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ORIGINAL RESEARCH

CRITICAL CARE CARDIOLOGY

Admission Total Leukocyte Count as a Predictor of Mortality in Cardiac Intensive Care Unit Patients

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ABSTRACT

BACKGROUND Inflammation is a sequela of cardiovascular critical illness and a risk factor for mortality.

OBJECTIVES This study aimed to evaluate the association between white blood cell count (WBC) and mortality in a broad population of patients admitted to the cardiac intensive care unit (CICU).

METHODS This retrospective cohort study included patients admitted to the Mayo Clinic CICU between 2007 and 2018. We analyzed WBC as a continuous variable and then categorized WBC as low ($<4.0 \times 10^3$/mL), normal (≥ 4.0 to $<11.0 \times 10^3$/mL), high (≥ 11.0 to $<22.0 \times 10^3$/mL), or very high ($\geq 22.0 \times 10^3$/mL). The association between WBC and in-hospital mortality was evaluated using multivariable logistic regression and random forest models.

RESULTS We included 11,699 patients with a median age of 69.3 years (37.6% females). Median WBC was 9.6 (IQR: 7.4-12.7). Mortality was higher in the low (10.5%), high (12.0%), and very high (33.3%) WBC groups relative to the normal WBC group (5.3%). A rising WBC was incrementally associated with higher in-hospital mortality after adjustment (AICc adjusted OR: 1.03 [95% CI: 1.02-1.04] per 1×10^3 increase in WBC). After adjustment, only the high (AICc adjusted OR: 1.37 [95% CI: 1.15-1.64]) and very high (AICc adjusted OR: 1.99 [1.47-2.71]) WBC groups remained associated with increased risk of in-hospital mortality.

CONCLUSIONS Leukocytosis is associated with an increased mortality risk in a diverse cohort of CICU patients. This readily available marker of systemic inflammation may be useful for risk stratification within the increasingly complex CICU patient population. (JACC Adv 2024;3:100757) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CA = cardiac arrest

CICU = cardiac intensive care unit

CS = cardiogenic shock

HF = heart failure

ICD = International Classification of Diseases

MI = myocardial infarction

NLR = neutrophil to lymphocyte ratio

SIRS = systemic inflammatory response syndrome

WBC = white blood cell count

Inflammation is an important pathophysiologic mechanism associated with adverse outcomes in patients admitted with acute cardiovascular disease or general critical illness.[1-3] A dysregulated systemic inflammatory response is hypothesized to play an integral role in several cardiovascular critical illness syndromes, including acute myocardial infarction (MI), decompensated heart failure (HF), cardiac arrest (CA), and cardiogenic shock (CS).[4-8] Research on novel inflammatory biomarkers and specific inflammatory pathway targets has yielded several promising investigative biomarkers, but these have not yet been routinely incorporated into clinical practice.[9] Therefore, identification of readily-available surrogate biomarkers for inflammation that predict prognosis in patients with cardiac critical illness is imperative.

Leukocytosis, defined as an elevated white blood cell count (WBC), is a simple marker of systemic inflammation and physiologic stress that has been associated with adverse outcomes in critically ill patient populations.[10] Leukocytosis has also been identified as a risk factor for mortality in specific subgroups of patients with acute cardiovascular disease, such as MI, HF, and CS.[10-12] However, little is known about the association between the WBC and outcomes across the spectrum of cardiac critical illness within the contemporary cardiac intensive care unit (CICU) patient population. Therefore, we sought to determine whether this readily available biomarker can facilitate prognostication in the modern CICU.

METHODS

STUDY POPULATION. This study was approved by the Mayo Clinic Institutional Review Board under a waiver of informed consent due to its minimal risk to patients. We included consecutive unique adults admitted to the Mayo Clinic CICU from January 1, 2007, to April 30, 2018, who had provided consent for their medical records to be used for research.[13,14] We excluded patients without available data for admission WBC value, which was defined as the WBC value recorded closest to CICU admission. We performed a subgroup analysis for patients in whom a complete admission WBC differential, which provides quantification of those cell lines which comprise the total WBC, was available.

DATA SOURCES. We electronically extracted demographic, clinical, and laboratory data from the medical record. Admission laboratory values were defined as the value closest to CICU admission or the first value after CICU admission. Missing data were excluded from the analysis; no imputation was performed. Except for lactate, discussed further below, variables with >50% missingness were excluded from the analysis. The Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation-III/IV scores, CICU Admission Risk Score (M-CARS), and Charlson Comorbidity Index were calculated using previously validated electronic algorithms.[13,15-18] Admission diagnoses were defined as all International Classification of Diseases-9/-10 diagnosis codes recorded within 1 day of CICU admission and were not mutually exclusive.[16] All-cause CICU and in-hospital mortality were extracted from the medical record.

CATEGORICAL WBC GROUPS. Patients were grouped according to the normal laboratory range for WBC count: low WBC ($<4.0 \times 10^3$/mL, leukopenia), normal WBC (≥ 4.0 to $<11.0 \times 10^3$/mL), high WBC (≥ 11.0 to $<22.0 \times 10^3$/mL, leukocytosis), and very high WBC ($\geq 22.0 \times 10^3$/mL, severe leukocytosis). WBC differential subgroups were similarly defined using the normal laboratory range, with the very high group being defined as a value greater than twice the upper limit of the normal range (Supplemental Table 1).

STATISTICAL ANALYSIS. Summary statistics were calculated as median (IQR) for continuous variables and number (percent) for categorical variables. Groups were compared using the Wilcoxon rank-sum test (continuous variables) or Pearson chi-square test (categorical variables). OR and 95% IQR CI values for the primary outcome of in-hospital mortality were estimated using logistic regression before and after multivariable adjustment. For continuous variables, we provided unit OR values; the WBC unit OR is reported per 1×10^3/mL increase in WBC. Candidate covariates for multivariable regression models included demographic, clinical, and laboratory variables.

