

Biomarkers for Lipid and Albumin Metabolism in Hospitalized Patients with Underlying Diseases and Community-Acquired Pneumonia Caused by Bacterial or SARS-CoV-2 Infection

Zheng Liu¹, Qian Wang¹, Hui Wang¹, Jing Li¹, Ying Yuan², Guo-zhen Yi¹

¹Department of Respiratory Medicine, the Petroleum Clinical Medical College of Hebei Medical University, Langfang, People's Republic of China;

²Department of Respiratory Medicine, the Langfang Third Hospital, Langfang, People's Republic of China

Correspondence: Zheng Liu, Department of Respiratory Medicine, the Petroleum Clinical Medical, College of Hebei Medical University, No. 51 of Xinkai Road, Guangyang District, Langfang, Hebei, 065000, People's Republic of China, Tel +863162077814, Email zhengl06drsun@163.com

Background: To look at the differences and similarities in albumin and lipid metabolism in non-severe COVID-19 infection, non-severe community-acquired pneumonia, and severe community pneumonia with underlying diseases, as well as the relationship between albumin and lipid metabolism and inflammatory mediators.

Methods: This retrospective analysis comprised 253 individuals with bacterial pneumonia and COVID-19 infection (1 May 2021–1 May 2022). Routine blood examination, blood lipid levels, albumin level, C-reactive protein (CRP) levels, coagulation function, cardiac enzymes, liver function, renal function, immunological function, and bacterial culture were also collected. Correlation analysis was performed using Spearman's test for lipid parameter and Inflammatory factors in the blood. Furthermore, the multiple linear regression (MLR) analysis was employed to analyze the multicollinearity in lipidomics data. The statistical analysis was performed using SPSS statistic version 19.0.

Results: There were 63 (24.90%) non-severe community-acquired pneumonia patients (NSCAP), 48 (18.97%) severe community-acquired pneumonia patients (SCAP), 112 (44.27%) non-severe COVID-19 infection patients (NSCOV), and 30 (11.86%) healthy volunteers (HV). In all, 45.59% (116/253) of the patients had underlying diseases. Patients with community-acquired pneumonia had lower albumin and cholesterol levels than those with non-severe COVID-19 infection and healthy controls ($t = -3.81, -2.09, P = 0.00, 0.04$). Albumin, triglyceride, cholesterol, and LDL-C levels in peripheral blood were considerably lower in the SCAP group than in the NSCAP group. Albumin, cholesterol, HDL-C, LDL-C, and aop-A were all inversely connected with CRP in the SCAP with underlying illness group, but cholesterol level was favorably correlated with lymphocyte count ($R = 0.36, P = 0.01$). Hypoproteinemia, hypotriglyceridemia, and an elevated neutrophil-to-lymphocyte count ratio are all risk factors for severe community-acquired pneumonia.

Conclusion: Hypoalbuminemia and abnormal lipid metabolism are important indicators of bacterial infection, especially severe bacterial pneumonia.

Keywords: bacterial pneumonia, COVID-19, hypoproteinemia, lipids

Background

Almost all chronic diseases, including cancer, arthritis, diabetes, cardiovascular disorders, chronic respiratory diseases, mood disorders, obesity, and inflammatory bowel disorders, are associated with chronic inflammation and elevated circulating levels of pro-inflammatory cytokines in the body.¹ This constant pathological rise in cytokines, termed cytokine storm or cytokine release syndrome, can result in systemic effects causing organ damage if it is not controlled.² When patients with these chronic conditions contract other acute infections such as community-acquired pneumonia or the novel coronavirus infection (also known as COVID-19), the COVID-19 pandemic caused by SARS-CoV-2 (a novel

coronavirus strain) has posed a severe threat to people globally. SARS-CoV-2 is a positive-sense single-stranded RNA virus characterized by the highly contagious severe acute respiratory syndrome (SARS) in humans.² By the April of 2022, over 500 million confirmed cases and over six million deaths have been reported globally by the World Health Organization.³ Although vaccines against COVID-19 have been authorized by the United States Food and Drug Administration (FDA),⁴ the variants of the novel coronavirus raise many new concerns because the vaccines are generally less effective in targeting variants such as Delta and Omicron compared to the original strain. COVID-19 has remained one of the most prevalent infectious diseases; even if the infection is mild or asymptomatic, individuals with a chronic condition or comorbidities tend to develop severe illness.^{5–7} In such cases, in addition to paying attention to clinical symptoms and imaging changes, it is particularly important to pay attention to inflammatory indicators. The main reason is that inflammatory factors can not only lead to an inflammatory storm but also increase the severity of chronic diseases, such as the increased circulating levels of inflammatory biomarker C-reactive protein, which are linked with increased risks of coronary heart disease, ischemic stroke, and mortality.⁸ There are several inflammatory factors associated with infection, but their specificity is poor, and comprehensive evaluation is lacking.

In infectious diseases, in addition to inflammatory factors, lipid and protein metabolism are also involved in disease progression. Lipids are critical cell-building blocks and inflammation that causes a number of changes in lipid metabolism.⁹ The key component of host cell and enveloped virus membranes is cholesterol, and it has been demonstrated to play a significant role in SARS-CoV-2 virus entrance into cells.¹⁰ Serum lipids, particularly low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), are continually interacting with lipid rafts in host cell membranes,^{11,12} and can alter virus-host cell interactions and disease severity. Several studies^{13,14} have found that there is a link between COVID-19 severity and low HDL-C blood levels.

Community-acquired pneumonia (CAP) is still a major public health concern worldwide, with significant morbidity and mortality rates, particularly among the elderly and people with underlying illnesses comorbidities.¹⁵ Furthermore, the degree of CAP clinical symptoms varies greatly.^{16,17} CAP is a global issue that remains unsolved due to the wide range of clinical symptoms and the lack of a specific definition of the causality. As a result, early illness detection in CAP patients can enhance their prognosis.^{18,19} Biomarkers in physiological fluids are increasingly being used to diagnose and predict the prognosis of lung infectious illnesses.²⁰ Lipids are important physiological components, and inflammation can cause a variety of lipid metabolic alterations.²¹ Albumin (Alb) accounts for nearly three-quarters of serum's antioxidant capacity.²² Hepatic production keeps albumin in the bloodstream, where it acts as an antioxidant and free radical scavenger in the interstitium and tissues.²³ However, albumin breaks down in an accelerated rate in inflammatory conditions, which might result in hypoalbuminemia.

In this paper, we discuss the discrepancies in albumin and lipid levels in non-critically infected individuals with underlying disorders (including COVID-19 infection and CAP) as well as critically ill patients with CAP are principally discussed. There is also discussion of the association between albumin and lipids such as cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and inflammatory mediators such as neutrophil count, lymphocyte count, C-reactive protein, D-dimer, and other parameters.

