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Evaluation of Nutrition Risk and Its Association With Mortality Risk in Severely and Critically Ill COVID-19 Patients

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Abstract

Background: The nutrition status of coronavirus disease 2019 patients is unknown. This study evaluates clinical and nutrition characteristics of severely and critically ill patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and investigates the relationship between nutrition risk and clinical outcomes. *Methods:* A retrospective, observational study was conducted at West Campus of Union Hospital in Wuhan. Patients confirmed with SARS-CoV-2 infection by a nucleic acid–positive test and identified as severely or critically ill were enrolled in this study. Clinical data and outcomes information were collected and nutrition risk was assessed using Nutritional Risk Screening 2002 (NRS). *Results:* In total, 413 patients were enrolled in this study, including 346 severely and 67 critically ill patients. Most patients, especially critically ill patients, had significant changes in nutrition-related parameters and inflammatory markers. As for nutrition risk, the critically ill patients had significantly higher proportion of high NRS scores ($P < .001$), which were correlated with inflammatory and nutrition-related markers. Among 342 patients with NRS score ≥3, only 84 (of 342, 25%) received nutrition support. Critically ill patients and those with higher NRS score had a higher risk of mortality and longer stay in hospital. In logistic regression models, 1-unit increase in NRS score was associated with the risk of mortality increasing by 1.23 times (adjusted odds ratio, 2.23; 95% CI, 1.10–4.51; $P = .026$). *Conclusions:* Most severely and critically ill patients infected with SARS-CoV-2 are at nutrition risk. The patients with higher nutrition risk have worse outcome and require nutrition therapy. (*JPEN J Parenter Enteral Nutr.* 2021;45:32–42)

Keywords

clinical outcomes; COVID-19; inflammatory marker; Nutritional Risk Screening 2002; nutritional status

Clinical Relevancy Statement

The novel coronavirus disease 2019 (COVID-19) has caused a pandemic throughout the world, posing unprecedented challenges to patients and healthcare systems. Meanwhile, the nutrition status of COVID-19 patients is unknown. The purpose of this observational study is to estimate the clinical characteristics and nutrition risk of severely and critically ill patients infected with severe acute respiratory syndrome coronavirus 2 and further investigate the relationship between nutrition risk and clinical outcomes. This study principally shows that a simple screening will help to detect the COVID-19 patients in need of nutrition therapy to improve clinical outcomes.

Introduction

An outbreak of novel coronavirus disease 2019 (COVID-19) caused by a newly recognized novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has spread rapidly nationwide and worldwide.[1-5] As of April 17, 2020, there were 2,000,000 confirmed cases and nearly 130,000 deaths globally.[6] The clinical spectrum of COVID-19 ranges from mild to critically ill pneumonia. The patients with severe illness who were aged over 60 years and those with underlying conditions (such as hypertension, diabetes, cardiovascular disease, and chronic respiratory disease) are at a higher risk of death and of great concern in clinical management and intensive care.

Previous studies showed that patients with severe pneumonia were at risk of protein-energy malnutrition, which severely impaired respiratory muscle contractility and the immune defense system.[7] COVID-19 patients also have some signs of malnutrition such as decreased serum albumin and prealbumin level and impaired liver and kidney function.[8] Nutrition risk screening and nutrition support have been recommended for critically ill COVID-19 patients.[9] However, clinical evidence of nutrition risk and its

association with clinical outcomes for COVID-19 patients is limited.

Therefore, we performed an observational study to comprehensively evaluate the clinical and nutrition characteristics of severely and critically ill COVID-19 patients based on clinical data and nutrition risk screening. We also investigated the relationship between nutrition risk and clinical outcomes in severely and critically ill patients. These findings will provide evidence for the role of nutrition strategies in achieving a beneficial outcome for severely and critically ill COVID-19 patients.