To evaluate the association between WBC and in-hospital mortality, we built a series of multivariable logistic regression models using different approaches to variable selection. First, we used traditional stepwise regression with forward variable selection and backward variable elimination to minimize the value of the corrected Akaike Information Criterion (AICc, more inclusive) and then repeated this stepwise regression to minimize the value of the Bayesian Information Criterion (more parsimonious). Second, we used adaptive machine learning-based penalized regression models, specifically the Least Absolute Shrinkage and Selection Operator (more

TABLE 1 Patient Characteristics, Hospital Course, Admission Diagnosis, Admission Labs

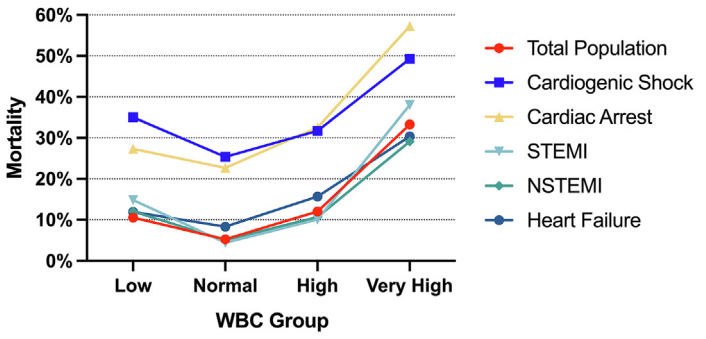
	Low (n = 247) (WBC <4)	Normal (n = 7,075) (WBC ≥4 & <11)	High (n = 3,962) (WBC ≥11 & <22)	Very High (n = 415) (WBC ≥ 22)	*P* Value
Patient characteristics					
Age, y	66.7 (56.9-77.0)	69.9 (58.8-79.5)	68.2 (56.7-78.5)	69.9 (57.7-79.0)	<0.001[a]
Female	104 (42.1)	2,636 (37.3)	1,494 (37.7)	150 (38.3)	0.46
Caucasian	216 (87.5)	6,530 (92.3)	3,687 (93.1)	381 (91.8)	0.01[a]
Hospital days prior to CICU	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	<0.001[a]
Day 1 SOFA	4 (2-6)	2 (1-4)	3 (1-6)	7 (4-10)	<0.001[a]
Comorbidity score	3 (1-5)	2 (0-4)	1 (0-3)	2 (0-4)	<0.001[a]
APACHE IV mortality prediction	0.10 (0.05-0.24)	0.08 (0.04-0.17)	0.12 (0.05-0.29)	0.40 (0.16-0.66)	<0.001[a]
MCARS	2 (1-3)	1 (0-3)	2 (1-4)	5 (3-7)	<0.001[a]
Braden score	18 (16-20)	18 (16-20)	17 (15-20)	14 (12-17)	<0.001[a]
Hospital course					
Dialysis in CICU	24 (9.7)	315 (4.5)	188 (4.8)	38 (9.2)	<0.001[a]
Invasive ventilation	33 (13.4)	702 (9.9)	994 (25.1)	227 (54.7)	<0.001[a]
Noninvasive ventilation	37 (15.0)	1,007 (14.2)	736 (18.6)	104 (25.1)	<0.001[a]
Intubation in CICU	6 (2.4)	155 (2.2)	212 (5.4)	34 (8.3)	<0.001[a]
In-hospital cath	125 (50.6)	4,056 (57.3)	2,459 (62.1)	217 (52.3)	<0.001[a]
In-hospital PCI	47 (19.0)	2,344 (56.9)	1,602 (40.4)	128 (30.8)	<0.001[a]
Vasoactive med use	72 (29.2)	1,523 (21.5)	1,139 (28.8)	222 (53.5)	<0.001[a]
pRBC transfusion	37 (15.0)	675 (9.5)	550 (13.9)	103 (24.8)	<0.001[a]
PAC in ICU	44 (17.8)	723 (10.2)	332 (8.4)	66 (15.9)	<0.001[a]
ICU IABP	14 (5.7)	519 (7.3)	421 (10.6)	63 (15.2)	<0.001[a]
In-hospital arrest	5 (2.0)	123 (1.8)	128 (3.3)	28 (6.8)	<0.001[a]
Admission diagnosis					
HF	134 (54.7)	3,410 (48.5)	1,960 (50.1)	240 (58.0)	0.001[a]
Cardiac arrest	22 (9.0)	546 (7.8)	644 (16.5)	164 (39.6)	<0.001[a]
Shock	32 (13.1)	660 (9.4)	858 (21.9)	190 (45.9)	<0.001[a]
Cardiogenic shock	20 (8.2)	524 (7.5)	701 (17.9)	150 (36.2)	<0.001[a]
Respiratory failure	66 (26.9)	1,214 (17.3)	1,312 (33.5)	252 (60.9)	<0.001[a]
ACS	52 (21.2)	2,588 (36.8)	2,102 (53.7)	207 (50.0)	<0.001[a]
STEMI	27 (10.9)	1,420 (20.1)	1,343 (34.1)	121 (29.2)	<0.001[a]
Non-STEMI	25 (10.2)	1,168 (16.6)	759 (19.3)	86 (20.8)	<0.001[a]
Sepsis	25 (10.2)	279 (4.0)	344 (8.8)	109 (26.3)	<0.001[a]
Admission labs					
WBC	3.3 (2.7-3.7)	8.0 (6.6-9.4)	13.6 (12.1-16.0)	26.0 (23.6-29.9)	<0.001[a]
Hemoglobin	10.5 (9.3-12.0)	12.0 (10.6-13.5)	12.5 (10.7-14.0)	12.0 (10.0-14.1)	<0.001[a]
Platelets	122.0 (76.0-169.0)	189.0 (151.0-233.0)	222.0 (178.0-275.0)	258.0 (185.0-332.0)	<0.001[a]
Sodium	138.0 (135.0-141.0)	139.0 (136.0-141.0)	138.0 (135.0-140.0)	137.0 (134.0-140.0)	<0.001[a]
Potassium	4.1 (3.7-4.5)	4.2 (3.9-4.6)	4.2 (3.9-4.7)	4.3 (3.8-4.9)	<0.001[a]
Bicarbonate	24.0 (22.0-27.0)	24.0 (22.0-27.0)	23.0 (20.0-25.0)	21.0 (18.0-24.0)	<0.001[a]
Creatinine	1.1 (0.8-1.6)	1.0 (0.8-1.4)	1.1 (0.8-1.5)	1.3 (0.9-1.7)	<0.001[a]
Anion gap	11.0 (9.0-14.0)	12.0 (9.0-14.0)	13.0 (10.0-15.0)	15.0 (12.0-17.0)	<0.001[a]
Albumin	3.3 (2.8-3.7)	3.4 (3.0-3.8)	3.3 (2.8-3.7)	3.0 (2.6-3.5)	<0.001[a]
Bilirubin	0.7 (0.5-1.4)	0.6 (0.4-1.0)	0.6 (0.4-1.0)	0.6 (0.4-1.1)	0.03[a]
ALT	22.0 (15.0-43.0)	28.0 (19.0-48.0)	39.0 (23.0-84.0)	61.5 (29.3-166.8)	<0.001[a]
Lactate	1.4 (0.9-2.6)	1.4 (1.0-2.2)	1.9 (1.3-3.3)	2.9 (1.6-4.9)	<0.001[a]
Initial troponin T	0.07 (0.00-0.27)	0.12 (0.02-0.67)	0.33 (0.07-1.50)	0.33 (0.09-1.5)	<0.001[a]

