Clinical Research in Cardiology (2020) 109:616–627
https://doi.org/10.1007/s00392-019-01549-0

ORIGINAL PAPER

Association between anemia and hematological indices with mortality among cardiac intensive care unit patients

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Received: 2 July 2019 / Accepted: 11 September 2019 / Published online: 18 September 2019

Abstract

Background Anemia and elevated red cell distribution width (RDW) or mean corpuscular volume (MCV) are associated with an adverse prognosis in patients with cardiovascular disease and critical illness. Limited data exist regarding these associations in unselected cardiac intensive care unit (CICU) patients.

Methods Retrospective cohort study of CICU patients between January 1, 2007, and December 31, 2015, with a hemoglobin (Hb) level measured at admission. Multivariable regression was performed to determine predictors of hospital mortality, and Kaplan–Meier analysis was used to determine post-discharge survival.

Results We included 9644 patients with a mean age of 67.5 ± 15.1 years, including 3604 (37.4%) females. The median (IQR) values of Hb, MCV and RDW were 12.2 g/dL (10.6, 13.7), 90.7 fL (87.3, 94.2) fL, and 14.1% (13.3, 15.8), respectively. Anemia (admission Hb < 12 g/dL) was present in 4434 (46%) patients. A total of 845 (8.8%) patients died in the hospital. Patients with anemia had higher hospital mortality (11.3% vs. 6.6%, unadjusted OR 1.82, 95% CI 1.58–2.10, $p < 0.001$). After multivariable regression, admission Hb and MCV were not significantly associated with hospital mortality (both $p > 0.1$), while admission RDW (adjusted OR 1.12 per 1%, 95% CI 1.07–1.18, $p < 0.001$) was significantly associated with hospital mortality. Hospital survivors with lower Hb, higher MCV, or higher RDW had lower post-discharge survival.

Conclusion Elevated RDW on admission was independently associated with higher hospital mortality in CICU patients. These data emphasize the importance of hematologic abnormalities for mortality risk stratification in CICU populations.

Hamza A. Rayes and Jacob C. Jentzer contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-019-01549-0) contains supplementary material, which is available to authorized users.

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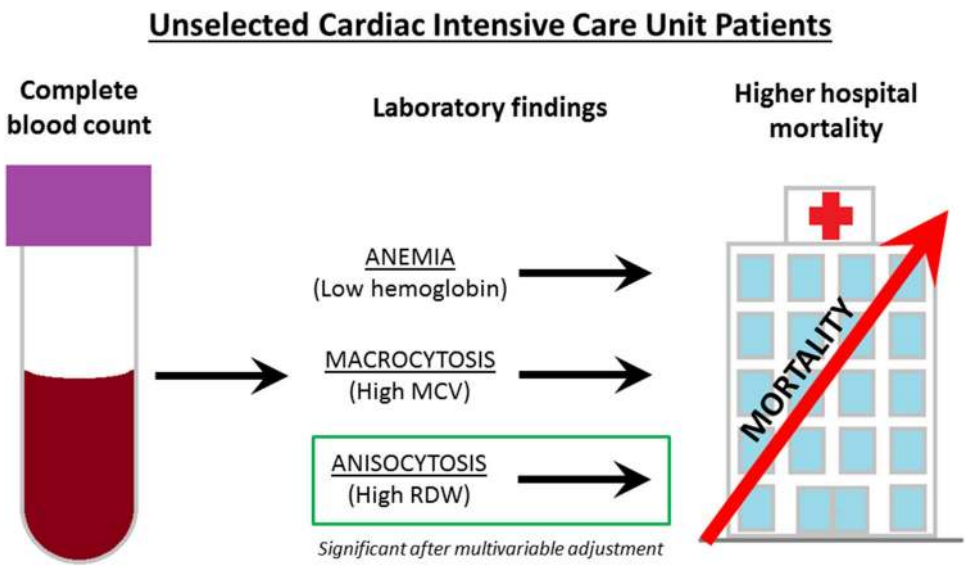
Graphic abstract



Keywords Red cell distribution width · Anemia · Mean corpuscular volume · Cardiac intensive care unit · Coronary care unit · Mortality

Introduction

Anemia is common among acutely ill cardiac patients, with a prevalence of up to 19% and up to 48% among patients with acute coronary syndrome (ACS) and acute heart failure (HF), respectively [1, 2]. Anemia is an independent predictor of adverse cardiovascular events, bleeding, and mortality in patients with acute cardiac disease [1–5]. In addition, abnormal values of hematological indices, including red cell distribution width (RDW) and mean corpuscular volume (MCV) have also been associated with worse outcome in patients with acute cardiac disease [6–12]. In general intensive care unit (ICU) populations, the presence of anemia has been associated with demand myocardial ischemia, ICU readmission, and increased mortality [13–15]. As in patients with cardiac disease, elevated RDW and MCV are also associated with worse outcomes in general ICU patients [16–18].

Despite the growing similarities between the cardiac intensive care unit (CICU) and medical ICU populations, CICU patients remain distinct due to their more prevalent cardiac comorbidities [19]. It remains uncertain whether predictors of mortality in general ICU patients without acute cardiac disease or in non-ICU patients with acute cardiac disease would apply similarly to the specialized CICU population. There is a paucity of published data available to describe the association between anemia, RDW, and MCV and adverse outcomes in CICU patients. This study was designed to test the hypothesis that anemia and abnormal values of RDW and MCV are associated with higher mortality in CICU patients.

Methods

Study population

This study was approved by the Institutional Review Board of Mayo Clinic as posing minimal risk to patients and was conducted under a waiver of informed consent (IRB # 16-000722). We retrospectively analyzed a database of consecutive unique adult (aged ≥ 18 years) patients admitted to the CICU at Mayo Clinic Hospital St. Mary's Campus whose entire CICU admission occurred between January 1, 2007, and December 31, 2015, as previously reported [20–22]. We only analyzed data from the first CICU admission during the study period to avoid mortality bias associated with CICU readmissions. According to Minnesota state law statute 144.295, patients must provide authorization to be included in observational research studies; patients who did not have Minnesota Research Authorization were excluded from the database. Patients who did not have available data for admission hemoglobin (Hb) level were excluded from this study.