Materials and Methods

Study Design and Participants

This retrospective, observational study was conducted at West Campus of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China), which was a designated hospital to treat COVID-19 patients. The inpatients admitted to the hospital from January 29, 2020, to February 19, 2020, who had been confirmed with SARS-CoV-2 infection by a nucleic acid–positive test and identified as severely or critically ill according to the diagnosis and treatment protocol for COVID-19 were enrolled in this study.[10,11] Patients were defined as severely ill if they met the following criteria: (1) respiratory distress (respiratory rate $\geq$ 30 breaths/min); (2) pulse oxygen saturation $\leq$93% on room air; (3) low arterial oxygenation ratio (PaO_2/fraction of inspired oxygen $\leq$ 300). Patients were defined as critically ill if the met the following criteria: (1) respiratory failure requiring a form of mechanical ventilation; (2) shock; (3) complications with other organ failure that require monitoring and treatment in the intensive care unit (ICU).[10,11] Patients who were pregnant, <18 years old, or admitted to the ICU were excluded from this study. Finally, 413 participants were included in the analysis.

This study was conducted in accordance with the Declaration of Helsinki and approved by The Ethics Committee of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology ([2020]0096-1). Informed consent was waived because of the rapid emergence of this infectious disease, and the analysis used anonymous clinical data. This trial was registered at the Chinese Clinical Trial Registry (ChiCTR2000030803).

Data Collection

Data on basic information (age, gender, and comorbidities) and medical history of present illness (onset date, symptoms from onset to admission, laboratory values, findings of chest computed-tomography examination and nucleic acid test, et al) on admission were retrospectively collected from electronic medical records for each participant. Any missing or uncertain records were reviewed and confirmed by discussion with involved healthcare providers. Laboratory variables were determined by standard clinical chemistry methods. For example, routine blood test was detected by BC-6800 Auto Hematology Analyzer (Mindray Biomedical Electronics Co Ltd, Shenzhen, China), coagulation function was determined by SF-8100 Automated Coagulation Analyzer (Beijing Succeeder Technology Inc, Beijing,

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China), interleukins were analyzed by BD FACSCanto II system (BD Biosciences, Franklin Lakes, NJ, USA), and other blood biochemical indicators were detected by LABOSPECT008AS Automatic Analyzer (Hitachi High-Tech, Tokyo, Japan). The reference values were exhibited in Table S1.

Nutrition Risk Assessment

Nutrition risk was assessed within 48 hours of admission by using Nutritional Risk Screening 2002 (NRS), which was recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the Chinese Society for Parenteral and Enteral Nutrition (CSPEN) to evaluate the nutrition risk for hospitalized patients, including COVID-19.[12-16] NRS includes an assessment of the patient's nutrition status (based on weight loss, body mass index [BMI], and food intake) and disease severity (stress metabolism due to the degree of disease). Each parameter is scored from 0 to 3 points, and patients receive an extra point if they are 70 years or older. According to the severity of COVID-19, it was proposed that patients with severe COVID-19 score 2 points and critically ill COVID-19 patients score 3 points. An NRS total score of $\geq$3 points was considered "at risk." The nutrition screening was performed by 2 trained specialists. Body weight and height were self-reported by patients.

Treatment and Nutrition Support

Treatment regimens including medication (such as antiviral, antibacterial, corticosteroid), respiratory support, and nutrition support (parenteral and/or enteral) during the entire hospital stay were recorded. Parenteral nutrition (PN) was defined as use of intravenous (peripheral or central) infusion of at least 2 of the energy-providing nutrients, including glucose, fat emulsion, and amino acids, for at least 3 days, supplying >10 kcal/kg/d of energy. Enteral nutrition (EN) was defined as the continuous use of commercial formulas via oral feeding or gavage for at least 3 days, providing >10 kcal/kg/d. Use of dietary supplements or microecological modulators such as probiotics and prebiotics was also recorded.

Outcomes

Hospital mortality was recorded. Information of clinical outcomes of each participant, either discharge or death date, was collected until March 31, 2020. The patients who met discharge standard of COVID-19 can be discharged from hospital. Hospital length of stay was calculated from the discharge date minus the date of admission.

Statistical Analysis

Prior to data analysis, all data were double-entered and logic-checked.