Values are median (IQR) or n (%). [a]$P \leq 0.05$.

ALT = alanine aminotransferase; ACS = acute coronary syndrome; APACHE = Acute Physiology and Chronic Health Evaluation; CICU = cardiac intensive care unit; HF = heart failure; IABP = intra-aortic balloon pump; ICU = intensive care unit; MCARS = Mayo Cardiac Intensive Care Unit Admission Risk Score; NSTEMI = non-ST-segment elevation myocardial infarction; PAC = pulmonary arterial catheter; PCI = percutaneous coronary intervention; pRBC = packed red blood cell; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; STEMI = ST-segment elevation myocardial infarction; WBC = white blood cell.

parsimonious) and the elastic net (more inclusive), both with 10-fold cross-validation to optimize the tuning parameters to maximize the area under the receiver-operator characteristic (C-statistic) value. For the subgroup analysis, the variables selected by the minimum AICc model were used to adjust the models containing WBC differential components; to facilitate comparison between these WBC differential

FIGURE 1 WBC Group Mortality by Admission Diagnosis



This figure demonstrates the unadjusted mortality in the admission diagnosis subgroup at each WBC subgroup. NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; WBC = white blood cell.

components, the values were standardized before regression to report an OR per 1 SD higher.

Subsequently, random forest models were built utilizing admission laboratory values alone, including total WBC and WBC differential components, and variable importance factors were evaluated to determine the strength of association between different laboratory values and mortality. These random forest models each contained 1,000 trees with 8 terms sampled per split. The maximum and minimum splits per tree were 2,000 and 10, respectively. The population was split into derivation (75%) and validation (25%) cohorts to optimize the performance of each random forest model, with performance from the validation cohort reported. Each variable's contribution to the random forest model is ranked according to G^2 test (the likelihood-ratio chi-square test). Statistical analyses were performed using JMP Statistical Software (Version 16.0.0, SAS Institute).

RESULTS

STUDY POPULATION. Out of 12,106 unique CICU patient-admissions, we included the 11,699 patients with available WBC data. Of the final study population, 10,195 (87.1%) had a complete WBC differential. A consortium diagram in accordance with the STROBE guidelines is provided as Supplemental Figure 1. This final study population had a median age of 69.3 years, 37.6% were female, and 92.4% identified as White. The median admission WBC was 9.6 $\times$ 10^3/mL (IQR: 7.4-12.7). The distribution of WBC groups was as follows: low WBC (leukopenia), 247 (2.1%); Normal WBC, 7,075 (60.5%); high WBC (leukocytosis), 3,962 (33.9%); and very high WBC (severe leukocytosis), 415 (3.5%). The WBC groups differed in most baseline characteristics, with higher illness severity, more critical care diagnoses, and greater utilization of critical care therapies as the WBC increased (Table 1). An admission diagnosis of sepsis was present in 26.3% of patients in the very high WBC group, compared to 4.0% of patients in the normal WBC group.

IN-HOSPITAL MORTALITY-UNADJUSTED ANALYSES OF CONTINUOUS WBC. In-hospital mortality occurred in 1,015 (8.7%) patients, including 616 (5.3%) who died during the CICU stay. The median WBC was higher in the hospital mortality group than the survivor group (12.6 $\times$ 10^3/mL [IQR: 8.8-17.6] vs 9.4 $\times$ 10^3/mL [IQR: 7.3-12.3], $P < 0.001$). The relationship between WBC and in-hospital mortality was curvilinear, demonstrating a J-shaped association. Overall, a higher WBC was incrementally associated with an increased risk of in-hospital mortality (unadjusted OR per 1 $\times$ 10^3 higher: 1.08; 95% CI: 1.07-1.09). Treating WBC as a quadratic polynomial improved the R^2 value for in-hospital mortality, and both WBC and WBC^2 were significantly associated with in-hospital mortality on logistic regression; this remained true after model adjustment with covariates selected by the minimum AICc model discussed further below. Our use of logistic regression to model the curvilinear association between WBC and mortality may be imperfect, but we note that despite the J-shaped association between WBC and mortality the prevalence and strength of association between high WBC and mortality resulted in a net direct association between WBC and mortality overall. Restricted cubic spline analysis demonstrated knot points of 4.9 $\times$ 10^3/mL and 10.0 $\times$ 10^3/mL, which were close to the upper and lower limits of the normal laboratory range.

IN-HOSPITAL MORTALITY-UNADJUSTED ANALYSES OF WBC GROUPS. In the total population, patients with normal WBC had the lowest mortality (reference group), followed by those with low WBC, high WBC, and very high WBC, as depicted in Supplemental Table 2 and Supplemental Figure 2. This association was maintained across all admission diagnoses (Figure 1), although in the STEMI admission diagnosis group, the mortality of the low WBC group exceeded that of the high WBC group.

