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ORIGINAL RESEARCH

Fibrinogen-to-Albumin Ratio is Associated with All-Cause Mortality in Cancer Patients

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Background: Past studies have identified fibrinogen-to-albumin ratio (FAR) as a novel prognostic immune biomarker in various diseases. Here, we investigated the prognostic value of FAR in all combined cancer mortality.

Methods: We extracted patient data from the Multiparameter Intelligent Monitoring in Intensive Care Database III. FAR was measured prior to hospital admission. Only first admission data from each patient were used. Baseline data were extracted within 24 h after admission. The clinical endpoints were 90- and 365-day all-cause cancer mortality. Cox proportional hazards models and subgroup analyses were used to determine the relationship between FAR and these clinical endpoints.

Results: A total of 652 eligible patients were enrolled. Upon adjusting for age and gender, multivariate analysis revealed correlation between higher FAR values and increased risk of all-cause mortality. After adjusting for more confounding factors, higher FAR values significantly correlated with 90- and 365-day all-cause mortality relative to low FAR values (tertile 3 vs tertile 1: HR, 95% CI: 1.65, 1.15–2.39; 1.52, 1.10–2.10).

Conclusion: Our findings indicate that FAR may predict the risk of cancer mortality and is an independent prognostic indicator of all-cause mortality in cancer patients.

Keywords: fibrinogen-to-albumin ratio, mortality, cancer, biomarker

Introduction

Cancer imposes a serious disease burden worldwide[1] and cancer mortality is projected to increase as the global population continues to age.[2] The top-10 cancer types are lung, esophageal, liver, cervical, stomach, breast, colorectal, lymphocytes, nasopharyngeal, and ovarian cancer. Five-year survival rates for all-combined cancer were only 30.82%.[3] The main cancer treatment methods are surgery, chemotherapy, and radiotherapy. However, despite cancer treatment advances, many cancers are associated with poor prognosis.[4,5] Thus, effective and noninvasive prognostic biomarkers are needed to guide personalized treatment and improve cancer outcomes.

Systemic inflammation status has emerged as an indicator of malignancy. More and more reliable evidence shows that cancer-related hypercoagulable state, inflammation and malnutrition are very common in cancer patients, and which are closely associated with cancer initiation, progression, metastasis, and resistance to chemotherapy.[6] Albumin and fibrinogen are two commonly used circulating inflammatory proteins. Fibrinogen is an acute-phase protein produced by the liver. The plasma level of fibrinogen increases in hypercoagulable state and inflammatory state.[7] A large amount of evidence shows that fibrinogen-related coagulation dysfunction is closely related to tumor angiogenesis, invasion, progression and metastasis.[8,9] Likewise, albumin is also produced by

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hepatocytes. Proinflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) inhibit albumin production through hepatocytes.[10] The decrease of plasma albumin level indicates high degree of inflammation, poor nutritional status and poor therapeutic effect. Albumin is a well-established prognostic factor for various disorders, including oral cavity cancer,[11] metastatic pathological femur fractures,[12] and amyotrophic lateral sclerosis.[13] The prognostic role of fibrinogen has also been reported in disorders like spontaneous intracerebral hemorrhage.[14] Therefore, fibrinogen and albumin better reflect the process of tumor inflammation. Moreover, fibrinogen-to-albumin ratio (FAR) has emerged as a prognostic immune biomarker in various diseases like gallbladder cancer,[15] breast cancer,[16] and ST-segment elevation myocardial infarction.[17]

However, the role of FAB in all-combined cancer mortality and its cancer prognostic value is unclear. Here, we examined the relationship between FAB and cancer mortality using data from MIMIC-III V1.3 database and its prognostic value in cancer.

Methods

Study Population

The research was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Data were downloaded from MIMIC-III version 1.4 database and included vital signs, medication, demographic data, and other essential data from patients admitted into intensive care (53,423 distinct admissions) at the Beth Israel Deaconess Medical Center (BIDMC, Boston) from 2001 to 2012.[18] Approval was obtained by the Massachusetts Institute of Technology and the Institutional Review Boards before applying the data. Requirement for individual patient consent was waived because the project did not affect clinical care and all protected health information was de-identified. All data accessed complies with relevant data protection and privacy regulations.

