



Red Cell Distribution Width as a Predictor of Functional Outcome in Rehabilitation of Older Stroke Patients

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Background: Red cell distribution width (RDW) is a prognostic marker in vascular diseases. While increased RDW predicts mortality and outcomes after ischemic stroke, evidence regarding its prognostic significance in stroke rehabilitation is lacking. Thus, the present study investigated the relationship of RDW with stroke, orthopedic, and deconditioning rehabilitation outcomes. **Methods:** This prospective comparative study included three groups (stroke, orthopedic, and deconditioning) of older adult patients hospitalized for rehabilitation. The patients in each group were divided into two subgroups according to whether they had high (>14.5%) or normal (≤14.5%) RDW levels on admission. Functional outcome was assessed by total and motor FIM (Functional Independence Measure) score changes and efficiency at admission and on discharge. **Results:** Of the 234 eligible patients, 108 (46.2%) had high RDW. Of the 50 stroke rehabilitation patients, 13 (26%) had high RDW. FIM change and efficiency scores were significantly lower in patients with high RDW only in the stroke rehabilitation group. However, multiple linear regression analysis showed that high RDW was not independently associated with total and motor FIM gain or total and motor FIM efficiency. **Conclusion:** High RDW levels on admission to rehabilitation were associated with poor rehabilitation outcome in stroke patients but were not an independent risk factor for rehabilitation outcomes.

Key Words: Stroke, Red cell distribution width, Rehabilitation, Recovery of function

INTRODUCTION

The red cell distribution width (RDW), the coefficient of variation of the red cell mean corpuscular volume (MCV), is a quantitative description of anisocytosis, or variation in red cell size. In general, a higher RDW reflects increased red blood cell destruction such as in hemolytic disorders and nutritional deficiency conditions, including iron, vitamin B12, and folate deficiency.

Recent studies have shown a strong independent association between higher RDW and the risks of adverse vascular outcomes in patients with various vascular diseases.¹⁾ Population studies have identified RDW as a predictor of all-cause²⁾ and cardiac mortality.³⁾ RDW has also been associated with worsened renal function,⁴⁾ evi-

dence of systemic inflammation,⁵⁾ and poor outcomes in a variety of disorders including stroke.⁶⁾ More recent evidence indicates the utility of RDW in predicting not only inflammation but also significant clinical outcomes, including post-operative mortality.⁷⁾ A higher likelihood of post-operative complications was reported in patients with higher RDW. RDW > 14.5% at the time of operation was linked to increased 1-year mortality in patients with partial prostheses in the setting of hip fractures.⁷⁾ Moreover, increasing RDW quartiles were associated with increased short- and long-term mortality in patients with hip fractures.⁸⁾

The emerging importance of RDW as a marker of potential high-risk patients has also been demonstrated in geriatric populations. RDW may be a part of risk assessment in older patients un-

dergoing surgery after a hip fracture.⁸⁾ Studies in geriatric populations have also identified RDW as a predictor of all-cause mortality,⁹⁾ as well as mortality in patients with ischemic stroke treated with intravenous thrombolysis,¹⁰⁾ older patients with sepsis¹¹⁾ and in older patients undergoing non-cardiac surgery.¹²⁾

The present study explored the prognostic potential of RDW for rehabilitation by investigating the associations between RDW and short-term functional outcomes among older patients hospitalized for rehabilitation.

MATERIALS AND METHODS

Setting and Study Design

Data were collected over a 6-month period at the Fliman Rehabilitation Geriatric Hospital (a 150-bed public geriatric facility affiliated with the Technion - Israel Institute of Technology, Medical School in Haifa, Israel. This study included all patients over 65 years of age admitted consecutively to the five geriatric rehabilitation wards. The only exclusion criteria were non-ambulatory status before hospitalization and unwillingness to participate. We obtained approval for the study from our local institutions and the Ministry of Health Helsinki committee. The study protocol was approved by the Institutional Review Board at Fliman Geriatric Hospital (No. 920150002).

