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SPECIAL ARTICLE

# Red cell distribution width as predictor for mortality in critically ill patients

**I.A. Meynaar[1,2], A.H.M. Knook[1], S. Coolen[3], H. Le[3], M.M.E.M. Bos[4], F. van der Dijs[3], M. von Lindern[5], E.W. Steyerberg[6]**

[1]Intensive Care Unit, [3]Department of Clinical Chemistry and [4]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, the Netherlands, [2]Intensive Care Unit, Haga Hospital, The Hague, the Netherlands, [5]Sanquin Research and Landsteiner Laboratory Amsterdam Medical Centre, Amsterdam University, Amsterdam, the Netherlands, [6]Department of Public Health, Erasmus MC – University Medical Centre Rotterdam, Rotterdam, the Netherlands, *corresponding author: e-mail: iwanmeynaar@gmail.com

## ABSTRACT

Background: The objective of this study was to evaluate whether the red cell distribution width (RDW) is a significant risk factor for hospital mortality in critically ill patients and to investigate whether RDW is a parameter indicating inflammation, or a risk factor independent of inflammation.

Methods: We studied all patients admitted to a ten-bed mixed intensive care unit in the Netherlands between May 2005 and December 2011 for whom RDW was available, and who had not received a blood transfusion in the preceding three months. Inflammation was measured by C-reactive protein and leucocyte count. Analyses included correlation, logistic regression analysis, and receiver-operating characteristic (ROC) curves.

Results: We included 2915 patients, of whom 387 (13.3%) did not survive to hospital discharge. In univariate analysis higher RDW values were associated with increased hospital mortality. In multivariate analysis RDW remained an independent risk factor for mortality after correction for APACHE II score, age, admission type and mechanical ventilation (odds ratio 1.04, 95% confidence interval 1.02-1.06, for each femtolitre of RDW). Adding RDW to APACHE II, however, increased the area under the ROC curve marginally (from 0.845 to 0.849, p<0.001). RDW was not correlated with C-reactive protein and leucocyte count, refuting the hypothesis that the association between RDW and outcome is mediated through inflammation.

Conclusion: In critically ill patients, the RDW on ICU admission was an independent predictor of mortality. Since RDW was not correlated with inflammation, the underlying mechanism of this association warrants further investigation.

## KEYWORDS

Anaemia, critical care, CRP, inflammation, outcome, RDW

## INTRODUCTION

Erythrocytes differ in size, getting gradually smaller during ageing. Their mean volume is quantified by the mean corpuscular volume (MCV) and the variation in size by the red cell distribution width (RDW). RDW is calculated automatically when a full blood count is requested, but the clinical usefulness of RDW is limited to the differential diagnosis of anaemia. Recent studies found associations of an increased variation in the size of the erythrocytes as measured by RDW with mortality irrespective of mean cellular volume (MCV) and haemoglobin levels. Associations were reported for patients with heart failure,[1-3] acute myocardial infarction,[1,4] community-acquired pneumonia,[5] pulmonary hypertension[6] and in the general population.[7-9] In three studies involving critically ill patients, an increased RDW was independently associated with increased mortality.[10-12] In patients with pulmonary hypertension, RDW was superior to N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in predicting outcome.[6] In patients with heart failure, RDW was as good as NT-pro-BNP and superior to New York Heart Association class, renal function and even ejection fraction in predicting outcome.[3,13] While the association between increased RDW and increased mortality seems to be an almost universal finding, the reason for this remains to be elucidated. One of the possible explanations, suggested by several authors, is that an increased RDW is caused by a state of

inflammation.[4] Lippi *et al*. found a correlation between RDW and erythrocyte sedimentation rate in their analysis of routinely acquired haematological data of outpatients.[14] Perlstein *et al*. found an association between RDW and C-reactive protein in a community-based cohort, but since no explanation for this association was given it is conceivable that the association was found by chance and for instance based on confounding.[9] Vitamin and nutritional deficiency, especially deficiencies in iron, folate and vitamin B12, can cause an increased RDW, but Perlstein *et al*. found RDW to be an independent predictor of mortality even after correction for vitamin deficiencies.[9] Bone marrow dysfunction, haemodilution, renal insufficiency and abnormalities of erythropoietin response have also been mentioned as possible explanations.[2,3]
The objective of this study was to evaluate the prognostic importance of increased red cell distribution width (RDW) with hospital mortality in critically ill patients. Specifically, we aimed to test the hypothesis that inflammation explains the association between RDW and mortality.