Methods

Study Design and Population

The prospective study was carried out at the Petroleum Clinical Medical College of Hebei Medical University in China between May 1st, 2021 and May 1st, 2022. The study was approved by the ethical committee of Hebei Medical University's Petroleum Clinical Medical College (No. 2016PHB202-01), and it was supported by clinical characteristics of sporadic and aggregated COVID-19 in Langfang [2020013002]. This trial was held in line with the Helsinki Declaration (as revised in 2013). Prior to clinical data collection and sample, subjects were provided with a written informed consent.

Infection with COVID-19 in non-critical patients results in mild/moderate disease characterized by fever, cough, intense asthenia, and a variety of symptoms caused by a replicative effect followed by a hyperimmune response, as their throat swab tested positive for SARS-CoV-2 on a real-time reverse transcriptase-polymerase chain reaction test.²⁴

Evidence of pulmonary infiltrates in the chest, as well as a chest radiograph revealing either a new patchy infiltrate, leaf or segment consolidation, ground-glass opacity, or interstitial alteration, were required for inclusion in the study.²⁵

The American Thoracic Society defined severe CAP (SCAP) as the presence of at least one major criterion or at least three minor criteria in 2007. The major criteria are invasive mechanical ventilation and septic shock with the need for vasopressors; the minor criteria included respiratory rate ≥ 30 breaths/minute, oxygenation index ≤ 250 , multipolar infiltrates, confusion or disorientation, uremia (BUN level ≥ 20 mg/dL), leukopenia (WBC count $< 4.0 \times 10^9/L$), thrombocytopenia (platelet count $< 100 \times 10^9/L$), hypothermia (core temperature $< 36^\circ C$), and hypotension necessitate aggressive fluid resuscitation.

The criteria of exclusion were 18 years of age or the presence of any of the following: pregnant or breastfeeding women, patients who underwent surgery within 3 months of beginning, patients with signs of nosocomial infections, and immunosuppressive diseases. Patients with malignant tumors, chronic neurological illnesses (such as Parkinson's disease or multiple system atrophy), end-stage renal or liver disease, and active tuberculosis or pulmonary cystic fibrosis were also excluded.

The following were the inclusion criteria for the control population: age 18 years old; no other respiratory diseases such as chronic bronchitis, bronchiectasis, or chronic obstructive pulmonary disease; no combined hematological tumors, solid tumors, long-term use of immunosuppressive agents and/or hormones, and other immunosuppressive states; no recent fever or respiratory symptoms such as cough, sputum, chest tightness, and dyspnea; positive bacterial culture; and no recent hospitalization history that is recent.

General information about the participants, including gender, age, comorbidities, laboratory data, and CT imaging data, such as regular blood examination, blood lipid levels, albumin levels, C-reactive protein (CRP) levels, coagulation function, myocardial enzymes, liver function, renal function, immunological function, and bacterial culture, were also gathered.

Statistical Analyses

Categorical variables are reported as percentages and examined with the chi-square test or Fisher's exact test. To assess the distribution of continuous variable data, the Kolmogorov–Smirnov test was performed. Continuous normally distributed variables are reported as mean standard deviation (mean SD) and evaluated using the Student's t-test or analysis of variance with post-hoc Tukey HSD test. To assess the strength and direction of the linear association between the abundance of target lipids and clinical manifestations, the two-tailed Spearman's rho test correlation coefficient (r) was performed. Furthermore, a stepwise technique was employed to perform multiple linear regression (MLR) analysis in addressing the multicollinearity inherent in lipidomic data. SPSS statistics version 19.0 was used for statistical testing analysis (IBM, NY, USA).

Results

Demographic and Clinical Characteristics of Participants

The study involved 253 people with complete data, including 63 with non-severe community-acquired pneumonia (NSCAP), 48 with severe community-acquired pneumonia (SCAP), 112 with non-severe COVID-19 infection (NSCOV), and 30 healthy volunteers (HV).

As indicated in Table 1, 45.59% (116/253) of the patients had underlying diseases. Among the patients with underlying disease, compared with the other three groups, there were more patients who were male and with advanced age in the severe pneumonia group ($P < 0.01$); however, the differences were not significant in terms of age, sex, and BMI among these three groups (NSCAP, NSCOV, and HV).

Laboratory Data

Metabolic Markers for Patients with Underlying Diseases

In the group of SCAP, the levels of albumin, cholesterol, and LDL-C in peripheral blood were significantly lower than those in the NSCAP and the NSCOV groups ($t = 4.18, 2.14, 2.65, 8.42, 4.74, 5.00, P = 0.00, 0.04, 0.01, 0.00, 0.00, 0.00$),

