Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Exploration of the Clinical Parameters as Predictive Biomarkers and Their Potential Roles in the Regulation of Inflammation in Elderly Septic Patients with Pneumonia

Jingjing Zhao[1], Junyu Wang[2,3], Bing Wei[2,3], Yugeng Liu[1–3]

[1]Department of Infectious Disease and Clinical Microbiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, 100043, People's Republic of China; [2]Emergency Medicine Clinical Research Center, Beijing Chaoyang Hospital, Capital Medical University, Beijing, 100043, People's Republic of China; [3]Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Clinical Center for Medicine in Acute Infection, Capital Medical University, Beijing, 100043, People's Republic of China

Correspondence: Bing Wei; Yugeng Liu, Emergency Medicine Clinical Research Center, Beijing Chaoyang Hospital, Capital Medical University, 5 Jing-Yuan Road, Beijing, 100043, People's Republic of China, Email dr_weibing@126.com; yugeng_liu@126.com

Background: The lack of knowledge on the characteristics, predictive values and potential roles of the clinical parameters for elderly septic patients with pneumonia hinders the application of precision medicine in sepsis and understanding of the possible mechanisms in the regulation of inflammation.

Methods: This study retrospectively studied elderly patients with sepsis, who were admitted to the emergency department of Beijing Chaoyang Hospital between October 2021 and June 2022, according to the sepsis-3.0 diagnostic criteria. Patients were divided into subgroups based on the clinical outcome at the 28-day interval and occurrence of pneumonia. Baseline characteristic data and the routine laboratory test results were collected or recorded within 24 h after admission to the emergency department. Logistic regression analysis, receiver operating characteristic curve (ROC) analysis and Pearson correlation analysis were conducted.

Results: In total, 138 elderly patients with sepsis were included in this study. Age, HGB, ALB, PCT/ALB ratio and PCT/CHOL ratio were risk factors associated with the occurrence of pneumonia in elderly patients with sepsis. The NEU/CHOL ratio possessed both diagnostic value in the survival group and prognostic value in the pneumonia group. Correlation analysis demonstrated characteristic links between HGB, ALB, lactate, NEU and lipids in different subgroups.

Conclusion: Our study for the first time revealed that levels of HGB and ALB, along with the ratios of PCT/ALB, PCT/CHOL, and NEU/CHOL, can serve as potential diagnostic and prognostic markers for elderly septic patients with and without pneumonia. The link between these clinical parameters may provide insights into their potential roles in the regulation of inflammation in sepsis.

Keywords: sepsis, HGB, ALB, lactate, lipids

Introduction

The global prevalence of infection in intensive care units (ICU) is estimated to be 30%. As an acute infection of the lung parenchyma, pneumonia is characterized by alveolar inflammation resulted from a predominantly bacterial or viral pathogen and listed as one of the vital causes of morbidity and mortality around the world.[1] It may cause sepsis and septic shock in the hospitalized patients, with a dramatically increased short-term mortality rate of up to 50% in ICU patients.[2,3] Sepsis is a clinical condition defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[4] As a major public health problem worldwide with a high incidence, sepsis remains one of the most prominent causes of death.[4,5] Age is an independent predictor for mortality in septic patients, especially for those over 65 years.[6] Elderly patients own fewer specific symptoms and lower immunity during sepsis, which result in higher mortality.[7] Early diagnosis and treatment of sepsis can reduce the patient mortality.[4] As pneumonia is also an important

Received: 20 February 2025
Accepted: 31 May 2025
Published: 7 June 2025

risk factor for sepsis, understanding the characteristics of sepsis complicated by pneumonia, is of great value for elderly patients in the clinical setting.[8]

Several parameters have been shown to be correlated with community-acquired pneumonia (CAP) or sepsis. Hemoglobin (HGB) plays a vital role in oxygen delivery, tissue perfusion and the management of critically ill patients with sepsis.[9,10] As an indicator for impaired immunological function, low levels of HGB have been observed in about 30% of patients with CAP and found to be related to increased mortality in hospitalized patients with CAP.[11,12] Albumin (ALB) acts as an antioxidant scavenger in the tissues and contributes to nearly three-quarters of antioxidant capacity in the serum.[13,14] It breaks down at an accelerated rate in inflammatory conditions and has been shown to be closely correlated with inflammation with respect to that hypoalbuminemia was frequently seen in patients with inflammatory diseases.[15–17] Serum lipids are critical in cell-building and changes in lipid metabolism correlate with inflammation.[18] Total cholesterol (CHOL) metabolism has been shown to be directly regulated by the interferon cytokine response, with upstream and downstream metabolites of the pathway directing immune effector functions and anti-infective activity.[19,20] Neutrophil (NEU) plays vital roles in the innate immune response to infection and its function is impaired with age. The aberrant NEU function seen in the elderly is further impaired by pulmonary infection, where increased severity of infection is associated with enhanced impairment of NEU function.[21] A number of ratio indicators, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), glucose-to-lymphocyte ratio (GLR), and lymphocyte-to-monocyte ratio (LMR), have been investigated for the prognosis of critically ill patients with CAP.[10,22] Also, procalcitonin-to-albumin ratio (PAR) can be used as an indicator for infection, inflammation, and nutritional status and a predictive biomarker of mortality in adult patients with sepsis-induced acute kidney injury.[23]

Despite the above findings, significance of the clinical parameters and their ratios as diagnostic and prognostic markers for elderly septic patients with and without pneumonia remains unknown. This study aimed to investigate the values of the clinical parameters and their ratios, along with the correlations between them, which may provide insights into their potential roles in the regulation of inflammation in sepsis complicated by pneumonia.

Patients and Methods

Ethics

This study received ethical approval (No. 2021-ke-636) from the Ethical Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University. In compliance with the Declaration of Helsinki, this study gained informed consent from all patients or their families.

