

## THE ROLE OF RED BLOOD CELL DISTRIBUTION WIDTH FOR PREDICTING 1-YEAR MORTALITY IN PATIENTS ADMITTED TO THE EMERGENCY DEPARTMENT WITH SEVERE DYSPNOEA

ULOGA ŠIRINE DISTRIBUCIJE ERITROCITA U PREDVIĐANJU JEDNOGODIŠNJEG MORTALITETA KOD PACIJENATA PRIMLJENIH U HITNU SLUŽBU ZBOG TEŠKE DISPNEJE

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### Summary

**Background:** Universally accepted and validated instruments for predicting the outcome of patients presenting to the emergency department (ED) with severe dyspnoea do not exist so far, nor are they regularly used by the emergency physicians. This study hence aimed to establish whether red blood cell distribution width (RDW) may be a predictive parameter of 1-year mortality in a population of patients admitted to the ED with severe dyspnoea attributable to different underlying disorders.

**Methods:** We retrospectively evaluated all the patients undergoing arterial blood gas analysis for severe dyspnoea (irrespective of the cause) during admission to ED of University Hospital of Verona from September 1, 2014 to November 31, 2014.

**Results:** The final study population consisted of 287 patients for whom complete clinical and laboratory information was available. Overall, 36 patients (12.5%) died after a 1-year follow-up. The RDW value was found to be considerably increased in patients who deceased during the follow-up compared to those who survived (17.2% versus 14.8%;  $p < 0.001$ ). In both univariate and multivariate analyses, the RDW value was found to be a significant predictor of 1-year mortality. In particular, patients with RDW  $\geq 15.0\%$  displayed a 72% increased risk of 1-year mortality after multiple adjustments.

### Kratak sadržaj

**Uvod:** Za sada ne postoje opšteprihvaćena i dokazana sredstva za predviđanje ishoda kod pacijenata koji se javljaju u hitnu službu (HS) zbog teških oblika dispneje, niti ih lekari u hitnoj službi redovno koriste. Cilj ove studije je stoga bio da se ustanovi da li širina distribucije eritrocita (eng. RDW) može poslužiti kao parametar za predviđanje mortaliteta u roku od godinu dana u populaciji pacijenata primljenih u HS sa teškom dispnejom usled različitih oboljenja.

**Metode:** Retrospektivna evaluacija je obuhvatila sve pacijente podvrgnute gasnoj analizi arterijske krvi zbog teške dispneje (bez obzira na uzorak) prilikom prijema u HS Univerzitetske bolnice u Veroni od 1. septembra 2014. do 31. novembra 2014.

**Rezultati:** Konačnu populaciju u ovoj studiji činilo je 287 pacijenata za koje su bili dostupni kompletni klinički i laboratorijski podaci. Ukupno 36 pacijenata (12,5%) umrlo je tokom jednogodišnjeg praćenja. Utvrđeno je da su vrednosti eritrocita bile značajno povišene kod pacijenata koji su preminuli tokom perioda praćenja u poređenju sa onima koji su preživeli (17,2% prema 14,8%;  $p = 0,001$ ). Univarijantna kao i multivarijantna analiza pokazale su da je vrednost eritrocita značajan prediktor jednogodišnjeg mortaliteta. Štaviše, pacijenti sa eritrocitima  $\geq 15,0\%$  imali su 72% veći rizik od smrtnog ishoda u roku od godinu dana, posle višestrukih prilagođavanja.

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**Conclusions:** The measurement of RDW, a very simple and inexpensive laboratory parameter, may represent an important factor for predicting medium-term mortality in patients presenting to the ED with severe dyspnoea.

**Keywords:** dyspnoea, red blood cell distribution width, mortality

## Introduction

Dyspnoea is conventionally defined as a subjective experience of breathing discomfort, which consists of qualitatively distinct sensations varying in intensity and perception of an inability to breathe comfortably (1, 2). This condition usually originates from a complex interplay among multiple physiological, psychological, social, and environmental factors, and is often accompanied by signs and symptoms of respiratory distress (1, 2). It has been established that the most informative approach to troubleshooting an acute respiratory failure entails a combination of clinical issues (i.e., uncomfortable abnormal awareness of breathing and/or respiratory rate  $\geq 25$ ) and results of arterial blood gas (ABG) analysis, typically showing at least one of the following: reduction in peripheral oxygen saturation ( $SpO_2 \leq 92\%$ ), arterial partial pressure of oxygen ( $pO_2 \leq 70$  mmHg), arterial partial pressure of  $CO_2$  ( $PaCO_2 \geq 45$  mmHg) and acidosis (i.e.,  $pH \leq 7.35$ ) (3).