## MATERIALS AND METHODS

### Setting

The study was conducted in the single mixed medical and surgical adult intensive care unit (ICU) of the Reinier de Graaf Hospital in Delft, the Netherlands. The hospital is a 500-bed teaching hospital covering all specialities except cardiac surgery and neurosurgery. The closed format ICU has ten beds and is intensivist-run with 24/7 availability. The intensivists decide on admission to and discharge from the ICU. The nurse to patient ratio is 1:2. During the study period APACHE II standardised mortality rate (SMR), the ratio between observed hospital mortality and expected hospital mortality according to APACHE II, was 0.73. The hospital has an ICU-based medical emergency team.

### Patient selection

All consecutive patients admitted to the ICU between 1 May 2005 and 31 December 2011, for whom a full blood count with RDW was available in the laboratory database, were entered into the study. If a patient was readmitted to the ICU during the study period, only the first admission was used. The need for ethical approval and informed consent was waived by the local medical ethics committee (METZ Zuid West Holland).

### Patient data

Demographic data, APACHE II scores, expected mortality and outcome data (ICU and hospital mortality) were collected on admission as part of the routine and mandatory data collection for the Dutch Intensive Care Registry (National Intensive Care Evaluation, NICE). Physiological data and data about patient history were collected on paper by the intensivist on call, demographic data and laboratory data were collected electronically. All data were entered into a dedicated ICU database (Mediscore, Itemedical, Tiel, the Netherlands). Data quality was checked regularly by external officials from NICE. In accordance with APACHE II and NICE definitions, patients were defined as medical patients if they had not undergone surgery in the preceding seven days and were not admitted to prepare them for surgery. Planned or elective surgery was defined as surgery according to the schedule, emergency or urgent surgery was defined as surgery that had not been planned beforehand. Patients fulfil APACHE II criteria when they have been treated in the ICU for at least eight hours, when they are 16 years or older and when they have not been admitted to the ICU before during this hospital admission.

### Laboratory investigations

The starting date of May 2005 was chosen because from that moment on RDW was measured automatically whenever haemoglobin (Hb) was requested. For all requested Hb values RDW, haematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were available in the laboratory database. Leucocyte count and CRP were not completely available. For the study we only included laboratory results from blood samples that were taken within 24 hours before until 24 hours after the time of admission to the ICU. RDW is the standard deviation of MCV and can be given in femtolitre (fl) as is done in this study. Some authors present RDW as the coefficient of variation which is calculated as 100 x (RDW/MCV). Normal values for Hb were 7.3-9.8 mmol/l (adult women) and 8.4-10.9 mmol/l (adult men), for Ht 0.36-0.48 l/l and 0.42-0.51 l/l respectively, for MCV 83-98 fl, for RDW 37.0-48.0 fl, for leucocyte count 3.5-11.0 x $10^9$/l, for MCH 1.60-2.06 mmol/cell, for MCHC 19.5-22.5 mmol/l and for CRP 0-10 mg/l. Haematological parameters were determined using XE-5000 analysers (Sysmex Corp., Tokyo, Japan). This analyser calculates the MCV, MCH and MCHC based on measurement of Hb and Ht. CRP was determined by a latex immunoassay using the Architect C16000(Abbott, Illinois, USA).

### Statistical analysis

The primary study endpoint was hospital mortality. We studied the association between hospital mortality and available potential risk factors for mortality, namely APACHE II score, age, mechanical ventilation during ICU treatment, sepsis on admission to the ICU, admission type, and also the laboratory parameters Hb, Ht, RDW, MCV, MCH, MCHC, leucocyte count and CRP. We only used

