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TITLE PAGE**Red cell distribution width improves prognostic performance of the Acute Physiology and Chronic Health Evaluation II score in obstetric patients admitted to intensive care unit**

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Abstract

Objectives: Red blood cell distribution width (RDW) has been shown to predict mortality in critically ill patients. The primary aim of this study was to examine the association between RDW and ICU mortality in obstetric critical care patients. The secondary aim was to investigate whether adding RDW to Acute Physiology and Chronic Health Evaluation II (APACHE II) improves the prognostic performance of APACHE II.

Setting: Single center, retrospective observational study in China.

Participants: A total of 447 consecutive obstetric patients admitted in the ICU from January 1, 2008 to December 31, 2013 were included. Patients were excluded if they had known hematologic diseases, history of recent blood transfusion, and patients who died or were discharged from ICU within 24 hours of admission.

Primary outcome measures: Each patient's ICU entrance characteristics including RDW were retrieved. APACHE II scores were calculated using the worst value of 12 acute physiological variables within 24 hours of presentation. The primary end point of the study was ICU mortality. The primary predictor of interest was RDW and APACHE II scores at ICU admission.

Results: A total of 376 patients were included in this present study. ICU mortality was 5.32%. A significant association was found between baseline RDW levels and ICU mortality (hazard ratio per percent increase in RDW, 1.21; 95% CI, 1.02 to 1.57). After categorization based on tertile of baseline RDW, as well as further adjustment for hematocrit and other risk factors, a

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3 graded independent association between RDW and mortality was observed
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5 ($P<0.001$). The addition of RDW to the APACHE II score improved the AUC
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7 for ICU mortality from 0.766 to 0.872 ($P<0.001$).
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10 **Conclusions:** RDW is an independent predictor for ICU mortality in Chinese
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12 obstetric critical care patients. Combining RDW to APACHE II scores could
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14 further improve its prognostic performance.
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18 **Key words:** APACHE-II score; Critical care; Mortality; Obstetrics; Red cell
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20 distribution width
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23 **Strengths and limitations of this study**

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25 • Red cell distribution width (RDW), a quantitative measure of erythrocyte size
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27 variability, is an independent prognostic outcome predictor in obstetric critical
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29 care patients.
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31 • RDW significantly improved the prognostic accuracy of the APACHE II score
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33 in obstetric critical care patients.
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35 • The study was a single-center study. It was very heterogenous, and patient
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37 numbers were relatively small, so large epidemiologic study may be required
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39 to validate the findings.
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Introduction

Despite the advances in the care of obstetric patients, maternal mortality ratio (MMR) has remained high, especially in developing countries.^{1,2} The use of scoring systems to assess severity and predict mortality may help identify obstetric patients who truly require intensive care.³ Acute Physiology and Chronic Health Evaluation II (APACHE II) scores are predictive scores for mortality that are widely used in the general population. However, results from obstetric patients have shown some inconsistencies; wherein, some studies have shown that these scores are a good predictor of illness severity, while more studies have shown that these scores overestimated mortality.^{4, 5, 6, 7-9} Further work is need to improve the prognostic accuracy of APACHE II scores in obstetric patients.

Red cell distribution width (RDW) is a parameter that is easy and inexpensive to obtain, and reflects the degree of heterogeneity of erythrocyte volume.¹⁰ RDW was used in the differential diagnosis of anemia in the past decades.¹¹ Recently, RDW has been shown to be a novel, independent prognostic marker for mortality, mainly in patients with cardiovascular disease and strokes, as well as in critically ill patients.¹²⁻¹⁹ However, few ICU subpopulations have been studied so far. The obstetric population is of special interest because of the limitations of existing scoring system, which largely are based on physiological parameters.

Therefore, we conducted a retrospective study to evaluate the prognostic value of RDW, and investigated whether adding RDW could improve the prognostic performance of APACHE-II scores in critically ill obstetric patients.

Methods

This study was approved by the Institutional Review Board of the Provincial Hospital Affiliated to Shandong University. Obstetric patients consecutively admitted in the ICU for at least 24 hours from January 1, 2008 to December 31, 2013 were included in this retrospective observational study. The requirement for patient consent was waived because this study did not affect the patient's clinical care, and all protected health information was deleted. Obstetric patients were defined as pregnant women or up to six weeks postpartum. This study was carried out at the Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China. The hospital is a 1500-bed tertiary academic hospital with 20 ICU beds. The hospital provides primary as well as tertiary care to an ethnically and socioeconomically diverse population within Shandong province and the surrounding region. The decision to transfer patients into the ICU was made by at least one senior critical care doctor and one senior obstetric doctor. Likewise, these doctors also made decisions to discharge patients or to transfer patients to general wards. Patients were excluded if they had known hematologic diseases (including leukemia, thrombotic thrombocytopenic purpura, and other hematologic diseases) or history of recent blood transfusion (less than two weeks). Patients who died or were discharged from the ICU within 24 hours of admission were excluded, because data was difficult to obtain from these patients.

Data collection

Demographic and clinical characteristics including age, gestational age, parity, pregnancy status at admission, diagnosis at entry and during ICU stay, and length of hospital stay were collected. The cesarean section was considered an emergency intervention. Diagnosis of acute kidney injury (AKI) was based on the Acute Kidney Injury Network (AKIN) criteria (20). AKI was defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, a percentage increase in serum creatinine of more than or equal to 50% (1.5 fold from baseline) within 48 hours, or reduction in urine output (documented oliguria of less than 0.5 ml/Kg per hour for more than six hours).²⁰ APACHE II scores were calculated using the worst value of 12 acute physiological variables within 24 hours of presentation. These variables included temperature, blood pressure, heart rate, respiratory rate, arterial oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood cell count, and Glasgow Coma scores. If the patient was sedated at the time of ICU admission, the last Glasgow Coma Scale obtained prior to sedation was collected. RDW, hemoglobin level, hematocrit and mean corpuscular volume (MCV) of all patients included in this study were determined at admission using a Beckman Coulter LH-750 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, California), as a part of the complete blood cell count. Normal reference range for RDW in the hospital laboratory is 10.9% to 15.4%.

Study outcomes

All patients were followed up during hospitalization. The primary end point of the study was ICU mortality. The primary predictor of interest was RDW and APACHE II scores at ICU admission.

Statistics

All continuous variables were presented as means \pm standard deviations, or medians with interquartile ranges as appropriate. Categorical data were summarized as number or percentage. We divided RDW into tertiles, and compared the demographics, diagnosis, clinical characteristics, laboratory test results, and APACHE-II scores of patients using analysis of variance or Kruskal-Wallis tests for continuous variables, and Chi-square or Fisher's exact tests for categorical variables. Univariate logistic regression analysis was conducted to examine the association between mortality and each of the predictors, separately. Multivariate logistic regression was further utilized to determine independent predictors of ICU mortality after adjusting for potential confounding factors. An appealing receiver operating characteristic (ROC) curve was used to examine the performance of APACHE-II scores and RDW in predicting ICU mortality. The curve represented a sensitivity plot *versus* 1-specificity. The area under the curve (AUC) was derived from the ROC curve, and the Youden index was adopted to define the optimal cut-off value.²¹ We also constructed an ROC curve for the combined APACHE-II score and RDW results for predicting ICU mortality according to the weighted sum formula derived from multivariate logistic regression: $\text{logit}(\text{mortality}) = 0.162 \times \text{APACHE-II score} + 0.203 \times \text{RDW} - 7.503$; wherein, $\text{logit}(\text{mortality})$ is the logarithm of the odds of a critically ill obstetric patient dying in the ICU. Differences between the AUC were detected by Delong's test.²² Two-sided *P*-values < 0.05 were considered statistically significant, and all analyses were performed with R software (<http://www.cran.r-project.org/>).

Results

Population

A total of 447 obstetric patients who were admitted to ICU were initially enrolled in this study. ICU admission rate was 21.73 per 1,000 births. Eight patients who were diagnosed with hematologic disease and 59 patients who received red blood cell transfusion within two weeks were excluded. Two patients who died within 24 hours after ICU admission were also excluded. Two patients were excluded for missing data. In the final analysis, 376 patients were included in this study.

Association between RDW and ICU mortality

A total of 20 deaths occurred in this cohort during the study period. ICU mortality was 5.32%, and RDW ranged from 10.7% to 24.0% (median, 14.8%; interquartile range, 13.4% to 16.0%).

Participants were divided into three categories on the basis of their baseline tertiles of RDW level: tertile I, 10.7%-13.9%; tertile II, 13.9%-15.6%; tertile III, 15.6%-20.4% (all $P < 0.001$). There was no difference in age, gestational weeks, primary reasons for ICU admission, AKI morbidity, as well as in the total length of stay in hospital (TLSH) among the three tertiles. Hb, MCV and HCT significantly decreased with the increase of RDW, while APACHE II scores and ICU mortality significantly increased with the increase of RDW (Table 1). A significant association was found between baseline RDW levels and ICU mortality (hazard ratio per percent increase in RDW, 1.21; 95% CI, 1.02 to 1.57).

Regression analysis for ICU mortality

Univariate logistic regression analysis demonstrated that patients with higher RDW, higher APACHE-II scores, higher AKI morbidity, and longer TLSH days had significantly greater death hazards (Table 2). Multivariate logistic regression analysis revealed that RDW, AKI and APACHE-II scores were independent predictors of ICU mortality (Table 3). The association of RDW and ICU mortality remained significant after adjusting for age, hemoglobin, MCV, hematocrit, APACHE-II score and AKI. RDW was a significant outcome predictor, which is independent of APACHE-II scores.

A ROC curve was drawn to evaluate the value for RDW and APACHE-II scores in predicting mortality (Figure 1). The AUC was calculated as 0.766 (95% CI, 0.705 to 0.826) for the APACHE-II score and 0.752 (95% CI, 0.684 to 0.862) for RDW. Optimal cut-off value of the APACHE-II score for predicting mortality was five points, which gave a sensitivity of 90.9% and a specificity of 60.7%. The optimal cut-off value of RDW was 16.1%, which gave a sensitivity of 68.2% and specificity of 77.9%. To further clarify whether RDW had an additive power with the APACHE-II score for ICU mortality, we combined RDW and the APACHE-II score to draw a third ROC curve, as shown in Figure 1. Compared with the APACHE-II score, adding RDW to APACHE-II scores improved the AUC from 0.766 to 0.872 ($P<0.001$). These results suggest that combining RDW and APACHE-II added to the ability to discriminate mortality risk.