IN-HOSPITAL MORTALITY-MULTIVARIABLE ANALYSES. The results of the multivariable logistic regression models are summarized in Table 2, and the final models were generally similar regardless of the variable selection method. All the multivariable models selected WBC for inclusion and demonstrated significant associations between WBC and adjusted in-hospital mortality. Adjusted unit OR values were

TABLE 2 Multivariable Regression Models

	Stepwise AICc ROC AUC: 0.91	Stepwise BIC ROC AUC: 0.91	Adaptive LASSO (KFold 10) ROC AUC: 0.91	Adaptive Elastic Net (KFold 10) ROC AUC: 0.91
Admission WBC (per 1 × 10^3/mL unit)	1.03 (1.02-1.04)[c]	1.03 (1.02-1.04)[c]	1.02 (1.01-1.03)[c]	1.02 (1.02-1.03)[c]
Admission: cardiac arrest	3.29 (2.67-4.06)[c]	3.19 (2.60-3.92)[c]	3.34 (2.65-4.21)[c]	3.26 (2.59-4.11)[c]
Dialysis in ICU	2.94 (2.26-3.83)[c]	2.87 (2.22-3.72)[c]	2.79 (2.04-3.81)[c]	2.86 (2.07-3.95)[c]
In-hospital arrest	2.57 (1.83-3.60)[c]	2.57 (1.83-3.61)[c]	2.26 (1.48-3.46)[b]	2.40 (1.56-3.69)[b]
Admission: shock	2.09 (1.70-2.56)[c]	2.17 (1.79-2.65)[c]	2.08 (1.63-2.64)[c]	2.05 (1.62-2.60)[c]
Intubation in CICU	2.09 (1.56-2.78)[c]	2.09 (1.57-2.78)[c]	2.00 (1.40-2.84)[c]	2.06 (1.43-2.96)[b]
Admission: respiratory failure	1.86 (1.53-2.27)[c]	1.94 (1.60-2.35)[c]	1.84 (1.48-2.29)[c]	1.86 (1.49-2.31)[c]
Vasoactive medication use	1.34 (1.23-1.45)[c]	1.32 (1.22-1.43)[c]	1.33 (1.20-1.46)[c]	1.34 (1.22-1.47)[c]
Admission: ACS	1.21 (1.00-1.47)	-	1.18 (0.95-1.47)	1.15 (0.93-1.43)
Admission: sepsis	1.22 (0.96-1.54)	-	1.15 (0.87-1.51)	1.15 (0.87-1.52)
Female	1.18 (1.00-1.39)	-	1.12 (0.94-1.34)	1.15 (0.96-1.38)
Day 1 SOFA	1.12 (1.09-1.16)[c]	1.13 (1.10-1.16)[c]	1.13 (1.09-1.17)[c]	1.12 (1.08-1.16)[c]
Hospital days prior to CICU	1.05 (1.03-1.07)[c]	1.05 (1.03-1.07)[c]	1.05 (1.01-1.07)[c]	1.04 (1.02-1.06)[b]
Comorbidity score	1.05 (1.02-1.08)[c]	-	1.04 (1.01-1.08)[b]	1.04 (1.01-1.08)
Age	1.03 (1.02-1.03)[c]	1.03 (1.02-1.03)[c]	1.03 (1.02-1.03)[c]	1.03 (1.02-1.03)[c]
PAC in ICU	-	-	0.99 (0.75-1.30)	-
ESRD on HD	-	-	-	0.95 (0.69-1.32)
Braden score	0.87 (0.84-0.89)[c]	0.86 (0.84-0.89)[c]	0.87 (0.84-0.90)[c]	0.86 (0.83-0.89)[c]
pRBC transfusion	0.76 (0.61-0.94)[a]	-	0.75 (0.59-0.95)[a]	0.83 (0.65-1.05)
Caucasian	0.69 (0.52-0.92)[a]	-	0.73 (0.53-1.01)	0.79 (0.57-1.09)
In-hospital PCI	0.67 (0.53-0.83)[c]	0.70 (0.56-0.86)[c]	0.69 (0.55-0.88)[b]	0.70 (0.55-0.89)[a]
In-hospital cath	0.54 (0.45-0.66)[c]	0.55 (0.45-0.66)[c]	0.55 (0.45-0.67)[c]	0.54 (0.44-0.66)[c]
Invasive ventilation	0.45 (0.35-0.59)[c]	0.42 (0.33-0.55)[c]	0.50 (0.36-0.68)[c]	0.45 (0.33-0.61)[c]
Noninvasive ventilation	-	-	-	-
Admission: HF	-	-	-	-
ICU IABP	-	-	-	-
Year of ICU admission	-	-	-	-

Values are OR (95% CI). [a]$P < 0.05$. [b]$P < 0.01$. [c]$P < 0.001$.

ACS = acute coronary syndrome; AICc = Akaike information criterion correction; BIC = Bayesian information criteria; CICU = cardiac intensive care unit; ESRD = end stage renal disease; HD = hemodialysis; HF = heart failure; IABP = intra-aortic balloon pump; ICU = intensive care unit; LASSO = least absolute shrinkage and selection operator; PAC = pulmonary arterial catheter; PCI = percutaneous coronary intervention; pRBC = packed red blood cell; ROC = receiver-operating curve; SOFA = sequential organ failure assessment; WBC = white blood cell.

