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A Prediction Model Incorporating Peripheral Eosinopenia as a Novel Risk Factor for Death After Hospitalization for *Clostridioides difficile* Infection

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Abstract

BACKGROUND AND AIMS: *Clostridioides difficile* infection (CDI) is associated with a range of outcomes, and existing prediction models for death among patients with CDI are imprecise. Peripheral eosinopenia has been proposed as a novel risk factor for death among patients with CDI but has not been incorporated into prediction models. This study aimed to develop and validate a prediction model for death among patients hospitalized with CDI that incorporated peripheral eosinopenia.

METHODS: Eosinopenia was defined as 0 eosinophils/ μL on the soonest peripheral blood drawn within the 48-hour window of the CDI test (before or after). Adults were eligible for the study if they were hospitalized at any one of 3 large, unaffiliated hospital networks, tested positive for CDI

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Ying Wang contributed to study conception/coordination, data analysis, manuscript writing, and revision. Hojjat Salmasian contributed to data acquisition/processing and manuscript revision. Aaron Schluger contributed to data analysis and manuscript writing. Angela Gomez-Simmonds contributed to manuscript revision. Alexa Choy contributed to data analysis. Jianhua Li contributed to data acquisition/processing. Jordan E. Axelrad contributed to data acquisition/processing and manuscript revision. Daniel E. Freedberg contributed to study conception/coordination/design, data analysis, manuscript writing, and revision.

Supplementary Materials

Material associated with this article can be found in the online version at <https://doi.org/10.1016/j.gastha.2021.10.002>.

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The authors disclose no conflicts.

Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:

The study data, analytic methods, and study materials will not be made available to other researchers.

by stool polymerase chain reaction, and received appropriate anti-CDI treatment. Patients were followed for all-cause death for up to 30 days.

RESULTS: There were 4518 unique hospitalized adults with CDI included (2142 in the derivation cohort and 2376 in the validation cohort). All-cause 30-day mortality was 9% and 10% in the cohorts. In the validation cohort, the factors most strongly associated with death were eosinopenia (adjusted odds ratio [aOR] 2.49, 95% confidence interval [CI] 1.77–3.50), albumin <3 g/dL (aOR 3.26, 95% CI 2.13–3.49), and creatinine >1.5 mg/dL (aOR 2.55, 95% CI 1.86–3.49). A 6-variable clinical prediction model was developed that improved on existing classification schemes for CDI severity (area under the receiver operating characteristic curve of 0.75 vs 0.68).

CONCLUSION: Among adults hospitalized with CDI, peripheral eosinopenia was associated with increased risk of all-cause 30-day mortality. A prediction model incorporating peripheral eosinopenia was developed to improve care for hospitalized patients with CDI through risk stratification.

Keywords

Peripheral Eosinopenia; *Clostridioides difficile* Infection (CDI); Prediction Model for *Clostridioides difficile* Infection Mortality

Introduction

Clostridioides difficile infection (CDI) is the leading cause of health care–associated infection, and the short-term mortality among those with health care–associated CDI ranges from 5% to 22% depending on the population studied.^{1–4} Guidelines from the Infectious Diseases Society of America (IDSA) and other organizations suggest categories of CDI severity for the purpose of risk-stratifying patients for adverse outcomes and making treatment decisions. If predictors for CDI-related mortality can be accurately identified, then resources can be appropriately directed toward the patients at the highest risk for adverse outcomes.

Leukocytosis and elevated creatinine are established predictors of CDI-related mortality and are incorporated into the severity categories of most guidelines^{5,6}; additionally, advanced age and low serum albumin identify patients with CDI at increased risk for death in multiple populations.⁷ However, whether these or other variables are optimal for defining CDI-associated mortality is unknown.

Recently, Kulaylat et al⁸ found that eosinopenia, defined as a peripheral eosinophil count of 0.0 cells/ μ L, is associated with mortality among patients with CDI. Although *C difficile* clinical prediction tools and guidelines have been previously tested to identify patients who are at increased risk for poor outcomes, none of these tools incorporate peripheral eosinopenia.^{9,10}

Our study aimed to develop and validate a clinical prediction score model using easily obtainable clinical and laboratory data, including peripheral eosinopenia, to identify the patients with CDI at the highest risk for death.

