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Coronavirus Pandemic

Nutritional status is closely related to the severity of COVID-19: a multi-center retrospective study

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Abstract

Introduction: Nutritional status has been defined as an individual's health condition. The relationship between the progression of COVID-19 and Nutritional status is still unclear. We analyzed the clinical characteristics of 342 coronavirus disease 2019 (COVID-19) patients, and analyzed the relationship between the progression of COVID-19 and Nutritional status.

Methodology: 342 COVID-19 were enrolled from ten different hospitals in China. The clinical characteristics were collected and analyzed.

Results: The body mass index (BMI) of the mild patients (Group A) was higher than those in severe patients (Group B) and critical patients (Group C); The lactate dehydrogenase (LDH) level of Group A was lower than those of the other two groups; Sex, age, and BMI, was strongly correlated with Clinical classification (CT); Among the laboratory test results, Neutrophil (NEU%), Aspartate aminotransferase (AST), LDH, and blood glucose (BG) were positively correlated with CT; Lymphocyte (LYM%), Platelet (PLT), Albumin (ALB), and Creatinine (Cr) were negatively correlated with CT. BMI, NEU%, LYM%, ALB, Cr, and PLT are all protective factors that affect CT.

Conclusion: People with poor nutritional status (lower BMI and ALB) have a higher risk of developing severe disease after infection with SARS-CoV-2. In the clinical treatment of COVID-19, individualized nutritional support is very important for the rehabilitation of patients.

Key words: Nutritional status; BMI; ALB; COVID-19.

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Introduction

Since December 2019 , the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) outbreak that started in Wuhan, China, has now spread to many countries. The World Health Organization (WHO) had named the disease caused by this pathogen coronavirus disease 2019 (COVID-19) [1]. As of July 9, 2020, a total of 654 patients had been diagnosed with COVID-19 in Jiangsu Province, China. All patients were subsequently discharged [2].

Research on the structure of SARS-CoV-2 has shown that it has high sequence homology with SARS-Cov and that RNA-dependent RNA polymerase (RdRp, also known as nsp12) is the core component of the coronavirus replication/transcription mechanism [3]. A study confirmed that the diagnostic accuracy of chest computed tomography (CT) for COVID-19 is comparable to that of real-time reverse transcription-polymerase chain reaction (RT-PCR) [4]. Traditional public health measures such as isolation, quarantine,

social distancing, and community containment play key roles in the prevention and control of COVID-19 [5].

Currently, the treatment of patients with COVID-19 remains very challenging, because there are no drugs or treatment plans that have precise effects. The pathogenic mechanism of COVID-19 has not yet been elucidated in vitro, which means that we cannot effectively prevent the continued aggravation of the disease. Some studies have confirmed that chloroquine and hydroxychloroquine have anti SARS-CoV-2 effects in vitro, but their safety remains to be evaluated [6,7]. A Chinese study reported that some Chinese herbal medicines are effective at treating COVID-19 [8]. However, the findings of many studies have not been verified by large-scale clinical trials, and their conclusions are still debatable. More importantly, the factors that affect the progression of COVID-19 patients are still unclear, and early clinical interventions cannot be performed on patients, which seriously affects the prognosis of patients. Therefore, if the factors that affect the progression of COVID-19 patients can be obtained, it is of great significance for preventing the progression of the disease and formulating an effective treatment plan.

In this study, we analyzed the clinical characteristics of 342 COVID-19 patients, and the factors that affect disease progression. We hope to provide new evidence to support the development of treatments and the understanding of the pathogenic mechanism.

Methodology

Study population

A total of 342 COVID-19 patients were enrolled from ten different hospitals in ten cities (Huaian, Suzhou, Changzhou, Xuzou, Yangzhou, Taizhou, Yancheng, Lianyungang, Suqian, Nantong) in Jiangsu Province China from January 1 to March 1, 2020. All patients were diagnosed according to the clinical guidelines of the People's Republic of China for COVID-19 [9]. The baseline clinical data and laboratory test results were collected and analyzed. This study obtained informed consent from the patients and approval from the hospital ethics committee (protocol number KY202003901).

Study design

According to the clinical guidelines [9], patients with fever, respiratory symptoms, and radiologically evidence of pneumonia were diagnosed with mild COVID-19 (Group-A); those who met any of the following conditions were diagnosed with severe COVID-19 (Group-B): 1. shortness of breath with a respiration rate ≥ 30 times/minute. 2. An oxygen saturation ≤ 93% at rest, 3. A PaO2/FiO2 ratio ≤ 300mmHg, 4. Evidence on pulmonary imaging that the lesion has progressed at least 50% within 24-48 hours; Patients meeting any of the following criteria were diagnosed with critical COVID-19 (Group C): 1. respiratory failure requiring mechanical ventilation; 2. shock; 3. failures of other organs requiring ICU monitoring and treatment.

This study investigated the differences in the baseline clinical data of the three groups of patients; A-Group = Mild patients: clinical symptoms are mild, no pneumonia manifested in imaging; B-Group = Severe patients: fever, respiratory symptoms, pneumonia manifested in imaging; C-Group = Critical patients: resting state RR ≥ 30 times/minute, oxygen saturation ≤ 93%, PaO2/FiO2 ≤ 300mmHg, the lung imaging showed obvious progression of > 50% within 24-48 hours. We summarized and compared the routine blood and liver and kidney function test results of all patients at admission, one week after treatment, and before discharge. With appropriate statistical methods, we analyzed the correlations between the above factors, and analyzed the strongly correlated factors through ordered logistics regression to verify their impacts on the clinical classification of COVID-19.

