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Red Cell Distribution Width and all cause mortality in critically ill patients

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Abstract

Red Cell Distribution Width (RDW) is a predictor of mortality in the general population. The prevalence of increased RDW and its significance in the intensive care unit are unknown.

Objective—To investigate the association between RDW at the initiation of critical care and all cause mortality

Design—Multicenter observational study

Setting—Two tertiary academic hospitals in Boston, Massachusetts

Patients—51,413 patients, age ≥ 18 years, who received critical care between 1997 and 2007

Measurements—The exposure of interest was RDW and categorized *a priori* in quintiles as ≤13.3%, 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%. Logistic regression examined death by days 30, 90 and 365 post-critical care initiation, in-hospital mortality and bloodstream infection. Adjusted odds ratios were estimated by multivariable logistic regression models. Adjustment included age, sex, race, Deyo-Charlson index, CABG, MI, CHF, hematocrit, WBC, MCV, BUN, red blood cell transfusion, sepsis and creatinine.

Interventions—None

Key Results—RDW was a particularly strong predictor of all cause mortality 30 days following critical care initiation with a significant risk gradient across RDW quintiles following

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multivariable adjustment: RDW 13.3–14.0% OR 1.19 (95% CI, 1.08–1.30; P<0.001); RDW 14.0–14.7% OR 1.28 (95% CI, 1.16–1.42; P<0.001); RDW 14.7–15.8% OR 1.69 (95% CI, 1.52–1.86; P<0.001); RDW > 15.8% OR 2.61 (95% CI, 2.37–2.86; P<0.001); all relative to patients with RDW ≤13.3%. Similar significant robust associations post multivariable adjustments are seen with death by days 90 and 365 post-critical care initiation as well as in-hospital mortality. In a sub-analysis of patients with blood cultures drawn (n= 18,525), RDW at critical care initiation was associated with the risk of bloodstream infection and remained significant following multivariable adjustment. The adjusted risk of bloodstream infection was 1.40- and 1.44-fold higher in patients with RDW values in the 14.7–15.8% and >15.8% quintiles, respectively, compared with those with RDW ≤13.3%. Estimating the ROC AUC shows that RDW has moderate discriminative power for 30-day mortality (AUC = 0.67).

Conclusion—RDW is a robust predictor of the risk of all cause patient mortality and bloodstream infection in the critically ill. RDW is commonly measured, inexpensive and widely available and may reflect overall inflammation, oxidative stress, or arterial underfilling in the critically ill.

Keywords

Red Cell Distribution Width; Intensive Care; Mortality; Bloodstream infection

Introduction

Red blood cell distribution width (RDW) is an expression of the variation in size of the red blood cells that make up the total population in an individual patient. RDW is calculated as the standard deviation in red blood cell (RBC) size divided by the mean corpuscular volume (MCV). The individual RBC sizes are determined in an automated fashion by flow cytometry. RDW is widely available, inexpensive and included in the complete blood count panel. The normal range of RDW is 11.5–14.5% with no clinical scenarios that produce RDW less than 11.5%. Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW. By its definition, the RDW is nonspecific as to the mean RBC size or the nature of the cells counted, and an elevated RDW is thus associated with multiple disease processes.

Although not routinely utilized in critical care, RDW is a strong predictor of mortality in the general population of adults aged 45 and older.(1) In outpatients, RDW predicts all-cause mortality in addition to risk of death from cardiovascular disease, cancer, and chronic lower respiratory tract disease, even after adjusting for anemia and related nutritional deficiencies.(2) In patients with symptomatic chronic congestive heart failure, an increased RDW is independently associated with all-cause mortality.(3) In acute heart failure, increased RDW at the time of hospital admission is associated with increased risk of 1-year mortality.(4) Further, higher baseline RDW independently predicts subsequent risk of both cardiovascular death and all-cause mortality in those with acute stroke.(5) Although the mechanism of a RDW-mortality association is unclear, the association may be related to inflammation and the contribution of inflammation to the pathophysiology of disease.(2, 6–8)

In general, RDW is reflective of inflammation.(2) In the general population and in those with heart failure, higher RDW is associated with increases in ESR and the inflammatory markers IL-6, C-reactive protein and receptors for TNF I and II. (9–12) Pro-inflammatory cytokines found in patients with SIRS including TNF-α, IL-6 and IL-1β are noted to suppress erythrocyte maturation, allowing newer, larger reticulocytes to enter the peripheral circulation and increase RDW.(13–14) Further, pro-inflammatory cytokines can have direct inhibitory effects on half-life of red blood cell circulation, and deformability of the red blood cell membrane which in turn can manifest as an increase in RDW.(13, 15–16) These observations provide support for the biologic plausibility of RDW as a marker of inflammation in critical illness.

Despite these observations, the prevalence of increased RDW and its significance in critical care are not well studied. In a study of 47 surgical ICU patients from 1994, South African investigators reported 82% of cohort patients had wider RDW than control subjects.(17) In a recent prospective single center study from China, investigators noted an 1.6 fold increase in hospital mortality (albeit inadequately adjusted) with increased RDW in 602 critically ill medical patients.(18) Taken together, increased RDW is present in the critically ill and may be associated with adverse outcomes.