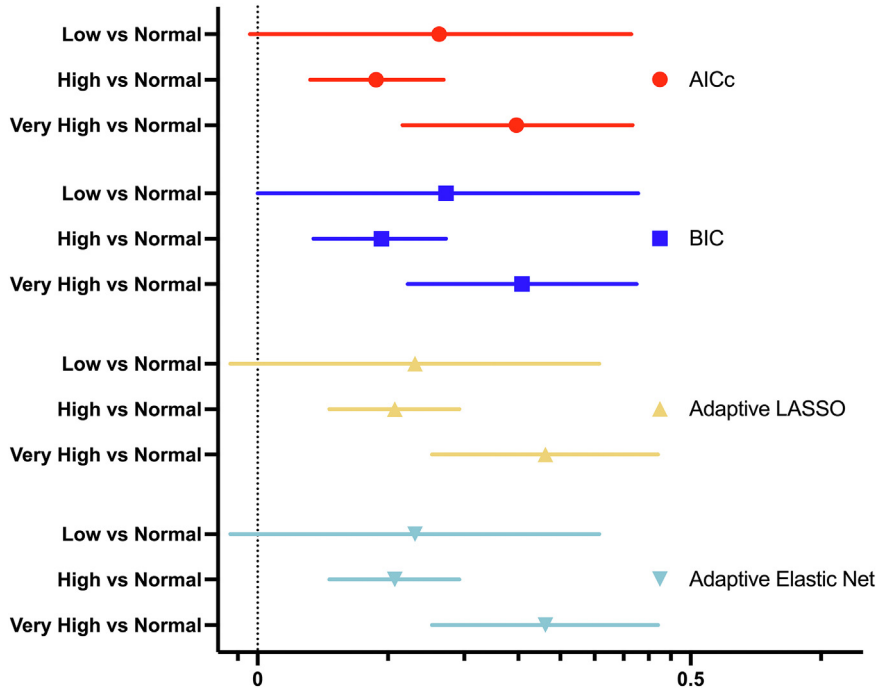
1.03 (95% CI: 1.02-1.04) per 1 × 10^3 WBC increase for the AIC and Bayesian Information Criterion models and 1.02 (CI: 1.01-1.03) per 1 × 10^3 WBC increase for the Least Absolute Shrinkage and Selection Operator and elastic net models (all $P < 0.001$). After multivariable adjustment, only the high WBC and very high WBC groups were associated with in-hospital mortality (**Figure 2**, Supplemental Table 3). OR point estimates for in-hospital mortality in the low WBC group were >1, but the confidence intervals were wide and crossed 1 (all $P \geq 0.05$).

IN-HOSPITAL MORTALITY–ANALYSIS BY WBC DIFFERENTIAL COMPONENTS. Subgroup analysis was performed utilizing data from the patients with admission WBC differential. Unadjusted and AICc-adjusted OR values per 1 SD increase of each component of the WBC differential are provided in **Table 3**. All components of the WBC differential were associated with in-hospital mortality on univariable analysis. The mortality risk increased with higher WBC, neutrophils, and monocytes and decreased with higher lymphocytes and eosinophils. However, the association between lymphocytes and eosinophils was no longer significant after adjustment ($P > 0.05$).

The categorical analysis of adjusted WBC differential components is provided in **Figure 3** and Supplemental Table 4. Similar to the adjusted analysis of WBC groups (Supplemental Table 3), the high (OR: 1.30 [95% CI: 1.06-1.61]) and very high (OR: 1.61 [95% CI: 1.24-2.09]) neutrophil groups remained significantly associated with mortality after adjustment. The low lymphocyte, low eosinophil, and very high monocyte groups also demonstrated a significant relationship with mortality after adjustment (**Figure 3**, Supplemental Table 4).

IN-HOSPITAL MORTALITY–RANDOM FOREST ANALYSIS. Random forest models ranking the strength of the association between mortality commonly available

FIGURE 2 Forest Plot of Adjusted WBC Group Mortality by Multivariable Regression Model



This figure provides the odds ratio per unit increase of WBC for the low, high, and very high WBC groups relative to the normal WBC group, after adjustment by each corresponding multivariable regression model. Each point indicates the OR with the 95% CI given by the corresponding horizontal line. The x-axis provides the odds ratio on a logarithmic scale. AICc = Akaike Information Criterion Correction; BIC = Bayesian Information Criterion; LASSO = Least Absolute Shrinkage and Selection Operator; WBC = white blood cells.

laboratory values are provided in Figure 4. In the overall cohort, the WBC was the second most important laboratory value for predicting in-hospital mortality after the anion gap. When all WBC differential components were included in place of the total WBC, the neutrophil count emerged as the most important laboratory value for predicting in-hospital mortality. When all WBC differential components were included with the total WBC, the WBC was the second most important laboratory value for predicting in-hospital mortality after BUN, and the neutrophil count was fifth.

DISCUSSION

In this large cohort of critically ill cardiac patients treated in a tertiary CICU, we demonstrated a robust association between WBC and mortality in the overall population and among each relevant admission diagnosis subgroup, including those with CS, CA, STEMI, non-STEMI, and HF. We observed a curvilinear (J-shaped) relationship between WBC and mortality, with elevated risk in patients having values lower or higher than the laboratory reference range; spline analysis identified knot points very close to the normal laboratory range cut-offs. The increased mortality risk was more prominent at higher WBC values, particularly after multivariable adjustment. This relationship was seen in unadjusted analysis of all subgroups except for the STEMI group; however, the difference between mortality in the low and high WBC STEMI groups was not statistically significant. We utilized several regression modeling approaches, including machine learning-based models, which yielded similar results. We consistently demonstrated a strong and incremental association between a higher WBC and increased risk of adjusted in-hospital mortality. Among the components of the WBC differential, a high absolute neutrophil count had the strongest association with mortality. Random forest machine learning models ranked WBC as the second most important common laboratory value for predicting mortality in our CICU patient population. Overall, we highlight the importance of leukocytosis

on CICU admission as a risk marker beyond traditional predictors in this critically ill cardiac population.

Leukocytosis is a fundamental sign of an acute stress reaction or systemic inflammation regardless of the precipitating insult and may serve as a barometer of overall systemic stress.[19] Leukocytosis has been associated with adverse outcomes in numerous populations with acute cardiac disease and noncardiovascular or mixed critical illness.[10-12,20,21] The consistent association between leukocytosis and mortality in the CICU population across subgroups supports the contention that a dysregulated immune response may contribute to mortality in diverse critical illness syndromes.[22] Nevertheless, it is possible that elevated WBC is an appropriate immunological response considering the severity of injury or contribution from additional diagnoses present at the time of CICU admission. By contrast, leukopenia can result from infectious or noninfectious systemic inflammatory response syndrome (SIRS) and blood dyscrasias.[23] In our unadjusted analyses, patients with leukopenia had higher mortality, consistent with a J-shaped association between WBC and mortality. However, this association no longer persisted after multivariable adjustment accounting for other relevant markers of prognosis, suggesting that leukopenia may be less useful for risk stratification. Due to the small size of the leukopenia group within our cohort, we could not exclude a clinically relevant association with mortality due to wide confidence intervals. Considering the constellation of pathology treated in the modern CICU,[14,24] the ubiquitously-available WBC may be valuable as an early prognostic biomarker regardless of the primary disease process.

