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Red blood cell distribution width: biomarker for red cell dysfunction and critical illness outcome?

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Abstract

Objective—Red blood cell distribution width (RDW) is reported to be an independent predictor of outcome in adults with a variety of conditions. We sought to determine if RDW is associated with morbidity or mortality in critically ill children.

Design—Retrospective observational study.

Setting—Tertiary pediatric intensive care unit.

Patients—All admissions to Saint Louis Children's Hospital Pediatric Intensive Care Unit between 1/1/2005 and 12/31/2012.

Interventions—We collected demographics, laboratory values, hospitalization characteristics and outcomes. We calculated the relative change in RDW (R-RDW) from admission (A-RDW) to the highest RDW during the first 7 days of hospitalization. Our primary outcome was ICU mortality or use of ECMO as a composite. Secondary outcomes were ICU- and ventilator-free days.

Measurements and main results—We identified 3,913 eligible subjects with an estimated mortality (by PIM2) of $2.94 \pm 9.25\%$ and an actual ICU mortality of 2.91%. For the study cohort, A-RDW was $14.12 \pm 1.89\%$ and R-RDW was $+2.63 \pm 6.23\%$. On univariate analysis, both A-RDW and R-RDW correlated with mortality or use of ECMO (OR=1.19 [95% CI: 1.12–1.27] and OR=1.06 [95% CI: 1.04–1.08], respectively, $p < 0.001$). After adjusting for confounding variables, including severity of illness, both A-RDW (OR=1.13, 95% CI 1.03–1.24) and R-RDW (OR=1.04, 95% CI 1.01–1.07) remained independently associated with ICU mortality or use of ECMO. A-

RDW and R-RDW both weakly correlated with fewer ICU-free ($r^2=0.038$) and ventilator-free days, ($r^2=0.05$), ($p<0.001$).

Conclusions—Independent of illness severity in critically ill children, A-RDW is associated with ICU mortality and morbidity. These data suggest that RDW may be a biomarker for RBC injury that is of sufficient magnitude to influence critical illness outcome, possibly via oxygen delivery impairment.

Keywords

Pediatrics; erythrocytes; erythrocyte indices; critical care; mortality; morbidity

Introduction

Red cell distribution width (RDW) is a standard parameter of the complete blood count (CBC) and indicates variability in red blood cell (RBC) size; RDW is calculated as the proportional variation in mean corpuscular volume (MCV) (normal range: 11.5% to 14.5%) (1). Increased RDW values reflect greater variability in RBC size, which generally indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes. Traditionally, RDW has been used in diagnosing of iron deficiency anemia, particularly when serum ferritin does not accurately indicate total iron stores. RDW is also elevated in other nutritional anemias such as folate or vitamin B12 deficiency. Recently, there has been increasing awareness of a positive association between RDW and risk of both morbidity and mortality in several disease states, principally in critically ill adults. These conditions include cardiovascular disease(2–4), community acquired pneumonia(5), acute stroke(6), chronic lung disease(7), sepsis(8–10), and with general critical illness(11–15).

Of note, mounting evidence suggests that, in the course of critical illness, RBCs acquire metabolic and structural injuries that impair oxygen (O_2) delivery and influence outcome. Such acquired RBC dysfunction is reported to result in: increased adhesion to endothelium, decreased deformability, decreased hemoglobin (Hb) content(16), increased O_2 affinity(17), constrained energy metabolism and impaired antioxidant capacity(18), as well as abnormal nitric oxide processing (and vascular signaling)(19). Each of these pathologies may adversely influence tissue O_2 delivery(20), by either impairing blood flow or O_2 release(17) itself. We considered the possibility that the changes in RDW observed in the critically ill may relate to these RBC injuries and thereby, serve as a biomarker for impaired RBC status with regard to O_2 delivery capacity and explain the observed association between this metric and outcome.

To our knowledge, only one moderate sized study has investigated the relationship between RDW and poor outcome in critically ill children(21). Examination of the association between RDW and outcome in this population adds to analyses of adult populations, given the reduced incidence of confounding chronic conditions and other co-morbidities and broadens external validity of prior reports. As such, and in preparation for prospective studies, we investigated the association of RDW with morbidity and mortality in a general critically ill pediatric population.

Materials and methods

We performed a retrospective analysis of all patients admitted between January 1, 2005 and December 31, 2012 to the pediatric intensive care unit (PICU) at Saint Louis Children's Hospital, a tertiary care children's hospital. Our institutional investigational review board approved the study protocol.