Dyspnoea is a frequent complaint in patients admitted to the emergency department (ED). It can be caused by a number of pulmonary and cardiac pathologies (e.g., infectious, obstructive and/or infiltrative lung diseases, pulmonary embolism, acute coronary syndrome or heart failure), as well as hematologic (e.g., anaemia), metabolic (e.g., diabetic ketoacidosis) or neuromuscular (e.g., myopathies) disorders. Several lines of evidence strongly confirm that the vast majority of ED admissions for severe dyspnoea can be linked with this heterogeneous group of conditions (4, 5). Although some clinical tools have been developed, such as the Likert or Visual Analog Scale (VAS), these are mostly aimed at predicting early dyspnoea improvement (6). Therefore, a universally accepted and validated instrument for predicting the outcome of dyspnoea in ED patients does not exist so far, nor is regularly used by emergency physicians (7, 8). This is especially disconcerting if one considers that the rate of missed diagnosis in the ED can be as high as 20%, whereas the in-hospital mortality rate of patients acutely admitted for dyspnoea is up to 16% (3). Notably, chief complaint of dyspnoea was also found to be a major determinant of unscheduled returns to the ED and consequent hospital admission, thus posing an additional organizational and economic burden on emergency physicians (9).

According to the Acute Heart Failure Syndromes International Working Group (10), dyspnoea is a subjective experience of disease, for which no objective

**Zaključak:** Merenje vrednosti eritrocita, kao vrlo jednostavnog i pristupačnog laboratorijskog parametra, može predstavljati važan faktor u predviđanju srednjoročnog mortaliteta kod pacijenata koji se javljaju u HS sa teškom dispnejom.

**Ključne reči:** dispneja, širina distribucije eritrocita, mortalitet

measure is an adequate substitute. The development of reliable tools for predicting clinical outcomes and appropriate therapeutic management both in the ED and in the extra-hospital setting after patients have been discharged remains hence challenging, and is still regarded as an unmet need (10).

The red blood cell distribution width (RDW) is a simple and inexpensive measure of anisocytosis (i.e., the heterogeneity of erythrocytes volumes), which is automatically generated by modern hematological analyzers within the parameters of the complete blood count (CBC). The value of the RDW can be rapidly and efficiently used in the ED for gathering useful diagnostic and prognostic information about a patient's status (11). In particular, an increased RDW value has been convincingly associated with the outcome of many acute and severe conditions such as acute coronary syndrome (12), heart failure (13), stroke (14), pulmonary embolism (15), severe acute allergic reactions (16) and acute pancreatitis (17) among others.

Therefore, the aim of this study was to establish whether anisocytosis may also be a predictive parameter of 1-year mortality in a population of patients admitted to the ED with severe dyspnoea.

## Materials and Methods

### Study population

We retrospectively evaluated all patients undergoing ABG analysis for severe dyspnoea during admission to the Emergency Department (ED) of University Hospital of Verona (Italy) from September 1, 2014 to November 31, 2014. Dyspnoea was defined as either sudden onset of shortness of breath or increase in the severity of chronic dyspnoea in the last 48 h. The emergency room belongs to a large urban university hospital in the town of Verona, with approximately 90,000 visits per year. Dyspnoea was clinically diagnosed by the emergency physicians in accord with the accepted definition of the American Thoracic Society (1), thus excluding chest pain or palpitation. Additional exclusion criteria were orotracheal intubation before ED admission and dyspnoea due to traumatic events or severe haemorrhage. Demographic, clinical and laboratory information were always collected at ED admission.