Data sources

Demographic, vital sign, laboratory, and other clinical and outcome data were extracted electronically from the medical

record, including procedures and therapies performed during the CICU and hospital stay. The admission value of all vital signs, clinical measurements, and laboratory values was used, defined as either the first value recorded after CICU admission or the value recorded closest to CICU admission. Although the WHO defines anemia as an admission Hb level < 12 g/dL in women and < 13 g/dL in men, we chose an operational definition of anemia as admission Hb < 12 g/dL regardless of gender [23]. Microcytosis was defined as an MCV < 80 fL and macrocytosis was defined as an MCV > 100 fL [23]. The Acute Physiology and Chronic Health Evaluation (APACHE)-III score, APACHE-IV predicted hospital mortality and Day 1 Sequential Organ Failure Assessment (SOFA) score were calculated for all patients using data from the first 24 h of CICU admission, with missing variables imputed as normal as the default; the mean and maximum values of all daily SOFA scores while the patient remained in the CICU were recorded [20–22, 24, 25]. The Charlson Comorbidity Index (CCI) and individual comorbidities were determined based on a previously-validated electronic algorithm [26]. Discharge diagnoses were identified using International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes, these diagnoses were not mutually exclusive, and the primary discharge diagnosis could not be determined.

Statistical analysis

The primary outcome was all-cause hospital mortality, and the secondary outcomes were CICU mortality and 5-year post-discharge mortality, based on the electronic review of the medical record. Groups were compared using Student *t* test and ANOVA for continuous variables and Pearson Chi-square test for categorical variables. Logistic regression was used to calculate the unadjusted odds ratio (OR) and 95% confidence interval (CI) values for hospital mortality. Optimal cutoffs for predicting hospital mortality were determined from receiver-operator characteristic curves based on the highest value of Youden's J index (sensitivity + specificity −1). Multivariable analysis was performed to determine adjusted OR values for hospital mortality using an adaptive elastic net penalized logistic regression model, with candidate variables including demographics, comorbidities, illness severity, and CICU therapies and complications; an interaction term between Hb and RDW was included in the model [27]. Optimal tuning parameters for the elastic net were selected by linear grid search in conjunction with tenfold cross-validation to maximize the AUROC. Kaplan–Meier survival analysis was used to compare 5-year post-discharge survival among patients surviving to hospital discharge (hospital survivors), with groups compared using the log-rank test. Cox proportional-hazards analysis was used to determine the associations between Hb, MCV, and RDW with post-discharge mortality after adjusting for predictors of hospital mortality. Two-tailed p values < 0.05 were considered statistically significant. Statistical analyses were performed using JMP version 13.0 Pro (SAS Institute, Cary, NC).

Results

Study population and baseline characteristics

We screened 12,904 CICU admissions and excluded 2900 as previously described, leaving 10,004 patients in the database [20–22]. An additional 360 patients were further excluded due to lack of available data on admission Hb level, leaving 9644 patients in the final study population (Supplemental Fig. 1). The median age of the study population was 69.1 years (IQR 57.8, 78.9) and comprised 3604 (37.4%) females. The median CCI was 2 (IQR 0, 4), with a median APACHE-III score of 58 (IQR 45, 74) corresponding to a median APACHE-IV predicted mortality of 9.5% (IQR 4.0, 22.8). The median admission Hb level was 12.2 g/dL (IQR 10.6, 13.7); 4434 (46.0%) patients met our operational definition of anemia (admission Hb < 12 g/dL), while 5402 (56.0%) met the WHO gender-specific definition of anemia (46.3% of women and 53.7% of men). Data on MCV were available in 9409 (97.5%) patients (Supplemental Fig. 1), and the median MCV was 90.7 fL (IQR 87.3, 94.2). Data on RDW were available in 9405 (97.5%) patients (Supplemental Fig. 1), and the median RDW was 14.1% (IQR 13.3, 15.6). Patients with anemia were older, more frequently female, had higher rates of comorbidities, greater illness severity and increased utilization of CICU therapies (all $p < 0.05$) compared to patients without anemia (Table 1); in addition, patients with anemia were more likely to have a discharge diagnosis of HF and less likely to have a discharge diagnosis of ACS. Significant differences were observed in baseline characteristics, comorbidities, illness severity and CICU therapies across RDW quartiles, reflecting higher illness severity, more extensive comorbidities, lower Hb and greater use of CICU therapies in patients with higher RDW (Supplemental Table 1); the prevalence of HF increased and the prevalence of ischemic heart disease decreased with rising RDW quartile. Patients with a discharge diagnosis of HF had lower Hb (11.7 vs. 12.4 g/dL) and higher RDW (15.7% vs. 14.2%), while patients with a discharge diagnosis of ACS had higher Hb (12.5 vs. 11.9 g/dL) and lower RDW (14.1% vs. 15.3%) (all $p < 0.001$); MCV differed minimally between these groups.

Table 1 Baseline characteristics of the study population, patients with and without anemia (admission hemoglobin < 12 g/dL)