Discussion

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3 The main finding of our study was that RDW was independently associated
4 with ICU mortality in obstetric critical care patients of China. This association
5 remained significant even after adjusting for APACHE-II scores, hemoglobin
6 levels, hematocrit and mean corpuscular volume. Combining RDW and the
7 APACHE-II score improved the prognostic accuracy of ICU mortality predicted
8 by APACHE-II alone in the study population.
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11 We found that RDW was independently associated with ICU mortality in a
12 Chinese obstetric ICU population. Patients were excluded if they had a history
13 of recent blood transfusions because RDW could be increased in anemia or
14 after blood transfusions.^{11, 23} In this present study, higher levels of RDW were
15 associated with ICU mortality even after adjusting for hemoglobin and
16 hematocrit. In addition, the independent association between RDW and ICU
17 mortality was not eliminated even after adjusting for other potential
18 confounders, including mean corpuscular volume, hemoglobin, hematocrit,
19 APACHE-II score, gestational age and AKI. Our results were consistent with
20 previous analyses of two large populations of critically ill patients.^{24, 25} Further,
21 our results were also similar to the findings obtained in a single-center
22 observational study in 2011;¹⁶ wherein, the independent association between
23 RDW and all-cause mortality in critically ill patients was shown.
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47 The important finding in our analysis was that combining RDW and
48 APACHE-II score performed better than APACHE-II score alone in predicting
49 ICU mortality in critically ill obstetric patients. The APACHE-II scoring system
50 developed in 1985 has shown a positive correlation with hospital mortality,
51 and was one of the most common models used for evaluating the severity of a
52 disease in critically ill patients.²⁶ Previous studies²⁷⁻²⁹ suggested APACHE II
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3 score was a good discriminator of illness severity in obstetric cohorts. The
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5 sensitivity and specificity of the APACHE II score was evaluated with the use
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7 of receiver operating characteristic curve analysis. In accordance with
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9 previous studies²⁷⁻²⁹, the APACHE-II score was also demonstrated to have a
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11 strong power to predict ICU mortality (AUC=0.766) in the present study.
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14 Despite its moderate discriminative power alone (AUC=0.752), adding RDW
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16 to the APACHE-II score resulted to a better increase in the AUC from 0.766 to
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18 0.872 ($P<0.001$). Combining RDW with APACHE-II score significantly
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20 improved prognostic performance in critically ill obstetric patients. Similarly,
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22 another study by Wang *et al.*¹⁶ also revealed that adding RDW to APACHE-II
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24 score significantly improves prognostic reliability of APACHE-II score in
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26 identifying critically ill patients. Since RDW is a simple, inexpensive, and
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28 widely available test as part of the complete blood count, these data may
29
30 have significant clinical implications for determining prognosis in critically ill
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32 obstetric patients.
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37 The pathophysiologic mechanism underlying the association of higher RDW
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39 with worse outcomes in critically ill obstetric patients remains unclear.
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41 Generally, the increase in RDW reflects either impaired erythropoiesis,
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43 abnormal red blood cell survival, or both. Metabolic abnormalities such as
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45 shortening of telomere length, poor nutritional status,^{30, 31} inflammation,³²⁻³⁴
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47 oxidative stress,^{35, 36} dyslipidemia, hypertension, erythrocyte fragmentation,
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49 and alteration of erythropoietin function might contribute to RDW increase.³⁷ In
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51 normal parturition, the increase of RDW might be related to stimulus-induced
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53 reticulocytosis in the last few weeks.²⁹ This might not be the case in our study;
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3 wherein, even if five patients with spontaneous onset of labor were excluded,
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5 RDW remained as a significant predictor of mortality.
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9 In this present study, the admission rate of 21.73 per 1,000 births was
10 relatively higher than those reported by other studies,³⁸⁻³⁹ and the mean
11 APACHE-II score was relatively lower compared with other groups.^{7, 16, 40} The
12 lack of a high dependency unit as a referral center in local areas for
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14 complicated pregnancies could partially explain these difference.
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19 This study had several limitations. First, we did not evaluate the evolution of
20 RDW, and thus, it remained unclear whether changes in RDW over time may
21 provide additional prognostic information. Second, we only used the
22 APACHE-II score to predict mortality in obstetric patients, which was limited
23 by spontaneous improvement after delivery in peripartum women,⁴¹⁻⁴⁷ and
24 inconsistent results.^{48, 49} Finally, our study was a single-center study. The
25 study was very heterogenous and patient numbers were relatively small, so
26 large epidemiologic study may be required to validate the findings.
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31 In summary, the single-center study in China demonstrated that RDW was
32 an independent predictor for mortality in obstetric critical care patients.
33 Combining RDW and the APACHE-II score improved prognostic accuracy
34 compared with the APACHE-II score model alone.
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50 Yufeng Chu and Hongsheng Ren conceived of the study, and participated in
51 its design and coordination. Mei Meng, Haiyan Zhou and Haiyan Zhou
52 extracted data and participated in study design. Yufeng Chu and Zhongshang
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3 Yuan performed the statistical analysis and drafted the manuscript. All authors
4
5 read and approved the final manuscript.
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8 **Competing interests**

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11 The authors declare that there is no conflict of interests regarding the
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13 publication of this paper.
14

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24 the Natural Science Foundation of Shandong Province of China
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26 (ZR2013HM062).
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30 **Data sharing statement**

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32 No additional unpublished data are available.
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37 **References**

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Table 1. Baseline clinical and laboratory characteristics by tertile of RDW at critical care initiation

	Tertile I	Tertile II	Tertile III	P-value
RDW (%)	10.7-13.9	13.9-15.6	15.6-20.4	<0.001
N	131	126	119	-
Age (years)	29.6 ± 4.3	29.3 ± 5.6	29.6 ± 5.9	0.84
Gestational age (weeks)	35 (32-37)	36 (33-39)	36 (32-38)	0.327
Primary diagnosis to ICU admission (n, %)				
Hypertensive disorder of pregnancy	50(38.17%)	55(43.65%)	52(43.70%)	0.417
HELLP Syndrome	12(9.16%)	10(7.94%)	8(6.72%)	0.322
Acute fatty liver of pregnancy	10(7.63%)	8(6.35%)	7(5.88%)	0.485
Obstetric sepsis	5(3.82%)	4(3.17%)	3(2.52%)	0.657
Cardiovascular disease	42 (32.06%)	31 (24.60%)	26 (21.85%)	0.162
Gastrointestinal disease	2 (1.53%)	5 (3.97%)	4 (3.36%)	0.476
Stroke	2 (1.53%)	3 (2.38%)	0 (0)	0.332
Pulmonary embolism	1 (0.76%)	0 (0)	1 (0.84%)	0.766
Others	7(5.34%)	10(7.94%)	18(15.13)	0.142
Hemoglobin (g/L)	109.5 ± 19.7	100.1 ± 20.7	92.5 ± 24.1	<0.001
MCV(fL)	89.8 ± 5.1	86.7 ± 6.0	83.6 ± 11.4	<0.001
HCT (%)	32.6 ± 5.8	30.5 ± 6.3	28.8 ± 6.9	<0.001
APACHE II score (points)	2 (2-6)	5 (3-6)	10 (6-22)	0.017
AKI (n, %)	14 (10.69%)	17 (13.49%)	14 (11.76%)	0.207
TLSH (days)	8 (7-12)	8 (6-13)	8 (7-12)	0.203
ICU Mortality (n, %)	0 (0%)	5 (3.97%)	15 (12.61%)	<0.001

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3 RDW, red cell distribution width; MCV, mean corpuscular volume; HCT,
4 hematocrit; APACHE-II score, Acute Physiology and Chronic Health
5 Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in
6 hospital. Values are presented as mean \pm standard deviations or number
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10 (percentage).
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Table 2. Univariate odds ratios of variables for predicting mortality

Variables	Odds ratio	95% CI	<i>P</i> -value
Age (years)	1.048	0.969-1.133	0.244
Hemoglobin (g/L)	0.997	0.977-1.017	0.763
MCV (fL)	0.962	0.919-1.006	0.098
Hematocrit (%)	0.997	0.934-1.064	0.929
APACHE-II score (points)	1.192	1.124-1.265	< 0.001
AKI (%)	16.61	6.580-42.014	< 0.001
TLSH (days)	0.803	0.691-0.933	0.004
gestational age (weeks)	1.023	0.920-1.138	0.677
RDW (%)	1.309	1.150-1.489	<0.001

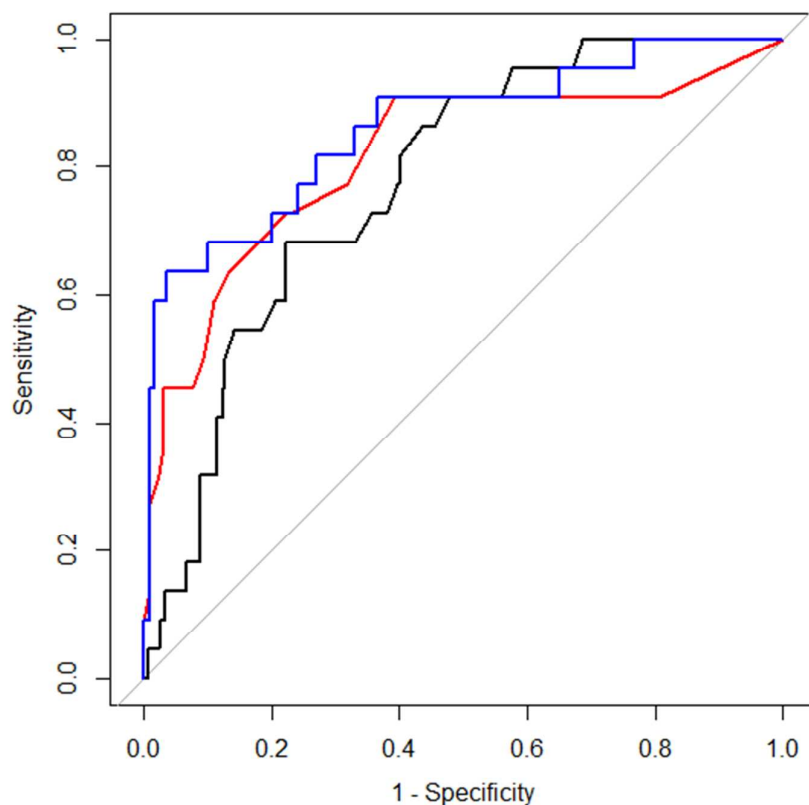
CI, confidence interval; RDW, red cell distribution width; MCV, mean corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in hospital.

Table 3. Independent predictors of mortality by multivariate logistic regression analysis

Variables	Odds ratio	95% CI	<i>P</i> value
APACHE-II (points)	1.189	1.071-1.319	0.001
AKI (%)	23.784	6.129-92.296	<0.001
RDW (%)	1.401	1.156-1.697	0.001

Independent variables include age, hemoglobin, MCV, hematocrit, APACHE-II score, AKI, TLSH, gestational age, and RDW. Due to the high correlation between hemoglobin and hematocrit, hemoglobin was first regressed on hematocrit; and placed the residual and hematocrit in the multivariate regression. RDW, red cell distribution width; MCV, mean corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in hospital.

Figure 1 ROC curve for Acute Physiology and Chronic Health Evaluation (APACHE) II score, red blood cell distribution width (RDW) and the combination of both in predicting ICU mortality.



— RDW (AUC 0.752 ± 0.062)

— APACHE-II score (AUC 0.766 ± 0.031)

— RDW+ APACHE-II score (AUC 0.872 ± 0.055)

RDW, red cell distribution width; MCV, mean corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in hospital.

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Clinical Usefulness of Red Blood Cell Distribution Width in Obstetric Patients admitted to Intensive Care Unit

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3 **1 TITLE PAGE**
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5 **2 Clinical Usefulness of Red Blood Cell Distribution Width in Obstetric**
6 **3 Patients admitted to Intensive Care Unit**
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21 Abstract

22 **Background:** Red blood cell distribution width (RDW) has been shown to
23 predict mortality in critically ill patients. The primary aim of this study was to
24 examine the association between RDW and hospital mortality in obstetric
25 critical care patients. The secondary aim was to investigate whether adding
26 RDW to Acute Physiology and Chronic Health Evaluation II (APACHE II)
27 improved the prognostic performance of APACHE II.

28 **Methods:** This is a single center, retrospective observational study. A total of
29 447 consecutive obstetric patients were included. Patients were excluded if
30 they had known hematologic diseases, history of recent blood transfusion,
31 and patients who died or were discharged from ICU within 24 hours of
32 admission. Each patient's ICU entrance characteristics were retrieved. We
33 modeled the association between RDW and mortality using multivariate
34 logistic regression. The receiver operating characteristic curve was used to
35 examine the performance of APACHE II score and RDW in predicting
36 mortality.

37 **Results:** A total of 376 patients were included in this present study. The
38 hospital mortality and maternal mortality were both 5.32%. A significant
39 association was found between baseline RDW levels and hospital or maternal
40 mortality (hazard ratio per percent increase in RDW, 1.21; 95% CI, 1.02 to
41 1.57). After categorization based on tertile of baseline RDW, as well as further
42 adjustment for hematocrit and other risk factors, a graded independent
43 association between RDW and mortality was observed ($P<0.001$). The

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3 44 addition of RDW to the APACHE II score improved the AUC for hospital or
4
5 45 maternal mortality from 0.766 to 0.872 ($P<0.001$).
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8 46 **Conclusions:** RDW is an independent predictor for hospital and maternal
9
10 47 mortality in obstetric critical care patients. Combining RDW to APACHE II
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12 48 scores could further improve its prognostic performance.
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15 49 **Key words:** APACHE-II score; Critical care; Mortality; Obstetrics; Red cell
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17 50 distribution width
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20 21 51 **Strengths and limitations of this study**

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23 52 • To our knowledge, this is the first report of red cell distribution width (RDW)
24
25 53 as an independent prognostic outcome predictor in obstetric critical care
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27 54 patients.
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29 55 • Since RDW is easy to obtain and highly reproducible, RDW has the
30
31 56 potentially clinical utility to predict outcome for obstetric critical care patients.
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33 57 • The study was a single-center study. It was very heterogenous, and patient
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35 58 numbers were relatively small, so large epidemiologic study might be required
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37 59 to validate the findings.
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61 Introduction

62 Despite the advances in the care of obstetric patients, maternal mortality ratio
63 (MMR) has remained high, especially in developing countries.^{1, 2} The use of
64 scoring systems to assess severity and predict mortality may help identify
65 obstetric patients who truly require intensive care.³ Acute Physiology and
66 Chronic Health Evaluation II (APACHE II) score is a predictive scores for
67 mortality that are widely used in ICUs. However, results from obstetric
68 patients have shown some inconsistencies; wherein, some studies have
69 shown that these scores are a good predictor of illness severity, while more
70 studies have shown that these scores overestimated mortality.^{4, 5, 6, 7-9} Further
71 work is needed to improve the prognostic accuracy of APACHE II scores in
72 obstetric patients.

