Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer

Junji Ichinose[1], Tomohiro Murakawa[2], Mitsuaki Kawashima[1], Kazuhiro Nagayama[1], Jun-ichi Nitadori[1], Masaki Anraku[1], Jun Nakajima[1]

[1]Department of Thoracic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [2]Department of Thoracic and Cardiovascular Surgery, Kansai Medical University, Hirakata City, Japan

Contributions: (I) Conception and design: J Ichinose; (II) Administrative support: T Murakawa, J Nakajima; (III) Provision of study materials or patients: J Ichinose, T Murakawa, J Nakajima; (IV) Collection and assembly of data: J Ichinose, T Murakawa, J Nakajima; (V) Data analysis and interpretation: J Ichinose; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Junji Ichinose, MD. Department of Thoracic Surgery, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: jichinose-tky@umin.ac.jp.

Background: The impact of red cell distribution width (RDW) on outcomes in elderly patients after surgery for non-small cell lung cancer (NSCLC) is not fully understood.

Methods: We retrospectively analyzed 992 NSCLC patients who underwent curative resection between 1998 and 2012. The following variables were included in the analyses to evaluate the role of RDW: age, gender, smoking index, leukocyte count, neutrophil to lymphocyte ratio (NLR), hemoglobin, platelet count, albumin, C-reactive protein, carcinoembryonic antigen, respiratory function, histology, T factor, N factor, surgical approach, surgical procedures, complications and prognosis.

Results: High RDW (>13.8) was an independent risk factor for morbidity [hazard ratio (HR) 2.1; P<0.01], recurrence (HR 2.0; P=0.01), overall survival (OS) (HR 2.1; P<0.01) and disease-free survival (DFS) (HR 2.0; P<0.01) in elderly patients (age ≥75 years, n=275), whereas it was not in younger patients (age <75 years, n=717). The surgical outcome was extremely poor in those older than 80 years with a RDW greater than 15% (morbidity, 56%; postoperative stay, 23 days; OS, 24%; DFS, 0%). RDW was unaffected by age (R =0.01; P=0.86) and elevated RDW without anemia was more prognostic than high RDW due to anemia in elderly patients.

Conclusions: High RDW was significantly associated with high morbidity and reduced survival in elderly patients who underwent resection for NSCLC. Therefore, this parameter should be taken into account when surgery is considered in the elderly.

Keywords: Lung cancer; red cell distribution width (RDW); elderly

Introduction

The preoperative assessment of surgical risk is critical especially when surgery is considered for complicated and high-risk cases. Owing to recent advances in less-invasive surgery, anesthesia, and perioperative managements, surgery can be performed in those who have comorbidities and are of advanced age. In this background, identifying a reliable preoperative parameter that can predict postoperative outcome is of importance.

In recent years, red cell distribution width (RDW) has been revealed to be a prognostic indicator for various diseases. RDW represents the volume variation among red blood cells, and is calculated by the following equation: RDW (%) = standard deviation of red cell volume ÷ mean cell volume ×100. RDW has been traditionally used in the

investigation of the etiology of anemia (1). The volume of erythrocytes is consistent, and RDW is normal in the case of anemia caused by rapid bleeding, whereas the increase of relatively large reticulocytes during the recovery process of anemia raises RDW in the case of slowly progressing anemia. RDW has recently been reported to also be an inflammatory indicator. There is mounting evidence linking elevated RDW and adverse outcomes in cardiac disease (2-4), pulmonary embolism (5), trauma (6), septic shock (7), acute pancreatitis (8), hepatitis (9), stroke (10), dementia (11), metabolic syndrome (12), and respiratory diseases such as non-small cell lung cancer (NSCLC) (13,14), chronic obstructive pulmonary disease (15), interstitial pneumonia (16) and sarcoidosis (17). High RDW has been associated with increased mortality and poor pulmonary function also in the general population (18-20).

The aim of this study was to investigate the prognostic impact of RDW on outcomes in elderly patients after surgery for NSCLC.