the laboratory results taken within 24 hours before to 24 hours after the time of admission to the ICU. Continuous data are reported as mean and standard deviation (SD) when normally distributed or otherwise as median and interquartile range (IQR) and compared using Student's t-test or Mann Whitney U test as appropriate. Normality was checked using histograms. Categorical data were compared using the Chi square test and by calculating odds ratios and 95% confidence intervals (CI). Univariate association between potential risk factors and mortality was done by stratified analysis using quartiles. Logistic regression analysis was used to study risk factors for hospital mortality. For logistic regression analysis APACHE II score, age, RDW, Ht, Hb, MCV, MCH, MCHC and CRP were entered as continuous variables. Sepsis on admission to the ICU (yes/no), mechanical ventilation during ICU treatment (yes/no), admission type (medical, planned surgery or emergency surgery) and leucocyte count (using quartiles) were entered as categorical variables. Improvement in model fit was statistically tested by likelihood ratio statistics and further quantified by the area under the receiver operating characteristic (AUC-ROC) curve. To avoid multicollinearity correlation between parameters this was checked using Pearson's R for normally distributed parameters or otherwise with Spearman's rho. To test the hypothesis that RDW is associated with increased mortality because RDW is associated with inflammation, the correlation between RDW and leucocyte count and correlation between RDW and CRP was quantified using Spearman's rho. Two-sided comparisons with 95% confidence intervals (95% CI) were used and p values of less than 0.05 were considered statistically significant. Data were analysed with SPSS 18.0 (SPSS, Chicago, IL, USA).

## RESULTS

Between May 2005 and December 2011 there were 4568 ICU admissions of 3954 individual patients. RDW was available for 3345 patients, and absent for 609 patients. We excluded the 330 patients who had received a blood transfusion in the three months preceding ICU admission. This left us with 2915 patients fulfilling inclusion criteria to be analysed. Basic characteristics are shown in *table 1*. The top 5 primary medical diagnoses were sepsis (n=224, 19.3%), respiratory disease (n=124, 10.7%), pneumonia (n=119, 10.3%), drug overdose (n=98, 8.5%) and cardiac arrest (n=94, 8.1%). The top 5 primary surgical diagnoses were gastrointestinal surgery (n=635, 36.1%), vascular surgery (n=507, 28.9%), sepsis (n=169, 9.6%), thoracic surgery for cancer (n=116, 6.6%) and renal/bladder surgery (n=115, 6.5%). Univariate analysis, using quartiles, indicated that hospital mortality was associated with haemoglobin, haematocrit, RDW, MCHC, leucocytes and CRP, but not with MCV and MCH (*table 2*). The association was linear except for leucocytes where the association was curvilinear: mortality was lowest in the range of 7.94-10.88 x $10^9$/l and higher below and above that range. High correlations were found between haemoglobin and haematocrit (R=0.975), between MCV and MCH (R=0.817), between MCH and MCHC (R=0.481) and between sepsis and CRP (R=0.478). We hypothesised that the increase in RDW would be a sign of inflammation and therefore there should be a correlation between RDW and CRP or leucocytes. However, the correlation between RDW and leucocytes was very low (Pearson R = 0.003) and the correlation between RDW and CRP (in 1743 patients with CRP available) was also low (Spearman's rho = 0.062), refuting this hypothesis.

Logistic regression analysis showed that RDW was the only haematological parameter that was an independent risk factor for mortality (*table 3*, Wald statistic 14, p<0.001). However, the APACHE II score (Wald statistic 176), age (Wald statistic 64), and mechanical ventilation (Wald statistic 31) were strong predictors. Addition of RDW to the APACHE II score only increased the AUC-ROC from 0.845 to 0.849 (p<0.001, likelihood ratio test). The interrelated parameters haemoglobin and haematocrit, MCV and MCHC, and leucocytes were not independently related to mortality in a model with age and APACHE II score. When we used CRP instead of sepsis in similar models (with 1682 patients in whom both APACHE II score and CRP were available) we found similar results: RDW remained an independent risk factor for mortality, while CRP was not (data not shown).

## DISCUSSION

The aim of our study was to evaluate the relevance of RDW as an independent risk factor for mortality of critically ill patients. In this retrospective study of patients in a mixed general ICU we found that an increased variation in the size of a patient's erythrocytes (RDW) at admission to the ICU was an independent prognostic factor for in-hospital mortality after correction for APACHE II score, age, mechanical ventilation, sepsis and admission type. However, adding RDW to APACHE II only marginally increased the area under the ROC curve for the prediction of mortality. Although it has been suggested that RDW reflects inflammation, we did not find a correlation between RDW and CRP or between RDW and leucocyte count.