Patient hemoglobin levels, MCV, and RDW were measured on admission. When more than two RDW measurements were available, the second was taken as the last RDW measurement during hospitalization. Anemia was defined as hemoglobin levels < 13 g/dL in men and 12 g/dL in women, based on the World Health Organization criteria.¹³⁾ RDW was reported as the coefficient of variation (in percent) of red blood cell volume. The normal range for RDW in our laboratory is 11.5% to 14.5%. We divided the patients into high (> 14.5%) or normal (\leq 14.5%) RDW groups based on measurements on admission.

Data Collection and Outcome Measures

We approached all potential participants in the hospital and assigned them to groups after the baseline evaluation. Patients were analyzed in three subgroups: namely, the stroke group (patients hospitalized for stroke rehabilitation), orthopedic group (patients hospitalized for orthopedic rehabilitation), and deconditioning group (patients hospitalized after deconditioning for general rehabilitation).

Baseline information was gathered during in-person interviews to ascertain ambulatory function just before hospitalization and associated comorbidities and to perform cognitive screening assessment. We applied the Clinical Dementia Rating (CDR) scale

to assess cognitive impairment.¹⁴⁾ Comorbid conditions were determined from the participant or proxy respondent (in interviews) and from medical records using a list derived from the Charlson Comorbidity Index.¹⁵⁾

In the stroke group, details of the stroke were gathered at the time of inclusion, including the National Institutes of Health Stroke Scale (NIHSS) score at arrival in the emergency room. The Functional Independence Measure (FIM) was the primary study outcome measure. The FIM is a performance-based disability measure that assesses the level of disability in terms of assistance required to perform basic activities of daily living.¹⁶⁾ The FIM consists of 18 items designed to assess the amount of assistance required for safely performing self-care (6 items), sphincter control (2 items), transfers (3 items), locomotion (2 items), communication (2 items), social adjustment and cooperation (3 items), and cognition and problem-solving (3 items). Good reliability and validity have been demonstrated in studies involving orthopedic conditions, older adults, and individuals with cognitive impairment. The validity and reliability of the FIM were also established specifically among adults receiving inpatient rehabilitation.¹⁵⁾ We also used the FIM motor score (13 items) because previous studies have reported low responsiveness for the FIM cognition score.¹⁶⁾ The FIM was completed by trained nurses at admission and discharge from rehabilitation. The rate of functional gain (FIM efficiency) was calculated as the total FIM change (discharge FIM score minus the admission FIM score) divided by the length of rehabilitation stay (days).

Statistical Analysis

Baseline characteristics were examined to determine pre-hospitalization functional status, comorbidities, and health status. Categorical data are presented as proportions. Chi-square tests were used to compare differences in categorical variables. The primary analysis examined recovery over time as measured according to FIM and FIM motor scores. We examined functional recovery at each evaluation point (admission and discharge) using all participants available at that time point. The overall changes within groups were examined by paired-sample t-test or Wilcoxon signed-rank test, while differences in changes between groups were assessed by independent sample t-test or Mann-Whitney U test. To test the associations between possible confounders and FIM measures, a multiple regression analysis was performed using possible confounders (congestive heart failure and baseline hemoglobin, albumin, and creatinine levels) with variables entered in a single stage. The p-value for statistical significance level was less than 0.05.

RESULTS

Data were available for 231 patients admitted, including 50 patients in the stroke group, 125 patients in the orthopedic group, and 56 in the deconditioning group. The demographic characteristics and clinical data of these patients are shown in Table 1.

We observed no significant differences in mean age or sex proportions between groups. In the stroke group, the baseline hemoglobin level was higher in patients with normal RDW compared to that in patients with high RDW (13.2 ± 1.9 vs. 11.3 ± 1.9 g/dL). Moreover, patients in the stroke group with normal RDW had a significantly higher albumin level, lower creatinine level, of better cognitive status (CDR). In the orthopedic group, patients with normal RDW had a significantly higher baseline hemoglobin level and lower Charlson Comorbidity Index. In the deconditioning group, patients with normal RDW had a significantly higher baseline hemoglobin level, lower Charlson Comorbidity Index, and higher percentage of patients with cancer.