Population Selection Criteria

Of the patients recorded in the MIMIC-III database, we selected cancer patients aged >18, who were first admitted into hospital for >1 day. Those lacking >5% of individual data or whose biopsies revealed hematological malignancy were excluded.

Data Extraction

Patient demographic data, including age, gender, ethnicity, vital signs, laboratory characteristics, comorbidities, and scoring systems were retrieved. Vital signs within 24 h after ICU admission included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate, respiratory rate, temperature, and SPO2. Comorbidities included congestive heart failure (CHF), coronary artery disease (CAD), atrial fibrillation (AFIB), stroke, renal disease, liver disease, pneumonia, respiratory failure, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS). Laboratory measurements included fibrinogen, albumin, bicarbonate, anion gap, creatinine, bilirubin, chloride, glucose, hematocrit, hemoglobin, platelet, sodium, potassium, blood urea nitrogen (BUN), white blood cell (WBC), lactate, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) in the first 24 h. The outcomes of our study were 90- and 1-year mortality rates. Patient day of admission was considered the start day of follow-up, and all participants were followed up for at least a year. Date of death was obtained from the Social Security Death Index records.

Statistical Analysis

Three subgroups were developed based on FAR. Continuous results were presented as the average value ± standard deviation (SD). Categorical data were presented as percentage or frequency. Kruskal–Wallis *H*-test and $\chi 2$ tests were used to compare baseline feature differences between the FAR subgroups for continuous variables and categorical variables. COX regression analysis was used to determine the association between FAR and cancer outcomes. The matched hazard ratio was changed by >10% upon adding covariances to the model.[19] There was no covariate adjustment in Model 1. Age and gender were adjusted in Model 2. Confounders like age, gender, anion gap, SBP, respiratory rate, hemoglobin, INR, temperature, SPO2, chronic conditions including AFIB (yes/no), renal disease, respiratory failure, ARDS (yes/no), and pneumonia were adjusted in Model 3. All analyses were done on R version 3.6.1. *P* values were two-sided and $p=<0.05$ was considered statistically significant.

Results

Subject Characteristics

A total of 652 cancer patients were included. Baseline clinical, laboratory, and demographic data are shown in Table 1. This analysis showed that the proportion of renal disease, pneumonia, respiratory failure, heart rate, respiratory rate, platelet count, and BUN level were elevated in the high-FAR group. SBP, MBP, serum albumin levels,

Table 1 Characteristics of the Study Patients According to Neutrophil Percentage-to-Albumin Ratios

