

# Red cell distribution width predicts out of hospital outcomes in critically ill emergency general surgery patients

Joaquim Michael Havens,<sup>1,2</sup> Anupamaa J Seshadri,<sup>1</sup> Ali Salim,<sup>1,2</sup> Kenneth B Christopher<sup>3,4</sup>

<sup>1</sup>Division of Trauma, Burns and Surgical Critical Care, Brigham and Women's Hospital, Boston, Massachusetts, USA

<sup>2</sup>Department of Surgery, Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, Massachusetts, USA

<sup>3</sup>Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

<sup>4</sup>The Nathan E. Hellman Memorial Laboratory Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

## Correspondence to

Dr Joaquim Michael Havens, Department of Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA; [jhavens@bwh.harvard.edu](mailto:jhavens@bwh.harvard.edu)

Received 22 November 2017

Revised 6 February 2018

Accepted 2 March 2018

## ABSTRACT

**Introduction** Red cell distribution width (RDW) is associated with mortality and bloodstream infection risk in critically ill patients. We hypothesized that an increase in RDW at hospital discharge in critically ill patients who received emergency general surgery (EGS) would be associated with increased mortality after hospital discharge.

**Methods** We performed a two-center observational study of patients treated in medical and surgical intensive care units. We studied 1567 patients, who received critical care between 1998 and 2012 who underwent EGS and survived hospitalization. The exposure of interest was RDW within 24 hours of hospital discharge and categorized a priori in quintiles as  $\leq 13.3\%$ , 13.3% to 14.0%, 14.0% to 14.7%, 14.7% to 15.8%, 15.8% to 17.0% and  $>17.0\%$ . The primary outcome was 90-day all-cause mortality. Adjusted ORs were estimated by multivariable logistic regression models with inclusion of covariate terms for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure.

**Results** The cohort patients were 51.4% male and 23.2% non-white. 23.9% had sepsis and the mean age was 58 years. 90-day postdischarge mortality was 6.8%. Patients with a discharge RDW 15.8% to 17.0% or RDW  $>17.0\%$  have an adjusted OR of 90-day postdischarge mortality of 3.64 (95% CI 1.04 to 12.68;  $p=0.043$ ) or 4.58 (95% CI 1.32 to 15.93;  $p=0.02$ ), respectively, relative to patients with a discharge RDW  $\leq 13.3\%$ . Further, patients with a discharge RDW  $\geq 15.8$  have an adjusted OR of 30-day hospital readmission of 2.12 (95% CI 1.17 to 3.83;  $p=0.013$ ) relative to patients with a discharge RDW  $\leq 13.3\%$ .

**Conclusions** In EGS patients requiring critical care who survive hospitalization, an elevated RDW at the time of discharge is a robust predictor of all-cause patient mortality and hospital readmission after discharge.

**Level of evidence** Level II, prognostic retrospective study.

## INTRODUCTION

Emergency general surgery (EGS) comprises a significant burden of medical care, constituting 7.2% of total hospital admissions in the USA with an increasing incidence over time.<sup>1</sup> Furthermore, EGS is known to lead to significant morbidity and mortality, with estimates of 12% to 15% 30-day mortality and 25% 1-year mortality.<sup>2</sup> Although it is evident that the mortality related to EGS is not

confined to the patient's hospital stay, the risk factors for postdischarge mortality are not yet well defined. Malnutrition at intensive care unit (ICU) admission,<sup>3</sup> increasing age and uninsured status<sup>4</sup> have been noted to correlate with increased mortality after EGS. However, further prognostic indicators may be helpful in better stratifying EGS patients at discharge for closer follow-up to improve mortality.

A recent study by Purtle *et al* defined a role for red cell distribution width (RDW) as a prognostic factor for mortality after hospital discharge in ICU patients.<sup>5</sup> RDW is a parameter that reflects the heterogeneity of erythrocyte volume, and elevated RDW has been shown to also have value in predicting mortality and adverse outcomes in multiple disease states including septic shock,<sup>6</sup> pulmonary embolism,<sup>7</sup> coronary artery disease<sup>8</sup> and heart failure.<sup>9</sup> EGS is often performed in critically ill patients and, like all trauma or surgery, leads to an inflammatory state.<sup>10</sup> The relationship between RDW and EGS has not been previously studied.

The aim of this study was to examine the relationship between RDW and mortality in critically ill EGS patients who survive to hospital discharge. We hypothesized that RDW will predict postdischarge mortality after EGS.

## MATERIALS AND METHODS

### Source population

We extracted administrative and laboratory data from patients admitted to two Boston hospitals: Brigham and Women's Hospital (BWH), with 777 beds, and Massachusetts General Hospital (MGH), with 999 beds. The two hospitals provide primary as well as tertiary care to an ethnically and socio-economically diverse population within eastern Massachusetts and the surrounding region.

### Data sources

Data on all patients admitted to BWH or MGH between November 2, 1997 and December 31, 2012 were obtained through the Research Patient Data Registry (RPDR), a computerized registry which serves as a central data warehouse for all inpatient and outpatient records at Partners Health-Care sites which includes BWH and MGH. The RPDR has been used for other clinical research studies.<sup>5 11-13</sup>

**To cite:** Havens JM, Seshadri AJ, Salim A, *et al*. *Trauma Surg Acute Care Open* 2018;**3**:e000147.

### Study population

During the study period, there were 2697 unique patients, age  $\geq 18$  years, who received critical care, underwent EGS within 48 hours of ICU admission and were assigned a diagnosis-related group code. ICU admission was analyzed by assignment of the Current Procedural Terminology (CPT) code 99291 (critical care, first 30–74 min) during hospitalization admission, a validated approach for ICU admission in the RPDR database.<sup>14</sup> Exclusions included: one patient who had white cell count over  $150\,000/10^9/L$ , as a high white cell count may skew the automatically calculated RDW<sup>15</sup>; 885 patients who did not have RDW drawn within 24 hours of hospital discharge and 244 patients who died as inpatients. Thus, 1567 patients constituted the total study population.