Statistical analysis

The data are expressed as the frequencies (n), percentages (%), and means ± standard deviations (SDs) and were analysed with R version 4.0.2. Count data were analyzed with the chi-square test. If measurement data conformed to a normal distribution, single-factor analysis of variance was used. The LSD-t test was used for comparisons within groups. The rank sum test was used for data that did not conform to a normal distribution. The correlations between different factors were analyzed by the Spearman method. The relationships between different factors and the clinical classification of COVID-19 was verified by ordered logistic regression analysis. A difference with $p < 0.05$ was considered statistically significant.

Statement of Ethics

This study was approved by the Ethics Committee of Taizhou People's Hospital.

Results

Clinical baseline data of patients

The 342 patients had 149 mild cases of COVID-19, 153 cases of severe COVID-19, and 40 cases of critical

COVID-19. There were more female than male in group with mild COVID-19 (Group A), and more males than females in the group with severe COVID-19 (Group B) and critical COVID-19 (Group-C) ($p < 0.05$); The mean age of Group C was 48.73 ± 12.52 years which was significantly higher than the mean ages of the other two groups ($p < 0.05$).

The body mass index (BMI) in Group C was 22.25 ± 4.09 kg/m2, which was significantly lower than the 24.22 ± 3.84 kg/m2 in Group A and 23.34 ± 3.26 kg/m2 in Group B ($p < 0.05$). Although the three groups had significant differences in the prevalence of diabetes, only 4 of the enrolled patients had diabetes. There were no significant differences in the proportions of patients with other chronic diseases such as hypertension and chronic liver disease ($p > 0.05$); There were no significant differences in smoking history and alcohol consumption ($p > 0.05$), and the proportion of patients with respiratory failure in Group C (47.92%) was significantly higher than the proportions in the other two groups ($p < 0.05$) (Table 1).

Comparison of clinical symptoms and treatment options

The proportions of patients in Group-C with fever, cough, sputum, chest tightness and shortness of breath symptoms were higher than those in the other two groups ($p < 0.05$); With regard to vital signs, the respiration rate of Group A was significantly lower than those in the other two groups ($p < 0.05$), and the blood oxygen saturation level of Group C was significantly lower than those of the other two groups; None of the patients in Group A received mechanical ventilation, and 35% of patients in Group C received mechanical ventilation; High percentages of patients in all three groups received interferon therapy, and 90% of patients in Group C received kelizhi treatment, which was a significantly higher proportion than those in the other two groups; The proportion of patients in Group C receiving moxifloxacin was significantly lower than those in the other two groups ($p < 0.05$); 67.5% of patients in Group C received glucocorticoid therapy, which was a significantly higher proportion than those in the other two groups ($p < 0.05$) (Table 2).

Comparison of routine blood results of patients after admission

Comparing the routine blood results of the three groups of patients after admission, we can see that the white blood cell (WBC) levels and neutrophil (NEU) levels (proportion and count) of Group C were higher than those of the other two groups ($p < 0.05$); The lymphocyte proportion (LYM%) of Group C was 12.71 ± 4.03%, which was significantly lower than in Group A (35.84 ± 11.71%) and that in Group B (26.89 ± 10.13%) ($p < 0.05$); The proportion of monocytes (MON) in Group C was 7.64 ± 3.37%, which was significantly lower than the 9.28 ± 3.56% in Group A, and 9.42 ± 3.52% in Group B ($p < 0.05$); The platelet

Table 1. Comparison of clinical baseline data of patients in different groups.

Value	A-Group	B-Group	C-Group	Statistics (χ^2 / F)	p-value
n	149	153	40		
Sex					
Female	82 (55.03%)	59 (38.56%)	15 (37.5%)	11.132	0.025
Male	66 (44.97%)	94 (61.44%)	25 (62.5%)		
Age (year)	41.61 ± 19.65 bc	46.31 ± 14.27 a	46.75 ± 14.94 a	3.397	0.035
BMI (kg / m^2)	24.22 ± 3.84 bc	23.34 ± 3.26 a	22.25 ± 4.09 a	5.367	0.005
Data	12.92 ± 4.25 bc	15.89 ± 5.13 ac	20.23 ± 5.18 ab	40.749	0.000
With chronic disease					
Hypertension					
Diabetes	0	2 (1.31%)	2 (5%)	6.866	0.032
Coronary heart disease	12 (8.05%)	8 (5.23%)	1 (2.5%)	2.087	0.352
COPD	10 (6.71%)	15 (9.80%)	2 (5%)	1.515	0.469
Cerebrovascular disease	3 (2.01%)	3 (1.96%)	0	0.811	0.667
Renal insufficiency	0	1 (0.65%)	0	1.239	0.538
Chronic liver disease	3 (2.01%)	1 (0.65%)	0	1.744	0.418
Malignant tumor	4 (2.68%)	4 (2.61%)	1 (2.5%)	0.005	0.998
Smoking history	5 (3.36%)	5 (3.27%)	2 (5%)	0.229	0.861
Alcohol history	7 (4.69%)	8 (5.23%)	3 (7.5%)	0.497	0.780
Clinical complications					
Respiratory failure	0	0	20 (50%)	117.572	0.000
Acute renal impairment	0	0	1 (2.5%)	7.572	0.023

*A-Group: Mild patients, B-Group: Severe patients, C-Group: Critical patients; BMI: Body Mass Index; Data: The time to a negative nucleic acid test; a: Compared with Group A $p < 0.05$; b: Compared with Group B $p < 0.05$; c: Compared with Group C $p < 0.05$.