### Laboratory testing

All patients finally included in the study underwent ABG testing at the time of ED admission, thus including the assessment of arterial pH,  $p\text{CO}_2$ ,  $p\text{O}_2$ , base excess (BE), bicarbonate and lactate (GEM Premier 4000, Instrumentation Laboratory, Lexington, MA, USA). An additional blood sample was taken for the assessment of the CBC (including haemoglobin and RDW) (Sysmex XE-2100; Sysmex Inc, Kobe, Japan) and creatinine (Jaffe compensated assay on Siemens Dimension Vista; Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The laboratory is certified according to the ISO 15189 standard, and the quality of data was validated throughout the study period by using internal quality control (IQC) procedures and participation to an External Quality Assessment (EQA) scheme (18).

### Study outcome

One-year mortality from original ED admission was identified as the primary endpoint of this retrospective investigation. Mortality was established upon scrutiny of digital medical records available in the hospital database. For patients without definitive information, direct contact was established by phone with the patients themselves or their relatives. This retrospective investigation did not require individual consent based on the institutional guidelines for waiving consent, was performed according to local ethical committee regulations in accord with the Helsinki declaration, and was finally cleared by the Institutional Review Board as a no-risk retrospective study.

### Statistical analysis

Continuous variables were expressed as median value and interquartile range (IQR); differences were evaluated with Mann–Whitney U test or Kruskal Wallis, when appropriate. Categorical variables were expressed as number and percentage; differences were analysed using Chi-square test and Fisher's Exact test. Univariate correlation analysis was assessed using Spearman's correlation. The diagnostic accuracy of RDW for predicting 1-year mortality was evaluated by means of receiver operating characteristics (ROC) analysis, and the most predictive RDW cut-off was chosen from analysis of the area under the curve (AUC). RDW was correlated with clinical outcomes both as a continuous and a categorical variable. Logistic binomial regression was used to evaluate independent effects of RDW on 1-year mortality after ED admission. Only variables found to be significantly associated with the risk of 1-year death in univariate analysis were entered into the multivariate model. Survival analysis was constructed using Kaplan Meier curves for cumulative risk study using

different RDW cut-off values. The statistical significance was set at  $p < 0.05$ . The statistical analysis was performed with SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) and with the statistical software package R version 2.12.2 (R Development Core Team, Auckland, New Zealand).

## Results

The final study population consisted of 287 patients who presented to the local ED for dyspnoea and for whom complete clinical and laboratory information was available. The main demographic, clinical and laboratory data are summarized in *Table I*. The median age of the entire patient cohort was 81 years (IQR, 69–88 years), whereas the median RDW value was 14.9% (IQR, 13.8–16.1%). Overall, 36 patients (12.5%) died during the 1-year follow-up. The value of RDW was found to be considerably increased in patients who deceased during follow-up compared to those who survived (17.2% versus 14.8%;  $p < 0.001$ ). The univariate correlation between RDW and ABG parameters is shown in *Table II*. The value of RDW at ED admission was found to be negatively correlated with  $\text{SpO}_2$ , bicarbonate and BE, whereas a strong and positive association was found with blood lactate. Interestingly, when patients were classified according to the  $p\text{O}_2$  values at admission, the value of RDW in the hypoxic group (i.e., patients with  $p\text{O}_2 < 60$  mmHg) was significantly higher than that of normoxic patients (15.5% versus 14.8%;  $p = 0.005$ ).

When expressed as a continuous variable, the RDW value was found to be a significant predictor of 1-year mortality in a univariate analysis, exhibiting an odds ratio (OR) of 1.74 (95% CI, 1.45–2.10;  $p < 0.001$ ). The AUC and the best RDW cut-off value for predicting 1-year mortality were 0.828 (95% CI, 0.759–0.897;  $p < 0.001$ ) and 15.0% (0.87 sensitivity and 0.59 specificity), respectively (*Figure 1*). Accordingly, a  $\text{RDW} \geq 15.0\%$  displayed an OR of 9.4 (3.8–23.5;  $p < 0.001$ ) for 1-year mortality. The use of a lower RDW threshold value (i.e., 14.2%) was characterized by greater sensitivity (i.e., 0.95) but much lower specificity (i.e., 0.36).