Thus we hypothesized that inflammation in the critically ill, reflected by a higher RDW, may increase the risk for bloodstream infections and be related to patient survival. To explore the role of increased RDW in the outcome of the critically ill, we performed a multicenter observational study of 51,785 critically ill patients hospitalized between 1997 and 2007. The objectives of this study were: 1) to determine the relationship between RDW at critical care initiation and all cause mortality; 2) to determine the association between RDW critical care initiation and bloodstream infection.

Materials and Methods

Source Population

We extracted administrative and laboratory data from individuals admitted to 2 academic teaching hospitals in Boston, Massachusetts. Brigham and Women's Hospital (BWH) is a 777-bed teaching hospital with 100 ICU beds. Massachusetts General Hospital (MGH) is a 902-bed teaching hospital with 109 ICU beds. The two hospitals provide primary as well as tertiary care to an ethnically and socioeconomically diverse population within eastern Massachusetts and the surrounding region.

Data Sources

Data on all patients admitted to BWH or MGH between November 2, 1997 and December 31, 2007 were obtained through a computerized registry which serves as a central clinical data warehouse for all inpatients and outpatients seen at these hospitals. The database contains information on demographics, medications, laboratory values, microbiology data, procedures and the records of inpatient and outpatients. Approval for the study was granted by the Institutional Review Board of BWH.

The following data were retrieved: Demographics, Vital status for up to 10 years following critical care initiation, Hospital admission and discharge date, laboratory values, blood bank reports, microbiology reports, Diagnosis Related Group (DRG) assigned at discharge, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes, and Current Procedural Terminology (CPT) codes for in-hospital procedures and services.

During the 10-year study period there were 54,392 unique patients, age ≥18 years, who were assigned the CPT code 99291 (critical care, first 30–74 minutes). 205 foreign patients without Social Security Numbers were identified and excluded as vital status in this study is determined by the Social Security Death Index. We also excluded 2,372 patients assigned CPT code 99291 who received care only in the Emergency Room, were not admitted and were not assigned a DRG. As a high white blood cell count may skew the automatically calculated RDW(19), 29 patients were excluded who had white blood cells over 150,000/ul. 166 patients were excluded for missing data. 51,413 patients constituted the study cohort.

Exposure of Interest and Comorbidities

The exposure of interest was RDW at critical care initiation and categorized *a priori* as ≤13.3%, 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, >15.8%.(3)

Sepsis was defined by the presence of any of the following ICD-9-CM codes: 038.0–038.9, 020.0, 790.7, 117.9, 112.5, and 112.81 3 days prior to critical care initiation to 7 days after critical care initiation.(20) Acute myocardial infarct is defined by ICD-9-CM 410.0–410.9(21) prior to or on day of critical care initiation. Congestive heart failure (CHF) is defined by ICD-9-CM 428.0–428.4 prior to or on the day of critical care initiation.(22) Number of organs with failure was adapted from Martin et al(20) and defined by a combination of ICD-9-CM and CPT codes relating to acute organ dysfunction assigned from 3 days prior to critical care initiation to 30 days after critical care initiation, as outlined in the Supplemental Digital Content.

Transfusion data was obtained via blood bank reports. Red blood cell transfusion unit amount, date and time were recorded. Only patients who received red blood cell transfusions in the 48 hours prior to critical care initiation and during the ICU stay were considered to have received transfusions.

Patient Type is defined as Medical or Surgical and incorporates the Diagnostic Related Grouping (DRG) methodology, devised by Centers for Medicare & Medicaid Services (CMS).(23) Procedures were determined by CPT codes as follows: CABG surgery performed on the day prior or day after critical care initiation (CPT codes 33510 to 33536).

The Deyo–Charlson index was used to assess the burden of chronic illness.(24) The Deyo–Charlson index consists of 17 co-morbidities, which are weighted and summed to produce a score each with an associated weight based on the risk of one-year mortality. This score ranges from 0 to 33, with higher scores indicating a higher burden. Thescore does not measure type or severity of acute illness.(24–25) We employed the ICD-9 coding algorithms developed by Quan et al(26) to derive a Deyo–Charlson index for each patient. The validity

of the algorithms for ICD-9 coding from administrative data is reported.(26) Due to relatively low representation, Deyo–Charlson index scores ≥ 5 were combined.

All patients who had blood cultures drawn 48 hours prior to 48 hours subsequent to critical care initiation were identified. Blood cultures were defined as positive if aerobic, anaerobic or fungal blood cultures grew identifiable organisms. Patients with positive blood cultures were considered to have bloodstream infections.(27–29)

Assessment of Mortality

Information on vital status for the study cohort was obtained from the Social Security Administration Death Master File. Data from the Social Security Administration Death Master File has a reported sensitivity for mortality up to 92.1% with a specificity of 99.9%, in comparison to >95% with National Death Index as the gold standard.(30–33) The administrative database from which our study cohort is derived is updated monthly using Social Security Administration Death Master File, which itself is updated weekly.(32, 34) Utilization of the Death Master File allows for long term follow-up of patients following hospital discharge. The censoring date was July 27, 2009.