Methods

Patient cohort

A total of 1,061 patients with NSCLC who underwent resection at our institute between 1998 and 2012 were retrospectively analyzed. Before the study, the Research Review Board of Tokyo University examined and approved our research protocol in accordance with the Declaration of Helsinki (project approval No. 2406). All patients undergoing surgery irrespective of this study provided written informed consent for the review of their medical charts before the surgery. A total of 69 patients were excluded, because their records regarding RDW could not be obtained (n=8) or because they had evidence of a small-cell carcinoma component (n=8), carcinoid (n=4), distant metastases (n=7), dissemination (n=22), malignant effusion (n=9), or N3 disease (n=11).

Data extraction

The following 18 variables were investigated as prognostic factors: RDW (%), age, gender, smoking index (pack-years), white blood cell count (WBC, $\times 10^3/\mu L$), neutrophil to lymphocyte ratio (NLR), hemoglobin (g/dL), platelet count ($\times 10^4/\mu L$), albumin (g/dL), C-reactive protein (CRP; mg/dL), carcinoembryonic antigen (CEA; ng/mL), %vital capacity (%VC; %), %forced expiratory volume

in one second (%FEV$_1$; %), histology, T factor, N factor, surgical approach and surgical procedures. Laboratory data were obtained within one month before surgery. All measurements were performed at a single laboratory and hematological parameters were analyzed using two automated hematology analyzers; Coulter Gen-S (Beckman Coulter) and Sysmex XE-2100 (Sysmex). The tumor stage was determined pathologically according to the seventh edition of the TNM staging system of the International Union Against Cancer (21), and the histologic tumor type was determined according to the third edition of the World Health Organization classification (22).

Outcomes

We evaluated morbidity, hospital mortality, and postoperative hospital stay as short-term outcomes and overall survival (OS) and disease-free survival (DFS) as long-term outcomes. Morbidity included prolonged air leakage (>7 days), bronchial fistula, pneumonia, pulmonary embolism, pyothorax, chylothorax, exacerbation of interstitial pneumonia, cardiovascular disease, arrhythmia, postoperative bleeding, reoperation, stroke and delirium. The OS was calculated from the date of surgery to the time of death. The DFS was measured from the date of surgery to the date of lung cancer recurrence or death from any cause. The interval between follow-up examinations was every 3 months for the first 2 years and every 4 months for up to 5 years. A full examination and a chest X-ray were performed at each visit, and a computed tomography (CT) scan was performed annually. Other investigations were performed when indicated.

Statistical analysis

Statistical analyses were performed using JMP 11 software (SAS Institute, Cary, NC, USA). The cutoff value of RDW was set at 13.8, which was the median value in the elderly patients (age ≥75 years). Another cutoff value of 15 was arbitrarily chosen. Comparisons of the clinicopathological features were analyzed using Student's t-test, Welch's method, or the χ^2 test. The OS and DFS were estimated by the Kaplan-Meier method and were compared by the log-rank test. Risk factors for morbidity and recurrence were analyzed by multiple logistic regression analysis, and prognostic factors for OS and DFS were assessed by Cox's proportional hazards regression model using the following binary variables: RDW (>13.8/≤13.8), sex (M/

F), smoking (yes/no), WBC ($>6\times10^3$/$\leq6\times10^3$/µL), NLR (>3/≤3), hemoglobin (<12/≥12 g/dL), platelet count ($>20\times10^4$/$\leq20\times10^4$/µL), albumin (<3.5/≥3.5 g/dL), CRP (>0.5/≤0.5 mg/dL), CEA (>5/≤5 ng/mL), adenocarcinoma (yes/no), %VC ($<80\%$/$\geq80\%$), %FEV$_1$ ($<80\%$/$\geq80\%$),T factor (T2–4/T1), N factor (N1–2/N0), approach (thoracoscopy/open) and sublobar resection (yes/no). Factors associated with higher levels of RDW were analyzed by multiple linear regression analysis using the following continuous and binary variables: age, gender (M/F), smoking index (pack-years), WBC, NLR, hemoglobin, platelet count, albumin, CRP, CEA, adenocarcinoma (yes/no), %VC, %FEV$_1$, T factor (T2–4/T1), N factor (N1–2/N0) and preoperative comorbidities such as interstitial pneumonia (yes/no), cardiovascular disease (yes/no), cerebrovascular disease (yes/no), diabetes mellitus (yes/no), autoimmune disease (yes/no) and history of malignancy (yes/no). The relationship between RDW, hemoglobin and age was evaluated by calculation of the Pearson correlation coefficient.

