Evaluation of the effects of red blood cell distribution width on survival in lung cancer patients

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Aim of the study: Data are available indicating that red blood cell distribution width (RDW) is higher in cancer patients compared to healthy individuals or benign events. In our study, we aimed to investigate the influence of different RDW levels on survival in lung cancer patients.

Material and methods: Clinical and laboratory data from 146 patients with lung cancer and 40 healthy subjects were retrospectively studied. RDW was recorded before the application of any treatment. Patients were categorised according to four different RDW cut-off values (median RDW, RDW determined by ROC curve analysis, the upper limit at the automatic blood count device, and RDW cut of value which used in previous studies). Kaplan-Meier survival analysis was used to examine the effect of RDW on survival for each cut-off level.

Results: The median age of patients was 56.5 years (range: 26–83 years). The difference in median RDW between patients and the control group was statistically significant (14.0 and 13.8, respectively, $p = 0.04$). There was no difference with regard to overall survival when patients with RDW ≥ 14.0 were compared to those with RDW < 14.0 ($p = 0.70$); however, overall survival was 3.0 months shorter in low values of its own group in each of the following cut-off values: ≥ 14.2 ($p = 0.34$), ≥ 14.5 ($p = 0.25$), ≥ 15 ($p = 0.59$), although no results were statistically significant.

Discussion: We consider that the difference between low and high RDW values according to certain cut-off values may reflect the statistics of larger studies although there is a statistically negative correlation between RDW level and survival.

Key words: prognosis, lung cancer, blood, RDW.

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Introduction

Lung cancer is the most common fatal cancer type [1]. Local recurrence or distant metastasis develops in approximately 40% of these patients despite treatments, even if at an early stage [2]. Most of the non-small cell lung cancer (NSCLC) patients have metastasis at the time of diagnosis. Treatment of stage IV disease is palliative chemotherapy [3]. However, objective response is possible in only 30% of the patients who receive chemotherapy. Five-year survival is approximately 15%, despite advancements in diagnosis and treatment [4]. Therefore, determining the influence of factors on overall survival is important.

Red blood cell distribution width (RDW) is a parameter that quantitatively reflects the change in sizes of circulating erythrocytes [5]. It is routinely used for discrimination of different anaemia types. The influence of chronic inflammation in the development and progression of cancers has been emphasised in many studies [6, 7]. In recent years, RDW has also been evaluated as a haematological and inflammatory parameter, and elevated RDW has been shown to be accompanied by all cause of mortality including cancer-related deaths and chronic lower respiratory tract infection-related deaths, besides increased risk for cardiovascular mortality [8, 9].

There are a limited number of studies investigating whether RDW is a factor determining mortality risk in lung cancer [10, 11]. Therefore, we planned to investigate the influence of different RDW levels in lung cancer in our study.

Material and methods

In our study, patients with a confirmed diagnosis of NSCLC histopathologically followed-up at our in medical oncology clinic between 2005 and 2011 were included. The clinicopathological characteristics, laboratory data, and treatment data of the patients were obtained by screening the hospital automation system and file archive system retrospectively. All patients were classified as stage I to stage IV, according to the guidelines of the tumour-node-metastasis (TNM) staging system of the Union for International Cancer Control (7th edition). Retrospective data of forty healthy subjects who were admitted to outpatient clinics for general control purposes were included in the study and RDW values of healthy control subjects were compared with the values of the patients. Any subjects who had additional diseases, especially anaemia, thyroid dysfunction, or lung cancer, and those who were using medicines that might affect RDW were excluded. The lymphocyte and platelet levels of patients before receiving any treatment, according to the

stage, were recorded. RDWs were analysed with an automated haematology analyser (Coulter Hmx; Beckman Coulter (UK) Ltd., High Wycombe, Bucks, UK). The reference range was 11.5% to 14.5%. Patients were categorised according to four different RDW cut-off values (median RDW, RDW value determined by ROC curve analysis, the upper limit at the automatic blood count device for RDW, and RDW cut-off value used in previous studies). Patients whose file information was missing or inaccessible were excluded. The current state of the patients was learned from hospital records or by calling the patients.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software program version 15.0 (SPSS Inc., Chicago, IL, USA). Chi-square or Fisher exact tests were used for comparative analysis of categorical data. A receiver operator characteristic (ROC) curve was used for assessment, e.g. the association between RDW and survival. The duration of overall survival (OS) was calculated from the date of pathologic diagnosis until death or until the date of the last follow-up visit. Overall survival was estimated using the Kaplan-Meier method, and the log-rank test was used for comparison of outcomes. A p-value < 0.05 was considered statistically significant.

