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Elevated red blood cell distribution width predicts mortality in acute exacerbation of COPD

Valoarea crescută a lărgimii distribuției eritrocitare prezice mortalitatea în exacerbările acute ale BPOC

Abstract

Objective: *Red blood cell distribution width (RDW) has been shown to predict clinical outcomes in many diseases. To our knowledge, the prognostic significance of RDW in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has not been reported so far. The aim of the present study is to investigate the relation of RDW to in-hospital mortality in patients with AECOPD.*
Methods: *We retrospectively reviewed hospital records of inpatients with AECOPD in two referral teaching hospitals in two provinces of east Azerbaijan and west Azerbaijan, Iran. Associations between RDW and in-hospital death were analyzed with using correlation, logistic regression analysis, and receiver operating characteristic (ROC) curves in SPSS software.*
Results: *We studied 330 patients, of whom 75 (22.7%) did not survive to hospital discharge. In univariate analysis higher RDW-SD values were associated with increased hospital mortality (30.2% vs. 15.8% p=0.002 odds ratio 2.31). Using the first quartile of RDW as reference, odds ratio (OR) mortality among patients in the highest RDW quartile was 5.34 (95% CI, 2.70-12.57; p = 0.001). In multivariate analysis RDW-SD remained an independent risk factor for mortality after correction for age, thrombocytopenia, leukocyte count, mean corpuscular volume, anemia. In receiver-operating curve analysis the AUC for RDW was 0.663, which was more than that of hemoglobin, platelets.*
Conclusion: *RDW on admission day proves to be a useful indicator to predict in-hospital death in AECOPD.*
Keywords: ***Red blood cell distribution width, COPD, AECOPD, in-hospital death, outcome***

Rezumat

Obiective: *A fost demonstrat faptul că lărgimea distribuției eritrocitare (RDW) prezice evoluția clinică în multe afecțiuni. După cunoștințele noastre, prognosticul și semnificația RDW în exacerbările acute de BPOC nu au fost clarificate și raportate până în acest moment. Scopul studiului de față este investigarea relației dintre RDW și mortalitatea intraspitalicească în cazul pacienților cu exacerbări acute ale BPOC.*
Metode: *Au fost analizate retrospectiv documentele medicale ale pacienților internați cu exacerbări de BPOC în două spitale universitare de referință din două provincii din Azerbaijan-ul de vest și de est, Iran. Asocierile dintre RDW și mortalitatea intraspitalicească au fost analizate utilizând corelația, analiza de regresie logistică și curbele ROC în programul SPSS.*
Rezultate: *Au fost analizate documentele a 330 pacienți, din care 75 (22.7%) au decedat în spital. În analiza univariată valorile mari ale distribuției eritrocitare (RDW-SD) au fost asociate cu o mortalitate intraspitalicească crescută (30.2% vs. 15.8% p=0.002 odds ratio 2.31). Prin utilizarea primei quartile a RDW ca referință, odds ratio (OR) al mortalității în rândul pacienților cu cea mai înaltă quartilă a RDW a fost de 5.34 (95% CI, 2.70-12.57; p = 0.001). În analiza multivariată RDW-SD a rămas un factor de risc independent pentru mortalitate după corecția pentru vârstă, trombocitopenie, numărul de leucocite, volumul corpuscular mediu, anemie. În analiza curbelor ROC AUC pentru RDW a fost 0.663, mai mare decât cea pentru hemoglobină, trombocite.*
Concluzii: *RDW la internare este un predictor util al mortalității intraspitalicești în cazul exacerbărilor BPOC.*
Cuvinte-cheie: ***lărgimea distribuției eritrocitare, BPOC, exacerbări BPOC, mortalitate intraspitalicească, rezultat***

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Introduction

Chronic obstructive pulmonary disease (COPD) ranked as the third most common cause of death worldwide after ischemic heart disease and stroke in 2010[1]. Clinically, acute exacerbations of COPD (AECOPD) are the most important events in the history of this disease, and its in-hospital mortality is reported at 2.5%[2], 7.25%[3], 7.4%[4], and 10%[5]. The identification of predictive markers for outcome in AECOPD patients following hospitalization may help the physicians in making better decisions and management. Many biomarkers are used for prediction of outcome, but some are expensive or are not available in many hospitals.

Red blood cell distribution width (RDW) in complete blood count (CBC) shows variations in size of circulating red blood cells (anisocytosis). RDW is used for the differential diagnosis of anemia.

RDW has also been shown as a possible marker for all-cause mortality[6,7]. In the Third National Health and Nutrition Examination Survey of 15 852 adults, mortality rates increased 5-fold from the lowest to the highest quintile of RDW[8].

Prior studies have investigated the association of RDW with mortality in internal medicine ward[9], critical care unites (adult and pediatric)[10-13], and emergency department[14].

