Red cell distribution width is associated with hospital mortality in unselected critically ill patients

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ABSTRACT

Background and objectives: Red cell distribution width (RDW) is a variability of red cell sizes and has been associated with outcomes in many clinical settings. Its prognostic value in intensive care unit (ICU) has been reported but requires confirmation. The study aimed to investigate the role of RDW in predicting hospital mortality in critically ill patients.

Methods: This is a retrospective study conducted in a 24-bed ICU of a tertiary teaching hospital. Data on demographic characteristics and laboratory measurements were collected from medical information database. Baseline variables were compared between survivors and nonsurvivors. The primary endpoint was hospital mortality; and ICU length of stays (LOS) were compared between patients with RDW >14.8% and ≤14.8%. The predictive value of RDW was also measured using receiver operating characteristic (ROC) curves. Two-sided P<0.05 was considered to be statistically significant.

Results: A total of 1,539 patients were enrolled during study period, including 1,084 survivors and 455 nonsurvivors. In univariate analysis, variables such as age, sex, primary diagnosis, C-reactive protein (CRP), RDW and albumin were significantly associated with hospital mortality. RDW remained significantly associated with mortality after adjustment for sex, age, Charlson index albumin and CRP, with an odds ratio of 1.1 (95% CI: 1.03-1.16). Diagnostic performance of RDW in predicting mortality appeared to be suboptimal (AU-ROC: 0.62). Changes in RDW during a short follow up period were not associated with mortality.

Conclusions: RDW measured on ICU entry is associated with hospital mortality. Patients with higher RDW will have longer LOS in ICU. Repeated measurements of RDW provide no additional prognostic value in critically ill patients.

KEYWORDS Red cell distribution width (RDW); intensive care unit (ICU); mortality; length of stay (LOS)

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Introduction

Red cell distribution width (RDW) is a measurement of the variability of red cell sizes and it increases in response to inflammatory stimulation or poor nutritional status (1,2). RDW has been linked to clinical outcomes in varieties of clinical settings. For instance, Nathan SD and coworkers (3) found that RDW is an independent predictor of outcome in patients with idiopathic pulmonary fibrosis; similar results have been replicated in many other diseases and settings including acute coronary syndrome, patients undergoing cardiopulmonary bypass surgery, community acquired pneumonia, acute cerebral infarction and bacteremia (4-7). These results render RDW a promising biomarker for risk stratification of patients.

In critical care setting, it is of vital importance to stratify patients on their entry to intensive care unit (ICU). This will help to make full use of the limited ICU resources, inform the anxious patients' relatives and institute appropriate medical treatment. Thus, continuous efforts have been made to find models or biomarkers that can provide information on the prognostication of critically ill patients. There are generally two types of methods used for the prediction of patients' mortality. One includes varieties of scores such as APACHE scores, SOFA and simplified acute physiology score (SAPS); the other includes biomarkers such as C-reactive protein (CRP) and soluble urokinase plasminogen activator receptor (8,9). Due to its promising results obtained in other clinical settings, RDW has also been investigated in ICU. However, these results are preliminary and further confirmations are needed. The present study aimed to investigate the prognostic value of RDW in critically ill patients. We hypothesized that (I) RDW measured on entry to ICU is predictive of the in-hospital mortality; (II)

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repeated measurements of RDW during ICU stay is of limited value due to the long lifespan of red blood cells.

Methods

The study was conducted in a 24-bed mixed ICU of a tertiary teaching hospital. This hospital had 1,980 open beds and provided medical care for over five million people in Jinhua region. Patients' electronic information was recorded in Haitai e-chart (provided by Haitai Medical information systems CO., LTD, Nanjing, P.R. China). These information included data on demographic characteristics, all laboratory findings, imaging studies and medications. The study was approved by IRB of our hospital. The study was approved by ethics committee of Jinhua municipal central hospital has therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki, and ethics committee of Jinhua municipal central hospital waived the need for written informed consent from the participants due to the retrospective nature of the study.

All patients that had been treated in ICU from October 2009 to December 2012 were considered to be eligible. Patients who had their medical records incomplete, transferred to other hospitals during the course of treatment, or signed do-not-resuscitation order were excluded. Such patients were labeled as "automatically discharged" in the Haitai medical system.