	Overall population ($n=9644$)	Patients without anemia ($n=5210$)	Patients with anemia ($n=4434$)	p value
Demographics				
Age	67.5 ± 15.1	64.8 ± 15.0	70.6 ± 14.7	< 0.001
Female gender	3604 (37.4%)	1448 (27.8%)	2156 (48.6%)	< 0.001
White race	8911 (92.4%)	4860 (93.3%)	4051 (91.4%)	< 0.001
BMI (kg/m^2)	29.6 ± 7.0	29.8 ± 6.8	29.3 ± 7.3	< 0.001
CICU length of stay	2.6 ± 4.6	2.4 ± 4.1	2.8 ± 5.2	< 0.001
Hospital length of stay	8.1 ± 13.3	6.4 ± 9.0	10.0 ± 16.9	< 0.001
CICU mortality	519 (5.4%)	229 (4.4%)	290 (6.5%)	< 0.001
Hospital mortality	845 (8.8%)	342 (6.6%)	503 (11.3%)	< 0.001
Severity of illness				
APACHE-III score	61.7 ± 25.2	56.3 ± 24.8	68.0 ± 24.2	< 0.001
APACHE-IV predicted mortality	0.172 ± 0.202	0.142 ± 0.193	0.207 ± 0.206	< 0.001
Day 1 SOFA score	3.6 ± 3.2	3.1 ± 3.1	4.3 ± 3.3	< 0.001
Maximum week 1 SOFA score	4.1 ± 3.4	3.5 ± 3.2	4.8 ± 3.5	< 0.001
Mean week 1 SOFA score	3.1 ± 2.7	2.6 ± 2.5	3.6 ± 2.8	< 0.001
Comorbidities				
Charlson comorbidity index	2.4 ± 2.6	1.7 ± 2.2	3.2 ± 2.9	< 0.001
Prior myocardial infarction	1919 (19.9%)	923 (17.8%)	996 (22.5%)	< 0.001
Prior heart failure	1901 (19.5%)	709 (13.6%)	1192 (26.9%)	< 0.001
Prior stroke	1179 (12.3%)	508 (9.8%)	671 (15.2%)	< 0.001
Prior chronic kidney disease	1971 (20.5%)	603 (11.6%)	1368 (30.9%)	< 0.001
Prior diabetes mellitus	2752 (28.6%)	1163 (22.4%)	1589 (35.9%)	< 0.001
Prior cancer	2053 (21.3%)	868 (16.7%)	1185 (26.8%)	< 0.001
Prior lung disease	1880 (19.5%)	835 (16.1%)	1045 (23.6%)	< 0.001
Prior liver disease	190 (2.0%)	64 (1.2%)	126 (2.8%)	< 0.001
Prior dialysis	562 (5.8%)	144 (2.8%)	418 (9.4%)	< 0.001
Discharge ICD-9 diagnoses				
Shock	1032 (10.7%)	454 (8.7%)	578 (13.0%)	< 0.001
Cardiogenic shock	809 (8.4%)	390 (7.5%)	419 (9.5%)	< 0.001
Cardiac arrest	769 (8.0%)	427 (8.2%)	342 (7.7%)	0.38
Acute coronary syndrome	4143 (43.0%)	2574 (49.5%)	1569 (35.4%)	< 0.001
Heart failure	3778 (39.2%)	1617 (31.1%)	2161 (48.8%)	< 0.001
Atrial fibrillation	3076 (31.9%)	1380 (26.5%)	1696 (38.3%)	< 0.001
Any organ failure	3471 (36.0%)	1388 (26.7%)	2083 (47.0%)	< 0.001
Multi-organ failure	1549 (16.1%)	607 (11.7%)	942 (21.3%)	< 0.001
Respiratory failure	1845 (19.1%)	812 (15.6%)	1033 (23.3%)	< 0.001
Acute kidney injury	2013 (20.9%)	666 (12.8%)	1347 (30.4%)	< 0.001
Sepsis	649 (6.7%)	186 (3.6%)	463 (10.4%)	< 0.001
Gastrointestinal bleeding	398 (4.1%)	104 (2.0%)	294 (6.6%)	< 0.001
Acute blood loss anemia	452 (4.7%)	135 (2.6%)	317 (7.2%)	< 0.001
Procedural bleeding	725 (7.5%)	341 (6.6%)	384 (8.7%)	< 0.001
Therapies and procedures				
Invasive ventilator	1581 (16.4%)	774 (14.9%)	807 (18.2%)	< 0.001
Noninvasive ventilator	1474 (15.3%)	635 (12.2%)	839 (18.9%)	< 0.001
Vasoactive drugs	2407 (25.0%)	1136 (21.8%)	1271 (28.7%)	< 0.001
> 1 vasoactive drug	1148 (11.9%)	522 (10.0%)	626 (14.1%)	< 0.001
Dialysis	479 (5.0%)	160 (3.1%)	319 (7.2%)	< 0.001
Coronary angiogram	5092 (52.8%)	3182 (61.1%)	1910 (43.1%)	< 0.001
PCI	3345 (34.7%)	2124 (40.8%)	1221 (27.5%)	< 0.001
Intra-aortic balloon pump	854 (8.9%)	483 (9.3%)	371 (8.4%)	0.12

Table 1 (continued)

	Overall population ($n=9644$)	Patients without anemia ($n=5210$)	Patients with anemia ($n=4434$)	p value
Pulmonary artery catheter	721 (7.5%)	339 (6.5%)	382 (8.6%)	<0.001
Red blood cell transfusion	1170 (12.1%)	198 (3.8%)	972 (21.9%)	<0.001
Admission laboratory values				
Admission hemoglobin (g/dL)	12.1 ± 2.1	13.7 ± 1.3	10.3 ± 1.2	<0.001
Admission MCV (fL)	90.7 ± 6.0	90.8 ± 5.2	90.6 ± 6.9	0.06
Microcytosis (MCV < 80 fL)	354 (3.7%)	94 (1.8%)	258 (6.0%)	<0.001
Macrocytosis (MCV > 100 fL)	526 (5.6%)	207 (4.1%)	391 (7.4%)	<0.001
Admission RDW (%)	14.8 ± 2.2	14.0 ± 1.6	15.6 ± 2.5	<0.001

Data represented as mean ± standard deviation for continuous variables and number (percent) for categorical variables. p value is for the comparison of patients with and without anemia, using the Student's t test for continuous variables and Chi-squared test for categorical variables

APACHE acute physiology and chronic health evaluation, *BMI* body mass index, *CICU* cardiac intensive care unit, *ICD* International Classification of Diseases, *MCV* mean corpuscular volume, *PCI* percutaneous coronary intervention, *RDW* red cell distribution width, *SOFA* sequential organ failure assessment