Patients and Inclusion Criteria

Patients with an acute change in total SOFA score ≥2 points and suspicion of infection were enrolled according to the Sepsis-3 criteria.[4] Those under the age of 60, or with malignant tumors, connective tissue diseases, hematological diseases, and those receiving immunosuppressive therapy were excluded. This single-center retrospective study was conducted at the emergency department of Beijing Chaoyang Hospital and a total of 220 septic patients (132 male and 88 female) entered the eligibility assessment of which 82 patients were excluded (Figure 1).

The diagnosis of pneumonia was based on a new pulmonary infiltrate on chest radiography, accompanied by symptoms and signs of a lower respiratory tract infection. A total of 138 patients (97 in the non-pneumonia group and 41 in the pneumonia group) were included in this study and further divided into four subgroups according to the occurrence of pneumonia or their survival status at the 28 day interval upon admission (Figure 1).

Data Collection and Laboratory Tests

The baseline data of the patients, such as gender and age, were collected and documented at the time of admission. Vital signs, such as systolic pressure (SBP), diastolic pressure (DBP), mean arterial pressure (MAP), were also collected. Scores, such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II, were calculated on admission for all enrolled patients.

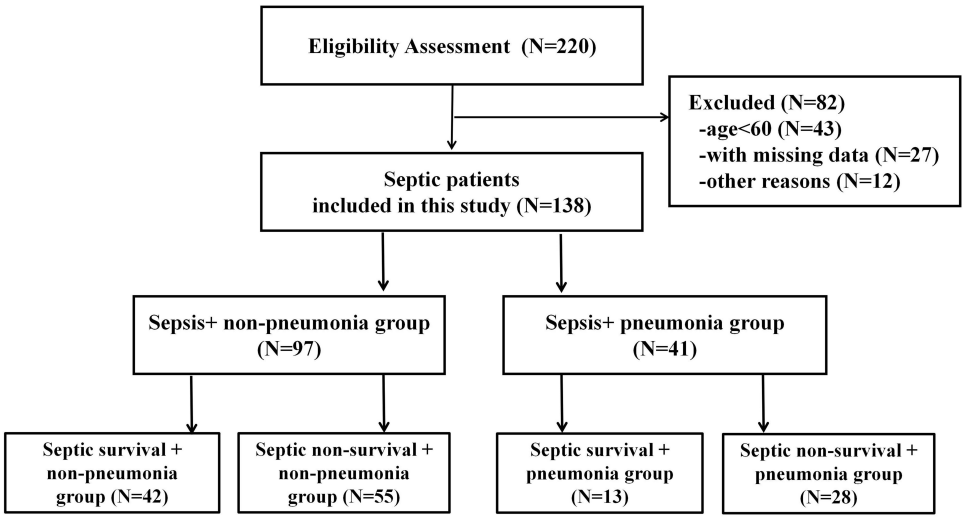

Figure 1 Flow chart of the patients in this study.

Blood samples were collected for all patients within 24 hours of admission to the emergency department for the measurement of the following parameters: lactate (Lac), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), hemoglobin (HGB), hematocrit (HCT), platelet counts (PLT), total bilirubin (TBIL), aspartate transaminase (AST), alanine transaminase (ALT), albumin (ALB), procalcitonin (PCT), C-reactive protein (CRP), white blood cell (WBC), lymphocyte count (LYM), monocyte count (MON), and neutrophil count (NEU).

Statistical Analysis

The SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations and analyses. The results were presented as medians with interquartile ranges or means with standard deviation where appropriate. Categorical variables were presented with absolute values and relative proportions. The Kolmogorov–Smirnov goodness of fit test was used for the examination of normality of the continuous variables. The Student's *t* test or Mann–Whitney *U*-test was performed accordingly for the data analysis. Categorical data were analyzed by the Pearson's chi square test. Statistical differences between the four subgroups for the clinical parameters were assessed with ANOVA, with post-hoc tests for two-group comparison. Correlations between different parameters were calculated by using Pearson correlation coefficients. Binary logistic regression analyses were performed to assess the independent relationship and screen the risk factors for occurrence of pneumonia in elderly septic patients. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of the biomarkers, and the area under the receiver operating characteristic curve (AUROC) was used to evaluate their predictive values. $P<0.05$ was considered statistically significant.

Results

Comparison of the Routine Clinical Parameters and the Parameter Ratios Between the Pneumonia Group and Non-Pneumonia Group

In total, 138 patients (79 male and 59 female) were included in this study, of whom 55 survived and 83 died within a 28-day period. As shown in Table 1, the mortality rate in the pneumonia group was higher than the non-pneumonia group (68.3% vs 56.7%, $P>0.05$). No significant differences existed in gender, SOFA and APACHE II between these two groups ($P>0.05$).

As shown in Table 1, there were no significant differences in the parameters of lactate, CHOL, HDL, LDL, SBP, DBP, WBC, HCT, PLT, TBIL, AST, CRP, LYM, MON, NEU between the pneumonia group (N=41) and the non-pneumonia

 https://doi.org/10.2147/JIR.S523902

Table 1 Clinical Data of the Septic Patients from the Non-Pneumonia Group and Pneumonia Group