End Points

The primary end point was 30 day mortality following critical care initiation. Other pre-specified end points included 90 day, 365 day, in-hospital mortality and bloodstream infection.

Statistical Analysis

Categorical covariates were described by frequency distribution, and compared across RDW groups using contingency tables and chi-square testing. Continuous covariates were examined graphically (e.g., histogram, box plot) and in terms of summary statistics (mean, SD, median, inter-quartile range), and compared across exposure groups using one-way ANOVA. Survival analyses considered death by days 30, 90 and 365 post-critical care initiation as well as in hospital mortality. In each instance, subjects were excluded if they were censored for incomplete data. 365 day follow-up was present for all 51,413 patients in the cohort.

Unadjusted associations between RDW groups and outcomes were estimated by contingency tables, chi square testing, by bivariable logistic regression analysis. Adjusted odds ratios were estimated by multivariable logistic regression models with inclusion of covariate terms thought to plausibly interact with both RDW and mortality or both RDW and bloodstream infection. Covariate terms included in the model included age, sex, race, Deyo-Charlson index, patient type (surgical versus medical), CABG, MI, CHF, hematocrit, transfusion, white blood count, MCV, blood urea nitrogen, sepsis and creatinine. For the primary model (30-day mortality), specification of each continuous covariate (as a linear versus categorical term) was adjudicated by the empiric association with the primary outcome using Akaike's Information Criterion; overall model fit was assessed using the Hosmer Lemeshow test. The Number of Organs with Failure variable was not adjusted for as it shares ICD-9 codes with the Deyo-Charlson Index.

Models for secondary analyses (90-day, 365-day and in-hospital mortality and bloodstream infection) were specified identically to the primary model in order to bear greatest analogy. We assessed possible effect modification of transfusion, anemia or sepsis on the risk of mortality and transfusion on the risk of bloodstream infection. We tested the significance of the interaction using the likelihood-ratio test. The discrimination of RDW for mortality was evaluated using receiver operating characteristics (ROC) curves. The area under the ROC curve (AUC) is an expression of the ability of RDW as a continuous variable to distinguish vital status at 30 days following critical care initiation.(35) All p-values presented are two-tailed; values below 0.05 were considered nominally significant. All analyses are performed using STATA 10.0MP (College Station, TX).

Results

Table 1 lists the main relevant characteristics of the 51,413 subject study cohort. Of the patients studied, 41.79% were women and 79.6% were white. The mean age at critical care initiation was 61.7 years (SD 18.3). 30 day all cause mortality was 14.2%. 50.5% of patients were assigned a Medical DRG. 15.4% of patients suffered an acute myocardial infarct. 5.5% of the cohort underwent CABG and 13.5% of patients were septic. 23.4% of patients were transfused red blood cells from 48 hours prior to critical care initiation throughout the ICU stay.

Patient characteristics of the study cohort were stratified according to RDW levels at critical care initiation (Table 2). Factors that significantly differed between stratified groups included age, gender, race, patient type, Deyo-Charlson Index, sepsis, acute MI, CABG, CHF, transfusion, creatinine, blood urea nitrogen, white blood cell count, hematocrit, and number of organs with failure. An increasing gradient across RDW quintiles is observed in patients with creatinine >1.3mg/dl, Blood Urea Nitrogen>20mg/dl, Sepsis, Deyo-Charlson Index ≥3, and number of organs with failure ≥2. (Table 2) In the multivariable adjusted analysis, age, patient type, Deyo-Charlson Index, creatinine, hematocrit, white blood cells, blood urea nitrogen, MCV, CABG, sepsis, and transfusions are all significantly associated with 30-day mortality.(Table 3)

RDW was a particularly strong predictor of all cause mortality with a significant risk gradient across RDW quintiles (Table 4). The risk of mortality 30 days following critical care initiation was 2.8- and 5.0-fold higher in patients with RDW values in the fourth and fifth highest quintiles, respectively, compared with those in the bottom quintile (RDW ≤13.3%). RDW in the cohort remains a significant predictor of risk of mortality following adjustment for age, sex, race, Deyo-Charlson index, patient type, CABG, MI, hematocrit, transfusion, creatinine, white blood count, MCV, blood urea nitrogen, sepsis and creatinine. The adjusted risk of mortality 30 days following critical care initiation was 1.7- and 2.6-fold higher in patients with RDW values in the fourth and fifth highest quintiles, respectively, compared with those in the bottom quintile (Table 5). Similar significant robust associations pre and post multivariable adjustments are seen with death by days 90 and 365 post-critical care initiation as well as in-hospital mortality (Tables 4 and 5).

In a subanalysis of patients with blood cultures drawn between 48 hours prior and 48 hours subsequent to critical care initiation (n= 18,525), RDW at critical care initiation was associated with a significant risk gradient for bloodstream infection across RDW quintiles. The risk of bloodstream infection was 1.8- and 2.0-fold higher in patients with RDW values in the fourth and fifth highest quintiles, respectively, compared with those in the bottom quintile (Table 6). RDW in the cohort remains a significant predictor of risk of bloodstream infection following multivariable adjustment for age, sex, race, Deyo-Charlson index, patient type, transfusion, creatinine and white blood count. The adjusted risk of bloodstream infection was 1.40- and 1.44-fold higher in patients with RDW values in the fourth and fifth highest quintiles, respectively, compared with those in the bottom quintile (Table 6). The most common organisms cultured from blood in the cohort include coagulase negative Staphylococcus, S. aureus, E. coli, E. faecium, E. faecalis, Candida albicans, Klebsiella pneumonia, E. cloacae, P. aeruginosa, Candida parapsilosis, Candida glabrata, and S. pneumoniae.

