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Eosinopenia and post-hospital outcomes in critically ill non-cardiac vascular surgery patients

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Abstract *Background and aims:* Eosinopenia is a marker for acute inflammation. We hypothesized that eosinopenia at Intensive Care Unit (ICU) admission in vascular surgery patients who receive critical care, would be associated with increased mortality following hospital discharge. *Methods and results:* We performed a two-center observational cohort study of critically ill, non-cardiac adult vascular surgery patients who received treatment in Boston between 1997 and 2012 and survived hospital admission. The consecutive sample included 5083 patients (male 57%, white 82%, mean age [SD] 61.6 [17.4] years). The exposure was Absolute eosinophil count measured within 24 h of admission to the ICU and categorized as ≤10 cells/μL, 11–50 cells/μL, 51–100 cells/μL, 101–350 cells/μL (normal range), and >350 cells/μL.

The primary outcome was all-cause mortality within 90 days of hospital discharge. The secondary outcome was discharge to home following hospitalization. 90-day post-discharge mortality was 6.7%, and 12.9% of patients were readmitted within 30 days. After multivariable adjustment, patients with eosinopenia (≤10 cells/μL) have a 90-day post-discharge mortality OR of 1.97 (95%CI 1.42, 2.73; $P < 0.001$) relative to patients with an absolute eosinophil count of 101–350 cells/μL. Further, after multivariable adjustment, patients with eosinopenia (≤10 cells/μL) have a 25% lower odds of discharge to home compared to patients with an absolute eosinophil count of 101–350 cells/μL [OR = 0.71 (CI 95% 0.59–0.85); $P < 0.001$].
Conclusion: Eosinopenia at ICU admission is a robust predictor of increased mortality and lower likelihood of discharge to home in vascular surgery patients treated with critical care who survive hospitalization.

Introduction

Intensive Care Unit (ICU) survivors have high post-hospital health-care resource use, substantial long-term morbidity and mortality [1,2]. Specific subsets of ICU survivors have magnified risks of adverse outcomes [3,4]. Critically ill vascular surgery patients undergo high-risk surgery with an

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increased baseline risk of adverse perioperative outcomes due to substantial comorbidities and age [5]. The identification of risk factors significantly associated with adverse health outcomes after discharge is important in high-risk populations. Risk factors for post-hospital adverse outcomes include comorbidity, severity of illness, acute organ failure, and facility type where discharged [6–9].

Biomarkers of systemic inflammation and oxidative stress show utility for early risk stratification in the critically ill and vascular surgery patient population [10–12]. In the early perioperative period following vascular surgery, a transient elevation of inflammatory markers [13,14] is consistently demonstrated. Chronic, low-grade, systemic inflammation heightens adverse outcome risk in adults with cardiovascular disease [15]. Existing indices may not have significant discriminative capacity for post-hospital outcomes in the vascular surgery population.

Determined from the absolute eosinophil count, eosinopenia is a marker for acute inflammation [16]. The absolute eosinophil count is determined using the leukocyte differential and total white blood cell count and is quickly measured, widely available and low-cost. Eosinopenia is a prognostic marker for sepsis and mortality of critically ill patients [17,18]. Eosinopenia is associated with increased risk of death after acute cerebral infarction [19] and bacteremia [20], and provides good discrimination between infection and non-infection at intensive care unit admission [21,22].

While studies suggest that biomarkers may be predictive of in-hospital outcomes, limited information exists on long term survival of critically ill patients following vascular surgery. We hypothesized that among non-cardiac vascular surgery patients who survived critical illness, eosinopenia at ICU admission would be associated with post-hospital mortality. To explore this hypothesis, we performed a two-center cohort study from 1997 to 2012 of 5083 adults who underwent non-cardiac vascular surgery requiring critical care.

Methods

Source population

We extracted administrative and laboratory data of patients admitted to two academic teaching hospitals in Boston, Massachusetts: Brigham and Women's Hospital (BWH), with 777 beds and Massachusetts General Hospital (MGH) with 999 beds. Both hospitals provide primary and tertiary care, vascular surgery and critical care within eastern Massachusetts and the surrounding region. BWH and MGH provide care to a socioeconomically and ethnically diverse population.