Table 1. General characteristics of all patients (n = 146)

Parameter		n	%
Median age (range)		56.5 (26–83)	
Gender	Female	15	10.3
	Male	131	89.7
ECOG	0–1	89	61.0
	2–3	57	39.0
Smokers	Yes	127	87.0
	No	19	13.0
Stage	I	21	15.2
	II	21	15.2
	III	46	33.3
	IV	50	36.2
Histology	Adenocarcinoma	61	41.8
	Squamous cell	57	39.0
	Large cell	4	2.7
	Other*	24	16.5
Treatment	Surgery	59	40.4
	Radiation	35	24.0
	Chemoradiation	19	13.0
	Chemotherapy	122	83.6
Surgical procedures	Lobectomy	39	26.7
	Pneumonectomy	18	12.3
	Wedge resection	2	1.4
Metastatic sites	Bone	16	11.0
	Liver	4	2.7
	Brain	12	8.2
	Adrenal	2	1.4
	Contralateral lung	4	2.7
	Multiple sites	19	13.0

** Adenosquamous, mixed, unknown subtypes, etc.*

Results

One hundred and forty-six patients were included in the study, whose entire set of parameters could be obtained. The median age of patients was 56.5 years (range: 26–83 years). One hundred and thirty-one patients (89.7%) were male. Fifty (36.2%) patients had metastasis at diagnosis. Adenocarcinoma (n = 61, 41.8%) and squamous cell carcinoma (n = 57, 39.0%) were the most frequent histological subtypes. The general characteristics of the patients are shown in Table 1. The median age of the healthy control group was 56.0 years (range: 30–78 years). There was no significant difference for median age between patients and the control group (p = 0.92). Thirty-two healthy subjects (80.0%) were male and eight were female (20.0%). There was no difference in gender proportion between patients and the control group (p = 0.11). Twenty-two control subjects (55.0%) were smokers, and the difference between the groups was statistically significant (p < 0.0001). The median RDW in the healthy control group was 13.8 years (range: 12.8–16.4 years). The difference for median RDW between patients and the control group was statistically significant (p = 0.04).

Patients were categorised according to four different RDW cut-off values. The median RDW value of 14.0 was used for the first classification. The group with RDW < 14.0 consisted of 62 patients (42.5%), and the group with RDW ≥ 14.0 consisted of 84 patients (57.5%). ROC curve analysis was used to determine the best value for overall survival for the second categorisation. Area under the curve (AUC) 0.565 (95% CI [confidence interval]: 0.453–0.676) was calculated according to this; the value of 14.2 was taken as the cut-off value of the second categorisation with 48% sensitivity and 64% specificity (Fig. 1). The RDW< 14.2 group consisted of 80 patients (54.8%) and the RDW ≥ 14.2 group consisted of 66 patients (45.2%). For the third categorisation, the upper limit on the automatic blood count device was used. The RDW < 14.5 group consisted of 87 patients (59.6%) and the RDW ≥ 14.5 group consisted of 59 patients (40.4%). The value used in previous studies, 15, was taken for the final categorisation [10, 12]. The RDW < 15.0 group consisted of 92 patients (63.0%), and the RDW ≥ 14.0 group consisted of 54 patients (37.0%).

There was not a difference between low and high values of the patients in Group 1 and Group 2 with regard to general characteristics. Of the patients in Group 3 and Group 4, the ones with low values were in earlier stages compared to the ones with high values and this difference was significant (p = 0.05), there was not a difference between low and high values with regard to other characteristics (Table 2).

In Group 1, median overall survival was estimated as 18 (95% CI: 6.4–12.7) months for the patients with RDW < 14.0 and 18.0 (95% CI: 12.7–23.3) months for the patients with RDW ≥ 14.0 (p = 0.70). In Group 2, while median overall survival was estimated at 19.0 (95% CI: 8.1–29.9) months in patients with RDW < 14.2, it was estimated at 16.0 (95% CI: 10.8–21.2) months in patients with RDW ≥ 14.2; however, the difference was not statistically significant (p = 0.34). In Group 4, while median overall survival