There is effect modification of the RDW-mortality association on the basis of anemia defined as hematocrit ≤ 36% (30-day mortality: interaction p=0.05; fully adjusted, data not shown). For 30-day mortality the risk associated with RDW of 13.3–14.0% and RDW of 14.0–14.7% relative to RDW of ≤ 13.3% is not significant in the presence of anemia (hematocrit ≤ 36%). The mortality risk associated with RDW > 14.7% is unchanged in the presence of hematocrit ≤ 36%. The number of patients with RDW > 14.7% and hematocrit ≤ 36 was 12,839 with 22.1% in-hospital mortality and 23.8% 30-day mortality.

There is no significant effect modification of the RDW-mortality association on the basis of transfusion (30-day mortality: interaction p=0.17; fully adjusted, data not shown). Finally, there is no significant effect modification of the RDW-bloodstream infection association on the basis of anemia (interaction p=0.29) or transfusion (interaction p=0.24); all fully adjusted, data not shown. There is no effect modification of the RDW-mortality association on the basis of sepsis in the primary outcome (30-day mortality: interaction p=0.46; fully adjusted, data not shown).

To assess discrimination of RDW for 30-day mortality we used receiver-operating-characteristic (ROC) curve analysis and determined the area under the curve (AUC), also known as a concordance (C) statistic. Estimating the AUC shows that RDW has moderate discriminative power for 30-day mortality (AUC = 0.67). RDW has marginal discriminative power for bloodstream infections (AUC = 0.57).

Discussion

The present study aimed to determine whether RDW was associated with all cause mortality following critical care initiation. The main findings of this study are the illustration of a graded independent relationship between RDW and all-cause mortality and also between RDW and bloodstream infection. RDW is a significant predictor of 30, 90, 365 day mortality post critical care initiation, in-hospital mortality and bloodstream infection. RDW remains a significant predictor of mortality and bloodstream infection following multivariable adjustments. The association between RDW and 30-day mortality is

independent of transfusion status. The RDW-mortality association is independent of anemia (hematocrit ≤ 36%) when RDW is over 14.7%. The RDW-bloodstream infection association is independent of transfusion status and anemia.

Sepsis significantly differed between RDW groups with a gradient of higher percentage of septic patients in the higher RDW quintiles.(Table 2). Patients with sepsis have a significantly increased odds of 30-day mortality following critical care.(Table 3) Despite these observations, there is no effect modification of the RDW-mortality association on the basis of sepsis in the primary outcome. The interaction tests suggest that the association between RDW quintiles and 30-day mortality is the same in septic patients as in non-septic patients.

In addition to adjusting for patients with myocardial infarct and congestive heart failure, we attempted to correct for known iatrogenic factors associated with an increase in RDW including red blood cell transfusion and white blood count. Adding exogenous RBCs through repeated transfusions is known to skew the RDW.(36) The vast majority of patients under study (n=39,521) did not receive transfusions 48 hours prior to critical care initiation or during the ICU stay. Since automated cell counters measure size by observing the change in resistance or light diffraction when an object enters the counting chamber, it is possible that particles other than single RBCs can make up the calculated RDW. Thus, fragmented schistocytes, cold-agglutinated RBCs, and even very high numbers of white blood cells (>150,000/ul) may skew the automatically calculated RDW.(19) In our study cohort, we excluded patients with white blood cells over 150,000/ul but were unable to adjust for fragmented schistocytes or cold-agglutinated red blood cells, factors that may interfere with the RDW.

The mechanism for a RDW-mortality association is not known. Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW. Elevations in RDW may have negative impact on patient survival by reflecting the extent of inflammation. An association between increased RDW and changes in inflammatory biomarkers has been studied in general patient populations. Higher RDW is associated with increasing levels of inflammation markers in outpatients.(9) A graded direct association was found in outpatients between RDW and ESR/hsCRP that was independent of age, sex, mean corpuscular volume, hemoglobin, and ferritin.(9)

Inflammation alters erythropoiesis by a variety of mechanisms, including direct myelosuppression of erythroid precursors, promotion of red cell apoptosis, reduction of erythropoietin production, reduced bioavailability of iron, and erythropoietin resistance in erythroid precursor cell lines.(37–38) Inflammatory cytokines suppress erythrocyte maturation, accentuated with sepsis(39), allowing newer, larger reticulocytes to enter the circulation and skew RDW.(14, 40) Thus, inflammation likely leads to an increased RDW from the release of immature red blood cells into the peripheral circulation.

