS ($p < 0.001$, HR = 2.635, 95% CI = 1.667–4.166) in advanced NSCLC.

Conclusion This is the first study to show that low HRR is associated with poor OS and PFS in patients with advanced NSCLC. Thus, hemoglobin and RDW which can be easily measured in routine practice may be used as a prognostic tool in these patients.

Keywords Non-small cell lung cancer · Hemoglobin · Red cell distribution width · Prognostic

Introduction

Lung cancers are the leading cause of cancer deaths, worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for > 80% of patients with newly diagnosed lung cancer and the 5-year overall survival (OS) rate is 17%, in spite of recent developments in therapeutic and diagnostic modalities [2]. Currently, management strategies for cancer focus on appropriately classifying patient according to their risks and the use of an appropriate prognostic factor to plan the next step of the treatment. Although a number of prognostic factors have been investigated in patients with NSCLC, prognostic factors other than the stage and performance status have remained controversial [3].

There may be limited number of specific tests to determine unique prognostic markers due to reasons associated with laboratory conditions or additional costs to the healthcare system. Complete blood counts (CBC) are feasible tests in routine clinical practice in cancer patients. A variety of studies and meta-analyses have been conducted to investigate the prognostic significance of complete blood count parameters in patients with lung cancer. In these studies neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume and neutrophil/monocyte ratio have been reported to be of prognostic significance [4–6].

Hemoglobin is a key CBC parameter and low hemoglobin concentrations are common in oncology diseases including lung, breast, gastric, ovary and cervical cancers [7–11]. There are studies demonstrating associations between hemoglobin concentrations and prognosis, particularly in patients with NSCLC. In these studies, low hemoglobin

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concentrations have been reported to be associated with poorer overall survival [12–14]. Another key CBC parameter, the red cell distribution width (RDW) is used to measure the variability in the size of red blood cells circulating in the peripheral blood. RDW has been investigated in oncology patients particularly after the demonstration of its prognostic significance in patients with cardiovascular [15], pancreas [16] and liver disorders [17]. Associations have been found between RDW and advanced tumor stage and invasiveness in lung, breast and kidney cancers [18–20]. Although individual prognostic significance of either hemoglobin or RDW has been demonstrated in many patients with the above-mentioned cancers, there are limited studies on hemoglobin/RDW ratio (HRR) and the significance of this ratio is not clear in lung cancers [21, 22]. Therefore, we aimed to assess potential associations between HRR and overall survival (OS) and progression-free survival (PFS) in our patients with advanced NSCLC.

Patients and methods

Patients with NSCLC attending Oncology Departments of Edirne State Hospital and Gazi University Faculty of Medicine between January 2014 and February 2018 were retrospectively assessed. Patients with histopathologically confirmed advanced NCSLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) aged over the age of 18 were included in the study. Exclusion criteria were a second primary cancer, absence of tissue sample, early-stage disease, use of targeted agents in patients with ALK/EGFR_ROS-1 positive cancers, any conditions and comorbidities (infections, inflammatory diseases, lymphoproliferative diseases, etc.) that might affect HRR or missing follow-up data.

Variables to be studied included age, sex, smoking status, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance score, weight loss (was defined as loss of more than 5 percent of usual body weight over 6 months), clinicopathological characteristics such as histological subtype, metastasis sites and laboratory data including complete blood count parameters and prior therapies. Complete blood counts were measured at diagnosis as a routine measure of clinical assessments. The ratio of hemoglobin–RDW was calculated according to the following formula: Hb (g / dL) divided by RDW (%). The median HRR was found to be 0.883 (range = 0.400–1.360). The cuff-value for HRR was taken as 0.88 and patients were divided into groups of low HHR and high HRR. In addition, Glasgow prognostic score (GPS) of each patient was calculated to assess systemic inflammatory status [23]. This study was conducted according to the principles of the Declaration of Helsinki should be included.

Data on the general health status of patients were obtained from both medical records of patients kept by the hospitals and records from central civil registry systems.