Unadjusted hospital mortality

A total of 519 (5.4%) patients died in the CICU, and 845 (8.8%) patients died in the hospital. Unadjusted CICU mortality was higher in patients with anemia (6.5% vs. 4.4%, unadjusted OR 1.52, 95% CI 1.28–1.82, $p<0.001$), as was unadjusted hospital mortality (11.3% vs. 6.6%, unadjusted OR 1.82, 95% CI 1.58–2.10, $p<0.001$). Similar results were observed when using the WHO gender-specific definition of anemia: both CICU mortality (6.4% vs. 4.1%, unadjusted OR 1.58, 95% CI 1.31–1.90, $p<0.001$) and hospital mortality (10.8% vs. 6.2%, unadjusted OR 1.84, 95% CI 1.58–2.14, $p<0.001$) were higher in patients with anemia. There was a stepwise increase in hospital mortality with decreasing admission Hb: ≥ 12 g/dL, 6.6%; 10.0–11.9 g/dL, 10.1%; 8.0–9.9 g/dL, 13.0%; < 8 g/dL 16.4% ($p<0.001$). Admission Hb was inversely associated with hospital mortality (unadjusted OR 0.87 per 1 g/dL, 95% CI 0.84–0.90, $p<0.001$), with an optimal cutoff of 11.5 g/dL for predicting hospital mortality. The unadjusted OR value for admission Hb was 0.84 per 1 g/dL (95% CI 0.78–0.90) among patients with anemia and 1.08 per 1 g/dL (95% CI 1.00–1.17) in patients without anemia, reflecting a U-shaped relationship between admission Hb and mortality (Fig. 1). Admission MCV was positively associated with hospital mortality (unadjusted OR 1.04

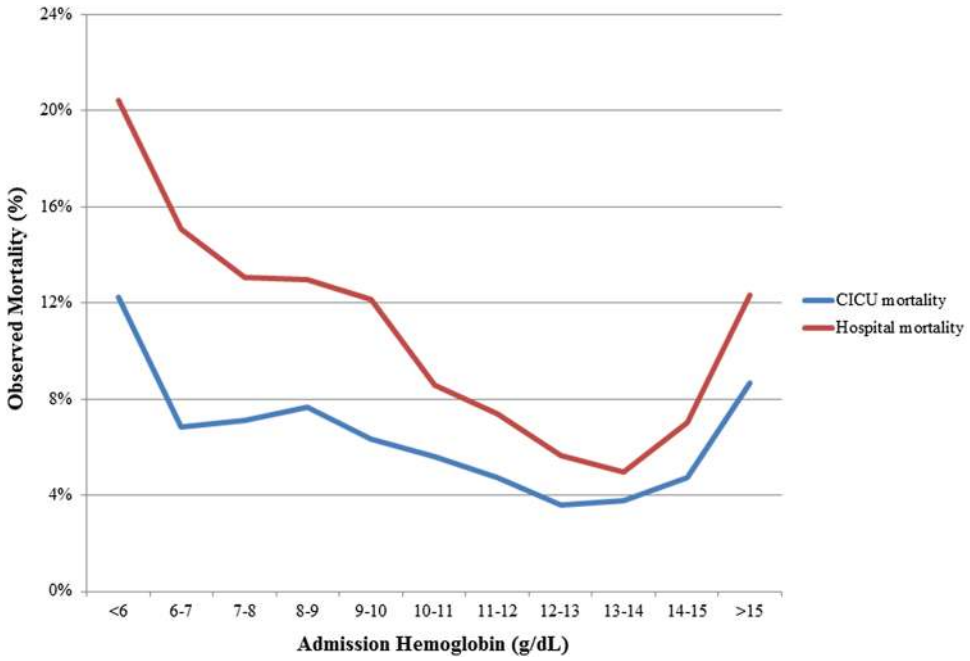


Fig. 1 CICU and hospital mortality as a function of admission hemoglobin. $p<0.001$ for both CICU and hospital mortality across groups using Chi-squared test. *CICU* cardiac intensive care unit

per 1 fL, 95% CI 1.02–1.05 $p < 0.001$), with an optimal cutoff of 94.6 fL for predicting hospital mortality. This relationship was similar among patients with anemia (OR 1.03 per 1 fL, 95% CI 1.02–1.05) and patients without anemia (OR 1.04 per 1 fL, 95% CI 1.01–1.06). A J-shaped relationship was observed between admission MCV and mortality (Fig. 2a); the MCV was associated with hospital mortality in patients with and without anemia, with mortality being highest in patients with macrocytic anemia (Fig. 2b). Admission RDW was positively associated with hospital mortality (unadjusted OR 1.20 per 1%, 95% CI 1.17–1.23, $p < 0.001$), with an optimal cutoff of 14.3% for predicting hospital mortality. This association that appeared to be stronger in patients without anemia (unadjusted OR 1.34 per 1%, 95% CI 1.28–1.41) compared to patients with anemia (unadjusted OR 1.11 per 1%, 95% CI 1.08–1.15). A progressive increase in mortality was observed with increasing decile of RDW, both in patients with and without anemia (Fig. 3).