Inflammation and immune suppression is observed with surgical procedures, trauma, burn injury, or hemorrhage which can predispose patients to nosocomial infections.(41–42) Septic patients also have decreases in immune responsiveness predisposing to nosocomial

infections.(43) T-Regulatory cells appear to play a major role in the suppression of immune reactivity in injury(44–45) and infection(46). In such inflammatory or injury states, a decrease in the counter-regulatory process from T-Regulatory cells may result in dysfunctional responses to sepsis, inflammation and injury. The observed correlations between RDW and inflammation (9–12) may result in the increased risk of bloodstream infection and mortality observed in our study.

Oxidative stress may also be a contributing factor for the RDW-mortality association. High oxidative stress is present in sepsis via the generation of reactive oxygen species by activated leukocytes.(47) High oxidative stress contributing to elevated RDW by reducing red blood cell survival, and increasing release of large premature red blood cells into the peripheral circulation.(48)

The RDW-mortality association in this study may also be related to the neurohumoral response to arterial underfilling. Such response involves arginine vasopressin (AVP), the renin angiotensin aldosterone system and the sympathetic nervous system.(61–63) Activation of the renin-angiotensin system triggers an acceleration of erythrocyte production resulting in an increased RDW via macrocytosis related to skipped cell divisions.(49–51) Such arterial underfilling states are common in cardiac failure and sepsis(66), conditions that contribute to mortality and are common to our cohort.

The limitations of our study stem from its retrospective observational design with its inherent biases. Our finding that RDW at critical care initiation is a significant predictor of mortality does not include physiologic data. In the administrative database used in this study APACHE scores are absent as both physiologic data and Glasgow Coma scale data is not available. APACHE and other physiological based scoring systems are strong predictors of mortality in the critically ill.(52) Adding a physiologic score in the analysis may cause an alteration in the observed RDW-mortality association. The Deyo-Charlson comorbidity index can be considered an alternative method of risk adjustment in the absence of physiologic data when age and gender data are utilized.(53) However, despite multivariable adjustment of potential confounders, the absence of physiologic data remains a limitation of our study.

Evaluating the sensitivity and specificity of the RDW with the use of receiver-operating-characteristic (ROC) curve analysis, estimating the area under the curve (AUC) shows that RDW has moderate discriminative power (AUC = 0.67). In comparison, a prior study of a heterogeneous critical care population demonstrated the discriminative power of APACHE II or SAPS II to distinguish in-hospital mortality the AUC was 0.84 and 0.85 respectively.(54) In our study due to data limitations we are unable to directly compare the discrimination of RDW for 30-day mortality versus APACHE or SAPS II.

Administrative coding data has been assessed for individual diseases(55–59) and comorbidity profiles.(60–61) There is controversy regarding the accuracy of ICD-9-CM coding for the identification of medical conditions.(20) The ICD-9-CM code 038.x is reported to have a high positive predictive value for the identification of true cases of sepsis(62), and a high sensitivity(63), specificity(20) and negative predictive value.(20) The

Deyo Charlson index algorithm used in this study(26) utilizes ICD-9 coding and is well studied and validated.(64–65)

The present study has several strengths. All-cause mortality is an unbiased and clinically relevant outcome in long-term observational studies.(66–67) Utilization of the Social Security Administration Death Master File allowed for complete 365 day follow up for the cohort following hospital discharge. Our study has sufficient numbers of patients to ensure adequate reliability of our mortality estimates (n = 51,413, in-hospital mortality rate = 12.8%). The basis of critical care initiation on CPT 99291 codes in our administrative dataset is validated.(68) Our use of previous records to define comorbidities increases their prevalence and results in a better risk adjustment.(57, 69) We include data for packed red blood cell transfusion prior to and during critical care, which is associated with respiratory failure and overall mortality in the critically ill.(70) Bloodstream infection and bloodstream infection rates are accepted end-points in critical care studies.(27–29) Finally, RDW measurement time is uniform relative to the onset of critical care initiation.

Conclusions

In aggregate, these data demonstrate that RDW at critical care initiation is very strongly associated with the risk of death and the risk of bloodstream infection in critical illness and that this risk is independent of other risk factors. RDW is not a surrogate for a single disease process but is more reflective several processes found in critically ill patients. In the heterogenous population under study, increased RDW likely reflects the presence of proinflammatory cytokines and chemokines, oxidative stress, or arterial underfilling or a combination thereof. Inflammation and or oxidative stress may also contribute to the association of RDW and risk of bloodstream infection.

RDW is an inexpensive and common measurement found on the complete blood count. While further research is needed to determine the mechanisms of the RDW-mortality association and the RDW-bloodstream infection association, this study provides support for future investigations to consider adding RDW to other established critical illness outcome markers to stratify critically ill patients at risk for infection and mortality.