Clinical Data	Sepsis+ Non-Pneumonia Group (N=97)	Sepsis+ Pneumonia Group (N=41)	*P*
Gender, n (%)			
Male	57 (58.8)	22 (53.7)	0.580
Female	40 (41.2)	19 (46.3)	
Survival, n (%)			
Survival	42 (43.3)	13 (31.7)	0.204
Non-survival	55 (56.7)	28 (68.3)	
Age, median (range)	71.0 (62.0, 81.0)	82.0 (68.5, 85.0)	0.010
SOFA	6.0 (5.0, 9.0)	7.0 (5.0, 10.0)	0.477
APACHE II	18.5 (13.0, 27.0)	21.0 (15.5, 24.0)	0.226
SBP (mmHg)	146.3±28.1	133.8±39.1	0.363
DBP (mmHg)	82.4±19.4	70.3±22.1	0.216
MAP (mmHg)	108.5±22.7	94.2±29.7	0.037
Lactate (mmol/L)	1.30 (1.10, 2.00)	1.20 (0.90, 1.75)	0.570
CHOL (mmol/L)	4.30±1.14	4.11±1.16	0.412
HDL (mmol/L)	1.30 (1.00, 1.64)	1.14 (0.87, 1.69)	0.430
LDL (mmol/L)	2.16 (1.59, 2.75)	2.00 (1.61, 2.73)	0.356
HGB (g/L)	135.50 (121.50, 148.00)	115.00 (96.00, 127.50)	0.011
HCT (%)	38.40 (32.55, 43.10)	35.75 (29.63, 42.05)	0.203
PLT ($\times 10^9$/L)	191.00 (147.00, 271.00)	179.00 (133.25, 272.75)	0.472
TBIL (μmol/L)	15.10 (11.00, 24.20)	13.50 (8.63, 17.95)	0.070
AST (IU/L)	26.90 (21.30, 38.30)	31.05 (18.20, 42.73)	0.835
ALT (IU/L)	24.50 (17.15, 34.30)	18.50 (14.88, 24.35)	0.014
ALB (g/L)	34.60 (26.65, 38.20)	25.60 (24.50, 37.00)	0.001
PCT (ng/mL)	0.05 (0.05, 0.40)	0.21 (0.05, 1.90)	0.041
CRP (mg/L)	21.00 (8.00, 86.00)	12.00 (7.00, 80.00)	0.964
WBC ($\times 10^9$/L)	8.50 (7.45, 11.30)	10.30 (8.15, 12.35)	0.206
LYM ($\times 10^9$/L)	1.33 (0.86, 2.25)	1.12 (0.83, 1.68)	0.113
MON ($\times 10^9$/L)	0.46 (0.38, 0.70)	0.55 (0.38, 0.74)	0.172
NEU ($\times 10^9$/L)	6.29 (4.91, 10.43)	7.16 (4.25, 10.76)	0.713
PCT/ALB	0.002 (0.001, 0.020)	0.009 (0.002, 0.052)	0.003
PCT/CHOL	0.0129 (0.0103, 0.1083)	0.0213 (0.0120, 0.3232)	0.010

Notes: n, number of patients; results were demonstrated as medians and interquartile ranges or means and standard deviations. *P*<0.05 was considered statistically significant.

Abbreviations: SOFA, the Sequential Organ Failure Assessment Score; APACHE II, the Acute Physiology and Chronic Health Evaluation II score; SBP, systolic pressure; DBP, diastolic pressure; MAP, mean arterial pressure; CHOL, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HGB, hemoglobin; HCT, hematocrit; PLT, platelet counts; TBIL, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; ALB, albumin; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; LYM, lymphocyte; MON, monocyte; NEU, neutrophil.

group (N=97) (P>0.05). There was a significant difference in age between these two groups (median value: 82.0 vs 71.0, P<0.05). MAP, HGB, ALT in the pneumonia group were significantly lower than those of the non-pneumonia group (mean or median value: 94.2 vs 108.5, 115.0 vs 135.5, 18.5 vs 24.5, P<0.05). The median values of PCT in the pneumonia group were higher than those of the non-pneumonia group (P<0.05). Compared with the non-pneumonia group (N=97), there were significantly higher levels in the ratios of PCT/ALB and PCT/CHOL in the pneumonia group (N=41) (both P<0.05) (Table 1).

Results from the Logistic Regression and ROC Curve Analysis

The logistic regression analysis found that age was independent risk factor associated with the occurrence of pneumonia in elderly patients with sepsis (OR=1.038, 95% CI [1.008, 1.070], P<0.05) (Table 2). HGB and ALB were protective

Table 2 Univariate Logistic Regression Analysis of Risk Factors for the Occurrence of Pneumonia in Elderly Patients with Sepsis

Factor	β	SE	Wald χ^2	OR	95% CI	*P*
HGB	−0.018	0.007	6.487	0.982	0.969, 0.996	0.011
ALT	−0.001	0.008	0.031	0.999	0.983, 1.014	0.861
ALB	−0.090	0.026	12.009	0.914	0.868, 0.962	0.001
PCT	0.323	0.185	3.053	1.381	0.961, 1.984	0.081
MAP	−0.022	0.015	2.165	0.978	0.949, 1.007	0.141
Age	0.037	0.015	6.073	1.038	1.008, 1.070	0.014

Note: *P*<0.05 was considered statistically significant.
Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; HGB, hemoglobin; ALT, alanine transaminase; ALB, albumin; PCT, procalcitonin; MAP, mean arterial pressure.

factors associated with the occurrence of pneumonia in elderly patients with sepsis (OR=0.982, 0.914, 95% CI [0.969, 0.996], [0.868, 0.962], P<0.05) (Table 2).

As shown in Table 3, the AUROCs of HGB, ALB and age were 0.638, 0.677, 0.640, respectively. ALB possessed the highest sensitivity of 84.0%, while HGB possessed a more balanced sensitivity and specificity of 62.8% and 67.5%, respectively.

Correlation Analyses of the Routine Clinical Parameters Between Different Subgroups

The parameter pairs with significance in correlation analyses were demonstrated in Tables 4 and 5. In the pneumonia group, lactate was correlated with HDL, HGB, HCT, PCT (r=0.717, −0.358, 0.672, 0.592, all P<0.05) and HDL was correlated with HGB, HCT, PCT (r=−0.466, 0.645, 0.595, all P<0.01). PLT was correlated with CRP and NEU (r=0.666, 0.552, both P<0.001) in the pneumonia group while PLT was correlated with LYM (r=0.252, P<0.05) in the non-pneumonia group (Table 4).

Table 3 Receiver Operating Characteristic Curve (ROC) Analysis and Predictive Values of HGB, ALB and Age as Risk Factors for the Occurrence of Pneumonia in Elderly Patients with Sepsis

Parameter	AUC	Sensitivity	Specificity	Cut-Off	95% CI	*P*-value
HGB	0.638	62.8%	67.5%	118.5	0.540, 0.737	0.011
ALB	0.677	84.0%	57.5%	26.4	0.569, 0.785	0.001
Age	0.640	58.5%	71.1%	78.5	0.541, 0.738	0.010

Note: *P*<0.05 was considered statistically significant.
Abbreviations: AUC, the area under curve; CI, confidence interval; HGB, hemoglobin; ALB, albumin.