This study confirms the findings of the three previous studies on RDW and outcome in critically ill patients.[10-12] Bazick *et al.* studied over 50,000 patients from two tertiary academic hospitals and found RDW to be a strong and

**Table 1.** *Patient characteristics*

| | All | Discharged alive | Died in hospital | P[2] |
|---|---|---|---|---|
| All patients | 2915 | 2528 (86.7%) | 387 (13.3%) | |
| Male | 1665 | 1447 (86.9%) | 218 (13.1%) | ns |
| | | | | |
| Medical | 1158 | 915 (79.0%) | 243 (21.0%) | <0.001 |
| Planned surgery | 1418 | 1330 (93.8%) | 88 (6.2%) | <0.001 |
| Urgent surgery | 339 | 283 (83.5%) | 56 (16.5%) | <0.001 |
| | | | | |
| Age (years) | 65.1 (16.0) | 63.9 (16.2) | 73.0 (12.3) | <0.001 |
| <50 | 484 | 467 (96.5%) | 17 (3.5%) | <0.001 |
| 50-59 | 443 | 404 (91.2%) | 39 (8.8%) | <0.001 |
| 60-69 | 653 | 585 (89.6%) | 68 (10.4%) | <0.001 |
| 70-79 | 841 | 711 (84.5%) | 130 (15.5%) | <0.001 |
| 80-89 | 450 | 332 (73.8%) | 118 (26.2%) | <0.001 |
| >=90 | 44 | 29 (65.9%) | 15 (34.1%) | <0.001 |
| | | | | |
| APACHE II exp mort[1] | 10% (5-24) | 9% (4-18) | 44% (21-72) | <0.001 |
| APACHE II score | 12.0 (7.4) | 12.1 (6.2) | 22.3 (8.8) | <0.001 |
| APACHE II 0-10 | 1154 | 1126 (97.6%) | 28 (2.4%) | <0.001 |
| APACHE II 11-20 | 1247 | 1104 (88.5%) | 143 (11.5%) | <0.001 |
| APACHE II 21-30 | 322 | 211 (65.5%) | 111 (34.5%) | <0.001 |
| APACHE II >30 | 107 | 29 (27.1%) | 78 (72.9%) | <0.001 |
| | | | | |
| No sepsis on admission | 2459 | 2188 (89.0%) | 271 (11.0%) | <0.001 |
| Sepsis on admission | 456 | 340 (74.6%) | 116 (25.4%) | <0.001 |
| No mechanical ventilation | 1846 | 1739 (94.2%) | 107 (5.8%) | <0.001 |
| Mechanical ventilation | 1069 | 2528 (86.7%) | 387 (13.3%) | <0.001 |
| LOS ICU (days) | 1.2 (0.8-3.3) | 1.0 (0.8-2.9) | 2.4 (0.9-6.0 | <0.001 |
| LOS hospital (days) | 10 (6-18) | 11 (7-19) | 7 (3-15) | <0.001 |
| | | | | |
| Haemoglobin (mmol/l) | 6.9 (1.3) | 6.9 (1.3) | 6.7 (1.5) | 0.002 |
| Haematocrit (l/l) | 0.33 (0.06) | 0.34 (0.06) | 0.33 (0.07) | 0.046 |
| MCV (fl) | 89.8 (6.0) | 89.7 (5.9) | 90.5 (6.7) | 0.023 |
| MCH (fmol/cell) | 1.86 (0.14) | 1.86 (0.14) | 1.85 (0.15) | ns |
| MCHC (mmol/l) | 20.7 (0.85) | 20.7 (0.83) | 20.5 (0.95) | <0.001 |
| RDW (fl) | 47.3 (6.4) | 46.9 (6.2) | 49.7 (6.9) | <0.001 |
| Leucocytes (x $10^9$/l) | 11.9 (6.1) | 11.8 (5.8) | 12.6 (8.0) | ns |
| CRP (mg/l)[3] | 48 (11-159) | 41 (9-152) | 88 (28-176) | <0.001 |

**Data are presented as mean (SD), median (IQR) or number (percentage) as appropriate. [1]for 2830 patients fulfilling APACHE II inclusion criteria; [2]Chi square test, t test or Mann Whitney U test as appropriate; [3]CRP was available in 1743 patients; CRP = C-reactive protein; Exp mort = expected mortality; LOS = length of stay; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; ns = not significant; RDW = red cell distribution width.**

independent predictor of mortality. Wang *et al.* found RDW not only to be an independent predictor for mortality but also for hospital length-of-stay in a single centre study involving 602 patients. In their multicentre study of 17,922 ICU patients, Hunziker *et al.* found that RDW improved prognostication of SAPS I score. Newer and more frequently used models such as SAPS II, APACHE II or APACHE IV, however, were not included in these studies. The present study is the first to evaluate the predictive properties of RDW in addition to the commonly used APACHE II model.