73 Red cell distribution width (RDW) is a parameter that is easy and
74 inexpensive to obtain, and reflects the degree of heterogeneity of erythrocyte
75 volume.¹⁰ RDW was used in the differential diagnosis of anemia in the past
76 decades.¹¹ Recently, RDW has been shown to be a novel, independent
77 prognostic marker for mortality, mainly in patients with cardiovascular disease
78 and strokes, as well as in critically ill patients.¹²⁻¹⁹ However, few ICU
79 subpopulations have been studied so far. The obstetric population is of
80 special interest because of the limitations of existing scoring system, which
81 largely are based on physiological parameters.

82 Therefore, we conducted a retrospective study to evaluate the prognostic
83 value of RDW, and investigated whether adding RDW could improve the
84 prognostic performance of APACHE-II scores in critically ill obstetric patients.

85

86 **Methods**

87 This study was approved by the Institutional Review Board of the Provincial
88 Hospital Affiliated to Shandong University. Obstetric patients consecutively
89 admitted in the ICU for at least 24 hours from January 1, 2008 to December
90 31, 2013 were included in this retrospective observational study. The
91 requirement for patient consent was waived because this study did not affect
92 the patient's clinical care, and all protected health information was deleted.
93 Obstetric patients were defined as pregnant women or up to six weeks
94 postpartum. This study was carried out at the Shandong Provincial Hospital
95 Affiliated to Shandong University, Jinan, China. The hospital is a 1500-bed
96 tertiary academic hospital with 20 ICU beds. The hospital provides primary as
97 well as tertiary care to an ethnically and socioeconomically diverse population
98 within Shandong province and the surrounding region. The decision to
99 transfer patients into the ICU was made by at least one senior critical care
100 doctor and one senior obstetric doctor. Likewise, these doctors also made
101 decisions to discharge patients or to transfer patients to general wards.
102 Patients were excluded if they had known hematologic diseases (including
103 leukemia, thrombotic thrombocytopenic purpura, and other hematologic
104 diseases) or history of recent blood transfusion (less than two weeks).
105 According to the APACHE II scores criterion of Knaus WA, 1985,²⁰ the
106 recorded value in our study was based on the most deranged reading during
107 each patient's initial 24h in an ICU, so we excluded the patients who died or
108 were discharged less than 24 hours.

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3 109 *Data collection*
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6 110 Demographic and clinical characteristics including age, gestational age, parity,
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8 111 pregnancy status at admission, diagnosis at entry and during ICU stay, and
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10 112 length of hospital stay were collected. The cesarean section was considered
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12 113 an emergency intervention. Diagnosis of acute kidney injury (AKI) was based
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14 114 on the Acute Kidney Injury Network (AKIN) criteria.²¹ AKI was defined as an
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16 115 absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, a
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18 116 percentage increase in serum creatinine of more than or equal to 50% (1.5
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20 117 fold from baseline) within 48 hours, or reduction in urine output (documented
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22 118 oliguria of less than 0.5 ml/Kg per hour for more than six hours).²¹ The
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24 119 pregnancy associated with cardiac disease include congenital and acquired
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26 120 heart disease during pregnancy. APACHE II scores were calculated using the
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28 121 worst value of 12 acute physiological variables within 24 hours of presentation.
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30 122 These variables included temperature, blood pressure, heart rate, respiratory
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32 123 rate, arterial oxygenation, arterial pH, serum sodium, serum potassium, serum
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34 124 creatinine, hematocrit, white blood cell count, and Glasgow Coma scores. If
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36 125 the patient was sedated at the time of ICU admission, the last Glasgow Coma
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38 126 Scale obtained prior to sedation was collected. RDW, hemoglobin level,
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40 127 hematocrit and mean corpuscular volume (MCV) of all patients included in this
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42 128 study were determined at admission using a Beckman Coulter LH-750
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44 129 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, California), as a part
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46 130 of the complete blood cell count. Normal reference range for RDW in the
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48 131 hospital laboratory is 10.9% to 15.4%.
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56 132 *Study outcomes*
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3 133 All patients were followed up during hospitalization. According to the rule of
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5 134 our department, all ICU patients would be followed up at 1, 6, and 12 months
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7 135 after discharge. The primary end points of the study were hospital mortality
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9 136 and maternal mortality. The primary predictor of interest was RDW measured
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11 137 at ICU admission.

138 *Statistics*

139 All continuous variables were presented as means \pm standard deviations, or
140 medians with interquartile ranges as appropriate. Categorical data were
141 summarized as number or percentage. We divided RDW into tertiles, and
142 compared the demographics, diagnosis, clinical characteristics, laboratory test
143 results, and APACHE-II scores of patients using analysis of variance or
144 Kruskal-Wallis tests for continuous variables, and Chi-square or Fisher's exact
145 tests for categorical variables. Univariate logistic regression analysis was
146 conducted to examine the association between mortality and each of the
147 predictors, separately. Multivariate logistic regression was further utilized to
148 determine independent predictors of ICU mortality after adjusting for potential
149 confounding factors. An appealing receiver operating characteristic (ROC)
150 curve was used to examine the performance of APACHE-II scores and RDW
151 in predicting ICU mortality. The curve represented a sensitivity plot *versus* 1-
152 specificity. The area under the curve (AUC) was derived from the ROC curve,
153 and the Youden index was adopted to define the optimal cut-off value.²² We
154 also constructed an ROC curve for the combined APACHE-II score and RDW
155 results for predicting ICU mortality according to the weighted sum formula
156 derived from multivariate logistic regression: $\text{logit}(\text{mortality}) = 0.162 \times$

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3 157 APACHE-II score + 0.203 x RDW - 7.503; wherein, logit (mortality) is the
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5 158 logarithm of the odds of a critically ill obstetric patient dying in the ICU.
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7 159 Differences between the AUC were detected by Delong's test which was a
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9 160 nonparametric approach and could generate an estimated covariance matrix
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11 161 by using the theory on generalized U-statistics.²³ Two-sided *P*-values <0.05
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13 162 were considered statistically significant, and all analyses were performed with
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15 163 R software (<http://www.cran.r-project.org/>).
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24 165 **Results**

25 166 *Population*

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28 167 A total of 447 obstetric patients who were admitted to ICU were initially
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30 168 enrolled in this study. ICU admission rate was 21.73 per 1,000 births. Eight
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32 169 patients who were diagnosed with hematologic disease and 59 patients who
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34 170 received red blood cell transfusion within two weeks were excluded. Two
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36 171 patients who died within 24 hours after ICU admission were also excluded.
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38 172 Two patients were excluded for missing data. In the final analysis, 376
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40 173 patients were included in this study.
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45 174 *Association between RDW and hospital mortality*

46
47 175 A total of 20 deaths occurred in this cohort during the study period. As
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49 176 mentioned before, all ICU patients would be followed up at 1, 6, and 12
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51 177 months after discharge. As we know, of the total of 376 obstetric patients who
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53 178 were admitted to ICU, all the death occurred in the ICU. That is to say, there
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55 179 was no death outside of hospital or ICU. Thus, the maternal mortality was
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3 180 equal to hospital mortality in this population. In this study, heart failure was the
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5 181 major cause of death in the cohort (n=8; 40.0%), followed by acute fatty liver
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7 182 of pregnancy (n=5; 25%), postpartum hemorrhage (n=2), hemorrhagic shock
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9 183 caused by liver tumor rupture (n=1), HELLP syndrome (n=1), acute pulmonary
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11 184 embolism (n=1), stroke (n=1), and liver failure caused by severe hepatitis B
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13 185 (n=1). The hospital mortality and maternal mortality were both 5.32%, and
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15 186 RDW ranged from 10.7% to 24.0% (median, 14.8%; interquartile range, 13.4%
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17 187 to 16.0%).
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21 188 Participants were divided into three categories on the basis of their baseline
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23 189 tertiles of RDW level: tertile I, 10.7%-13.9%; tertile II, 13.9%-15.6%; tertile III,
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25 190 15.6%-20.4% (all $P<0.001$). There was no difference in age, gestational
26
27 191 weeks, primary reasons for ICU admission, AKI morbidity, as well as in the
28
29 192 total length of stay in hospital (TLSH) among the three tertiles. Hb, MCV and
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31 193 HCT significantly decreased with the increase of RDW, while APACHE II
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33 194 scores and hospital mortality significantly increased with the increase of RDW
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35 195 (Table 1). A significant association was found between baseline RDW levels
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37 196 and hospital mortality (hazard ratio per percent increase in RDW, 1.21; 95%
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39 197 CI, 1.02 to 1.57).
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44 198 *Regression analysis for hospital mortality*

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47 199 Univariate logistic regression analysis demonstrated that patients with higher
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49 200 RDW, higher APACHE-II scores, higher AKI morbidity, and longer TLSH days
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51 201 had significantly greater death hazards (Table 2). Multivariate logistic
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53 202 regression analysis revealed that RDW, AKI and APACHE-II scores were
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55 203 independent predictors of hospital mortality (Table 3). The association of
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3 204 RDW and hospital mortality remained significant after adjusting for age,
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5 205 hemoglobin, MCV, hematocrit, APACHE-II score and AKI. RDW was a
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7 206 significant outcome predictor, which is independent of APACHE-II scores.
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11 207 A ROC curve was drawn to evaluate the value for RDW and APACHE-II
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13 208 scores in predicting mortality (Figure 1). The AUC was calculated as 0.766
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15 209 (95% CI, 0.705 to 0.826) for the APACHE-II score and 0.752 (95% CI, 0.684
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17 210 to 0.862) for RDW. Optimal cut-off value of the APACHE-II score for
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19 211 predicting mortality was five points, which gave a sensitivity of 90.9% and a
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21 212 specificity of 60.7%. The optimal cut-off value of RDW was 16.1%, which gave
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23 213 a sensitivity of 68.2% and specificity of 77.9%. To further clarify whether RDW
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25 214 had an additive power with the APACHE-II score for hospital mortality, we
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27 215 combined RDW and the APACHE-II score to draw a third ROC curve, as
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29 216 shown in Figure 1. Compared with the APACHE-II score, adding RDW to
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31 217 APACHE-II scores improved the AUC from 0.766 to 0.872 ($P<0.001$). These
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33 218 results suggested that combining RDW and APACHE-II added to the ability to
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35 219 discriminate mortality risk. As in multivariate logistic regression analysis, AKI
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37 220 was another strong predictor for hospital mortality. We conducted the ROC
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39 221 curve analysis using all three variables including RDW, APACHE-II and AKI.
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41 222 Adding AKI improved the AUC from 0.872 to 0.884 ($P>0.05$), however, when
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43 223 we compared them by Delong's test, no significance can be found.
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50 51 225 **Discussion**

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55 226 The main finding of our study was that RDW was independently associated
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57 227 with hospital and maternal mortality in obstetric critical care patients . The
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3 228 association remained significant even after adjusting for APACHE-II scores,
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5 229 hemoglobin levels, hematocrit and mean corpuscular volume. Combining
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7 230 RDW and the APACHE-II score improved the prognostic accuracy of hospital
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9 231 mortality predicted by APACHE-II alone in the study population.

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12 232 We found that RDW was independently associated with hospital and
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14 233 maternal mortality in a Chinese obstetric ICU population. Patients were
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16 234 excluded if they had a history of recent blood transfusions because RDW
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18 235 could be increased in anemia or after blood transfusions.^{11, 24} In this present
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20 236 study, higher levels of RDW were associated with hospital and maternal
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22 237 mortality even after adjusting for hemoglobin and hematocrit. In addition, the
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24 238 independent association between RDW and hospital mortality or maternal
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26 239 mortality was not eliminated even after adjusting for other potential
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28 240 confounders, including mean corpuscular volume, hemoglobin, hematocrit,
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30 241 APACHE-II score, gestational age and AKI. Our results were consistent with
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32 242 previous analyses of two large populations of critically ill patients.^{25, 26} Further,
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34 243 our results were also similar to the findings obtained in a single-center
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36 244 observational study in 2011;¹⁶ wherein, the independent association between
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38 245 RDW and all-cause mortality in critically ill patients was shown.

