Red cell distribution width and all-cause mortality in critically ill patients*

Heidi S. Bazick, MD; Domingo Chang, MD; Karthik Mahadevappa, MBBS; Fiona K. Gibbons, MD; Kenneth B. Christopher, MD, FASN, FCCP

Objective: **Red cell distribution width is a predictor of mortality in the general population. The prevalence of increased red cell distribution width and its significance in the intensive care unit are unknown. The objective of this study was to investigate the association between red cell distribution width at the initiation of critical care and all cause mortality.**

Design: **Multicenter observational study.**

Setting: **Two tertiary academic hospitals in Boston, MA.**

Patients: **A total of 51,413 patients, aged ≥18 yrs, who received critical care between 1997 and 2007.**

Interventions: **None.**

Measurements and Main Results: **The exposure of interest was red cell distribution width as a predictor of mortality in the general population. The prevalence of increased red cell distribution width and its significance in the intensive care unit are unknown and categorized *a priori* in quintiles as ≤13.3%, 13.3% to 14.0%, 14.0% to 14.7%, 14.7% to 15.8%, and >15.8%. Logistic regression examined death by days 30, 90, and 365 postcritical care initiation, inhospital mortality, and bloodstream infection. Adjusted odds ratios were estimated by multivariable logistic regression models. Adjustment included age, sex, race, Deyo–Charlson index, coronary artery bypass grafting, myocardial infarction, congestive heart failure, hematocrit, white blood cell count, mean corpuscular volume, blood urea nitrogen, red blood cell transfusion, sepsis, and creatinine. Red cell distribution width was a particularly strong predictor of all-cause mortality 30 days after critical care initiation with a significant risk gradient across red cell distribution width quintiles after multivariable adjustment: red cell distribution width 13.3% to 14.0% (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.08–1.30; $p < .001$); red cell distribution width 14.0% to 14.7% (OR, 1.28; 95% CI, 1.16–1.42; $p < .001$); red cell distribution width 14.7% to 15.8% (OR, 1.69; 95% CI, 1.52–1.86; $p < .001$); red cell distribution width >15.8% (OR, 2.61; 95% CI, 2.37–2.86; $p < .001$), all relative to patients with red cell distribution width ≤13.3%. Similar significant robust associations postmultivariable adjustments are seen with death by days 90 and 365 postcritical care initiation as well as inhospital mortality. In a subanalysis of patients with blood cultures drawn (n = 18,525), red cell distribution width at critical care initiation was associated with the risk of bloodstream infection and remained significant after multivariable adjustment. The adjusted risk of bloodstream infection was 1.40- and 1.44-fold higher in patients with red cell distribution width values in the 14.7% to 15.8% and >15.8% quintiles, respectively, compared with those with red cell distribution width ≤13.3%. Estimating the receiver operating characteristic area under the curve shows that red cell distribution width has moderate discriminative power for 30-day mortality (area under the curve = 0.67).**

Conclusion: **Red cell distribution width is a robust predictor of the risk of all-cause patient mortality and bloodstream infection in the critically ill. Red cell distribution width is commonly measured, inexpensive, and widely available and may reflect overall inflammation, oxidative stress, or arterial underfilling in the critically ill. (Crit Care Med 2011; 39:1913–1921)**

KEY WORDS: red cell distribution width; intensive care; mortality; bloodstream infection

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 SD in red blood cell (RBC) size divided by the mean corpuscular volume. 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% to 14.5% with no clinical scenarios that produce RDW <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 used in critical care, RDW is a strong predictor of mortality in the general population of adults aged ≥45 yrs (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

***See also p. 2005**.

From the Department of Anesthesiology (HSB) and the Pulmonary Division (FKG), Massachusetts General Hospital, Boston, MA; and the Renal Division (DC, KM, KBC), Brigham and Women's Hospital, Boston, MA.

Dr. Christopher is supported by National Institutes of Health grant K08AI060881.