We identified potential subjects by querying the Virtual PICU Systems (VPS) clinical database. VPS is a national database of pediatric critical care units that collect clinical data for the purpose of improving quality, benchmarking with peers and establishing best practices. It is a collaboration amongst the National Association of Children's Hospitals and Related Institutions, National Outcomes Center of Children's Hospital and Health System in Wisconsin, and Children's Hospital Los Angeles (VPS, LLC, Alexandria, VA)(22). All patients admitted to our PICU during the study period were included. Exclusion criteria were: (1) the following ICD9 admission diagnoses: anemia, malignancy, epilepsy or seizures, organ or tissue transplant recipients, as well as admission for routine short term planned post-operative care, (2) lack of a CBC in the first 7 days of PICU stay, and (3) history of RBC transfusion within 14 days prior to PICU admission or during the first 7 days following PICU admission.

We obtained the following data: (1) demographics: age, sex, weight, admission diagnoses, admission date, cardiac surgery or ECMO, admission severity of illness using the Pediatric Index of Mortality 2 score (PIM2) (a validated score used to estimate mortality risk on PICU admission utilizing physiological and laboratory variables collected within 1 hour after admission)(23) and (2) hospitalization characteristics: number of PICU days, number of ventilator days, length of hospital stay, PICU mortality, discharge date and destination, and initial vital signs. We obtained laboratory results from the Clinical Investigation Data Exploration Repository (CIDER) at Washington University in St. Louis(24). We collected subjects' CBCs on admission and during the first 7 days from admission to the PICU. During the study period, CBCs were analyzed using Sysmex XE-2100™ automated hematology system (Sysmex America, Inc.). History of RBC transfusion was identified using the SLCH blood bank database (CERNER millennium). Admission RDW (A-RDW) was determined from the first CBC collected in the first 24 hours in PICU for all the patient cohort including subjects who received ECMO support. To evaluate RDW change, we calculated the difference between the admission RDW (A-RDW) and the highest RDW in the first 7 days after admission. We divided that difference by the A-RDW to calculate the relative change in RDW (R-RDW). If any exclusion criteria were met prior day 7, the highest RDW up until that day was used for the R-RDW calculation.

Our primary outcome was a composite metric of death during PICU admission and/or use of ECMO. To evaluate the relationship between RDW and our primary outcome, we first performed a univariate analysis for all variables and then a multivariate analysis to control for severity of illness by PIM2. To evaluate the independent contribution of A-RDW to the primary outcome, we apportioned our cohort by RDW quartiles and then performed an inter-quartile comparison of severity of illness, estimated mortality and actual mortality. We calculated standardized mortality ratios (SMR)(25) for the cohort by indexing the observed

mortality to that predicted by PIM2(26). To evaluate the impact of A-RDW on estimation of mortality, we plotted receiver operating characteristic (ROC) curves for PIM2, A-RDW and then by combining A-RDW with PIM2.

Our secondary outcomes included ICU-free days and ventilator-free days. ICU-free days were defined as the number of days between transfer to a regular ward and 28 days after PICU admission. Subjects were assigned zero ICU-free days if they died in the PICU or had a PICU length of stay more than 28 days. Ventilator-free days were defined as the number of days between successful discontinuation of mechanical ventilatory support and 28 days after PICU admission. Subjects were assigned zero ventilator-free days if they died in PICU or were on mechanical ventilatory support for greater than 28 days.

Statistical analyses

Wilcoxon Rank-sum test was used to compare continuous nonparametric data and Chi-square or Fisher's exact tests were used to compare categorical data, as appropriate. We first developed simple logistic regression models for death or use of ECMO using the following variables; weight, gender, age, history of trauma, PIM2, PRISM III (Pediatric Risk of Mortality III) and PELOD (Pediatric Logistic Organ Dysfunction) scores using Pearson correlations and simple linear regression. We then developed a stepwise multivariate logistic regression model to determine which variables were independently associated with ICU mortality and use of ECMO. All variables with $p < 0.2$ by univariate analysis for the primary outcome were considered for the multivariate model. PIM2 was chosen to adjust for severity of illness instead of PRISM III to minimize the number of subjects with missing data for this metric. The area under the curve for multivariate models was calculated to demonstrate the strength of the models developed. Data is presented as mean $\pm$ standard deviation, unless otherwise noted. We used $p < 0.05$ to indicate statistical significance. Analyses were performed with SAS 9.4 statistical software, (SAS® Cary, NC). Receiver Operator Characteristics (ROCs) were constructed for variables associated with the death, followed by Area Under the Curve (AUC) comparison with STATA 12.1 (StataCorp LP, College Station, TX). SMR and statistical significance between actual and estimated mortality (PIM2) were calculated using OpenEpi(27); Spearman correlation between the errors in PIM2 estimated mortality and A-RDW were performed with R version 3.1.1(28).