Methods

Setting

This was a 3-center retrospective study that included Columbia University Medical Center (CUMC), Brigham and Women's Hospital (BWH), and NYU Langone Health (NYU). The study timeframe was from January 2010 to June 2018 for CUMC and NYU and from June 2015 to December 2018 for BWH. This timeframe was selected because it reflected center-specific periods when relevant variables were complete within the electronic health record and when use of the Cepheid stool polymerase chain reaction (PCR) to diagnose CDI was universal across all 3 institutions. This study was approved by the institutional review boards of CUMC, BWH, and NYU.

Population

Patients who were hospitalized at any one of the 3 participating institutions were considered for the study if they had a positive *C difficile* PCR for the toxin B gene performed on an unformed stool specimen and received appropriate anti-CDI treatment (including oral vancomycin, oral metronidazole, and intravenous metronidazole and fidaxomicin) within 48 hours of the index test (both before and after). Patients with community-acquired and with health care-associated CDI were included in the primary analysis, and stratified sensitivity analyses were subsequently performed. Patients were excluded from the study if they did not have a peripheral eosinophil count measured within 48 hours of the index *C difficile* test. For patients with multiple positive stool tests for *C difficile*, the first test was chosen to study unique individuals.

Primary Outcome

The primary outcome was death from any cause within 30 days after the index CDI test. CDI-attributable mortality was initially considered as a primary outcome, but this was abandoned because of difficulty in adjudicating the cause of death.¹¹ Secondary outcomes included colectomy and death within 90 days after the index CDI test. To evaluate the cause of death, a manual chart review was performed among the patients who died within the derivation cohort (CUMC). Death was determined from the hospital electronic medical record (EMR), which interfaces with the national social security death index at all 3 participating institutions.

Covariates

Using automated electronic queries, peripheral eosinopenia and the following covariates were extracted and examined: demographics (age, sex, and self-identified race/ethnicity), comorbidities based on the Charlson comorbidity index,^{12,13} and vital signs/laboratory results using the worst values within the 48-hour window of the index test (before or after). Peripheral eosinopenia was classified categorically as by Kulaylet et al based on a peripheral eosinophil count of 0.0 cells/ μL on the automated differential from the peripheral blood drawn within the 48-hour window of the index test. Age was classified into approximate tertiles using categories of age 18–55 years, 56–75 years, and older than 76 years. Laboratory values were classified categorically based on institutional laboratory reference

ranges for normal or, in the case of serum creatinine and white blood cell (WBC) count, based on the cutoffs used in the IDSA/Society for Healthcare Epidemiology of America (SHEA) CDI disease severity criteria which are a WBC count $\geq 15,000$ cells/mL and a serum creatinine >1.5 mg/dL.⁵ Use of vasopressors and/or hospitalization in an intensive care unit (ICU) within 48 hours of the positive CDI test were also evaluated as predictor variables for death, based on the IDSA/SHEA guideline which uses hypotension to define the highest category of CDI disease severity. Vasopressor use was classified as present if vasopressors were used at any dose or for any duration, and otherwise, vasopressor use was classified as absent.

Statistical Approach

The final data set was divided a priori into 2 cohorts, a derivation cohort using the data from CUMC and a validation cohort using combined data from BWH and NYU. Using the derivation cohort, a multivariable logistic regression model was developed, modeling 30-day mortality as a function of peripheral eosinopenia and the other covariates at the time of CDI testing. Clinical prediction tools must consider both model performance and parsimony¹⁴; to strive toward both of these, we used 2 strategies for modeling. First, we used 10-fold cross validation and a bootstrapping approach to select model variables and build a model with the best fit for the outcome, regardless of model complexity. Second, to optimize parsimony, we produced a reduced model through stepwise subtraction of variables, retaining only those with an independent relationship with 30-day mortality ($P < .05$ for each variable). β -coefficients from this reduced logistic regression model were then used to develop a clinical prediction tool by translating coefficients into point scores (rounded to the nearest 0.5).¹⁴ The final clinical prediction tool was then validated in the separate cohort of patients from BWH and NYU. Using the validation cohort, sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC) were calculated to evaluate the tool's ability to predict 30-day mortality.