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Table 1

Patient Characteristics of the Study Population

N	51,413
Age years-*mean(SD)*	61.7(18.3)
Gender-no.(%)	
Male	29,930(58.21)
Female	21,483(41.79)
Race-no.(%)	
White	40,938(79.63)
Non-white	10,475(20.37)
Type-no.(%)	
Medical	25,972(50.52)
Surgical	25,441(49.48)
RDW-no.(%)	
≤13.3%	13,511(26.28)
13.3–14%	12,495(24.30)
14–14.7%	7,745(15.06)
14.7–15.8%	7,225(14.05)
>15.8%	10,437(20.30)
Blood Urea Nitrogen-no.(%)	
≤10 mg/dl	6,792(13.21)
10–20 mg/dl	23,158(45.04)
20–40 mg/dl	14,753(28.70)
>40 mg/dl	6,710(13.05)
Creatinine-no.(%)	
≤1.0 mg/dl	26,844(52.21)
1.0–1.3 mg/dl	10,959(21.32)
1.3–2.0 mg/dl	7,646(14.87)
>2.0 mg/dl	5,964(11.60)
White Blood Cells-no.(%)	
≤4	1,684(3.28)
4–10	21,206(41.25)
>10	28,523(55.48)
Hematocrit-no.(%)	
≤30 %	10,964(21.33)
30–33 %	6,876(13.37)
33–36 %	7,437(14.47)
36–39 %	8,379(16.30)
39–42 %	7,926(15.42)
>42 %	9,831(19.12)
Transfusions-no.(%)	
0	39,395(76.62)

1	2,141(4.16)
2	2,514(4.89)
3	1,314(2.56)
≥4	6,050(11.77)
Sepsis-no.(%)	6,963(13.54)
Bloodstream Infections-no.(%)	
Absent	15,463(83.47)
Present	3,062(16.53)
No. Organs with Failure-no.(%)	
0	18,110(35.22)
1	16,890(32.85)
2	9,480(18.44)
3	4,410(8.58)
≥4	2,523(4.91)
CABG-no.(%)	2,815(5.48)
MI-no.(%)	7,912(15.39)
CHF-no.(%)	11,428 (22.23)
Deyo-Charlson Index-no.(%)	
0	5,649(10.99)
1	7,906(15.38)
2	10,003(19.46)
3	9,179(17.85)
4	7,395(14.38)
≥5	11,281(21.9)
Mortality Rates-no.(%)	
30-day	7,277(14.15)
90-day	9,597(18.67)
365-day	13,507(26.27)
In-hospital	6,580(12.80)

Table 2

Stratified Patient Characteristics of the Study Population

	RDW% at at critical care initiation					
	≤13.3	**13.3–14.0**	**14.0–14.7**	**14.7–15.8**	**>15.8**	**P-value**
N	13,511	12,495	7,745	7,225	10,437	
Age-mean(SD)	53.7(19.7)	62.4(18.1)	65.9(16.6)	66.7(16.1)	64.7(15.9)	<0.001
Gender-no.(%)						<0.001
Male	8,541(63.2)	7,529(60.3)	4,377(56.5)	3,940(54.5)	5,543(53.1)	
Female	4,970(36.8)	4,966(39.7)	3,368(43.5)	3,285(45.5)	4,894(46.9)	
Race-no.(%)						<0.001
White	10,524(77.9)	9,985(79.9)	6,285(81.2)	5,881(81.4)	8,263(79.2)	
Non-White	2,987(22.1)	2,510(20.1)	1,460(18.9)	1,344(18.6)	2,174(20.8)	
Patient type-no.(%)						<0.001
Medical	7,002(51.8)	6,134(49.1)	3,616(46.7)	3,396(47.0)	5,824(55.8)	
Surgical	6,509(48.2)	6,361(50.9)	4,129(53.3)	3,829(53.0)	4,613(44.2)	
Deyo-Charlson Index (%)						<0.001
0	3,118(23.1)	1,541(12.3)	488(6.3)	290(4.0)	212(2.0)	
1	3,290(24.4)	2,256(18.1)	1,000(12.9)	710(9.8)	650(6.2)	
2	2,893(21.4)	2,744(22.0)	1,595(20.6)	1,250(17.3)	1,521(14.6)	
3	1,962(14.5)	2,264(18.1)	1,523(19.7)	1,462(20.2)	1,968(18.9)	
4	1,146(8.5)	1,672(13.4)	1,239(16.0)	1,290(17.9)	2,048(19.6)	
≥5	1102(8.2)	2,018(16.2)	1900(24.5)	2223(30.8)	4038(38.7)	
Bloodstream Infections-no.(%)						<0.001
Absent	431(14.0)	460(15.0)	454(14.8)	629(20.5)	1096(35.7)	
Present	3347(21.6)	2709(17.4)	2286(14.7)	2801(18.0)	4383(28.2)	
Sepsis-no.(%)	771(5.7)	1,107(8.9)	971(12.5)	1,350(18.7)	2,764(26.5)	<0.001
Acute MI-no.(%)	2,017(14.9)	2,130(17.1)	1,281(16.5)	1,075(14.9)	1,409(13.5)	<0.001
CHF-no.(%)	1,468(10.9)	2,353(18.8)	1,995(25.8)	2,171(30.1)	3,441(33.0)	<0.001
CABG-no.(%)	472(3.5)	685(5.5)	568(7.3)	564(7.8)	526(5.0)	<0.001
Transfusions-no.(%)						<0.001
0 units	13555(89.3)	8907(82.4)	5660(73.3)	5025(65.0)	6248(63.0)	