Data sources

Data on all patients admitted to the BWH or MGH between 1997 and 2012 were extracted through the Research Patient Data Registry (RPDR). The RPDR is a computerized registry which serves as a central data warehouse for all inpatient and outpatient records at Partners HealthCare sites which include BWH and MGH. The RPDR has been utilized in previous clinical research studies [11,23–25]. Partners Human Research Committee approved this study. The IRB approval included a waiver of the requirement to obtain informed consent because the risk to study subjects, including risk to privacy, was deemed to be minimal, obtaining informed consent of study subjects was not feasible and the rights and welfare of the subjects would not be adversely affected by the waiver.

Study population

During the study period, there were 7608 patients, age $\geq$18 years, who received critical care and were assigned Current Procedural Terminology (CPT) codes for vascular surgery in the six days prior to ICU admission to 2 days after (Appendix 1). ICU admission was determined by assignment of the CPT code 99291 (critical care, first 30–74 min) during hospital admission, a validated approach for ICU admission in the RPDR database [24]. Exclusions included: 961 patients who died as in-patients; 242 patients with a hospital readmission including an ICU stay; 72 patients with end-stage renal disease; and 1250 patients in whom eosinophil count was not obtained within 24 h of ICU admission. Thus, 5083 patients constituted the total study population.

Exposure of interest and comorbidities

The exposure of interest, absolute eosinophil count within 48 h of ICU admission, was categorized *a priori* as $\leq$ 10 cells/μL, 11–50 cells/μL, 51–100 cells/μL, 101–350 cells/μL, and $>$350 cells/μL [20,26]. Vascular procedures were categorized according to their Current Procedural Terminology (CPT) code and by their anatomical site such as neck, upper extremity, abdomen, lower extremity, or as amputations, compartment syndrome, and venous procedures [27].

We utilized the Deyo-Charlson index to assess the burden of chronic illness by employing ICD-9 coding algorithms, which are well studied and validated [28]. Patient DRG Type is defined as Medical or Surgical and incorporates the Diagnostic Related Grouping (DRG) methodology. Sepsis was defined as the presence of ICD-9 codes 038, 995.91, 995.92, or 785.52, from 3 days prior to 7 days after critical care initiation [29]. Number of organs with failure was adapted from Martin et al. [30]. They were defined by a combination of ICD-9-CM and CPT codes relating to acute organ dysfunction assigned from 3 days prior to critical care initiation to 30 days after critical care initiation [31,32]. Noncardiogenic acute respiratory failure was identified by the presence of ICD-9 codes for respiratory failure or pulmonary edema (518.4, 518.5, 518.81, and 518.82) and mechanical ventilation (96.7$\times$), excluding congestive heart failure (428.0–428.9) following hospital admission [33]. Patients were considered to have exposure to inotropes and vasopressors if pharmacy records from 3 days prior to 7 days after critical care initiation showed evidence of the use of dopamine, dobutamine,

epinephrine, norepinephrine, phenylephrine, milrinone or vasopressin. The acute organ failure score is an ICU risk-prediction score derived and validated from demographics (age, race), patient DRG type and ICD-9-CM code based comorbidity, sepsis, and acute organ failure covariates which have similar discrimination for 30 day mortality as Acute Physiology and Chronic Health Evaluation (APACHE) II [25]. Changes from the expected hospital length of stay (LOS) were computed as the difference between the actual LOS and the geometric mean LOS for each DRG as determined by the Centers for Medicare & Medicaid Services [34]. Inter-facility transfer was defined as transfer of patient from an acute care hospital to either hospital under study [35]. Red Cell Distribution Width was determined at ICU admission.

Assessment of mortality

The vital status of patients in this study cohort was obtained from the Social Security Administration Death Master File. The accuracy of the Social Security Administration Death Master File was previously validated for in-hospital and out-of-hospital mortality in our administrative database [24]. The censoring date was December 31, 2013.

End points

The primary endpoint was all-cause, out-of-hospital mortality at 90 days. Secondary endpoint was discharge to home. Discharge disposition data was determined from hospital records.