Table 2. General characteristics of patients according to RDW groups

Parameter	Group 1			Group 2			Group 3			Group 4		
	< 14 (*n* = 62) *n*	≥ 14 (*n* = 84) *n*	*p*	< 14.2 (*n* = 80) *n*	≥ 14.2 (*n* = 66) *n*	*p*	< 14.5 (*n* = 87) *n*	≥ 14.5 (*n* = 59) *n*	*p*	< 15 (*n* = 92) *n*	≥ 15 (*n* = 54) *n*	*p*
Age*												
< 57	32	41	0.86	39	34	0.87	45	28	0.74	46	27	1.00
≥ 57	30	43		41	32		42	31		46	27	
Gender												
Female	5	10	0.58	8	7	0.90	8	7	0.59	9	6	0.78
Male	57	74		72	59		79	52		83	48	
ECOG												
0–1	36	25	0.86	47	39	0.86	51	35	0.96	54	32	0.96
2–3	50	32		32	25		34	23		36	21	
Stage												
I–III	40	48	0.30	53	35	0.09	58	30	0.05	62	28	0.02
IV	20	35		25	30		27	28		28	27	
Histology												
Adenocarcinoma	24	37		35	26		38	23		40	21	
Squamous cell	23	34	0.41	30	27	0.86	31	26	0.58	33	24	0.58
Other**	15	13		15	13		18	10		19	9	
Treatment												
Surgery	55	29	0.12	44	22	0.13	39	20	0.23	36	18	0.22
Radiation	64	20	0.96	50	16	0.94	44	15	0.84	40	14	0.69
Chemoradiation	73	11	0.97	59	7	0.47	53	6	0.46	49	5	0.44
Chemotherapy	12	72	0.50	11	55	0.95	11	48	0.65	9	45	0.95

**Age variable was categorised by median age as < 57 and ≥ 57 years*
***Adenosquamous, mixed, large cell, unknown subtypes, etc.*

was 19.0 (95% CI: 8.7–29.3) months in patients with RDW < 15, it was estimated at (95% CI: 11.0–21.0) months in patients with RDW ≥ 15 (p = 0.25); however, the difference was not statistically significant (p = 0.59) (Fig. 2).

Discussion

Studies are available revealing the association between RDW and mortality in benign conditions like heart failure and chronic obstructive pulmonary disease [13, 14]. Data are also available indicating that RDW is higher in cancer patients compared to healthy individuals or in benign conditions [12, 15–17]. In a study conducted with symptomatic multiple myeloma patients, RDW value was categorised according to 14.5, the upper limit of reference value of the automated blood counter of the hospital. However, no difference was detected between the patients whose RDW was low (≤ 14.5) and high (> 14.5) with regard to overall survival (p = 0.236) [18]. Data are limited and conflicting about the association between RDW and overall survival in patients with solid cancers [10–12].

In a prospective study that aimed at comparing cancer patients and non-cancer patients with regard to RDW levels, cancer patients who had involuntary weight loss were shown to have higher RDW levels than those with non-cancer diseases (p = 0.02) [12]. However, in subgroup analysis done on 67 cancer patients, the influence of RDW on survival was investigated and a significant difference was not observed between dying and surviving patients after six months of follow-up with regard to RDW (median was taken as 15 for cut-off) (p = 0.083). In our study, although a difference was detected between patients with low and high RDW levels with regard to three-month survival in groups 2, 3, and 4, this difference did not reach statistical significance. One of the two studies of the influence of RDW on survival in solid tumours was conducted on lung cancer patients. In that study, patients were classified according to upper limit of the automated blood count device in the hospital (RDW < 15 and ≥ 15) [10]. In