In the stroke group, total and motor FIM changes were significantly higher in the low RDW group (32.4 ± 18.2 vs. 18.1 ± 12.9 and 26.5 ± 16.0 vs. 15.2 ± 13.1 , respectively; $p = 0.012$ and $p = 0.028$, respectively); additionally, these patients had higher total (1.17 ± 0.88 vs. 0.57 ± 0.62 ; $p = 0.015$) and motor (0.99 ± 0.74 vs. 0.47 ± 0.58 ; $p = 0.027$) FIM efficiency scores compared to those in the high RDW group (Table 2). In contrast, in the orthopedic and deconditioning groups, we observed no significant differences in FIM gains and efficiency between the high and low RDW groups.

As the group of stroke patients with normal RDW had a lower prevalence of anemia, higher albumin levels, and lower creatinine levels, we performed multiple linear regression analysis to test for predictors of high FIM change and FIM efficiency scores. As the confounders included as covariates are influenced by age, we checked and found no multicollinearity (Table 3). Our results suggested that high RDW was not independently associated with worse total and motor FIM change scores (β coefficient = -4.76 , $p = 0.47$ and β coefficient = -2.47 , $p = 0.68$, respectively). High RDW was also not independently associated with worse total and motor FIM efficiency scores (β coefficient = -0.18 , $p = 0.58$ and β coefficient = -0.10 , $p = 0.72$, respectively). None of the other variables tested, including age, sex, congestive heart failure, and baseline hemoglobin, albumin, and creatinine levels were predictive of higher FIM change or efficiency.

DISCUSSION

The present prospective study of a consecutive cohort of patients

hospitalized for rehabilitation focused on the relationship between RDW and rehabilitation outcome as assessed by FIM score. The results showed significant differences in functional gains during rehabilitation between patients with normal and high RDW hospitalized for stroke rehabilitation. We found that high RDW was associated with small gain and low efficiency of total and motor FIM during rehabilitation. The association between high RDW and functional gains was not observed in other rehabilitation patients (orthopedic and deconditioning). To our knowledge, this is the first study to compare the effects of high RDW on rehabilitation outcomes in these patients and to suggest its negative effects on functional outcomes. These results did not remain statistically significant after multiple regression analysis accounting for the effects of confounders including age, sex, and baseline hemoglobin, albumin, and creatinine levels. This finding supports the assumption that high RDW is not an independent risk factor of rehabilitation outcomes in stroke patients.

Most previous investigations of RDW in stroke patients were retrospective studies in patients with acute ischemic stroke that analyzed RDW as a predictor of long-term mortality.^{6,17} Among patients with ischemic stroke, higher RDW was predictive of higher mortality. Previous studies reported an association between higher RDW and worse functional outcome 3 months⁶ and 1 year¹⁰ after the stroke; however, the relative weights of mortality and rehabilitation on that outcome from these studies remain unclear.

Despite our finding that high RDW was associated with small gain and low efficiency of total and motor FIM during rehabilitation in stroke patients multiple linear regression analysis did not support its role as a specific predictor of stroke rehabilitation outcome. We propose that the role of RDW as a predictor of successful rehabilitation is not specifically implicated in the pathogenesis or process of stroke and that it should instead be interpreted as a general prognostic marker as it was associated with mortality in the general population,⁹ patients with ischemic heart disease,¹⁸ and those with metabolic syndrome¹⁹ and heart failure, among others. Other factors, including oxidative stress, impaired iron mobilization, inflammation, undernutrition, and impaired renal function are some of the pathophysiological mechanisms postulated as mediators of the association between elevated RDW and clinical endpoints.^{4,5,18,20}

The underlying mechanisms by which RDW predicts adverse clinical endpoints remain unknown. Red blood cell transports oxygen to tissues such as peripheral muscle. Increased RDW signifies increased numbers of red blood cells with incomplete oxygen binding to hemoglobin such as premature erythrocytes in iron deficiency anemia. Higher RDW levels may affect oxygen transport capacity, resulting in adverse clinical outcomes.²¹ Recent studies