Statistical analysis

A "Statistical Package for Social Sciences" version 18 for Windows was used for all statistical analyses. A p value less than 0.05 was considered to be statistically significant. Visual (histograms, probability graphics) and analytic (the Kolmogorov–Smirnov test or the Shapiro–Wilk test) methods were used to determine if variables were normally distributed. Continuous variables were summarized as median and the Mann–Whitney U test was used for comparisons between cases and controls. The Chi-square test or Fisher's exact test was used in intergroup comparisons in terms of clinicopathological characteristics. The Kaplan–Meier method was used for survival analysis and the log-rank test was used to compare subgroups. The possible factors determined by univariate analyses were introduced with the Cox regression analysis (with backward selection) to identify independent predictors of overall survival and progression-free survival. Hazard ratios (HR) were presented along with two-sided p values and 95% confidence intervals (95% CI). Overall survival (OS) was defined as the time from advanced disease to the date to the last follow-up visit or death from any causes. Progression-free survival (PFS) is defined as the time from the date of the onset of chemotherapy (first-line chemotherapy) to disease progression or to the date of death.

Results

Patient characteristics and treatments

A total of 153 patients were included in the study. The baseline clinical and pathological characteristics of the patients are summarized in Table 1. The median age of the patients at admission was 64 years (range = 41–84 years) and 139 of the patients were male and 14 were female. 84% of patients had a history of smoking (active/ex-smoker) and 13% had a history of alcohol. 53% of the patients had comorbidities, most notably diabetes mellitus and essential hypertension. The most common histopathological subtype was adenocarcinoma and 46% of the patients had a history of weight loss at diagnosis. The most common sites of metastasis (in order) were contralateral lung (39%) and pleura (30%) and 47% of patients had 2 or more metastatic sites. The median hemoglobin concentration in the overall patient group was found to be 12.8 g/dL (range = 7.1–18.3 g/dL) and anemia was detected in 53 patients (Hgb < 11 g/dL for female patients and Hgb < 12 g/dL for male patients). The median RDW was found to be 14.4 (%) (range = 9.5–19.4%). 76% of patients in

Table 1 Demographic characteristics of the patients

Characteristics	Low HRR $N=70$ (%)	High HRR $N=83$ (%)	Total $N=153$ (%)	p value
Age (mean, years)	65.7	63.1	64.3	0.19
Gender				
Female	6 (9)	8 (10)	14 (9)	0.82
Male	64 (91)	75 (90)	139 (93)	
Smoking				
Yes	59 (84)	69 (83)	128 (83)	0.84
No	11 (16)	14 (17)	25 (16)	
Alcohol				
Yes	10 (14)	10 (12)	20 (13)	0.68
No	60 (86)	73 (88)	133 (87)	
ECOG				
0–1	35 (50)	51 (61)	86 (56)	0.15
2–4	35 (50)	32 (39)	67(44)	
Weight loss				
Yes	43 (61)	28 (34)	71 (46)	**0.001**
No	27 (39)	55 (66)	82 (54)	
Comorbidity				
Yes	40 (57)	41 (49)	81 (53)	0.33
No	30 (43)	42 (51)	72 (47)	
GPS				
0	25 (36)	58 (70)	83 (54)	**< 0.001**
1–2	45 (64)	25 (30)	70 (46)	
NLR (median)	5.4	4.0	4.3	**0.009**
PLR (median)	231	190	208	**0.02**
Histological subtype				
Adenocarcinoma	37 (53)	51 (61)	88 (57)	0.56
Squamous cell carcinoma	30 (43)	29 (35)	59 (39)	
Large cell carcinoma	3 (4)	3 (4)	6 (8)	
Location of metastases at diagnosis				
Contralateral lung	26 (37)	33 (40)	59 (39)	0.74
Liver	20 (29)	22 (27)	42 (28)	0.77
Plevra	19 (27)	27 (33)	46 (30)	0.46
Adrenal	16 (23)	22 (27)	38 (25)	0.6
Bone	21 (30)	18 (22)	39 (26)	0.24
Others	14 (20)	14 (17)	28 (18)	0.61

ECOG Eastern Cooperative Oncology Group, *GPS* Glasgow prognostic score, *HRR* hemoglobin/ red cell distribution width ratio, *HR* hazard ratio, *CI* confidence interval, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio

Statistically significant p values ($p<0.05$) are shown in bold

the overall group received first-line chemotherapy while 19% of patients received second-line chemotherapy. The most commonly used first-line chemotherapy regimen (65%) was the platinum-doublet regimen.