Results

We screened 17,351 patients admitted to the PICU between January 2005 and December 2012; of these, 3,913 subjects met study criteria and were analyzed (Figure 1). Table 1 indicates demographics and admission CBC values. For the full cohort, Hb was 11.93 ± 2.39 gm/dL with an RDW of $14.12 \pm 1.89\%$ and the relative RDW change over the first 7 days after PICU admission was $+2.63 \pm 6.23\%$. The PICU length of stay (LOS) was 2.85 ± 4.45 days, with 24.02 ± 6.48 ICU-free days and 25.67 ± 6.15 ventilator-free days. The PIM2 score for the cohort was -4.59 ± 1.40 , with an estimated mortality of $2.94\% \pm 9.25$. There were 114 PICU deaths in the cohort, with an actual mortality of 2.91%; 20 subjects (0.51%) received ECMO support, of whom, 6 subjects died (30%). Of our total cohort, 164 subjects (4.19%) underwent cardiopulmonary bypass (CPB) on the first ICU day. There was no

difference in A-RDW for subjects who underwent CPB on ICU day 1 vs the remainder of our cohort (13.92 ± 1.45 vs 14.13 ± 1.91 respectively, $p = 0.517$). Subjects who underwent CPB on ICU day 1 had a significantly higher R-RDW compared to the remainder of our cohort (4.06 ± 6.37 vs 2.1 ± 5.06 respectively, $p < 0.001$). There was no statistically significant difference in mortality between subjects who underwent CPB on ICU day 1 and the remainder of our cohort (1.22% vs 2.99% respectively, $p = 0.187$)”.

We divided our cohort into quartiles by A-RDW as follows: 1st quartile: $<12.9\%$, 2nd quartile: $12.9 - 13.5\%$, 3rd quartile: $13.6 - 14.8\%$ and 4th quartile: $>14.9\%$. We observed a statistically significant difference between the 1st and 4th quartiles for the majority of patient and hospitalization characteristics (Table 1). Subjects in the 4th quartile were younger, had lower Hb levels, and increased severity of illness and mortality. Additionally, RBC metrics differed significantly between quartiles: subjects in the 4th quartile had higher mean corpuscular volume (MCV) and lower mean corpuscular hemoglobin concentration (MCHC), although the mean corpuscular hemoglobin (MCH) did not differ (Figure 2). We considered younger subject age in the 4th quartile confounded the relationship between A-RDW and outcomes. In fact, when analyzed within the 1st and 4th quartiles, we found no relationship between age and RDW (data not shown).

On univariate analysis, we observed a significant correlation between A-RDW, R-RDW and PIM2 with ICU mortality or use of ECMO (Table 2, Figure 3A). On multivariate analysis, after adjustment for severity of illness with PIM2, both A-RDW and R-RDW remained independently associated with ICU mortality or use of ECMO, with an Odd's ratio (OR) of 1.127 (95% Confidence Interval (CI): 1.025 – 1.238, $p = 0.01$) and 1.037 (95% CI: 1.010 – 1.065, $p < 0.01$), respectively (Figure 3B).

Compared to those in the 1st A-RDW quartile, subjects in the 4th A-RDW quartile had higher PIM2 scores and estimated mortality ($p < 0.001$), actual mortality ($p < 0.001$) and use of ECMO ($p < 0.005$) (Table 1 and Figure 4A). We calculated SMR for the entire cohort as well as for sub-cohorts apportioned by A-RDW quartiles. Although the SMR for the total cohort was 0.991, SMR increased with RDW progression: SMR for the 1st A-RDW quartile was 0.878, while SMR for the 4th A-RDW quartile was 1.102 (Figure 4B). When compared by categorical analysis, differences in the ratio of observed and expected mortality between A-RDW-based sub-cohorts were not significant; however, we also tested the residual errors in predicted mortality per PIM2 for association with each subject's actual A-RDW value, and this association was significant and in line with the trend seen in Figure 4A ($p = 0.011$ for rank-based association between model residuals and A-RDW). Generally, a well-fitting model should not generate systematic trends of residuals across values of a predictor variable; therefore, this analysis provides strong evidence that patients with low A-RDW tend to have mortality rates lower than predicted by PIM2, while those with higher A-RDW tend to have higher mortality than predicted by PIM2. In ROC analyses of the relationship between RDW and mortality, the AUC for A-RDW was 0.611 (95% CI: 0.076–0.218) while the AUC for PIM2 was 0.901 (95% CI: 0.908–1.166). Combining A-RDW and PIM2 nominally increased the AUC to 0.905 (95% CI: 0.903–1.161, NS) (Figure 4C). With regard to our secondary outcomes, subjects in the highest A-RDW quartile had significantly lower ICU- and ventilator-free days ($p < 0.001$, table 1). Comparing all sub-cohorts apportioned by

A-RDW, subjects in the 3rd and 4th A-RDW quartiles had significantly lower ICU-free and ventilator-free days compared to those in the 1st and 2nd quartiles ($p<0.001$). Additionally, linear regression analysis demonstrated a (significant, but weak) correlation between ICU-free days and A-RDW (r^2 0.038, $p<0.001$) and R-RDW (r^2 0.050, $p<0.001$) and between ventilator-free days and A-RDW (r^2 0.025, $p<0.001$) and R-RDW (r^2 0.035, $p<0.001$).