Table 1 Relation of categorical variable to in-hospital death

	Death in hospital N (%)	Discharged alive N (%)	Total N (%)	P value	Odds ratio (95% CI)
Male **Female**	49 (65.3) 26 (34.7)	133 (52.2) 122 (47.8)	182 (55.2) 148 (44.8)	0.044	NS
Comorbidity* NO Yes Diabetes mellitus Hypertension CHF and coronary disease	 31 (9.5) 162 (64.0) 12(20) 36(21.45) 16(23.9)	 91 (27.7) 44 (51.7) 48(80) 132(78.6) 51(76.1)	 122 (37.2) 206 (62.8) 60(18.2) 168(50.9) 67(20.3)	 0.42 0.311 0.329 0.64	 NS
Anemia Yes No	 38 (35.8) 37 (16.5)	 68 (64.2) 187 (83.5)	 106 (32.1) 224 (67.9)	0.000	2.82 (1.66-4.80)
RDW-SD>46 RDW-SD<46	48 (30.2) 27 (15.8)	111 (69.8) 144 (84.2)	159 (48.2) 171 (51.8)	0.002	2.31 (1.35-3.93)
Thrombocytopenia Non-thrombocytopenia	41 (32.8) 34 (16.6)	84 (67.2) 171 (83.4)	125(37.9) 205(62.1)	0.001	2.45(1.45-4.14)
RDW quartiles 1st quartile 2nd quartile 3rd quartile 4th quartile	 8 (9.8) 18 (21.7) 19 (22.9) 30 (36.6)	 74 (90.2) 65 (78.3) 64 (77.1) 52 (63.4)	 82 (24.8) 83 (25.2) 83 (25.2) 82 (24.8)	0.001	Ref=I 2.60(1.05-6.30) 2.75(1.130-6.70) 5.34(2.70-12.57)

*Presence of any one or more of hypertension, diabetes mellitus, congestive heart failure, stable ischemic heart disease; RDW: red cell distribution width

Table 2 Relation of continues variables to in-hospital death

	Death in hospital	Discharged alive	Total	P value
Age mean± SD Median	73.39± 10.07 73	68.55± 10.73 68	69.65±10.76 70	0.001
Hb Mean± SD (l) Median	12.55±3.18 12.5	13.92± 2.53 13.5	13.66± 2.75 13.4	0.000
MCV Mean± SD Median	88.04± 8.61 88	90.55± 9.22 91.30	89.98± 9.14 90.75	0.037
RDW-SD Mean± SD Median	46.96± 18.39 51.100	36.35± 20.17 41.6	38.76±20.25 45.45	0.000
RDW-CV Mean± SD Median	18.28± 6.42 16.4	16.12± 3.74 14.85	16.72± 4.75 13.5	0.002
Platelet count mean Median	150293±85743 143000	186447±90872 182000	178,205± 90878 175,000	0.002
WBC	11194± 5876 11300	8827± 3612 8300	9365± 4339 8600	0.000

Hb: haemoglobin in mg/dl; RDW-SD: Red cell distribution width-standard deviation in femtoliter; WBC: white blood cells count/ml

Many studies have described RDW as a prognostic marker in several cardiovascular disease including congestive heart failure[15], coronary artery disease[16], carotid atherosclerosis[17], peripheral artery disease[18], and cerebrovascular accidents[19].

RDW has also been described to be predictive of mortality in hip fracture[20,21] pancreatitis[22], acute kidney injury[23], haemodialysis[24], necrotizing fasciitis[25], infective endocarditis[26], sepsis[27] and even organophosphate poisoning[28]. In respiratory medicine area, the relation of higher RDW with mortality have been shown for lung cancer[29,30], pulmonary hypertension[31], pulmonary embolism[32,33], acute dyspnea[34], community acquired pneumonia[35] and stable COPD patients[36] but not AECOPD.

To the best of our knowledge, there is only one published article, by Seyhan et al.[36], that has investigated and shown that elevated RDW levels have been associated with increased mortality risk in stable COPD patients.

As relation between RDW and in-hospital mortality in AECOPD has not been reported in the literature so far, the aim of this study is to find whether there is any relationship.

Table 3 Multivariate binary logistic regression analysis

	B	Wald	P value	Exp (B)
Gender(male)	0.532	2.839	0.092	1.702
Age	0.046	9.294	0.002	1.047
anemia	-0.923	8.583	0.003	0.397
MCV	-0.027	2.581	0.108	0.973
Platelet	0.000	10.341	0.001	1.000
RDW-SD	0.025	9.515	0.002	1.025
WBC	0.000	18.740	0.000	1.000
Constant	-3.383	3.084	0.079	0.034

Methods and material

This is a retrospective cohort study at two referral teaching hospitals in two provinces in Iran, Imam-Reza hospital in Tabriz, and Imam-Khomeini hospital in Urmia. We reviewed hospital charts of 330 hospitalized patients with primary and final diagnosis of AECOPD. Patients whose primary or final diagnosis was not AECOPD were excluded. Patients with haematologic and oncologic disease were excluded. The admission day CBC parameters, age, sex, were recorded. Outcomes of discharged alive or death in-hospital were recorded.