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	RDW% at at critical care initiation					
	≤13.3	**13.3–14.0**	**14.0–14.7**	**14.7–15.8**	**>15.8**	**P-value**
1 units	428(2.8)	370(3.4)	331(4.3)	408(5.3)	604(6.1)	
2 units	454(3.0)	458(4.2)	377(4.9)	457(5.9)	768(7.7)	
3 units	186(1.2)	221(2.1)	213(2.8)	293(3.8)	401(4.0)	
≥4 units	565(3.7)	855(7.9)	1145(14.8)	1585(20.4)	1900(19.2)	
Creatinine-no.(%)						<0.001
≤1 mg/dl	8,778(65.0)	6,984(55.9)	3,820(49.3)	3,214(44.5)	4,048(38.8)	
1.0–1.3 mg/dl	3,143(23.3)	3,045(24.4)	1,717(22.2)	1,393(19.3)	1,661(15.9)	
1.3–2.0 mg/dl	1,184(8.8)	1,687(13.5)	1,390(18.0)	1,430(19.8)	1,955(18.7)	
>2 mg/dl	406(3.0)	779(6.2)	818(10.6)	1,188(16.4)	2,773(26.6)	
Blood Urea Nitrogen-no.(%)						<0.001
≤10 mg/dl	2,340(17.3)	1,638(13.1)	942(12.2)	803(11.1)	1,069(10.2)	
10–20 mg/dl	7,955(58.9)	6,376(51.0)	3,319(42.9)	2,548(35.3)	2,960(28.4)	
20–40 mg/dl	2,767(20.5)	3,557(28.5)	2,495(32.2)	2,532(35.0)	3,402(32.6)	
>40 mg/dl	449(3.3)	924(7.4)	989(12.8)	1,342(18.6)	3,006(28.8)	
White Blood Cells-no.(%)						<0.001
≥4	165(1.2)	212(1.7)	251(3.2)	272(3.8)	784(7.5)	
4–10	5,623(41.6)	5,396(43.2)	3,253(42.0)	2,913(40.3)	4,021(38.5)	
>10	7,723(57.2)	6,887(55.1)	4,241(54.8)	4,040(55.9)	5,632(54.0)	
Hematocrit-no.(%)						<0.001
≤30%	987(7.3)	1,720(13.8)	1,756(22.7)	2,198(30.4)	4,303(41.2)	
30–33%	927(6.9)	1,351(10.8)	1,170(15.1)	1,333(18.5)	2,095(20.1)	
33–36%	1,578(11.7)	1,772(14.2)	1,236(16.0)	1,211(16.8)	1,640(15.7)	
36–39%	2,691(19.9)	2,275(18.2)	1,265(16.3)	1,001(13.9)	1,147(11.0)	
39–42%	3,092(22.9)	2,376(19.0)	1,061(13.7)	737(10.2)	660(6.3)	
>42%	4,236(31.4)	3,001(24.0)	1,257(16.2)	745(10.3)	592(5.7)	
No. of organs with failure-no.(%)						<0.001
0	6,524(48.3)	5,085(40.7)	2,461(31.8)	1,794(24.8)	2,246(21.5)	
1	4,334(32.1)	4,186(33.5)	2,721(35.1)	2,484(34.4)	3,165(30.3)	
2	1,800(13.3)	2,013(16.1)	1,511(19.5)	1,637(22.7)	2,519(24.1)	
3	605(4.5)	821(6.6)	679(8.8)	845(11.7)	1,460(14.0)	

	RDW% at at critical care initiation					
	≤13.3	**13.3–14.0**	**14.0–14.7**	**14.7–15.8**	**>15.8**	**P-value**
≥4	248(1.8)	390(3.1)	373(4.8)	465(6.4)	1,047(10.0)	

Note: The means are shown in the table unless it is noted as %, then the percentage is shown. Transfusions variable indicates RBC transfusions for the 48 hours prior to or during ICU stay.

Table 3

Multivariable Adjusted Associations between covariates and 30-day mortality

	OR	95% CI	P
RDW-no.(%)			
≤13.3%	1	Reference	
13.3–14%	1.19	1.08–1.30	<0.001
14–14.7%	1.28	1.16–1.42	<0.001
14.7–15.8%	1.69	1.53–1.86	<0.001
>15.8%	2.61	2.37–2.86	<0.001
Age (per 1 year)	1.02	1.01–1.02	<0.001
Gender			
Male	1	Reference	
Female	1.02	0.97–1.08	0.4
Race			
White	1	Reference	
Non-White	1.06	0.99–1.14	0.08
Patient Type			
Medical	1	Reference	
Surgical	0.65	0.61–0.69	<0.001
Deyo-Charlson Index			
0	1	Reference	
1	1.69	1.43–1.99	<0.001
2	2.14	1.83–2.51	<0.001
3	2.21	1.88–2.59	<0.001
4	2.42	2.05–2.85	<0.001
≥5	2.09	1.78–2.45	<0.001
Creatinine			
≤1.0 mg/dl	1.06	0.98–1.14	0.2
1.0–1.3 mg/dl	1	Reference	
1.3–2.0 mg/dl	1.20	1.10- 1.31	<0.001
>2.0 mg/dl	1.14	1.03–1.27	0.01
Hematocrit (%)			
≤30	1.03	0.93–1.13	0.6
30–33	1.12	1.01–1.24	0.03
33–36	1.09	0.99–1.21	0.07
36–39	1.01	0.91–1.11	0.9
39–42	0.93	0.84–1.03	0.2
>42	1	Reference	
White Blood Cell			
$<4 \times 10^3/mm^3$	2.03	1.79–2.30	<0.001
$4–12 \times 10^3/mm^3$	1	Reference	
$>12 \times 10^3/mm^3$	1.80	1.69–1.90	<0.001