It has been suggested that the association between RDW and mortality can be explained by RDW being a marker of inflammation. However, we found no correlation between RDW and available markers of inflammation. RDW may also be increased by blood transfusions, by the presence of anaemia and by dietary status (iron, folate and vitamin B12). In our study, patients with one or more blood transfusions in the three months preceding admission to the ICU were excluded, but information on iron deficiency, folate or vitamin B12 was not available. An increase in RDW without a change in MCV implies an increase in

**Table 2.** *Univariate analysis of haematological parameters and mortality*

| | Number | Hospital mortality | OR (95% CI) | P |
|---|---|---|---|---|
| RDW <43.20 fl | 714 | 53 (7.4%) | Ref= 1 | <0.001 |
| RDW 43.20-46.09 fl | 734 | 80 (10.9%) | 1.53 (1.06-2.19) | <0.001 |
| RDW 46.10-49.69 fl | 729 | 84 (11.5%) | 1.62 (1.13-2.34) | <0.001 |
| RDW >49.70 fl | 738 | 170 (23.0%) | 3.73 (2.79-5.18) | <0.001 |
| | | | | |
| Haematocrit ≥0.37 | 807 | 100 (12.4%) | Ref=1 | 0.001 |
| Haematocrit 0.33-0.36 | 719 | 85 (11.8%) | 0.95 (0.70-1.29) | 0.001 |
| Haematocrit 0.29-0.32 | 848 | 101 (11.9%) | 0.96 (0.71-1.28) | 0.001 |
| Haematocrit <0.29 | 541 | 101 (18.7%) | 1.62 (1.20-2.19) | 0.001 |
| | | | | |
| Haemoglobin ≥7.8 mmol/l | 740 | 90 (12.2%) | Ref=1 | <0.001 |
| Haemoglobin 6.9-7.7 mmol/l | 737 | 83 (11.3%) | 0.92 (0.67-1.26) | <0.001 |
| Haemoglobin 6.0-6.8 mmol/l | 774 | 93 (12.0%) | 0.99 (0.72-1.34) | <0.001 |
| Haemoglobin <6.0 mmol/l | 664 | 121 (18.2%) | 1.61 (1.20-2.16) | <0.001 |
| | | | | |
| Leucocytes <7.94 | 728 | 109 (15.0%) | 1.73 (1.25-2.39) | <0.001 |
| Leucocytes 7.94-10.88 | 725 | 67 (9.2%) | Ref=1 | <0.001 |
| Leucocytes 10.89-14.51 | 731 | 88 (12.0%) | 1.34 (0.96-1.88) | <0.001 |
| Leucocytes ≥14.52 | 730 | 123 (16.8%) | 1.99 (1.45-2.73) | <0.001 |
| | | | | |
| CRP <11 mg/l[1] | 430 | 33 (7.7%) | Ref=1 | <0.001 |
| CRP 11-47 mg/l | 440 | 79 (18.0%) | 2.63 (1.71-4.05) | <0.001 |
| CRP 48-158 mg/l | 434 | 97 (22.4%) | 3.46 (2.27-5.27) | <0.001 |
| CRP >=159 mg/l | 439 | 98 (22.3%) | 3.46 (2.27-5.26) | <0.001 |
| | | | | |
| MCV <86.20 fl | 713 | 96 (13.5%) | Ref=1 | ns |
| MCV 86.20-89.59 fl | 744 | 86 (11.6%) | 0.84 (0.62-1.15) | ns |
| MCV 89.60-93,09 fl | 721 | 88 (12.2%) | 0.89 (0.66-1.22) | ns |
| MCV ≥93.10 fl | 737 | 117 (15.9%) | 1.21 (0.91-1.63) | ns |
| | | | | |
| MCH ≥1.94 | 740 | 95 (12.8%) | Ref=1 | ns |
| MCH 1.860-1.939 | 729 | 95 (13.0%) | 1.02 (0.75-1.38) | ns |
| MCH 1.781-1.859 | 715 | 85 (11.9%) | 0.92 (0.67-1.25) | ns |
| MCH <1.781 | 728 | 112 (15.4%) | 1.23 (0.92-1.66) | ns |
| | | | | |
| MCHC ≥21.30 | 729 | 75 (10.3%) | Ref=1 | <0.001 |
| MCHC 20.70-21.29 | 826 | 90 (10.9%) | 1.07 (0.77-1.47) | <0.001 |
| MCHC 20.20-20.69 | 675 | 91 (13.5%) | 1.36 (0.98-1.88) | <0.001 |
| MCHC <20.20 | 681 | 130 (19.1%) | 2.06 (1.52-2.79) | <0.001 |