(PLT) count level in Group C was 183.05 ± 67.27 $\times 10^9$/L, which was significantly lower than the 209.7 ± 66.88 $\times 10^9$/L in Group A and 176.77 ± 70.38 $\times 10^9$/L in Group B ($p < 0.05$).

The Alanine aminotransferase (ALT) level in Group C was 40.33 ± 33.91 U/L, which was significantly higher than the 29.13 ± 21.92 U/L in Group A and 31.21 ± 20.21 U/L in Group B; The Aspartate aminotransferase (AST) level in Group C was 38.08 ± 27.68 U/L, which was significantly higher than the 26.88 ± 17.16 U/L in Group A and 29.74 ± 17.34 U/L in Group B; The ɣ-glutamyl transpeptidase (ɣ-GGT) level in Group C was 45.85 ± 34.61U/L, which was significantly higher than the 26.46 ± 17.06 U/L in Group A and 39.14 ± 52.76 U/L ($p < 0.05$) U/L in Group B; The lactate dehydrogenase (LDH) level of Group C was 295.00 (202.00 – 450.25) U/L, which was significantly higher than the 196.80 (158.00 – 285.50) U/L in Group A and 267.00 (188.50 - 413.00) U/L in Group B; The Albumin (ALB) level in Group C was 37.69 ± 4.78 g/L, which was significantly higher than the 42.49 ± 5 g/L in Group A and 39.87 ± 6.09 U/L in Group B; The Blood glucose (BG) level in Group C was higher than those in the other two groups ($p < 0.05$) and the blood calcium level in Group A was higher than those in the other two groups ($p < 0.05$) (Table 3).

Table 2. Comparison of admission symptoms and treatment options for patients of different clinical types.

Value	A-Group	B-Group	C-Group	Statistics (χ^2 / F)	p-value
n	149	153	40		
Admission symptoms					
Fever	65 (43.62%)	134 (87.58%)	37 (92.5%)	79.889	0.000
Cough	35 (23.49%)	91 (59.48%)	28 (70.00%)	50.906	0.000
Expectoration	30 (20.13%)	49 (32.03%)	19 (47.5%)	13.090	0.001
Chest tightness	1 (0.67%)	4 (2.61%)	16 (40.00%)	90.604	0.000
Headache	10 (6.71%)	7 (4.58%)	2 (5.00%)	0.683	0.711
Sore throat	11 (7.38%)	15 (9.80%)	8 (20.00%)	5.613	0.060
Vomit	0 (0%)	4 (2.61%)	2 (5.00%)	5.762	0.056
Diarrhea	6 (4.03%)	9 (5.88%)	0 (0%)	2.698	0.260
Muscle ache	21 (14.09%)	11 (7.19%)	3 (7.50%)	4.286	0.117
Fatigue					
Vital signs					
Breath rate	18.4 ± 2.01 bc	19.93 ± 8.45a	20.58 ± 4.21 a	3.441	0.033
Blood pressure (high pressure)	126.41 ± 15.35	129.71 ± 13.43	126.68 ± 18.05	2.011	0.135
Blood pressure (low pressure)	81.19 ± 9.49	82.6 ± 10.17	81.83 ± 10.43	0.761	0.468
Heart rate	85.91 ± 12.11	88.17 ± 13.53	90.33 ± 10.88	2.395	0.093
Blood oxygen saturation	97.91 ± 1.31c	98.15 ± 1.58c	96.75 ± 2.86 ab	11.059	0.000
Life support					
Nasal feeding	34 (22.81%)	127 (83.01%)	37 (92.50%)	134.432	0.000
Oxygen mask	0 (0%)	5 (3.27%)	22 (55.00%)	139.337	0.000
Non-invasive mechanical ventilation	0 (0%)	2 (1.31%)	38 (95.00%)	77.765	0.000
Invasive mechanical ventilation	0 (0%)	1 (0.65%)	2 (5.00%)	9.226	0.010
Blood purification	0 (0%)	0 (0%)	1 (2.50%)	7.572	0.023
ECMO	0 (0%)	0 (0%)	1 (2.50%)	7.572	0.023
Anti-viral drug					
Interferon	107 (71.81%)	66 (43.13%)	21 (52.50%)	25.614	0.000
Kreiz	102 (68.46%)	112 (73.20%)	36 (90.00%)	7.444	0.024
Abidor	58 (38.93%)	70 (45.75%)	25 (62.50%)	7.204	0.027
Antibacterial drugs				39.759	0.000
Ceftriaxone	22 (14.77%)	6 (3.92%)	2 (5.00%)		
Moxifloxacin	94 (63.09%)	130 (84.97%)	32 (8.00%)		
Cefoperazone sulbactam	0 (0%)	5 (3.27%)	3 (7.50%)		
Carbapenems	1 (0.67%)	2 (1.31%)	0 (0%)		
Other	6 (4.03%)	3 (1.96%)	1 (2.50%)		
Glucocorticoid	22 (14.77%)	46 (3.01%)	27 (67.50)	44.435	0.000

*A-Group: Mild patients, B-Group: Severe patients, C-Group: Critical patients; a: Compared with Group A $p < 0.05$; b: Compared with Group B $p < 0.05$; c: Compared with Group C $p < 0.05$.