Discussion

Our evaluation of over 3,000 critically ill children confirms reports in other populations that RDW is independently associated with ICU mortality and morbidity. Of note, the prior study of critically ill children was limited to 596 subjects and did not exclude those with recent RBC transfusion, hemoglobinopathies or anemia on admission(21). In our larger, more focused cohort, we observed that both A-RDW and R-RDW positively associated with mortality or use of ECMO and that this association persisted after correction for illness severity (PIM2). Overall, the likelihood of ICU mortality or use of ECMO rose 12.7% for every 1% increase in A-RDW (OR 1.127). Further, for every 1% relative increase in RDW during the first 7 days of PICU stay (R-RDW), the likelihood of ICU mortality or use of ECMO rose by 3.7% (OR 1.037).

Our findings are consistent with previous analyses of general populations of critically ill adults(8, 11, 13–15), which consistently demonstrate a positive association between RDW and 30 day hospital mortality, 90 day mortality and 365 day mortality. Similar associations have been reported for select critically ill adult populations, such as those with septic shock(10). Two prior reports (together, including 800 subjects) evaluated the relationship between RDW and outcome in children undergoing surgery for congenital heart disease and found that RDW was positively associated with both mortality and length of ICU stay(29, 30) (however, it should be noted that cardiopulmonary bypass may affect RDW, in proportion to bypass duration). Only one study excluded patients with history of recent RBC transfusion(29). Moreover, we excluded patients with anemia or cancer on admission, due to concerns that these diagnoses would confound the relationship between RDW and outcome; therefore, our results should not be generalized to these subpopulations without further study. This study is the first to show an association between A-RDW and a composite primary outcome of death or use of ECMO support. This outcome, in our view, better captures subjects' severity of illness than the use of ICU mortality alone. Previous pediatric studies have shown an association between RDW and ICU length of stay. We present the first study to show an association between A-RDW and ICU-free days and ventilator-free days. These outcomes account for ICU death and are therefore more standardized measures of ICU morbidity.

We observed that A-RDW only nominally increased the predictive power of a validated severity of illness score (PIM2) for mortality. This observation is in contrast with previous reports in adults(8, 13), which demonstrated that adding A-RDW to Acute Physiology and Chronic Health Evaluation II (APACHEII)(8, 13), Simplified Acute Physiology Score (SAPS)(31) and APACHEIII(32) increased predictive power for both ICU and hospital mortality. Examined differently, however, we observed that PIM2 reliability varied in a systematic, but balanced, fashion when examined by RDW quartile. For our full cohort, the

PIM2-based standardized mortality ratio (SMR) approached 1 and PIM2 was 99.1% accurate in estimating mortality. When examined by RDW quartile, however, PIM2 overestimated mortality in the lowest quartile (by 12.2%) and underestimated mortality in the highest quartile (by 10.2%). This RDW-based bias was found to be significant in testing the association between individual A-RDW and the magnitude and direction of the error in PIM2 predicted mortality: higher A-RDW values were associated with higher mortality than predicted by PIM2, while patients with lower A-RDW values had lower mortality than predicted. Although the absolute number of events (e.g. deaths) was not sufficient to establish statistical reliability in our categorical analysis (given the low mortality in our population), this observation reinforces the finding in our regression models that RDW may serve as a biomarker for a physiologic disturbance that influences outcome. It may be that elevated RDW is most relevant in the PICU subpopulation with sepsis or MODS; as such it may add more value to metrics such as SOFA or MODS scores.

We lack a mechanistic explanation for the established association between RDW and clinical outcome. It has been speculated that the relationship could be explained by the effect of inflammatory cytokines, such as TNF- α , IL-6, and IL-1 β , upon RBC survival and maturation, or with entrance of larger juvenile cells (reticulocytes) into the peripheral circulation, thus increasing RDW(33, 34). However, when examined, prior reports have failed to show an association between elevated RDW and increased inflammatory cytokines(15). Of note, in the highest RDW quartile, we observed increased RBC size (higher MCV) with reduced Hb concentration (MCHC) – although absolute Hb content (MCH) did not change. Notably, these changes do not meet criteria for iron, folate or B12 deficiencies, which have also been suggested as cause for increased RDW in the critically ill. Moreover, others have shown that the RDW-mortality association persists even after correction for iron, folate and vitamin B12 deficiency(35). Rather, as suggested by others (above), these RBC metrics may indicate an increase in immature RBCs (larger in size with less concentrated Hb) that might be associated with increased RBC turnover. Alternatively, this pattern may instead arise from RBC injuries that impair control of volume homeostasis (e.g. hydration) in mature cells, as discussed below.