Characteristics	Neutrophil Percentage-to-Albumin Ratios			
	<20.5 (n = 313)	**≥20.5, <25.0 (n = 313)**	**≥25.0 (n = 314)**	***P* value**
Age, years	66.5 ± 14.8	67.2 ± 15.0	67.0 ± 14.2	0.839
Gender, n (%)				0.893
Female	139 (44.4)	140 (44.7)	145 (46.2)	
Male	174 (55.6)	173 (55.3)	169 (53.8)	
Ethnicity, n (%)				0.328
White	221 (70.6)	224 (71.6)	224 (71.3)	
Black	34 (10.9)	20 (6.4)	28 (8.9)	
Other	58 (18.5)	69 (22.0)	62 (19.7)	
NPAR	16.7 ± 4.2	22.6 ± 1.3	31.3 ± 7.1	<0.001
SBP, mmHg	130.5 ± 17.8	129.4 ± 17.5	121.4 ± 17.7	<0.001
DBP, mmHg	64.5 ± 11.1	64.8 ± 11.7	61.5 ± 11.0	<0.001
MBP, mmHg	83.5 ± 11.4	83.7 ± 12.0	79.3 ± 11.3	<0.001
Heart rate, beats/minute	80.4 ± 16.2	81.8 ± 14.5	87.6 ± 17.4	<0.001
Respiratory rate, beats/minute	18.4 ± 3.5	18.4 ± 3.4	20.3 ± 4.7	<0.001
Temperature, °C	36.9 ± 0.6	37.0 ± 0.6	36.9 ± 0.8	0.861
SPO2, %	97.5 ± 1.9	97.8 ± 2.1	97.5 ± 2.6	0.307
Comorbidities, n (%)				
Congestive heart failure	28 (8.9)	26 (8.3)	52 (16.6)	0.001
Coronary artery disease	43 (13.7)	64 (20.4)	56 (17.8)	0.082
Atrial fibrillation	84 (26.8)	90 (28.8)	108 (34.4)	0.100
Renal disease	27 (8.6)	35 (11.2)	64 (20.4)	<0.001
Liver disease	13 (4.2)	10 (3.2)	22 (7.0)	0.067
Pneumonia	72 (23.0)	84 (26.8)	126 (40.1)	<0.001
Malignancy	52 (16.6)	38 (12.1)	48 (15.3)	0.267
Respiratory failure	79 (25.2)	101 (32.3)	184 (58.6)	<0.001
COPD	1 (0.3)	3 (1.0)	4 (1.3)	0.416
Laboratory parameters				
Neutrophil percentage, %	66.9 ± 18.9	83.3 ± 7.5	85.4 ± 7.2	<0.001
Albumin, g/dl	4.0 ± 0.6	3.7 ± 0.4	2.8 ± 0.5	<0.001
Bicarbonate, mg/dl	25.8 ± 3.7	25.3 ± 3.5	24.3 ± 4.8	<0.001
Anion gap, mmol/l	16.8 ± 3.8	16.9 ± 3.8	17.5 ± 5.1	0.110
Creatinine, mEq/l	1.4 ± 2.5	1.5 ± 1.8	2.0 ± 1.7	<0.001
Chloride, mmol/l	106.6 ± 6.1	107.2 ± 6.7	108.8 ± 7.4	<0.001
Glucose, mg/dl	178.5 ± 87.1	192.5 ± 81.9	196.7 ± 94.2	0.025
Hematocrit, %	38.3 ± 6.1	38.3 ± 5.3	35.2 ± 6.1	<0.001
Hemoglobin, g/dl	13.0 ± 2.1	13.0 ± 1.9	11.7 ± 2.2	<0.001
Platelet, 10^9 /l	246.3 ± 112.6	258.6 ± 105.3	250.6 ± 144.0	0.446
Sodium, mmol/l	141.5 ± 5.3	141.6 ± 5.4	141.5 ± 5.6	0.972
Potassium, mmol/l	4.4 ± 0.8	4.4 ± 0.8	4.7 ± 0.9	<0.001
BUN, mg/dl	24.1 ± 19.1	24.4 ± 16.7	38.5 ± 29.3	<0.001
WBC, 10^9 /l	13.9 ± 21.5	14.0 ± 6.1	15.9 ± 8.9	0.109
PT, second	15.9 ± 9.2	15.8 ± 9.1	20.0 ± 14.4	<0.001
APTT, second	35.4 ± 21.2	37.1 ± 26.4	50.2 ± 36.5	<0.001
INR	1.5 ± 1.2	1.5 ± 1.4	2.0 ± 1.9	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Neutrophil Percentage-to-Albumin Ratios			
	<20.5 (n = 313)	≥20.5, <25.0 (n = 313)	≥25.0 (n = 314)	*P* value
Scoring systems				
APSIII	42.9 ± 19.9	43.3 ± 20.0	57.9 ± 24.8	<0.001
SAPSII	35.9 ± 13.8	38.4 ± 13.1	46.4 ± 14.6	<0.001
30-day mortality, n (%)	67 (21.4)	77 (24.6)	100 (31.8)	0.009
90-day mortality, n (%)	78 (24.9)	92 (29.4)	125 (39.8)	<0.001
365-day mortality, n (%)	97 (31.0)	107 (34.2)	145 (46.2)	<0.001

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; WBC, white blood cell; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; APSIII, acute physiology score III; SAPSII, Simplified Acute Physiology Score II.

bicarbonate, bilirubin, glucose, hemoglobin, potassium, lactate, and APTT were decreased (p=<0.05 for all).