Table 1 Demographic and Clinical Characteristics of 253 Study Participants

Characteristic	SCAP (N=48)		NSCAP (N=63)		NSCOV (N=112)		HV (N=30)	p value
	NUD (N=0)	UD (N= 48)	NUD (N=29)	UD (N=34)	NUD (N=78)	UD (N=34)		
Male sex	0 (0.00%)	31 ^b (12.25%)	19 (7.51%)	19 (7.51%)	35 (13.83%)	22 (8.69%)	11 (4.35%)	<0.01
Age, years								
≥65	0 (0.0%)	38 ^{bc} (15.02%)	2 (0.79%)	23 (9.09%)	11 (4.35%)	22 (8.69%)	3 (1.19%)	<0.01
<65	0 (0.00%)	10 (3.95%)	27 (10.67%)	11 (4.35%)	67 (26.48%)	20 (7.09%)	27 (10.67%)	
BMI,kg/m ²								
<30	0 (0.00%)	44 ^d (17.39%)	27 (10.67%)	30 (11.86%)	71 (28.06%)	42 (26.09%)	27 (10.67%)	>0.05
≥30	0 (0.00%)	4 (1.58%)	2 (0.79%)	4 (1.58%)	7 (2.77%)	6 (2.13%)	3 (1.19%)	
Laboratory results								
NE (×10 ⁹ /L)	0 (0.00%)	9.77 ^{bc} ±5.65	5.17 ^{ab} ±3.06	5.99 ^b ±3.93	2.71±1.55	3.01±1.19	3.26±2.05	<0.05
LY (×10 ⁹ /L)	0 (0.00%)	1.07 ^b ±0.90	1.51±0.53	1.34±0.72	1.67±0.57	1.64±0.58	1.61±0.70	<0.01
NLR (%)	0 (0.00%)	15.27 ^{bc} ±13.38	4.05 ^b ±3.00	6.43 ^b ±6.41	2.00±1.97	2.33±2.34	2.63±2.44	<0.01
MONO (×10 ⁹ /L)	0 (0.00%)	0.88 ^b ±1.53	1.05 ^b ±1.71	0.74 ^b ± 0.99	0.61±0.60	3.02±1.29	0.54±0.24	<0.05
CRP (mg/L)	0 (0.00%)	87.65 ^b ±83.51	86.58 ^b ±48.73	71.20 ^b ±68.20	10.54±29.55	6.18±6.70	8.26±8.96	<0.05
Alb (g/L)	0 (0.00%)	25.00 ^{bcd} ±4.34	38.63 ^b ±4.28	35.84 ^b ±4.82	40.27±3.39	39.88±3.89	41.72±3.60	<0.01
Total cholesterol (mmol/L)	0 (0.00%)	3.44 ^{bc} ±0.99	4.11±0.91	4.09 ^b ±1.19	4.29±0.94	4.37±1.07	4.14±0.90	<0.01
Triglyceride (mmol/L)	0 (0.00%)	1.08 ^c ±0.50	1.17±0.52	1.37±0.76	1.33±0.89	1.52±0.61	1.17±0.77	<0.01
HDL-C (mmol/L)	0 (0.00%)	0.93±0.35	0.94 ^b ±0.27	0.89±0.24	1.08±0.31	0.95 ^d ±0.26	1.06±0.24	<0.05
LDL-C (mmol/L)	0 (0.00%)	1.92 ^{bc} ±0.78	2.65±0.75	2.59±1.01	2.72±1.73	2.74±0.83	2.46±0.70	<0.05
apo-A (mmol/L)	0 (0.00%)	0.93±0.25	0.92±0.17	0.91±0.21	-	0.59±0.57	-	<0.05
apo-B (mmol/L)	0 (0.00%)	0.75±0.22	0.97±0.36	0.86±0.27	-	6.72 ^d ±2.94	-	<0.05
apo-A/B	0	1.29±0.39	0.97±0.27	1.17±0.47	-	17.81±5.59	-	<0.05
D-Dimer (mg/L)	0 (0.00%)	1.49 ^{bc} ±1.56	0.39±0.21	0.67 ^b ±0.68	0.47 ^a ±0.56	-	-	>0.05
Glucose (mmol/L)	0 (0.00%)	7.55±4.14	4.99±0.97	6.38±3.10	5.77±2.04	-	0.69±0.12	<0.01
Hospital stays(days)	0 (0.00%)	17.48 ^c ±10.66	6.38 ^b ±3.20	8.53 ^b ±3.95	18.11±5.27	-	5.50±1.61	

Notes: ^aCompared with HV; ^bcompared with NSCOV; ^ccompared to NSCAP; ^d compared underlying disease to non-underlying disease; P < 0.05 was statistically significant.

Abbreviations: NUD, non-underlying disease; UD, underlying disease; BMI, body mass index; NE, neutrophil count; LY, lymphocyte count; NLR, neutrophil count to lymphocyte count ratio; MONO, monocyte count; CRP, C-reactive protein; ALB, albumin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; apo-A, apolipoprotein A; apo-B, apolipoprotein B; SCAP, severe CAP; NSCAP, non-severe CAP; NSCOV, non-severe COVID-19; HV, healthy volunteers.

and the level of triglyceride in the SCAP group was lower than that in the NSCAP ($t = 3.69$, $P = 0.00$) and was not statistically significant in the NSCOV group ($t = 1.66$, $P = 0.10$). The levels of blood glucose and HDL-C were not statistically significant in SCAP group, NSCAP, and NSCOV groups ($t = -1.39$, -4.31 , -0.49 , -0.91 , $P = 0.17$, 0.67 , 0.63 , 0.37). The levels of apo-A and apo-B were not statistically significant between the NSCAP group and SCAP group ($t = -0.43$, 1.94 , $P = 0.67$, 0.06).

The levels of albumin and cholesterol in peripheral blood were significantly lower in the NSCAP group than in the NSCOV group ($t = -3.81$, -2.09 , $P = 0.00$, 0.04), while blood triglyceride, LDL, HDL, and glucose were not statistically significant ($t = 1.36$, -1.66 , 0.00 , 0.91 , $P = 0.23$, 0.10 , 1.00 , 0.37).

Inflammatory Biomarkers or Other Indicators for Patients with Underlying Diseases

The neutrophil count and the ratio of neutrophil count to lymphocyte count in patients with an underlying disease were substantially greater in the SCAP group than in the NSCAP and NSCOV groups ($t = -3.25$, -3.26 , -7.03 , -5.12 , all $P = 0.00$). The levels of lymphocyte count, monocyte count, C-reactive protein, and D-dimer were statistically different between the SCAP and NSCOV groups ($t = -3.23$, -6.65 , 6.30 , 3.18 , all $P = 0.00$). The NSCAP group and the NSCOV group had statistically significant differences in neutrophil count, the ratio of neutrophil count to lymphocyte count, monocyte count, C-reactive protein, and length of hospital stay ($t = 4.18$, 3.38 , -8.17 , 5.53 , -8.10 , all $P = 0.00$). However, no statistically significant was observed in C-reactive protein, lymphocyte count, monocyte count, D-dimer, and length of hospital stay between the SCAP group and the NSCAP group ($t = -0.96$, 1.44 , -0.46 , -2.90 , -4.29 , $P = 0.34$, 0.15 , 0.65 , 0.01 , 0.00), and there was no significant statistical difference in lymphocyte count and D-dimer between the NSCAP group and the NSCOV group ($t = -1.91$, 0.43 , $P = 0.06$, 0.67).

Patients without Underlying Diseases

Apart from the D-dimer, which was higher in the group NSCOV than in the group of HV ($t = 4.19$, $P = 0.04$), no other measure showed a statistically significant difference between the two groups. The NSCAP group had lower HDL-C, albumin, length of hospital stays, and age levels than the NSCOV group ($t = -2.27, -2.07, -11.52, -234$, $P = 0.03, 0.04, 0.00, 0.02$). The NSCAP group had a higher neutrophil count and neutrophil count to lymphocyte count ratio than the NSCOV group ($t = 5.05, 6.02, 4.44$, all $P = 0.00$).

Compared with the HV group, the C-reactive protein level, neutrophil count, and neutrophil count and lymphocyte count ratios, were significantly higher ($t = 4.39, 3.21, 2.76$, all $P = 0.00$), while age and blood glucose level were lower compared to the HV group ($t = -4.36, -3.16$, $P = 0.00, 0.00$).