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41 246 The important finding in our analysis was that combining RDW and
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43 247 APACHE-II score performed better than APACHE-II score alone in predicting
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45 248 hospital mortality or maternal mortality in critically ill obstetric patients. The
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47 249 APACHE-II scoring system developed in 1985 has shown a positive
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49 250 correlation with hospital mortality, and was one of the most common models
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51 251 used for evaluating the severity of a disease in critically ill patients.²⁰ Previous
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3 252 studies²⁷⁻²⁹ suggested APACHE II score was a good discriminator of illness
4
5 253 severity in obstetric cohorts. The sensitivity and specificity of the APACHE II
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7 254 score was evaluated with the use of receiver operating characteristic curve
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9 255 analysis. In accordance with previous studies²⁷⁻²⁹, the APACHE-II score was
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11 256 also demonstrated to have a strong power to predict hospital mortality or
12
13 257 maternal mortality (AUC=0.766) in the present study. Despite its moderate
14
15 258 discriminative power alone (AUC=0.752), adding RDW to the APACHE-II
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17 259 score resulted to a better increase in the AUC from 0.766 to 0.872 ($P<0.001$).
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21 260 Combining RDW with APACHE-II score significantly improved prognostic
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23 261 performance in critically ill obstetric patients. Similarly, another study by Wang
24
25 262 *et al.*¹⁶ also revealed that adding RDW to APACHE-II score significantly
26
27 263 improved prognostic reliability of APACHE-II score in identifying critically ill
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29 264 patients. Since RDW is a simple, inexpensive, and widely available test as
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31 265 part of the complete blood count, these data may have significant clinical
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33 266 implications for determining prognosis in critically ill obstetric patients.
34
35 267 However, no significant improvement on prognostic performance was
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37 268 observed when AKI was associated with RDW and APACHE-II score, even
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39 269 though AKI was another strong predictor for hospital mortality in multivariate
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41 270 logistic regression analysis. The reason was not clear, and further study
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43 271 would be needed.

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48 272 The pathophysiologic mechanism underlying the association of higher RDW
49
50 273 with worse outcomes in critically ill obstetric patients remains unclear.
51
52 274 Generally, the increase in RDW reflects either impaired erythropoiesis,
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54 275 abnormal red blood cell survival, or both. Metabolic abnormalities such as
55
56 276 shortening of telomere length, poor nutritional status,^{30, 31} inflammation,³²⁻³⁴

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3 277 oxidative stress,^{35, 36} dyslipidemia, hypertension, erythrocyte fragmentation,
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5 278 and alteration of erythropoietin function might contribute to RDW increase.³⁷ In
6
7 279 normal parturition, the increase of RDW might be related to stimulus-induced
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9 280 reticulocytosis in the last few weeks.²⁹ This might not be the case in our study;
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11 281 wherein, even if five patients with spontaneous onset of labor were excluded,
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13 282 RDW remained as a significant predictor of mortality.

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17 283 There were 20570 births from 2008 to 2013 in Shandong Provincial Hospital
18
19 284 and 447 ICU admissions. A total of 28 deaths occurred in the hospital during
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21 285 the 6-year study period resulting in a maternal mortality rate of 136 per
22
23 286 100,000 births. There were 22 deaths occurred in the ICU, and the others
24
25 287 occurred in emergency room (n=2) and maternity ward (n=4). In this present
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27 288 study, the admission rate of 21.73 per 1,000 births was relatively higher than
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29 289 those reported by other studies,³⁸⁻³⁹ and the mean APACHE-II score was
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31 290 relatively lower compared with other groups.^{7, 16, 40} The lack of a high
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33 291 dependency unit as a referral center in local areas for complicated
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35 292 pregnancies could partially explain these difference.

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40 293 This study had several limitations. First, we did not evaluate the evolution of
41
42 294 RDW, and thus, it remained unclear whether changes in RDW over time may
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44 295 provide additional prognostic information. Second, we only used the
45
46 296 APACHE-II score to predict mortality in obstetric patients, which was limited
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48 297 by spontaneous improvement after delivery in peripartum women,⁴¹⁻⁴⁷ and
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50 298 inconsistent results.^{48, 49} Finally, our study was a single-center study. The
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52 299 study was very heterogenous and patient numbers were relatively small, so
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54 300 large epidemiologic study may be required to validate the findings.

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3 301 In summary, the single-center study in China demonstrated that RDW was
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5 302 an independent predictor for mortality in obstetric critical care patients.
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7 303 Combining RDW and the APACHE-II score improved prognostic accuracy
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9 304 compared with the APACHE-II score model alone.
10

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34 314 **Conflict of Interests**

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37 315 The authors declare that there is no conflict of interests regarding the
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39 316 publication of this paper.
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41 317 **References**

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459 **Table 1. Baseline clinical and laboratory characteristics by tertile of**
 460 **RDW at critical care initiation**

	Tertile I	Tertile II	Tertile III	P-value
RDW (%)	10.7-13.9	13.9-15.6	15.6-20.4	<0.001
N	131	126	119	-
Age (years)	29.6 ± 4.3	29.3 ± 5.6	29.6 ± 5.9	0.84
Gestational age (weeks)	35 (32-37)	36 (33-39)	36 (32-38)	0.327
Primary diagnosis to ICU admission (n, %)				
Hypertensive disorder of pregnancy	50(38.17%)	55(43.65%)	52(43.70%)	0.417
HELLP Syndrome	12(9.16%)	10(7.94%)	8(6.72%)	0.322
Acute fatty liver of pregnancy	10(7.63%)	8(6.35%)	7(5.88%)	0.485
Obstetric sepsis	5(3.82%)	4(3.17%)	3(2.52%)	0.657
Cardiovascular disease	42 (32.06%)	31 (24.60%)	26 (21.85%)	0.162
Gastrointestinal disease	2 (1.53%)	5 (3.97%)	4 (3.36%)	0.476
Stroke	2 (1.53%)	3 (2.38%)	0 (0)	0.332
Pulmonary embolism	1 (0.76%)	0 (0)	1 (0.84%)	0.766
Others	7(5.34%)	10(7.94%)	18(15.13)	0.142
Hemoglobin (g/L)	109.5 ± 19.7	100.1 ± 20.7	92.5 ± 24.1	<0.001
MCV(fL)	89.8 ± 5.1	86.7 ± 6.0	83.6 ± 11.4	<0.001
HCT (%)	32.6 ± 5.8	30.5 ± 6.3	28.8 ± 6.9	<0.001
APACHE II score (points)	2 (2-6)	5 (3-6)	10 (6-22)	0.017
AKI (n, %)	14 (10.69%)	17 (13.49%)	14 (11.76%)	0.207
TLSH (days)	8 (7-12)	8 (6-13)	8 (7-12)	0.203
Hospital Mortality (n, %)	0 (0%)	5 (3.97%)	15 (12.61%)	<0.001

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3 461 RDW, red cell distribution width; MCV, mean corpuscular volume; HCT,
4 462 hematocrit; APACHE-II score, Acute Physiology and Chronic Health
5 463 Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in
6 464 hospital. Values are presented as mean \pm standard deviations or number
7 465 (percentage).
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467 **Table 2. Univariate odds ratios of variables for predicting mortality**

Variables	Odds ratio	95% CI	<i>P</i> -value
Age (years)	1.048	0.969-1.133	0.244
Hemoglobin (g/L)	0.997	0.977-1.017	0.763
MCV (fL)	0.962	0.919-1.006	0.098
Hematocrit (%)	0.997	0.934-1.064	0.929
APACHE-II score (points)	1.192	1.124-1.265	< 0.001
AKI (%)	16.61	6.580-42.014	< 0.001
TLSH (days)	0.803	0.691-0.933	0.004
gestational age (weeks)	1.023	0.920-1.138	0.677
RDW (%)	1.309	1.150-1.489	<0.001

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469 CI, confidence interval; RDW, red cell distribution width; MCV, mean
 470 corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology
 471 and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total
 472 length of stay in hospital.

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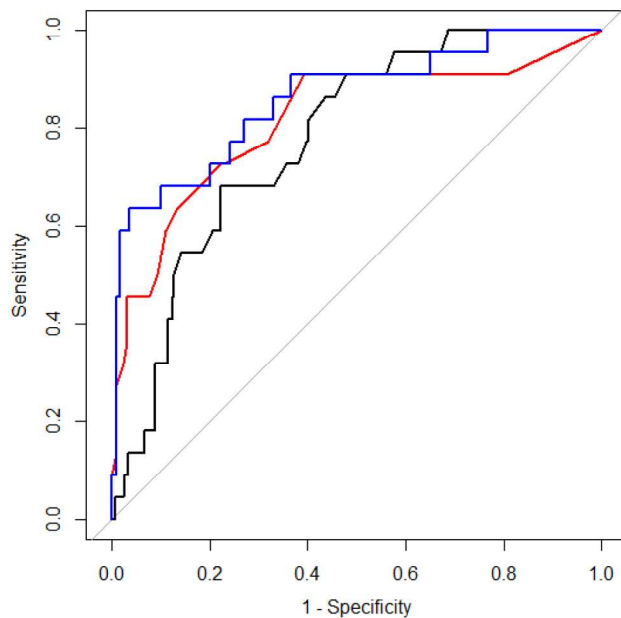
474 **Table 3. Independent predictors of mortality by multivariate logistic**
 475 **regression analysis**

Variables	Odds ratio	95% CI	<i>P</i> value
APACHE-II (points)	1.189	1.071-1.319	0.001
AKI (%)	23.784	6.129-92.296	<0.001
RDW (%)	1.401	1.156-1.697	0.001

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477 Independent variables include age, hemoglobin, MCV, hematocrit, APACHE-II
 478 score, AKI, TLSH, gestational age, and RDW. Due to the high correlation
 479 between hemoglobin and hematocrit, hemoglobin was first regressed on
 480 hematocrit; and placed the residual and hematocrit in the multivariate
 481 regression. RDW, red cell distribution width; MCV, mean corpuscular volume;
 482 HCT, hematocrit; APACHE-II score, Acute Physiology and Chronic Health
 483 Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in
 484 hospital.

Figure 1 ROC curve for Acute Physiology and Chronic Health Evaluation (APACHE) II score, red blood cell distribution width (RDW) and the combination of both in predicting hospital mortality.



— RDW (AUC 0.752 ± 0.062)

— APACHE-II score (AUC 0.766 ± 0.031)

— RDW+ APACHE-II score (AUC 0.872 ± 0.055)

RDW, red cell distribution width; MCV, mean corpuscular volume; HCT, hematocrit;

APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AKI, acute

kidney injury; TLSH, total length of stay in hospital.

179x220mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-8
		(b) Describe any methods used to examine subgroups and interactions	7-8
		(c) Explain how missing data were addressed	7-8
		(d) If applicable, explain how loss to follow-up was addressed	7-8
		(e) Describe any sensitivity analyses	7-8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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RDW as a risk factor in obstetric patients admitted to the ICU – a single center, retrospective cohort study.