Association Between FAR and Cancer Outcomes

Here, different models were established to evaluate the independent effects of FAR and cancer outcomes after adjusting for other potential confounders. Effect sizes (HR) and 95% Cis are displayed in Table 2. We stratified FAR levels by tertiles to assess if FAR was associated with 90- and 365-day all-cause mortality. In model I, after adjusting for age and gender, higher FAR values correlated with elevated risk of all-cause mortality. In model II, after adjusting for age, gender, anion gap, diastolic blood pressure, respiratory rate, hemoglobin, INR, temperature, SPO2, atrial fibrillation, renal disease, respiratory failure, ARDS, and pneumonia, higher FAR values significantly correlated with high risk of 90- and 365-day all-cause mortality relative to low FAR levels (tertile 3 vs tertile 1: HR, 95% CI: 1.65, 1.15–2.39; 1.52, 1.10–2.10).

Subgroup Analyses

Subgroup analysis of the association between FAR and 90-day all-cause mortality (Table 3) revealed no interactions in most strata (p=0.0506–0.9372). Patients with a DBP ≥60 mmHg, MBP ≥76mmHg, hemoglobin ≥11.2g/dl, bicarbonate ≥24 mg/dl, and glucose ≥180mg/dl had significantly higher risk of 90-day mortality with FAR ≥0.192 (HR, 95% CI: 3.47, 1.91–6.31; 3.43, 1.95–6.02; 3.78, 2.16–6.62; 3.20, 1.77–5.78; 3.02, 1.81–5.04, respectively). Similarly, patients with a chloride <109 mmol/l and respiratory failure (no) showed increased risk with a FAR ≥0.192 (HR, 95% CI: 1.91, 1.18–3.10 and 2.51, 1.55–4.06).

Discussion

A positive association between FAR and cancer mortality was expressed within our study. Our findings show that FAR may predict risk of cancer mortality. The results showed that higher FAR values correlated with increased all-cause mortality in 90- and 365-day after adjusting several variables. Similar observations were found in the model that adjusted for more confounding factors, indicating that FAR is still an independent and effective tumor prognostic marker. Although several previous studies have shown that FAR was associated with mortality in certain cancers, such as stage IB-IIA cervical cancer and resectable gastric cancer,[20,21] evidence of this association is limited. The majority of prior studies focused on FAR's single-type cancer association. As the association between FAR and all-cancer mortality is unclear at this moment, we focused on this relationship.

Fibrinogen, a protein used in blood coagulation, is also responsible for the mediation between hemostatic components and cancer biology. Fibrinogen has been shown via mechanisms, such as angiogenesis stimulation, platelet adhesion promotion, and tumor cell proliferation/migration via growth factor bondage to promote tumor growth.[22] An analysis of 1196 patients with GC revealed that elevated fibrinogen positively correlates with poor survival.[23] Circulation of albumin and prealbumin can be used to evaluate nutritional and immunity status. Albumin may restrain tumor progression stabilizing DNA replication and enhancing immune response.[24] Albumin, which accumulates at inflammation and tumor sites, can be used to deliver anti-inflammatory and anticancer drugs.[25,26] Additionally, albumin levels are correlated with poor prognosis in cancer due to malnutrition and postoperative complications.[27] FAR, which is mechanistically important

Table 2 HRs (95% CIs) for All-Cause Mortality Across Groups of Neutrophil Percentage-to-Albumin Ratios

NAR	Non-Adjusted		Model I		Model II	
	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value	HR (95% CIs)	*P* value
30-day all-cause mortality						
Tertiles						
<20.5	1.0(ref)		1.0(ref)		1.0(ref)	
≥20.5, <25.0	1.17 (0.85, 1.63)	0.3389	1.11 (0.80, 1.55)	0.5175	1.10 (0.79, 1.54)	0.5670
≥25.0	1.55 (1.13, 2.11)	0.0058	1.52 (1.11, 2.07)	0.0083	1.45 (1.05, 2.00)	0.0254
P trend	0.0044		0.0054		0.0196	
90-day all-cause mortality						
Tertiles						
<20.5	1.0(ref)		1.0(ref)		1.0(ref)	
≥20.5, <25.0	1.21 (0.90, 1.64)	0.2102	1.16 (0.86, 1.57)	0.3421	1.15 (0.85, 1.56)	0.3719
≥25.0	1.71 (1.29, 2.26)	0.0002	1.67 (1.26, 2.22)	0.0004	1.60 (1.19, 2.15)	0.0020
P trend	0.0001		0.0002		0.0013	
365-day all-cause mortality						
Tertiles						
<20.5	1.0(ref)		1.0(ref)		1.0(ref)	
≥20.5, <25.0	1.14 (0.87, 1.50)	0.3539	1.08 (0.82, 1.42)	0.5774	1.08 (0.81, 1.42)	0.6105
≥25.0	1.63 (1.26, 2.11)	0.0002	1.60 (1.24, 2.07)	0.0003	1.50 (1.15, 1.97)	0.0030
P trend	<0.0001		0.0001		0.0017	