### Exposure of interest and comorbidities

We examined RDW within 24 hours of hospital discharge. This was categorized a priori in quintiles as  $\leq 13.3\%$ , 13.3% to 14.0%, 14.0% to 14.7%, 14.7% to 15.8%, 15.8% to 17.0%, and  $>17.0\%$ .<sup>5</sup> EGS was defined as seven surgical procedures shown to encompass the majority of relevant emergency operations<sup>16</sup> occurring within 48 hours of ICU admission. These procedures include appendectomy, cholecystectomy, lysis of peritoneal adhesions, laparotomy, partial colectomy, operative management of peptic ulcer disease, and small bowel resection. Initiation of critical care was defined as the presence of CPT code 99291 (critical care, first 30–74 min), an approach validated in our administrative database.<sup>14</sup> Sepsis was defined by the presence of International Classification of Diseases ninth revision (ICD-9) codes 038, 995.91, 995.92, or 785.52, from 3 days prior to initiation of critical care to 7 days after.<sup>17</sup> We used the Deyo-Charlson Index to assess the burden of chronic illness<sup>18</sup> using ICD-9 coding algorithms which has been previously validated.<sup>19,20</sup> Patient type is defined as medical or surgical and incorporates the Diagnostic Related Grouping (DRG) methodology.<sup>21</sup> The number of organs with failure was previously described by Martin *et al*<sup>22</sup> and defined by a combination of ICD-9-clinical modification and CPT codes relating to acute organ dysfunction assigned from 3 days before the initiation of critical care to 30 days after.<sup>23,24</sup> Changes from the expected hospital length of stay (LOS) were analyzed by calculating the difference between the actual LOS and the geometric mean LOS for each DRG as analyzed by the Centers for Medicare and Medicaid Services.<sup>25</sup>

Patients were considered to have exposure to inotropes and vasopressors if they received dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, milrinone or vasopressin anytime from 3 days prior to the initiation of critical care and 7 days after. As adding exogenous red blood cells (RBCs) through repeated transfusions is reported to increase the RDW,<sup>15</sup> transfusion data were obtained via blood bank reports.

### Assessment of mortality

Information on vital status for the study cohort was obtained from the Social Security Administration Death Master File. The accuracy of the Social Security Administration Death Master File for in-hospital and out of hospital mortality in our administrative database is validated.<sup>14</sup> Hundred percent of the cohort had vital status present at 365 days after hospital discharge.

### End points

The primary outcome was all-cause 90-day postdischarge mortality. Secondary outcomes included 365-day postdischarge

mortality, unplanned 30-day and 90-day hospital readmission<sup>26,27</sup> and discharge to a care facility. Hospital readmission was analyzed from hospital admission data as previously described<sup>28</sup> and defined as a subsequent or unscheduled admission to BWH or MGH after the index hospitalization.<sup>28–30</sup> We excluded readmissions with DRG codes that are associated with planned readmissions in addition to DRGs for transplantation, procedures related to pregnancy, and psychiatric issues as previously described.<sup>28,31</sup> Discharge care facility data were analyzed from hospital records.<sup>32</sup>

### Power calculations and statistical analysis

Based on our prior work,<sup>5</sup> we anticipated that absolute 90-day posthospital discharge mortality would increase 12.7% in patients with discharge RDW  $>15.8\%$  compared with those with discharge RDW  $\leq 13.3\%$ . With an alpha error level of 5% and a power of 90%, the sample size thus required for our primary end point (90-day posthospital discharge mortality) was 114 in the RDW  $>15.8\%$  group and 114 in the RDW  $\leq 13.3\%$  group.

Categorical variables were described by frequency distribution and compared across RDW groups using contingency tables and  $\chi^2$  testing. Continuous variables were compared across exposure groups using one-way analysis of variance. Unadjusted associations between covariates and mortality were estimated by bivariable logistic regression models. Adjusted ORs were estimated by multivariable logistic regression models with inclusion of covariate terms thought to plausibly be associated with both RDW levels and 90-day postdischarge mortality. Overall fit of the models was assessed using the Hosmer-Lemeshow test and the Bayesian information criterion.

We evaluated the possible effect modification of sepsis, hospital, acute kidney injury, year of hospitalization or total number of packed RBC (PRBC) units transfused on the risk of mortality using the likelihood-ratio test. We evaluated for confounding by running the adjusted model with and without terms for calendar quarter of hospital discharge and LOS. We calculated receiver operator characteristic curves to analyze the discriminating power of discharge RDW for predicting 90-day postdischarge mortality. The *coefplot* command was used to graphically represent the continuous relationship between discharge RDW level and risk of 90-day postdischarge mortality.<sup>33</sup> Locally weighted scatter plot smoothing (LOWESS)<sup>34,35</sup> was used to demonstrate the relationship between change in RDW and hospital LOS. We evaluated the difference in discrimination between discharge RDW and LOS via the DeLong method.<sup>36</sup>

Mixed-effect logistic regression models<sup>37,38</sup> using both fixed and random-effects were used to evaluate the association between changes in RDW and 90-day postdischarge mortality using the STATA *xtmelogit* command<sup>39</sup> with the dates of RDW for the individual patients as the random effect. We assessed the following variables for confounding: age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure. The model used a fixed effect for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure; an independent covariance structure of the random effects and Gaussian-distributed random intercepts and slopes. We used negative binomial regression (overdispersed Poisson regression) models to describe how changes in RDW varied with hospital LOS. All p values are two-tailed, with values  $<0.05$  were considered statistically significant. All analyses were performed using STATA V.14.1MP statistical software.