Additional analyses were conducted. First, within the validation cohort, the final model was re-run for the composite outcome of mortality or colectomy within 90 days. Next, we stratified patients based on community-acquired CDI versus health care-associated CDI using a cutoff of a positive test within <72 hours of hospital admission to define community-associated CDI. Finally, to evaluate the cause of death, a manual chart review was performed within the derivation cohort of the 199 patients who died within 30 days of CDI testing using the approach suggested by Brooks et al.¹⁵ All statistical testing was carried out using Stata 16 (StataCorp, College Station, TX), and all analyses were performed 2-sided at the alpha 0.05 level of significance.

Results

Outcomes and Patient Characteristics

Of the patients considered for this study, 29.5% were excluded because of lack of the peripheral eosinophil count within 48 hours of the diagnosis of CDI. A total of 4518 patients were included in the study (CUMC: 2142 and BWH/NYU: 2376). Thirty-day mortality was similar between the cohorts at 9% and 10% for the derivation and validation cohorts,

respectively (Table 1). Other patient characteristics were relatively similar between the 2 study cohorts. In addition, we stratified patients by peripheral eosinopenia, with 1856 patients in the eosinopenia group and 2662 patients in the noneosinopenia group (Table A3). Overall, patients in the eosinopenia group were more likely to have abnormal vital signs (temperature and heart rate), as well as abnormal laboratory values including WBC count, platelet count, total bilirubin, and albumin.

Derivation Cohort

Using the data from the derivation cohort (CUMC), a multivariable logistic regression model was constructed for 30-day mortality as a function of the predictor variables, which had been selected based on prior associations with increased risk of death among patients with CDI⁷ (Table A1). First, a cross-validation approach was used to optimize model performance. This model included all predictor variables except for mean arterial pressure. Second, a reduced model was developed that optimized parsimony and included only the predictor variables that were independently associated with 30-day mortality. This reduced model included eosinopenia (adjusted odds ratio [aOR] 1.65, 95% confidence interval [CI] 1.18–2.31), age, WBC count, albumin, creatinine, and ICU stay (Table A1).

Clinical Prediction Model

The parsimonious model was used to develop a clinical prediction tool that included the same 6 variables as the final model, which were weighed based on the strength of their relationship with death (Table 2). In this tool, hospitalization in the ICU received 5 points, age ≥ 76 years old received 3 points, and all other predictor variables received 2 points.

Validation Cohort

Next, the clinical prediction model was tested within an independent validation cohort that included combined patient data from BWH and NYU ($n = 2376$). The model was applied to the validation cohort, generating a total prediction score for each patient that ranged from 0 to 16. Thirty-day mortality ranged from 0% among 141 patients (5.9% of the cohort) with a score of 0–45% among 40 patients (1.7% of the cohort) with a score of 16 (Figure). The sensitivity and specificity of the clinical prediction tool within the validation cohort are shown in Table 3. At a prediction score of 6 or less, model sensitivity was 85% with a specificity of 50%. At a score of 8 or greater, sensitivity and specificity were 62% and 72%, respectively. The AUROC associated with this risk score model was 0.75 (Figure A1). A 5-variable model, omitting peripheral eosinopenia, had an AUROC of 0.73.

Performance Differences Between Models

To assess for a difference in performance between this parsimonious model and the more complete model built using a bootstrapping approach, we similarly derived a prediction tool using the variables from the bootstrapped model. Although this model included a total of 12 variables, the overall performance was minimally improved compared with the parsimonious model (AUROC 0.79, Figure A1). Conversely, these models were substantially improved compared with a simplified model that included only leukocytosis and elevated creatinine (AUROC 0.68), as suggested by current guidelines (Figure A1).

Multivariable Model Within the Validation Cohort

Using data from the validation cohort, a multivariable logistic regression model was built based on the clinical prediction tool. Eosinopenia at the time of CDI testing was an independent predictor of 30-day mortality (aOR 2.49, 95% CI 1.77–3.50). Similarly, leukocytosis (aOR 1.60, 95% CI 1.17–2.20), low albumin (aOR 3.26, 95% CI 2.13–4.98), creatinine >1.5 mg/dL (aOR 2.55, 95% CI 1.86–3.49), and older age (aOR 1.88, 95% CI 1.22–2.90 for age 56–75 years; aOR 2.20, 95% CI 1.38–3.51 for age ≥76 years) were all associated with death within 30 days (Table 4).