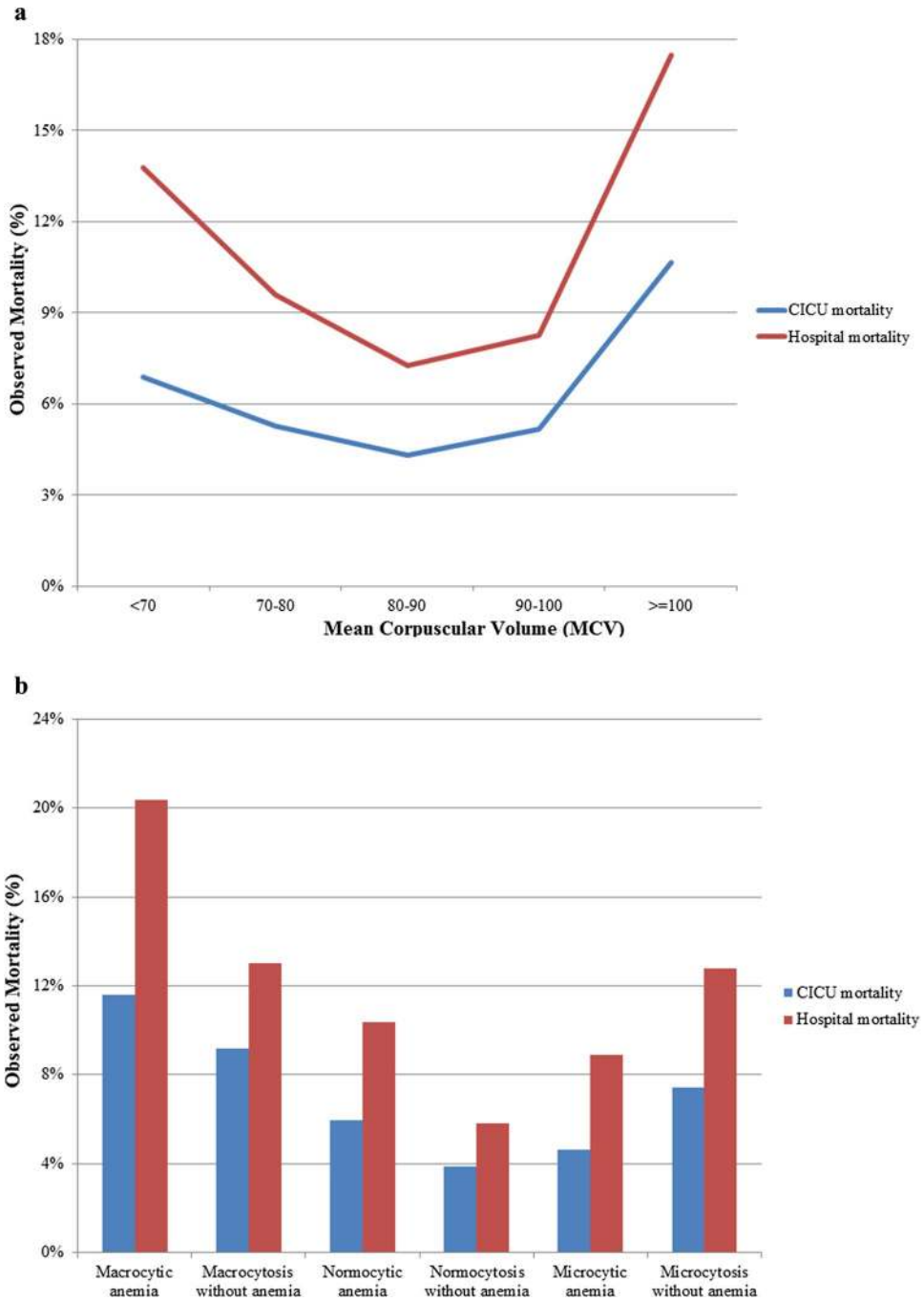


Fig. 2 **a** CICU and hospital mortality as a function of admission MCV. $p < 0.001$ for both CICU and hospital mortality across groups using Chi-squared test. *CICU* cardiac intensive care unit, *MCV* mean corpuscular volume. **b** CICU and hospital mortality in patients with microcytosis (MCV < 80 fL), macrocytosis (MCV > 100 fL) and normocytosis (MCV 80–100 fL), with and without anemia. $p < 0.001$ for both CICU and hospital mortality between groups using Chi-squared test. *CICU* cardiac intensive care unit, *MCV* mean corpuscular volume

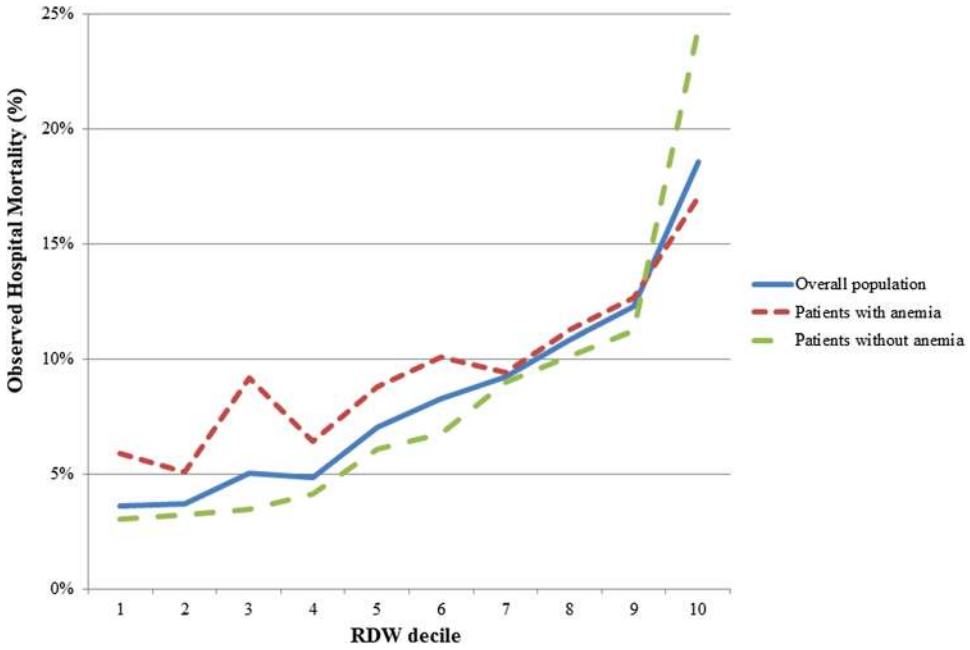


Fig. 3 Hospital mortality as a function of admission RDW decile in the overall population, patients with anemia, and patients without anemia. $p < 0.001$ for hospital mortality trends across RDW declines in each group. *RDW* red cell distribution width

Adjusted hospital mortality

On multivariable regression adjusting for demographics, comorbidities, vital signs, laboratory data, discharge diagnoses and APACHE-III score (Table 2), neither admission Hb level nor anemia (both $p > 0.99$) was associated with hospital mortality. Likewise, admission MCV (adjusted OR 1.01 per 1 fL, 95% CI 1.00–1.03, $p = 0.11$) was not significantly associated with hospital mortality. By contrast, admission RDW remained strongly associated with hospital mortality after multivariable adjustment (adjusted OR 1.15 per 1%, 95% CI 1.10–1.21, $p < 0.001$). There was a positive statistical interaction between admission Hb and RDW ($p = 0.005$).