A relationship between inflammation and mortality in acute cardiac illness has been previously established, with acute MI as a prototypical example.[4,10-12,25,26] During acute MI, releasing damage-associated molecular patterns from cardiomyocytes after ischemic injury activates the innate immune system and cytokine release that can worsen the myocardial injury and trigger SIRS.[22,27] Van Diepen et al[4] identified SIRS positivity in 25% of patients admitted for treatment of STEMI and 90-day mortality was higher in the SIRS population. Of the 4 SIRS criteria, only WBC remained significantly associated with 90-day mortality after multivariable adjustment.[4] In a prior analysis from this CICU population, SIRS was present at the time of CICU admission in approximately one-third of patients provided additional risk stratification beyond conventional risk factors across the spectrum of shock severity; patients with SIRS had higher in-hospital and 1-year mortality.[23]

TABLE 3 Unadjusted and AICc Adjusted Standardized WBC Differential Component Mortality

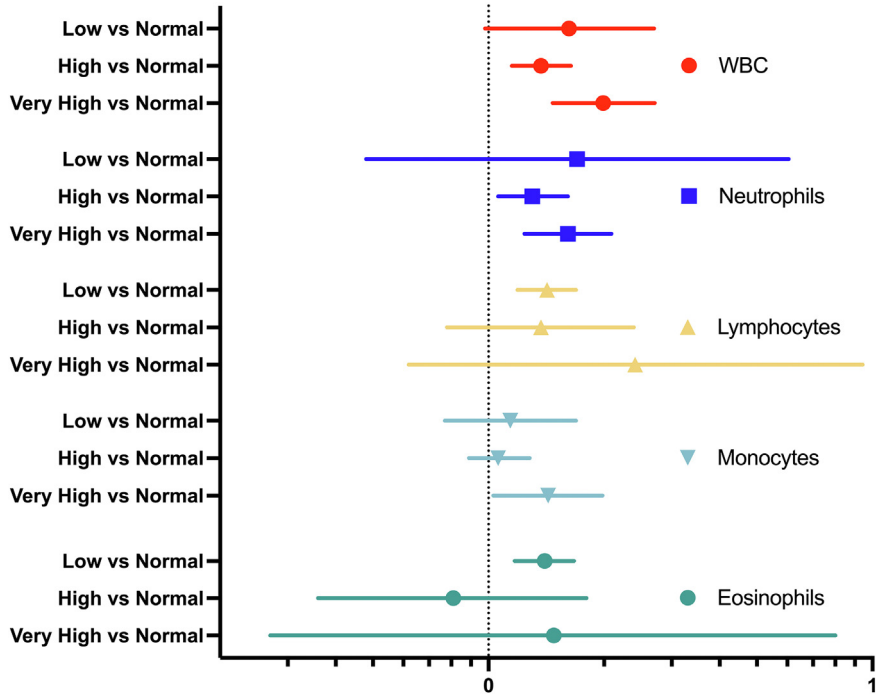
Cell Line	Unadjusted OR	*P* Value	AICc Adjusted OR	*P* Value	Unadjusted ROC AUC
WBC	1.69 (1.59-1.80)	≤0.001[a]	1.15 (1.07-1.23)	≤0.001[a]	0.65
Neutrophil	1.75 (1.65-1.86)	≤0.001[a]	1.19 (1.11-1.28)	≤0.001[a]	0.68
Lymphocyte	0.55 (0.47-0.65)	≤0.001[a]	0.87 (0.74-1.02)	0.09	0.62
Monocyte	1.28 (1.20-1.35)	≤0.001[a]	1.09 (1.02-1.17)	0.01[a]	0.56
Eosinophil	0.67 (0.59-0.75)	≤0.001[a]	0.92 (0.82-1.02)	0.12	0.62

Values are OR (95% CI) unless otherwise indicated. As WBC and WBC differential component values were standardized before regression, the presented OR values are per each standard deviation higher. [a]$P \leq 0.05$.
AICc = Akaike information criterion correction; ROC = receiver operating curve; WBC = white blood cell count.

Other measures of inflammation have been examined for prognostication in the CICU population and relevant subgroups. In a prior analysis from this CICU cohort, a higher neutrophil-to-lymphocyte ratio (NLR), a proposed marker of systemic stress and inflammation derived from the WBC differential, was associated with increased mortality risk even when patients were stratified by shock severity.[28] Notably, both the NLR and the WBC remained incrementally associated with higher adjusted mortality after inclusion in the same multivariable model, emphasizing the added prognostic relevance of the WBC differential beyond the WBC itself.[28] In the present analysis, the absolute neutrophil count carried the strongest association with mortality of the WBC differential components; insofar as a high neutrophil count or a low lymphocyte count was associated with higher mortality, the present study further validates the use of the NLR for risk stratification. Neutrophilic inflammation is typically associated with lymphopenia and eosinopenia, and our analysis suggests that neutrophilic leukocytosis is the form of leukocytosis that carries the greatest adverse prognosis in the CICU.