Table 4 Correlation Analysis Between Lactate, HGB, Lipids and Other Parameters for Septic Patients from the Non-Pneumonia Group and Pneumonia Group

Group	Parameter Pair	r	*P*
Sepsis+ non-pneumonia (N=97)	HGB-CHOL	0.307	0.003
	ALB-CHOL	0.257	0.014
	PLT-CHOL	0.248	0.019
	HDL-CHOL	0.377	<0.001
	HDL-LDL	0.620	<0.001
	PLT-WBC	0.316	0.002
	PLT-LYM	0.252	0.022

(*Continued*)

https://doi.org/10.2147/JIR.S523902

Table 4 (Continued).

Group	Parameter Pair	r	*P*
Sepsis+ pneumonia (N=41)	Lactate-HDL	0.717	<0.001
	Lactate-HGB	−0.358	0.023
	Lactate-HCT	0.672	<0.001
	Lactate-PCT	0.592	<0.001
	HGB-CHOL	0.403	0.012
	HCT-CHOL	0.502	0.001
	CRP-CHOL	−0.353	0.030
	HGB-HDL	−0.466	0.003
	HCT-HDL	0.645	<0.001
	PCT-HDL	0.595	<0.001
	PLT-WBC	0.486	0.002
	PLT-CRP	0.666	<0.001
	PLT-NEU	0.552	<0.001

Note: *P*<0.05 was considered statistically significant.
Abbreviations: HGB, hemoglobin; CHOL, total cholesterol; ALB, albumin; PLT, platelet counts; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; WBC, white blood cell; LYM, lymphocyte count; HCT, hematocrit; PCT, procalcitonin; CRP, C-reactive protein; NEU, neutrophil count.

Table 5 Correlation Analysis Between Lactate, HGB, Lipids and Other Parameters for the Septic Survivals or Non-Survivals from the Non-Pneumonia Group and Pneumonia Group

Group	Parameter Pair	r	*P*
Septic survival + non-pneumonia (N=42)	Lactate-HDL	0.621	<0.001
	Lactate-LDL	0.517	0.006
	Lactate-HCT	−0.391	0.018
	HGB-CHOL	0.359	0.037
	HDL-LDL	0.752	<0.001
	ALB-LDL	−0.423	0.018
	PLT-WBC	0.395	0.013
	PLT-ALB	−0.437	0.005
	PLT-HCT	−0.360	0.024
	PLT-NEU	0.630	<0.001
Septic survival + pneumonia (N=13)	Lactate-NEU	0.869	0.001
	CHOL-HCT	0.626	0.039
	CHOL-CRP	−0.620	0.042
	HDL-LDL	0.834	0.003
	HDL-CRP	−0.792	0.006
	PLT-CRP	0.907	<0.001
	PCT/ALB-APACHE II	0.732	0.007
Septic non-survival + non-pneumonia (N=55)	CHOL-HDL	0.439	0.001
	HGB-CHOL	0.274	0.043
	PLT-CHOL	0.277	0.041
	HDL-LDL	0.531	<0.001
	HDL-ALT	−0.318	0.018
	PLT-WBC	0.269	0.047

(*Continued*)

Table 5 (Continued).

Group	Parameter Pair	r	*P*
Septic non-survival + pneumonia (N=28)	Lactate-HDL	0.800	<0.001
	Lactate-HGB	−0.398	0.036
	Lactate-PCT	0.638	<0.001
	CHOL-LDL	0.559	0.002
	HGB-HDL	−0.486	0.009
	HCT-HDL	0.771	<0.001
	PCT-HDL	0.697	<0.001
	PLT-WBC	0.492	0.009
	PLT-NEU	0.494	0.008

Note: *P*<0.05 was considered statistically significant.
Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HCT, hematocrit; HGB, hemoglobin; CHOL, total cholesterol; ALB, albumin; PLT, platelet counts; WBC, white blood cell; NEU, neutrophil count; CRP, C-reactive protein; PCT, procalcitonin; PCT/ALB, the ratio of PCT to ALB; APACHE II, the Acute Physiology and Chronic Health Evaluation II score; ALT, alanine transaminase.

In the pneumonia group of non-survivors (N=28), lactate was correlated with HDL, HGB, PCT (r=0.800, −0.398, 0.638, all P<0.05) and HDL was correlated with HGB, HCT, PCT (r=−0.486, 0.771, 0.697, all P<0.01). In the pneumonia group of survivors (N=13), lactate was correlated with NEU (r=0.869, P=0.001) and CRP was correlated with CHOL, HDL, PLT (r=−0.620, −0.792, 0.907, all P<0.05). In the non-pneumonia group of survivors (N=42), lactate was correlated with HDL, LDL, HCT (r=0.621, 0.517, −0.391, all P<0.05) while PLT was correlated with ALB, HCT, NEU (r=−0.437, −0.360, 0.630, all P<0.05). PLT was correlated with NEU both in the non-pneumonia group of survivors (N=42) and the non-survival group with pneumonia (N=28) (P<0.01) (Table 5). The PCT/ALB ratio was found to be correlated with the APACHE II scores in the pneumonia group of survivors (N=13) (P<0.01) (Table 5). A diagram which reflects the correlations between the parameters of different subgroups has been shown in Figure 2.

Comparison of the Routine Clinical Parameters and the Parameter Ratios Between Different Subgroups

Compared with the group of non-pneumonia survivors (N=42), there was significantly lower levels of ALB in the group of pneumonia survivors (N=13) (median value: 28.7 vs 36.3, P<0.05) (Table 6). The SOFA and APACHE II scores were both shown to be significantly increased in the non-pneumonia group of non-survivors (P<0.05) (Table 6).