Demographic data abstracted from e-chart included age, sex, diagnosis, use of mechanical ventilation (MV) and the use of continuous renal replacement therapy (CRRT). Laboratory data included hemoglobin, CRP, mean corpuscular volume (MCV) and albumin. These variables were measured on entry to ICU. RDW was included in the complete blood cell count (CBC) and was routinely measured for each patient treated in ICU. It was measured in automatic hematology analyzer. The normal reference of RDW in our laboratory was 11.6-14.8%. All consecutive measurements of RDW were abstracted from the database. Because physiology-based scores for the measurement of illness severity were not routinely recorded in our e-chart, we used the well validated Charlson comorbidity index for risk adjustment (10,11). Patients were followed during their hospital stay. The primary endpoint was in-hospital mortality and the secondary study endpoint was ICU length of stay (LOS). For patients readmitted to ICU within seven days, the ICU LOS was the sum of the two ICU LOSs; for patients readmitted to ICU beyond seven days, only the first ICU LOS was used for analysis.

Statistical analysis

Continuous variables were tested for normality by using skewness and kurtosis test. Normally distributed data were expressed as mean ± SD (standard deviation) and compared between groups by using *t*-test; skewed data were expressed as median and interquartile range (IQR) and tested using Wilcoxon rank-sum test. Demographic data and baseline variables were compared between survivors and nonsurvivors. Multivariable logistic regression model was used to screen independent variables that were associated with in-hospital mortality. Variables with P<0.1 in the univariate analysis were entered into the multivariable model. Hosmer-Lemeshow method was used to test the goodness-of-fit of the regression model. Diagnostic performance of CRP, RDW, albumin, Charlson index and their combination in discriminating survivors and nonsurvivors were evaluated by using receiver operating characteristic (ROC) curve (12). Logistic regression model was used to obtain coefficients (β) for each variable. Then a new variable Y was calculated according to the equation: $Y= \exp(\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\ldots\ \beta_nX_n)/1+\exp(\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\ldots\ \beta_nX_n)$; where *X* denotes each included variables, and in the present situation it refers to CRP, RDW, albumin and Charlson index. ICU LOS was compared between patients with RDW >14.8% and ≤14.8% by using Log-rank test. To exclude potential confounding effect of death on the analysis of ICU LOS, patients died in ICU were excluded from analysis (e.g., patients who died shortly after ICU entry appears to have a very short LOS in ICU, which will erroneously render this group of patients to have a good clinical outcome). Changes in RDW (ΔRDW) were calculated on 3, 6, 10, 13, 17 and 20 days during ICU stay. Patients were divided into two groups with ΔRDW >0 or ≤0 to examine whether the changes in RDW during ICU stay were associated with in-hospital mortality. All statistical analyses were performed using StataSE 11.2 (College Station, Texas 77845 USA). Conventional two-tailed P<0.05 was considered to be statistically significant.

Results

A total of 1,539 patients were eligible for the current analysis during study period. Demographic data and baseline characteristics were shown in Table 1. During their hospital stay, there were 1,084 survivors and 455 nonsurvivors. Male patients were more likely to die than female patients (69.06% *vs.* 63.82%, P=0.047). Nonsurvivors were significantly older than survivors (63.1 *vs.* 61.2 years, P=0.046). The Charlson indices were significantly higher in the nonsurvivors than survivors (median: 2 *vs.* 1, P<0.001). The primary diagnoses were not equally distributed between the two groups. There were more patients with primary diagnoses of cardiovascular diseases (23.43% *vs.* 13.85%, P<0.001), trauma (14.58% *vs.* 5.93%, P<0.001) in survivor group than in nonsurvivor group; conversely, there were more patients with the primary diagnoses of neurosurgical disorders (26.37% *vs.* 19.19%, P=0.002), post cardiac arrest (2.64% *vs.* 0.18%, P<0.001), multi-organ failure (2.2% *vs.* 0.83%, P=0.028), shock (3.96% *vs.* 1.85%, P=0.016) and renal failure

Table 1. Baseline characteristics of included patients.