Power calculations and statistical analysis

For our power calculation, based on our previous work and that of others [17,36,37], we assumed the 90-day post-discharge mortality rate to have a two-fold absolute increase in the patients with an absolute eosinophil count of $\leq$10 cells/μL compared to patients with an eosinophil count of 101–350 cells/μL. We assumed an absolute eosinophil count of 101–350 cells/μL would have a 90-day post-discharge mortality of 5% [38], and the ratio of patients with absolute eosinophil count of $\leq$10 cells/μL to those with 101–350 cells/μL was 5:1. With an alpha error level of 5% and a power of 80%, the minimum sample size required for our primary end point is 1560 total patients (1300 with absolute eosinophil count of 101–350 cells/μL and 260 patients with $\leq$10 cells/μL).

The frequency distribution and the comparison across eosinophil categories were used to describe categorical covariates using contingency tables and chi-square testing. Continuous covariates were assessed graphically and in terms of summary statistics (mean, SD, median, interquartile range) when appropriate. Using one-way analysis of variance, continuous covariates were compared across exposure groups. Bivariable logistic regression was used to estimate the unadjusted associations between eosinophil categories and mortality. Adjusted odds ratios were estimated by multivariable logistic regression models with inclusion of *a priori* determined covariate terms thought to plausibly associate with both eosinophils and mortality to avoid over-adjustment bias and unnecessary adjustment [39]. Covariate terms included age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital.

For the primary model (90-day, out-of-hospital mortality), specification of each continuous covariate (as linear vs categorical term) was adjudicated by the empiric association with the primary outcome using Akaike's Information Criterion. The Hosmer-Lemeshow test was used to assess the overall fit of the model. Unadjusted event rates were calculated with the use of the Kaplan-Meier methods and compared with the use of the log-rank test. We assessed possible effect modification of year of hospital admission and malignancy on the risk of mortality using the likelihood-ratio test. Models for secondary analyses (discharge to home) were specified identically to the primary model to bear greatest analogy. Area under the receiver operating characteristic curve (AUC) was constructed to analyze the discriminating power of absolute eosinophil count at admission for predicting 90-day, out-of-hospital mortality. The continuous adjusted relationship between absolute eosinophil count and risk of 90-day post-discharge mortality was graphically represented utilizing the coefplot command [40]. Pearson's product-moment correlation was run to assess the relationship between absolute eosinophil count and Red Cell Distribution Width at ICU admission. All p-values were two-tailed and considered statistically significant if values were less than 0.05. All analyses were performed using STATA 12.0 MP statistical software (Stata Corp., College Station, TX).

Results

Table 1 shows characteristics of the study population. Most patients were male (57%), white (82%) and the majority had surgically related DRGs (83%). The mean age at hospital admission was 61.4 (SD 17.4) years. 16.7% of the cohort were inter-facility transfers. Post-hospital discharge mortality rates were 6.7% at 90-days, 9.6% at 180 days and 13.0% at 365 days. 90-day readmission rate was 20.9%. The vascular surgery procedure classes in the cohort included abdomen (33%), amputations (2%), compartment syndrome (2%), lower extremity (9%), neck (8%), upper extremity (32%) and venous (13%). Sixty-four percent of the vascular procedures were endovascular. Details of the vascular surgery procedures are outlined in Supplemental Table 1. Age, Deyo-Charlson Index, acute organ failure, malignancy, acute kidney injury, sepsis, acute organ failure score, change in expected length of stay, discharge to home and hospital readmission are significant predictors of 90-day post-discharge mortality (Table 1). Patients with Absolute Eosinophil Count $\leq$10 cells/μL are younger, more often female, have fewer prior vascular surgery, more sepsis, have higher length of stay and greater 90-day post-discharge mortality (Table 2).

Table 1 Characteristics and unadjusted association of potential prognostic determinants with 90-day post discharge mortality.[a].