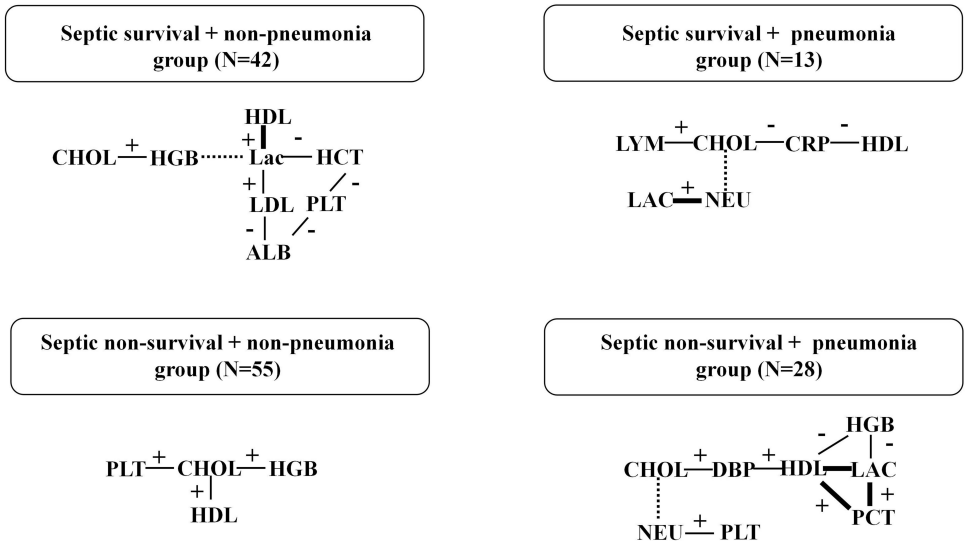

Figure 2 Correlation network between the clinical parameters in the different subgroups.

https://doi.org/10.2147/JIR.S523902

Table 6 Clinical Data with Significant Differences of Between Septic Patients from Different Subgroups

Clinical Data	Septic Survival + Non-Pneumonia Group (N=42)	Septic Survival + Pneumonia Group (N=13)	*P*
ALB (g/L)	36.30 (33.60, 39.40)	28.70 (20.85, 36.78)	0.006
PCT/CHOL	0.0125 (0.0106, 0.2300)	1.0677 (0.0124, 2.2102)	0.008
NEU/CHOL	1.50 (0.96, 2.59)	2.87 (1.54, 4.05)	0.037
Clinical Data	**Septic Survival + Non-Pneumonia Group (N=42)**	**Septic Non-Survival + Non-Pneumonia Group (N=55)**	***P***
APACHE II	16.0 (12.0, 18.0)	22.0 (17.0, 29.0)	<0.001
SOFA	3.8±1.8	8.6±3.3	<0.001
Clinical Data	**Septic Survival + Pneumonia Group (N=13)**	**Septic Non-Survival + Pneumonia Group (N=28)**	***P***
NEU/CHOL	2.95 (1.70, 4.87)	1.74 (0.83, 2.26)	0.048

Note: *P*<0.05 was considered statistically significant.
Abbreviations: ALB, albumin; PCT, procalcitonin; CHOL, total cholesterol; NEU, neutrophil count; SOFA, the Sequential Organ Failure Assessment Score; APACHE II, the Acute Physiology and Chronic Health Evaluation II score; PCT/ALB, the ratio of PCT to ALB.

As shown in Table 6, compared with the non-pneumonia group of survivors (N=42), there were significantly higher levels of the ratios of PCT/CHOL and NEU/CHOL in the pneumonia group of survivors (N=13) (both P<0.05). The pneumonia group of non-survivors (N=28) possessed lower levels of the NEU/CHOL ratio compared with the pneumonia group of survivors (N=13) (P<0.05).

ROC Curve Analysis of the Parameter Ratios Between Different Subgroups

As shown in Table 7, the PCT/ALB ratio and PCT/CHOL ratio can be used to distinguish the non-pneumonia group (N=97) and pneumonia group (N=41) with the AUROCs of 0.694 and 0.643, respectively (both P<0.05). And the sensitivity and specificity of the PCT/ALB ratio were 75.6% and 69.1% for distinguishing these two groups. The ratios of PCT/ALB, PCT/CHOL and NEU/CHOL can be used to distinguish the non-pneumonia group of survivors (N=42) and pneumonia group of survivors (N=13) (all P<0.05, AUROC value: 0.761, 0.744, 0.733). The specificity of PCT/CHOL ratio and the sensitivity of PCT/ALB in distinguishing these two groups can be 95.0% and 77.8%, respectively. The AUROC of the NEU/CHOL ratio in distinguishing the pneumonia group of survivors (N=13) and non-survivors (N=28) can reach 0.761 with the sensitivity and specificity of 70.0% and 82.1%, respectively (Table 7).

Table 7 Receiver Operating Characteristic Curve (ROC) Analysis and Predictive Values of Parameter Ratios for the Occurrence of Pneumonia or Survival in Septic Patients from Different Subgroups

Group	Parameter Ratio	AUROC	Sensitivity	Specificity	*P*
Non-pneumonia group (N=97) vs pneumonia group (N=41)	PCT/ALB	0.694	75.6%	69.1%	<0.001
	PCT/CHOL	0.643	71.8%	54.9%	0.010
Survival + non-pneumonia group (N=42) vs Survival + pneumonia group (N=13)	PCT/ALB	0.761	77.8%	70.0%	0.027
	PCT/CHOL	0.744	55.6%	95.0%	0.038
	NEU/CHOL	0.733	66.7%	85.0%	0.048
Survival + pneumonia group (N=13) vs Non-survival + pneumonia group (N=28)	NEU/CHOL	0.761	70.0%	82.1%	0.016

Note: *P*<0.05 was considered statistically significant.
Abbreviations: PCT, procalcitonin; ALB, albumin; CHOL, total cholesterol; NEU, neutrophil count; HGB, hemoglobin; AUROC, the area under the receiver operating characteristic curve; PCT/ALB, the ratio of PCT to ALB.