Definition of terms

RDW-SD in femtoliter (fL) is an actual measurement of the width of the RBC size-distribution histogram. This parameter is therefore not influenced by the average RBC size (mean corpuscular volume, MCV).

RDW-CV (expressed in %) is calculated from standard deviation and MCV.

RDW-CV (%) = 1 standard deviation of RBC volume/ MCV × 100%

Of note, since RDW-CV is mathematically derived from MCV, it is therefore affected by the average RBC size (MCV).

In this study MCV has significant relation to mortality, to prevent the confounding effect of MCV on RDW, we emphasized most on RDW-SD.

Analysis

Statistical analyses were performed using SPSS 23.0 software. P<0.05 was considered statistically significant. Categorical data were analyzed using chi-square tests and expressed as frequency percentage and odds ratios. Quantitative data are expressed as mean and standard deviation (SD) and median. To compare groups, independent t-test is used in data with normal distribution and Mann–Whitney U-test is used in data without a normal distribution. Those parameters with p value < 0.05 in univariate analysis were entered into binary logistic regression analysis with the "Enter" method. We used a receiver-operating characteristic (ROC) curve to assess the discriminating performance of RDW to predict death in AECOPD, and the cut-off values for RDW with sensitivity and specificity were calculated.

Results

We studied 330 patients with AECOPD. Based on patient deaths within hospital, patients were classified as death groups (75 patients 22.7%) and survivor groups (255 patients 77.3%). Of all patients, 48.2% had higher than normal RDW-SD. Tables 1 and 2 show a comparison of the two groups. As shown in the tables, anemia, RDW, MCV, age, WBC, platelet, and sex were statistically significant (p value < 0.05). In the death group, the mean value of RDW-SD value was significantly higher than in discharged patients (46.96 ± 18.39 fL vs. 36.35 ± 20.17 fL, P < 0.01). Using the first quartile of RDW as reference, odds ratio (OR) mortality among patients in the highest RDW quartile was 5.34 (2.70-12.57) (95% CI, 2.70-12.57; p = 0.001). In a binary-logistic-regression analysis, the higher RDW-SD group remained strong as a significant predictor of in-hospital mortality even after adjustment for age, gender, haemoglobin, and WBC count (Table 3).

Receiver-operating-characteristic curve analysis was used to evaluate the values for RDW-SD to predict mortality in AECOPD patients (Figure 1). RDW-SD had an area under the curve value (AUC) of 0.663 (95% CI, 0.597–0.729). Cut-off value of 46 (upper limit normal for RDW-SD) showed sensitivity of 64% and specificity of 58% for predicting in-hospital death. AUC for haemoglobin (0.365) was less than RDW (0.663). In bivariate correlation analysis RDW-SD values were negatively correlated with haemoglobin (r = –1.42, P = 0.01) but not with age (r = 0.003, p = 0.964) and WBC count (r = –0.005, p = 0.96).

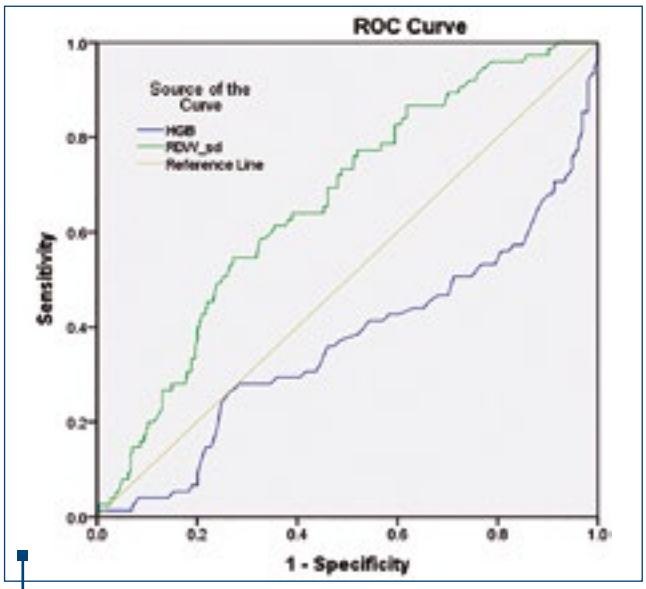

Figure 1. *Receiver operative curve analysis for RDW-SD and hemoglobin*

Discussion

The major finding of the present study was RDW was higher in patients with in-hospital death. To the best of our knowledge, this is the first report on the prognostic significance of RDW in AECOPD.