	Alive N = 4742	Expired[a] N = 341	Total N = 5083	P-value	Unadjusted OR (95%CI) for 90-day Post Discharge Mortality
Age years-mean ± SD	60.7 ± 17.4	72 ± 13.6	61.4 ± 17.4	<0.001†	1.05 (1.04, 1.06)
Male Gender-no.(%)	2708 (57)	182 (53)	2890 (57)	0.18	0.86 (0.69, 1.07)
Non-White Race-no.(%)	851 (18)	47 (14)	898 (18)	0.052	0.73 (0.53, 1.00)
Surgical Patient Type-no.(%)	3934 (83)	292 (86)	4226 (83)	0.20	1.22 (0.90, 1.67)
Prior Vascular Surgery-no.(%)	572 (12)	46 (13)	618 (12)	0.44	1.14 (0.82, 1.57)
Deyo-Charlson index-no.(%)				<0.001	
0–1	1279 (26.97)	30 (8.8)	1309 (25.75)		1.00 (Referent)
2–3	2049 (43.21)	105 (30.79)	2154 (42.38)		2.19 (1.45, 3.30)
4–6	1219 (25.71)	169 (49.56)	1388 (27.31)		5.91 (3.98, 8.78)
≥7	195 (4.11)	37 (10.85)	232 (4.56)		8.09 (4.88, 13.40)
Number of organs with acute failure-no.(%)				<0.001	
0	1515 (32)	52 (15)	1567 (31)		1.00 (Referent)
1	1659 (35)	117 (34)	1776 (35)		2.06 (1.47, 2.87)
2	994 (21)	107 (31)	1101 (22)		3.14 (2.23, 4.41)
3	400 (8)	49 (14)	449 (9)		3.57 (2.38, 5.35)
≥4	174 (4)	16 (5)	190 (4)		2.68 (1.50, 4.79)
Malignancy-no.(%)	770 (16)	131 (38)	901 (18)	<0.001	3.22 (2.55, 4.06)
Acute Kidney Injury-no.(%) [b]	246 (6)	25 (10)	271 (6)	0.010	1.75 (1.14, 2.71)
Sepsis-no.(%)	372 (8)	48 (14)	420 (8)	<0.001	1.92 (1.39, 2.66)
Noncardiogenic acute respiratory failure-no.(%)	419 (9)	31 (9)	450 (9)	0.87	1.03 (0.70, 1.51)
Vasopressors/Inotropes-no.(%)	2301 (49)	154 (45)	2455 (48)	0.23	0.87 (0.70, 1.09)
Acute Organ Failure Score-mean±SD[c]	7.8 ± 3.8	10.3 ± 3.7	8.0 ± 3.9	<0.001†	1.17 (1.14, 1.21)
Absolute Eosinophil Count-median [IQR]	0.10 [0.03, 0.19]	0.08 [0.02, 0.17]	0.09 [0.03, 0.19]	0.0011‡	0.54 (0.24, 1.23)
Absolute Eosinophil Count-mean±SD	0.14 (0.31)	0.12 (0.17)	0.14 (0.30)	0.33	0.54 (0.24, 1.23)
Red Cell Distribution Width-mean±SD[d]	14.2 ± 1.6	15.4 ± 2.0	14.3 ± 1.7	<0.001†	1.35 (1.29, 1.42)
Change in Expected Length of Stay-median [IQR]	4.0 [0.4, 10.5]	8.3 [1.3, 17.7]	4.2 [0.5, 11.0]	<0.001‡	1.02 (1.01, 1.02)
Discharge to Home-no.(%)	2332 (49)	88 (26)	2420 (48)	<0.001	0.36 (0.28, 0.46)
90-Day Readmission-no.(%)	969 (20)	91 (27)	1060 (21)	0.006	1.42 (1.10, 1.82)

Data presented as no. (%) unless otherwise indicated. P determined by chi-square except for † determined by ANOVA or ‡ determined by Kruskal-Wallis test.

[a] Expired within 90-days following hospital discharge.

[b] Acute Kidney Injury is RIFLE class injury or failure and available on 4232 patients.

[c] 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.

[d] Red Cell Distribution Width at ICU admission is available on 5011 patients.

Primary outcome

Eosinopenia was a robust predictor of mortality (Table 3 and Fig. 1). The odds of 90-day mortality in the ≤10 cells/μL eosinophil group was 75% higher than that of those in the 101–350 cells/μL eosinophil group. Eosinopenia remained a significant predictor of odds of mortality after adjustment for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital. The adjusted odds of 90-day mortality in the ≤10 cells/μL eosinophil group was 97% higher than that of those in the 101–350 cells/μL eosinophil group (Table 3). The AUC for the prediction model for 90-day post-discharge mortality was 0.77 (95%CI 0.75–0.80). The prediction model showed good calibration (HL χ^2 8.0, P = 0.43). There was no significant effect modification of the eosinophil 90-day post-discharge mortality association on the basis of RDW (P-interaction = 0.26), year of hospitalization (P-interaction = 0.76) or malignancy (P-interaction = 0.21). Additional adjustment of the model for sepsis or RDW did not materially alter the point estimates (Table 3, Models 2 and 3).