Sensitivity Analyses and Cause of Death

Within the validation cohort, the final model was re-run for the composite outcome of mortality or colectomy within 90 days. Extending the study period resulted in an additional number of 133 deaths (36.3% of overall deaths) which occurred from 31 to 90 days after the index *C difficile* test. There were no substantive changes in the estimates for the predictor variables, although the association between eosinopenia and the composite outcome was slightly attenuated (aOR 2.00, 95% CI 1.48–2.70). Next, we stratified patients based on community-acquired CDI versus health care-associated CDI using a cutoff of a positive test within <72 hours of hospital admission to define community-associated CDI.¹ The association between eosinopenia and day mortality was similar among those with community-acquired CDI (n = 1414, aOR 2.79, 95% CI 1.72–4.53) and health care-associated CDI groups (n = 962, aOR 2.34, 95% CI 1.44–3.82). Finally, to evaluate the cause of death, a manual chart review was performed within the derivation cohort of the 199 patients who died within 30 days of CDI testing using the approach suggested by Brooks et al.¹⁵ The leading causes of death were sepsis (41%), respiratory failure (10%), and cardiac causes (9.0%) (Table A2).

Discussion

In this multicenter retrospective study, we developed a clinical prediction model for death among hospitalized patients with CDI that incorporated a novel risk factor, peripheral eosinopenia. Kulaylat et al⁸ first suggested that eosinopenia has prognostic value in CDI; our study validates their result and extends it by incorporating eosinopenia into a simple, 6-variable clinical prediction model. This clinical prediction model improves on the current IDSA/SHEA classification scheme for severity of CDI. At a specificity of 50%, this model has 85% sensitivity for death, whereas the existing classification scheme has a sensitivity of 75%. At a prediction score cutoff of 4, model sensitivity improves to 96% with a specificity of 25%. The model may inform future decision-making about hospitalized patients with CDI, with model cutoffs selected depending on the decision at hand (eg, a more specific cutoff for whether to use a new therapy with potential risks and a more sensitive cutoff for whether to triage patients to a higher level of monitoring).

There are several reasons to strive toward a more accurate classification of risk for death among hospitalized patients with CDI. CDI varies in clinical presentation, and PCR-based testing for *C difficile*, which is typically reported as positive versus negative rather than semi-quantitatively, does not distinguish between patients who are colonized

and those who are infected.^{16,17} If patients can be identified who are at the increased risk for poor outcomes, then more resources can be allocated toward those patients such as prioritization for more intensive monitoring (eg, for stepdown or ICU units). In the past, guidelines have suggested that CDI severity should determine whether metronidazole is added to vancomycin for treatment (ie, that patients with more severe CDI should receive both antibiotics and that those with less severe CDI should receive vancomycin monotherapy). WBC count >15,000 cells/mL and creatinine >1.5 mg/dL have been used as the factors to determine CDI severity; this study suggests that other factors, including peripheral eosinopenia, better predict CDI severity.^{5,18} Looking forward, as new therapies for CDI become available, the patients who are at the highest risk for poor outcomes could reasonably be prioritized for these therapies based on our clinical prediction model. Such prioritization will be especially important if new therapies have high cost or potential adverse effects.

The mechanism linking peripheral eosinopenia with mortality in CDI is uncertain, but mouse models show that *C difficile* binary toxin can deplete circulating eosinophils by binding Toll-like receptor 2 on eosinophils to induce apoptosis.¹⁹ Alternatively, the relationship between eosinopenia and death may be nonspecific to CDI; supporting this conclusion, peripheral eosinopenia has also been associated with death among unselected critically ill patients without CDI.²⁰ The cause of death is notoriously difficult to ascertain retrospectively, but the plurality of deaths in this study was due to sepsis.²¹ Future studies that gather biospecimens may wish to further interrogate the mechanisms by which eosinophils may confer protection against death among patients with CDI.