Comparison of routine blood results one week after admission

After one week of treatment, WBC and NEU%, in Group C patients were still higher than those in the other two groups ($p < 0.05$); The proportion of lymphocytes in Group C was 18.1 ± 10.88%, which was still significantly lower than that in Group A (29.55 ± 10.85%) and that in Group B (24.73 ± 10.35%) ($p < 0.05$); The ALT level in Group C was 41.93 ± 40.48 U/L, which was higher than that in Group A (27.49 ± 20.5 U/L) and Group B (36.07 ± 34.36 U/L) ($p < 0.05$); Similarly, the levels of ɣ-GGT, LDH, BG, and blood urea nitrogen(BUN) in Group C were higher than those in the other two groups ($p < 0.05$); The ALB level in Group C was 36.91 ± 6.5 g/L, which was significantly lower than that in Group A (40.67 ± 6.65 g/L) and Group B (37.79 ± 6.03 g/L) ($p < 0.05$) (Table 4).

Comparison of routine blood results before discharge

Before discharge, the proportion and count of neutrophils in Group C were higher than those in the other two groups ($p < 0.05$) and the proportion and count of lymphocytes in Group C were still lower than those in the other two groups ($p < 0.05$).

In terms of liver and kidney functioning, the levels of ALT and AST in Group C were significantly higher than those in the other two groups ($p < 0.05$); The levels of ɣ-GGT and LDH in Group C were still higher than those in the other two groups ($p < 0.05$), while the level

Table 3. Comparison of laboratory tests in different groups (the first time).

Value	A-Group	B-Group	C-Group	Statistics (χ^2 / *F*/Z)	*p*-value
n	149	153	40		
WBC (10^9/L)	5.42 ± 2.06 bc	4.65 ± 1.54 ac	9.39 ± 3.83 ab	77.968	0.000
NEU%	59.89 ± 13.59 bc	62.9 ± 11.71 ac	76.66 ± 10.98 ab	28.480	0.000
LYM%	35.84 ± 11.71 bc	26.89 ± 10.13 ac	12.71 ± 4.03 ab	84.818	0.000
MON%	9.28 ± 3.56 c	9.42 ± 3.52 c	7.64 ± 3.37 ab	4.223	0.015
NEU (10^9/L)	3.37 ± 1.93 c	3.01 ± 1.32 ac	4.42 ± 2.64 ab	9.931	0.000
LYM (10^9/L)	1.73 ± 0.74 bc	1.2 ± 0.55 a	1.11 ± 0.49 a	32.322	0.000
MON (10^9/L)	0.48 ± 0.51	0.42 ± 0.18	0.34 ± 0.15	2.713	0.068
RBC (10^12/L)	4.65 ± 0.58	4.53 ± 0.58	4.56 ± 0.56	1.752	0.175
Hb (g/L)	138.89 ± 17.6	137.82 ± 17.17	138.73 ± 16.3	0.153	0.858
HCT (%)	40.56 ± 4.8	40.45 ± 4.68	40.56 ± 4.7	0.023	0.977
PLT (10^9/L)	209.7 ± 66.88 bc	176.77 ± 70.38 a	183.05 ± 67.27 a	9.120	0.000
RDW (%)	18.95 ± 11.8 bc	24.37 ± 13.61 ac	16.45 ± 9.79 ab	10.323	0.000
MPV (fL)	10.63 ± 1.22	10.84 ± 1.29	10.63 ± 1.58	1.076	0.342
PDW (fL)	14.33 ± 2.51	15.65 ± 20.26	14.09 ± 2.54	0.426	0.653
PCT (%)	0.22 ± 0.08	0.19 ± 0.07	0.19 ± 0.06	6.155	0.002
ALT (U/L)	29.13 ± 21.92 c	31.21 ± 20.21 c	40.33 ± 33.91 ab	3.775	0.024
AST (U/L)	26.88 ± 17.16 c	29.74 ± 17.34 c	38.08 ± 27.68 ab	5.656	0.004
ALP (U/L)	68.37 ± 28.23	66.35 ± 26.96	60.38 ± 16.93	1.431	0.240
ɣ-GGT (U/L)	26.46 ± 17.06 bc	39.14 ± 52.76 a	45.85 ± 34.61 a	5.966	0.003
LDH (U/L)	196.80 (158.00-285.50) b	267.00 (188.50-413.00) a	295.00 (202.00-450.25)	25.637	0.000
Tbil **(umol/L)**	13.1 ± 13.02	11.58 ± 6.81	12.42 ± 5.64	0.883	0.415
ALB (g/L)	42.49 ± 5.00 bc	39.87 ± 6.09 ac	37.69 ± 4.78 ab	15.64	0.000
GLB (g/L)	28.16 ± 4.75	27.75 ± 4.48	28.78 ± 3.72	0.896	0.409
BG (mmol/L)	5.9 ± 1.83 c	6.17 ± 1.79 c	7.26 ± 2.93 ab	7.540	0.001
BUN (mmol/L)	4.25 ± 1.19	4.11 ± 1.36	4.02 ± 5.2	0.250	0.779
Cr (mmol/L)	64.3 ± 19.61 c	67.06 ± 19.26 c	31.14 ± 19.61 ab	56.496	0.000
UA (mmol/L)	276.33 ± 101.83	257.43 ± 106.08	250.61 ± 87.45	1.733	0.178
TG (mmol/L)	1.74 ± 1.48	1.58 ± 1.14	1.47 ± 0.98	0.948	0.389
TC (mmol/L)	3.78 ± 1.23	3.74 ± 1.26	3.96 ± 1.00	0.527	0.591
Ca (mmol/L)	2.27 ± 0.15 bc	2.13 ± 0.25 ac	2.18 ± 0.12 ab	19.206	0.000
P (mmol/L)	1.18 ± 0.27	1.13 ± 0.26	1.12 ± 0.28	1.503	0.224
K (mmol/L)	4.02 ± 0.46	3.95 ± 0.47	4.07 ± 0.58	1.200	0.302
Na (mmol/L)	138.96 ± 3.35	136.82 ± 16.2	138.61 ± 3.69	1.470	0.231
Cl (mmol/L)	103.05 ± 3.51	100.6 ± 16.36	102.4 ± 3.86	1.831	0.162

*A-Group: Mild patients, B-Group: Severe patients, C-Group: Critical patients; a: Compared with Group A $p < 0.05$; b: Compared with Group B $p < 0.05$; c: Compared with Group C $p < 0.05$.

of ALB in the Group C was lower than those in the other two groups ($p < 0.05$) (Table 5).