**Table 1** Characteristics and unadjusted association of potential prognostic determinants with 90-day post discharge mortality\*

	Alive, n=1460	Expired*, n=107	Total, n=1567	P values	Unadjusted or (95% CI) for 90-day postdischarge mortality
Age (years), mean±SD	57.5±18.8	68.8±15.4	58.3±18.8	<0.001†	1.04 (1.02 to 1.05)
Male (gender), no. (%)	747 (51)	59 (55)	806 (51)	0.43	1.17 (0.79 to 1.74)
Non-white (race) no. (%)	352 (24)	11 (10)	363 (23)	0.001	0.36 (0.19 to 0.68)
Surgical patient type, no. (%)	1324 (91)	95 (89)	1419 (91)	0.52	0.81 (0.43 to 1.52)
Deyo-Charlson Index, no. (%)					1.04 (1.02 to 1.05)
0–1	491 (34)	18 (17)	509 (33)	<0.001	1.00 (Referent)
2–3	523 (36)	33 (31)	556 (35)		1.72 (0.96 to 3.10)
4–6	354 (24)	36 (34)	390 (25)		2.77 (1.55 to 4.96)
≥7	92 (6)	20 (19)	112 (7)		5.93 (3.02 to 11.64)
RDW at hospital admission, mean±SD	14.65±1.75	16.06±2.37	14.75±1.84	<0.001†	1.35 (1.24 to 1.48)
Number of organs with acute failure, no. (%)					
0	307 (21)	13 (12)	320 (20)	0.001	1.00 (Referent)
1	414 (28)	24 (22)	438 (28)		1.37 (0.69 to 2.73)
2	397 (27)	29 (27)	426 (27)		1.73 (0.88 to 3.37)
3	207 (14)	19 (18)	226 (14)		2.17 (1.05 to 4.49)
≥4	135 (9)	22 (21)	157 (10)		3.85 (1.88 to 7.87)
Malignancy, no. (%)	522 (36)	59 (55)	581 (37)	<0.001	2.21 (1.49 to 3.28)
Acute kidney injury, no. (%)§	117 (9)	20 (24)	137 (10)	<0.001	2.39 (1.57 to 3.63)
Sepsis, no. (%)	336 (23)	39 (36)	375 (24)	0.002	1.92 (1.27 to 2.90)
Vasopressors/inotropes, no. (%)	724 (50)	64 (60)	788 (50)	0.041	1.51 (1.01 to 2.26)
Acute organ failure score, mean±SD¶	7.76±4.55	10.66±4.59	7.96±4.61	<0.001†	1.33 (1.23 to 1.45)
RDW at hospital discharge, mean±SD	15.32±1.90	16.69±2.26	15.42±1.95	<0.001†	2.06 (1.39 to 3.06)
Length of stay, median (IQR)	11 (7–21)	15 (10–27)	12 (7–21)	<0.001‡	1.02 (1.01 to 1.03)
Change in expected length of stay, median (IQR)	2.8 (–1.0 to 11.7)	7.5 (0.7–21.5)	3.1 (–0.9 to 12.1)	0.002‡	2.09 (1.40 to 3.10)
Discharge to care facility, no. (%)	483 (33)	54 (50)	537 (34)	<0.001	1.37 (0.69 to 2.73)
90-day readmission, no. (%)	421 (29)	49 (46)	470 (30)	<0.001	1.73 (0.88 to 3.37)

Data presented as no. (%) unless otherwise indicated.

\*Expired within 90 days after hospital discharge.

†P analyzed by X<sup>2</sup> except for analyzed by analysis of variance.

‡P analyzed by X<sup>2</sup> except for analyzed by Kruskal-Wallis test.

§Acute kidney injury is RIFLE class injury or failure and available on 1341 patients.

¶The acute organ failure score is a severity of illness risk-prediction score ranging from 0 to 30 points with 30 having the highest risk for mortality.

## RESULTS

Patient characteristics of the study cohort were stratified according to 90-day postdischarge mortality (table 1). In the study cohort, the mean (SD) age at hospital admission was 58.3 (18.8) years. Most patients were male (51%) and white (77%). The median (IQR) change in RDW from hospital admission to hospital discharge was 0.4% (–0.1%–1.3%). The median (IQR) LOS was 12 (7–21) days and the median (IQR) for total transfused RBCs was 0 (0, 6) units. Cohort patients (42.1%) received at least 1 PRBC unit during hospitalization and before discharge RDW was analyzed. In those who received at least 1 PRBC unit, the median (IQR) for total transfused RBCs was 8 (4–17) units. The number of red cell transfusions decreased during the time of the study (Kruskal-Wallis equality-of-populations rank test  $p=0.031$ ).

In the study cohort, the 90-day and 365-day postdischarge mortality rates were 6.8% and 16.0%, respectively. Age, race, Deyo-Charlson index, RDW at hospital admission, acute organ failures, malignancy, sepsis, LOS, changes in expected LOS and RDW at hospital discharge were significantly associated with 90-day postdischarge mortality (table 1). Patient characteristics of the study cohort were stratified according to discharge

RDW levels (table 2). Factors that differed with RDW categories included age, gender, Deyo-Charlson index, acute organ failures, malignancy, sepsis, LOS, changes in expected LOS and the mortality, readmission and discharge to facility outcomes (table 2).