This work was performed at The Nathan E. Hellman Memorial Laboratory, Renal Division, Brigham and Women's Hospital, Boston, MA.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: kbchristopher@partners.org

DOI: 10.1097/CCM.0b013e31821b85c6

admission is associated with increased risk of 1-yr mortality (4). Furthermore, 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 erythrocyte sedimentation rate and the inflammatory markers interleukin-6, C-reactive protein, and receptors for tumor necrosis factor I and II (9–12). Proinflammatory cytokines found in patients with systemic inflammatory response syndrome including tumor necrosis factor-α, interleukin-6, and interleukin-1β are noted to suppress erythrocyte maturation, allowing newer, larger reticulocytes to enter the peripheral circulation and increase RDW (13, 14). Furthermore, proinflammatory cytokines can have direct inhibitory effects on the 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 biological 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 intensive care unit (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 a 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; and 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 two academic teaching hospitals in Boston, MA. Brigham and Women's Hospital is a 777-bed teaching hospital with 100 ICU beds. Massachusetts General Hospital 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 Brigham and Women's Hospital or Massachusetts General Hospital 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 Brigham and Women's Hospital.

The following data were retrieved: demographics, vital status for up to 10 yrs following critical care initiation, hospital admission and discharge date, laboratory values, blood bank reports, microbiology reports, diagnosis-related group assigned at discharge, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, and current procedural terminology (CPT) codes for inhospital procedures and services.

During the 10-yr study period, there were 54,392 unique patients, aged ≥18 yrs, who were assigned the CPT code 99,291 (critical care, first 30–74 mins). Two hundred five foreign patients without Social Security Numbers were identified and excluded because vital status in this study is determined by the Social Security Death Index. We also excluded 2372 patients assigned CPT code 99,291 who received care only in the emergency room, were not admitted, and were not assigned a diagnosis-related group. Because a high white blood cell count may skew the automatically calculated RDW (19), 29 patients were excluded who had white blood cells >150,000/μL. One hundred sixty-six patients were excluded for missing data. A total of 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% to 14.0%, 14.0% to 14.7%, 14.7% to 15.8%, and >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 before 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) before or on the day of critical care initiation. Congestive heart failure is defined by ICD-9-CM 428.0–428.4 before or on the day of critical care initiation (22). Number of organs with failure was adapted from a study by 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 before critical care initiation to 30 days after critical care initiation as outlined in the Supplemental Digital Content.

Transfusion data were obtained by 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 hrs before 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 diagnosis-related group methodology devised by Centers for Medicare & Medicaid Services (23). Procedures were determined by CPT codes as follows: coronary artery bypass grafting (CABG) surgery performed on the day before or day after critical care initiation (CPT codes 33,510–33,536).

The Deyo–Charlson index was used to assess the burden of chronic illness (24). The Deyo–Charlson index consists of 17 comorbidities, which are weighted and summed to produce a score each with an associated weight based on the risk of 1-yr mortality. This score ranges from 0 to 33 with higher scores indicating a higher burden. The score does not measure type or severity of acute illness (24, 25). We used the ICD-9 coding algorithms developed in the study 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 are reported (26). As a result of the relatively low representation, Deyo–Charlson index scores ≥5 were combined.

All patients who had blood cultures drawn 48 hrs before 48 hrs 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). Use of the Death Master File allows for long-term follow-up of patients after hospital discharge. The censoring date was July 27, 2009.

End Points. The primary end point was 30-day mortality after critical care initiation. Other prespecified end points included 90-day, 365-day, inhospital 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, interquartile range) and compared across exposure groups using one-way analysis of variance. Survival analyses considered death by days 30, 90, and 365 postcritical care initiation as well as inhospital mortality. In each instance, subjects were excluded if they were censored for incomplete data. Three hundred sixty-five-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, and 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 vs. medical), CABG, myocardial infarction, congestive heart failure, hematocrit, transfusion, white blood count, mean corpuscular volume, blood urea nitrogen, sepsis, and creatinine. For the primary model (30-day mortality), specification of each continuous covariate (as a linear vs. 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 because it shares ICD-9 codes with the Deyo–Charlson index.