Table 1. Baseline clinical characteristics by rehabilitation group according to baseline RDW

Variable	Stroke group (n = 50)			Orthopedic group (n = 125)			Deconditioning group (n = 56)		
	Normal RDW (n = 37)	High RDW (n = 13)	p-value	Normal RDW (n = 65)	High RDW (n = 60)	p-value	Normal RDW (n = 21)	High RDW (n = 35)	p-value
Sociodemographic characteristics									
Age (yr)	75.6 ± 7.6	79.8 ± 7.0	0.100	77.8 ± 9.4	78.2 ± 9.3	0.830	75.5 ± 10.2	77.7 ± 8.3	0.370
Female	16 (43.2)	8 (61.5)	0.260	22 (66.2)	40 (66.7)	1.000	9 (43.0)	15 (43.0)	1.000
Chronic diseases and medication use									
NIHSS score at the ER	12.69 ± 5.81	13.21 ± 3.89	0.320	-	-	-	-	-	-
Number of chronic diseases	4.51 ± 1.17	4.92 ± 1.04	0.270	4.60 ± 1.43	4.93 ± 1.57	0.220	4.57 ± 1.17	4.51 ± 1.38	0.650
Charlson Comorbidity Index	2.43 ± 1.80	2.85 ± 1.90	0.370	2.34 ± 2.30	3.40 ± 2.36	0.008	3.14 ± 1.65	4.06 ± 1.78	0.060
Delirium	1 (2.7)	1 (7.7)	1.000	5 (7.7)	3 (5.0)	0.400	0 (0.0)	3 (8.6)	0.280
Post-stroke state	12 (32.4)	5 (38.5)	0.740	10 (15.4)	11 (18.3)	0.420	6 (28.6)	6 (17.1)	0.330
CHF	4 (10.8)	6 (46.2)	0.046	17 (26.2)	25 (41.7)	0.070	9 (43.0)	20 (57.1)	0.300
Diabetes mellitus	13 (35.1)	6 (46.2)	0.520	25 (36.1)	32 (53.3)	0.110	13 (62.0)	16 (45.7)	0.240
Cancer	9 (24.3)	1 (7.7)	0.260	11 (16.9)	14 (23.3)	0.300	3 (14.3)	18 (51.4)	0.009
COPD	1 (2.7)	2 (15.4)	0.160	7 (10.8)	3 (5.0)	0.330	2 (9.5)	5 (14.3)	0.700
Parkinson disease	1 (2.7)	0 (0.0)	1.000	3 (4.6)	0 (0.0)	0.250	2 (9.5)	2 (5.7)	0.630
Blood analysis									
Baseline hemoglobin (g/dL)	13.2 ± 1.9	11.3 ± 1.9	0.003	10.8 ± 1.7	10.2 ± 1.1	0.040	11.7 ± 1.7	10.5 ± 1.2	0.002
Anemia (WHO)	16 (43.2)	10 (77.0)	0.037	58 (89.2)	58 (96.7)	0.100	16 (76.2)	35 (100.0)	0.005
Mean corpuscular volume (µm ³)	86.7 ± 3.87	84.4 ± 4.4	0.130	88.1 ± 4.0	86.1 ± 6.5	0.320	86.9 ± 4.6	85.6 ± 6.4	0.410
Albumin (g/dL)	3.66 ± 0.45	3.22 ± 0.54	0.009	3.31 ± 0.40	3.21 ± 0.38	0.160	3.22 ± 0.39	3.00 ± 0.44	0.070
CRP (mg/dL)	22.1 ± 25.7	33.4 ± 48.9	0.380	59.1 ± 44.3	51.4 ± 50.1	0.160	35.2 ± 33.6	31.0 ± 25.9	0.930
Creatinine (mg/dL)	1.18 ± 1.15	1.23 ± 1.87	0.007	1.0 ± 0.93	1.26 ± 1.30	0.370	1.03 ± 0.63	1.18 ± 0.84	0.950
Psychosocial functioning									
No cognitive impairment (CDR=0)	7 (19.0)	2 (15.4)	0.024	21 (32.3)	18 (30.0)	0.770	5 (23.8)	9 (25.7)	0.990
Mild cognitive impairment (CDR=0.5)	13 (35.0)	4 (30.8)		19 (29.2)	23 (38.3)		5 (23.8)	10 (28.6)	
Cognitive impairment (CDR=1)	10 (77.0)	4 (30.8)		13 (20.0)	12 (20.0)		6 (28.6)	10 (28.6)	
Cognitive impairment (CDR=2)	7 (19.0)	0 (0.0)		10 (15.4)	6 (10.0)		4 (19.0)	5 (14.3)	
Cognitive impairment (CDR=3)	0 (0.0)	3 (23.1)		0 (0.0)	1 (1.7)		1 (4.8)	1 (2.9)	
Rehabilitation period									
Hospitalization period (day)	35.7 ± 17.6	42.1 ± 18.8	0.310	35.3 ± 18.8	39.0 ± 18.2	0.110	31.9 ± 10.9	38.8 ± 20.9	0.500