Secondary outcome

The odds of a hospital discharge to home in the ≤10 cells/μL eosinophil group was 29% lower than that of those in the 101–350 cells/μL eosinophil group (Table 4). Following adjustment, the odds of discharge to home in the ≤10 cells/μL eosinophil group remained 29% lower compared to those of the 101–350 cells/μL eosinophil group (Table 4).

Sensitivity analysis

We next analyzed the association of the absolute eosinophil count within 48 h of ICU admission and 90-day post-discharge mortality in critically ill population with (N = 5083) and without (N = 63,291) vascular surgery patients. Critically ill vascular surgery patients have higher comorbidity than those without vascular surgery (chi^2 P < 0.001). In both cohorts, eosinopenia is

Table 2 Patient characteristics by Absolute Eosinophil Count

	Absolute Eosinophil Count cells/μL.					
N	≤10	11–50	51–100	101–350	>350	P-value
	743	879	940	2161	360	
Age-mean ± SD	58.1 ± 18.1	59.4 ± 17.6	60.9 ± 17.4	63.3 ± 16.8	63.3 ± 17.4	<0.001†
Male Gender-no.(%)	379 (51)	492 (56)	523 (56)	1261 (58)	235 (65)	<0.001
Non-White Race-no.(%)	124 (17)	166 (19)	200 (21)	350 (16)	58 (16)	0.009
Surgical Patient Type-no.(%)	616 (83)	710 (81)	769 (82)	1826 (85)	305 (85)	0.084
Prior Vascular Surgery-no.(%)	70 (9)	83 (9)	104 (11)	304 (14)	57 (16)	<0.001
Endovascular-no.(%)	396 (53)	522 (59)	556 (59)	1171 (54)	191 (53)	0.007
Deyo-Charlson index-no.(%)						0.001
0-1	179 (24)	239 (27)	275 (29)	548 (25)	68 (19)	
2-3	334 (45)	381 (43)	393 (42)	901 (42)	145 (40)	
4-6	200 (27)	231 (26)	232 (25)	603 (28)	122 (34)	
≥7	30 (4)	28 (3)	40 (4)	109 (5)	25 (7)	
Number of organs with acute failure -no.(%)						<0.001
0	195 (26)	264 (30)	311 (33)	699 (32.35)	98 (27.22)	
1	241 (32)	287 (33)	326 (35)	775 (35.86)	147 (40.83)	
2	170 (23)	205 (23)	204 (22)	446 (20.64)	76 (21.11)	
3	94 (13)	83 (9)	69 (7)	176 (8.14)	27 (7.5)	
≥4	43 (6)	40 (5)	30 (3)	65 (3)	12 (3.33)	
Malignancy-no.(%)	166 (22)	170 (19)	182 (19)	329 (15)	54 (15)	<0.001
Acute Kidney Injury-no.(%)[a]	165 (22)	151 (17)	187 (20)	526 (24)	93 (26)	<0.001
Sepsis-no.(%)	97 (13)	78 (9)	61 (6)	157 (7)	27 (8)	<0.001
Noncardiogenic acute respiratory failure -no.(%)	74 (10)	114 (13)	83 (9)	154 (7)	25 (7)	<0.001
Vasopressors/Inotropes -no.(%)	395 (53)	446 (51)	426 (45)	1022 (47)	166 (46)	0.007
Acute Organ Failure Score-mean±SD	8.2 ± 4.0	8.1 ± 4.0	7.7 ± 3.9	7.9 ± 3.8	8.2 ± 3.7	0.03†
Red Cell Distribution Width-mean±SD[b]	14.6 ± 2.0	14.2 ± 1.8	14.1 ± 1.6	14.3 ± 1.6	14.5 ± 1.7	<0.001†
Change in Expected Length of Stay-median [IQR]	6.2 [1.4, 14.5]	5.0 [0.7, 12.9]	3.9 [0.4, 10.0]	3.7 [0.4, 10.1]	4.3 [0.7, 10.7]	<0.001‡
Discharge to Home-no.(%)	315 (42)	398 (45)	437 (46)	1097 (51)	173 (48)	0.001
90-day Readmission-No.(%)	155 (21)	180 (20)	193 (21)	460 (21)	72 (20)	0.97
90-day post-discharge Mortality-no.(%)	71 (10)	66 (8)	61 (6)	123 (6)	20 (6)	0.005
365-day post-discharge Mortality-no.(%)	110 (15)	127 (14)	120 (13)	254 (12)	49 (14)	0.14

Data presented as n (%) unless otherwise indicated. P determined by chi-square except for † determined by ANOVA or ‡ determined by Kruskal-Wallis test.