Models for secondary analyses (90-day, 365-day, and inhospital mortality and bloodstream infection) were specified identically to the primary model 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 characteristic curves. The area under the receiver operating characteristic curve (AUC) is an expression of the ability of RDW as a continuous variable to distinguish vital status at 30 days after critical care initiation (35). All p values presented are two-tailed; values $<.05$ 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 yrs (SD 18.3). Thirty-day all-cause mortality was 14.2%. A total of 50.5% of patients were assigned a medical diagnosis-related group. A total of 15.4% of patients had an acute myocardial infarction. A total of 5.5% of the cohort underwent CABG and 13.5% of patients were septic. A total of 23.4% of patients were transfused red blood cells from 48 hrs before 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, sex, race, patient type, Deyo–Charlson index, sepsis, acute myocardial infarction, CABG, congestive heart failure, 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 >1.3 mg/dL, blood urea nitrogen >20 mg/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, mean corpuscular volume, 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 after 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 $\leq 13.3\%$). RDW in the cohort remains a significant predictor of risk of mortality after adjustment for age, sex, race, Deyo–Charlson index, patient type, CABG, myocardial infarction, hematocrit, transfusion, creatinine, white blood count, mean corpuscular volume, blood urea nitrogen, sepsis, and creatinine. The adjusted risk of mortality 30 days after 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 postmultivariable adjustments are seen with death by days 90 and 365 postcritical care initiation as well as inhospital mortality (Tables 4 and 5).

In a subanalysis of patients with blood cultures drawn between 48 hrs before and 48 hrs 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 after 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*, *Staphylococcus aureus*, *Escherichia coli, Enterococcus faecium, Enterococcus faecalis, Candida albicans, Klebsiella pneumonia, Enterobacter cloacae, Pseudomonas aeruginosa, Candida parapsilosis, Candida glabrata*, and *Staphylococcus pneumoniae*.

There is effect modification of the RDW–mortality association on the basis of anemia defined as hematocrit $\leq 36\%$ (30-day mortality: interaction $p = .05$; fully adjusted, data not shown). For 30-day mortality, the risk associated with RDW of 13.3% to 14.0% and RDW of 14.0% to 14.7% relative to RDW of $\leq 13.3\%$ is not significant in the presence of anemia (hematocrit $\leq 36\%$). The mortality risk associated with RDW $>14.7\%$ is unchanged in the presence of hematocrit $\leq 36\%$. The number of patients with RDW $>14.7\%$ and hematocrit ≤ 36 was 12,839 with 22.1% inhospital mortality and 23.8% 30-day mortality.

Table 1. Patient characteristics of the study population

No.	51,413
Age, yrs, mean (SD)	61.7 (18.3)
Sex, no. (%)	
Male	29,930 (58.21)
Female	21,483 (41.79)
Race, no. (%)	
White	40,938 (79.63)
Nonwhite	10,475 (20.37)
Type, no. (%)	
Medical	25,972 (50.52)
Surgical	25,441 (49.48)
Red cell distribution width, 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/d	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. of 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)
Coronary artery bypass grafting, no. (%)	2,815 (5.48)
Myocardial infarction, no. (%)	7,912 (15.39)
Congestive heart failure, 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)
Inhospital	6,580 (12.80)

There is no significant effect modification of the RDW–mortality association on the basis of transfusion (30-day mortality: interaction $p = .17$; fully adjusted, data not shown). Finally, there is no significant effect modification of the RDW–bloodstream infection association on the basis of anemia (interaction $p = .29$) or transfusion (interaction $p = .24$; 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 $p = .46$; fully adjusted, data not shown).

To assess discrimination of RDW for 30-day mortality, we used receiver operating characteristic curve analysis and determined the 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 after 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-, and 365-day mortality postcritical care initiation, inhospital mortality, and bloodstream infection. RDW remains a significant predictor of mortality and bloodstream infection after 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 >14.7%. The RDW–bloodstream infection association is independent of transfusion status and anemia.

Sepsis significantly differed between RDW groups with a gradient of a higher percentage of septic patients in the higher RDW quintiles.(Table 2). Patients with sepsis have a significantly increased odds of 30-day mortality after 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 nonseptic patients.

In addition to adjusting for patients with myocardial infarction 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 hrs before critical care initiation or during the ICU stay. Because 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/μL) may skew the automatically calculated RDW (19). In our study cohort, we excluded patients with white blood cells >150,000/μL but were unable to adjust for fragmented schistocytes or cold-agglutinated RBCs, 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 a 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 erythrocyte sedimentation rate/high-sensitivity C-reactive protein 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 (13, 14). Thus, inflammation likely leads to an

Table 2. Stratified patient characteristics of the study population red cell distribution width percentage at critical care initiation