Values are presented as mean ± standard deviation or number (%).

RDW, red cell distribution width; NIHSS, National Institutes of Health Stroke Scale; ER, emergency room; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; WHO, World Health Organization; CRP, C-reactive protein; CDR, Clinical Dementia Rating scale.

Table 2. Functional recovery of the participants (high vs. normal RDW) over time (unadjusted associations)

Variable	Stroke group (n = 50)			Orthopedic group (n = 125)			Deconditioning group (n = 56)		
	Normal RDW (n = 37)	High RDW (n = 13)	p-value	Normal RDW (n = 65)	High RDW (n = 60)	p-value	Normal RDW (n = 21)	High RDW (n = 35)	p-value
Total FIM change	32.4 ± 18.2	18.1 ± 12.9	0.012	25.8 ± 13.0	17.6 ± 14.0	0.111	29.4 ± 16.1	26.0 ± 17.8	0.530
Motor FIM change	26.5 ± 16.0	15.2 ± 13.1	0.028	21.9 ± 11.9	25.4 ± 12.3	0.113	25.4 ± 13.5	20.2 ± 13.8	0.160
Total FIM efficiency	1.17 ± 0.88	0.57 ± 0.62	0.015	0.94 ± 0.70	0.93 ± 0.65	0.800	1.17 ± 1.00	0.86 ± 0.77	0.120
Motor FIM efficiency	0.99 ± 0.74	0.47 ± 0.58	0.027	0.80 ± 0.70	0.78 ± 0.56	0.860	1.02 ± 0.86	0.65 ± 0.57	0.210

Values are presented as mean ± standard deviation.

RDW, red cell distribution width; FIM, Functional Independence Measure.

$$\text{FIM efficiency} = \frac{\text{Total FIM change}}{\text{Length of rehabilitation stay (day)}}$$

Table 3. Associations between baseline characteristics and study outcomes in the stroke group (normal and high RDW, adjusted analyses)

Characteristic	Total FIM change		Total FIM efficiency		Motor FIM change		Motor FIM efficiency	
	β coefficient (95% CI)	p-value	β coefficient (95% CI)	p-value	β coefficient (95% CI)	p-value	β coefficient (95% CI)	p-value
High RDW	-4.76 (17.90, 8.40)	0.47	-0.18 (-0.83, 0.47)	0.58	-2.47 (-14.38, 9.44)	0.68	-0.10 (-0.64, 0.45)	0.72
Female	4.65 (-6.00, 15.30)	0.38	0.27 (-0.26, 0.79)	0.31	2.67 (-6.97, 12.31)	0.58	0.22 (-0.22, 0.67)	0.31
Age	0.0003 (-0.67, 0.67)	0.99	-0.002 (-0.04, 0.03)	0.92	-0.14 (-0.75, 0.47)	0.65	-0.006 (-0.03, 0.02)	0.65
CHF	-12.15 (-25.65, 1.35)	0.08	-0.48 (-1.14, 0.19)	0.15	-10.35 (-22.57, 1.87)	0.09	-0.44 (-0.99, 0.13)	0.13
Baseline hemoglobin	1.44 (-2.05, 4.92)	0.41	0.035 (-0.14, 0.21)	0.68	1.60 (-1.56, 4.74)	0.32	0.04 (-0.10, 0.18)	0.59
Albumin	3.82 (-9.53, 17.17)	0.57	0.27 (-0.39, 0.93)	0.41	2.27 (-9.82, 14.36)	0.71	0.18 (-0.38, 0.73)	0.52
Creatinine	0.33 (-3.83, 4.48)	0.88	-0.041 (-0.25, 0.16)	0.69	-0.30 (-4.06, 3.46)	0.87	-0.06 (-0.23, 0.11)	0.49