The association between RDW and 1-year death outcome remained statistically significant in a multivariate analysis (*Table III*), wherein  $\text{RDW} \geq 15.0\%$  displayed an adjusted OR of 1.72 (95% CI, 1.37–2.16;  $p < 0.001$ ). Interestingly, 1-year mortality could also be significantly predicted by blood lactate, heart rate and  $\text{SpO}_2$ . The survival curve analysis according to RDW value  $\geq 15.0\%$  is shown in *Figure 2*. Notably, in the entire patient sample (*Figure 2a*) as well as in patients with respiratory distress (i.e., defined as  $p\text{O}_2 < 60$  mmHg or  $\text{SpO}_2 < 90\%$ ) ( $n = 95$ ; *Figure 2b*), a  $\text{RDW} \geq 15.0\%$  was associated with much shorter survival.

**Table I** Demographic, clinical and laboratory data of the study population, entailing 287 patients admitted to the emergency department (ED) for severe dyspnoea.

Variable, n (%)	Alive after 1 year	Deceased after 1 year	p
Patients, n	251 (87.5%)	36 (12.5%)	
Diagnosis			0.123
Pulmonary embolism	21 (8.4)	1 (2.8)	
Heart failure	88 (35.1)	12 (33.3)	
Pneumonia	54 (21.5)	9 (25)	
Asthma	13 (5.2)	1 (2.8)	
COPD	35 (13.9)	5 (13.9)	
Pneumothorax	3 (1.2)	0 (0)	
Sepsis	10 (4)	7 (19.4)	
Bronchitis	27 (10.8)	1 (2.8)	
Age, years	80 (68–88)	86 (73–90)	0.001
Gender, females	124 (49.4)	18 (50)	1.000
Comorbidities			
Hypertension	169 (67.9%)	22 (64.7%)	0.713
Chronic Heart Failure	46 (18.5%)	14 (41.2%)	0.005
Arrhythmia	60 (23.9%)	8 (22.2%)	1.000
Ischemic heart disease	58 (23.1%)	11 (30.6%)	0.403
Vascular Disease History	37 (14.7%)	10 (22.8%)	0.056
Valvular heart disease	28 (11.2%)	5 (13.9%)	0.582
COPD	60 (23.9%)	7 (19.4%)	0.675
Previous stroke	21 (8.4%)	4 (11.1%)	0.533
Cancer	36 (14.3%)	9 (25%)	0.137
Laboratory data			
Haemoglobin, g/L	126 (112–141)	103 (94.5–126)	0.001
Creatinine, $\mu$ mol/L	106 (82–140)	151 (108–306)	0.008
RDW, %	14.8 (13.7–15.8)	17.2 (15.8–18.5)	0.001
Sodium	138.7 (135.4–141)	137.4 (131.7–(141.7)	0.249
Potassium	3.9 (3.6–4.2)	4.1 (3.6–4.7)	0.124
Arterial Blood Gas Analysis			
PO <sub>2</sub> , mmHg	61.6 (51.4–73.4)	50.6 (42–53.6)	0.238
PCO <sub>2</sub> , mmHg	36.5 (30.8–43.9)	36.2 (27.7–41.7)	0.126
Lactate, mmol/L	1.3 (1.1–2.1)	2.7 (1.6–5.8)	0.001
BE, mmol/L	1.2 (-0.8–3.2)	- 1 (-6.8–1.3)	0.004
Bicarbonate, mmol/L	24.5 (22–27.6)	23.4 (17.8–26.8)	0.104
SpO <sub>2</sub> , % 80 (68–88)	91.7 (86.5–95.2)	87.1 (59.7–94.5)	0.041

BE, base excess; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width; PO<sub>2</sub>, arterial partial pressure of oxygen; SpO<sub>2</sub>, peripheral oxygen saturation; PCO<sub>2</sub>, arterial partial pressure of CO<sub>2</sub>

**Table II** Univariate correlation between red blood cell distribution width (RDW) and arterial blood gas (ABG) analysis.