	≤13.3	13.3–14.0	14.0–14.7	14.7–15.8	>15.8	*p*
No.	13,511	12,495	7,745	7,225	10,437	
Age, yrs, mean (SD)	53.7 (19.7)	62.4 (18.1)	65.9 (16.6)	66.7 (16.1)	64.7 (15.9)	<.001
Sex, no. (%)						<.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. (%)						<.001
White	10,524 (77.9)	9,985 (79.9)	6,285 (81.2)	5,881 (81.4)	8,263 (79.2)	
Nonwhite	2,987 (22.1)	2,510 (20.1)	1,460 (18.9)	1,344 (18.6)	2,174 (20.8)	
Patient type, no. (%)						<.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 (%)						<.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	1,102 (8.2)	2,018 (16.2)	1,900 (24.5)	2,223 (30.8)	4,038 (38.7)	
Bloodstream infections, no. (%)						<.001
Absent	431 (14.0)	460 (15.0)	454 (14.8)	629 (20.5)	1,096 (35.7)	
Present	3,347 (21.6)	2,709 (17.4)	2,286 (14.7)	2,801 (18.0)	4,383 (28.2)	
Sepsis, no. (%)	771 (5.7)	1,107 (8.9)	971 (12.5)	1,350 (18.7)	2,764 (26.5)	<.001
Acute myocardial infarction, no. (%)	2,017 (14.9)	2,130 (17.1)	1,281 (16.5)	1,075 (14.9)	1,409 (13.5)	<.001
Congestive heart failure, no. (%)	1,468 (10.9)	2,353 (18.8)	1,995 (25.8)	2,171 (30.1)	3,441 (33.0)	<.001
Coronary artery bypass grafting, no. (%)	472 (3.5)	685 (5.5)	568 (7.3)	564 (7.8)	526 (5.0)	<.001
Transfusions, no. (%)						<.001
0 units	13,555 (89.3)	8,907 (82.4)	5,660 (73.3)	5,025 (65.0)	6,248 (63.0)	
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)	1,145 (14.8)	1,585 (20.4)	1,900 (19.2)	
Creatinine, no. (%)						<.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. (%)						<.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. (%)						<.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. (%)						<.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. (%)						<.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)	
≥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 Percent, then the percentage is shown. Transfusions variable indicates red blood cell transfusions for the 48 hrs before or during intensive care unit stay.

increased RDW from the release of immature RBCs 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 (40, 41). Septic patients also have decreases in immune responsiveness predisposing to nosocomial infections (42). T-regulatory cells appear to play a major role in the suppression of immune reactivity in injury (43, 44) and infection (45). 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

Table 3. Multivariable adjusted associations between covariates and 30-day mortality

	Odds Ratio	95% Confidence Interval	*p*
Red cell distribution width, no. (%)			
≤13.3%	1	Reference	
13.3–14%	1.19	1.08–1.30	<.001
14–14.7%	1.28	1.16–1.42	<.001
14.7–15.8%	1.69	1.53–1.86	<.001
>15.8%	2.61	2.37–2.86	<.001
Age per 1 yr	1.02	1.01–1.02	<.001
Sex			
Male	1	Reference	
Female	1.02	0.97–1.08	.4
Race			
White	1	Reference	
Nonwhite	1.06	0.99–1.14	.08
Patient type			
Medical	1	Reference	
Surgical	0.65	0.61–0.69	<.001
Deyo–Charlson index			
0	1	Reference	
1	1.69	1.43–1.99	< 0.001
2	2.14	1.83–2.51	<.001
3	2.21	1.88–2.59	<.001
4	2.42	2.05–2.85	<.001
≥5	2.09	1.78–2.45	<.001
Creatinine			
≤1.0 mg/dL	1.06	0.98–1.14	.2
1.0–1.3 mg/dL	1	Reference	
1.3–2.0 mg/dL	1.20	1.10–1.31	<.001
>2.0 mg/dL	1.14	1.03–1.27	.01
Hematocrit (%)			
≤30	1.03	0.93–1.13	.6
30–33	1.12	1.01–1.24	.03
33–36	1.09	0.99–1.21	.07
36–39	1.01	0.91–1.11	.9
39–42	0.93	0.84–1.03	.2
>42	1	Reference	
White blood cell			
$<4 \times 10^3/mm^3$	2.03	1.79–2.30	<.001
$4–12 \times 10^3/mm^3$	1	Reference	
$>12 \times 10^3/mm^3$	1.80	1.69–190	<.001
Blood urea nitrogen			
<10 mg/dL	0.81	0.73–0.91	<.001
10–20 mg/dL	1	Reference	
20–40 mg/dL	1.29	1.20–1.39	<.001
>40 mg/dL	1.72	1.55–1.90	<.001
Mean corpuscular volume per 1 femtoliter	1.03	1.03–1.04	<.001
Sepsis[a]	1.92	1.80–2.05	<.001
Acute myocardial infarction[a]	1.02	0.95–1.10	.5
Congestive heart failure[a]	0.93	0.87–0.99	.03
Coronary artery bypass grafting[a]	0.34	0.28–0.40	<.001
Transfusions			
0 units	1	Reference	
1 units	1.18	1.05–1.34	.008
2 units	1.09	0.97–1.23	.2
3 units	1.07	0.91–1.25	.4
≥4 units	1.14	1.05–1.25	.003