In patients with CS, vasodilation resulting from systemic inflammation can compromise hemodynamic compensation and contribute to a downward spiral of worsening shock.[22] Accordingly, elevated cytokine levels have been associated with more severe shock and worse prognosis in patients resuscitated from CA.[29] Inflammation plays an integral role in the pathogenesis of acute HF, partly due to adverse effects on ventricular function.[30] Furthermore, inflammation after ACS, measured by C-reactive protein, is associated with an increased risk of developing HF and mortality.[31] Administration of anakinra, an interleukin-1 receptor antagonist, leads

FIGURE 3 AICc Adjusted Mortality by WBC Differential Component



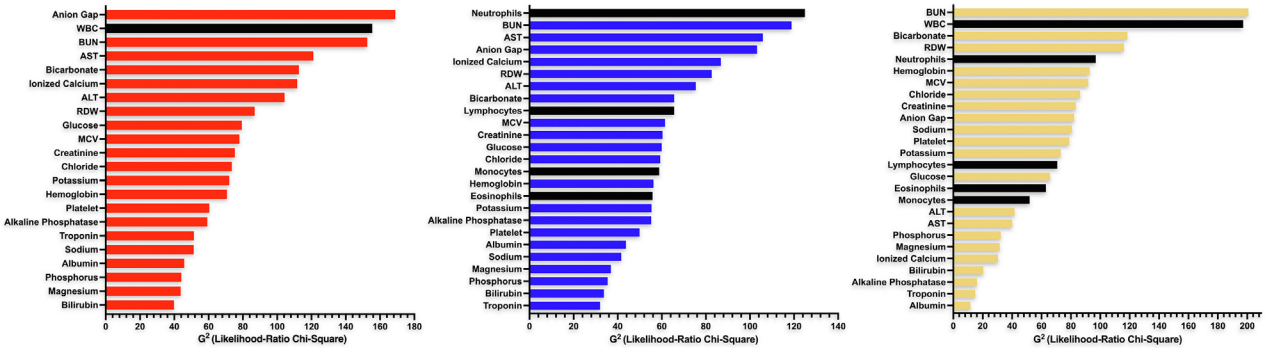
This figure provides the OR per unit increase of WBC and each component of the WBC differential for the low, high, and very high groups relative to the corresponding normal leukocyte range, after AICc adjustment. Each point indicates the OR with the 95% CI given by the corresponding horizontal line. The x-axis provides the odds ratio on a logarithmic scale. AICc = Akaike information criterion correction.

to a reduction in post-STEMI inflammation, measured by C-reactive protein, and is associated with reduced risk of post-MI HF and mortality.[32]

There is an immediate need for readily available biomarkers for prognostic use in the diverse CICU patient population. Comparison of common admission laboratory values via the use of random forest models demonstrated that the strength of the association between WBC and mortality was second only to the anion gap for mortality prediction. Neutrophil count, the greatest contributor to total WBC, was the most important of the WBC differential components and a strong predictor of mortality. In the random forest model containing all components of the WBC differential, the strength of the association between WBC and mortality surpassed that of the individual WBC differential components and was second only to BUN; neutrophil count ranked fifth. Anion gap and BUN are known laboratory predictors of mortality in this CICU population that were included in the M-CARS, a novel prognostic risk score that outperforms standard ICU risk scores in this cohort.[13] Anion gap and bicarbonate are likely surrogate markers for concomitant lactic acidosis; because lactate was available for only approximately 25% of patients, we had to exclude it from the random forest analysis. However, we previously confirmed the prognostic utility of lactate for predicting mortality in an unselected CICU patient population[33] and CS.[34] We suspect that the WBC count was not originally identified for inclusion in the M-CARS because of its curvilinear relationship with mortality, which was unmasked using the nonlinear random forest approach. Future CICU mortality prediction models may benefit from including a marker of inflammation, such as WBC, along with lactate to capture both the hypoperfusion and inflammation hypothesized to contribute to CICU patient mortality. Biomarker-based approaches to phenotyping and subgrouping may support recent efforts to individualize clinical care and trials in CICU patients.[35,36]

STUDY LIMITATIONS. Our study had several limitations necessitating external validation.[24] Our mixed

FIGURE 4 **Variable Importance of WBC Differential Components from Random Forest Model of Laboratory Values**



The red graph (left) demonstrates the strength of the association between mortality WBC in comparison to other common laboratory values in the total population. The blue graph (center) demonstrates the association between mortality and each component of the WBC Differential in the population with WBC differential data available. The yellow graph (right) demonstrates the association between mortality and each component of the WBC differential, including total WBC, in the population with WBC differential data available. Together, these models demonstrate the strength of the association between total WBC and each component of the WBC differential relative to other relatively available laboratory values. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; MCV = mean corpuscular volume; RDW = red cell distribution width; WBC = white blood cell.

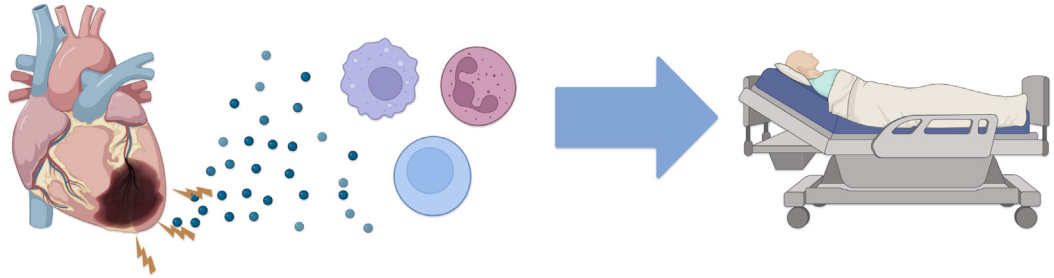
CICU population included patients with diverse admission diagnoses, including sepsis and respiratory failure, which should be considered when applying our results to a more limited cardiac population. As we performed a retrospective review of a pre-existing database, missing data may potentially bias the results; however, only a relative minority of patients lacked an admission WBC value, and WBC differentials were available for the vast majority of patients in our study. To perform our analysis, we utilized a hybrid approach to causal inference by integrating predictive analytic techniques for model building. To accomplish this, we built a series of models using different techniques for variable selection to confirm that WBC count remained significantly associated with mortality regardless of the model type and covariates included. We did not determine the adjustment variables a priori. While we believe this led to better models, we recognize that not including variables with weak associations with mortality (eg, sex and race) could have affected the observed associations. As with any observational study, residual confounding is possible, and causation cannot be determined. Indeed, patients with high and very high WBC were sicker and it is likely that (neutrophilic) leukocytosis is simply a marker reflecting greater overall severity of illness that drives adverse outcomes. In addition, we cannot determine whether the predominant driver of leukocytosis was physiologic stress, infection, or noninfectious inflammation, which precludes us from knowing whether an elevated WBC is a specific marker of increased systemic inflammation per se. Of note, out of consideration that the underlying pathophysiology and consequences of leukopenia and leukocytosis may differ depending on the underlying etiology of shock (eg, septic vs cardiogenic), a sensitivity analysis excluding those patients with an admission diagnosis of sepsis was performed without significantly altering our findings. We lacked data on specific inflammatory biomarkers or consistent testing for the presence of infection, precluding us from drawing inferences regarding specific underlying mechanisms of WBC abnormalities. Finally, we did not have preadmission laboratory values, and we could not identify patients with chronically abnormal WBC, such as those with preexisting hematologic malignancy, chronic infectious diseases such as HIV, or other blood dyscrasias.