### Primary outcome

Discharge RDW was a strong predictor of mortality (figure 1 and table 3). The odds of 90-day mortality in the discharge RDW 15.8% to 17.0% and RDW >17.0% groups was 6.9-fold and 7.9-fold, respectively, that of those with RDW ≤13.3%. Discharge RDW remained a significant predictor of odds of mortality after adjustment for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure. The adjusted odds of 90-day mortality in the discharge RDW 15.8% to 17.0% and RDW >17.0% groups was 3.6-fold and 4.6-fold, respectively, that of those with RDW ≤13.3% (table 3). The area under the curve (AUC) for the prediction model for 90-day postdischarge mortality was 0.77. The prediction model showed good calibration (Hosmer-Lemeshow  $\chi^2$  7.4,  $p=0.49$ ). There was no significant effect modification of the RDW 90-day postdischarge

**Table 2** Patient characteristics by RDW category group hospital discharge RDW

	≤13.3	13.3–14.0	14.0–14.7	14.7–15.8	15.8%–17.0%	>17.0%	P values
n	154	223	263	381	274	272	
Age, mean±SD	44.07±19.70	55.57±19.08	59.64±19.5	60.49±17.94	62.25±16.88	60.31±16.66	<0.001*
Male gender, no. (%)	102 (66)	127 (57)	135 (51)	188 (49)	134 (49)	120 (44)	<0.001
Non-white race, no. (%)	55 (36)	46 (21)	59 (22)	95 (25)	52 (19)	56 (21)	0.002
Surgical patient type, no. (%)	140 (91)	199 (89)	245 (93)	347 (91)	240 (88)	248 (91)	0.35
Deyo-Charlson index, n (%)							
0–1	86 (56)	90 (40)	83 (32)	114 (30)	75 (27)	61 (22)	<0.001
2–3	49 (32)	72 (32)	111 (42)	133 (35)	91 (33)	100 (37)	
4–6	10 (6)	45 (20.18)	58 (22.05)	112 (29.4)	79 (28.83)	86 (31.62)	
≥7	9 (6)	16 (7)	11 (4.18)	22 (5.77)	29 (10.58)	25 (9.19)	
RDW at hospital admission, mean±SD	12.81±0.53	13.51±0.71	14.10±0.93	14.80±1.20	15.49±1.52	16.63±2.38	<0.001*
Number of organs with acute failure no. (%)							
0	85 (55)	76 (34)	52 (20)	52 (14)	27 (10)	28 (10)	<0.001
1	41 (27)	77 (35)	77 (29)	125 (33)	70 (26)	48 (18)	
2	20 (13)	44 (20)	76 (29)	112 (29)	85 (31)	89 (33)	
3	3 (2)	20 (9)	35 (13)	58 (15)	55 (20)	55 (20)	
≥4	5 (3)	6 (3)	23 (9)	34 (9)	37 (14)	52 (19)	
Malignancy, no. (%)	16 (10)	66 (30)	104 (40)	157 (41)	114 (42)	124 (46)	<0.001
Acute kidney injury, no. (%)†	6 (4)	6 (3)	21 (10)	27 (8)	35 (15)	42 (18)	<0.001
Sepsis, no. (%)	7 (5)	27 (12)	45 (17)	103 (27)	91 (33)	102 (38)	<0.001
Vasopressors/inotropes, no. (%)	29 (19)	77 (35)	130 (49)	210 (55)	168 (61)	174 (64)	<0.001
Acute organ failure score, mean±SD	4.02±3.94	6.53±3.93	7.76±4.37	8.37±4.44	9.49±4.45	9.41±4.48	<0.001*
Length of stay, median (IQR)	5 (3–7)	8 (5–11)	11 (7–17)	13 (8–23)	19 (10–33)	18 (12–33)	<0.001‡
Change in expected length of stay, median (IQR)	–0.7 (–3.0 to 0.7)	0.2 (–2.3 to 3.4)	2.5 (–1.1 to 8.1)	5.3 (–0.3 to 14.8)	9.0 (1.3–24.9)	8.9 (2.6–4.7)	<0.001 ‡
Discharge to care facility, no. (%)	15 (10)	49 (22)	84 (32)	144 (38)	124 (45)	121 (44)	<0.001
90-day readmission, no. (%)	20 (13)	49 (22)	71 (27)	128 (34)	107 (39)	95 (35)	<0.001
90-day postdischarge mortality, no. (%)	3 (2)	4 (2)	11 (4)	19 (5)	33 (12)	37 (14)	<0.001
365-day postdischarge mortality, no. (%)	5 (3)	20 (9)	31 (12)	58 (15)	64 (23)	73 (27)	<0.001

Data presented as no. (%) unless otherwise indicated.

\*P analyzed for X<sup>2</sup> except for analyzed by analysis of variance.

‡P analyzed for X<sup>2</sup> except for analyzed by Kruskal-Wallis test.

†Acute kidney injury is RIFLE class injury or failure. Information on acute kidney injury available on 1341 patients.

RDW, red cell distribution width.

mortality association on the basis of sepsis (p-interaction=0.55), hospital (p-interaction=0.24), acute kidney injury (p-interaction=0.29), year of hospitalization (p-interaction=0.11) or total number of PRBC units transfused (p-interaction=0.85). Additional adjustment of the model for calendar quarter of hospital discharge or LOS did not materially alter the point estimates. Similar robust crude and adjusted discharge RDW-mortality associations are present at 365 days after hospital discharge (data not shown).