Correlation in Patients without Underlying Diseases

Among patients without underlying diseases, the albumin level was positively correlated with vaccination history and cholesterol levels in the NSCOV group ($R = 0.44, 0.35$, $P < 0.01$) and was negatively related to age and the level of CRP ($R = -0.32, -0.34$, $P = 0.01, 0.01$), while the level of albumin correlated negatively with age, cholesterol, LDL-C, monocyte count, and D-dimer in the NSCAP group ($R = -0.47, -0.41, -0.50, -0.53, -0.38$, $P = 0.01, 0.03, 0.01, 0.00, 0.04$, respectively).

Blood glucose level correlated positively with triglyceride and the levels of cholesterol ($R = 0.29, 0.30$, $P = 0.01, 0.01$) in the NSCOV group.

In the NSCOV group, besides albumin and blood glucose, the cholesterol level was related to other lipid parameters (HDL-C, LDL-C, and triglyceride) ($R = 0.23, 0.23, -0.35$, $P < 0.05$); HDL was negatively correlated with age and lymphocyte count ($R = -0.25, -0.41$, $P = 0.00, 0.00$). LDL-C was positively correlated with monocyte count ($R = 0.35$, $P < 0.01$).

Aside from albumin, cholesterol level in the NSCAP group was negatively connected with hospital stay length ($R = -0.49$, $P = 0.01$) and positively correlated with age, triglyceride, aop-A, and aop-B ($R = 0.41, 0.38, 0.46, 0.77$, $P = 0.03, 0.04, 0.01, 0.00$). The triglyceride level was shown to be positively connected with BMI and LDL ($R = 0.49, 0.42$, $P = 0.01, 0.03$) and negatively correlated with hospital stay length and HDL-C ($R = -0.42, -0.46$, $P = 0.02, 0.01$). HDL-C was found to be positively connected to aop-A ($R = 0.88, 0.00$) and negatively related to D-dimer ($R = -0.46$, $P = 0.01$). LDL was shown to be adversely connected with length of hospital stay and albumin ($R = -0.43, -0.50$, $P = 0.02, 0.01$) but favorably correlated with age and monocyte count ($R = 0.44, 0.40$, $P = 0.02, 0.03$) (Figure 1).

CRP was inversely connected with vaccination ($R = -0.38$, $P = 0.01$) and favorably correlated with age, creatinine level, and neutrophil count in the NSCOV group ($R = 0.37, 0.31, 0.67$, $P = 0.01, 0.01, 0.00$, respectively). D-dimer was associated with age and the neutrophil count to lymphocyte count ratio ($R = 0.24, 0.38$, $P = 0.03, 0.01$), but not with lymphocyte count ($R = -0.32$, $P = 0.01$).

CRP level was positively connected with D-dimer, neutrophil count, and lymphocyte count ratio in the NSCAP group ($R = 0.56, 0.57$, $P = 0.01, 0.01$) and negatively correlated with lymphocyte count ($R = -0.60$, $P = 0.01$).

Correlation Analysis of Patients with Underlying Diseases in Each Group

Albumin was found to be positively connected with BMI ($R = 0.35$, $P = 0.04$) and negatively correlated with CRP ($R = -0.44$, $P = 0.01$) in individuals with underlying illnesses. In the NSCOV group, blood glucose levels were favorably linked with BMI and LDL ($R = 0.34, 0.34$, $P = 0.05$).

In the NSCAP group, albumin level was positively correlated with cholesterol, HDL-C, LDL-C, lymphocyte count, and aop-A ($R = 0.41, 0.57, 0.36, 0.61, 0.66$, $P = 0.02, 0.00, 0.04, 0.00, 0.00$, respectively) and negatively correlated with length of hospital stay, creatinine, CRP, neutrophil count, and lymphocyte count ratio ($R = -0.37, -0.45, -0.35, -0.42$, $P = 0.03, 0.01, 0.04, 0.01$, respectively). Blood glucose level was positively correlated with creatinine, triglyceride, and monocyte count ($R = 0.81, 0.75, 0.68$, $P < 0.01$).

Cholesterol level was positively correlated with body mass index, albumin, triglyceride, LDL-C, lymphocyte count, and aop-B. ($R = 0.52, 0.41, 0.54, 0.97, 0.45, 0.96$, $P = 0.00, 0.02, 0.00, 0.00, 0.01, 0.00$, respectively). Triglycerides were