Results

The clinicopathological data of 992 patients were analyzed. The median value of RDW was 13.5. The normal value of RDW was set at 12.0–15.9 in our institution. RDW was higher than 15.9 in 73 (7.4%) patients and lower than 12.0 in 5 (0.5%) patients. The morbidity, the 30-day mortality and the hospital mortality in the total cohort were 195 (20%), 1 (0.1%) and 11 (1.1%), respectively. The median follow-up time was 47 months. The recurrence of lung cancer was detected in 238 (24%) patients during follow-up.

In the study cohort, 275 (28%) cases were 75 years of age or older. The elderly patients were divided into two groups according to the RDW value. The relationships between RDW and other characteristics in the elderly patients were shown in *Table 1*. High RDW was significantly associated with low albumin, T stage >1 and morbidity. The 30-day and hospital mortality were 1 (0.8%) and 4 (3.0%) in the high RDW group and 0 and 1 (0.7%) in the low RDW group, respectively.

Multiple logistic regression analysis using the 17 variables listed in the Methods section revealed that high RDW was an independent risk factor for morbidity in the elderly patients [hazard ratio (HR) 2.1; P<0.01], whereas it was not in the younger patients (*Table 2*). The OS and DFS curves for high and low RDW are shown in *Figure 1*. The survival outcomes with high RDW

were poorer than those with low RDW, especially in the elderly patients (5-year OS, 59% *vs*. 81%, P<0.01; 5-year DFS, 48% *vs*. 70%, P<0.01). Cox regression analysis revealed that high RDW was an independent prognostic factor in the elderly patients (OS: HR 2.1, P<0.01; DFS: HR 2.0, P<0.01), whereas it was not in the younger patients (*Table 3*). Multiple logistic regression analysis revealed that high RDW was also a risk factor for recurrence in the elderly patients (HR 2.0; P=0.01), but not in the younger patients.

Figure 2 showed that there was little correlation between RDW and age (R =0.15; P<0.01). Especially in the elderly patients, RDW was revealed to be unaffected by age (R =0.01; P=0.86). *Table 1* also showed that there was no significant difference in age between the high RDW group and the low RDW group. Factors associated with higher levels of RDW in the elderly patients were analyzed using multiple linear regression analysis using the 21 variables listed in the Methods section (*Table 4*). High RDW was associated with low hemoglobin, high NLR, histology other than adenocarcinoma, absence of diabetes mellitus and past history of malignancy. To eliminate the confounding bias of anemia, all analyses were repeated excluding the patients with anemia (hemoglobin <12, <11, or <10 g/dL), and the same results were obtained (data not shown). The correlation between RDW and hemoglobin was weaker in elderly patients (R =−0.27) than in younger patients (R =−0.49). The differences in the prognostic significance of RDW according to age and hemoglobin are shown in *Figure 3*. High RDW without anemia had little influence on prognosis of younger patients, but in elderly patients, elevated RDW without anemia was more prognostic than high RDW due to anemia.