	All (n=1,539)	Survivors (n=1,084)	Nonsurvivors (n=455)	P
Sex (male, %)	1,026 (65.35)	709 (63.82)	317 (69.06)	0.047
Age (years)	61.8±19.3	61.2±19.0	63.1±20.0	0.046
Charlson index (median; IQR)	1 (0-2)	1 (0-2)	2 (0-3)	<0.001
Primary diagnosis (n, %)				<0.001
Pulmonary	260 (16.89)	171 (15.77)	89 (19.56)	0.082
Cardiovascular	317 (20.60)	254 (23.43)	63 (13.85)	<0.001
Trauma	185 (12.02)	158 (14.58)	27 (5.93)	<0.001
Neurosurgical	328 (21.31)	208 (19.19)	120 (26.37)	0.002
Post-CPR	14 (0.91)	2 (0.18)	12 (2.64)	<0.001
Multi-organ failure	19 (1.23)	9 (0.83)	10 (2.20)	0.028
Pancreatitis	23 (1.49)	14 (1.29)	9 (1.98)	0.320
Abdominal	168 (10.92)	124 (11.44)	44 (9.67)	0.289
Unclassified	105 (6.82)	72 (6.64)	33 (7.25)	0.693
Shock	38 (2.47)	20 (1.85)	18 (3.96)	0.016
Obstetrics	17 (1.10)	15 (1.38)	2 (0.44)	0.103
Renal	65 (4.22)	37 (3.41)	28 (6.15)	0.016
Use of MV (n, %)	795 (51.66)	490 (45.20)	305 (67.03)	<0.001
Use of CRRT (n, %)	177 (11.50)	82 (7.56)	95 (20.88)	<0.001
Hemoglobin (g/L)	106.2±23.7	107.8±22.7	102.7±25.4	<0.001
Mean corpuscular volume (fL)	91.0±6.7	90.9±6.4	91.3±7.4	0.240
RDW (median, IQR, %)	14 (13.1, 15.2)	13.8 (13, 14.8)	14.5 (13.4, 15.8)	<0.001
CRP (mg/L, median, IQR)	46.3 (11.8, 112.95)	38 (9.4, 99.2)	72.3 (25, 147)	<0.001
Albumin (g/L)	30.3±6.7	31.1±6.3	28.4±7.3	<0.001

Abbreviations: IQR, interquatile range; CPR, cardiopulmonary resuscitation; RDW, red cell distribution width; CRP, C-reactive protein; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

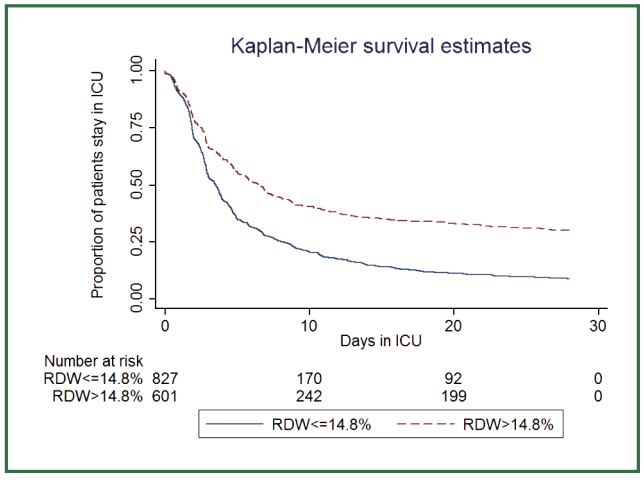

Figure 1. Kaplan-Meier survival curves for the comparison of intensive care unit length of stay between patients with RDW >14.8% and ≤14.8%. The analysis was restricted to patients who were discharged alive. The result showed that patients with RDW >14.8% had significantly longer length of stay in ICU than those with normal RDWs (Log-rank test, P<0.001). RDW, red cell distribution width; ICU, intensive care unit.

(6.15% *vs.* 3.14%, P=0.016) in nonsurvivor group than survivor group. More patients in the nonsurvivor group used MV (67.03% *vs.* 45.20%, P<0.001) and CRRT (20.88% *vs.* 7.56%, P<0.001) than survivor group. Hemoglobin levels were significantly higher in the survivor group than that in the nonsurvivor group (107.8±22.7 *vs.* 102.7±25.4 g/L, P<0.001). MCVs were similar between survivors and nonsurvivors. RDWs were significantly higher in nonsurvivors (14.5% *vs.* 13.8%, P<0.001). Figure 1 displays the Kaplan-Meier survival estimates for the ICU LOS in patients with RDW >14.8% and ≤14.8%. The result showed that patients with RDW >14.8% had significantly longer LOS in ICU (Log-rank test, P<0.001).