It is commonly appreciated that RBCs may acquire metabolic and structural injuries that impair performance (e.g. O₂ delivery). In the setting of critical illness, it is also apparent that O₂ delivery constraint may influence outcome. Acquired RBC injuries in the critically ill population are commonly observed, with the following reports of specific alterations that impair O₂ delivery: increased adhesion to endothelium(36), decreased deformability, decreased hemoglobin (Hb) content(16, 37), increased O₂ affinity(17, 38), constrained energy metabolism and impaired antioxidant capacity(18), as well as abnormal nitric oxide processing (and vascular signaling)(19). Each of these pathologies adversely influence tissue O₂ delivery(20), by diminishing either blood flow or O₂ release(17) itself. It is important to note that the circulating RBC population is comprised by subpopulations of differing physiological reserve/resilience (e.g. juvenile vs senescent cells); exposure to stress in the setting of differing resilience is expected to increase diversity of physiologic parameters. It may be reasonable to consider that such acquired RBC injuries therefore increase size heterogeneity of the circulating RBC pool (and thus, be reflected by increased RDW). More specifically, concurrent increase in RDW and MCV, with reduced MCHC (as we observed)

may arise from impaired RBC volume homeostasis (e.g. a population of overhydrated cells); moreover, loss of volume homeostasis may be attributable to RBC energy failure and impaired cation gradient maintenance(39). RBC hydrocytosis (over-hydration) typically arises from increased intracellular sodium flux, which has been associated with RBC energy failure or injury to proteins involved in volume regulation, including the following: the Na^+/K^+ ATPase pump, the Anion Exchange Protein 1 (AE1 or Band 3), the Gardos channel, and Peizo1 (a mechanosensitive ion channel), GLUT1, and ABCB6 (ATP-binding cassette) (40). As such, we hypothesize that increased RDW is a biomarker for impaired RBC energetics, which would both: (1) disrupt RBC volume regulation (leading to the specific pattern of altered RBC metrics we observed) and (2) result in the RBC injuries associated with O_2 delivery failure (and therefore, worsened outcomes).

We propose that the observed independent relationship between RDW and outcome may be explained by either: (1) underlying pathology that results in a functional RBC injury (e.g. reduced capacity for O_2 delivery) that is sufficient to alter the course of critical illness and consequently, RDW may serve as a biomarker for clinically significant RBC impairment *or*, that (2) RDW demonstrates fidelity to the severity of underlying pathology, but does not connote impairment in RBC performance that is causally linked to outcome. We will examine these possibilities in future work by prospectively testing the relationship between RDW, RBC energetics and antioxidant systems, specific injuries to key RBC regulatory proteins noted above, physiologic measures of RBC performance and outcome in critically ill children.

Conclusion

In conclusion, RDW is independently associated with ICU mortality and morbidity in critically ill children, suggesting a possible causal relationship between RBC performance and outcome. The mechanism for this relationship between RBC size heterogeneity and outcome is unclear; we propose that this association may be explained by accrued RBC injuries that impair O_2 delivery in the setting of critical illness – and that RDW may serve as a biomarker for red cell injury. Further study is warranted to understand the impact of critical illness on RBC function and life span, the fidelity and utility of RDW as a putative biomarker for such, and the potential impact of RBC performance failure upon clinical outcomes.

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References

1. Constantino B. Red cell distribution width, revisited. *Laboratory Medicine*. 2013; 44
2. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB. Investigators C. Red cell distribution width as a novel

- prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *Journal of the American College of Cardiology*. 2007; 50:40–47. [PubMed: 17601544]
3. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, Lenihan DJ, Oren RM, Wagoner LE, Schwartz TA, Adams KF Jr. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *Journal of Cardiac Failure*. 2010; 16:230–238. [PubMed: 20206898]
 4. van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi JL Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. *European Journal of Heart Failure*. 2010; 12:129–136. [PubMed: 20026456]
 5. Lee JH, Chung HJ, Kim K, Jo YH, Rhee JE, Kim YJ, Kang KW. Red cell distribution width as a prognostic marker in patients with community-acquired pneumonia. *American Journal of Emergency Medicine*. 2013; 31:72–79. [PubMed: 22867824]
 6. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. *J Neurol Sci*. 2009; 277:103–108. [PubMed: 19028393]
 7. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med*. 2009; 169:588–594. [PubMed: 19307522]
 8. Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. *J Intensive Care Med*. 2013; 28:307–313. [PubMed: 22809690]
 9. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, Han SH, Yoo TH, Kim YS, Kang SW, Oh HJ. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. *Critical Care*. 2013; 17:R282. [PubMed: 24321201]
 10. Lorente L, Martin MM, Abreu-Gonzalez P, Sole-Violan J, Ferreres J, Labarta L, Diaz C, Gonzalez O, Garcia D, Jimenez A, Borreguero-Leon JM. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. *Public Library of Science One*. 2014; 9:e105436. [PubMed: 25153089]
 11. Purtle SW, Moromizato T, McKane CK, Gibbons FK, Christopher KB. The association of red cell distribution width at hospital discharge and out-of-hospital mortality following critical illness. *Crit Care Med*. 2014; 42:918–929. [PubMed: 24448196]
 12. Zhang Z, Xu X, Ni H, Deng H. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. *J Thorac Dis*. 2013; 5:730–736. [PubMed: 24409348]
 13. Wang F, Pan W, Pan S, Ge J, Wang S, Chen M. Red cell distribution width as a novel predictor of mortality in ICU patients. *Ann Med*. 2011; 43:40–46. [PubMed: 20961272]
 14. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. *Crit Care Med*. 2011; 39:1913–1921. [PubMed: 21532476]
 15. Meynaar IA, Knook AH, Coolen S, Le H, Bos MM, van der Dijs F, von Lindern M, Steyerberg EW. Red cell distribution width as predictor for mortality in critically ill patients. *Neth J Med*. 2013; 71:488–493. [PubMed: 24218427]
 16. Condon MR, Kim JE, Deitch EA, Machiedo GW, Spolarics Z. Appearance of an erythrocyte population with decreased deformability and hemoglobin content following sepsis. *Am J Physiol Heart Circ Physiol*. 2003; 284:H2177–2184. [PubMed: 12742829]
 17. Eel Ibrahim D, McLellan SA, Walsh TS. Red blood cell 2,3-diphosphoglycerate concentration and in vivo P50 during early critical illness. *Crit Care Med*. 2005; 33:2247–2252. [PubMed: 16215378]
 18. Rogers SC, Said A, Corcuera D, McLaughlin D, Kell P, Doctor A. Hypoxia limits antioxidant capacity in red blood cells by altering glycolytic pathway dominance. *FASEB J*. 2009; 23:3159–3170. [PubMed: 19417084]
 19. Doctor A, Platt R, Sheram ML, Eischeid A, McMahon T, Maxey T, Doherty J, Axelrod M, Kline J, Gurka M, Gow A, Gaston B. Hemoglobin conformation couples erythrocyte S-nitrosothiol content to O₂ gradients. *Proc Natl Acad Sci U S A*. 2005; 102:5709–5714. [PubMed: 15824313]
 20. Said A, Rogers S, Doctor A. Red cell physiology and signaling relevant to the critical care setting. *Current Opinion Pediatrics*. 2015; 27:267–276.

21. Ramby AL, Goodman DM, Wald EL, Weiss SL. Red Blood Cell Distribution Width as a Pragmatic Marker for Outcome in Pediatric Critical Illness. *Public Library of Science One*. 2015; 10:e0129258. [PubMed: 26057629]
22. Wetzel RC, Sachedeva R, Rice TB. Are all ICUs the same? *Paediatric Anaesthesia*. 2011; 21:787–793. [PubMed: 21554489]
23. Slater A, Shann F, Pearson G. G Paediatric Index of Mortality Study. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med*. 2003; 29:278–285. [PubMed: 12541154]
24. Washington University in St. Louis, Center for Biomedical informatics, Clinical Investigation Data Exploration Repository, project number 966, created at 9/25/2013, doi:/10.7936/B6CR0000. 2010;
25. Goncalves JP, Severo M, Rocha C, Jardim J, Mota T, Ribeiro A. Performance of PRISM III and PELOD-2 scores in a pediatric intensive care unit. *Eur J Pediatr*. 2015; 174:1305–1310. [PubMed: 25875250]
26. Curtin LR, Klein RJ. Direct standardization (age-adjusted death rates). *Healthy People 2000 Stat Notes*. 1995:1–10.
27. DAG, SKM, SMM. [Accessed 01/29/2016] OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. <http://www.openepi.com/>. Available at
28. R. C. Team. R: A language and environment for statistical computing. Available at: <http://http://www.R-project.org/>. Accessed
29. Massin MM. Relation between red cell distribution width and clinical outcome after surgery for congenital heart disease in children. *Pediatr Cardiol*. 33:1021–1025.
30. Polat V, Iscan S, Etli M, El Kilic H, Gursu O, Eker E, Ozdemir F. Red cell distribution width as a prognostic indicator in pediatric heart disease and after surgery. *Biomed Research International*. 2014; 2014:681679. [PubMed: 24745021]
31. Hunziker S, Celi LA, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. *Critical Care*. 2012; 16:R89. [PubMed: 22607685]
32. Loveday S, Sinclair L, Badrick T. Does the addition of RDW improve current ICU scoring systems? *Clinical Biochemistry*. 2015; 48:569–574. [PubMed: 25869493]
33. Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med*. 2003; 31:S651–657. [PubMed: 14724462]
34. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005; 352:1011–1023. [PubMed: 15758012]
35. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med*. 2009; 169:515–523. [PubMed: 19273783]
36. Goyette RE, Key NS, Ely EW. Hematologic changes in sepsis and their therapeutic implications. *Semin Respir Crit Care Med*. 2004; 25:645–659. [PubMed: 16088507]
37. Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. Red blood cell rheology in sepsis. *Intensive Care Med*. 2003; 29:1052–1061. [PubMed: 12802488]
38. Textoris J, Martin C, Leone M. Oxygen blood transport during experimental sepsis: effect of hypothermia*. *Crit Care Med*. 2012; 40:1017–1018. [PubMed: 22343864]
39. Flatt JF, Bawazir WM, Bruce LJ. The involvement of cation leaks in the storage lesion of red blood cells. *Front Physiol*. 2014; 5:214. [PubMed: 24987374]
40. Gallagher PG. Disorders of red cell volume regulation. *Curr Opin Hematol*. 2013; 20:201–207. [PubMed: 23519154]