Notes: Models were derived from Cox proportional hazards regression models. Non-adjusted model adjust for: none. Adjust I model adjust for: age, ethnicity and gender. Adjust II model adjust for: age, gender, ethnicity, sodium, chloride, congestive heart failure, coronary artery disease, atrial fibrillation, renal disease, liver disease, chronic obstructive pulmonary disease.

Abbreviations: HR, hazard ratio; CI, confidence interval.

for nutrition, coagulation, and systemic inflammation, is strongly correlated with the tumor cell survival, intraversion and adhesiveness leading to increased metastatic potential.[28] This may explain why FAR can be a strong prognostic tool in cancer patients.

FAR's prognostic role was previously applied to several cancers, ranging from esophageal squamous cell carcinoma[29] to metastatic colorectal cancer.[30] Liu et al recently identified FAR as an inflammatory factor, illustrating the status of ankylosing spondylitis.[31] Observations of FAR's prognostic role were expressed proceeding percutaneous coronary intervention in patients with non-ST elevation acute coronary syndrome.[32] Via meta-analysis Zhang et al discovered a strong correlation between FAR and positive lymph node metastasis, distant metastasis, deeper infiltration, and advanced clinical stage.[33] Yu et al were recently able to independently predict resistance to chemotherapeutic drugs and advanced epithelial ovarian cancer prognosis via a biomarker constructed by and albumin-to-fibrinogen ratio. Similarly, within our study, the results showed that higher FAR values were independently associated with increased all-cause mortality at 90 and 365 days of all-cancer, which is consistent with above research results.

The main strengths of our study are its large sample size and in-depth analysis. In addition, this is the first study of the association between FAR and risk of mortality in ICU cancer patients. However, some limitations of the study were worth noting. First, due to its retrospective nature, the study cannot prove a causal relationship between mortality and cancer. Second, although we adjusted for possible risk factors, additional confounders like proinflammatory factors, and unknown factors cannot be ruled out. Third, FAR was assessed for only the first 24 h of admission and the relationship between subsequent FAR and prognosis was not evaluated. The baseline assessment used may increase the risk of misclassification bias.

Conclusions

Our data indicated that FAR is an independent prognostic indicator of all-cause mortality in cancer. However, the prospective cohort studies are needed to validate our conclusions.

Table 3 Subgroup Analysis of the Associations Between the Neutrophil Percentage-to-Albumin Ratios and 30-Day All-Cause Mortality