Post-discharge survival

Among 8799 (91.2%) patients surviving to hospital discharge, 3537 (40.2%) died during a mean follow-up of 3.4 years; 1229 (14.0%) hospital survivors had post-discharge follow-up less than 1 year, including loss to follow-up. Post-discharge survival decreased in a stepwise fashion as a function of decreasing quartile of admission Hb (Fig. 4a, $p < 0.001$ by log-rank). Post-discharge survival differed based on the presence or absence of anemia and the admission MCV (Fig. 4b, $p < 0.001$ by log-rank); survival was highest among patients with normocytosis or microcytosis without anemia and lowest among patients with macrocytic anemia. Post-discharge survival decreased in a stepwise fashion as a function of increasing quartile of admission Hb (Fig. 4c, $p < 0.001$ by log-rank). On Cox proportional-hazards analysis adjusting for predictors of hospital mortality (Table 2), admission Hb (adjusted HR 0.92 per 1 g/dL, 95% CI 0.90–0.94), MCV (adjusted HR 1.02 per 1 fL, 95% CI 1.01–1.02), and RDW (adjusted HR per 1% 1.13, 95% CI 1.11–1.15) were all significantly ($p < 0.001$) associated with post-discharge mortality among hospital survivors.

Discussion

To our knowledge, this is the largest study to examine the associations between hematologic indices with hospital and post-discharge mortality in unselected CICU patients. Anemia (admission Hb < 12 g/dL) was present in almost 50% of patients in this CICU population and predicted higher unadjusted hospital and post-discharge mortality. Admission Hb demonstrated a reverse J-shaped relationship with hospital mortality, but this relationship did not persist after multivariable adjustment. Admission MCV showed a J-shaped association with hospital mortality, and patients with macrocytic anemia were at higher risk of hospital and post-discharge death. An elevated admission RDW was associated with higher hospital and post-discharge mortality, and RDW remained a significant predictor of hospital mortality after multivariable adjustment. The association between RDW and mortality was influenced by the presence or absence of anemia, as evidenced by the significant statistical interaction term on multivariable regression. The relationship between RDW and mortality appeared stronger in patients without anemia, suggesting that elevated RDW was a relevant prognostic factor and not merely a marker of anemia. Admission Hb, MCV, and RDW were all significantly associated with adjusted post-discharge mortality among hospital survivors. Patients with HF had lower Hb and higher RDW, as opposed

Table 2 Predictors of hospital mortality using multivariable regression using an adaptive elastic net penalty algorithm and predictors of post-discharge mortality using Cox proportional-hazards analysis

Variable	Inpatient mortality (regression)			Post-discharge mortality (Cox)		
	Adjusted OR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
Comorbidities and severity of illness						
Age (per 1 year)	1.03	1.02–1.04	< 0.001	1.03	1.02–1.03	< 0.001
Inpatient days prior to CICU	1.01	0.98–1.03	0.63	1.00	0.98–1.01	0.63
Charlson Comorbidity Index	1.02	0.98–1.07	0.31	1.12	1.10–1.14	< 0.001
Prior stroke	1.04	0.74–1.44	0.83	1.02	0.91–1.14	0.74
APACHE-III score (per 1 unit)	1.02	1.02–1.03	< 0.001	1.01	1.00–1.01	< 0.001
Admission vital signs						
Systolic BP (per 1 mmHg)	1.00	0.99–1.00	0.13	1.00	1.00–1.00	0.02
Heart rate (per 1 BPM)	1.01	1.00–1.01	0.02	1.00	1.00–1.00	0.01
Respiratory rate (per 1 BPM)	1.01	0.99–1.03	0.47	1.01	1.00–1.02	0.02
Admission laboratory values						
Hemoglobin (per 1 g/dL)*	––	––	––	0.92	0.90–0.94	< 0.001
MCV (per 1 fL)	1.01	1.00–1.03	0.11	1.02	1.01–1.02	< 0.001
RDW (per 1%)	1.15	1.10–1.21	< 0.001	1.13	1.11–1.15	< 0.001
Anion gap (per 1 mEq/L)	1.04	1.01–1.07	0.008	0.99	0.98–1.00	0.21
Chloride (per 1 mEq/L)	0.96	0.94–0.98	< 0.001	0.97	0.96–0.98	< 0.001
Neutrophil count (per 1000/mm^3)	1.03	1.01–1.07	0.002	1.00	0.99–1.01	0.89
BUN (per 1 mg/dL)	1.01	1.00–1.01	0.06	1.00	1.00–1.01	< 0.001
Procedures and therapies						
# vasoactive drugs (per 1 drug)	1.45	1.30–1.62	< 0.001	1.04	0.98–1.11	0.17
Dialysis in CICU	2.00	1.35–2.96	< 0.001	1.58	1.33–1.88	< 0.001
Pulmonary artery catheter	0.75	0.51–1.09	0.14	0.86	0.73–1.02	0.08
Coronary angiogram	0.93	0.70–1.23	0.59	0.91	0.82–1.01	0.08
PCI	0.74	0.54–1.01	0.05	0.80	0.71–0.89	< 0.001
Discharge ICD9 diagnoses						
Shock	1.32	0.94–1.85	0.11	0.96	0.82–1.13	0.66
Hypertension	0.55	0.43–0.70	< 0.001	0.84	0.77–0.91	< 0.001
Cardiomyopathy	0.76	0.56–1.04	0.08	1.02	0.90–1.16	0.73
Heart failure	0.82	0.63–1.06	0.14	1.26	1.14–1.39	< 0.001
Atrial fibrillation	0.79	0.63–1.01	0.06	1.10	1.01–1.20	0.03
Cardiac arrest	3.56	2.59–4.89	< 0.001	1.00	0.82–1.20	0.96
Acute coronary syndrome	1.08	0.79–1.48	0.63	1.08	0.97–1.21	0.17
Coronary artery disease	0.69	0.53–0.90	0.007	0.94	0.85–1.04	0.22
Acute kidney injury	1.06	0.81–1.37	0.69	1.02	0.91–1.12	0.75
Respiratory failure	2.21	1.68–2.90	< 0.001	1.18	1.06–1.32	0.003
Procedural bleeding	1.47	0.97–2.23	0.07	0.82	0.69–0.97	0.02