Correlation analysis of clinical data (at admission)

The correlation analysis of clinical characteristics in 342 COVID-19 patients showed that sex (r = 0.17), BMI (r = 0.15), and age (r = 0.16) were correlated with the clinical classification of COVID-19 (CT); Among the laboratory test indicators, NEU%, AST, LDH, and BG were positively correlated with the clinical classification of COVID-19, NEU% had the strongest correlation (r = 0.29); LYM%, PLT, ALB, Creatinine (Cr) were all negatively correlation with the clinical classification of COVID-19, and LYM% had the strongest correlation (r = -0.56), followed by ALB (r = -0.32); Factors with a strong correlation with the time to a negative nucleic acid test (Data) were the clinical classification of COVID-19, NEU%, LYM%, LDH, ALB, and BG; The time to a negative nucleic acid test (Data) was positively correlated with the clinical classification of COVID-19, NEU%, and LDH, and the clinical classification had the strongest correlation (r = 0.42), LYM%, ALB, and BG were all negatively correlated with the time to a negative nucleic acid test. Among them, LYM% had the strongest correlation (r = -0.3), followed by ALB (r = -0.21) (Figure 1).

Ordered logistics regression analysis of related factors

After entering 8 different factors into the ordered logistics regression analysis model, sex and BG were found to have limited impacts on the severity of the disease; LDH is a risk factor affecting the severity of

Table 4. Comparison of laboratory test results of patients in different groups (A week later).

Value	A-Group	B-Group	C-Group	Statistics ($\chi^2/F/Z$)	p-value
n	149	153	40		
WBC (10^9/L)	5.46 ± 1.82 c	5.55 ± 2.62 c	7.2 ± 3.51 ab	8.620	0.000
NEU.%	60.1 ± 11.69 bc	65.07 ± 12.64 ac	73.75 ± 12.87 ab	20.725	0.000
LYM.%	29.55 ± 10.85 bc	24.73 ± 10.35 ac	18.1 ± 10.88 ab	20.423	0.000
MON.%	8.79 ± 2.50	8.82 ± 3.33	7.75 ± 3.23	2.227	0.109
NEU (10^9/L)	3.31 ± 1.4 bc	3.82 ± 2.48 ac	5.57 ± 3.52 ab	15.931	0.000
LYM (10^9/L)	1.6 ± 0.82 bc	1.26 ± 0.58 ac	1.11 ± 0.63 ab	12.75	0.000
MON (10^9/L)	0.47 ± 0.17	0.47 ± 0.21	0.50 ± 0.23	0.453	0.636
RBC (10^12/L)	4.55 ± 0.58	4.46 ± 0.59	4.56 ± 0.58	1.016	0.363
Hb (g/L)	136.34 ± 17.04	134.42 ± 22.46	138.9 ± 16.15	0.939	0.392
HCT (%)	39.88 ± 4.7	40.04 ± 6.18	40.16 ± 4.65	0.055	0.946
PLT (10^9/L)	217.4 ± 70.32	200.71 ± 73.89	224.93 ± 87.99	2.743	0.066
RDW (%)	21.53 ± 13.1	23.62 ± 13.66	18.38 ± 11.23	2.770	0.064
MPV (fL)	10.65 ± 1.27	10.6 ± 1.23	10.43 ± 1.17	0.501	0.607
PDW (fL)	14.03 ± 2.59	13.89 ± 3.37	13.88 ± 2.55	0.096	0.908
PCT (%)	0.22 ± 0.06	0.21 ± 0.07	0.23 ± 0.08	1.785	0.169
ALT (U/L)	27.49 ± 20.5 bc	36.07 ± 34.36 ac	41.93 ± 40.48 ab	5.057	0.007
AST (U/L)	24.05 ± 15.21	29.58 ± 24.26	28.19 ± 16.68	2.987	0.052
ALP (U/L)	69.38 ± 36.67	65.83 ± 29.78	60.9 ± 18.77	1.229	0.294
ɣ-GGT (U/L)	29.4 ± 20.31 bc	35.24 ± 30.72 ac	43.48 ± 34.86 ab	4.648	0.010
LDH (U/L)	205.00 (153.00-347.50) b	255.00 (179.50-433.50) a	264.00 (179.50-578.75)	13.504	0.001
TBil **(umol/L)**	18.32 ± 37.93	20.36 ± 48.92	14.55 ± 9.11	0.330	0.719
ALB (g/L)	40.67 ± 6.65 bc	37.79 ± 6.03 a	36.91 ± 6.50 a	9.993	0.000
GLB (g/L)	27.66 ± 4.67	26.9 ± 6.08	27.72 ± 7.18	0.766	0.466
BG (mmol/L)	5.98 ± 2.49 bc	6.5 ± 3.47 ac	7.28 ± 2.89 ab	3.105	0.046
BUN (mmol/L)	4.42 ± 1.23 bc	4.34 ± 1.4 ac	6.05 ± 5.08 ab	10.933	0.000
Cr (mmol/L)	67.77 ± 20.74	69.51 ± 21.63	67.69 ± 25.94	0.275	0.759
UA (mmol/L)	252.86 ± 103.24	249.24 ± 92.23	253.57 ± 81.46	0.063	0.939
TG (mmol/L)	2.00 ± 1.23	1.92 ± 1.09	1.88 ± 0.98	0.246	0.782
TC (mmol/L)	4.13 ± 3.35	7.15 ± 37.15	4.16 ± 0.98	0.600	0.549
Ca (mmol/L)	2.24 ± 0.21 bc	2.18 ± 0.28 a	2.13 ± 0.13 a	4.642	0.010
P (mmol/L)	1.20 ± 0.34	1.15 ± 0.31	1.19 ± 0.27	0.984	0.375
K (mmol/L)	3.96 ± 0.47	3.94 ± 0.52	3.88 ± 0.36	0.471	0.625
Na (mmol/L)	137.74 ± 11.58	137.31 ± 15.81	137.64 ± 2.97	0.042	0.959
Cl (mmol/L)	103.26 ± 5.66	102.73 ± 5.73	100.76 ± 3.5	3.265	0.039