Figure 1. Consort diagram for cohort accrual

We screened all PICU admissions from January, 2005 through December, 2012. Using the VPS database, patients with admission diagnoses of anemia, malignancy, seizures or history of organ transplant were excluded. Repeat encounters were excluded as were those lacking admission laboratory data. We also excluded all who had received red blood cell transfusions during the 2-week period prior to PICU admission or 1 week after admission. *CBC*: complete blood count, *VPS*: virtual PICU systems.

Figure 2. RBC metrics for the sub-cohorts apportioned by A-RDW quartiles
Box and whisker plot of MCV, MCH and MCHC for the sub-cohorts apportioned by A-RDW quartiles. We observed a significant increase in MCV and decrease in MCHC in the 4th A-RDW, while no difference was noted in MCH (One way ANOVA, $p < 0.001$). *MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, A-RDW: red cell distribution width on ICU admission.*

Figure 3.

(A) Odds ratio for mortality or use of ECMO by univariate analysis. All patient variables were analyzed for association with mortality or the need for ECMO support. Odds ratios with 95% CI were calculated for all variables including: weight in kg, age in years, first systolic blood pressure on admission to the PICU, highest and lowest heart rates in the first 12 hours on admission to the PICU, PIM 2 score on admission to the PICU, number of ICU free and ventilator free days, CBC data: admission WBC count, admission RDW, highest RDW in first 7 days on admission to the PICU, relative change in RDW in the first 7 days on admission to the PICU, admission Hb, admission HCT, admission MCV, admission MCH, admission MCHC, admission RBC count, admission platelet count and admission MPV. **(B) Odds ratio for mortality or use of ECMO by multivariate analysis.** Odds ratios for death or the use of ECMO were repeated after controlling for PIM2. Both A-RDW and R-RDW continued to correlate with mortality or use of ECMO support, with OR of 1.127 and 1.037 respectively. *ECMO: extracorporeal membrane oxygenation, PIM 2: pediatric index of mortality 2, WBC: white blood cell count, RDW: red cell distribution width, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RBC: red blood cell, MPV: mean platelet volume.*

Figure 4.

(A) Interquartile comparison of actual and estimated mortality and use of ECMO.

There were significantly higher rates of all three outcomes in subjects in the 4th A-RDW quartile as compared to those in the 1st A-RDW quartile (t test). **(B) Interquartile comparison of standardized mortality ratios.**

Standardized mortality ratios (ratio of actual/PIM2 estimated mortality) indicated that PIM2 overestimated mortality in subjects in the 1st and 2nd A-RDW quartiles and underestimated mortality in patients in the 3rd and 4th A-RDW quartiles, suggesting a relationship between A-RDW and patient outcome. Chi square and *p* values comparing observed and estimated mortality are tabulated. **(C) Receiver operator characteristics curves for death or use of ECMO.** Receiver operator characteristics curves for the incidence of death was calculated for A-RDW, PIM2 score and the combination of PIM2 and A-RDW. AUC was 0.611 for A-RDW, 0.901 for PIM2 and 0.904 for the combined model of A-RDW and PIM2. *ECMO: extracorporeal membrane oxygenation, PIM2: Pediatric Index of Mortality 2, A-RDW: red cell distribution width on ICU admission, R-RDW: relative change in RDW.*

Table 1

Cohort demographics admission CBC values and outcomes.