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3 **1 TITLE PAGE**
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5 **2 RDW as a risk factor in obstetric patients admitted to the ICU – a single**
6 **3 center, retrospective cohort study.**
7

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2
3 **Abstract**
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6 **Background:** Red blood cell distribution width (RDW) has been shown to
7
8 predict mortality in critically ill patients. The primary aim of this study was to
9
10 examine the association between RDW and hospital mortality in obstetric
11
12 critical care patients. The secondary aim was to investigate whether adding
13
14 RDW to Acute Physiology and Chronic Health Evaluation II (APACHE II)
15
16 improved the prognostic performance of APACHE II.
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19
20 **Methods:** This is a single center, retrospective observational study. Patients
21
22 were excluded if they had known hematologic diseases, history of recent
23
24 blood transfusion, and patients who died or were discharged from ICU within
25
26 24 hours of admission were also excluded. Each patient's ICU entrance
27
28 characteristics were retrieved. Multivariate logistic regression was used to
29
30 determine the association between RDW and mortality. The receiver
31
32 operating characteristic curve was used to examine the performance of
33
34 APACHE II score and RDW in predicting mortality.
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38 **Results:** A total of 376 patients were included in this present study and the
39
40 hospital mortality was 5.32%. A significant association was found between
41
42 baseline RDW levels and hospital mortality (odds ratio per percent increase in
43
44 RDW, 1.21; 95% CI, 1.02 to 1.57). After categorization based on tertile of
45
46 baseline RDW, as well as further adjustment for hematocrit and other risk
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48 factors, a graded independent association between RDW and mortality was
49
50 observed ($P<0.001$). The addition of RDW to the APACHE II score improved
51
52 the AUC for hospital mortality from 0.766 to 0.872 ($P<0.001$).
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3 43 **Conclusions:** RDW is an independent predictor for hospital mortality in
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5 44 obstetric critical care patients. Combining RDW to APACHE II scores could
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7 45 further improve its prognostic performance.
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10 46 **Key words:** APACHE-II score; Critical care; Mortality; Obstetrics; Red cell
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12 47 distribution width
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14 48 **Strengths and limitations of this study**

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18 49 • To our knowledge, this is the first report of red cell distribution width (RDW)
19
20 50 as an independent prognostic outcome predictor in obstetric critical care
21
22 51 patients.
23
24 52 • The advantage of RDW is that it is easy to obtain and highly reproducible,
25
26 53 therefore, RDW may have the potential clinical utility to predict outcome for
27
28 54 obstetric critical care patients.
29
30 55 • Results discussed in this study are coming from a single-center with
31
32 56 relatively small patient numbers and high variability. A larger population based
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34 57 cohort study might greatly strengthen our findings.
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58 Introduction

59 Maternal mortality ratio (MMR) remain high despite the advances in the
60 critical care of obstetric patients, especially in developing countries.^{1, 2} The
61 use of scoring systems to assess severity and predict mortality may help
62 identify obstetric patients who truly require intensive care.³ Acute Physiology
63 and Chronic Health Evaluation II (APACHE II) score is a predictive scores for
64 mortality that are widely used in ICUs. However, results from obstetric
65 patients were inconsistencies; wherein, some studies have shown that these
66 scores are a good predictor of illness severity, more recent studies have
67 shown that these scores overestimated mortality.^{4, 5, 6, 7-9} Further work is
68 needed to improve the prognostic accuracy of APACHE II scores in obstetric
69 patients.

70 Red cell distribution width (RDW) is a parameter that is easy and
71 inexpensive to obtain, and reflects the degree of heterogeneity of erythrocyte
72 volume.¹⁰ RDW was used in the differential diagnosis of anemia in the past
73 decades.¹¹ Recently, RDW has been shown to be a novel, independent
74 prognostic marker for mortality, mainly in patients with cardiovascular disease
75 and strokes, as well as in critically ill patients.¹²⁻¹⁹ However, few ICU
76 subpopulations have been studied so far. The obstetric population is of
77 special interest because of the limitations of existing scoring system, which
78 are largely based on physiological parameters.

79 Therefore, we conducted a retrospective study to evaluate the prognostic
80 value of RDW, and investigated whether adding RDW could improve the
81 prognostic performance of APACHE-II scores in critically ill obstetric patients.

82

83 Methods

84 This study was approved by the Institutional Review Board of the Provincial
85 Hospital Affiliated to Shandong University. Obstetric patients consecutively
86 admitted in the ICU for at least 24 hours from January 1, 2008 to December
87 31, 2013 were included in this retrospective observational study. The
88 requirement for patient consent was waived because this study did not affect
89 the patient's clinical care, and all protected health information was deleted.
90 Obstetric patients were defined as pregnant women or up to six weeks
91 postpartum. This study was carried out at the Shandong Provincial Hospital
92 Affiliated to Shandong University, Jinan, China. The hospital is a 1500-bed
93 tertiary academic hospital with 20 ICU beds. The hospital provides primary as
94 well as tertiary care to an ethnically and socioeconomically diverse population
95 within Shandong province and the surrounding region. The decision to
96 transfer patients into the ICU was made by at least one senior critical care
97 doctor and one senior obstetric doctor. Likewise, these doctors also made
98 decisions to discharge patients or to transfer patients to general wards.
99 Patients were excluded if they had known hematologic diseases (including
100 leukemia, thrombotic thrombocytopenic purpura, and other hematologic
101 diseases) or history of recent blood transfusion (less than two weeks).
102 According to the APACHE II scores criterion of Knaus WA, 1985,²⁰ the
103 recorded value in our study was based on the most deranged reading during
104 each patient's initial 24h in an ICU, so we excluded the patients who died or
105 were discharged less than 24 hours.

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3 106 *Data collection*
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6 107 Demographic and clinical characteristics including age, gestational age, parity,
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8 108 pregnancy status at admission, diagnosis at entry and during ICU stay, and
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10 109 length of hospital stay were collected. The cesarean section was considered
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12 110 an emergency intervention. The pregnancy associated with cardiac disease
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14 111 include congenital and acquired heart disease during pregnancy. Diagnosis of
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16 112 acute kidney injury (AKI) was based on the Acute Kidney Injury Network (AKIN)
17
18 113 criteria.²¹ AKI was defined as an absolute increase in serum creatinine of
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20 114 more than or equal to 0.3 mg/dl, a percentage increase in serum creatinine of
21
22 115 more than or equal to 50% (1.5 fold from baseline) within 48 hours, or
23
24 116 reduction in urine output (documented oliguria of less than 0.5 ml/Kg per hour
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26 117 for more than six hours).²¹ APACHE II scores were calculated using the worst
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28 118 value of 12 acute physiological variables within 24 hours of presentation.
29
30 119 These variables included temperature, blood pressure, heart rate, respiratory
31
32 120 rate, arterial oxygenation, arterial pH, serum sodium, serum potassium, serum
33
34 121 creatinine, hematocrit, white blood cell count, and Glasgow Coma scores. If
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36 122 the patient was sedated at the time of ICU admission, the last Glasgow Coma
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38 123 Scale obtained prior to sedation was collected. RDW, hemoglobin level,
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40 124 hematocrit and mean corpuscular volume (MCV) of all patients included in this
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42 125 study were determined at admission using a Beckman Coulter LH-750
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44 126 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, California), as a part
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46 127 of the complete blood cell count. Normal reference range for RDW in the
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48 128 hospital laboratory is 10.9% to 15.4%. In addition, we got the number of birth
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50 129 (from January 1, 2008 to December 31, 2013) from hospital database in order
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52 130 to count ICU admission rate in the hospital.
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131 *Study outcomes*

132 All patients were followed up during hospitalization. The primary end point of
133 the study was hospital mortality. The primary predictor of interest was RDW
134 measured at ICU admission.

135 *Statistics*

136 All continuous variables were presented as means \pm standard deviations, or
137 medians with interquartile ranges as appropriate. Categorical data were
138 summarized as number or percentage. We divided RDW into tertiles, and
139 compared the demographics, diagnosis, clinical characteristics, laboratory test
140 results, and APACHE-II scores of patients using analysis of variance or
141 Kruskal-Wallis tests for continuous variables, and Chi-square or Fisher's exact
142 tests for categorical variables. Univariate logistic regression analysis was
143 conducted to examine the association between mortality and each of the
144 predictors, separately. Multivariate logistic regression was further utilized to
145 determine independent predictors of ICU mortality after adjusting for potential
146 confounding factors. An appealing receiver operating characteristic (ROC)
147 curve was used to examine the performance of APACHE-II scores and RDW
148 in predicting hospital mortality. The curve represented a sensitivity plot
149 *versus* 1-specificity. The area under the curve (AUC) was derived from the
150 ROC curve, and the Youden index was adopted to define the optimal cut-off
151 value.²² We also constructed an ROC curve for the combined APACHE-II
152 score and RDW results for predicting hospital mortality according to the
153 weighted sum formula derived from multivariate logistic regression: logit
154 (mortality) = 0.162 x APACHE-II score + 0.203 x RDW - 7.503; wherein, logit

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3 155 (mortality) is the logarithm of the odds of a critically ill obstetric patient dying in
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5 156 the ICU. Differences between the AUC were detected by Delong's test which
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7 157 was a nonparametric approach and could generate an estimated covariance
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9 158 matrix by using the theory on generalized U-statistics.²³ Two-sided *P*-values
10
11 159 <0.05 were considered statistically significant, and all analyses were
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14 160 performed with R software (<http://www.cran.r-project.org/>).
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162 **Results**

163 *Population*

164 A total of 20570 births was reported from January 1, 2008 to December 31,
165 2013 in Shandong Provincial Hospital, among which 447 obstetric patients
166 were admitted to ICU. ICU admission rate was 21.73 per 1,000 births in the
167 hospital. 8 patients who were diagnosed with hematologic disease and 59
168 patients who received red blood cell transfusion within two weeks were
169 excluded. 2 patients who died within 24 hours after ICU admission were also
170 excluded. 2 patients were excluded for missing data. Thus, in the final
171 analysis, a total of 376 patients were included in this study.

172 *Association between RDW and hospital mortality*

173 A total of 20 deaths occurred in this cohort during the study period. In this
174 study, heart failure was the major cause of death in the cohort (n=8; 40.0%),
175 followed by acute fatty liver of pregnancy (n=5; 25%), postpartum hemorrhage
176 (n=2), hemorrhagic shock caused by liver tumor rupture (n=1), HELLP
177 syndrome (n=1), acute pulmonary embolism (n=1), stroke (n=1), and liver

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3 178 failure caused by severe hepatitis B (n=1). The hospital mortality was 5.32%,
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5 179 and RDW ranged from 10.7% to 24.0% (median, 14.8%; interquartile range,
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7 180 13.4% to 16.0%).
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11 181 Participants were divided into 3 categories on the basis of their baseline
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13 182 tertiles of RDW level: tertile I, 10.7%-13.9%; tertile II, 13.9%-15.6%; tertile III,
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15 183 15.6%-20.4% (all $P<0.001$). There was no difference in age, gestational
16
17 184 weeks, primary reasons for ICU admission, AKI morbidity, as well as in the
18
19 185 total length of stay in hospital (TLSH) among the 3 tertiles. Hb, MCV and HCT
20
21 186 significantly decreased with the increase of RDW, while APACHE II scores
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23 187 and hospital mortality significantly increased with the increase of RDW (Table
24
25 188 1). A significant association was found between baseline RDW levels and
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27 189 hospital mortality (odds ratio per percent increase in RDW, 1.21; 95% CI, 1.02
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29 190 to 1.57).
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33 191 *Regression analysis for hospital mortality*

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36 192 Univariate logistic regression analysis demonstrated that patients with higher
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38 193 RDW, higher APACHE-II scores, higher AKI morbidity, and longer TLSH days
39
40 194 had significantly greater death hazards (Table 2). Multivariate logistic
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42 195 regression analysis revealed that RDW, AKI and APACHE-II scores were
43
44 196 independent predictors of hospital mortality (Table 3). The association of
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46 197 RDW and hospital mortality remained significant after adjusting for age,
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48 198 hemoglobin, MCV, hematocrit, APACHE-II score and AKI. RDW was a
49
50 199 significant outcome predictor, which is independent of APACHE-II scores.
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55 200 A ROC curve was drawn to evaluate the value for RDW and APACHE-II
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57 201 scores in predicting mortality (Figure 1). The AUC was calculated as 0.766
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3 202 (95% CI, 0.705 to 0.826) for the APACHE-II score and 0.752 (95% CI, 0.684
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5 203 to 0.862) for RDW. Optimal cut-off value of the APACHE-II score for
6
7 204 predicting mortality was 5 points, which gave a sensitivity of 90.9% and a
8
9 205 specificity of 60.7%. The optimal cut-off value of RDW was 16.1%, which gave
10
11 206 a sensitivity of 68.2% and specificity of 77.9%. To further clarify whether RDW
12
13 207 had an additive power with the APACHE-II score for hospital mortality, we
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15 208 combined RDW and the APACHE-II score to draw a third ROC curve, as
16
17 209 shown in Figure 1. Compared with the APACHE-II score, adding RDW to
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19 210 APACHE-II scores improved the AUC from 0.766 to 0.872 ($P<0.001$). These
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21 211 results suggested that combining RDW and APACHE-II added to the ability to
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23 212 discriminate mortality risk. As in multivariate logistic regression analysis, AKI
24
25 213 was another strong predictor for hospital mortality. We conducted the ROC
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27 214 curve analysis using all three variables including RDW, APACHE-II and AKI.
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29 215 Adding AKI improved the AUC from 0.872 to 0.884 ($P>0.05$), however, no
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31 216 significant difference was observed between the AUC derived from all three
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33 217 variables or that derived only from RDW and APACHE-II. The Delong's Z
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35 218 statistic and P value were equal to -0.668 and 0.504 respectively.

219 Discussion

220 The main finding of our study was that RDW was independently associated
221 with hospital mortality in obstetric critical care patients . The association
222 remained significant even after adjusting for APACHE-II scores, hemoglobin
223 levels, hematocrit and mean corpuscular volume. Combining RDW and the
224 APACHE-II score improved the prognostic accuracy of hospital mortality as
225 predicted by APACHE-II alone in the study population.