Adjusted odds ratio (OR) and 95% confidence interval (CI) values are shown

APACHE acute physiology and chronic health evaluation, *BUN* blood urea nitrogen, *CICU* cardiac intensive care unit, *MCV* mean corpuscular volume, *PCI* percutaneous coronary intervention, *RDW* red cell distribution width

*Admission Hb was not selected for inclusion in the final regression model for hospital mortality

to patients with ACS, implying an association between myocardial dysfunction and these hematologic abnormalities. These data emphasize the importance of easily-available hematologic laboratory data for risk stratification of CICU patients and highlight the interactions between hematologic abnormalities and acute cardiovascular disease outcomes.

Anemia has been associated with adverse outcomes across a broad spectrum of patients with acute cardiovascular disease and critical illness [1–5, 15]. We observed the same curvilinear relationship between admission Hb and unadjusted hospital mortality in our CICU population, as was previously reported in ACS patients [4]. However, after

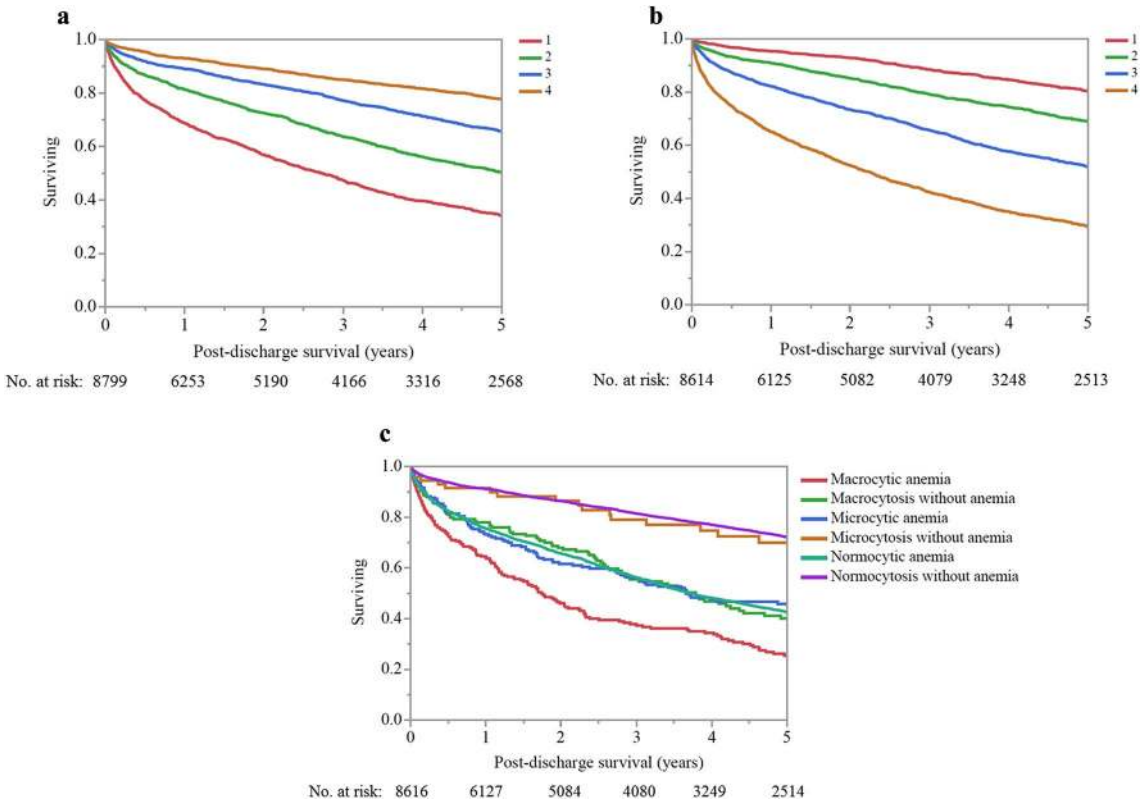


Fig. 4 **a** Kaplan–Meier curves demonstrating post-hospital survival among hospital survivors, grouped by admission hemoglobin quartile, based on a median of 12.2 (IQR 10.6–13.7) g/dL. $p < 0.001$ between groups by log-rank. **b** Kaplan–Meier curves demonstrating post-hospital survival among hospital survivors, grouped by RDW quartile based on a mean RDW of 14.1% (IQR 13.3–15.6). $p < 0.001$ between groups by log-rank. RDW, red cell distribution width. **c** Kaplan–Meier curves demonstrating post-hospital survival among hospital survivors, grouped by admission MCV and the presence of anemia (admission hemoglobin < 12 g/dL). $p < 0.001$ between groups by log-rank. *MCV* mean corpuscular volume

multivariable adjustment we did not observe an association between admission Hb and hospital mortality in this large CICU population, potentially suggesting that anemia may be a marker of sicker CICU patients rather than a directly pathological entity in many cases [15]. Our findings imply that acutely raising the Hb level, for instance by transfusion, may not necessarily reduce mortality in CICU patients, consistent with prior studies that have failed to demonstrate improved outcomes using higher Hb thresholds for transfusion among patients with acute cardiovascular disease [28]. This highlights the importance of ongoing studies such as the Myocardial Ischemia and Transfusion trial (MINT, NCT02981407) to define the role of transfusion in acutely-ill cardiac patients with anemia.