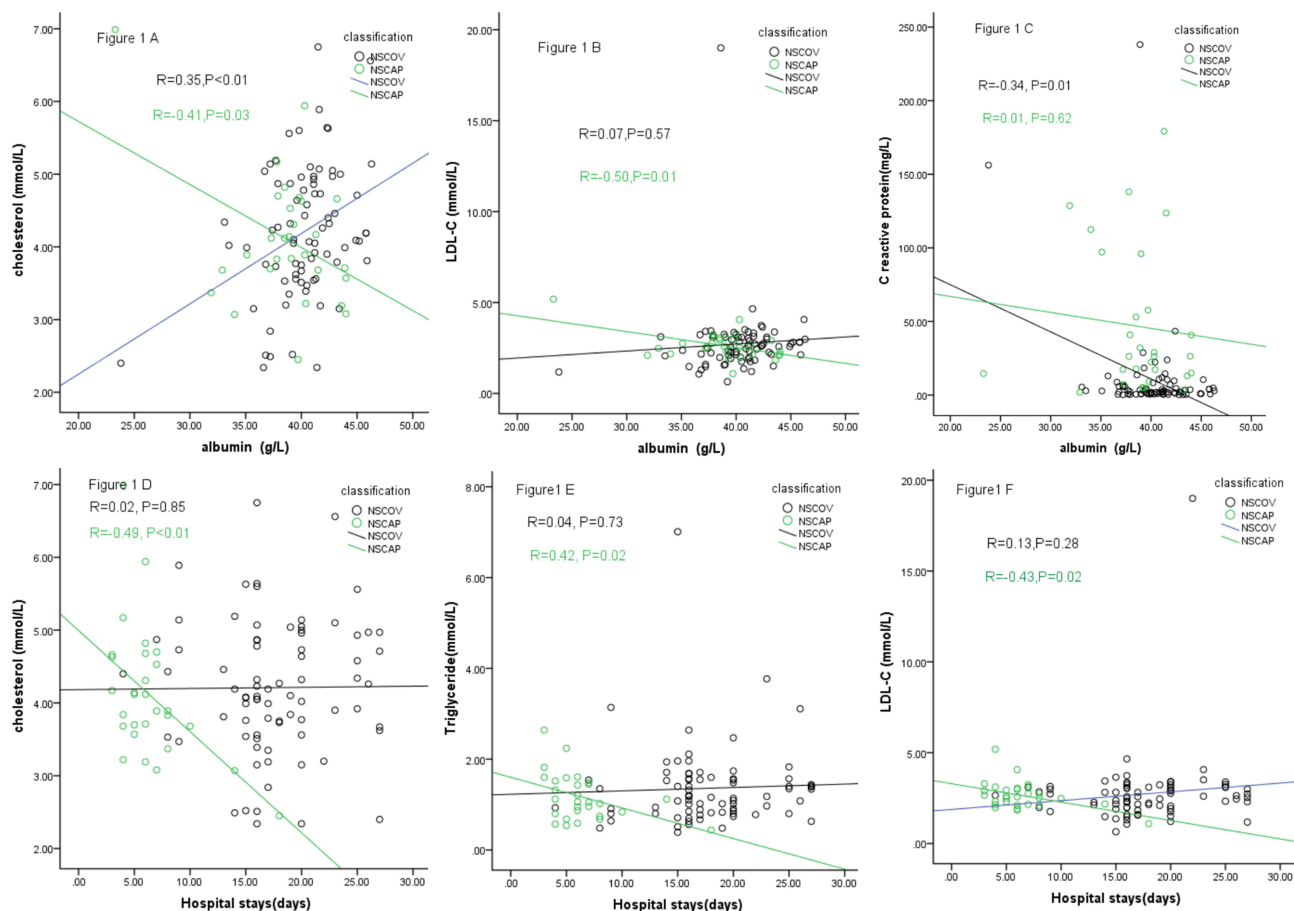


Figure 1 In patients without underlying disease, (A) albumin levels were positively correlated with cholesterol levels in the NSCOV group ($R=0.35, P<0.01$). (B) Albumin and low-density lipoprotein levels were negatively correlated in NSCAP group ($R=-0.50, P=0.01$) but not in NSCOV group ($R=0.07, P=0.57$). (C) There was a negative correlation between albumin level and C-reactive protein in NSCOV group ($R=-0.34, P=0.01$), while there was no correlation between albumin level and C-reactive protein in NSCAP group ($R=0.01, P=0.62$). (D-F) In the NSCAP group, cholesterol, triglyceride, and LDL-C levels were negatively correlated with length of hospital stay ($R=-0.49, -0.42, -0.43, P<0.01, 0.02, 0.02$).

positively correlated with creatinine, blood sugar, cholesterol, LDL-C, lymphocyte count, and aop-B ($R = 0.59, 0.75, 0.54, 0.47, 0.34, 0.58, P = 0.00, 0.00, 0.00, 0.00, 0.05, 0.00$, respectively). HDL-C was positively correlated with aop-A levels ($R = 0.89, P = 0.00$) and negatively correlated with creatinine and D-dimer ($R = 0.47, 0.42, P = 0.01, 0.01$). LDL-C were positively correlated with body mass index, albumin, cholesterol, triglycerides, lymphocyte count, and aop-B ($R = 0.53, 0.38, 0.97, 0.47, 0.43, 0.97, P = 0.00, 0.04, 0.00, 0.01, 0.01, 0.00$, respectively) and was negatively correlated with the ratio of neutrophil count to lymphocyte count ($R = -0.34, P = 0.05$). CRP level was correlated with age, neutrophil count, and the ratio of neutrophil count to lymphocyte count ($R = 0.39, 0.51, 0.62, P = 0.02, 0.00, 0.00$). It was negatively correlated with albumin, lymphocyte count, and aop-A ($R = -0.35, -0.45, -0.44, P = 0.04, 0.01, 0.01$, respectively).

Albumin levels in the SCAP group were positively connected with cholesterol, HDL-C, LDL-C, aop-A, and aop-B ($R = 0.38, 0.41, 0.37, 0.51, 0.31, P = 0.01, 0.00, 0.00, 0.03$, respectively) and negatively correlated with CRP ($R = -0.36, P = 0.03$).

In addition to albumin, cholesterol levels were shown to be positively connected with HDL-C, LDL-C, aop-A, aop-B, and lymphocyte count ($R = 0.64, 0.90, 0.71, 0.89, 0.36, P = 0.01$) and negatively correlated with CRP and neutrophil count ($R = -0.37, -0.39, P = 0.01, 0.01$) (See Figure 2).

Triglyceride showed a negative relationship with age and HDL-C ($R = -0.30, -0.47, P = 0.04, 0.01$). There was no correlation between triglyceride and cholesterol, albumin, inflammatory markers, blood glucose, D-dimer, etc.