The outcomes of the subdivided groups according to age (≥80, 75–79, and ≤74 years) and RDW (>15, 13.9–15, and <13.9) are shown in *Figure 4*. In the patients aged 80 years or older (n=90), a RDW of >15 was significantly associated with high morbidity and long postoperative hospital stay. The prognosis of this highest-risk group (n=16) was extremely poor (5-year OS, 24%; 5-year DFS, 0%). This group had frequent preoperative comorbidities (81%; history of malignancy in ten cases, cardiovascular disease in four cases, and interstitial pneumonia in three cases), frequent complications (56%; pneumonia in five cases, pyothorax in one case, prolonged air leakage in one case, postoperative bleeding in one case, exacerbation of interstitial pneumonia in one case, stroke in one case, and delirium in one case)

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Table 1 The relationships between RDW and other characteristics in elderly patients

Variables	High RDW group (n=133), median [range] or n (%)	Low RDW group (n=142), median [range] or n (%)	P
RDW (%)	14.6 [13.9–26.8]	13.3 [11.8–13.8]	<0.001
Age (years)	78 [75–90]	78 [75–90]	0.59
Gender, male	89 (67%)	87 (61%)	0.40
Smoking index (pack-years)	31 [0–180]	21 [0–180]	0.08
WBC ($\times 10^3$/μL)	5.8 [1.2–3]	6.0 [3.1–12]	0.42
NLR	2.4 [0.4–31]	2.4 [0.9–13]	0.34
Hemoglobin (g/dL)	12.3 [8.4–15.8]	12.6 [9.7–16.6]	0.08
Platelet count ($\times 10^4$/μL)	22.8 [6.5–55]	22.0 [7.5–39]	0.08
Albumin (g/dL)	3.8 [2.9–4.7]	3.9 [2.8–4.7]	<0.05
CRP (mg/dL)	0.2 [0–6.3]	0.2 [0–6.7]	0.10
CEA (ng/mL)	5.2 [1.2–96]	4.3 [1.2–56]	0.30
%VC (%)	97 [67–163]	104 [65–150]	0.09
%FEV$_1$ (%)	102 [57–202]	108 [43–161]	0.21
Histology, Ad	88 (66%)	104 (73%)	0.25
T factor, T1	56 (42%)	78 (55%)	<0.05
N factor, N0	110 (83%)	124 (87%)	0.37
Approach, thoracoscopy	81 (61%)	89 (63%)	0.86
Sublobar resection, yes	31 (23%)	45 (32%)	0.16
Morbidity, yes	46 (35%)	26 (18%)	<0.01
Postoperative stay (days)	11 [4–97]	10 [3–170]	0.09
Hospital mortality, yes	4 (3.0%)	1 (0.7%)	0.33
Recurrence, yes	31 (23%)	24 (17%)	0.24

RDW, red cell distribution width; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen; VC, vital capacity; FEV1.0, forced expiratory volume in one second; Ad, adenocarcinoma.

and a high risk of recurrence (56%).

Discussion

In this study, high RDW was found to be an independent risk factor for morbidity, OS, and DFS in elderly patients who underwent resection for NSCLC, whereas it was not in younger patients. The outcomes were extremely poor, especially in the highest-risk group (age ≥80 years and RDW >15).

The difference in the prognostic significance of RDW according to age has rarely been described. In our study, the correlation between RDW and adverse outcome was mostly due to anemia in younger patients. However, RDW is particularly worthy of measurement in elderly patients, because elevated RDW in the elderly had a stronger influence on prognosis in cases without anemia.