We next evaluated the potential correlation between red cell transfusion and increase in RDW in our cohort. A Pearson's product-moment correlation was run to assess the relationship between number of transfused RBC units during hospitalization and the change in RDW from hospital admission to hospital discharge in the cohort (n=1567). There was a very weak positive correlation between number of transfused PRBC units and change in RDW (r=0.08, p=0.0145) with the number of transfused PRBC units explaining only 0.06% of the variation in RDW.

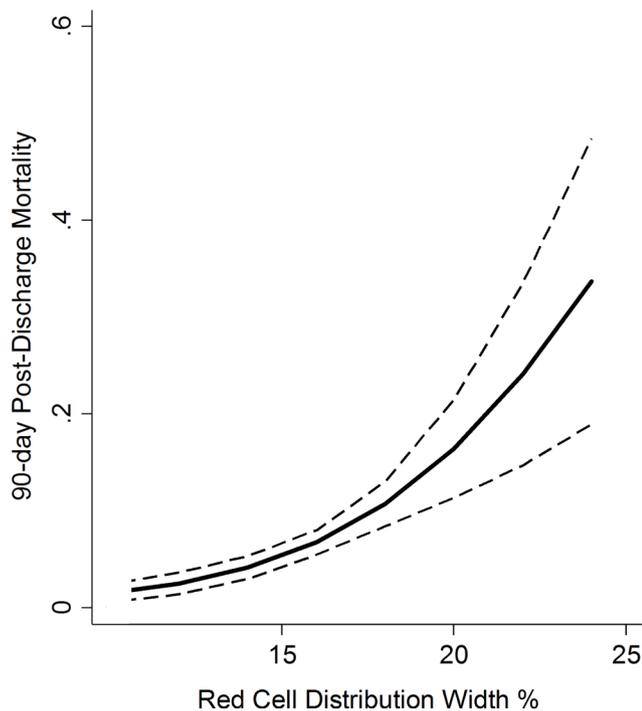
Further, to evaluate the association of the change in RDW during hospitalization and 90-day postdischarge mortality, we studied measures of RDW at hospital admission and at hospital

discharge. In a mixed-effect logistic regression model adjusted for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure, the adjusted odds of 90-day postdischarge mortality is 0.93 (95% CI 0.82 to 1.07) for each 1% increase in RDW during hospitalization (p=0.316) compared with the 90-day postdischarge mortality in the entire cohort. Thus, in our cohort, the change in RDW is not associated with change in adverse outcome after hospital discharge.

We next evaluated discharge RDW stratified by RDW at ICU admission due to our prior findings that RDW at ICU admission is associated with mortality.<sup>13</sup> The data show that the discharge RDW-90-day postdischarge mortality association is preserved after censoring for elevated RDW >17.0% at ICU admission (n=1385). The adjusted ORs of 90-day mortality in the discharge RDW 15.8% to 17.0% and RDW >17.0% groups was 3.5 (95% CI 0.99 to 12.21) and 3.7 (95% CI 1.02 to 13.14), respectively, that of those with RDW ≤13.3%.

### Secondary outcome

The odds of 30-day readmission in the discharge RDW 15.8% to 17.0% and RDW >17.0% groups was 3.3-fold and 2.8-fold,



**Figure 1** Regression coefficient plot representing multivariate estimates of the hospital discharge red cell distribution width 90-day postdischarge mortality association with 95% CIs (dashes). Multivariate estimates adjusted for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure.

respectively, that of those with RDW  $\leq 13.3\%$  (table 4). Discharge RDW remained a significant predictor of odds of readmission after adjustment for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure. The adjusted odds of 30-day readmission in the discharge RDW 15.8% to 17.0% and RDW  $>17.0\%$  groups was 2.3-fold and 1.9-fold, respectively, that of those with RDW  $\leq 13.3\%$  (table 4). Similar robust crude and adjusted discharge RDW readmission associations are present at 90 days after hospital discharge. Further, robust crude and adjusted associations between discharge RDW group and discharge facility are present (table 4).

Finally, we explored the relationship between RDW and LOS. In a negative binomial regression adjusted for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure, we find that for every 1-day increase in LOS, the change of RDW increases by 0.2% (incident rate ratio (IRR) 1.002 (95% CI 1.001 to 1.003)) (figure 2). LOS was next compared with discharge RDW as an exposure in models adjusted by age, gender, race, Deyo-Charlson index, acute organ failures and

sepsis with 90-day postdischarge mortality as the outcome. The discriminatory ability of LOS for 90-day postdischarge mortality as quantified using the c-statistic (AUC=0.729) was less than that of discharge RDW (AUC=0.765) with the difference being significant ( $\chi^2(1)=6.80$ ,  $p=0.0091$ ). This indicates that discharge RDW has significantly superior discrimination than LOS for 90-day postdischarge mortality.

### DISCUSSION

EGS has been shown to confer significant morbidity and mortality, not only during the patient’s hospital stay but also after discharge.<sup>1,2</sup> Therefore, the discovery of predictive factors to stratify EGS patients to better identify those who would benefit from closer follow-up may help prevent adverse outcomes.

There is no current gold standard predictor for mortality after discharge in EGS patients. Our group has identified that patients who are malnourished at the time of ICU admission after EGS have increased 90-day mortality.<sup>3</sup> Although this is a helpful metric that could potentially change management both when in the hospital and in outpatient care, this requires an in-depth evaluation and often the expertise of a dietician. Although increasing age and uninsured status have been found to be correlated with worse outcomes after EGS, these are less specific metrics to use for stratification of patients post-discharge for more intensive follow-up.<sup>4</sup> Therefore, we investigated the potential of RDW as a more specific, one-time laboratory value for use as a prognostic marker for postdischarge mortality.