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3 226 We found that RDW was independently associated with hospital mortality in
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5 227 a Chinese obstetric ICU population. Patients were excluded if they had a
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7 228 history of recent blood transfusions because RDW could be increased in
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9 229 anemia or after blood transfusions.^{11, 24} In this present study, higher level of
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11 230 RDW was associated with hospital mortality even after adjusting for
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13 231 hemoglobin and hematocrit. In addition, the independent association between
14
15 232 RDW and hospital mortality was not eliminated even after adjusting for other
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17 233 potential confounders, including mean corpuscular volume, hemoglobin,
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19 234 hematocrit, APACHE-II score, gestational age and AKI. Our results were
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21 235 consistent with two previous population studies on critically ill patients.^{25, 26} In
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23 236 addition, our results were also in line with the findings obtained in a single-
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25 237 center observational study in 2011¹⁶, which showed independent association
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27 238 between RDW and all-cause mortality in critically ill patients.

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32 239 Our unique findings indicated that combining RDW and APACHE-II score
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34 240 performed better than APACHE-II score alone in predicting hospital mortality
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36 241 in critically ill obstetric patients. The APACHE-II scoring system developed in
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38 242 1985 has shown a positive correlation with hospital mortality, and was one of
39
40 243 the most common models used for evaluating the severity of a disease in
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42 244 critically ill patients.²⁰ Previous studies²⁷⁻²⁹ suggested APACHE II score was a
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44 245 good discriminator of illness severity in obstetric cohorts. The sensitivity and
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46 246 specificity of the APACHE II score was evaluated with the use of receiver
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48 247 operating characteristic curve analysis. In accordance with previous studies²⁷⁻
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50 248 ²⁹, the APACHE-II score was also demonstrated to have a good ability to
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52 249 predict hospital mortality (AUC=0.766) in the present study. Despite its
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54 250 moderate discriminative power alone (AUC=0.752), adding RDW to the

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3 251 APACHE-II score resulted to a better increase in the AUC from 0.766 to 0.872
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5 252 ($P<0.001$). Combining RDW with APACHE-II score significantly improved
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7 253 prognostic performance in critically ill obstetric patients. Similarly, another
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9 254 study by Wang *et al.*¹⁶ also revealed that adding RDW to APACHE-II score
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11 255 significantly improved prognostic reliability of APACHE-II score in identifying
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13 256 critically ill patients. Since RDW is a simple, inexpensive, and widely available
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15 257 test as part of the complete blood count, these data may have significant
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17 258 clinical implications for determining prognosis in critically ill obstetric patients.
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19 259 However, no significant improvement on prognostic performance was
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21 260 observed when AKI was associated with RDW and APACHE-II score, even
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23 261 though AKI was another strong predictor for hospital mortality in multivariate
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25 262 logistic regression analysis.
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30 263 The pathophysiologic mechanism underlying the association of higher RDW
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32 264 with worse outcomes in critically ill obstetric patients remains unclear.
33
34 265 Generally, the increase in RDW reflects either impaired erythropoiesis,
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36 266 abnormal red blood cell survival, or both. Metabolic abnormalities such as
37
38 267 shortening of telomere length, poor nutritional status,^{30, 31} inflammation,³²⁻³⁴
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40 268 oxidative stress,^{35, 36} dyslipidemia, hypertension, erythrocyte fragmentation,
41
42 269 or alteration of erythropoietin function might contribute to RDW increase.³⁷ In
43
44 270 normal parturition, the increase of RDW might be related to stimulus-induced
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46 271 reticulocytosis in the last few weeks.²⁹ This might not be the case in our study;
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48 272 wherein, even if five patients with spontaneous onset of labor were excluded,
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50 273 RDW remained as a significant predictor of mortality.
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3 274 In this present study, the admission rate of 21.73 per 1,000 births was
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5 275 relatively high,³⁸⁻³⁹ and the mean APACHE-II score was relatively low
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7 276 compared with other studies.^{7, 16, 40} The lack of a high dependency unit as a
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10 277 referral center in local areas for complicated pregnancies could partially
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12 278 explain these difference.

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15 279 This study had several limitations. First, we did not evaluate the evolution of
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17 280 RDW, and thus, it remained unclear whether changes in RDW over time may
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19 281 provide additional prognostic information. Second, we only used the APACHE-
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21 282 II score to predict mortality in obstetric patients, which was limited by
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23 283 spontaneous improvement after delivery in peripartum women,⁴¹⁻⁴⁷ and
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25 284 inconsistent results.^{48, 49} Finally, our study was a single-center study. The
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28 285 study was very heterogeneous and the case number was relatively small, in
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30 286 future, a large population based study may validate and strengthen our
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32 287 findings.

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36 288 In summary, the single-center study in China demonstrated that RDW was
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38 289 an independent predictor for mortality in obstetric critical care patients.
39
40 290 Combining RDW and the APACHE-II score improved prognostic accuracy
41
42 291 compared with the APACHE-II score model alone.

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10 301 **Conflict of Interests**

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13 302 The authors declare that there is no conflict of interests regarding the
14
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16 303 publication of this paper.
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446 **Table 1. Baseline clinical and laboratory characteristics by tertile of**
 447 **RDW at critical care initiation**

	Tertile I	Tertile II	Tertile III	P-value
RDW (%)	10.7-13.9	13.9-15.6	15.6-20.4	<0.001
N	131	126	119	-
Age (years)	29.6 ± 4.3	29.3 ± 5.6	29.6 ± 5.9	0.84
Gestational age (weeks)	35 (32-37)	36 (33-39)	36 (32-38)	0.327
Primary diagnosis to ICU admission (n, %)				
Hypertensive disorder of pregnancy	50(38.17%)	55(43.65%)	52(43.70%)	0.417
HELLP Syndrome	12(9.16%)	10(7.94%)	8(6.72%)	0.322
Acute fatty liver of pregnancy	10(7.63%)	8(6.35%)	7(5.88%)	0.485
Obstetric sepsis	5(3.82%)	4(3.17%)	3(2.52%)	0.657
Cardiovascular disease	42 (32.06%)	31 (24.60%)	26 (21.85%)	0.162
Gastrointestinal disease	2 (1.53%)	5 (3.97%)	4 (3.36%)	0.476
Stroke	2 (1.53%)	3 (2.38%)	0 (0)	0.332
Pulmonary embolism	1 (0.76%)	0 (0)	1 (0.84%)	0.766
Others	7(5.34%)	10(7.94%)	18(15.13)	0.142
Hemoglobin (g/L)	109.5 ± 19.7	100.1 ± 20.7	92.5 ± 24.1	<0.001
MCV(fL)	89.8 ± 5.1	86.7 ± 6.0	83.6 ± 11.4	<0.001
HCT (%)	32.6 ± 5.8	30.5 ± 6.3	28.8 ± 6.9	<0.001
APACHE II score (points)	2 (2-6)	5 (3-6)	10 (6-22)	0.017
AKI (n, %)	14 (10.69%)	17 (13.49%)	14 (11.76%)	0.207
TLSH (days)	8 (7-12)	8 (6-13)	8 (7-12)	0.203
Hospital Mortality (n, %)	0 (0%)	5 (3.97%)	15 (12.61%)	<0.001

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3 448 Note: RDW, red cell distribution width; MCV, mean corpuscular volume; HCT,
4 449 hematocrit; APACHE-II score, Acute Physiology and Chronic Health
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6 450 Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in
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8 451 hospital. Values are presented as mean \pm standard deviations or number
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10 452 (percentage).
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454 **Table 2. Univariate odds ratios of variables for predicting mortality**

Variables	Odds ratio	95% CI	<i>P</i> -value
Age (years)	1.048	0.969-1.133	0.244
Hemoglobin (g/L)	0.997	0.977-1.017	0.763
MCV (fL)	0.962	0.919-1.006	0.098
Hematocrit (%)	0.997	0.934-1.064	0.929
APACHE-II score (points)	1.192	1.124-1.265	< 0.001
AKI (%)	16.61	6.580-42.014	< 0.001
TLSH (days)	0.803	0.691-0.933	0.004
gestational age (weeks)	1.023	0.920-1.138	0.677
RDW (%)	1.309	1.150-1.489	<0.001

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456 Note: CI, confidence interval; RDW, red cell distribution width; MCV, mean
 457 corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology
 458 and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total
 459 length of stay in hospital.

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461 **Table 3. Independent predictors of mortality by multivariate logistic**
 462 **regression analysis**

Variables	Odds ratio	95% CI	<i>P</i> value
APACHE-II (points)	1.189	1.071-1.319	0.001
AKI (%)	23.784	6.129-92.296	<0.001
RDW (%)	1.401	1.156-1.697	0.001

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464 Note: Independent variables include age, hemoglobin, MCV, hematocrit,
 465 APACHE-II score, AKI, TLSH, gestational age, and RDW. Due to the high
 466 correlation between hemoglobin and hematocrit, hemoglobin was first
 467 regressed on hematocrit; and placed the residual and hematocrit in the
 468 multivariate regression. RDW, red cell distribution width; MCV, mean
 469 corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology
 470 and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total
 471 length of stay in hospital.

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473 Figure legend:
474 Figure 1: ROC curve for APACHE II score, RDW, and the combination of both
475 in predicting hospital mortality.

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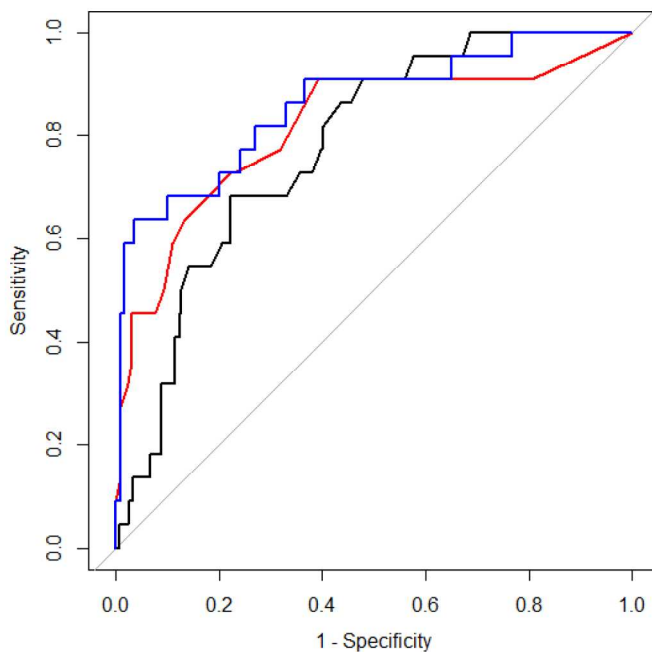


Figure 1

ROC curve for APACHE II score, RDW, and the combination of both in predicting hospital mortality. Compared with the APACHE-II score, adding RDW to APACHE-II scores improved the AUC from 0.766 to 0.872 ($P < 0.001$). — RDW (AUC 0.752 ± 0.062); — APACHE-II score (AUC 0.766 ± 0.031); — RDW+APACHE-II score (AUC 0.872 ± 0.055); ROC, receiver operating characteristic; AUC, area under the curve; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; RDW, red cell distribution width.

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Red blood cell distribution width as a risk factor for in-hospital mortality in obstetric patients admitted to Intensive care unit – a single center, retrospective cohort study.