[a]Referent is absence of condition.

Note: Estimates for each variable are adjusted for all other variables in the table. Transfusions variable indicates red blood cell transfusions from 48 hrs before critical care initiation throughout the intensive care unit stay.

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 through the generation of reactive oxygen species by activated leukocytes (46). High oxidative stress contributing to elevated RDW by reducing RBC survival and increasing release of large premature red blood cells into the peripheral circulation (47).

The RDW–mortality association in this study may also be related to the neurohumoral response to arterial underfilling. Such response involves arginine vasopressin, the renin–angiotensin–aldosterone system, and the sympathetic nervous system (48–50). Activation of the renin–angiotensin system triggers an acceleration of erythrocyte production resulting in an increased RDW through macrocytosis related to skipped cell divisions (51–53). Such arterial underfilling states are common in cardiac failure and sepsis (54), 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 physiological data. In the administrative database used in this study, Acute Physiology and Chronic Health Evaluation scores are absent because both physiological data and Glasgow Coma Scale data are not available. Acute Physiology and Chronic Health Evaluation and other physiological-based scoring systems are strong predictors of mortality in the critically ill (55). Adding a physiological 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 physiological data when age and sex data are used (56). However, despite multivariable adjustment of potential confounders, the absence of physiological data remains a limitation of our study.

Evaluating the sensitivity and specificity of the RDW with the use of receiver operating characteristic curve analysis, estimating the 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 Acute Physiology and Chronic Health Evaluation II or Simplified Acute Physiology Score II to distinguish inhospital mortality; the AUC was 0.84 and 0.85, respectively (57). In our study, as a result of data limitations, we are unable to directly compare the discrimination of RDW for 30-day mortality vs. Acute Physiology and Chronic Health Evaluation or Simplified Acute Physiology Score II.

Administrative coding data has been assessed for individual diseases (58–62) and comorbidity profiles (48, 63). There

Table 4. Unadjusted associations between red cell distribution width at critical care initiation and outcomes

	Odds Ratio	95% Confidence Interval	p
30-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.52	1.40–1.66	<.001
RDW 14.0–14.7%	1.91	1.74–2.10	<.001
RDW 14.7–15.8%	2.84	2.60–3.11	<.001
RDW >15.8%	5.02	4.64–5.44	<.001
90-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.59	1.47–1.72	<.001
RDW 14.0–14.7%	2.25	2.06–2.44	<.001
RDW 14.7–15.8%	3.28	3.02–3.56	<.001
RDW >15.8%	6.24	5.80–6.71	<.001
365-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.69	1.58–1.81	<.001
RDW 14.0–14.7%	2.53	2.35–2.72	<.001
RDW 14.7–15.8%	3.79	3.53–4.07	<.001
RDW >15.8%	7.36	6.90–7.85	<.001
Inhospital mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.44	1.31–1.57	<.001
RDW 14.0–14.7%	1.93	1.75–2.13	<.001
RDW 14.7–15.8%	2.78	2.53–3.05	<.001
RDW >15.8%	4.79	4.41–5.20	<.001

RDW, red cell distribution width.
Note: Referent in each case is RDW ≤13.3%.