*A-Group: Mild patients, B-Group: Severe patients, C-Group: Critical patients; a: Compared with Group A $p < 0.05$; b: Compared with Group B $p < 0.05$; c: Compared with Group C $p < 0.05$.

the disease (OR = 1.003, 95%, CI = 1.002-1.005); BMI, NEU%, LYM%, ALB, Cr, and PLT are all protective factors that affect the clinical classification of COVID-19 (CT), of which LYM% is associated with the highest risk (β = -0.256, OR = 0.774, 95% CI = 0.728-0.822) (Table 6).

Discussion

COVID-19 is currently widespread worldwide. Although most patients with COVID-19 have mild symptoms or are asymptomatic, the mechanism underlying the progression of COVID-19 patients from infection to serious illness or even death is still unclear. Because the pathophysiological mechanism by which SARS-CoV-2 causes pneumonia is not yet clear, there is currently no specific treatment available. Determining the relevant factors that affect disease progression after infection with SARS-CoV-2 through retrospective studies is very important for determining pathogenesis of COVID-19 [10].

This multi-centre retrospective study confirmed that there were more females than males in the mild COVID-19 group (Group A), and more males than females in severe COVID-19 group (Group B) and the critical COVID-19 group(Group C) ($p < 0.05$); The average age in Group A was lower than those in the other two groups ($p < 0.05$); Although the three groups had significant differences in the prevalence of diabetes, only 4 of the enrolled patients had diabetes. We found that the BMI of patients in the A-Group was

Table 5. Laboratory test results of patients in different groups before discharge (before discharge).

Value	A-Group	B-Group	C-Group	Statistics ($\chi^2/F/Z$)	P-value
n	149	153	40		
WBC (10^9/L)	7.03 ± 2.83	6.13 ± 2.16	6.32 ± 3.15	1.709	0.183
NEU.%	67.68 ± 14.82 bc	61.38 ± 12.51 a	65.04 ± 13.83 a	4.773	0.009
LYM.%	22.91 ± 11.43 bc	28.33 ± 10.48 ac	24.26 ± 11.69 ab	6.638	0.001
MON.%	8.05 ± 3.15	8.55 ± 2.60	8.4 ± 2.90	0.516	0.597
NEU (10^9/L)	5.22 ± 2.98 bc	3.98 ± 2.13 ac	4.42 ± 3.24 ab	3.275	0.039
LYM (10^9/L)	1.5 ± 0.75c	1.6 ± 0.62c	1.39 ± 0.61 ab	4.112	0.017
MON (10^9/L)	0.55 ± 0.27	0.51 ± 0.20	0.5 ± 0.20	0.867	0.421
RBC (10^12/L)	4.24 ± 0.77	4.32 ± 0.73	4.24 ± 0.70	0.621	0.538
Hb (g/L)	131.34 ± 25.26	130.97 ± 18.62	130.49 ± 16.74	0.044	0.957
HCT (%)	40.84 ± 14.48	38.89 ± 8.55	37.82 ± 5.57	2.175	0.115
PLT (10^9/L)	255.57 ± 96.62	244.62 ± 78.27	237.09 ± 70.91	0.998	0.370
RDW (%)	27.27 ± 51.75	20.26 ± 28.35	21.61 ± 12.89	1.058	0.348
MPV (fL)	10.06 ± 1.40	10.58 ± 1.68	10.43 ± 1.29	1.936	0.146
PDW (fL)	13.09 ± 2.64	13.39 ± 2.57	12.99 ± 2.66	0.939	0.392
PCT (%)	0.24 ± 0.10	0.24 ± 0.07	0.24 ± 0.06	0.108	0.898
ALT (U/L)	56.65 ± 57.86 bc	35.98 ± 32.14 a	39.21 ± 29.08 a	5.567	0.004
AST (U/L)	32.03 ± 22.4	33.37 ± 40.44	28.91 ± 25.89	0.707	0.494
ALP (U/L)	60.02 ± 18.76	66.88 ± 50.89	69.06 ± 47.75	0.592	0.554
ɣ-GGT (U/L)	50.28 ± 40.95 bc	35.48 ± 27.47 ac	37.79 ± 30.06 ab	3.743	0.025
LDH (U/L)	173.00 (137.75-222.00) b	254.00 (173.00-408.00) a	253.50 (177.00-543.00)	36.025	0.000
TBil **(umol/L)**	25.88 ± 46.09	35.55 ± 57.99	25.64 ± 48.81	1.460	0.234
ALB (g/L)	33.83 ± 7.55	35.44 ± 10.81	34.08 ± 7.53	1.025	0.360
GLB (g/L)	28.77 ± 7.45	28.7 ± 8.08	28.2 ± 7.27	0.187	0.829
BG (mmol/L)	7.17 ± 4.70	8.11 ± 7.37	6.52 ± 4.61	2.600	0.076
BUN (mmol/L)	5.52 ± 2.83 bc	4.29 ± 1.33 a	4.23 ± 1.44 a	10.750	0.000
Cr (mmol/L)	60.45 ± 26.66	60.05 ± 25.52	61.39 ± 23.00	0.113	0.893
UA (mmol/L)	263.64 ± 103.33	243.58 ± 97.58	255.89 ± 107.83	0.853	0.427
TG (mmol/L)	2.81 ± 1.31	5.33 ± 31.34	11.24 ± 52.76	1.105	0.332
TC (mmol/L)	4.19 ± 0.89	3.96 ± 1.14	7 ± 36.79	0.622	0.537
Ca (mmol/L)	2.15 ± 0.15	2.24 ± 0.46	2.18 ± 0.25	1.872	0.155
P (mmol/L)	1.27 ± 0.30	1.27 ± 0.47	1.22 ± 0.36	0.618	0.540
K (mmol/L)	3.85 ± 0.99b	3.68 ± 1.03a	3.95 ± 0.82	3.100	0.046
Na (mmol/L)	130.37 ± 36.79	122.34 ± 45.5	131.73 ± 32.18	2.312	0.101
Cl (mmol/L)	104.74 ± 9.33	107.84 ± 12.14	105.23 ± 8.97	2.827	0.061