In multivariable model, RDW was independently associated with in-hospital mortality (OR: 1.1, P=0.002). Other variables including albumin, CRP, use of MV and CRRT were also independently associated with mortality (Table 2). The regression model was well fitted as demonstrated by Hosmer-Lemeshow χ^2=11.17 (P=0.19). Variables independently associated with in-hospital mortality were assessed for their ability in discriminating survivors and nonsurvivors. However, there individual discriminating abilities were suboptimal and of limited

Table 2. Logistic regression analysis of association of red cell distribution width with in-hospital mortality.

Variables	Odds ratio	Lower 95% CI	Upper 95% CI	P value
RDW	1.110	1.040	1.180	0.001
Sex (male as reference)	0.850	0.660	1.100	0.219
Age	0.997	0.990	1.004	0.400
Charlson index	1.050	0.980	1.130	1.146
Use of MV	2.360	1.840	3.020	<0.001
Use of CRRT	2.580	1.810	3.680	<0.001
Albumin	0.960	0.940	0.980	<0.001
CRP	1.003	1.001	1.005	0.001
Hemoglobin	1.002	0.996	1.008	0.470

Abbreviations: RDW, red blood cell distribution width; CRP, C-reactive protein; CI, confidence interval; MV, mechanical ventilation; CRRT, continuous renal replacement therapy. Goodness-of-fit test for the regression model (Hosmer-Lemeshow χ^2=11.17; P=0.19).

Table 3. Diagnostic performance of variables in predicting in-hospital mortality.

Variables	Area	Standard error	95% confidence interval
RDW	0.6202	0.016	0.589-0.651
CRP	0.6093	0.016	0.578-0.640
Charlson index	0.5980	0.015	0.568-0.628
Albumin	0.6134	0.016	0.583-0.644
Y	0.6618	0.016	0.631-0.693

Note: Y refers to the combination of RDW, CRP, albumin and charlson index in predicting mortality. The regression model was Y= exp (−1.630539+0.1072033* RDW +0.003924* CRP-0.0407945* albumin+ 0.0743247* charlson index)/{1+[exp (−1.630539+0.1072033* RDW +0.003924* CRP-0.0407945* albumin +0.0743247* charlson index)]}. RDW, red blood cell distribution width; CRP, C-reactive protein.

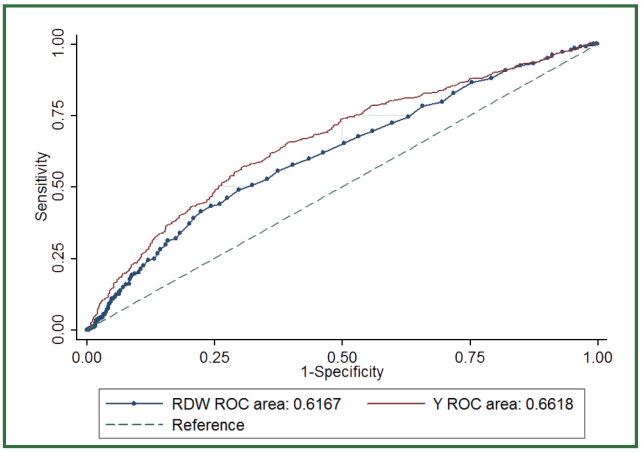

Figure 2. Receiver operating characteristic (ROC) curves showing the diagnostic performance of RDW in predicting hospital mortality. The results showed that RDW measured on ICU entry had moderate discriminating power and the combination of C-reactive protein, Charlson index and albumin significantly improved the diagnostic performance, but slightly in magnitude. Y is a new parameter calculated by combining all variables (e.g., RDW, C-reactive protein, Charlson index and albumin) in a regression model. RDW, red cell distribution width; ICU, intensive care unit.

clinical utility. The areas under ROC curve (AU-ROC) for RDW, CRP, Charlson index and albumin were 0.62, 0.61, 0.60 and 0.61, respectively (Table 3 and Figure 2). The combination of these variables significantly improved the discriminating power, but slightly in magnitude (AUC =0.66, 95% CI: 0.631-0.693).