Table 5. Adjusted associations between red cell distribution width at critical care initiation and outcomes

	Odds Ratio	95% Confidence Interval	p
30-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.19	1.08–1.30	<.001
RDW 14.0–14.7%	1.28	1.16–1.42	<.001
RDW 14.7–15.8%	1.69	1.52–1.86	<.001
RDW >15.8%	2.61	2.37–2.86	<.001
90-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.18	1.09–1.29	<.001
RDW 14.0–14.7%	1.40	1.28–1.54	<.001
RDW 14.7–15.8%	1.79	1.63–1.96	<.001
RDW >15.8%	3.04	2.79–3.31	<.001
365-day mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.21	1.12–1.30	<.001
RDW 14.0–14.7%	1.47	1.36–1.60	<.001
RDW 14.7–15.8%	1.92	1.77–2.09	<.001
RDW >15.8%	3.41	3.16–3.69	<.001
Inhospital mortality			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.12	1.01–1.23	.03
RDW 14.0–14.7%	1.26	1.13–1.40	<.001
RDW 14.7–15.8%	1.54	1.39–1.71	<.001
RDW >15.8%	2.27	2.06–2.50	<.001

RDW, red cell distribution width.
Note: Referent in each case is RDW ≤13.3%. Estimates adjusted for age, sex, race, Deyo–Charlson index, patient type (surgical vs. medical), coronary artery bypass grafting, myocardial infarction, congestive heart failure, hematocrit, transfusion (from 48 hrs before critical care initiation throughout the intensive care unit stay), white blood count, mean corpuscular volume, blood urea nitrogen, sepsis, and creatinine.

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 (49) and a high sensitivity (50), specificity (20), and negative predictive value (20). The Deyo–Charlson index algorithm used in this study (26) uses 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 (54, 66). Use of the Social Security Administration Death Master File allowed for complete 365-day follow-up for the cohort after hospital discharge. Our study has sufficient numbers of patients to ensure adequate reliability of our mortality estimates (n = 51,413, inhospital mortality rate = 12.8%). The basis of critical care initiation on CPT 99,291 codes in our administrative data set is validated (67). Our use of previous records to define comorbidities increases their prevalence and results in a better risk adjustment (60, 68). We include data for packed RBC transfusion before and during critical care, which is associated with respiratory failure and overall mortality in the critically ill (69). 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. Although 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.

Table 6. Unadjusted and adjusted associations between red cell distribution width at critical care initiation and bloodstream infection

	Odds Ratio	95% Confidence Interval	*p*
Unadjusted			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.30	1.13–1.50	<.001
RDW 14.0–14.7%	1.56	1.35–1.81	<.001
RDW 14.7–15.8%	1.75	1.52–2.01	<.001
RDW >15.8%	1.96	1.73–2.23	<.001
Adjusted			
RDW ≤13.3%	1.00	1.0–1.0	
RDW 13.3–14.0%	1.19	1.03–1.38	.02
RDW 14.0–14.7%	1.34	1.15–1.56	<.001
RDW 14.7–15.8%	1.40	1.20–1.63	<.001
RDW >15.8%	1.44	1.24–1.66	<.001

RDW, red cell distribution width.

Note: Referent in each case is RDW ≤13.3%. Estimates adjusted for age, sex, race, Deyo–Charlson index, patient type (surgical vs. medical), coronary artery bypass grafting, myocardial infarction, congestive heart failure, hematocrit, transfusion (from 48 hrs before critical care initiation throughout the intensive care unit stay), white blood count, mean corpuscular volume, blood urea nitrogen, and creatinine.

ACKNOWLEDGMENTS

This article is dedicated to the memory of our dear friends and colleagues Keith Alan Landesman, MD, and Nathan Edward Hellman, MD, PhD. We express deep appreciation to Steven M. Brunelli, MD, MSCE, for statistical expertise and analysis.