**[1]C-reactive protein (CRP) was available in 1743 patients. All parameters except mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MVC) are associated with mortality. The association is linear (mortality either increases or decreases with increasing value of the parameter) except for leucocytes where the association is curvilinear (mortality is lowest in the range of 7.94-10.88 and is higher below and above that range). MCHC = mean corpuscular haemoglobin concentration; ns = not significant; RDW = red cell distribution width.**

the number of smaller and an increase in the number of larger erythrocytes in the blood. The increased number of smaller erythrocytes may be explained by an increase in vesicle shedding by erythrocytes potentially due to membrane damage inflicted by alterations in the injured tissue capillary bed. Thus, accelerated vesicle shedding enhances erythrocyte clearance. To compensate this clearance may result in enhanced, erythrocyte production and the release of relatively large reticulocytes from the bone marrow. Future measurement of reticulocyte counts may indicate whether an increased RDW indicates enhanced ageing and reticulocyte release. Hence, the functional implications of RDW as an independent risk factor for mortality and morbidity needs further study.

From a prediction perspective it appears that RDW is helpful in refining prognostic estimates for mortality and length of stay, but only to a minor extent (small increase in ROC area). Since RDW is a cheap laboratory

**Table 3.** *Logistic regression analysis in 2830 patients fulfilling APACHE II criteria of all significant predictors of mortality*

| | Wald | p | OR (95% CI) |
|---|---|---|---|
| APACHE II | 176 | <0.001 | 1.14 (1.12-1.16) |
| Age | 64 | <0.001 | 1.04 (1.03-1.06) |
| Mechanical ventilation | 31 | <0.001 | 2.32 (1.72-3.12) |
| RDW | 14 | <0.001 | 1.04 (1.02-1.06) |
| Admission type | 12 | 0.003 | |
| -Urgent vs planned surgery (=ref) | 7 | 0.008 | 1.76 (1.16-2.66) |
| -Medical vs planned surgery (=ref) | 10 | 0.002 | 1.68 (1.21-2.33) |

**Final model, showing that even after correction for APACHE II score, age, mechanical ventilation and admission type, red cell distribution width (RDW) is an independent risk factor for mortality. When sepsis, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration or leucocytes were entered in this model instead of RDW, none of these were significant risk factors (data not shown).**

measurement, its addition to risk prediction algorithms may still be cost-effective.[15] However, to achieve a significant improvement in current prediction scores of APACHE II and other prognostic factors, a larger set of new biomarkers is required.

We acknowledge several weaknesses and limitations in our study. Firstly, we performed a retrospective study and some possibly interesting data are lacking: reticulocyte count, iron status, folate and vitamin B12. Secondly, regarding the association between RDW and CRP, the latter was only available for 60% of patients and it is most likely that these patients were more seriously ill. Also the absence of other markers of inflammation, such as procalcitonin or interleukin-6, hampered further evaluation of the relationship between RDW and inflammation. The strengths of our study include the prospective collection of clinical and laboratory data, and the observation that different statistical analyses produced similar results.[16]

## CONCLUSION

In conclusion, an increased variation in the size of erythrocytes on admission to the ICU, as indicated by RDW, is an independent prognostic factor for hospital mortality in critically ill patients. However, adding RDW to the APACHE II score only marginally improves mortality prediction. The biological mechanism behind this association is not one arising from inflammation as expressed by leucocyte count or CRP. This calls for further studies with more patients. Since RDW only marginally improves the prediction of mortality, a possible role of RDW in outcome prediction also warrants further analysis.

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