Although it has been demonstrated that higher RDW is associated with adverse outcomes in various diseases, the mechanism underlying this association remains unclear. The major causes of anisocytosis include iron deficiency anemia, megaloblastic anemia, immune hemolytic anemia, myelodysplastic syndrome, and liver disease. This suggests that high RDW is caused by systemic inflammation,
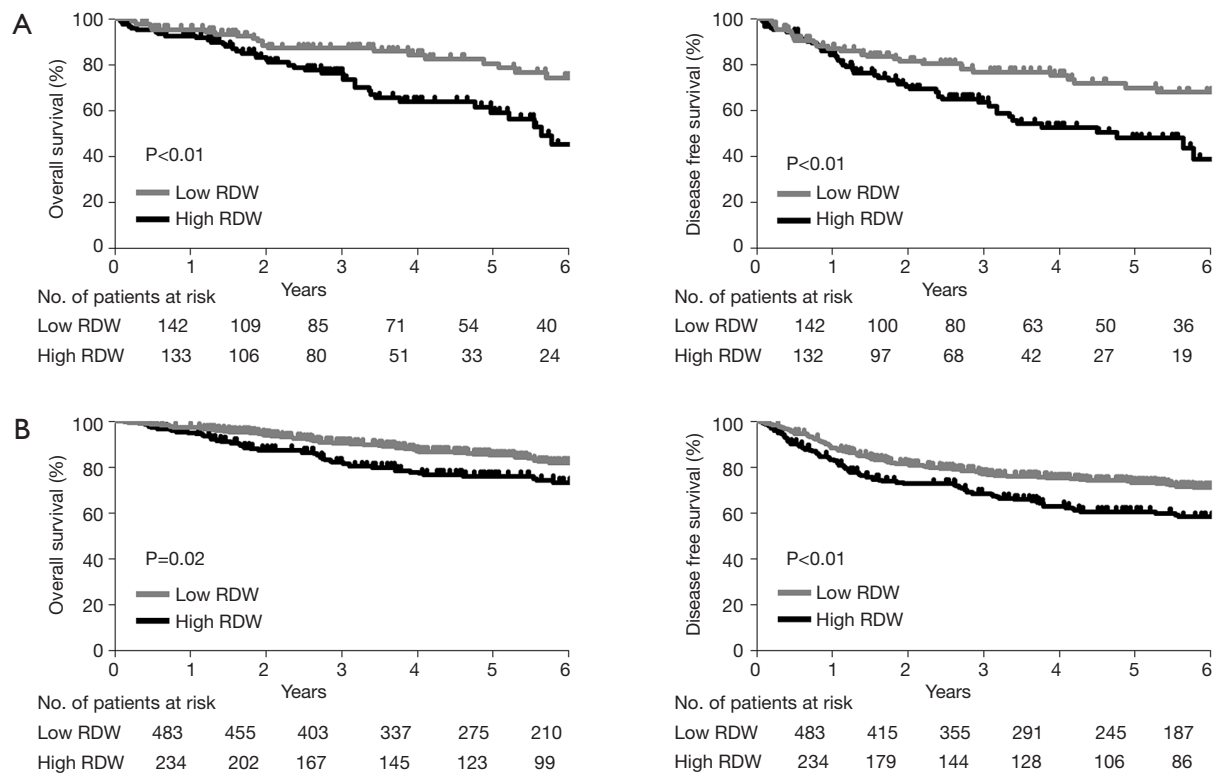
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Figure 1 The overall survival (OS) and disease-free survival (DFS) curves of resected NSCLC for high RDW (>13.8) and low RDW (≤13.8). (A) The 5-year survival rates for high and low RDW in elderly patients were OS: 59% and 81%, and DFS: 48% and 70%, respectively; (B) the 5-year survival rates for high and low RDW in younger patients were OS: 76% and 85%, and DFS: 61% and 73%, respectively. P values were calculated using log-rank tests. NSCLC, non-small cell lung cancer; RDW, red cell distribution width.

Table 2 Risk factors for morbidity

Variables	HR	95% CI	P
Age ≥75 years			
RDW (>13.8)	2.1	1.2–3.9	0.01
Sublobar resection (yes)	0.3	0.2–0.7	<0.01
NLR (>3)	2.2	1.2–4.0	<0.01
Age <75 years			
RDW (>13.8)	1.2	0.8–1.9	0.40
Gender (male)	1.9	1.1–3.4	0.03
Smoking (yes)	1.8	1.0–3.4	0.04
Approach (thoracoscopy)	0.5	0.3–0.8	<0.01

The 17 variables listed in the Methods section were analyzed using multiple logistic regression analysis. HR, hazard ratio; CI, confidence interval; RDW, red cell distribution width; NLR, neutrophil to lymphocyte ratio.