In addition to eosinopenia, age, low albumin, elevated creatinine, elevated WBC count, and hospitalization in the ICU at the time of CDI testing were all independently associated with death. Prior studies have shown similar associations.^{22–24} These variables are likely to be nonspecific with CDI and rather serve to mark patients with acute and/or chronic illness. Interestingly, these variables, rather than the Charlson comorbidity index (a weighted score of medical comorbidities), better predicted death. All the variables utilized by our clinical prediction model are routinely measured in hospitalized patients, enhancing the generalizability of the study results.

This study has several strengths. It was large, with nearly 5000 patients studied across 3 unaffiliated medical systems. It focused on death as an endpoint, which is unlikely to be misclassified and of obvious clinical importance. It used a transparent modeling strategy, with derivation and validation cohorts that were distinct and defined a priori. There are also limitations. Stool PCR testing was used to classify patients as having CDI. PCR-based testing is now the most common means of diagnosing CDI, but does not well distinguish infection from colonization.^{17,25} To address this limitation, we required that patients also receive appropriate anti-CDI treatment (eg, oral vancomycin) to verify that providers were sufficiently convinced of the CDI diagnosis that they were willing to initiate treatment. For those patients with multiple stool PCR tests in the EMR, the first test was chosen to study unique individuals. It is possible that some patients may have prior *C difficile* tests that were not captured in our EMR, and therefore, a small proportion of our patients may have had recurrent rather than incident CDI. The decision was made to combine community-acquired

and health care–associated CDI in the primary analysis, although sensitivity analyses suggested that the eosinopenia–death relationship remained in both instances. Finally, the study evaluated all-cause mortality, and we cannot know with certainty the extent to which CDI contributed to each death. Because all-cause mortality was the study’s outcome of interest, high model specificity is unlikely.

In sum, this study found that peripheral eosinopenia was associated with increased risk for death among hospitalized patients with CDI. This relationship was robust and held true for both community-acquired and health care–associated CDI. A clinical prediction model for death was developed that included eosinopenia, age, creatinine, albumin, WBC count, and hospitalization in the ICU. This prediction model may be useful for future studies or guidelines seeking to risk-stratify hospitalized patients with CDI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

aOR	adjusted odds ratio
AUROC	area under the receiver operating characteristic curve
BWH	Brigham and Women’s Hospital
CDI	<i>Clostridioides difficile</i> infection
CI	confidence interval
CUMC	Columbia University Medical Center
EMR	electronic medical record
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
MAP	mean arterial pressure
PCR	polymerase chain reaction
WBC	white blood cell

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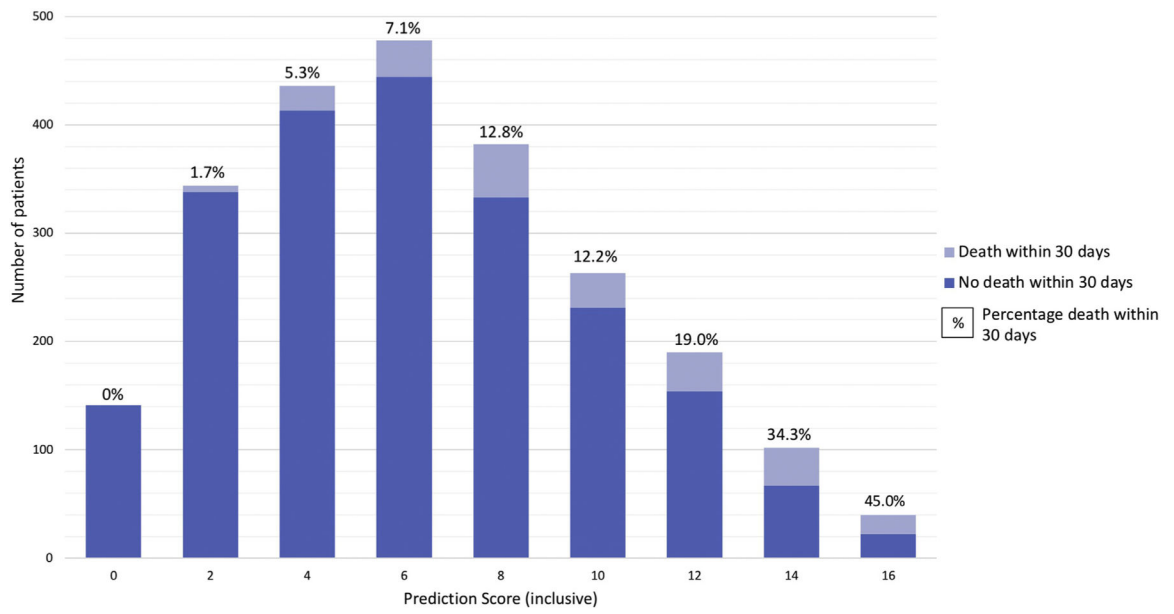