RDW is a laboratory value that is commonly obtained in postsurgical patients that has prognostic value in multiple disease states. RDW is a precise quantitation of RBC heterogeneity available on virtually all automated hematology analyzers and included in the complete blood count. RDW is a reflection of subtle changes in the red cell volume (mean corpuscular volume (MCV)) and size (anisocytosis). RDW is calculated as the variation in the distribution of RBC volumes divided by the width of the RBC histogram at 1 SD from the mean divided by  $MCV \times 100$  and reported as a percentage. The normal RDW-CV is 11.5% to 14.5%. Variation in size of RBCs (anisocytosis) with a normal MCV occurs in subclinical deficiency of iron, folate or B12, as well as Sickle cell disease, and myelodysplastic syndrome.

An elevated RDW after RBC transfusion reflects the heterogeneity in size of the transfused donor and the recipient RBC populations.<sup>40</sup> Packed RBCs have MCV values in the normal range even during 42 days of storage.<sup>41</sup> After the first 24 hours after transfusion, RBCs commonly survive 90 days.<sup>42</sup> Patients with RBC transfusions can have increases in the RDW if the

**Table 3** Unadjusted and adjusted associations between RDW category and 90-day postdischarge mortality (n=1567)

	$\leq 13.3$	13.3–14.0	14.0–14.7	14.7–15.8	15.8–17.0%	$>17.0\%$	AUC	HL- $\chi^2$	BIC
90-day postdischarge mortality	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p			
Crude	1.00 (referent)*	0.92 (0.20 to 4.17), 0.91	2.20 (0.60 to 8.00), 0.23	2.64 (0.77 to 9.06), 0.12	6.89 (2.08 to 22.87), 0.002	7.93 (2.40 to 26.16), 0.001	0.69	0.99	774
Adjusted†	1.00 (referent)*	0.59 (0.13 to 2.72), 0.50	1.35 (0.36 to 5.11), 0.66	1.58 (0.44 to 5.67), 0.48	3.64 (1.04 to 12.68), 0.043	4.58 (1.32 to 15.93), 0.017	0.77	0.49	801

\*Referent in each case is RDW $\leq 13.3$ .

†Estimates adjusted for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure.

AUC, area under the receiver operating characteristic curve; BIC, Bayesian information criterion; HL- $\chi^2$ , Hosmer-Lemeshow  $\chi^2$  goodness-of-fit test; RDW, red cell distribution width.

**Table 4** Unadjusted and adjusted associations between red blood distribution width (RDW) category, discharge to facility and hospital readmission (n=1567)

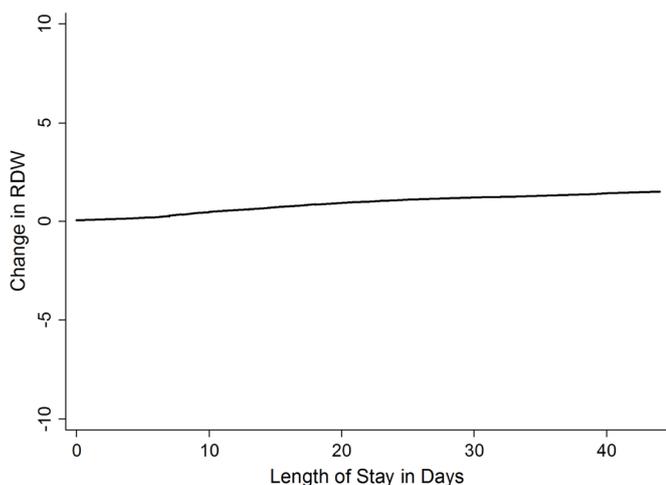
	≤13.3	13.3 to 14.0	14.0 to 14.7	14.7 to 15.8	15.8% to 17.0%	>17.0%
	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), p	OR (95% CI), P	OR (95% CI), p
<b>30-day hospital readmission</b>						
Crude	1.00 (referent)*	1.29 (0.67 to 2.47), 0.44	1.83 (1.00 to 3.36), 0.052	2.79 (1.58 to 4.91), <0.001	3.25 (1.82 to 5.82), <0.001	2.76 (1.54 to 4.97), 0.001
Adjusted†	1.00 (referent)*	1.12 (0.58 to 2.16), 0.74	1.47 (0.78 to 2.76), 0.24	2.19 (1.20 to 3.98), 0.010	2.33 (1.26 to 4.33), 0.007	1.91 (1.02 to 3.58), 0.043
<b>90-day hospital readmission</b>						
Crude	1.00 (referent)*	1.89 (1.07 to 3.33), 0.028	2.48 (1.44, 4.26), 0.001	3.39 (2.02 to 5.68), <0.001	4.29 (2.53 to 7.28), <0.001	3.60 (2.11 to 6.12), <0.001
Adjusted†	1.00 (referent)*	1.60 (0.90 to 2.86), 0.11	1.94 (1.10, 3.41), 0.022	2.51 (1.46 to 4.32), 0.001	2.90 (1.66 to 5.09), <0.001	2.30 (1.31 to 4.06), 0.004
<b>Discharge to facility</b>						
Crude	1.00 (referent)*	2.61 (1.40 to 4.85), 0.002	4.35 (2.40 to 7.86), <0.001	5.63 (3.18 to 9.97), <0.001	7.66 (4.27 to 13.73), <0.001	7.43 (4.14 to 13.31), <0.001
Adjusted†	1.00 (referent)*	1.65 (0.85 to 3.19), 0.14	2.17 (1.15 to 4.10), 0.017	2.54 (1.37 to 4.71), 0.003	3.03 (1.61 to 5.69), 0.001	2.99 (1.58 to 5.64), 0.001

\*Referent in each case is RDW≤13.3.