Table 3 Prognostic factors for overall survival and disease-free survival

Variables	OS			DFS		
	HR	95% CI	P	HR	95% CI	P
Age ≥75 years						
Univariate analysis						
RDW (>13.8)	2.3	1.4–3.9	<0.01	2.0	1.3–3.2	<0.01
Multivariate analysis						
RDW (>13.8)	2.1	1.3–3.6	<0.01	2.0	1.3–3.2	<0.01
Gender (male)	2.5	1.4–4.9	<0.01	1.8	1.1–2.9	0.02
T factor (T2–4)	2.4	1.5–4.1	<0.01	2.5	1.5–4.2	<0.01
N factor (N1–2)				2.6	1.5–4.4	<0.01
Sublobar resection (yes)				1.8	1.1–2.9	0.02
Age <75 years						
Univariate analysis						
RDW (>13.8)	1.5	1.1–2.2	0.02	1.6	1.2–2.0	<0.01
Multivariate analysis						
RDW (>13.8)	0.9	0.6–1.3	0.61	1.1	0.9–1.5	0.37
T factor (T2–4)	2.0	1.3–3.1	<0.01	2.3	1.7–3.3	<0.01
N factor (N1–2)	2.8	1.9–4.1	<0.01	2.9	2.2–3.9	<0.01
CEA (>5 ng/mL)	1.8	1.2–2.6	<0.01	1.8	1.4–2.4	<0.01
Albumin (<3.5 g/dL)	3.0	1.6–5.4	<0.01			
Smoking (yes)	1.8	1.2–3.0	<0.01			
NLR (>3)				1.6	1.2–2.1	<0.01

The 17 variables listed in the Methods section were analyzed using stepwise Cox regression analysis. OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval; RDW, red cell distribution width; CEA, carcinoembryonic antigen; NLR, neutrophil to lymphocyte ratio.

Table 4 Factors associated with higher levels of RDW in the elderly

Variables	Coefficient	SE	t	P
Hemoglobin (g/dL)	−0.46	0.09	−5.3	<0.01
NLR	0.13	0.05	2.7	0.01
Histology (Ad)	−0.32	0.14	−2.4	0.02
Diabetes mellitus (yes)	−0.37	0.17	−2.2	0.03
History of malignancy (yes)	0.28	0.13	2.3	0.03