[a] Acute Kidney Injury is RIFLE class injury or failure. Information on acute kidney injury available on 4232 patients.

[b] Red Cell Distribution Width at ICU admission is available on 5011 patients.

a significant predictor of odds of mortality after adjustment for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index and sepsis (Supplemental Table 2). For the ≤10 cells/μL eosinophil group, the effect size (odds ratio) of the vascular patients was higher than the non-vascular critically ill (2.08 vs 1.90). This indicates that absolute eosinophil count is a more robust predictor in critically ill patients who undergo vascular surgery.

Subanalysis

There was a no correlation between absolute eosinophil count and Red Cell Distribution Width at ICU admission, r

Table 3 Unadjusted and adjusted associations between Absolute Eosinophil Count and 90-day post-discharge mortality (N = 5083).

90-day post-discharge mortality	≤10	11–50	51–100	101–350	>350
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
Crude	1.75 (1.29, 2.37) <0.001	1.35 (0.99, 1.83) 0.61	1.15 (0.84, 1.58) 0.39	1.00 (Referent)[a]	0.98 (0.60, 1.59) 0.92
Adjusted[b]	1.97 (1.42, 2.73) <0.001	1.44 (1.04, 2.00) 0.029	1.30 (0.93, 1.81) 0.12	1.00 (Referent)[a]	0.88 (0.54, 1.46) 0.63
Adjusted[c]	1.93 (1.39, 2.68) <0.001	1.43 (1.03, 2.26) 0.034	1.31 (0.94, 1.82) 0.12	1.00 (Referent)[a]	0.89 (0.54, 1.46) 0.66
Adjusted[d]	1.79 (1.28, 2.49) 0.001	1.42 (1.01, 1.98) 0.041	1.33 (0.95, 1.85) 0.095	1.00 (Referent)[a]	0.89 (0.54, 1.47) 0.64

Note.

[a] Referent in each case is Absolute Eosinophil Count 101–350 cells/μL.

[b] Model 1: Estimates adjusted for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital.

[c] Model 2: Estimates adjusted for covariates in Model 1 and additionally for sepsis.

[d] Model 3: Estimates adjusted for covariates in Model 1 and additionally for Red Cell Distribution Width at ICU admission.

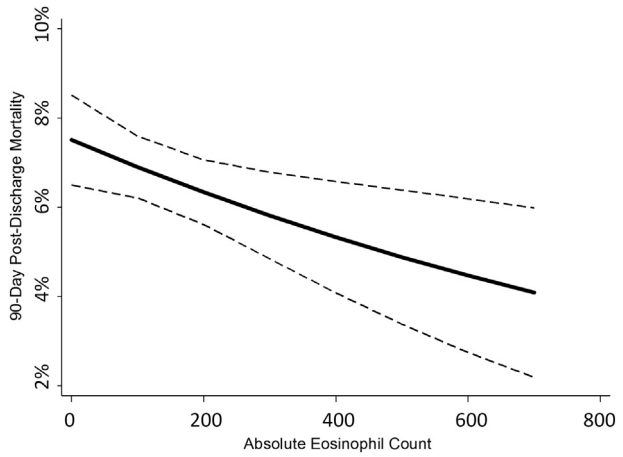

Figure 1 Coefficient plot. Plot representing multivariate estimates of the absolute eosinophil count-mortality association with confidence intervals (dashes). Multivariate estimates adjusted for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital.

(5,009) = 0.002, p = 0.88, with RDW explaining 0% of the variation in absolute eosinophil count. To evaluate the robustness of the absolute eosinophil count-post-discharge mortality association in the presence of chronic inflammation, we restricted the cohort to those patients with elevated RDW at ICU admission (RDW≥14.8%, N = 1530). In this smaller cohort, following adjustment for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital, the odds of 90-day post-discharge mortality in patients with absolute eosinophil counts ≤10 cells/μL was 2.3 fold higher compared to those with absolute eosinophil counts of 101–350 cells/μL [OR = 2.27 (95%CI 1.47, 3.52; P < 0.001)].