Pearson's correlation	RDW	p
ABG parameters		
pO <sub>2</sub>	- 0.090	0.129
pCO <sub>2</sub>	- 0.097	0.102
SpO <sub>2</sub>	- 0.137	0.023
Bicarbonate	- 0.173	0.009
Lactate	0.228	0.001
BE	- 0.109	0.045
Na	- 0.17	0.780
K	0.108	0.087

BE, base excess; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width; PO<sub>2</sub>, arterial partial pressure of oxygen; SpO<sub>2</sub>, peripheral oxygen saturation; PCO<sub>2</sub>, arterial partial pressure of CO<sub>2</sub>

**Table III** Multivariate analysis including the significant predictors of 1-year mortality after emergency department (ED) admission for severe dyspnoea from the univariate analysis.

Variables	Coefficient	Odds Ratio	95% CI	p
RDW	0.543	1.722	1.371–2.162	0.001
Lactate	0.411	1.508	1.174–1.937	0.001
Heart rate >100	0.855	2.352	0.884–6.260	0.087
SpO <sub>2</sub> < 90%RDW	0.992	2.696	1.017–7.144	0.046

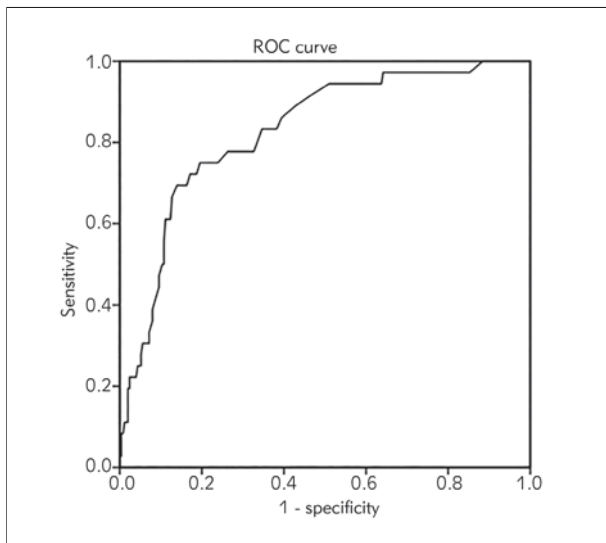
BE, base excess; COPD, chronic obstructive pulmonary disease; RDW, red blood cell distribution width; SpO<sub>2</sub>, peripheral oxygen saturation

**Discussion**

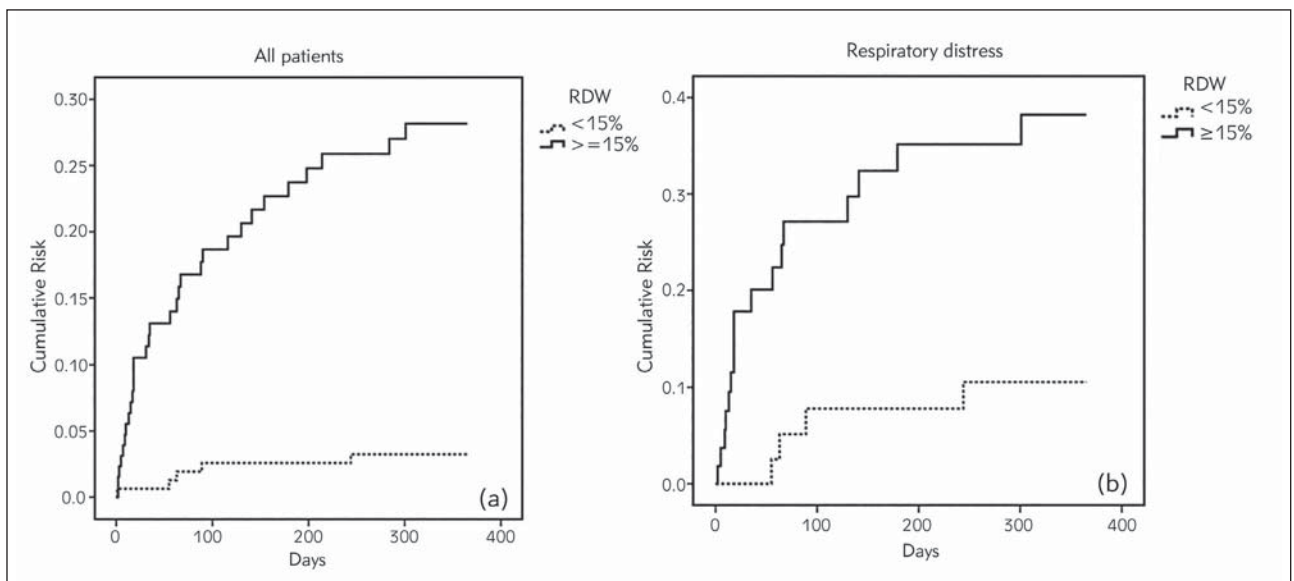
Dyspnoea is a complex symptom, which often anticipates or reflects a critical threat to homeostasis, and is hence frequently associated with impaired performance and decreased quality of life (2). Despite the underlying causes of dyspnoea being indeed multiple, multifaceted and frequently interplaying, the outcome of patients presenting to the ED with severe dyspnoea remains importantly prejudiced by high