Clinicopathological and therapeutic characteristics in the low and High HRR groups

A total of 70 patients were included in the low HRR group and 83 patients were included in the high HRR group. We investigated potential associations between HRR and other clinicopathological characteristics in our patients with advanced NSCLC. Weight loss at diagnosis ($p=0.001$), neutrophil/lymphocyte ratio (NLR) ($p=0.009$) and platelet/lymphocyte ratio (PLR) ($p=0.02$) were higher in the low HRR group while the rate of patients who had a GPS of 0 was higher in the high HRR group (P = 0 < 001). Regarding treatment lines; 82% of patients in the high HRR group and 69% of patients in the low HRR group received first-line chemotherapy. The rate of patients receiving second-line

chemotherapy was 25% and 10% in the high HRR group and low HRR group, respectively.

Survival analysis

The median follow-up duration in the overall group was 6 months (range = 0.7–32.7 months). 107 patients died from lung cancer-related causes during the follow-up. In overall group, the median OS was 7.1 months (range = 0.7–36 months) and the median PFS was 5.3 months (range = 0.6–25 months). The median OS was 5.6 (95% CI 4.4–6.8 months) in the low HRR group and 13.9 months (95% CI 5.4–22.5 months) in the high HRR group, respectively ($p < 0.001$). The median PFS was 5.1 months (95% CI 3.3–6.9 months) in the low HRR group and 8.6 months (95% CI 4.8–12.4 months) in the high HRR group, respectively ($p < 0.001$). The Kaplan–Meier survival curves of both groups are shown in Figs. 1 and 2.

Factors affecting survival in the overall group were analyzed in a univariate analysis. Factors significantly affecting survival include a low HRR ($p < 0.001$), an ECOG performance score of 2–4 ($p < 0.001$), a GPS of 1 or 2 ($p < 0.001$), weight loss ($p < 0.001$), a median NLR of ≥4.3 ($p = 0.004$), and ≥2 metastatic sites. Although not significant, age>65 years showed a tendency towards statistical significance ($p = 0.08$). A multivariate analysis was performed with factors which were found to be significant in the univariate analysis. Independent prognostic markers which were found to be significant for a shorter overall survival included an ECOG performance score between 2

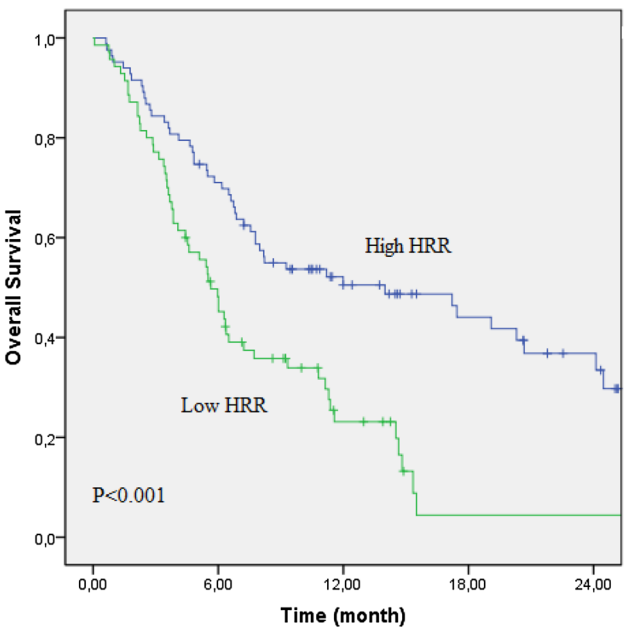

Fig. 1 Kaplan–Meier Curve for Overall Survival of Low HRR and High HRR group

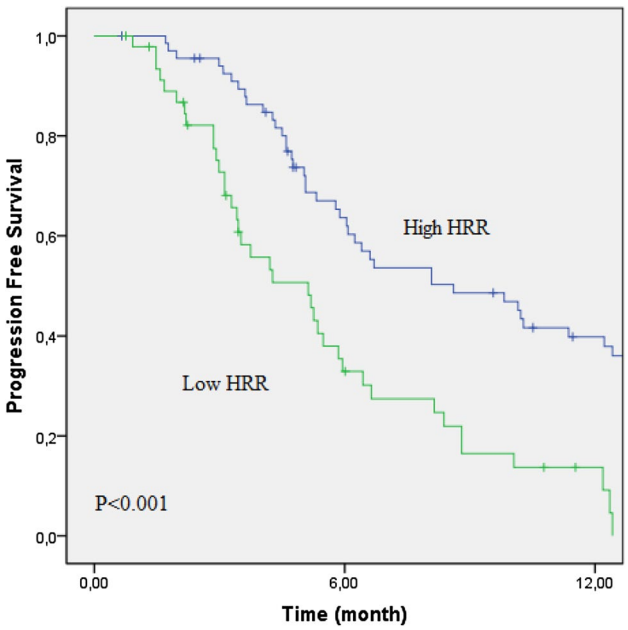

Fig. 2 Kaplan–Meier curve for progression-free survival of low HRR and High HRR group