RDW, red cell distribution width; FIM, Functional Independence Measure; CI, confidence interval; CHF, congestive heart failure.

demonstrated inverse correlations between peak oxygen uptake and RDW, with peak oxygen uptake increasing and RDW decreasing before and after exercise training.²²⁾ A previous study showed that higher RDW levels were related to impaired exercise capacity and that exercise training decreased RDW in patients with chronic heart failure.²³⁾ These findings suggest that the mechanisms of RDW as a predictor of adverse clinical endpoints may be connected to erythrocyte proliferation in the bone marrow.

The mechanisms underlying the association between RDW and outcome of stroke rehabilitation but not in orthopedic or deconditioning rehabilitation are not fully understood. We hypothesize that, because erythropoiesis is affected by numerous chronic disease factors including inflammation, kidney diseases, malignancies, autoimmune diseases as well as oxidative stress and different acute-phase inflammatory markers, RDW mirrors chronic disease (as reflected in our data) and may, thus, be viewed as a nonspecific but outcome-relevant “chronic disease marker”. Such a marker may be better reflected in chronic atherosclerotic patients, such as those with stroke.

Previous studies have analyzed the effects of RDW on survival. Most studies reporting the relationship between RDW and age found that a higher RDW was consistently associated with older

age, which is a major determinant of survival. Assessment of the interaction between these variables revealed that the role of RDW in predicting mortality depends on age and confirmed the association between higher RDW values and increased mortality in most cases in older patients. This important bias needs to be addressed in studies analyzing the effect of RDW on survival.

The strengths of the present study are its prospective design including a large sample of patients who had experienced a stroke and underwent a rehabilitation program in a ward dedicated to the rehabilitation of older stroke patients. To the best of our knowledge, this study is the first to focus on the specific role of RDW value in rehabilitation. Another strength of the study was the use of the FIM as a structured assessment tool. This scale has benefits over other widely used scales.^{24,25)} The use of the FIM to analyze our data was advantageous as it shows lower ceiling and floor effects compared to those of other scales. Thus, the FIM likely measured the functional gains during rehabilitation with greater accuracy.

However, this study also has several limitations that should be considered. First, the study cohort was restricted to older patients hospitalized for rehabilitation. Assessing the possibility that RDW value may provide prognostic information for rehabilitation only

in this cohort excluded a number of community-dwelling older adults and younger people who experienced a stroke but were not hospitalized in an institution dedicated to stroke rehabilitation. Second, although the natural history of functional recovery was described, the mediators of improvement cannot be concluded. For example, whether rehabilitation therapy or expertise were similar between groups was unknown, although we compared the time, in days, that patients spent in rehabilitation and in our hospital. Such patients usually receive the same rehabilitation program.

In conclusion, older patients with high RDW before being hospitalized for stroke rehabilitation had less recovery of functional status compared to adults who suffered a stroke but had normal RDW. However, high RDW was not an independent risk factor for rehabilitation outcomes.

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CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, EZ, EA; Data curation, EZ, YP; Investigation, EZ, IS, YP, RS, SC, BNF, EA; Methodology, EZ, IS, EA; Project administration, EZ, EA; Supervision, EA; Writing-original draft, EZ, RS, SC, BNF, EA; Writing-review and editing, EA.

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