Koma et al.[30] carried out a retrospective study of 332 patients with lung cancer reported that the survival rates were lower in the high RDW group than in the low RDW group. Multivariate analysis showed higher RDW is a significant prognostic factor.

In a prospective study of 136 patients with acute pulmonary thromboembolism, high RDW was independently associated with increased acute pulmonary embolism related mortality (Hazard ratio 15.5)[33].

In patients with pulmonary hypertension, RDW was superior to N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in predicting outcome[31].

In a cohort study in which RDW was measured in 1,840 patients with various forms of newly diagnosed or progressive cancer after remission, high RDW value was found to be a significant predictor of mortality[37]

Vashistha et al.[24] with studying of 109,675 adult on haemodialysis reported higher mortality in patients with elevated RDW, and RDW was stronger predictor of death than anemia.

In Zhang et al.[38] study of 122 patients with traumatic brain injury, high RDW had a positive predictive value (PPV), negative predictive value (NPV) 65.4%, 95.7%.

Shteinshnaider et al.[9] reported that among 586 internal medicine inpatients, the mortality rates were 51.1% in elevated RDW vs. 20.3% ($p < 0.001$) in patients with normal RDW. Every 1% increment of RDW on admission was associated with relative risk of 1.21 for predicting mortality.

In a retrospective analysis of 907 patients with acute dyspnea who visited an emergency department, there was a stepwise increase of 30-day mortality risk from lowest to highest RDW tertiles[34].

The precise mechanism for the association between high RDW and mortality in these diverse conditions remains unclear, however, it is assumed to be related to chronic inflammation, which interferes with erythropoiesis and causes anisocytosis[39]. Studies showed that RDW positively correlated with inflammatory indices such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and inflammatory cytokines in a large cohort of unselected outpatients[40], systemic lupus erythematous patients[41], rheumatoid arthritis[42], and obese adolescents[43].

It is proposed that RBCs as biomarker of progression in chronic or acute diseases with oxidative alterations[44]. It is well recognised that COPD is associated with oxidative stress imbalance.

RDW increases in the anemia of chronic diseases, independent of iron status. It is explained that inflammation processes promote deaths of RBCs and alter erythropoiesis and RBCs membrane deformability[45]. Some inflammatory mediators influence iron metabolism and suppress erythropoietin-induced maturation of RBCs. COPD is considered an inflammatory disease. Therefore, it can be assumed RDW values reflect the inflammation status of AECOPD. Another possible explanation for relation of elevated RDW is that malnutrition is one of comorbidities in COPD, which is directly caused by COPD[46]. Nutritional deficiencies result in impaired formation of erythrocytes, which leads to a heterogeneous RBC population and an increase in RDW.

The third explanation for the association of high RDW may be right ventricular failure. In patients with COPD, the levels of RDW predicted the presence of right ventricular failure with a sensitivity of 70% and specificity of 93.1%[47].

Age was an independent predictor of in-hospital mortality in multivariate logistic analysis. Most other studies have similar results[4,48]. RDW retains its significance in multivariate analysis. RDW is a strong and consistent predictor of total and cause-specific mortality in older adults in community-based[8] samples and hospital[49] studies.

In our study, thrombocytopenia, leukocytosis, and anemia retain their significant value in logistic regression analysis. Their significant role in AECOPD had been shown in other studies[50,51].

RDW as a prognostic factor for patients with AECOPD has two advantages. First, it is an inexpensive index without extra-cost, because CBC is a routine test for patients with AECOPD. It is easily available and can be tested even in a community hospital. Second, the lifespan of red blood cells is approximately 120 days. Therefore, RDW may have less biological variation than ESR, CRP, WBC platelets, and may reflect the long duration of the patient's condition.

Seyhan et al.[36], with a study of 270 stable COPD patients, reported that elevated RDW levels were associated with increased mortality risk. Taken together these two studies, we conclude RDW may be a potent marker of mortality not only in stable COPD but also in AECOPD.

The major limitation of this study is its retrospective design. The other weakness of our study is that we did not use the Charlson comorbidity index[52] for evaluation of comorbid conditions. Finally, we didn't measure well recognised inflammatory markers. However, we think that this retrospective cohort has adequate effect size to suggest a reasonable strength of evidence for prognostic relation of RDW with mortality. Future studies are suggested with prospective design with measurement of inflammatory markers, such as Procalcitonin, IL-6, and CRP with evaluation of comorbidities with Charlson index.

Conclusion:

We demonstrated elevated RDW predicts an increased risk of in-hospital death in AECOPD. Because testing for RDW values in AECOPD patients is an affordable method that will not require any additional costs either for patient or hospital, the potential prognostic value of RDW should be integrated into the comprehensive management of patients with ACOPD. Further studies are required to elucidate its underlying mechanism. ■

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