Parameter (mean $\pm$ SD unless otherwise noted)	Full cohort	1st quartile RDW<12.9% n = 925	4th quartile RDW>14.8% n = 988	<i>p value</i> *
Age, years	7.45 $\pm$ 6.67	10.84 $\pm$ 5.97	3.99 $\pm$ 5.88	< 0.001
Gender (n, % males)	2208, 56.43	492, 53.11	543, 54.96	0.437
Weight, Kg	30.9 $\pm$ 27.51	41.65 $\pm$ 23.72	18.05 $\pm$ 24.30	< 0.001
WBC, 10 ³ /mL	13.93 $\pm$ 12.73	13.03 $\pm$ 6.63	15.64 $\pm$ 22.03	< 0.001
RBC, 10 ⁶ /mL	4.16 $\pm$ 0.76	4.19 $\pm$ 0.61	4.02 $\pm$ 0.91	< 0.001
Hemoglobin, gm/dL	11.93 $\pm$ 2.39	12.28 $\pm$ 1.91	11.76 $\pm$ 3.19	< 0.001
Hematocrit, %	35.17 $\pm$ 6.72	35.49 $\pm$ 5.26	35.24 $\pm$ 9.0	0.48
RDW, %	14.12 $\pm$ 1.89	12.47 $\pm$ 0.28	16.64 $\pm$ 2.05	<0.001
Relative change in RDW, %	2.63 $\pm$ 6.23	2.65 $\pm$ 4.39	1.93 $\pm$ 8.17	0.01
MCH, pgm	28.74 $\pm$ 2.96	29.26 $\pm$ 1.73	29.33 $\pm$ 4.52	0.65
MCHC, gm/dL	33.88 $\pm$ 1.38	34.57 $\pm$ 1.05	33.27 $\pm$ 1.74	< 0.001
MCV, fL	84.8 $\pm$ 7.95	84.68 $\pm$ 4.84	87.94 $\pm$ 11.79	< 0.001
Platelet, 10 ³ /mL	280.87 $\pm$ 129.53	262.28 $\pm$ 98.76	291.68 $\pm$ 156.54	< 0.001
LOS, days	2.85 $\pm$ 4.45	2.46 $\pm$ 5.25	4.31 $\pm$ 5.73	< 0.001
ICU-free days	24.02 $\pm$ 6.48	25.26 $\pm$ 5.25	22.13 $\pm$ 7.81	< 0.001
Ventilator-free days	25.67 $\pm$ 6.15	26.64 $\pm$ 4.96	24.22 $\pm$ 7.49	< 0.001
ECMO (n, %)	20, 0.51	1, 0.11	13, 1.32	0.002
PIM2 score	-4.59 $\pm$ 1.40	-4.81 $\pm$ 1.35	-4.21 $\pm$ 1.40	< 0.001
PIM2 Estimated mortality (%)	2.94 $\pm$ 9.25	2.22 $\pm$ 7.25	3.86 $\pm$ 10.28	< 0.001
PICU Actual Mortality (%)	2.91	1.95	4.25	0.004
SMR	0.998	0.878	1.102	

* T test between 1st and 4th quartiles.

LOS = Length of PICU stay, HCT = hematocrit, Hb = hemoglobin, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RBC = red blood cell count, RDW = red cell distribution width, R-RDW = relative change in RDW in first 7 days, WBC = white blood cell count, LOS = Length of stay, PIM2 = Pediatric Index of Mortality 2, SMR = Standardized mortality ratio.

Table 2

Odds ratios for mortality or use of ECMO by univariate analysis

Variable	Odds ratio	95% CI	p value
Weight	0.994	0.987 ± 1.001	0.110
Age	0.980	0.954 ± 1.007	0.143
First systolic blood pressure	0.987	0.973 ± 1.001	0.076
Peak heart rate (first 12 hours)	1.017	1.011 ± 1.022	<0.001
Lowest heart rate (first 12 hours)	0.990	0.984 ± 0.996	0.001
PIM2 score	2.759	2.439 ± 3.121	<0.001
ICU-free days	0.708	0.668 ± 0.750	<0.001
Ventilator-free days	0.733	0.702 ± 0.766	<0.001
Admission WBC	1.007	1.000 ± 1.015	0.058
A-RDW	1.190	1.115 ± 1.270	<0.001
Peak RDW (first 7 days)	1.181	1.107 ± 1.261	<0.001
R-RDW	1.059	1.035 ± 1.083	<0.001
Admission hemoglobin	1.026	0.954 ± 1.104	0.483
Admission hematocrit	1.022	0.997 ± 1.049	0.090
Admission MCV	1.046	1.026 ± 1.066	<0.001
Admission MCHC	0.787	0.710 ± 0.872	<0.001
Admission MCH	1.068	1.009 ± 1.130	0.022
Admission RBC count	1.004	0.795 ± 1.268	0.973
Admission platelet count	0.999	0.997 ± 1.000	0.058
Admission MPV	1.284	1.085 ± 1.520	0.003

PIM2 = Pediatric Index of Mortality 2, WBC = white blood cell count, A-RDW = red cell distribution width on admission to the PICU, R-RDW = relative change in red cell distribution width in first 7 days of PICU stay, MCV = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCH = mean corpuscular hemoglobin, RBC = red blood cell, MPV = mean platelet volume.