†Estimates adjusted for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure.

MCV of the donor and recipient cells are different. Patients with a normal MCV and no anisocytosis should not have an increase in RDW after RBC transfusion as the MCV of transfused cells is normal.

An elevated RDW is indicative of impaired erythropoiesis. Therefore, it is a secondary marker of inflammation, malnutrition, or impaired renal function, as inadequate production of erythropoietin can lead to elevated RDW.<sup>43</sup> As such, this marker has generated interest as a biomarker for cardiovascular conditions including coronary artery disease, peripheral vascular disease, and stroke.<sup>8,9,44</sup> Furthermore, elevated RDW at the onset of critical care has been linked to an increased risk of 30-day mortality, and elevated RDW at discharge after critical illness has been shown to be correlated with increased mortality 30 days after discharge.<sup>5,13</sup> Therefore, as EGS often involves a combination of critical illness, malnutrition, and inflammation, RDW is a logical potential biomarker to help predict postdischarge mortality in this cohort.



**Figure 2** Change in red cell distribution width (RDW) versus length of stay. Locally weighted scatter plot smoothing used to represent the association between the length of stay and change in RDW.

Our study demonstrates that those patients in the two highest quintiles of RDW values had a significantly increased odds of 90-day mortality, 6.9-fold and 7.9-fold of those in the lowest quintile. This remained a significant predictor of mortality after adjustment for age, race, gender, Deyo-Charlson Index, sepsis and number of organs with acute failure. Moreover, those patients in the top two quintiles of RDW had a significantly increased risk of 30-day readmission as compared with those in the lowest quartile. This shows a clear correlation between elevated RDW in the EGS patient cohort and increased post-discharge morbidity and mortality. Although it is unclear as to the direct mechanism of this correlation, it is likely that RDW is a bellwether for ongoing inflammation and malnutrition in these patients that leads to worse outcomes. The benefit of using this particular metric is that it requires a single lab draw at discharge that is likely being performed for other reasons in these patients. Therefore, it is a quick and easily interpretable value that can change the patient's postdischarge follow-up to flag complications early and prevent increased mortality.

This study has several methodological strengths that include the use of a previously validated approaches to the definition of EGS,<sup>16</sup> comorbidities,<sup>18-20</sup> acute organ failure<sup>22</sup> and sepsis.<sup>17</sup> Additionally, all-cause mortality was analyzed using a validated method based on the Social Security Administration Death Master File, allowing for the determination of patients survival status after hospital discharge.<sup>14</sup> We have sufficient power to detect a clinically relevant difference in 90-day post-discharge mortality. All cohort patients under study had vital status follow-up for at least 365 days.

The limitations of this study must also be considered. As with all observational studies, these data may be limited by potential confounding, reverse causation and the lack of randomly distributed exposure. Despite adjustment for multiple potential confounders, it is possible that residual confounding contributed to adverse outcomes in our cohort. Due to study design, our ability to make causal inference is limited. Finally, although we adjusted for a severity of illness score that has similar performance to Acute Physiology and Chronic Health Evaluation II score,<sup>45</sup> we were unable to directly adjust for

physiologic-based severity of illness scores which are strong predictors of critical illness outcome.<sup>46</sup>

In summary, RDW is an easily interpretable, cost-effective metric that can help predict postdischarge mortality in patients who undergo EGS. This biomarker can be used to stratify patients to identify those high-risk patients who may benefit from closer follow-up to avoid further morbidity and mortality after discharge. Further studies are required to better delineate the underlying mechanism of this correlation and the clinical impact of using this metric in practice. Furthermore, the mechanism of this correlation is particularly important to analyze whether this is a clinically modifiable factor which could have therapeutic value in addition to prognostic value.

**Acknowledgements** This article is dedicated to the memory of our dear friend and colleague Nathan Edward Hellman, MD, PhD. The authors thank Shawn Murphy and Henry Chueh and the Partners HealthCare Research Patient Data Registry group for facilitating use of their database.

**Contributors** JMH, AS and KBC contributed equally to the conception and design. JMH, AJS and KBC contributed equally to the acquisition, analysis and interpretation of data. All authors drafted and critically revised the manuscript and read and given final approval for the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent** Not required.