	No. of Patients	Neutrophil Percentage-to-Albumin Ratios			*P* for Interaction
		<20.5	≥20.5, <25.0	≥25.0	
Age, years					0.2351
<69.2	470	1.0(ref)	1.71 (0.98, 2.97)	2.15 (1.28, 3.60)	
≥69.2	470	1.0(ref)	0.84 (0.56, 1.27)	1.19 (0.81, 1.76)	
Gender					0.8199
Female	424	1.0(ref)	1.26 (0.80, 2.00)	1.69 (1.10, 2.61)	
Male	516	1.0(ref)	1.09 (0.69, 1.74)	1.39 (0.89, 2.17)	
Ethnicity					0.1416
White	669	1.0(ref)	1.12 (0.76, 1.65)	1.47 (1.02, 2.13)	
Black	82	1.0(ref)	4.60 (0.89, 23.72)	4.58 (0.95, 22.07)	
Other	189	1.0(ref)	0.90 (0.47, 1.72)	1.34 (0.72, 2.51)	
SBP, mmHg					0.5523
<127	469	1.0(ref)	1.13 (0.67, 1.88)	1.63 (1.04, 2.56)	
≥127	470	1.0(ref)	1.21 (0.79, 1.86)	1.47 (0.94, 2.32)	
DBP, mmHg					0.1894
<63	469	1.0(ref)	0.78 (0.48, 1.27)	1.30 (0.85, 1.98)	
≥63	470	1.0(ref)	1.66 (1.05, 2.61)	1.85 (1.17, 2.93)	
MBP, mmHg					0.3216
<82	469	1.0(ref)	0.89 (0.54, 1.47)	1.40 (0.91, 2.15)	
≥82	470	1.0(ref)	1.45 (0.93, 2.24)	1.72 (1.09, 2.70)	
Respiratory rate, beats/minute					0.6852
<18	469	1.0(ref)	1.34 (0.84, 2.12)	1.74 (1.08, 2.80)	
≥18	469	1.0(ref)	1.00 (0.63, 1.59)	1.30 (0.86, 1.96)	
Temperature, °C					0.2201
<36.9	466	1.0(ref)	1.57 (0.98, 2.51)	1.69 (1.08, 2.66)	
≥36.9	467	1.0(ref)	0.89 (0.56, 1.40)	1.45 (0.94, 2.21)	
SPO2, %					0.3479
<98	469	1.0(ref)	1.12 (0.66, 1.88)	1.67 (1.04, 2.70)	
≥98	470	1.0(ref)	1.14 (0.75, 1.74)	1.38 (0.92, 2.07)	
Sodium, mmol/l					0.6897
<140	423	1.0(ref)	1.42 (0.85, 2.38)	1.83 (1.11, 3.01)	
≥140	514	1.0(ref)	1.02 (0.66, 1.57)	1.37 (0.92, 2.05)	
Potassium, mmol/l					0.4276
<4.3	427	1.0(ref)	1.24 (0.76, 2.02)	2.09 (1.30, 3.37)	
≥4.3	510	1.0(ref)	1.13 (0.73, 1.77)	1.26 (0.84, 1.90)	
Chloride, mmol/l					0.5696
<107	439	1.0(ref)	1.05 (0.65, 1.69)	1.84 (1.17, 2.89)	
≥107	498	1.0(ref)	1.29 (0.81, 2.04)	1.39 (0.90, 2.15)	
WBC, 10^9 /l					0.0215
<13.1	462	1.0(ref)	1.57 (0.94, 2.64)	2.42 (1.47, 3.98)	
≥13.1	475	1.0(ref)	0.85 (0.55, 1.30)	1.00 (0.67, 1.48)	

(*Continued*)

Table 3 (Continued).