REFERENCES

1. Patel KV, Ferrucci L, Ershler WB, et al: Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med* 2009; 169:515–523
2. Perlstein TS, Weuve J, Pfeffer MA, et al: Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009; 169:588–594
3. Felker GM, Allen LA, Pocock SJ, et al: Red cell distribution width as a novel prognostic marker in heart failure: Data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol* 2007; 50:40–47
4. van Kimmenade RR, Mohammed AA, Uthamalingam S, et al: Red blood cell distribution width and 1-year mortality in acute heart failure. *Eur J Heart Fail* 2010; 12:129–136
5. Ani C, Ovbiagele B: Elevated red blood cell distribution width predicts mortality in persons with known stroke. *J Neurol Sci* 2009; 277:103–108
6. Brody JS, Spira A: State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006; 3:535–537
7. Libby P: Inflammation in atherosclerosis. *Nature* 2002; 420:868–874
8. Morrow DA, de Lemos JA: Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation* 2007; 115:949–952
9. Lippi G, Targher G, Montagnana M, et al: Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; 133:628–632
10. Allen LA, Felker GM, Mehra MR, et al: Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J Card Fail* 2010; 16:230–238
11. Patel KV, Seminba RD, Ferrucci L, et al: Red cell distribution width and mortality in older adults: A meta-analysis. *J Gerontol A Biol Sci Med Sci* 2010; 65:258–265
12. Forhecz Z, Gombos T, Borgulya G, et al: Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J* 2009; 158:659–666
13. Pierce CN, Larson DF: Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion* 2005; 20:83–90
14. Scharte M, Fink MP: Red blood cell physiology in critical illness. *Crit Care Med* 2003; 31:S651–S657
15. Chiari MM, Bagnoli R, De Luca PD, et al: Influence of acute inflammation on iron and nutritional status indexes in older inpatients. *J Am Geriatr Soc* 1995; 43:767–771
16. Weiss G, Goodnough LT: Anemia of chronic disease. *N Engl J Med* 2005; 352:1011–1023
17. Viljoen M, Coetzee IH, Roux LJ, et al: Anemia in surgical intensive care patients. *Haematologica* 1994; 79:19–24
18. Wang F, Pan W, Pan S, et al: Red cell distribution width as a novel predictor of mortality in ICU patients. *Ann Med* 2011; 43:40–46
19. Evans TC, Jehle D: The red blood cell distribution width. *J Emerg Med* 1991; 9:71–71
20. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
21. Trespalacios FC, Taylor AJ, Agodoa LY, et al: Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int* 2002; 62:1799–1805
22. Mamdani M, Juurlink DN, Lee DS, et al: Cyclo-oxygenase-2 inhibitors versus nonselective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: A population-based cohort study. *Lancet* 2004; 363:1751–1756
23. Rapoport J, Gehlbach S, Lemeshow S, et al: Resource utilization among intensive care patients. Managed care vs traditional insurance. *Arch Intern Med* 1992; 152:2207–2212
24. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987; 40:373–383
25. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619
26. Quan H, Sundararajan V, Halfon P, et al: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43:1130–1139
27. Shorr AF, Jackson WL, Kelly KM, et al: Transfusion practice and blood stream infections in critically ill patients. *Chest* 2005; 127:1722–1728
28. Blaine KP, Tuohy MJ, Wilson D, et al: Progression to bacteremia in critical care patients colonized with methicillin-resistant *Staphylococcus aureus* expressing Panton-Valentine leukocidin. *Diagn Microbiol Infect Dis* 2010; 68:28–33
29. Miller RS, Norris PR, Jenkins JM, et al: Systems initiatives reduce healthcare-associated infections: A study of 22,928 device days in a single trauma unit. *J Trauma* 2010; 68:23–31
30. Cowper DC, Kubal JD, Maynard C, et al: A primer and comparative review of major US mortality databases. *Ann Epidemiol* 2002; 12:462–468
31. Sohn MW, Arnold N, Maynard C, et al: Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr* 2006; 4:2
32. Schisterman EF, Whitcomb BW: Use of the Social Security Administration Death Master File for ascertainment of mortality status. *Popul Health Metr* 2004; 2:2
33. Newman TB, Brown AN: Use of commercial record linkage software and vital statistics to identify patient deaths. *J Am Med Inform Assoc* 1997; 4:233–237
34. Social Security Administration's Death Master File. Available at: http://www.ntis.gov/products/ssa-dmf.aspx. Accessed July 10, 2010
35. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36
36. Bessman JD, Gilmer PR Jr, Garder FH: Improved classification of anemias by MCV and RDW. *Am J Clin Pathol* 1983; 80:322–326
37. Ghali JK: Anemia and heart failure. *Curr Opin Cardiol* 2009; 24:172–178
38. Laftah AH, Sharma N, Brookes MJ, et al: Tumour necrosis factor alpha causes hypo-