Discussion

In this study, we investigated whether eosinopenia, at ICU admission in critically ill vascular surgery patients, was associated with post-hospital discharge outcomes. Our novel observations show that eosinopenia at ICU admission in vascular surgery patients is associated with a significant increase in the odds of post-discharge hospital mortality and a decrease in the odds of a hospital to home discharge. While we cannot infer causation from our observational study, the eosinopenia-mortality association does have biologic plausibility.

Identification of a robust risk factor for ICU survivorship outcomes that is routinely measured and inexpensive may enhance the development of risk prediction scores for out-of-hospital outcomes.

Eosinopenia during acute inflammation is an old observation, first noted in the 1880s [41]. Eosinophils are multifunctional leucocytes that are part of the normal mucosal immune system and play vital roles in numerous inflammatory responses [42]. Early during inflammation, chemotactic factors such as complement 5a and fibrin fragments are released in the circulation, recruiting eosinophils to major organs and rapidly dropping the peripheral eosinophil count [16,43–45]. The rapid disappearance of eosinophils from the circulation implies both intense acute inflammation and sequestration of the eosinophils outside the circulation.

Eosinopenia, defined as an absolute eosinophil count ≤10 cells/ul, is an early marker for adverse outcomes in critically ill patients [17,18]. Eosinopenia has good discrimination for infection in critically ill patients at ICU admission [21,22,46] and is associated with elevated in-hospital mortality in critically ill medical patients [17,22,47]. Sustained eosinopenia is associated with decreased survival in bacteremia [20] even though eosinopenia fails to discriminate well between systemic inflammatory response syndrome and sepsis [21,48]. Eosinopenia may be a suitable biomarker for the intensity of inflammation in vascular surgery patients as this population has a higher baseline systemic inflammatory burden.

The role of the immune system in chronic disease differs from acute illness. From our subanalysis, it appears that the absolute eosinophil count and RDW are not correlated and likely provide different information regarding acute and chronic inflammation respectively. Further it appears that eosinopenia is a more robust predictor of mortality in critical illness survivors who undergo vascular surgery a group with high comorbidity. The depth of eosinopenia is likely reflective of the intensity of acute inflammation, which itself is associated with adverse outcomes. The response to chronic inflammation is a suppression of erythropoiesis and erythrocyte maturation, decrease in erythrocyte survival and a resultant increase in the RDW [49]. Our observation of the distinction between the absolute eosinophil count and RDW may assist in the construction of a composite risk score utilizing commonly

Table 4 Unadjusted and adjusted associations between Absolute Eosinophil Count and Discharge to Home (N = 5083).

	≤10	11–50	51–100	101–350	>350
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
Discharge to Home					
Crude	0.71 (0.60, 0.84) <0.01	0.80 (0.69, 0.94) 0.006	0.84 (0.72, 0.98) 0.029	1.00 (Referent)[a]	0.90 (0.72, 1.12) 0.34
Adjusted[b]	0.71 (0.59, 0.85) <0.001	0.81 (0.68, 0.96) 0.014	0.84 (0.71, 0.98) 0.031	1.00 (Referent)[a]	0.89 (0.71, 1.13) 0.35

Note:
[a] Referent in each case is Absolute Eosinophil Count 101–350 cells/μL.
[b] Model 4: Estimates adjusted for age, race, patient DRG type (medical vs. surgical), Deyo-Charlson index, prior vascular surgery, vascular surgery class, inter-facility transfer status and inpatient hospital.

obtained covariates to enhance clinical utility. In patient-provider discussions in the ICU regarding goals of treatment and long-term prognosis, information regarding the intensity of inflammation reflected by eosinopenia may be of value. Patients known to have eosinopenia at ICU admission may benefit from a more intensive rehabilitation and follow-up regime after hospital discharge.