	No. of Patients	Neutrophil Percentage-to-Albumin Ratios			*P* for Interaction
		<20.5	≥20.5, <25.0	≥25.0	
Platelet, 10^9 /l					0.4410
<239	463	1.0(ref)	1.09 (0.68, 1.75)	1.59 (1.04, 2.43)	
≥239	474	1.0(ref)	1.28 (0.80, 2.02)	1.52 (0.96, 2.40)	
Hematocrit, %					0.3502
<37.4	463	1.0(ref)	0.98 (0.60, 1.62)	1.37 (0.89, 2.11)	
≥37.4	474	1.0(ref)	1.35 (0.87, 2.10)	1.74 (1.09, 2.77)	
Hemoglobin, g/dl					0.9761
<12.6	454	1.0(ref)	1.20 (0.73, 1.98)	1.49 (0.96, 2.32)	
≥12.6	483	1.0(ref)	1.16 (0.75, 1.80)	1.61 (1.02, 2.55)	
Creatinine, mEq/l					0.0650
<1.1	446	1.0(ref)	1.46 (0.87, 2.44)	2.17 (1.29, 3.65)	
≥1.1	491	1.0(ref)	1.00 (0.65, 1.55)	1.15 (0.78, 1.69)	
BUN, mg/dl					0.1011
<24	440	1.0(ref)	1.59 (0.98, 2.59)	1.90 (1.09, 3.32)	
≥24	497	1.0(ref)	0.87 (0.56, 1.37)	1.14 (0.78, 1.68)	
Anion gap, mmol/l					0.5589
<16	362	1.0(ref)	1.02 (0.53, 1.94)	1.35 (0.74, 2.47)	
≥16	574	1.0(ref)	1.23 (0.84, 1.81)	1.64 (1.14, 2.36)	
Bicarbonate, mg/dl					0.5392
<25	398	1.0(ref)	1.00 (0.62, 1.63)	1.17 (0.74, 1.84)	
≥25	538	1.0(ref)	1.26 (0.80, 1.98)	1.83 (1.19, 2.82)	
Glucose, mg/dl					0.1462
<164	467	1.0(ref)	0.94 (0.53, 1.65)	1.80 (1.10, 2.95)	
≥164	470	1.0(ref)	1.16 (0.76, 1.75)	1.25 (0.84, 1.87)	
PT, second					0.5228
<14	456	1.0(ref)	1.06 (0.65, 1.72)	1.24 (0.72, 2.15)	
≥14	471	1.0(ref)	1.31 (0.83, 2.05)	1.49 (1.00, 2.22)	
APTT, second					0.5421
<30	461	1.0(ref)	0.90 (0.56, 1.44)	1.09 (0.64, 1.85)	
≥30	464	1.0(ref)	1.62 (1.01, 2.57)	1.77 (1.17, 2.68)	
INR					0.2899
<1.3	446	1.0(ref)	0.89 (0.55, 1.44)	1.11 (0.64, 1.91)	
≥1.3	481	1.0(ref)	1.51 (0.96, 2.38)	1.65 (1.10, 2.50)	
CHF					0.1365
No	834	1.0(ref)	1.27 (0.91, 1.79)	1.73 (1.25, 2.41)	
Yes	106	1.0(ref)	0.38 (0.10, 1.45)	0.71 (0.29, 1.77)	
AFIB					0.9222
No	658	1.0(ref)	1.22 (0.82, 1.82)	1.54 (1.05, 2.26)	
Yes	282	1.0(ref)	1.07 (0.60, 1.89)	1.49 (0.88, 2.51)	
CAD					0.0806
No	777	1.0(ref)	1.37 (0.96, 1.95)	1.58 (1.12, 2.22)	
Yes	163	1.0(ref)	0.53 (0.23, 1.23)	1.35 (0.66, 2.76)	

(*Continued*)

Table 3 (Continued).

	No. of Patients	Neutrophil Percentage-to-Albumin Ratios			*P* for Interaction
		<20.5	≥20.5, <25.0	≥25.0	
Malignancy					0.5813
No	802	1.0(ref)	1.24 (0.87, 1.76)	1.54 (1.10, 2.17)	
Yes	138	1.0(ref)	0.78 (0.31, 1.99)	1.56 (0.74, 3.30)	
Liver disease					0.0806
No	895	1.0(ref)	1.10 (0.78, 1.54)	1.52 (1.10, 2.09)	
Yes	45	1.0(ref)	4.28 (1.10, 16.67)	1.81 (0.49, 6.70)	
Renal disease					0.1191
No	814	1.0(ref)	1.30 (0.91, 1.85)	1.69 (1.20, 2.39)	
Yes	126	1.0(ref)	0.55 (0.23, 1.31)	0.74 (0.37, 1.50)	
Respiratory failure					0.7417
No	576	1.0(ref)	1.07 (0.71, 1.61)	1.46 (0.95, 2.25)	
Yes	364	1.0(ref)	1.30 (0.74, 2.27)	1.42 (0.86, 2.35)	
Pneumonia					0.0696
No	658	1.0(ref)	1.42 (0.96, 2.09)	1.91 (1.31, 2.80)	
Yes	282	1.0(ref)	0.68 (0.36, 1.27)	0.93 (0.55, 1.59)	
COPD					0.3686
No	932	1.0(ref)	1.18 (0.85, 1.65)	1.55 (1.13, 2.12)	
Yes	8	1.0(ref)	0.37 (0.02, 5.97)	0.77 (0.07, 8.58)	
SAPSII					0.3904
<38	437	1.0(ref)	1.63 (0.91, 2.91)	1.32 (0.65, 2.71)	
≥38	503	1.0(ref)	0.85 (0.57, 1.26)	0.99 (0.70, 1.42)	
APSIII					0.7695
<43	459	1.0(ref)	1.39 (0.81, 2.37)	1.80 (1.01, 3.24)	
≥43	481	1.0(ref)	1.08 (0.71, 1.63)	1.09 (0.75, 1.58)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; CHF, congestive heart failure; AFIB, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SAPSII, simplified acute physiology score.

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