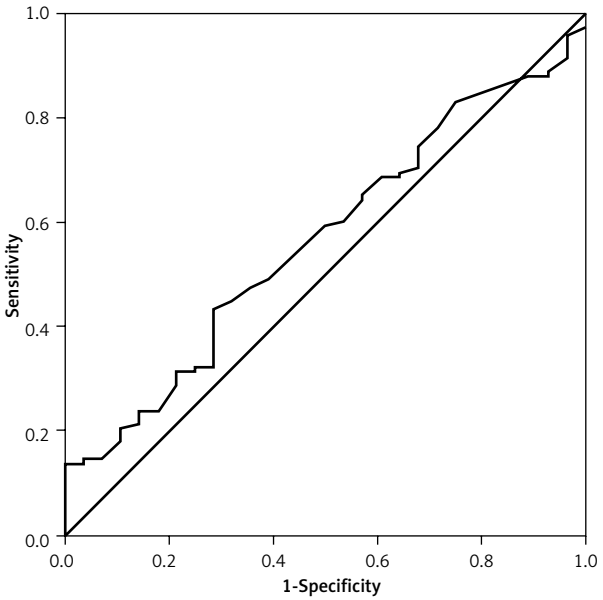

Fig. 1. The ROC curves for RDW

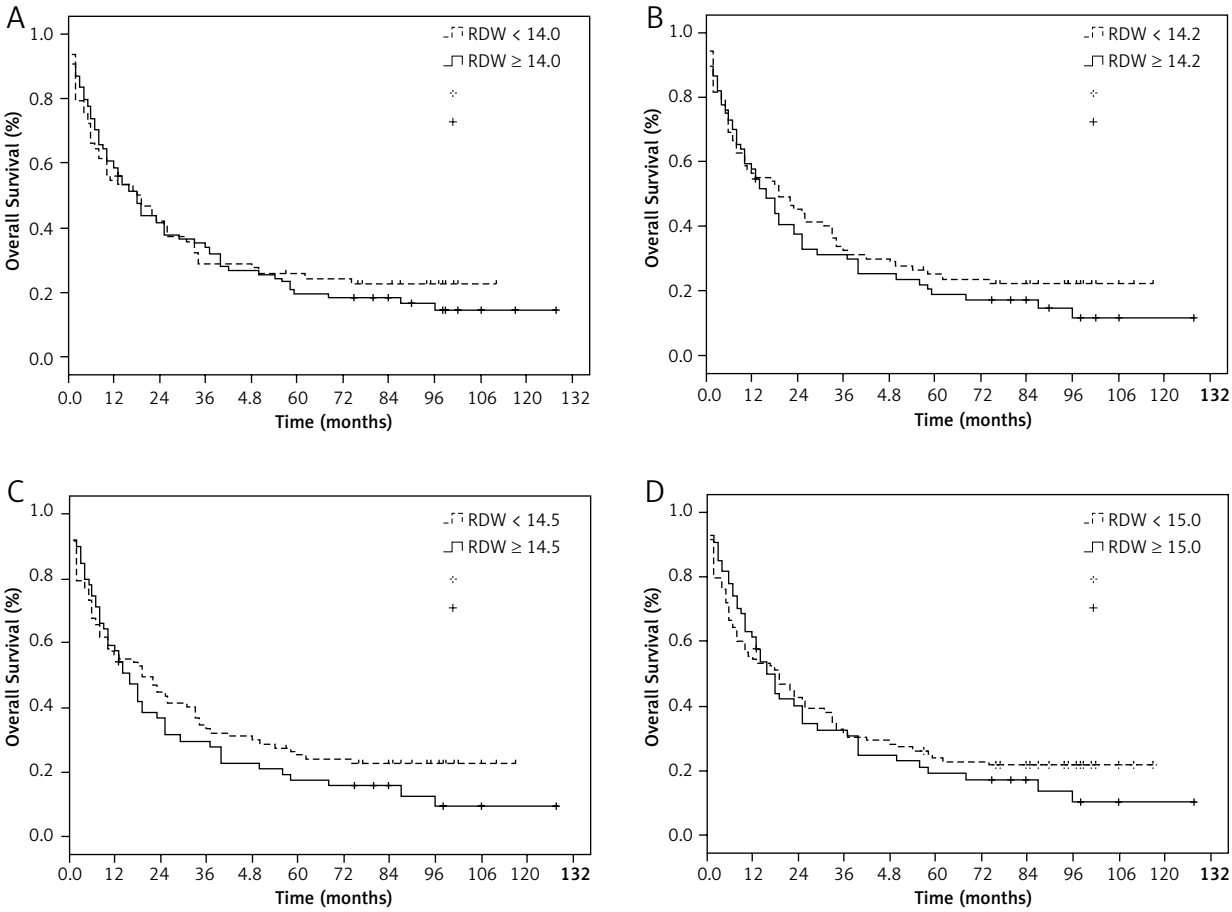

Fig. 2. Kaplan-Meier survival curves for overall survival of patients with Group 1 (A), Group 2 (B), Group 3 (C), and Group 4 (D)

the study, high RDW values were found to be related with poor prognosis ($p = 0.002$). Another large study was conducted by Warwick *et al*. in operated non-small cell lung cancer patients [11]. In the study, RDW levels were analysed by dividing subjects to four groups through graphics (Group 1 < 13.5, Group 2 13.5–14.2, Group 3 14.2–15.3, and Group > 15.3). In that study, preoperative RDW > 15.3 was found to be related with mortality ($p < 0.0001$).

Our study is one of the few studies about the association between RDW and survival in solid tumours. In conclusion, although it is a statistically negative study about RDW level and survival, the difference between arms in Group 2 and Group 3 is striking in Kaplan-Meier curves. This suggests that the negative result is a reflection of the small number of patients.

The authors declare no conflict of interest.

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