morbidity and mortality rates. The unquestionable importance of accurate and timely management of patients is confirmed by recent evidence that inappropriate treatment of severe dyspnoea may be associated with approximately 3-time higher mortality (3). In an attempt to both improve clinical outcomes and limit overcrowding in the ED, some clinical decision aids and prediction tools have been proposed to assist emergency physicians in meeting these demands. Although these prediction tools have proven useful in acute care management, thus allowing rapid decisions and overall improving ED efficiency (8), they are mostly specific for certain associated conditions (i.e., acute coronary syndrome, asthma, etc.) and are not designed to provide risk stratification and mortality prediction in all patients presenting to the ED with dyspnoea.

The results of our retrospective investigation, which included a relatively ample number of patients admitted to the ED with severe dyspnoea, suggest that RDW is associated to, and may hence independently predict, the risk of 1-year mortality in such patients. Notably, the risk of death in univariate analysis was found to be up to 9-time higher in patients with  $RDW \geq 15.0\%$ , and remained nearly 2-time higher after adjustment in multivariate analysis, thus providing further support to the important role that anisocytosis may play in the pathogenesis of many severe pathologies (19). Interestingly, the RDW value at ED admission was also found to be associated with a worse respiratory status, as attested by the negative correlation with  $SpO_2$ , bicarbonate and BE, along with the positive association with blood lactate.



**Figure 1** Receiver operating characteristics (ROC) curve analysis of red blood cell distribution width (RDW) for predicting 1-year mortality in patients admitted to the emergency department with severe dyspnoea.



**Figure 2** Survival curve analysis of 1-year mortality according to RDW value in patients admitted to the emergency department with severe dyspnoea.



A strict relationship exists between oxygen and erythropoiesis. Blood oxygenation is a major determinant of the renal synthesis of the hormone erythropoietin, which both promotes the release of immature erythrocyte precursors from the bone marrow and enhances survival of reticulocytes into the circulation (20). Hypoxemia, along with the consequent enhancement of erythropoietin production, are followed by a relatively persistent increase in RDW values, mostly sustained by the release of large red blood cells from the bone marrow, which ultimately contribute to increase the heterogeneity of erythrocyte volumes (21). In a pathophysiological perspective, it is hence conceivable that severe respiratory distress and the related hypoxemia may contribute to generate a consistent perturbation of erythrocyte biology, mirrored by enhanced anisocytosis, which might ultimately expose the patients with severe dyspnoea to a greater risk of future chronic illness and mortality.

Overall, the results of our retrospective investigation not only confirm but also extend those of the only study in which the relationship between RDW

and mortality risk had been previously assessed in a general population of patients presenting to the ED with severe dyspnoea. Briefly, Hong et al. (22) retrospectively analysed short-term mortality in 907 patients admitted to the ED with acute dyspnoea, and found that those with RDW values in the highest tertile had a 7-fold higher risk of 30-day mortality than those in the lowest tertile, after adjustment for other risk factors.

In conclusion, and in accord with previous evidence provided by Hong et al., (22) our findings suggest that the measurement of RDW, a very simple and inexpensive laboratory parameter, may represent an important factor for predicting short- and medium-term mortality in patients with severe dyspnoea regardless of the underlying condition.

### Conflict of interest statement

The authors stated that they have no conflicts of interest.

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