Table 4 shows the association of changes in RDW with in-hospital mortality. Repeated measurements of RDW were arbitrarily selected on day 3, 6, 10, 13, 17 and 20 during ICU stay. The results showed that none of these ΔRDWs was associated with in-hospital mortality, indicating that repeated measurements of RDW are of limited value in critical care setting. Post hoc subgroup analysis was performed to investigate whether the association of RDW with mortality differed across different ICU populations (Figure 3). The results showed that RDW was significantly higher in nonsurvivors than that in survivors in subgroups of cardiovascular disease (WMD: 1.1%; 95% CI: 0.53-1.67%), abdominal surgery (WMD: 0.9%; 95% CI: 0.1-1.7%) and neurosurgery (WMD: 0.8%; 95% CI: 0.4-1.2%). There was a trend towards higher RDW in nonsurvivors in subgroups of CRRT (WMD: 0.4%; 95% CI: −0.22-1.02%) and pulmonary diseases (WMD: 0.4%; 95% CI: −0.13-0.93%). However, in trauma patients, there was a trend towards higher RDW in survivors than nonsurvivors (WMD: −0.1%; 95% CI: −0.72-0.52%).

Table 4. Association of changes in RDW with in-hospital mortality.

Days of measurement (No. of observations)	ΔRDW >0 (mortality rate %)	ΔRDW ≤0 (mortality rate %)	P value
3 (1,532)	28.94	29.51	0.806
6 (1,440)	27.87	28.22	0.883
10 (1,326)	27.47	25.37	0.386
13 (1,171)	22.80	27.52	0.065
17 (1,026)	25.71	24.62	0.689
20 (902)	23.08	25.51	0.395

Abbreviation: RDW, red blood cell distribution width. Note, ΔRDW is calculated by RDW measured on a certain day minus that measured on ICU entry. Statistical inference was based on χ^2 test.

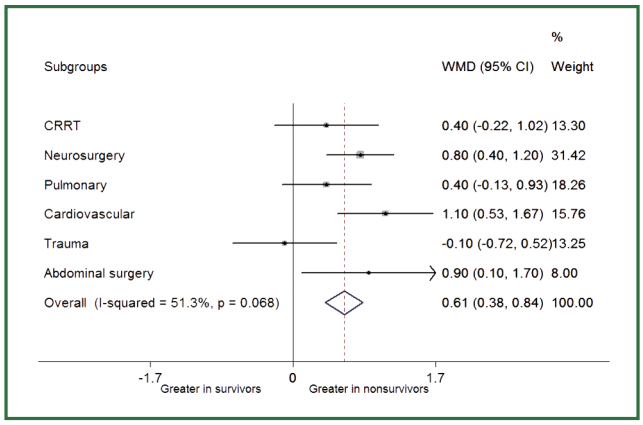

Figure 3. Post hoc analysis by restricting to subgroups of trauma, continuous renal replacement therapy (CRRT), neurosurgery, pulmonary diseases, cardiovascular disorders and abdominal surgery.

Discussion

Our study confirmed previous finding that RDW was associated with clinical outcomes in critically ill patients. Specifically, our study showed that higher RDW was associated with increased in-hospital mortality and prolonged ICU LOS. However, the ability of RDW in distinguishing survivors from nonsurvivors was suboptimal, and the repeated measurements of RDW offered no additional clinical value in predicting outcomes.

The first report on the association of RDW with clinical outcome in critically ill patients used ICU mortality as the primary study end point; as a result, patients were regarded to have a favorable outcome if they were successfully discharged from ICU (13). However, many patients die in floor ward after they are successfully discharged from ICU. Even when their illness deteriorates, these patients and their next-of-kin refuse to enter ICU again. Furthermore, the authors did not explicitly clarify the definition of ICU death in the situation of ICU readmission. In a recent study, Badawi O and coworkers found that ICU readmission was experienced by 3% of ICU patients (14). Thus, we feel that use of in-hospital mortality as the primary end point is more reasonable in the situation that patients are discharged prematurely due to limited ICU resources. However, the choice of study endpoint seems to have no impact on the result and our finding is consistent with that reported by Wang F and colleagues (13). In a large multicenter cohort study, Bazick HS and colleagues (15) also showed a strong association of RDW with all cause mortality at different follow-up time points. However, diagnostic statistics such as AUC, sensitivity and specificity were not reported in that study, which limited the clinical application of their results. Nonetheless, our study shows that the discriminating power of RDW is of limited clinical utility due to a very low AUC. RDW only adds slightly to the discriminating power of conventional variables such as Charlson index, CRP and albumin. Such low predictive value may be explained by the heterogeneity of the study population. In a study including only patients with septic shock, Sadaka F and colleagues (16) showed a much better discrimination of RDW for mortality. Further studies are needed to investigate whether analysis restricting to certain subgroup can improve the diagnostic performance of RDW. Furthermore, the discriminating power of RDW is confounded by other measured and unmeasured risk factors for mortality, including physiological disease severity scores, comorbidities and inflammatory biomarkers.