CONCLUSIONS

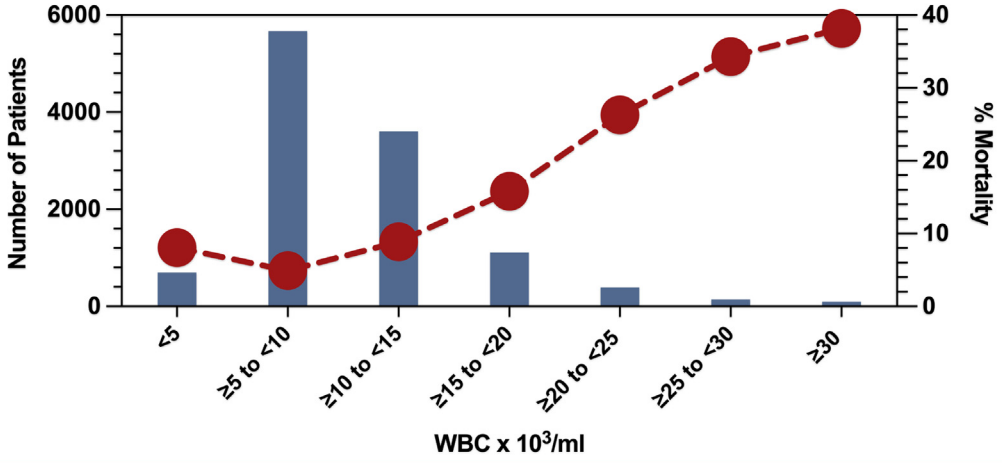
A higher WBC was incrementally associated with increased in-hospital mortality in a diverse CICU patient population, with consistent findings after adjustment and in relevant subgroups. Our findings support the hypothesis that inflammation is integral to the pathophysiology of cardiovascular critical illness. WBC is a readily available laboratory value that may be useful for facilitating prognostication across the heterogenous and complex modern CICU patient population (**Central Illustration**). Future CICU-

CENTRAL ILLUSTRATION **Admission Total Leukocyte Count as a Predictor of Mortality in Cardiac Intensive Care Unit Patients**

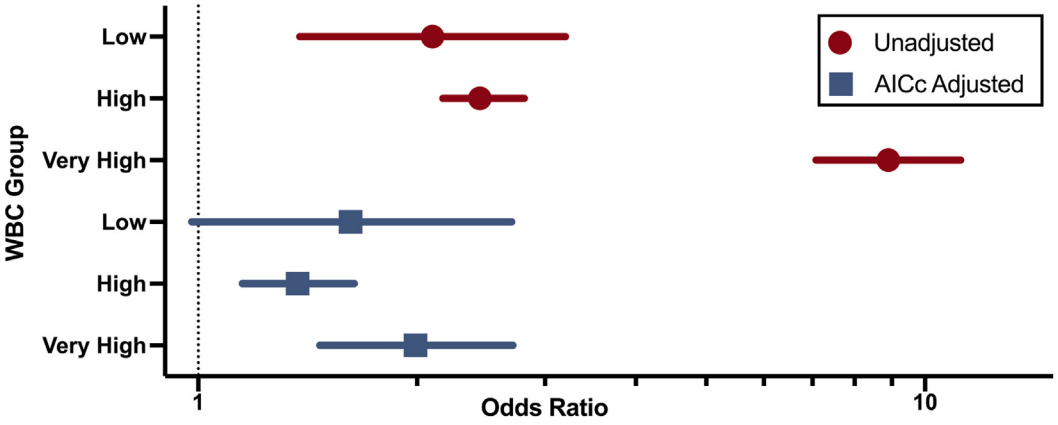
Myocardial Injury → Inflammatory Mediator Release → Inflammation and Leukocyte Activation → Secondary Tissue and Organ Injury Critical Illness



In a Diverse 11,699 Cardiac Intensive Care Unit Patient Cohort: Admission White Blood Cell Count Was Associated With Higher Adjusted In-Hospital Mortality



Leukopenia Was Associated With Higher Mortality Before Adjustment: After Multivariable Adjustment, Only Leukocytosis Remained Associated With Higher In-Hospital Mortality



Smith RJ, et al. JACC Adv. 2024;3(1):100757.

Myocardial injury is associated with inflammatory mediator release, such as damage-associated molecular patterns and cytokines. The resultant inflammation, often evidenced by leukocytosis, may contribute to adverse outcomes. In a large cohort of unselected CICU patients with diverse conditions, we observed a strong, consistent, incremental association between an increased white blood cell (WBC) count on admission and higher adjusted in-hospital mortality. Patients with low WBC counts had higher mortality before adjustment. Leukocytosis is an important risk marker in cardiac intensive care unit patients, which could imply the presence of harmful excess inflammation and greater physiologic stress. The top panel was created with BioRender.com. AICc = Akaike information criterion correction.

specific risk stratification tools may benefit from including WBC, recognizing its nonlinear association. It remains to be established whether CICU patients with leukocytosis have a systemic inflammatory process that anti-inflammatory therapies could modify.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: WBC is a readily available biomarker that may be useful for prognostication in the modern CICU patient population. Elevated WBC is incrementally associated with increased risk of mortality across diverse admission diagnoses.

TRANSLATIONAL OUTLOOK: Further studies are warranted to investigate whether these findings can be utilized to create a predictive model for use in critically ill patients admitted to the CICU.

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KEY WORDS CICU, inflammation, mortality, WBC

APPENDIX For supplemental tables and figures, please see the online version of this paper.