	OR	95% CI	P
Blood Urea Nitrogen			
<10 mg/dl	0.81	0.73–0.91	<0.001
10–20 mg/dl	1	Reference	
20–40 mg/dl	1.29	1.20–1.39	<0.001
>40 mg/dl	1.72	1.55–1.90	<0.001
MCV (per 1 femtoliter)	1.03	1.03–1.04	<0.001
Sepsis[*]	1.92	1.80–2.05	<0.001
AMI[*]	1.02	0.95–1.10	0.5
CHF[*]	0.93	0.87–0.99	0.03
CABG[*]	0.34	0.28–0.40	<0.001
Transfusions			
0 units	1	Reference	
1 units	1.18	1.05–1.34	0.008
2 units	1.09	0.97–1.23	0.2
3 units	1.07	0.91–1.25	0.4
≥4 units	1.14	1.05–1.25	0.003

Note: Estimates for each variable are adjusted for all other variables in the table. Transfusions variable indicates RBC transfusions from 48 hours prior to critical care initiation throughout the ICU stay.

[*] Referent is absence of condition.

Table 4

Unadjusted associations between RDW at critical care initiation and outcomes

	OR	95% CI	P
30-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.52	1.40–1.66	<0.001
RDW 14.0–14.7%	1.91	1.74–2.10	<0.001
RDW 14.7–15.8%	2.84	2.60–3.11	<0.001
RDW >15.8%	5.02	4.64–5.44	<0.001
90-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.59	1.47–1.72	<0.001
RDW 14.0–14.7%	2.25	2.06–2.44	<0.001
RDW 14.7–15.8%	3.28	3.02–3.56	<0.001
RDW >15.8%	6.24	5.80–6.71	<0.001
365-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.69	1.58–1.81	<0.001
RDW 14.0–14.7%	2.53	2.35–2.72	<0.001
RDW 14.7–15.8%	3.79	3.53–4.07	<0.001
RDW >15.8%	7.36	6.90–7.85	<0.001
In-hospital mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.44	1.31–1.57	<0.001
RDW 14.0–14.7%	1.93	1.75–2.13	<0.001
RDW 14.7–15.8%	2.78	2.53–3.05	<0.001
RDW >15.8%	4.79	4.41–5.20	<0.001

Note: Referent in each case is RDW ≤13.3%.

Table 5

Adjusted associations between RDW at critical care initiation and outcomes

	OR	95% CI	P
30-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.19	1.08–1.30	<0.001
RDW 14.0–14.7%	1.28	1.16–1.42	<0.001
RDW 14.7–15.8%	1.69	1.52–1.86	<0.001
RDW >15.8%	2.61	2.37–2.86	<0.001
90-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.18	1.09–1.29	<0.001
RDW 14.0–14.7%	1.40	1.28–1.54	<0.001
RDW 14.7–15.8%	1.79	1.63–1.96	<0.001
RDW >15.8%	3.04	2.79–3.31	<0.001
365-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.21	1.12–1.30	<0.001
RDW 14.0–14.7%	1.47	1.36–1.60	<0.001
RDW 14.7–15.8%	1.92	1.77–2.09	<0.001
RDW >15.8%	3.41	3.16–3.69	<0.001
In-hospital mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.12	1.01–1.23	0.03
RDW 14.0–14.7%	1.26	1.13–1.40	<0.001
RDW 14.7–15.8%	1.54	1.39–1.71	<0.001
RDW >15.8%	2.27	2.06–2.50	<0.001

Note: Referent in each case is RDW ≤13.3%. Estimates adjusted for age, sex, race, Deyo-Charlson index, patient type (surgical versus medical), CABG, MI, CHF, hematocrit, transfusion (from 48 hours prior to critical care initiation throughout the ICU stay), white blood count, MCV, blood urea nitrogen, sepsis and creatinine.

Table 6

Unadjusted and Adjusted associations between RDW at critical care initiation and bloodstream infection

	OR	95% CI	P
Unadjusted			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.30	1.13–1.50	<0.001
RDW 14.0–14.7%	1.56	1.35–1.81	<0.001
RDW 14.7–15.8%	1.75	1.52–2.01	<0.001
RDW >15.8%	1.96	1.73–2.23	<0.001
Adjusted			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.19	1.03–1.38	0.02
RDW 14.0–14.7%	1.34	1.15–1.56	<0.001
RDW 14.7–15.8%	1.40	1.20–1.63	<0.001
RDW >15.8%	1.44	1.24–1.66	<0.001

Note: Referent in each case is RDW ≤13.3%. Estimates adjusted for age, sex, race, Deyo-Charlson index, patient type (surgical versus medical), CABG, MI, CHF, hematocrit, transfusion (from 48 hours prior to critical care initiation throughout the ICU stay), white blood count, MCV, blood urea nitrogen, and creatinine.