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	APACHE-II score, Critical care, Mortality, OBSTETRICS, Red cell distribution width

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Manuscripts

1 **TITLE PAGE**

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6 **Red blood cell distribution width as a risk factor for in-hospital mortality**
7 **in obstetric patients admitted to Intensive care unit – a single center,**
8 **retrospective cohort study.**

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3 **Abstract**
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6 **Background:** Red blood cell distribution width (RDW) has been shown to
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8 predict mortality in critically ill patients. To our knowledge, it has not been
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10 evaluated whether RDW is associated with clinical outcomes of obstetric
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12 patients requiring critical care.
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16 **Methods:** This is a single-center, retrospective observational study of
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18 obstetric patients admitted to intensive care unit (ICU). Patients were
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20 excluded from the analysis if they had known hematologic diseases or
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22 recently underwent blood transfusion. Patients who died or were discharged
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24 from ICU within 24 hours of admission were also excluded. Patient clinical
25
26 characteristics at ICU admission were retrieved from medical chart. Multiple
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28 logistic regression was used to estimate odds ratios (OR) and 95%
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30 confidence intervals (95% CI) for in-hospital mortality associated with RDW.
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32 The receiver operating characteristic curve was used to examine the
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34 performance of RDW, alone or in combination with Acute Physiology and
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36 Chronic Health Evaluation II score (APACHE II), in predicting in-hospital
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38 mortality.
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41 **Results:** A total of 376 patients were included in this study. The hospital
42
43 mortality was 5.32%. A significant association was found between baseline
44
45 RDW levels and hospital mortality (odds ratio per percent increase in RDW,
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47 1.21; 95% CI, 1.02 to 1.57). Further adjustment for hematocrit and other
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49 potential confounders did not appreciably alter the result ($P<0.001$). The area
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51 under the curve (AUC) for in-hospital mortality by RDW was similar to that by
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3 46 APACHE II score (0.752 vs 0.766). Combination of these two factors resulted
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5 47 in substantial improvement in risk prediction, with AUC of 0.872 ($P<0.001$).
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8 **Conclusions:** This study suggests that RDW is an independent predictor for
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10 48 in-hospital mortality among ICU-admitted obstetric patients. Combining RDW
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12 49 and APACHE II scores could significantly improve in-hospital prognostic
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14 50 prediction among these critically-ill obstetric patients.
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18 **Key words:** APACHE-II score; Critical care; Mortality; Obstetrics; Red cell
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20 52 distribution width
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23 54 **Strengths and limitations of this study**

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26 55 • To our knowledge, this is the first report of red cell distribution width (RDW)
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28 56 as an independent prognostic predictor of clinical outcomes in obstetric
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30 57 critical care patients.
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32 58 • The study finding suggests that RDW, a routinely measured clinical
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34 59 laboratory test with high reproducibility, may have direct clinical implications
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36 60 and may aid the improvement of critical care for obstetric patients.
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38 61 • This is a single-center study. Replication in other populations/settings is
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40 62 warranted.
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63 Introduction

64 Maternal mortality ratio (MMR) remains high, despite the advances in the
65 critical care of obstetric patients, especially in developing countries.^{1, 2} The
66 use of scoring systems to assess its severity and predict mortality may help
67 identify obstetric patients who truly require intensive care.³ Acute Physiology
68 and Chronic Health Evaluation II (APACHE II) score is a predictive score for
69 mortality that are widely used in ICUs. However, results from obstetric
70 patients requiring critical care have been mixed. Some studies suggest this is
71 a good predictor for illness severity, but other more recent studies have
72 shown that this score has overestimated mortality risk.^{4, 5, 6, 7-9} Therefore,
73 there is a real need to identify new factors in order to improve the assessment
74 of illness severity and prediction of clinical outcomes for critically-ill obstetric
75 patients.

76 Red cell distribution width (RDW), a routinely measured clinical laboratory
77 test with high reproducibility, reflects the degree of heterogeneity of
78 erythrocyte volume.¹⁰ RDW has been used to differentiate anemia types over
79 the past decades.¹¹ Recently, RDW has been shown to be a novel,
80 independent prognostic marker for mortality, mainly in patients with
81 cardiovascular disease and strokes, as well as in critically ill patients.¹²⁻¹⁹
82 However, to our knowledge, no study has directly examined the prognostic
83 performance of RDW among obstetric patients requiring critical care.

84 In the study, we conducted a retrospective cohort study of ICU-admitted
85 obstetric patients to evaluate whether RDW at ICU admission was associated
86 with in-hospital mortality and examined the performance of RDW, alone or in

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3 87 combination with Acute Physiology and Chronic Health Evaluation II score
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5 88 (APACHE II), in predicting risk for in-hospital mortality.
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8 89 **Methods**
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11 90 The study was carried out at the Shandong Provincial Hospital Affiliated to
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13 91 Shandong University, Jinan, China. The hospital is a 1500-bed tertiary
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15 92 academic hospital with 20 ICU beds, which provides primary as well as
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17 93 tertiary care to an ethnically and socioeconomically diverse population within
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19 94 Shandong province and the surrounding region. The study was approved by
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21 95 the Institutional Review Board of the hospital. Obstetric patients consecutively
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23 96 admitted in the ICU for at least 24 hours from January 1, 2008 to December
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25 97 31, 2013 were included in this retrospective observational study. The
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27 98 requirement for patient consent was waived given the retrospective nature of
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29 99 this study design, i.e., no direct/indirect patient care intervention, and that all
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31 100 identifiable information was removed. Obstetric patients were defined as
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33 101 pregnant women or up to six weeks postpartum. The decision to transfer
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35 102 patients into the ICU was made by at least one senior critical care doctor and
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37 103 one senior obstetric doctor. Likewise, these doctors also made decisions to
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39 104 discharge patients or to transfer patients to general wards. Patients were
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41 105 excluded if they had known hematologic diseases (including leukemia,
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43 106 thrombotic thrombocytopenic purpura, and other hematologic diseases) or
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45 107 history of recent blood transfusion (less than two weeks). According to the
46
47 108 APACHE II score criterion of Knaus WA, 1985,²⁰ the recorded value in our
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49 109 study was based on the most deranged reading during each patient's initial
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3 110 24h in an ICU, so patients who died or were discharged less than 24 hours
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5 111 were excluded from the study.
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8 112 *Data collection*
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11 113 Demographic and clinical characteristics including age, gestational age, parity,
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13 114 pregnancy status at admission, diagnosis at entry and during ICU stay, and
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15 115 length of hospital stay were all collected. Cesarean section was considered an
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17 116 emergency intervention. The pregnancy associated with cardiac disease
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19 117 include congenital and acquired heart disease during pregnancy. Diagnosis of
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21 118 acute kidney injury (AKI) was based on the Acute Kidney Injury Network (AKIN)
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23 119 criteria.²¹ AKI was defined as an absolute increase in serum creatinine of
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25 120 more than or equal to 0.3 mg/dl, a percentage increase in serum creatinine of
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27 121 more than or equal to 50% (1.5 fold from baseline) within 48 hours, or
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29 122 reduction in urine output (documented oliguria of less than 0.5 ml/Kg per hour
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31 123 for more than six hours).²¹ APACHE II scores were calculated using the worst
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33 124 value of 12 acute physiological variables within 24 hours of presentation.
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35 125 These variables included temperature, blood pressure, heart rate, respiratory
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37 126 rate, arterial oxygenation, arterial pH, serum sodium, serum potassium, serum
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39 127 creatinine, hematocrit, white blood cell count, and Glasgow Coma scores. If
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41 128 the patient was sedated at the time of ICU admission, the last Glasgow Coma
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43 129 Scale obtained prior to sedation was collected. RDW, hemoglobin level,
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45 130 hematocrit and mean corpuscular volume (MCV) of all patients included in this
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47 131 study were determined at admission using a Beckman Coulter LH-750
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49 132 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, California), as a part
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51 133 of the complete blood cell count. Normal reference range for RDW in the
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3 134 hospital laboratory is between 10.9% and 15.4%. In addition, we obtained the
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5 135 number of birth (from January 1, 2008 to December 31, 2013) from hospital
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7 136 database in order to calculate ICU admission rate in the hospital.
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10 137 *Study outcomes*
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13 138 All patients were followed up during hospitalization. The primary end point of
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15 139 the study was in-hospital mortality. The primary predictor of interest was RDW
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17 140 measured at ICU admission.
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21 141 *Statistics*
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24 142 All continuous variables were presented as means \pm standard deviations, or
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26 143 medians with interquartile ranges as appropriate. Categorical data were
27
28 144 summarized as number or percentage. Patient characteristics across tertiles
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30 145 of RDW were compared using analysis of variance or Kruskal-Wallis tests for
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32 146 continuous variables and Chi-square or Fisher's exact tests for categorical
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34 147 variables. Logistic regression analysis was conducted to estimate odds ratios
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36 148 (OR) and 95% confidence intervals (95% CI) for in-hospital mortality
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38 149 associated with RDW and other clinical parameters after adjustment for
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40 150 potential confounding factors. The receiver operating characteristic (ROC)
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42 151 curve was used to examine the performance of RDW, alone or in combination
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44 152 with other clinical parameters such as APACHE II score, in predicting in-
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46 153 hospital mortality. The curve represented a sensitivity plot *versus* 1-specificity.
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48 154 The area under the curve (AUC) was derived from the ROC curve, and the
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50 155 Youden index was adopted to define the optimal cut-off value.²² We also
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52 156 constructed an ROC curve for the combined APACHE-II score and RDW
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54 157 results for predicting in-hospital mortality according to the weighted sum
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3 158 formula derived from multivariate logistic regression: $\text{logit}(\text{mortality}) = 0.162 \times$
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5 159 APACHE-II score + $0.203 \times \text{RDW} - 7.503$; wherein, $\text{logit}(\text{mortality})$ is the
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7 160 logarithm of the odds of a critically ill obstetric patient dying in the ICU.
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10 161 Differences between the AUC were detected by Delong's test, which was a
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12 162 nonparametric approach and could generate an estimated covariance matrix
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14 163 by using the theory on generalized U-statistics.²³ Two-sided P -values <0.05
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16 164 were considered statistically significant. All analyses were performed with R
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18 165 software (<http://www.cran.r-project.org/>).
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167 **Results**

168 *Population*

169 A total of 20570 births were reported from January 1, 2008 to December 31,
170 2013 in Shandong Provincial Hospital, among which 447 obstetric patients
171 were admitted to the ICU. ICU admission rate was 21.73 per 1,000 births in
172 the hospital. 8 patients who were diagnosed with hematologic disease and 59
173 patients who received red blood cell transfusion within two weeks were
174 excluded. 2 patients who died within 24 hours after ICU admission were also
175 excluded. Also 2 patients were excluded for missing data. Thus, in the final
176 analysis, a total of 376 patients were included in this study.

177 *Association between RDW and hospital mortality*

178 A total of 20 deaths occurred in this cohort during the study period. In this
179 study, heart failure was the major cause of death in the cohort ($n=8$; 40.0%),
180 followed by acute fatty liver of pregnancy ($n=5$; 25%), postpartum hemorrhage

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3 181 (n=2; 10%), hemorrhagic shock caused by liver tumor rupture (n=1; 5%),
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5 182 HELLP syndrome (n=1; 5%), acute pulmonary embolism (n=1; 5%), stroke
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7 183 (n=1; 5%), and liver failure caused by severe hepatitis B (n=1; 5%). The in-
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10 184 hospital mortality was 5.32%.

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12
13 185 RDW ranged from 10.7% to 24.0% (median, 14.8%; interquartile range,
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15 186 13.4% to 16.0%). Table 1 shows the comparison of patient clinical
16
17 187 characteristics across tertiles of RDW. RDW levels were inversely associated
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19 188 with levels of Hb, MCV and HCT, but positively associated with APACHE II
20
21 189 score and in-hospital mortality. No difference was found in distributions of age,
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23 190 gestational weeks, primary reasons for ICU admission, AKI morbidity, or the
24
25 191 total length of stay in hospital (TLSH) across RDW tertiles.

26 27 28 29 192 *Regression analysis for in-hospital mortality*

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32 193 Univariate logistic regression analysis demonstrated that patients with higher
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34 194 RDW, higher APACHE-II scores, higher AKI morbidity, and longer TLSH days
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36 195 had significantly greater death hazards (Table 2). Per percent increase in
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38 196 RDW was associated with 21% increase in the risk, with OR of 1.21 (95% CI,
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40 197 1.02 to 1.57).

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43 198 Multivariate logistic regression analysis revealed that RDW, AKI and
44
45 199 APACHE-II scores were independent predictors of in-hospital mortality (Table
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47 200 3). The association of RDW and in-hospital mortality remained significant after
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49 201 adjusting for age, hemoglobin, MCV, hematocrit, APACHE-II score and AKI.
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51 202 RDW was a significant outcome predictor, which is independent of APACHE-II
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53 203 scores.
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3 204 A ROC curve was drawn to evaluate the value for RDW and APACHE-II
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5 205 scores in predicting mortality (Figure 1). RDW and APACHE-II score were
6
7 206 equally sensitive in prognostic prediction, with AUC of 0.766 (95% CI, 0.705 to
8
9 207 0.826) for the APACHE-II score and 0.752 (95% CI, 0.684 to 0.862) for RDW.
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11 208 Optimal cut-off value of the APACHE-II score for predicting mortality was 5
12
13 209 points, which yielded sensitivity and specificity of 90.9% and 60.7%. The
14
15 210 optimal cut-off value of RDW was 16.1%, which resulted in sensitivity and
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17 211 specificity of 68.2% and 77.9%, respectively. We further combined RDW and
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19 212 the APACHE-II score to draw a third ROC curve, as shown in Figure 1,
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21 213 yielding much greater discriminatory capacity for in-hospital mortality, with
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23 214 AUC of 0.872. As shown in the multiple logistic regression analysis (Table 2),
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25 215 AKI was also significantly associated with in-hospital mortality. However, no
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27 216 appreciable improvement of prognostic performance was observed when
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29 217 further incorporating AKI into the prediction model. AUC derived from all three
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31 218 variables was 0.884. The Delong's Z statistic was -0.668 and P value was
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33 219 0.504.