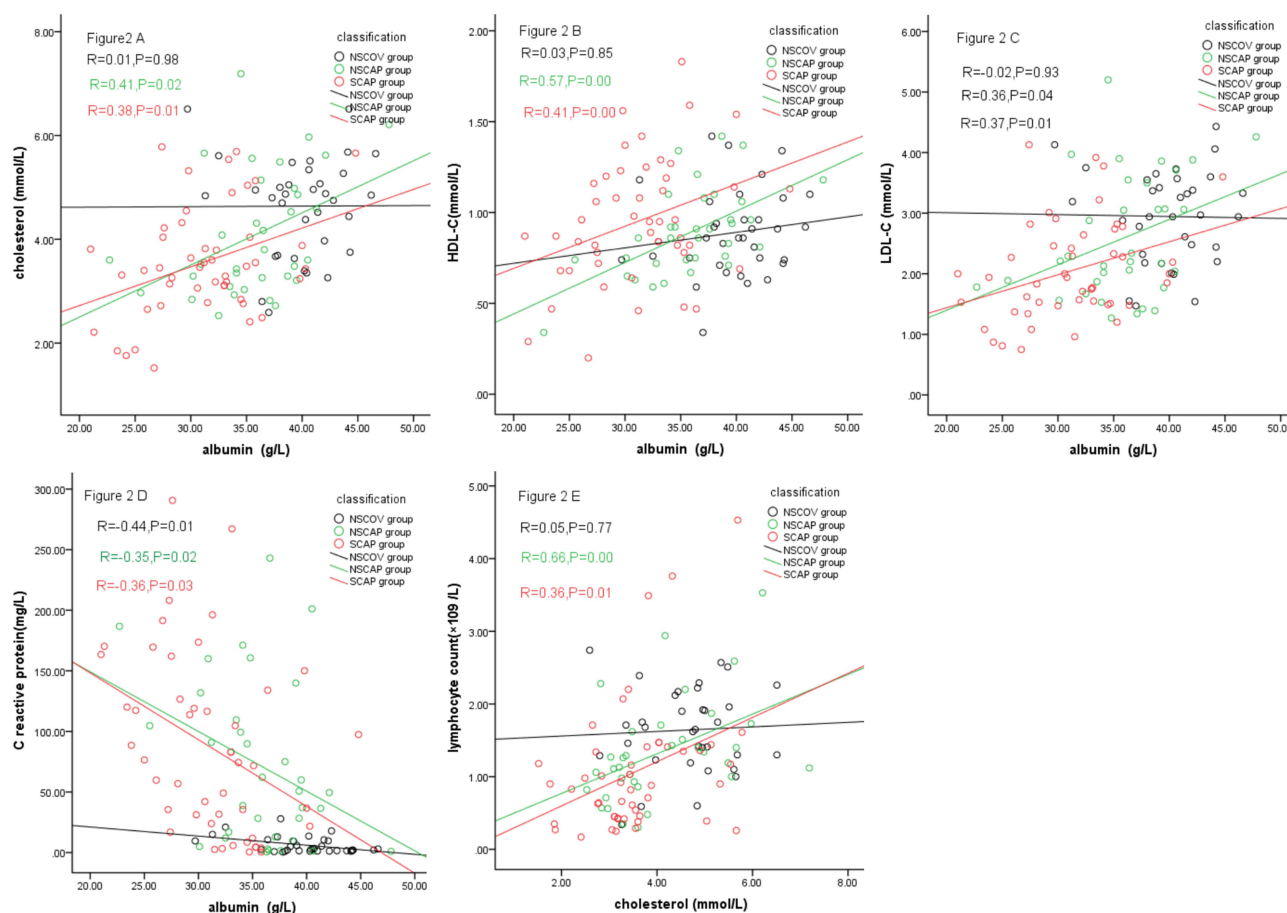


Figure 2 Analysis of related indicators of patients with underlying diseases in the three groups. (A–D) In NSCAP and SCAP groups, albumin level was positively correlated with cholesterol, HDL-C and LDL-C levels ($R=0.41, 0.57, 0.36, P=0.02, 0.00, 0.04$), ($R=0.38, 0.41, 0.37, P=0.01, 0.00, 0.01$). In NSCOV group, albumin level was not correlated with cholesterol, HDL-C and LDL-C levels ($R=0.01, 0.03, 0.02, P=0.98, 0.85, 0.93$). There was a negative correlation between albumin level and C-reactive protein in the three groups ($R=-0.44, -0.35, -0.36, P=0.01, 0.04, 0.03$). (E) There was a positive correlation between cholesterol level and lymphocyte count in NSCAP and SCAP groups ($R=0.66, 0.36, P=0.00, 0.01$), while there was no correlation between cholesterol level and lymphocyte count in NSCOV group ($R=0.05, P=0.77$).

In addition to CRP, there was indication of relationship that is negative with cholesterol and albumin; CRP was also negatively correlated with HDL-C, LDL-C, and aop-A ($R=-0.33, -0.45, -0.46, P=0.01, 0.00, 0.00$, respectively) and positively correlated with neutrophil count and blood glucose ($R=0.32, 0.31, P=0.03, 0.03$, respectively).

In binary logistic regression analysis, admission to patients with non-severe community-acquired pneumonia, albumin was a prognostic factor for patients with underlying diseases ($P=0.01, OR=0.79, 95\% CI 0.68-0.94$), while blood glucose was a negative factor ($P=0.00, OR=3.55, 95\% CI 1.71-7.35$). Albumin level was a protective factor ($P=0.01, OR=0.89, 95\% CI 0.82-0.97$), while cholesterol level was a negative factor ($P=0.00, OR=7.56, 95\% CI 3.35-16.08$) in patients in the NSCOV group.

In this study, the logistic regression results of severe community-acquired pneumonia with underlying diseases revealed that albumin and triglyceride levels were protective factors ($P=0.03, OR=0.83, 95\% CI 0.70-0.98; P=0.01, OR=0.12, 95\% CI 0.03-0.57$), while the ratio of neutrophil count to lymphocyte count and length of hospital stay were aggravating factors ($P=0.01, OR=1.18, 95\% CI 1.05-1.33$ and $P=0.00, OR=136, 95\% CI 1.13-1.64$).

Discussion

One of the top causes of death globally is pneumonia. In addition to infections and inflammation, underlying diseases and patients' nutritional metabolism can also affect the prognosis of pneumonia. The results of this study revealed that albumin, cholesterol, and LDL-C levels in peripheral blood were significantly lower in the severe community-acquired pneumonia (SCAP) group with underlying disease than in the non-severe community-acquired pneumonia (NSCAP)

group and the non-severe COVID-19 infection (NSCOV) group. The level of triglyceride in the SCAP group was lower than that in the NSCAP group. Albumin levels in the SCAP group were positively connected with cholesterol, HDL-C, LDL-C, aop-A, and aop-B and negatively correlated with CRP. The level of cholesterol was shown to be positively connected to lymphocyte count and negatively related to CRP and neutrophil count. The logistic regression results of severe community-acquired pneumonia with underlying illnesses revealed that hypoalbuminemia and low triglycerides, an elevated neutrophil-to-lymphocyte ratio, and a prolonged hospital stay were aggravating variables.

Lipid Metabolism

There is essential role that lipids play in respiratory infections. Recent research has showed that cholesterol is absorbed by alveolar epithelial type II cells and alveolar macrophages from circulating high-density and low-density lipoprotein.²⁶ Alveolar epithelial type II cells are also important in alveolar damage repair and homeostasis maintenance.²⁷ The pulmonary surfactant, which is a component of both the innate and adaptive immune systems, is 90% lipids.^{28,29} As a result, reduced cholesterol levels may be related to alveolar epithelial type II cell and alveolar macrophage dysfunction, reducing CAP recovery. Furthermore, plasma accounts for more than 80% of total lung cholesterol.³⁰ Lower HDL-C levels have been linked to COVID-19 infection, severity, and death.³¹ HDL-C contributes significantly to host resistance to bacterial, viral, and parasitic infections,³² and it possesses a variety of qualities such as anti-inflammatory, anti-thrombotic, and anti-oxidative properties.³³ HDL-C and its structural component, apoA-1, have been proven to have anti-inflammatory properties.^{34,35}

In our study, irrespective of whether there was an underlying disease, there was no obvious difference in lipid metabolism between the NSCOV group and healthy control group. Low HDL-C levels have been linked to serious disease and mortality in patients of COVID-19, implying that the dynamic change in HDL-C levels could be used as one of the observation indicators for the development of mild to severe disease in COVID-19 patients.

The essential factors influencing the prognosis of pneumonia include fundamental disorders such as coronary heart disease and diabetes. The administration of COVID-19 vaccination is effective in preventing COVID-19 infection and decreasing the occurrence of severe pneumonia. The correlation analysis revealed a relationship between the COVID-19 vaccination injection and cholesterol levels.

Among patients with underlying disorders, the NSCAP group had significantly lower cholesterol than that in the NSCOV group, while the neutrophil count and the neutrophil-to-lymphocyte ratio were significantly higher. SCAP participants had lower cholesterol, LDL-C, and triglyceride levels than NSCAP participants.