and 4 ($p < 0.001$), weight loss ($p = 0.002$), a GPS of 1 or 2 ($p = 0.007$), a low HRR ($p = 0.03$) and ≥2 metastatic sites ($p < 0.001$) (Table 2).

A total of 115 patients received first-line chemotherapy. Factors affecting PFS in these patients were assessed by univariate and multivariate analyses (Table 3). In the univariate analysis, factors which were found to be significant were an ECOG performance score of 2–4 ($p = 0.03$), a GPS of 1–2 ($p = 0.02$), weight loss ($p = 0.01$), a low HRR ($p < 0.001$). In the multivariate analysis, only a low HRR was found to be associated with shorter PFS. ≥2 metastatic sites showed a tendency towards statistical significance both in univariate and multivariate analyses ($p = 0.07$).

Discussion

In this study, we aimed to assess the prognostic significance of HRR at diagnosis, in patients with advanced NSCLC. Study patients were assigned to the high HRR group and low HRR group based on the median HRR. Prognosis was poorer in patients with the low HRR group compared to the patients in the high HRR group. Based on the multivariate analysis of the factors which were found to be significant in the univariate analysis, OS and PFS were statistically significantly shorter in patients who had lower HRR. Therefore, HRR at diagnosis may be used as a factor predictive of survival in patients with NSCLC before the treatment.

RDW is measured in routine clinical practice to determine variations in red blood cell size and is usually used in

Table 2 Univariate and multivariate statistical analysis of overall survival

Characteristics	Number of patients *N* (%)	Univariate analysis for OS	*P* value (univariate)	Multivariate analysis
Age (median, years)				
>65	65 (42)	6.5	**0.08**	$p = 0.83$, HR = 1.044, 95% CI = 0.702–1.552
≤65	88 (58)	9.3		
Gender				
Female	14 (9)	10.8		
Male	139 (93)	7.5	0.63	
Smoking				
Yes	128 (83)	6.8	0.26	
No	25 (16)	10.8		
ECOG				
0–1	86 (56)	14.6	**< 0.001**	***p* < 0.001**, HR = 2.947, 95% CI = 1.939–4.480
2–4	67(44)	4.1		
Weight loss				
Yes	71 (46)	4.6	**< 0.001**	***p* = 0.002**, HR = 1.977, 95% CI = 1.277–3.060
No	82 (54)	14.8		
Comorbidity				
Yes	81 (53)	7.7	0.34	
No	72 (47)	7.5		
GPS				
0	83 (54)	11.9	**< 0.001**	***p* = 0.007**, HR = 1.767, 95% CI = 1.169–2.672
1–2	70 (46)	5		
Histological subtype				
Adenocarcinoma	88 (57)	7.7	0.69	
Squamous cell carcinoma	59 (39)	7.2		
Large cell carcinoma	6 (8)	6.5		
NLR				
≥4.3	78 (51)	6	**0.004**	$p = 0.15$, HR = 1.343, 95% CI = 0.896–2.013
<4.3	75 (49)	11.2		
PLR				
≥208	77 (50)	6.6	0.15	
<208	76 (50)	11.1		
HRR				
Low HRR	70 (46)	5.6	**< 0.001**	***p* = 0.03**, HR = 1.607, 95% CI = 1.041–2.480
High HRR	83 (54)	13.9		
Number of metastatic sites				
1	81 (53)	15.5	**< 0.001**	***p* < 0.001**, HR = 3. 279, 95% CI = 2.156–4.989
2	72 (47)	5		