34 35 36 37 38 39 220 **Discussion**

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42 221 The main finding of our study was that RDW was independently associated
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44 222 with in-hospital mortality in obstetric critical care patients . The association
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46 223 remained significant after adjusting for APACHE-II scores, hemoglobin levels,
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48 224 hematocrit and mean corpuscular volume. revealed the first evidence that the
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50 225 prognostic performance of RDW for in-hospital mortality among ICU-admitted
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52 226 obstetric patients was similar to APACHE-II score, a widely-accepted
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3 227 predictor of clinical outcomes in critically ill patients. Combination of RDW and
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5 228 APACHE-II score provided even greater predictive power than either alone.
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8 229 RDW has been associated with all-cause mortality in critically ill
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10 230 patients.^{16,24,25} We for the first time specifically evaluated the association
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12 231 among obstetric patients requiring critical care. We found that RDW was
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14 232 independently associated with in-hospital mortality in these patients. Patients
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16 233 were excluded if they had a history of recent blood transfusions because
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18 234 RDW could be increased in anemia or after blood transfusions.^{11, 26} In this
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20 235 present study, higher level of RDW was associated with in-hospital mortality
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22 236 even after adjusting for hemoglobin and hematocrit. In addition, the
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24 237 independent association between RDW and hospital mortality was not
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26 238 eliminated after further adjusting for other potential confounders such as
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28 239 mean corpuscular volume, hemoglobin, hematocrit, APACHE-II score,
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30 240 gestational age and AKI. Our findings indicated that combining RDW and
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32 241 APACHE-II score performed better than APACHE-II score alone in predicting
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34 242 in-hospital mortality in critically ill obstetric patients.
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40 243 The APACHE-II scoring system developed in 1985 has shown a positive
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42 244 correlation with hospital mortality, and was one of the most common models
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44 245 used for evaluating the severity of a disease in critically ill patients.²⁰ The
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46 246 sensitivity and specificity of the APACHE II score was evaluated with the use
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48 247 of receiver operating characteristic curve analysis in the present study. In
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50 248 accordance with previous studies²⁷⁻²⁹, the APACHE-II score was
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52 249 demonstrated to have a moderate discriminative ability to predict in-hospital
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54 250 mortality (AUC=0.766), similar to that for RDW (AUC=0.752). Combining
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3 251 RDW with APACHE-II score significantly improved prognostic performance
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5 252 (AUC=0.872). Similarly, another study by Wang *et al.*¹⁶ also revealed that
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7 253 adding RDW to APACHE-II score significantly improved prognostic reliability
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9 254 of APACHE-II score in identifying critically ill patients. Therefore, RDW, a
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11 255 simple, inexpensive, and widely available clinical test as part of the complete
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13 256 blood count, may have significant clinical implications for determining
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15 257 prognosis in critically ill obstetric patients. AKI was also significantly
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17 258 associated with in-hospital mortality. However, no significant improvement of
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19 259 prognostic performance was observed when further incorporating AKI into the
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21 260 prediction model.
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26 261 The pathophysiologic mechanism underlying the association of higher RDW
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28 262 with worse outcomes in critically ill obstetric patients remains unclear.
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30 263 Generally, the increase in RDW reflects either impaired erythropoiesis,
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32 264 abnormal red blood cell survival, or both. Metabolic abnormalities such as
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34 265 shortening of telomere length, poor nutritional status,^{30, 31} inflammation,³²⁻³⁴
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36 266 oxidative stress,^{35, 36} dyslipidemia, hypertension, erythrocyte fragmentation,
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38 267 or alteration of erythropoietin function might contribute to RDW increase.³⁷ In
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40 268 normal parturition, the increase of RDW might be related to stimulus-induced
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42 269 reticulocytosis in the last few weeks.³⁰ This might not be the case in our study;
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44 270 wherein, even if five patients with spontaneous onset of labor were excluded,
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46 271 RDW remained as a significant predictor of mortality.
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51 272 In this present study, the admission rate of 21.73 per 1,000 births was
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53 273 relatively high,^{27,38} and the mean APACHE-II score was relatively low
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55 274 compared with other studies.^{7, 16, 39} The lack of a high dependency unit as a
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3 275 referral center in local areas for complicated pregnancies could partially
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5 276 explain these difference.
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8 277 This study had several limitations. First, this work did not evaluate potential
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10 278 changes in RDW over time which may provide additional prognostic
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12 279 information. Second, only the APACHE-II score was used to predict mortality
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14 280 in obstetric patients, which was limited by spontaneous improvement after
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16 281 delivery in peripartum women,⁴⁰⁻⁴⁶ and inconsistent results.^{47, 48} Finally, the
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18 282 study was a single-center study. It is warranted to examine the association in
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20 283 different study settings/populations with a larger sample size.
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24 284 In summary, the study suggested that RDW may be an independent
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26 285 predictor for in-hospital mortality in obstetric patients requiring clinical care.
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28 286 Combining RDW and APACHE-II score significantly improved prognostic
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30 287 assessment among critically ill obstetric patients, which may have direct
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32 288 clinical implications and may aid the improvement of critical care for obstetric
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34 289 patients.
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38 290 **Contributorship statement**

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41 291 Yufeng Chu and Hongsheng Ren conceived of the study, and participated in
42
43 292 its design and coordination. Mei Meng, Haiyan Zhou and Chunting Wang
44
45 293 extracted data and participated in study design. Yufeng Chu, Zhongshang
46
47 294 Yuan and Gong Yang performed the statistical analysis and drafted the
48
49 295 manuscript. All authors read and approved the final manuscript.
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53 296 **Competing Interests**

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3 297 The authors declare that there is no competing interests regarding the
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5 298 publication of this paper.
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8
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30 **308 Data sharing statement**

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33 309 No additional unpublished data are available.
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450 **Table 1. Baseline clinical and laboratory characteristics by tertile of**
 451 **RDW at critical care initiation**

	Tertile I	Tertile II	Tertile III	P-value
RDW (%)	10.7-13.9	13.9-15.6	15.6-20.4	<0.001
N	131	126	119	-
Age (years)	29.6 ± 4.3	29.3 ± 5.6	29.6 ± 5.9	0.84
Gestational age (weeks)	35 (32-37)	36 (33-39)	36 (32-38)	0.327
Primary diagnosis to ICU admission (n, %)				
Hypertensive disorder of pregnancy	50(38.17%)	55(43.65%)	52(43.70%)	0.417
HELLP Syndrome	12(9.16%)	10(7.94%)	8(6.72%)	0.322
Acute fatty liver of pregnancy	10(7.63%)	8(6.35%)	7(5.88%)	0.485
Obstetric sepsis	5(3.82%)	4(3.17%)	3(2.52%)	0.657
Cardiovascular disease	42 (32.06%)	31 (24.60%)	26 (21.85%)	0.162
Gastrointestinal disease	2 (1.53%)	5 (3.97%)	4 (3.36%)	0.476
Stroke	2 (1.53%)	3 (2.38%)	0 (0)	0.332
Pulmonary embolism	1 (0.76%)	0 (0)	1 (0.84%)	0.766
Others	7(5.34%)	10(7.94%)	18(15.13)	0.142
Hemoglobin (g/L)	109.5 ± 19.7	100.1 ± 20.7	92.5 ± 24.1	<0.001
MCV(fL)	89.8 ± 5.1	86.7 ± 6.0	83.6 ± 11.4	<0.001
HCT (%)	32.6 ± 5.8	30.5 ± 6.3	28.8 ± 6.9	<0.001
APACHE II score (points)	2 (2-6)	5 (3-6)	10 (6-22)	0.017
AKI (n, %)	14 (10.69%)	17 (13.49%)	14 (11.76%)	0.207
TLSH (days)	8 (7-12)	8 (6-13)	8 (7-12)	0.203
Hospital Mortality (n, %)	0 (0%)	5 (3.97%)	15 (12.61%)	<0.001

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3 452 Note: RDW, red cell distribution width; MCV, mean corpuscular volume; HCT,
4 453 hematocrit; APACHE-II score, Acute Physiology and Chronic Health
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6 454 Evaluation II score; AKI, acute kidney injury; TLSH, total length of stay in
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8 455 hospital. Values are presented as mean \pm standard deviations or number
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10 456 (percentage).
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458 **Table 2. Univariate odds ratios of variables for predicting mortality**

Variables	Odds ratio	95% CI	<i>P</i> -value
Age (years)	1.048	0.969-1.133	0.244
Hemoglobin (g/L)	0.997	0.977-1.017	0.763
MCV (fL)	0.962	0.919-1.006	0.098
Hematocrit (%)	0.997	0.934-1.064	0.929
APACHE-II score (points)	1.192	1.124-1.265	< 0.001
AKI (%)	16.61	6.580-42.014	< 0.001
TLSH (days)	0.803	0.691-0.933	0.004
Gestational age (weeks)	1.023	0.920-1.138	0.677
RDW (%)	1.309	1.150-1.489	<0.001

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460 Note: CI, confidence interval; RDW, red cell distribution width; MCV, mean
 461 corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology
 462 and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total
 463 length of stay in hospital.

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465 **Table 3. Independent predictors of mortality by multivariate logistic**
 466 **regression analysis**

Variables	Odds ratio	95% CI	<i>P</i> value
APACHE-II (points)	1.189	1.071-1.319	0.001
AKI (%)	23.784	6.129-92.296	<0.001
RDW (%)	1.401	1.156-1.697	0.001

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468 Note: Independent variables include age, hemoglobin, MCV, hematocrit,
 469 APACHE-II score, AKI, TLSH, gestational age, and RDW. Due to the high
 470 correlation between hemoglobin and hematocrit, hemoglobin was first
 471 regressed on hematocrit; and placed the residual and hematocrit in the
 472 multivariate regression. RDW, red cell distribution width; MCV, mean
 473 corpuscular volume; HCT, hematocrit; APACHE-II score, Acute Physiology
 474 and Chronic Health Evaluation II score; AKI, acute kidney injury; TLSH, total
 475 length of stay in hospital.

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477 Figure legend:
478 Figure 1: ROC curve for APACHE II score, RDW, and the combination of both
479 in predicting hospital mortality.

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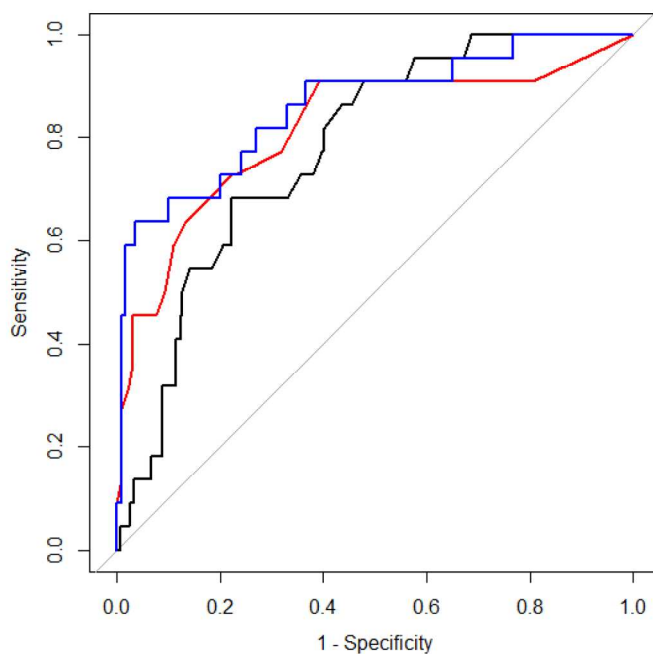


Figure 1

ROC curve for APACHE II score, RDW, and the combination of both in predicting hospital mortality. Compared with the APACHE-II score, adding RDW to APACHE-II scores improved the AUC from 0.766 to 0.872 ($P < 0.001$). — RDW (AUC 0.752 ± 0.062); — APACHE-II score (AUC 0.766 ± 0.031); — RDW+APACHE-II score (AUC 0.872 ± 0.055); ROC, receiver operating characteristic; AUC, area under the curve; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; RDW, red cell distribution width.

173x177mm (300 x 300 DPI)