Hypoalbuminemia

The prognosis of pneumonia is closely related to a patient's nutritional state. Malnutrition can weaken the immune system and exacerbate pneumonia,³⁶ due to the immune system's inability to operate optimally. Hypoalbuminemia has been associated with the development and severity of infectious illnesses, and albumin is required for healthy innate and adaptive immune responses. Albumin has the ability to defend against inflammatory processes, as well as the ensuing microcirculation and tissue damage.³⁷ As a carrier molecule, albumin is involved in drug transport and excretion.³⁸ Albumin dynamics involve trans-capillary leak and breakdown, culminating in hypoalbuminemia, which is linked to poorer outcomes across a wide range of illnesses.²³ Hypoalbuminemia has been linked to a poor prognosis for community-acquired pneumonia.^{39,40} Furthermore, the role of ALB as a mediator of pro-inflammatory chemicals and inflammation should be investigated further.⁴¹ At the same time, increased vascular permeability can induce a shift in ALB distribution between intravascular and extravascular compartments.⁴² The development and severity of community-acquired pneumonia (CAP) are connected to hypoalbuminemia.⁴³

Consequently, hypoproteinemia is prevalent in sepsis patients and a robust predictor of morbidity.⁴⁴ In this study, individuals with non-severe and severe community-acquired pneumonia had significantly lower albumin levels than patients with non-severe COVID-19 infection and underlying illnesses. Hypoproteinemia was positively connected with CRP and neutrophil levels in both the non-severe and severe community-acquired pneumonia groups, according to the correlation analysis. Low albumin levels were statistically common risk variables in patients with community-acquired

pneumonia (severe and non-severe) and COVID-19 infection, according to multivariate analysis, and these findings are consistent with relevant literature.⁴⁵

Hypoalbuminemia in severe pneumonia may be caused by the fact that albumin physiology is important in both an effective host immunological response to infections and the destructive consequence of immune dysregulation caused by cytokine storm.^{43,46} Lower serum albumin levels are related to worse outcomes in COVID-19 patients.⁴⁴ The viral load of SARS-CoV-2 identified in patients' respiratory tracts was connected to lung disease severity in a case series of 12 patients, and serum albumin and indicators of systemic inflammation were highly correlated with acute lung injury.⁴⁵ In this study, all patients of COVID-19 showed mild signs, and their albumin levels were comparable to those of healthy controls. The various causes are connected to the virus's virulence and the severity of the disease.

The Relationship Between Lipids, Albumin, and Inflammatory Factors

Regardless of underlying illness, albumin levels were inversely correlated with CRP. In non-severe COVID-19 patients with underlying diseases, an elevated cholesterol level was not associated with disease recovery, as determined by logistic regression.

Cholesterol, LDL-C, and albumin levels were negatively linked with length of hospital stay in non-severe CAP patients without underlying illness. LDL-C and albumin levels were also found to be inversely associated. The ratio of D-dimer and neutrophil count to lymphocyte count were both favorably connected with CRP levels, while D-dimer was negatively correlated with HDL-C.

Cholesterol, LDL-C, and albumin levels were negatively linked with length of hospital stay in non-severe CAP patients without underlying illness. LDL-C and albumin levels were also found to be inversely associated. The ratio of D-dimer and neutrophil count to lymphocyte count were both favorably connected with CRP levels, while D-dimer was negatively correlated with HDL-C.

Cholesterol and albumin levels were shown to be positively connected with lymphocyte counts and negatively correlated with CRP and neutrophil counts in SCAP patients. According to logistic regression analysis, low albumin levels, low triglyceride levels, an elevated neutrophil count to lymphocyte count ratio, and a prolonged hospital stay were risk factors for poor SCAP prognosis.

However, this study has a few limitations that need to be acknowledged. First of all, the sample size could be increased to represent a more generalized population. For the same reason, another limitation of this study is related to the lack of participant data post-treatment. Furthermore, it would be better if our study included data on patients who are seriously ill due to COVID-19 infection.

Despite the limitations, the data were collected come from medical examinations and clinical analyses; hence, the results of the study can be considered reliable and accurate.

In conclusion, our findings confirm the statement that patients with community-acquired pneumonia had lower levels of albumin and cholesterol than those with non-severe COVID-19 infection and healthy controls. Albumin, cholesterol, LDL-C levels, and inflammatory factors such as lymphocyte count, neutrophil count, neutrophil count to lymphocyte count ratio, and C-reactive protein are strongly correlated with disease severity in community-acquired pneumonia with underlying disease. Compared to non-severe community-acquired pneumonia, hypoproteinemia, hypotriglyceridemia, and increased ratio of neutrophil count to lymphocyte count are risk factors for severe community-acquired pneumonia.

Abbreviations

BMI, body mass index; NE, neutrophil count; LY, lymphocyte count; NLR, neutrophil count to lymphocyte count ratio; MONO, Monocyte count; CRP, C-reactive protein; ALB, albumin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; apo-A, apolipoprotein A; apo-B, apolipoprotein B; SCAP, severe community-acquired pneumonia.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of the Petroleum Clinical Medical College of Hebei Medical University (No. 2016PHB202-01). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Funding

This study was supported by clinical characteristics of sporadic and aggregated COVID-19 in Langfang [2020013002].

Disclosure

The authors report no conflicts of interest in this work.