Discussion

Sepsis is estimated to account for worldwide incident cases of about 50 million, resulting in approximately 5 million deaths each year.[24–26] Age is an independent predictor of mortality for patients with sepsis, of whom the mortality rate of patients between the age of 60–64 years is 26% and that of patients aged over 85 years reaches 38%.[27,28] And age was an independent risk factor associated with the occurrence of pneumonia in elderly patients with sepsis, which may reflect a deterioration of immune function with the increase of age. As it is difficult to diagnose elderly patients with sepsis due to their relatively few specific symptoms, it is vital to evaluate potential biological markers with diagnostic or prognostic values for the elderly. As CAP is the leading cause of sepsis and also a risk factors for sepsis, understanding the clinical characteristics of sepsis complicated by pneumonia is of great value for elderly patients. And there is an urgent demand to unravel the molecular processes that underlie the disease severity and determine adverse outcomes.[29] Our study for the first time explored the clinical parameters and their ratios as potential diagnostic and prognostic markers for elderly septic patients with and without pneumonia. The correlations between them may provide insights into their potential roles in the regulation of inflammation in sepsis complicated by pneumonia.

HGB is a main carrier of oxygen and its level decrease correlates with oxygen deficiency as well as the hypoxic and ischemic injury in the body. Several studies have investigated the prognostic values of HGB in sepsis. The level of HGB has been identified as an indicator for predicting long-term outcomes in sepsis. And septic patients with early HGB levels below 8 g/dL had significantly lower survival rates.[30] For the ICU patients with sepsis, the HGB level was strongly correlated with the in-hospital mortality, and significant associations were observed between HGB levels and the 14-day mortality risk or 1-year mortality risk in CAP patients.[31,32] In our study, the level of HGB was found to be an indicator of the occurrence of pneumonia in elderly patients with sepsis. We conclude that several possible mechanisms may explain the relationship between HGB and pneumonia in sepsis. First of all, HGB exerts a vital role in anti-inflammation by defending against bacteria and enhancing the function of leucocytes.[33] Secondly, HGB impacts on the absorption and metabolism of antibiotics with respect to that decreased level of HGB significantly attenuate the anti-infection of antibiotics.[34] Thirdly, HGB is zinc-containing enzyme related to low-grade inflammation.[35] All these factors may influence the clinical progression to pneumonia and the outcome of the elderly septic patients.

ALB plays important roles in acid-base physiology and fluid distribution.[36] It also acts as an antioxidant and free radical scavenger in the blood and tissues.[14] In inflammatory conditions, however, ALB breaks down in an accelerated rate which might result in hypoalbuminemia.[15–17] Septic patients possess lower plasma ALB levels than non-septic patients.[37] Serum lipids are critical in cell-building and changes in lipid metabolism correlate with inflammation.[18] HDL aids with the removal of bacterial toxins and participates in the pathophysiology of sepsis. CHOL is the key component of enveloped virus membranes and host cells which has been shown to play a significant role in SARS-CoV-2 virus entry into cells.[38] A recent research based on systematic review, meta-analysis, and perspective of observational studies has shown that HDL, LDL, and CHOL levels either prior to or early during sepsis and critical illness are adversely prognostic.[22] A retrospective analysis on bacterial pneumonia and COVID-19 infection showed that patients with CAP had lower ALB and CHOL levels than healthy controls and those with non-severe COVID-19 infection. The serum ALB, triglyceride (TG), CHOL, and LDL levels were considerably lower in the severe community acquired pneumonia patients (SCAP) group than in the non-severe community-acquired pneumonia patients (NSCAP) group.[39] In our research, serum ALB levels were significantly lower in the pneumonia group than those in the non-pneumonia group of elderly septic patients, indicating the diagnostic value of ALB for the occurrence of pneumonia.

Both the PCT/ALB ratio (PAR) and CRP/ALB ratio (CAR) have been shown to possess the ability to identify sepsis in neonates with pneumonia.[40,41] Despite these findings, no reports have been made on elderly septic patients with pneumonia. In this study, several parameter ratios have been evaluated based on the insights from the correlation analysis of the different subgroups and proven to have predictive values either for the disease subtypes, severity or adverse outcomes. The PCT/ALB ratio plays a role in distinguishing the non-pneumonia group and pneumonia group. Also, correlated with the APACHE II scores in the pneumonia group of survivors (N=13), the PCT/ALB ratio possesses the predictive value for the disease severity for this subgroup of patients.

As NEU and CHOL are both correlated with control of infection and regulation of inflammation, we wondered whether the ratios of NEU to CHOL and PCT to CHOL can be used as diagnostic and prognostic markers for elderly septic patients with and without pneumonia. Our results demonstrated that the NEU/CHOL ratio was adversely prognostic in the pneumonia group of elderly septic patients. We conclude that the NEU/CHOL ratio can be a novel indicator of the inflammation and infection status of the elderly septic patients with pneumonia, which greatly influences the disease progression and mortality. Also, our data confirmed the diagnostic values of the NEU/CHOL ratio and the PCT/CHOL ratio in distinguishing the pneumonia group and non-pneumonia group of survivors.