The 21 variables listed in the Methods section were analyzed using multiple linear regression analysis. SE, standard error; RDW, red cell distribution width; NLR, neutrophil to lymphocyte ratio; Ad, adenocarcinoma.
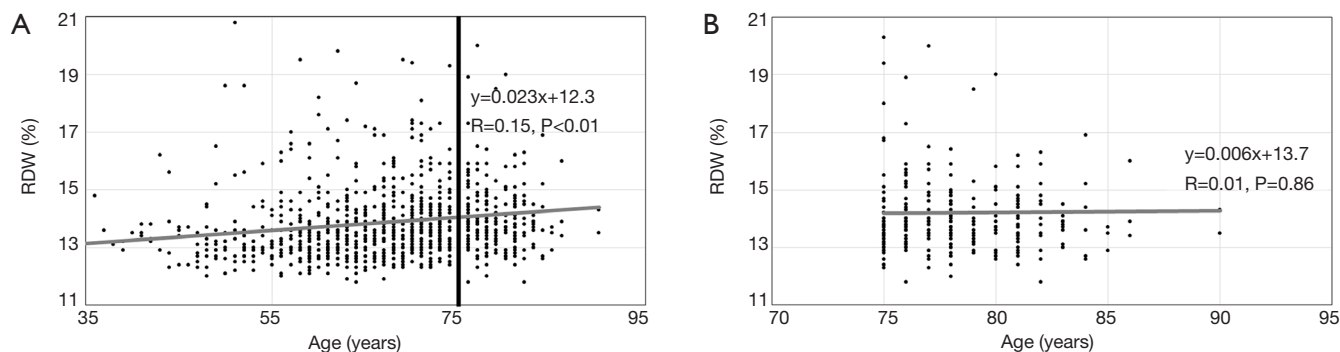
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Figure 2 The relation between RDW and age in the total cohort (A) and in the elderly patients (B). There was no correlation between RDW and age in the elderly patients. RDW, red cell distribution width.
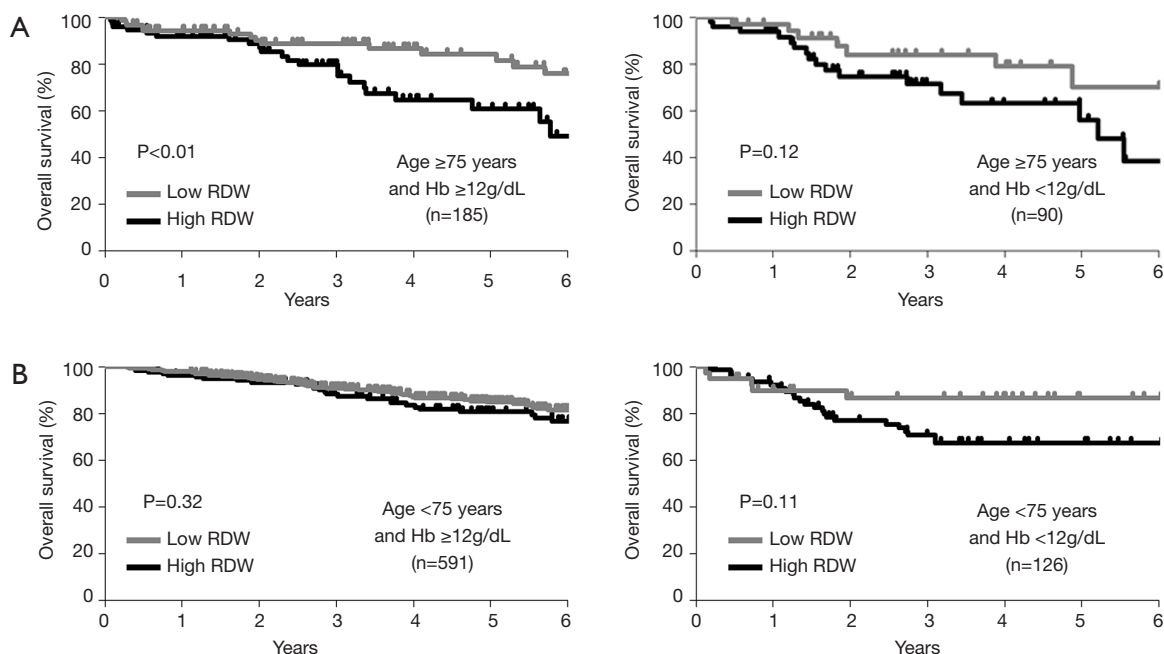

Figure 3 Differences in the prognostic significance of RDW according to age and presence/absence of anemia. The overall survival curves of the elderly (A) and younger patients (B) with or without anemia who underwent resection for NSCLC for high RDW (>13.8) and low RDW (≤13.8). P values were calculated using log-rank tests. RDW, red cell distribution width; NSCLC, non-small cell lung cancer; Hb, hemoglobin.

nutritional deficiency, and bone marrow dysfunction. Larger variation of red blood cell volume is strictly associated with decreased erythrocyte deformability, which in turn impairs blood flow through microcirculation (23). Oxidative stress was also revealed to be involved in the association between elevated RDW and clinical endpoints (24,25). In our study, higher RDW was associated with low hemoglobin, high NLR, histology other than adenocarcinoma, past history of malignancy, and absence of diabetes mellitus in elderly

patients. An association between diabetes mellitus and low RDW was also reported in a previous study (26).