Statistically significant *p* values ($p < 0.05$) are shown in bold

ECOG Eastern Cooperative Oncology Group, *GPS* Glasgow prognostic score, *HRR* hemoglobin/ red cell distribution width ratio, *HR* hazard ratio, *CI* confidence interval, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *OS* overall survival

differentiating anemia types. The association between high RDW levels and increased mortality has been demonstrated in non-oncological disorders of cardiovascular, cerebrovascular, respiratory and hepatic systems [24–27]. Recently, the use of RDW in malignant tumors has attracted attention. Relevant studies have been performed in patients with ovarian, endometrial, liver and lung cancers [28–31]. Studies of RDW have been mainly reported in lung cancer. Koma et al. reported a study in a heterogeneous group of 332 patients with early/advanced small cell lung cancer and non-small cell lung cancer. This study demonstrated an association between higher RDW values and poorer survival [29]. Only patients with resected tumors were included in other studies in lung cancers. In one of these studies, Warwick et al.

Table 3 Univariate and multivariate statistical analysis of progression-free survival

Characteristics	Number of patients *N* (%)	Univariate analysis for PFS	*p* value (univariate)	Multivariate analysis
Age (median, years)				
>65	41(36)	6	0.92	
≤65	74 (64)	6		
Gender				
Female	11 (10)	5.7	0.49	
Male	104 (90)	6		
Smoking				
Yes	92 (80)	5.3	0.53	
No	23 (20)	6.2		
ECOG				
0–1	70 (61)	6.7	**0.03**	***p*** **= 0.16**, HR = 1.397, 95% CI = 0.872–2.241
2–4	45 (39)	5.3		
Weight loss				
Yes	42 (37)	4.6	**0.01**	***p*** **= 0.28**, HR = 1.325, 95% CI = 0.794–2.212
No	73 (63)	8		
Comorbidity				
Yes	56(49)	5.8	0.96	
No	59(51)	6.4		
GPS				
0	70 (61)	6.6	**0.02**	***p*** **= 0.32**, HR = 1.266, 95% CI = 0.790–2.031
1–2	45 (39)	5		
Histological subtype				
Adenocarcinoma	68 (59)	6.2		
Squamous cell carcinoma	43 (37)	6.4		
Large cell carcinoma	4 (4)	5.4		
NLR				
≥ 4.3	55 (48)	5.8	0.37	
< 4.3	60 (52)	6.6		
PLR				
≥ 208	57 (50)	6	0.97	
< 208	58 (50)	6.4		
HRR				
Low HRR	47 (41)	5.1	**< 0.001**	***p*** **< 0.001**, HR = 2.635, 95% CI = 1.667–4.166
High HRR	68 (59)	8.6		
Number of metastatic sites				
1	65(57)	8.1	0.07	***p*** **= 0.07**, HR = 1.469, 95% CI = 0.963–2.242
≥ 2	50 (43)	5.1		

ECOG Eastern Cooperative Oncology Group, *GPS* Glasgow prognostic score, *HRR* hemoglobin/red cell distribution width ratio, *HR* hazard ratio, *CI* confidence interval, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *PFS* progression-free survival

Statistically significant *p* values ($p < 0.05$) are shown in bold

divided patients with resected NSCLC into 4 groups based on RDW levels (Group 1 < 13.5, Group 2 13.5–14.2, Group 3 14.2–15.3, and Group 4 > 15.3). In this study RDW values higher than > 15.3 were found to be associated with mortality [18]. In the second study, Ichinose et al. grouped patients with resected NSCLC according to the median RDW value (> 13.8/≤13.8). In this study, higher RDW values were found to be associated with decreased survival and increased morbidity in 275 patients aged 75 years and older [32]. Although the mechanism underlying the association between RDW and survival has remained unclear in these studies, the increases in RDW values are believed to be triggered by iron, folic acid and vitamin B12 deficiencies caused by poor nutrition and chronic inflammation [33–35].