Serum levels of lactate are elevated as a result of increased catecholamine secretion, impaired pyruvate dehydrogenase activity, tissue hypoperfusion, and increased immune cell activation in sepsis.[42] Increased serum levels and impaired clearance of lactate are independently associated with higher mortality in patients with sepsis.[43,44] The role of lactate in inflammation is not fully clear for the fact that the concurrent pro-inflammatory and anti-inflammatory effects of lactate acid were both reported in sepsis.[45,46]

As the clinical parameters are cross-linked at different levels in vivo in the regulation of inflammation in sepsis, we performed the correlation analysis aiming at investigating the relationships between these clinical parameters. Correlations between several parameters in each subgroup have been shown in this study. The characteristic correlation between HGB-CHOL was confirmed both in the non-pneumonia group of survivors and non-survivors. The correlations between HCT-CHOL-LYM have been shared by the pneumonia group of survivors and non-survivors. The correlation between WBC-PLT has been shared by the pneumonia and non-pneumonia group of non-survivors. In the pneumonia group of non-survivors, there were characteristic correlations between lactate, HDL, HGB and PCT, compared with the other subgroups. In this study, interestingly, we observed strong correlations between lactate and NEU in the pneumonia group of survivors (r=0.869) and between lactate and HDL in the pneumonia group of non-survivors (r=0.800). One previous study has found that the neutrophil count in sputum is associated with increased sputum glucose and sputum L-lactate in cystic fibrosis.[47] L-Lactate might be a marker of inflammation, as it is produced from glucose by polymorphonuclear neutrophils (PMNs) in cystic fibrosis (CF) lungs.[47] This reflects that lactate and NEU may have a cause–effect relationship, which may influence the clinical outcome when the correlation between lactate and NEU was unbalanced or out of control. The detailed mechanisms still need further investigation by animal model studies. However, the association between lactate and HDL has not yet been mentioned by other reports. Altogether, these characteristic correlation network between the parameters in different subgroups, especially those between lactate, HGB, HDL, NEU and CHOL, may provide novel insights into their potential roles in the regulation of inflammation in sepsis with pneumonia.

This study also has limitations, such as the relatively small sample size, lack of healthy controls and the fact that it was a single-center study. Also, sample size calculation was not conducted for the lack of an expected estimate of Spearman correlation coefficient either from previous similar research or expert opinion. Further multi-center studies with larger sample sizes are still needed to the validation of the values of the parameter ratios. Future research should focus on the cause–effect relationships between these clinical parameters and more studies should be performed to verify the regulatory mechanisms in in vitro cell models or in vivo animal models.

Conclusion

Our study for the first time revealed that levels of HGB and ALB, along with the ratios of PCT/ALB, PCT/CHOL, and NEU/CHOL, can serve as potential diagnostic and prognostic markers for elderly septic patients with and without pneumonia. The link between these clinical parameters may provide insights into their potential roles in the regulation of inflammation in sepsis.

Data Sharing Statement

Dr Jingjing Zhao can be contacted for a reasonable request of the data and materials.

Ethics Approval and Consent to Participate

This study has been approved by the Ethics Committee of Beijing Chaoyang Hospital (No. 2021-ke-636) and was in compliance with the Declaration of Helsinki. Informed consent has been obtained from all patients or their families before the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Torres A, Cilloniz C, Niederman MS, et al. Pneumonia. *Nat Rev Dis Primers*. 2021;7(1):25. doi:10.1038/s41572-021-00259-0
2. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386(9998):1097–1108. doi:10.1016/S0140-6736(15)60733-4
3. Woodhead M, Welch CA, Harrison DA, et al. Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC case mix programme database. *Crit Care*. 2006;10(Suppl 2):S1. doi:10.1186/cc4927
4. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
5. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):762–774. doi:10.1001/jama.2016.0288
6. Martin-Loeches I, Guia MC, Vallecoccia MS, et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multi-center cohort study. *Ann Intensive Care*. 2019;9(1):26. doi:10.1186/s13613-019-0495-x
7. Wu CC, Lan HM, Han ST, et al. Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann Intensive Care*. 2017;7(1):91. doi:10.1186/s13613-017-0316-z
8. Liu GB, Cui XQ, Wang ZB, et al. Detection of serum procalcitonin and hypersensitive C-reactive protein in patients with pneumonia and sepsis. *J Biol Regul Homeost Agents*. 2018;32(5):1165–1169.
9. Hayden SJ, Albert TJ, Watkins TR, et al. Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med*. 2012;185(10):1049–1057. doi:10.1164/rccm.201110-1915CI
10. Warner MA, Hanson AC, Frank RD, et al. Prevalence of and Recovery from Anemia following hospitalization for critical illness among adults. *JAMA Network Open*. 2020;3(9):e2017843. doi:10.1001/jamanetworkopen.2020.17843
11. Nair GB, Niederman MS. Updates on community acquired pneumonia management in the ICU. *Pharmacol Ther*. 2021;217:107663. doi:10.1016/j.pharmthera.2020.107663
12. Reade MC, Weissfeld L, Angus DC, et al. Te prevalence of anemia and its association with 90-day mortality in hospitalized community-acquired pneumonia. *BMC Pulm Med*. 2010;10:15. doi:10.1186/1471-2466-10-15
13. Roche M, Rondeau P, Singh NR, et al. The antioxidant properties of serum albumin. *FEBS Lett*. 2008;582(13):1783–1787. doi:10.1016/j.febslet.2008.04.057
14. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and Clinical Significance. *J Parenter Enter Nutr*. 2019;43(2):181–193. doi:10.1002/jpen.1451
15. Eckart A, Struja T, Kutz A, et al. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: a prospective study. *Am J Med*. 2020;133(6):713–722e7. doi:10.1016/j.amjmed.2019.10.031
16. Arnau-Barres I, Guerri-Fernandez R, Luque S, et al. Serum albumin is a strong predictor of sepsis outcome in elderly patients. *Eur J Clin Microbiol Infect Dis*. 2019;38(4):743–746. doi:10.1007/s10096-019-03478-2
17. Gui Y, Xu Y, Yang P. Predictive value of the platelet to-albumin ratio (par) on the risk of death at admission in patients suffering from severe fever with thrombocytopenia syndrome. *J Inflamm Res*. 2021;14:5647–5652. doi:10.2147/JIR.S335727
18. Zhang C, Wang K, Yang L, et al. Lipid metabolism in inflammation-related diseases. *Analyst*. 2018;143(19):4526–4536. doi:10.1039/c8an01046c
19. Robertson KA, Ghazal P. Interferon control of the sterol metabolic network: bidirectional molecular circuitry-mediating host protection. *Front Immunol*. 2016;7:634. doi:10.3389/fimmu.2016.00634
20. Fessler MB. The intracellular cholesterol landscape: dynamic integrator of the immune response. *Trends Immunol*. 2016;37(12):819–830. doi:10.1016/j.it.2016.09.001
21. Sapey E, Patel JM, Greenwood HL, et al. Pulmonary infections in the elderly lead to impaired neutrophil targeting, which is improved by simvastatin. *Am J Respir Crit Care Med*. 2017;196(10):1325–1336. doi:10.1164/rccm.201704-0814OC
22. Qiu Y, Su Y, Tu GW, et al. Neutrophil-to-lymphocyte ratio predicts mortality in adult renal transplant recipients with severe community-acquired pneumonia. *Pathogens*. 2020;9(11):913. doi:10.3390/pathogens9110913