Unlike our results for hospital mortality, a lower admission Hb was associated with higher post-discharge mortality among hospital survivors. A prior study by Uscinska, et al. found that lower Hb levels and decreased markers of iron stores were associated with lower long-term survival in their cohort of 392 CICU patients [7]. Anemia and iron deficiency have been identified as relevant prognostic variables and important targets for therapy in patients with HF [29, 30]. Chronic iron deficiency typically produces microcytosis with an elevated RDW, although macrocytosis can be seen during acute blood loss due to regenerative reticulocytosis [30]. In our CICU population, macrocytosis appeared to be more strongly associated with adverse outcomes than microcytosis, raising important questions about the underlying pathophysiology that drives the associations between anemia, MCV and outcomes.

The association between MCV and mortality has not been previously explored in unselected CICU patients, and our results suggest that an elevated MCV is more significantly associated with post-discharge than hospital mortality. Huang et al. demonstrated an association between higher MCV and higher RDW with increased unadjusted hospital mortality among acute MI patients in the ICU; as in our study, Hb levels were associated with unadjusted mortality but not adjusted mortality [12]. The mean corpuscular Hb concentration was inversely related to adjusted hospital mortality in their population, and RDW was associated with adjusted 1-year mortality. Similarly, Ueda et al.

demonstrated that an elevated MCV is associated with mortality among patients with acute HF [6]. Prior studies have shown associations between elevated MCV with mortality and ICU readmission in other ICU populations [14, 16]. Bazick et al. previously demonstrated a higher MCV to be associated with increased hospital mortality in a cohort of 51,143 mixed ICU patients (including 15% with MI and 22% with HF), after performing multivariable adjustment [16]. Numerous potential pathophysiologic mechanisms may explain the association between elevated MCV and adverse outcomes, including altered hematopoiesis due to intrinsic bone marrow abnormalities, organ dysfunction, drugs, toxins, and nutritional deficiency which may influence macrocyte morphology and produce concomitant cytopenias [23]. An elevated MCV may represent myelodysplastic syndrome or clonal hematopoiesis of indeterminate potential (CHIP), the latter of which has been associated with an increased risk of cardiovascular events and highlighted as a potent emerging cardiovascular risk factor [31, 32].

RDW was one of the most significant predictors of the adjusted hospital and post-discharge mortality in this CICU cohort and appeared to be more strongly associated with mortality among patients without anemia, even though patients with anemia had higher RDW. These findings in a mixed CICU population may be expected given the consistent association between an elevated RDW and increased mortality in patients with acute cardiovascular disease and general ICU patients [9–11, 14, 16–18]. A prior study by Hu, et al. demonstrated an association between elevated RDW with hospital mortality and AKI in 412 CICU patients, even after adjustment for illness severity and other variables, higher RDW was associated with lower long-term survival [8]. These authors found a positive correlation between RDW and the APACHE-II score, suggesting that RDW correlates with illness severity yet provides additional prognostic value. Prior studies in patients with acute myocardial infarction have consistently demonstrated that an elevated RDW is associated with higher mortality, even after adjustment for relevant risk scores [10]. Similar associations between elevated RDW and death have been reported in patients with acute HF, including patients with and without anemia [9]. In one of the largest studies examining RDW in critically ill patients, Bazick et al. reported a strong independent relationship between RDW and mortality [16]. As in our study, patients with elevated RDW were older, had greater comorbidities, more frequently had sepsis, had a worse renal function and lower Hb levels, and had a higher prevalence of organ failure.

Several potential hypotheses have been proposed to explain the association between elevated RDW and mortality, which is undoubtedly multifactorial and likely mediated by higher illness severity and worse underlying cardiac substrate [9, 10, 16, 17]. The factors which may drive both altered hematopoiesis and adverse outcomes include increased inflammation or oxidative stress (as suggested by studies showing correlations between RDW and C-reactive protein) and the effects of multi-organ dysfunction (including AKI) and baseline comorbidities on bone marrow function and hematopoiesis [9, 10, 15–17]. While an elevated RDW clearly portends higher hospital and post-discharge mortality risk independent of anemia, it remains uncertain how to leverage this information to optimize treatment for CICU patients.

Limitations

This study has a number of relevant limitations that apply similarly to other retrospective cohort analyses, particularly the potential for additional unmeasured confounding variables. The CICU population at Mayo Clinic may differ from other populations in terms of baseline demographics and case mix [19]. We focused on admission laboratory values to predict mortality and were not able to determine whether changes in these variables during hospitalization influenced mortality risk. We did not have data available on pre-admission laboratory values, prior hematologic abnormalities, preceding transfusion, blood cell morphology, hemolysis, reticulocytosis, bleeding, iron studies, or vitamin levels. This prevented us from determining the causes and chronicity of anemia, elevated MCV, or elevated RDW in our patients, and from defining how these hematologic abnormalities may have led to higher mortality. Likewise, we did not have echocardiographic data available to better elucidate the relationships between HF and myocardial dysfunction with abnormal hematologic parameters. Our post-discharge mortality analysis should be considered exploratory, as the use of electronic health record review to determine patient death may underestimate post-discharge mortality by potentially failing to capture patients dying in other health systems. We did not have data available to determine cause of death, preventing us from providing specific insights about the mechanisms that could have linked abnormal hematologic indices with mortality risk.

Conclusions

Anemia is common among CICU patients and is associated with higher unadjusted short-term and long-term mortality, but this relationship seems to be mediated primarily by illness severity and comorbidities. By contrast, elevated RDW was strongly associated with higher hospital mortality after adjusting for relevant covariates, as shown in other populations of cardiac and ICU patients. Anemia, MCV, and RDW were able to risk-stratify post-discharge mortality among hospital survivors. Incorporation of RDW into

future severity of illness scores may be useful for enhancing mortality risk stratification. Future studies are needed to understand the relationship between RDW and outcomes in CICU patients to determine whether RDW reflects specific underlying pathophysiology or simply greater illness severity and to better define the underlying pathophysiology linking abnormal hematopoiesis and outcomes in patients with acute cardiovascular disease.

Acknowledgements The authors would like to acknowledge the dedicated physicians, nurses and allied health staff comprising the multidisciplinary team that cares for our CICU patients each day.

Funding No extramural funding was involved in the conduct of this research.

Compliance with ethical standards

Conflict of interest The authors report no relevant conflicts of interest.

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