Anemia is common among cancer patients, with a prevalence of 30% [36]. An association between decreased hemoglobin concentration and shorter survival has been reported in patients with lung, prostate, cervical, ovarian, head/neck and hematological malignancies [37–39]. In a study conducted in patients with lung cancer, Gauthier et al. reported associations between low baseline hemoglobin (< 12 g/L.) and increased hospitalization and poor quality of life in 476 patients with resected NSCLC. In this study, a tendency towards poorer overall survival was observed in patients with low baseline hemoglobin level [13]. 611 patients with early/advanced small cell lung cancer and non-small cell lung cancer were included in another study. Patients were divided into two groups based on the presence or absence of anemia (Hgb < 13 g/dL in male patients and Hgb < 12 g/dL in female patients). Anemia at diagnosis has been reported as an independent prognostic marker based on the multivariate analysis of the data from this study [12]. Only patients with adenocarcinoma subtype were included in a study in 306 patients with NSCLC and patients were assigned into normal hemoglobin and low hemoglobin groups (Hgb < 12 gL in male patients and Hgb < 11 g/dL in female patients). Low hemoglobin levels at diagnosis have been reported to be a poor prognostic marker in patients with adenocarcinoma [14]. In the above-mentioned studies, the absence of a standard cut-off value to define low hemoglobin levels is remarkable. In addition, even though an association is found between hemoglobin levels and prognosis, the mechanism underlying this association is not clear. Possible explanations are: (1) Cytokines released by tumor cells (interleukin-6 and tumor necrosis factor-α), (2) Impaired response of erythroid progenitor cells to erythropoietin and erythropoietin suppression, (3) Low hemoglobin levels may be a result of the changes in the hematopoietic environment. Furthermore, low hemoglobin levels may accelerate tumoral angiogenesis by leading to hypoxia, and hypoxia may also increase the resistance of tumor cells against chemotherapy and radiotherapy and, may result in a poorer survival by decreasing the effectiveness of treatment [40–42].

Although prognostic value of either RDW or hemoglobin has been reported individually in patients with lung cancer, prognostic effect of HRR in this patient group has remained unclear and as far as we know, prognostic effect of HRR in patients with NSCLC has been demonstrated for the first time in our study. Actually, only two studies on HRR have been conducted so far. The first study was conducted in 362 patients who had received curative treatment for esophageal cancer. In this study, Sun et al. reported that neither hemoglobin nor RDW was significant individually in terms of survival; however, HRR was a predictor of overall survival [21]. The second study has been reported recently and was conducted in patients with head and neck cancers who underwent surgery with curative intent. A total of 205 patients were included in this study. This study demonstrated that low HRR was of prognostic significance for event-free survival (EFS) rather than overall survival [22]. In line with the above-mentioned studies, a low HRR was found to be an independent predictor of overall survival in our study. Given the prognostic significance of either hemoglobin or RDW established separately in studies in lung cancer, the demonstration of the prognostic significance of HRR in our study, may not be surprising. However, what made the difference in our study was the value of HRR as an independent predictor of PFS in patients who received chemotherapy. Furthermore, both hemoglobin and RDW can be affected by conditions other than cancer. Therefore, HRR may minimize any potential bias and may be used as a parameter more reliable than either hemoglobin or RDW.

In our study, statistically significant associations were found between low HRR values and prognostic factors such as higher median NLR and PLR, a GPS of 1 or 2 and weight loss. On the other hand, an association between Low HRR values and more advanced stages and nodal involvement was reported in the study conducted by Sun et al. [21]. Thus, low HRR may be an indicator of aggressive tumor behavior. Considering previous studies, these findings may provide further support to studies which have demonstrated close associations between low hemoglobin or high RDW values and aggressive tumor behavior [43, 44].

Various prognostic indices including serum NLR, PLR, CRP (C-reactive protein), GPS have been investigated in patients with lung cancer and these indices have been reported to be prognostic [23, 45, 46]. Although the prognostic effect of NLR and PLR could not be demonstrated in the multivariate analysis of our study, the present study demonstrated that HRR was an independent prognostic factor along with GPS. Albumin concentrations and CRP which are used in the calculation of the GPS score are not parameters to be tested in patients with lung cancer, in routine clinical practice. Therefore, HRR which can be calculated using complete blood count parameters alone can be used as an easy, appropriate, feasible and economical parameter in this patient group.

Our study has several limitations. The essential limitation of this study is its retrospective design, which made impossible to exclude any conditions that may affect the outcomes, including inflammatory diseases or autoimmune conditions. Another limitation of the study was the absence of a standard cut-off value as each of the previous study had determined a cut-off value using different statistical methods.

In conclusion, our study is the first study investigating the prognostic significance of HRR in patients with NSCLC. In the multivariate analysis, HRR was found to be an independent prognostic marker for both OS and PFS, Thus, HRR may be used as an inexpensive, easy and feasible prognostic factor in clinical practice in patients with advanced NSCLC.

Compliance with ethical standards

Conflict of interest All authors report no conflicts of interest relevant to this article.

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