Figure.
Number of patients at each prediction score (validation cohort, n = 2376 total).

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Table 1.

Clinical and Demographic Characteristics of the Derivation and Validation Cohorts

Baseline characteristics	CUMC (n = 2142) n (%)	BWH and NYU (n = 2376) n (%)
Eosinopenia	686 (32)	1170 (49)
Sex		
Female	1100 (51)	1287 (54)
Male	1042 (49)	1089 (46)
Age		
18–55 y	650 (30)	691 (29)
56–75 y	870 (41)	1073 (45)
76 y	622 (29)	612 (26)
Race/ethnicity		
White	667 (31)	1743 (73)
Black	241 (11)	237 (10)
Hispanic	384 (18)	116 (5)
Other/unclassified	850 (40)	280 (12)
Charlson comorbidity index		
0–3 points	785 (37)	970 (41)
4–6 points	812 (38)	909 (38)
>7 points	545 (25)	496 (21)
Vital signs		
Temperature <35, >38 °C	250 (27)	439 (24)
Heart rate >100 beats/min	1223 (67)	870 (48)
MAP <65 mmHg	725 (40)	466 (26)
Laboratory results		
WBC count >15 × 10 ³ /μL	841 (39)	696 (29)
Hematocrit <37.2%	1974 (92)	1294 (90)
Platelet count <156 × 10 ³ /μL	800 (37)	942 (40)
Total bilirubin >1.3 mg/dL	304 (20)	132 (12)
Albumin <3 g/dL	614 (32)	1168 (60)
Creatinine >1.5 mg/dL	887 (42)	678 (29)
Vasopressor use	274 (13)	489 (21)
ICU stay	709 (33)	602 (25)
Outcomes		
Mortality at 30 d	199 (9)	233 (10)
Colectomy	8 (0.4)	42 (2)

MAP, mean arterial pressure.

Table 2.

Clinical Prediction Scale

Variable	Score
Eosinopenia	2
Age	
18–55 y	–
56–75 y	2
76 y	3
Laboratory results	
WBC count $>15 \times 10^3/\mu\text{L}$	2
Albumin <3 g/dL	2
Creatinine >1.5 mg/dL	2
ICU stay	5
Total prediction score	18

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Table 3. Sensitivity and Specificity at Different Cutoff Values for the Clinical Prediction Score (BWH/NYU)

Prediction score	Sensitivity	Specificity	True		False	
			Positive	Negative	Positive	Negative
0	1.00	0.00	233	0	2143	0
2	1.00	0.07	233	141	2002	0
4	0.96	0.25	224	545	1598	9
6	0.85	0.50	198	1066	1077	35
8	0.62	0.72	145	1550	593	88
10	0.45	0.86	105	1845	298	128
12	0.29	0.94	67	2022	121	166
14	0.12	0.98	29	2102	41	204
16	0.05	1.00	11	2136	7	222

Table 4.

Multivariable Model for the Relationship Between Eosinopenia and 30-D Mortality (BWH/NYU)

Variable	Full model (odds ratio, 95% CI)
Eosinophil count	
>0	Reference
= 0	2.49 (1.77–3.50)
Age	
18–55 y	Reference
56–75 y	1.88 (1.22–2.90)
76 y	2.20 (1.38–3.51)
Laboratory results	
WBC count $>15 \times 10^3/\mu\text{L}$	1.60 (1.17–2.20)
Albumin <3 g/dL	3.26 (2.13–4.98)
Creatine >1.5 mg/dL	2.55 (1.86–3.49)
ICU stay	1.84 (1.34–2.53)

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