References

- Suryavanshi SV, Kovalchuk I, Kovalchuk O. Cannabinoids as Key Regulators of Inflammasome Signaling: a Current Perspective. *Front Immunol.* 2020;11:613613.
- Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med.* 2020;383:2255–2273.
- Miossec P. Understanding the cytokine storm during COVID-19: contribution of preexisting chronic inflammation. *Eur J Rheumatol.* 2020;7:S97–S98.
- Food and Drug Administration. FDA Takes Key Action in Fight Against COVID-19 by Issuing Emergency Use Authorization for First COVID-19 Vaccine; 2020.
- Schiffirin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. *Am J Hypertens.* 2020;33:373–374.
- Haitao T, Vermunt JV, Abeykoon J, et al. COVID-19 and Sex Differences: mechanisms and Biomarkers. *Mayo Clin Proc.* 2020;95:2189–2203.
- Saha S, Al-Rifai RH, Saha S. Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression. *J Diabetes Metab Disord.* 2021;1:1–12.
- Kaptoge S, Di Angelantonio E, Lowe G, et al.; The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375:132–140.
- Zhang C, Wang K. Lipid metabolism in inflammation-related diseases. *Analyst.* 2018;143:4526–4536.
- Sun X, Whittaker GR. Role for influenza virus envelope cholesterol in virus entry and infection. *J Virol.* 2003;77:12543–12551.
- Song J, Ping LY, Duong DM, et al. Native low density lipoprotein promotes lipid raft formation in macrophages. *Mol Med Rep.* 2016;13:2087.
- Peng Y, Akmentin W, Connelly MA, Lund-Katz S, Phillips MC, Williams DL. Scavenger receptor BI (SR-BI) clustered on microvillar extensions suggests that this plasma membrane domain is a way station for cholesterol trafficking between cells and high-density lipoprotein. *Mol Biol Cell.* 2004;15:384–396.
- Feingold KR Lipid and Lipoprotein Levels in Patients With COVID-19 Infections; 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK564657/>. Accessed 16 October, 2021.
- Sun JT, Chen Z, Nie P, et al. Lipid profile features and their associations with disease severity and mortality in patients with COVID-19. *Front Cardiovasc Med.* 2020;7:584987.
- Wunderink RG, Waterer G. Advances in the causes and management of community acquired pneumonia in adults. *BMJ.* 2017;10(358):j2471.
- Salluh JJ, Soares M, Povoa P. Corticosteroids in severe community-acquired pneumonia: the path we choose depends on where we want to get. *Crit Care.* 2011;15(2):137.
- Chalmers JD. Identifying severe community-acquired pneumonia: moving beyond mortality. *Thorax.* 2015;70(6):515–516.
- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200:e45–67.
- Chalmers JD. Identifying severe community-acquired pneumonia: moving beyond mortality. *Thorax.* 2015;70:515–516.
- Upadhyay S, Niederman MS. Biomarkers: what is their benefit in the identification of infection, severity assessment, and management of community-acquired pneumonia? *Infect Dis Clin North Am.* 2013;27:19–31.
- Zhang C, Wang K, Yang L, et al. Lipid metabolism in inflammation-related diseases. *Analyst.* 2018;143:4526–4536.
- Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. *FEBS Lett.* 2008;582:1783–1787.
- Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and Clinical Significance. *J Parenter Enter Nutr.* 2019;43:181–193.
- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): a Review. *JAMA.* 2020;324:782–793.
- Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med.* 2001;163(7):1730–1754.
- Chien YF, Chen CY, Hsu CL, Chen KY, Yu CJ. Decreased serum level of lipoprotein cholesterol is a poor prognostic factor for patients with severe community-acquired pneumonia that required intensive care unit admission. *J Crit Care.* 2015;30:506–510.
- Garcia O, Hiatt MJ, Lundin A, et al. Targeted type 2 alveolar cell depletion provides a dynamic functional model for lung injury. *Am J Respir Cell Mol Biol.* 2015.
- Mb F, Rs S. Surfactant lipids at the host-environment interface. Metabolic sensors, suppressors, and effectors of inflammatory lung disease. *Am J Respir Cell Mol Biol.* 2016;54:624–635.
- Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. *Ann Am Thorac Soc.* 2015;12:765.
- Turley SD, Andersen JM, Dietsch' JM. Rates of sterol synthesis and uptake in the major organs of the rat in vivo. *J Lipid Res.* 1981;22:551–569.
- Vignesh C, Harinivaas S, Amudha K, et al. Association of Lipid Levels With COVID-19 Infection, Disease Severity and Mortality: a Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2022;9. doi:10.3389/fcvm.2022.862999
- Tanaka S, Couret D, Tran-Dinh A, et al. High-density lipoproteins during sepsis: from bench to bedside. *Crit Care.* 2020;24:1–11.

33. Georgila K, Vyrla D, Drakos E. Apolipoprotein A-I (ApoA-I), immunity, inflammation and cancer. *Cancers*. 2019;11:1097.
34. Van Lenten BJ, Wagner AC, Navab M, et al. D-4F, an apolipoprotein A-I mimetic peptide, inhibits the inflammatory response induced by influenza A infection of human type II pneumocytes. *Circulation*. 2004;110:3252–3258.
35. Van Lenten BJ, Wagner AC, Nayak DP, Hama S, Navab M, Fogelman AM High-Density Lipoprotein Loses Its Anti-Inflammatory Properties During Acute Influenza A Infection; 2001. Available from: <http://www.circulationaha.org>. Accessed 11 October, 2021.
36. Maruyama T, Gabazza EC, Morser J, Takagi T, Taguchi O. Community-acquired pneumonia and nursing home-acquired pneumonia in the very elderly patients. *Respir Med*. 2010;104:584–592.
37. Hariri G, Joffe J, DeRyckere S, et al. Albumin infusion improves endothelial function in septic shock patients: a pilot study. *Intensive Care Med*. 2018;44:669–671.
38. Bihari S, Bannard-Smith J, Bellomo R. Albumin as a drug: its biological effects beyond volume expansion. *Crit Care Resusc*. 2020;22:257–265.
39. Gariballa S, Forster S, Walters S, Powers H. A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. *Am J Med*. 2006;119:693–699.
40. Nancy T, Yuichiro S, Junya O, et al. Clinical characteristics and risk factors for mortality in patients with community-acquired staphylococcal Pneumonia. *Nagoya J Med Sci*. 2022;84:247–259.
41. Zhang H, Voglis S, Kim CH, Slutsky AS. Effects of albumin and ringer's lactate on production of lung cytokines and hydrogen peroxide after resuscitated hemorrhage and endotoxemia in rats. *Crit Care Med*. 2003;31:1515–1522.
42. Pimienta G, Heithoff DM, Mahan MJ, Marth JD, Smith JW. Plasma proteome signature of sepsis: a functionally connected protein network. *Proteomics*. 2019;19(5):e1800389. doi:10.1002/pmic.201800389
43. Washio Y, Ito A, Kumagai S, Ishida T, Yamazaki A. A model for predicting bacteremia in patients with community-acquired pneumococcal pneumonia: a retrospective observational study. *BMC Pulm Med*. 2018;18:24.
44. Wiedermann CJ Hypoalbuminemia as surrogate and culprit of infections. *Int J Mol Sci*. 2021;22(9):548.
45. Granata G, Bartoloni A, Codeluppi M, et al. The Burden of Clostridioides Difficile Infection during the COVID-19 Pandemic: a Retrospective Case-Control Study in Italian Hospitals (CloVid). *J Clin Med*. 2020;9:3855.
46. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med*. 2020;383:2255.

Publish your work in this journal

The Journal of Inflammation Research is an international, peer-reviewed open-access journal that welcomes laboratory and clinical findings on the molecular basis, cell biology and pharmacology of inflammation including original research, reviews, symposium reports, hypothesis formation and commentaries on: acute/chronic inflammation; mediators of inflammation; cellular processes; molecular mechanisms; pharmacology and novel anti-inflammatory drugs; clinical conditions involving inflammation. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-inflammation-research-journal>