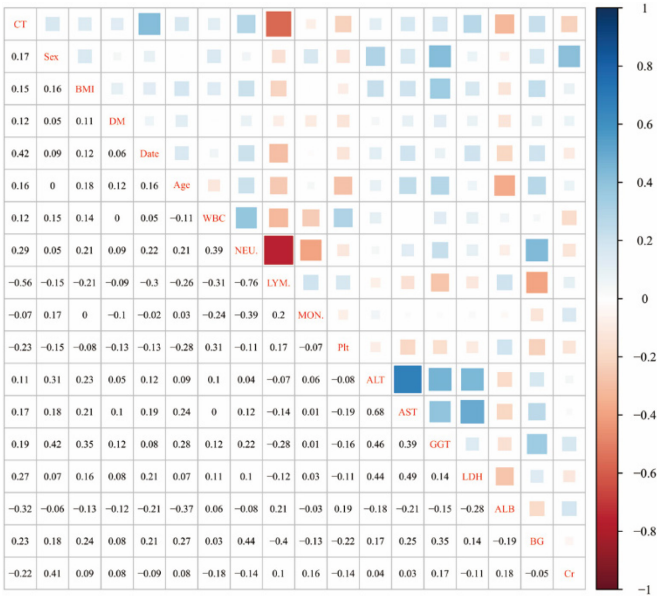
*A-Group: Mild patients, B-Group: Severe patients, C-Group: Critical patients; a: Compared with Group A $p < 0.05$; b: Compared with Group B $p < 0.05$; c: Compared with Group C $p < 0.05$.

higher than that in the Group B, and the BMI in Group B was higher than that in Group C. Therefore, we doubt whether the nutritional status of the patient correlated with disease severity.

The patients we included all had typical clinical symptoms and radiological evidence of pneumonia. The treatment plans were formulated according to the guidelines. A large proportion of severe and critically ill patients received combined antiviral therapy (interferon, kreats, Arbidol). A large proportion of patients were had bacterial infections, and they were given antimicrobial treatment. Some studies have confirmed that COVID-19 patients have a higher risk of bacterial infections, and some patients even have bacterial and fungal infections. Therefore, it is necessary to pay close attention to the emergence of mixed infections during clinical treatment [11]. Most importantly, 67.5% of the critically ill patients (Group C) were treated with glucocorticoids (prednisolone 20 mg ivgtt q12h). Several clinical trials and meta-analyses have indicated that corticosteroids are associated with increased mortality, a tendency for requiring mechanical ventilation, and relatively longer hospitalizations for patients with SARS, MERS, and H1N1 [12]. However, the effectiveness and safety of glucocorticoids for the treatment of viral pneumonia are still unclear, and further research is needed. Eventually, all patients enrolled in this study were cured and discharged.

When the patients were admitted to the hospital, the blood lymphocytes levels (proportion and count) of the Group B patients were significantly lower than those of the Group A patients, and those of the Group C patients were lower than those of Group B patients. This is consistent with the results reported in related studies [13]. Patients with COVID-19 experience a decrease in lymphocytes early in the disease course. The levels of white blood cells and neutrophils in the Group C patients were significantly higher than those in the other two groups of patients. The above results reconfirm that COVID-19 patients have a higher risk of bacterial

Figure 1. Correlation analysis of clinical difference data of 342 COVID-19 patients.



CT: (the clinical classification of COVID-19); DM: Diabetes; Data: The time to a negative nucleic acid test; BG: Blood glucose. In this study, r ≥ 0.2 is considered to have a high correlation.

infection [14]. The platelet level of Group A patients was significantly higher than those of the other two groups. COVID-19 patients have low PLT counts and prolonged prothrombin times, which may be related to the pathogenesis of COVID-19, further research is needed to confirm this [15].