**Ethics approval** Partners Human Research Committee Institutional Review Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- Gale SC, Shafi S, Dombrovskiy VY, Arumugam D, Crystal JS. The public health burden of emergency general surgery in the United States: a 10-year analysis of the Nationwide Inpatient Sample – 2001 to 2010. *J Trauma Acute Care Surg* 2014;77:202–8.
- Watt DG, Wilson MS, Shapter OC, Patil P. 30-Day and 1-year mortality in emergency general surgery laparotomies: an area of concern and need for improvement? *Eur J Trauma Emerg Surg* 2015;41:369–74.
- Havens JM, Columbus AB, Seshadri AJ, Olufajo OA, Mogensen KM, Rawn JD, Salim A, Christopher KB. Malnutrition at intensive care unit admission predicts mortality in emergency general surgery patients. *JPEN J Parenter Enteral Nutr* 2016;014860711667659.
- Shah AA, Haider AH, Zogg CK, Schwartz DA, Haut ER, Zafar SN, Schneider EB, Velopulos CG, Shafi S, Zafar H, Efron DT. National estimates of predictors of outcomes for emergency general surgery. *J Trauma Acute Care Surg* 2015;78:482–91.
- 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;42:918–29.
- Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, Kang KW, Kim J, Rhee JE. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. *Am J Emerg Med* 2013;31:545–8.
- Ozsu S, Abul Y, Gunaydin S, Orem A, Ozlu T. Prognostic value of red cell distribution width in patients with pulmonary embolism. *Clin Appl Thromb Hemost* 2014;20:365–70.
- Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. for the Cholesterol and Recurrent Events (CARE) Trial Investigators. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation* 2008;117:163–8.
- Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB. CHARM Investigators. 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;50:40–7.
- Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. *Injury* 2007;38:1336–45.
- Hivert MF, Grant RW, Shrader P, Meigs JB. Identifying primary care patients at risk for future diabetes and cardiovascular disease using electronic health records. *BMC Health Serv Res* 2009;9:170.
- Hug BL, Lipsitz SR, Seger DL, Karson AS, Wright SC, Bates DW. Mortality and drug exposure in a 5-year cohort of patients with chronic liver disease. *Swiss Med Wkly* 2009;139:737–46.
- 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;39:1913–21.
- Zager S, Mendu ML, Chang D, Bazick HS, Braun AB, Gibbons FK, Christopher KB. Neighborhood poverty rate and mortality in patients receiving critical care in the academic medical center setting. *Chest* 2011;139:1368–79.
- Evans TC, Jehle D. The red blood cell distribution width. *J Emerg Med* 1991;9(Suppl 1):71–4.
- Scott JW, Olufajo OA, Brat GA, Rose JA, Zogg CK, Haider AH, Salim A, Havens JM. Use of national burden to define operative emergency general surgery. *JAMA Surg* 2016;151:e160480.
- Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion* 2005;20:83–90.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
- Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82.
- Rapoport J, Gehlbach S, Lemeshow S, Teres D. Resource utilization among intensive care patients. Managed care vs traditional insurance. *Arch Intern Med* 1992;152:2207–12.
- Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
- Beier K, Eppanapally S, Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of "normal" creatinine. *Crit Care Med* 2011;39:305–13.
- Müller MC, Juffermans NP. Anemia and blood transfusion and outcome on the intensive care unit. *Crit Care* 2010;14:438. author reply 438.
- Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, et al. Red cell distribution width and mortality in older adults: a meta-analysis. *J Gerontol Ser A Biol Sci Med Sci* 2010;65:258–65.
- Casey K, Hernandez-Boussard T, Mell MW, Lee JT. Differences in readmissions after open repair versus endovascular aneurysm repair. *J Vasc Surg* 2013;57:89–95.
- Martin RC, Brown R, Puffer L, Block S, Callender G, Quillo A, Scoggins CR, McMasters KM. Readmission rates after abdominal surgery: the role of surgeon, primary caregiver, home health, and subacute rehab. *Ann Surg* 2011;254:591–7.
- Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res* 1998;18:555–9.
- Bateman AP, McArdle F, Walsh TS. Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Crit Care Med* 2009;37:1906–12.
- Rogiers P, Zhang H, Leeman M, Nagler J, Neels H, Mélot C, Vincent JL. Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997;23:159–62.
- Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA* 2010;303:849–56.
- Semba RD, Patel KV, Ferrucci L, Sun K, Roy CN, Guralnik JM, Fried LP. Serum antioxidants and inflammation predict red cell distribution width in older women: the Women's Health and Aging Study I. *Clin Nutr* 2010;29:600–4.
- Jann B. Plotting regression coefficients and other estimates. *Stata J* 2014;14:708–37.
- Cleveland W. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc* 1979;74:829–36.
- Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. *J Am Stat Assoc* 1988;83:596–610.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
- Hedeker D. A mixed-effects multinomial logistic regression model. *Stat Med* 2003;22:1433–46.
- Hartzel J, Agresti A, Caffo B. Multinomial logit random effects models. *Stat Modelling* 2001;1:81–102.



- 39 Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, Perera R, Primrose JN, Mant D. Blood CEA levels for detecting recurrent colorectal cancer. *Cochrane Database Syst Rev* 2015;CD011134.
- 40 Bessman JD, Gilmer PR, Gardner FH. Improved classification of anemias by MCV and RDW. *Am J Clin Pathol* 1983;80:322–6.
- 41 Pertinhez TA, Casali E, Baroni F, Berni P, Baricchi R, Spisni A. A comparative study of the effect of leukoreduction and pre-storage leukodepletion on red blood cells during storage. *Front Mol Biosci* 2016;3:13.
- 42 Luten M, Roerdinkholder-Stoelwinder B, Bost HJ, Bosman GJ. Survival of the fittest? Survival of stored red blood cells after transfusion. *Cell Mol Biol* 2004;50:197–203.
- 43 Montagnana M, Danese E. Red cell distribution width and cancer. *Ann Transl Med* 2016;4:399.
- 44 Isik T, Ayhan E, Kurt M, Tanboga IH, Kaya A, Aksakal E. Is red cell distribution width a marker for the presence and poor prognosis of cardiovascular disease? *Eurasian J Med* 2012;44:169–71.
- 45 Elias KM, Moromizato T, Gibbons FK, Christopher KB. Derivation and validation of the acute organ failure score to predict outcome in critically ill patients: a cohort study. *Crit Care Med* 2015;43:856–64.
- 46 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.