RDW is a quantitative measurement of anisocytosis and is calculated by dividing standard deviation of red blood cell volume with MCV. It increases in varieties of pathological conditions. The underlying mechanism of the association of RDW with mortality is largely unknown. However, several plausible hypotheses have been proposed, and inflammatory response and oxidative stress are among the most popular ones (17). Semba RD and colleagues (18) demonstrated that serum selenium level was an independent predictor of RDW, and this was mediated via interleukin-6 mediated inflammatory pathway. In our study, we found that the well known inflammatory biomarker CRP was also significantly increased in non-survivors. This is in support of the notion that increased inflammatory response is a harbinger of adverse clinical outcome (19,20).

ICU patients are exposed to increased oxidative stress and inflammation response, both of which are responsible for the observed increase in RDW (21).

Another finding in the present study is that the measurement of RDW in a short interval offers no additional clinical value. This is reasonable since the lifespan of red blood cell is 120 days in normal population and even in pathological conditions the lifespan can only drop to 30 days (22). Thus, its change within 28 days (a study period that is commonly used in critical care setting) is not clinically meaningful. Repeated measurements may be more meaningful in chronic health conditions in which patients are followed for longer period of time. In a community-based study, Semba RD and colleagues (18) made a series of measurements of RDW over a period of 24 months. They found that serum selenium level was in linear correlation with RDW over time. In another study involving cardiac failure patients, Oh J and colleagues found that it was the change in RDW between hospital admission and one month after discharge that could predict cardiovascular events, while the change of RDW between admission and discharge had no significant association with cardiovascular events (23). Although the authors did not mention the erythrocyte lifespan as a potential explanation for this observation, we proposed that an interval of 30 days between two measurements of RDW may be necessary to make this clinically meaningful.

The results of subgroup analysis are generally in line with that reported in literature. For instance, Oh HJ and colleagues (24) reported that RDW was an independent predictor of 28-day mortality in patients with CRRT. In patients with cardiovascular diseases, there are numerous studies being published all consistently showing a significant link between RDW and mortality (25-27). The same result is replicated in our investigation. An interesting finding in the study is that RDW tends to be higher in survivors than non-survivors in trauma patients; although the low statistical power due to limited sample size may explain such conflicting finding; we proposed other possible explanations. First, trauma patients usually require large volumes of blood transfusion that will introduce large number of deformed erythrocytes (28,29). As a result, the first measurement of RDW on ICU entry appears to be increased because the patient receives liberal blood transfusion in emergency department. Probably, the higher RDWs can reflect adequate resuscitation with packed RBCs, which results in higher survival rate. Secondly, since RDW reflects the host inflammatory response (30,31), more intensive response may help to control or prevent subsequent infection during ICU stay. However, the result of this post hoc subgroup analysis is hypothesis-generating and further well designed investigations are needed to validate the result.

Our study contains several limitations. First, the proportion of patients with sepsis was unknown. This was due to the fact that the diagnosis of sepsis was not routinely recorded in our administrative database. Abstraction of data on sepsis from medical chart would distort the result. Second, the study is retrospective in nature, and bears the risk of potential bias. However, we tried to attenuate the risk by using multivariate analysis. Third, study population in the study is heterogeneous, which is a potential explanation for the low discriminating power of RDW as discussed previously.

Conclusively, in accordance with previous findings, the present study confirms that increased RDW measured on ICU entry is associated with higher hospital mortality. However, its diagnostic performance in predicting mortality is suboptimal. Repeated measurements of RDW in a short follow up period provide no additional value.

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