Consistent with related reports, the ALT and AST levels of COVID-19 patients were significantly elevated [16]. Abnormal liver enzymes levels are relatively common in severe infectious diseases [17,18]. The LDH level of Group A patients was lower than that of the Group B, and that of the Group C was higher than that of Group B patients. The ALB level of the Group B patients was significantly lower than that of the Group A patients, and that of the Group C patients was significantly lower than that of the Group B patients. The BUN and Cr levels of Group C patients

Table 6. Ordered logistics regression analysis.

Factors	*β*	*S.E*	*Wald*	*P-value*	*OR*	*95%CI*	
						low	up
Sex	-0.001	0.038	0.001	0.985	0.999	0.927	2.93
BMI	-0.129	0.041	9.737	0.002	0.879	0.811	0.953
NEU%	-0.126	0.024	27.13	0.000	0.882	0.84	0.924
LYM%	-0.256	0.031	69.191	0.000	0.774	0.728	0.822
LDH	0.003	0.001	14.432	0.000	1.003	1.002	1.005
ALB	-0.052	0.023	4.887	0.027	0.949	0.907	0.994
BG	-0.001	0.071	0.001	0.984	0.999	0.87	1.149
Cr	-0.032	0.006	25.592	0.000	0.968	0.957	0.981

were significantly lower than those of the other two groups (although the comparison of the three groups of patients did not show a significant different, the BUN level in Group C patients was still numerically lower than those of the other two groups). The random BG level of Group A patients was also significantly lower than those of the other two groups. After 1 week of treatment, the differences among the three groups of patients were still significant, however before discharge, there were no significant differences in WBC, PLT, AST, ALP, ALB, BG, and Cr among the three groups of patients.

To verify whether the different factors (at the time of admission) are related to disease severity, we conducted a correlation matrix analysis, and the results showed that the baseline clinical data such as sex, age, and BMI were strongly correlated with disease severity. Among the laboratory test results, NEU%, AST, LDH, and BG were positively correlated with CT (the clinical classification of COVID-19); LYM%, PLT, ALB, and Cr were all negatively correlated with CT. Data (The time to a negative nucleic acid test) was positively correlated with CT, NEU%, LDH. LYM%, ALB, and BG were all negatively correlated with Data. Finally, we performed ordered logistic regression analysis of the factors with strong correlations with disease severity to verify the causality. The results indicated that LDH is a risk factor affecting the severity of the disease (OR = 1.003, 95%, CI = 1.002-1.005); NEU%, LYM%, ALB, Cr, and PLT are all protective factors that affect disease severity.

Nutritional status has been defined as an individual's health condition, it is influenced by the intake and utilization of nutrients [19]. Through the above statistical analysis, we found that the factors that reflect the nutritional status of patients such as LDH ALB, Cr, and BMI have an important causal relationship with the severity of COVIDS-19. BMI and ALB are direct indicators of the current nutritional status of patients. Nutrition status can be defined in different ways. In clinical practice, body mass index (BMI) is often used as a parameter of nutritional status. BMI < 18.5 is generally accepted as underweight, BMI 18.5–25 as normal weight and BMI > 25 as overweight. Serum albumin (ALB) is generally accepted parameter of nutritional status, and it is affected by low-protein feeding [20]. Studies have confirmed that patients with an abnormal BMI are relatively more likely to contract infectious diseases. The BMI on the risk of admission for an infectious disease is unclear, and is difficult to study given the risk of confounding. Butler-Laporte G's study confirmed that an increased BMI was associated with increased risks of admission for infectious disease and mortality [21]. Bhasin A found that younger patients with COVID-19 had a higher mean BMI than older patients with COVID-19 [22]. A study demonstrated that in adults with clinically defined sepsis, patients with higher body mass had lower short-term mortality than patients with normal body mass [23]. Some studies also found that elderly COVID-19 patients have a poor nutritional status and high mortality [24]. A meta-analysis confirmed that thirty-four percent of patients had ALB levels lower than the normal range [25]. Muhammad SA's study confirmed that ALB can induce the differentiation of T cells and regulate the activity of cytotoxic T cells [26]. Patients with a poor nutritional status have longer hospital stays and a higher risk of re-admission than patients with a normal nutritional status, and our research confirms this [27]. LDH is involved in the metabolism of glycolysis in the human body, and the expression level of serum Cr indirectly reflects the patients' protein metabolic. Cr and LDH only reflect the patient's metabolic state to a certain extent. Because the nutritional status is related to the intake and utilization of nutrients, the abnormality of Cr and LDH indirectly reflects the abnormal nutritional status of the patient, but the two indicators that most directly reflect the nutritional status of the patient are BMI and ALB. The hyperfunction of CD4+ and CD8+ T cells is associated with the pathogenesis of extremely severe SARS-CoV-2 infection [28]. Mandarano's study indicated that the activation of T cells is closely related to glycolysis [29]. When glucose metabolism is disordered, increased pyruvate production affects the immune activity of macrophages [30]. Therefore, we believe that some COVID-19 patients with poor nutritional status may also have metabolism abnormalities that affect their immune systems.

Conclusions

In summary, people with a poor nutritional status (lower BMI and ALB) have a higher risk of developing severe disease after infection with SARS-CoV-2. Such patients may have metabolic abnormalities that affect their metabolism of nutrients such as sugar or protein. Low nutritional status likely affects the body's immune system before the patient shows clinical symptoms. In the clinical treatment of COVID-19, individualized nutritional support is very important for the rehabilitation of patients.

Limitations

Although this study was a multi-center study, it was not a randomized controlled experiment. There may have been some statistical bias, and further verification and analyses are needed in the future.

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Authors' Contributions

Dr. Li Yang completed the data sorting and writing of this article; All authors provided original data and participated in article design. All authors have read and agreed to the published version of the manuscript.

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