ferraemia and reduced intestinal iron absorption in mice. *Biochem J* 2006; 397:61–67
39. Rogiers P, Zhang H, Leeman M, et al: Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997; 23: 159–162
40. Mannick JA, Rodrick ML, Lederer JA: The immunologic response to injury. *J Am Coll Surg* 2001; 193:237–244
41. Moore FA, Sauaia A, Moore EE, et al: Postinjury multiple organ failure: A bimodal phenomenon. *J Trauma* 1996; 40:501–510; discussion 510–512
42. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348:138–150
43. Kinsey GR, Sharma R, Huang L, et al: Regulatory T cells suppress innate immunity in kidney ischemia–reperfusion injury. *J Am Soc Nephrol* 2009; 20:1744–1753
44. Murphy TJ, Ni Choileain N, Zang Y, et al: CD4+CD25+ regulatory T cells control innate immune reactivity after injury. *J Immunol* 2005; 174:2957–2963
45. McHugh RS, Shevach EM: The role of suppressor T cells in regulation of immune responses. *J Allergy Clin Immunol* 2002; 110: 693–702
46. Kolls JK: Oxidative stress in sepsis: A redox redux. *J Clin Invest* 2006; 116:860–863
47. Ghaffari S: Oxidative stress in the regulation of normal and neoplastic hematopoiesis. *Antioxid Redox Signal* 2008; 10:1923–1940
48. Kieszak SM, Flanders WD, Kosinski AS, et al: A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol* 1999; 52:137–142
49. Eaton S, Burnham E, Martin GS, et al: The ICD-9 code for septicemia maintains a high positive predictive value for clinical sepsis. *Am J Respir Crit Care Med* 2002; 165:A471
50. Ollendorf DA, Fendrick AM, Massey K, et al: Is sepsis accurately coded on hospital bills? *Value Health* 2002; 5:79–81
51. Vlahakos DV, Kosmas EN, Dimopoulou I, et al: Association between activation of the renin–angiotensin system and secondary erythrocytosis in patients with chronic obstructive pulmonary disease. *Am J Med* 1999; 106:158–164
52. Lord BI: Kinetics of the recognizable erythrocyte precursor cells. *Clin Haematol* 1979; 8:335–350
53. Kato H, Ishida J, Imagawa S, et al: Enhanced erythropoiesis mediated by activation of the renin–angiotensin system via angiotensin II type 1a receptor. *FASEB J* 2005; 19: 2023–2025
54. Gottlieb SS: Dead is dead—Artificial definitions are no substitute. *Lancet* 1997; 349: 662–663
55. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
56. Quach S, Hennessy DA, Faris P, et al: A comparison between the APACHE II and Charlson Index Score for predicting hospital mortality in critically ill patients. *BMC Health Serv Res* 2009; 9:129
57. Beck DH, Smith GB, Pappachan JV, et al: External validation of the SAPS II, APACHE II and APACHE III prognostic models in South England: A multicentre study. *Intensive Care Med* 2003; 29:249–256
58. Goldstein LB: Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: Effect of modifier codes. *Stroke* 1998; 29:1602–1604
59. Iezzoni LI, Burnside S, Sickles L, et al: Coding of acute myocardial infarction. Clinical and policy implications. *Ann Intern Med* 1988; 109:745–751
60. Lee DS, Donovan L, Austin PC, et al: Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care* 2005; 43:182–188
61. Levy AR, Tamblyn RM, Fitchett D, et al: Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. *Can J Cardiol* 1999; 15:1277–1282
62. Winkelmayer WC, Schneeweiss S, Mogun H, et al: Identification of individuals with CKD from Medicare claims data: A validation study. *Am J Kidney Dis* 2005; 46:225–232
63. Humphries KH, Rankin JM, Carere RG, et al: Co-morbidity data in outcomes research: Are clinical data derived from administrative databases a reliable alternative to chart review? *J Clin Epidemiol* 2000; 53:343–349
64. Moreno RP, Metnitz PG, Almeida E, et al: SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; 31:1345–1355
65. Sibbald W: Evaluating critical care-using health services research to improve quality. *In:* Update in Intensive Care Medicine. Vincent J-L (Ed). Heidelberg, Springer-Verlag, 2001
66. Lauer MS, Blackstone EH, Young JB, et al: Cause of death in clinical research: Time for a reassessment? *J Am Coll Cardiol* 1999; 34: 618–620
67. Zager S, Mendu M, Chang D, et al: Neighborhood poverty rate and mortality in patients receiving critical care in the academic medical center setting. *Chest* 2011 Mar 31 [Epub ahead of print]
68. Preen DB, Holman CD, Spilsbury K, et al: Length of comorbidity lookback period affected regression model performance of administrative health data. *J Clin Epidemiol* 2006; 59:940–946
69. Kor DJ, Gajic O: Blood product transfusion in the critical care setting. *Curr Opin Crit Care* 2010; 16:309–316