23. Wu J, Wang X, Zhou M, et al. The value of lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio in differentiating pneumonia from upper respiratory tract infection (URTI) in children: a cross-sectional study. *BMC Pediatr*. 2021;21(1):545. doi:10.1186/s12887-021-03018-y
24. Saeed K, Wilson DC, Bloos F, et al. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. *Crit Care*. 2019;23(1):40. doi:10.1186/s13054-019-2329-5
25. Kumar S, Tripathy S, Jyoti A, Singh SG. Recent advances in biosensors for diagnosis and detection of sepsis: a comprehensive review. *Biosens Bioelectron*. 2019;124–125:205–215. doi:10.1016/j.bios.2018.10.034
26. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet*. 2020;395(10219):200–211. doi:10.1016/S0140-6736(19)32989-7
27. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med*. 2006;34(1):15–21. doi:10.1097/01.ccm.0000194535.82812.ba
28. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med*. 2007;35(5):1244–1250. doi:10.1097/01.CCM.0000261890.41311.E9
29. Aliberti S, Dela Cruz CS, Amati F, et al. Community-acquired pneumonia. *Lancet*. 2021;398(10303):906–919. doi:10.1016/S0140-6736(21)00630-9
30. Qi D, Peng M. Early hemoglobin status as a predictor of long-term mortality for sepsis patients in intensive care units. *Shock*. 2021;55(2):215–223. doi:10.1097/SHK.0000000000001612
31. Muady GF, Bitterman H, Laor A, et al. Hemoglobin levels and blood transfusion in patients with sepsis in internal medicine departments. *BMC Infect Dis*. 2016;16(1):569. doi:10.1186/s12879-016-1882-7
32. Xu Y, Fang J, Kang X, et al. The U-shaped association between hemoglobin concentrations and all-cause death risk in patients with community-acquired pneumonia. *Lab Med*. 2024:lmae079. doi:10.1093/labmed/lmae079
33. Jiang Y, Jiang FQ, Kong F, et al. Inflammatory anemia-associated parameters are related to 28-day mortality in patients with sepsis admitted to the ICU: a preliminary observational study. *Ann Intensive Care*. 2019;9(1):67. doi:10.1186/s13613-019-0542-7
34. Chuma M, Makishima M, Imai T, et al. Relationship between hemoglobin levels and vancomycin clearance in patients with sepsis. *Eur J Clin Pharmacol*. 2019;75(7):929–937. doi:10.1007/s00228-019-02661-w
35. Bhandari R, Basnet K. A case report on zinc phosphide ingestion resulting to acute pancreatitis. *Ann Med Surg*. 2022;78:103859. doi:10.1016/j.amsu.2022.103859
36. Vincent JL, Russell JA, Jacob M, et al. Albumin administration in the acutely ill: what is new and where next? *Crit Care*. 2014;18(4):231. doi:10.1186/cc13991
37. Omiya K, Sato H, Sato T, et al. Albumin and fibrinogen kinetics in sepsis: a prospective observational study. *Crit Care*. 2021;25(1):436. doi:10.1186/s13054-021-03860-7
38. Sun X, Whittaker GR. Role for influenza virus envelope cholesterol in virus entry and infection. *J Virol*. 2003;77(23):12543–12551. doi:10.1128/jvi.77.23.12543-12551.2003
39. Liu Z, Wang Q, Wang H, et al. Biomarkers for lipid and albumin metabolism in hospitalized patients with underlying diseases and community-acquired pneumonia caused by bacterial or SARS-CoV-2 infection. *J Inflamm Res*. 2023;16:1135–1145. doi:10.2147/JIR.S399921
40. Li T, Li X, Zhu Z, et al. Clinical value of procalcitonin-to-albumin ratio for identifying sepsis in neonates with pneumonia. *Ann Med*. 2023;55(1):920–925. doi:10.1080/07853890.2023.2185673
41. Kang P, Kang W, Li Y, et al. C-reactive protein-to-albumin ratio as an early biomarker to identify sepsis in neonates with pneumonia. *Mediators Inflamm*. 2022;2022:4711018. doi:10.1155/2022/4711018
42. Caslin HL, Abebayehu D, Pinette JA, et al. Lactate is a metabolic mediator that shapes immune cell fate and function. *Front Physiol*. 2021;12:688485. doi:10.3389/fphys.2021.688485
43. Nichol A, Bailey M, Egi M, et al. Dynamic lactate indices as predictors of outcome in critically ill patients. *Crit Care*. 2011;15(5):R242. doi:10.1186/cc10497
44. Marty P, Roquilly A, Vallée F, et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in Intensive Care Unit: an observational study. *Ann Intensive Care*. 2013;3(1):3. doi:10.1186/2110-5820-3-3
45. Ivashkiv LB. The hypoxia-lactate axis tempers inflammation. *Nat Rev Immunol*. 2020;20(2):85–86. doi:10.1038/s41577-019-0259-8
46. Brooks GA. The science and translation of lactate shuttle theory. *Cell Metab*. 2018;27(4):757–785. doi:10.1016/j.cmet.2018.03.008
47. Nielsen BU, Kolpen M, Jensen PØ, et al. Neutrophil count in sputum is associated with increased sputum glucose and sputum L-lactate in cystic fibrosis. *PLoS One*. 2020;15(9):e0238524. eCollection 2020. doi:10.1371/journal.pone.0238524