The interesting characteristic of RDW was that high RDW seemed to represent not only increased surgical risk but also a potential hazard of recurrence of NSCLC. High RDW may be associated with impaired antitumor immunity, and that may explain why high RDW was closely associated with a past history of malignancy. Further work is needed to elucidate the exact mechanism by which RDW
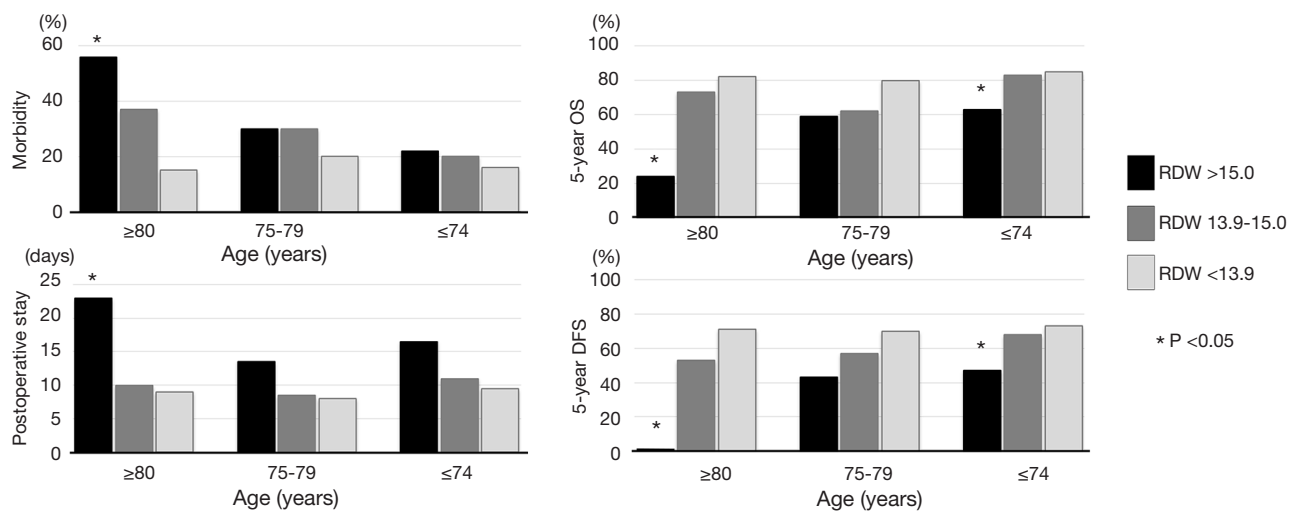
Figure 4 Surgical outcomes according to age and RDW. P values were calculated using logistic regression analysis for morbidity, Student's *t*-tests for postoperative stay, and log-rank tests for survival analyses. *, significantly different from the other two groups (P<0.05). RDW, red cell distribution width; OS, overall survival; DFS, disease free survival.

impacts prognosis.

RDW is a particularly useful prognostic indicator because of its cost-effectiveness, simplicity and predictive ability of both short- and long-term outcomes. RDW is a simple item included in usual complete blood counts and no additional examination, cost, calculation, or detailed medical history is required. Our results appear to be common among surgeries for other malignancies as well as NSCLC. The prognostic significance of RDW in other diseases should be evaluated in future studies.

There are some limitations to the present study. The study design was retrospective and observational, and this was a single-institution study. This study did not include the non-surgically treated patients, and therefore, the influence of selection bias should be considered. Our results can be applied only for surgically treated patients. An additional limitation is that serum levels of factors that can influence RDW (e.g., iron, vitamin B12, and folic acid) were not determined.

On the basis of the extremely poor outcomes observed for the highest-risk group (age ≥80 years and RDW >15) in our study, surgical indication for these patients should be carefully assessed and limited resection might be beneficial. Moreover, RDW should be taken into account when a clinical trial of surgical treatment for the elderly is designed. The role of preoperative RDW as a predictive factor needs to be further tested in a prospective study in the future.

In conclusion, high RDW appears to be a risk factor indicating postoperative morbidity and reduced survival in elderly patients with NSCLC. The results from this study should be further tested in a prospective manner so that surgical/medical oncologists can take this parameter into account when surgical intervention is considered in the elderly.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Before the study, the Research Review Board of Tokyo University examined and approved our research protocol in accordance with the Declaration of Helsinki (project approval No. 2406). All patients undergoing surgery irrespective of this study provided written informed consent for the review of their medical charts before the surgery.

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