The present study may have limitations. Post-discharge outcomes may be influenced by other variables independent of the absolute eosinophil count, which could bias estimates. Ascertainment bias may be present as not all critically ill vascular surgery patients have absolute eosinophil count measured, as it is included in the white blood cell differential. Our two-center study may not be generalizable to all centers. Utilization of ICD-9-CM codes to determine comorbidities will underestimate the true incidence, which is likely higher. Despite multivariable adjustment for potential confounders, residual confounding may be present. Though we are unable to adjust for physiologic based severity of illness scores, we have adjusted for an ICU-risk prediction score validated against APACHE II [25]. However, the absence of physiologic data is a potential limitation of our study.

In conclusion, eosinopenia is a robust predictor for post-hospital mortality and hospital discharge disposition in critically ill vascular surgery patients. The low cost, wide availability and facile interpretation of the absolute eosinophil count would tend to favor its adoption over more impractical and expensive tests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.05.061.

Appendix

Supplemental Methods

Current Procedural Terminology (CPT) codes

Neck

Endovascular

34001, 36100, 37195.

Open

35001, 35002, 35005, 35180, 35188, 35201, 35231, 35261, 35301, 35390, 35501, 35506, 35508, 35509, 35601, 35606, 35642, 35691, 35693, 35695, 35694, 35701, 35800, 35901, 37600, 37605, 37606, 37609, 37615.

Upper extremity

Endovascular

0033T, 0034T, 34101, 34111, 35458, 35475, 35484, 35494, 36120, 36140, 36145, 36215, 36216, 36217, 36218, 36870.

Open

35011, 35013, 35045, 35206, 35207, 35236, 35266, 35311, 35321, 35507, 35511, 35515, 35516, 35518, 35521, 35526, 35612, 35616, 35621, 35623, 35626, 35645, 35650, 35875, 35876, 36819, 36820, 36821, 36825, 36830, 36831, 36832, 36833, 36834, 37607.

Thorax

Endovascular

0035T, 0036T, 0037T, 34051, 36013.

Compartment syndrome

Upper extremity

24495, 25020, 25023.

Lower extremity

27025, 27600, 27601, 27602, 27892, 27893, 27894.

Amputations

Upper extremity

23900, 23920, 23921, 24900, 24920, 24925, 24930, 24931, 25900, 25905, 25907, 25909, 25915, 25920, 25922, 25924, 25927, 25929, 25931, 26910, 26951, 26952.

Lower extremity

27290, 27295, 27590, 27591, 27592, 27594, 27596, 27598, 27880, 27881, 27882, 27884, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825.

Abdomen

Endovascular

34151, 34800, 34802, 34803, 34804, 34805, 34808, 34813, 34820, 34825, 34826, 34900, 35400, 35450, 35452, 35454, 35471, 35472, 35473, 35480, 35481, 35482, 35490, 35492, 36160, 36200, 36245, 36246, 36247, 36248.

Open

34830, 34831, 34832, 34833, 34834, 35081, 35082, 35091, 35092, 35102, 35103, 35111, 35112, 35121, 35122, 35131, 35132, 35182, 35189, 35221, 35251, 35281, 35331, 35341, 35351, 35355, 35361, 35363, 35531, 35536, 35541, 35546, 35548, 35549, 35551, 35560, 35563, 35565, 35631, 35636, 35651, 35641, 35646, 35647, 35663, 35665, 35840, 35870, 35907, 37617, 37799.

Lower extremity

Endovascular

34201, 34203, 35456, 35459, 35470, 35474, 35483, 35485, 35493, 35495, 36002, 37201, 37202, 37203, 37204, 37205, 37206, 37207, 37208, 37209, 37250, 37251.

Open

34812, 35141, 35142, 35151, 35152, 35184, 35190, 35226, 35256, 35286, 35371, 35372, 35381, 35533, 35556, 35558, 35566, 35571, 35583, 35585, 35587, 35654, 35656, 35661, 35666, 35671, 35681, 35682, 35683, 35685, 35686, 35700, 35721, 35741, 35761, 35860, 35879, 35881, 35903, 37618.

Venous

34401, 34421, 34451, 34471, 34490, 34501, 34502, 34510, 34520, 34530, 35460, 35476, 36005, 36011, 36012, 36468, 36469, 36470, 36471, 37140, 37145, 37160, 37180, 37181, 37620, 37650, 37660, 37720, 37730, 37735, 37760,

37780, 37785, 37500, 37565, 36010, 36800, 36810, 36815, 36835, 36860, 36861, 36014, 36015, 36822, 36823.

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