Continuous variables were described using mean, median, and interquartile range values (P_{25}–P_{75}). Categorical variables were described as frequency rates (%). Means for continuous variables were compared using independent group *t*-test when the data were normally distributed between severely and critically ill groups or using the Mann-Whitney *U* test otherwise. Proportions for categorical variables were compared by χ^2 test or Fisher exact test between the 2 groups. Spearman correlation test was used to analyze the association between NRS score and blood biomarkers. To present the results visually, Kaplan-Meier survival curves were used to visualize the results. Logistic regression models and linear regression models were used to analyze the association between NRS score (treated as a continuous variable) and outcomes after adjusting the covariates.

All statistical analyses were performed using the SPSS software, version 22.0. A two-sided α of <.05 was considered statistically significant.

Results

In all, 413 patients admitted to West Campus of Union Hospital from January 29, 2020, to February 19, 2020, because of SARS-CoV-2 infection were enrolled in this study. Of these patients, 346 were diagnosed as severely ill and 67 as critically ill.

Demographics, Characteristics, and Clinical Features of Severely and Critically Ill COVID-19 Patients

Demographics characteristics and clinical features of patients were displayed in Table 1. The average age was 60.31 $\pm$ 12.68 years, and 212 (of 413; 51%) of them were men. The average BMI of patients was 23.73 $\pm$ 3.24 kg/m^2; 35% (130 of 413) were overweight (24.0 $\leq$ BMI $\leq$ 27.9 kg/m^2) and 9% (33 of 413) were obese (BMI $\geq$ 28.0 kg/m^2) according to the Chinese BMI cutoffs.[17]

On average, time from illness onset to admission was 11.26 $\pm$ 6.23 days. In addition, 175 (of 413; 42%) patients had 1 or more comorbidities. The most common comorbidities were hypertension (115 of 413; 28%), diabetes (47 of 413; 11%), and cardiovascular diseases (44 of 413; 11%). Fever (340 of 413; 82%), cough (313 of 413; 76%), impaired appetite (246 of 413; 60%), and dyspnea (170 of 413; 41%) were the most common symptoms at onset of illness. Compared with patients with severe illness, patients who were critically ill were significantly older ($P = .003$) and more likely to report sputum production ($P = .037$). Other characteristics and symptoms had no significant difference between the 2 groups.

All patients received antiviral agents, and some patients received empirical antibacterial agents (318 of 413; 77%)

Table 1. Demographics, Characteristics, and Clinical Features of Severely and Critically Ill Patients With Coronavirus Disease 2019[a].

Characteristics	All cases (n = 413)	Severe cases (n = 346)	Critical illness cases (n = 67)	*P*-value[b]
Age, y (n)	60.31 ± 12.68 (413)	59.49 ± 12.29 (346)	64.55 ± 13.91 (67)	.003
Sex, male	212 (51%)	175 (51%)	37 (55%)	.486
BMI, kg/m^2 (n)	23.73 ± 3.24 (376)	23.73 ± 3.25 (314)	23.78 ± 3.27 (62)	.937
<18.5	16 (4%)	14 (4%)	2 (3%)	.916
18.5–23.9	197 (52%)	165 (53%)	30 (48%)	
24.0–27.9	130 (35%)	108 (34%)	23 (38%)	
≥28.0	33 (9%)	27 (9%)	7 (11%)	
Days from illness onset to admission, d (n)	11.26 ± 6.23 (408)	11.34 ± 6.38 (342)	10.82 ± 5.37 (66)	.532
Respiratory rate, bpm (n)	24.88 ± 28.05 (385)	23.34 ± 21.36 (322)	32.71 ± 49.35 (63)	.144
Systolic pressure, mm Hg (n)	132.70 ± 23.16 (334)	131.39 ± 18.89 (280)	139.54 ± 37.88 (54)	.128
Diastolic pressure, mm Hg (n)	79.48 ± 15.01 (334)	79.84 ± 13.66 (280)	77.61 ± 20.73 (54)	.450
Any comorbidity	175 (42%)	140 (41%)	35 (52%)	.074
Diabetes	47 (11%)	38 (11%)	9 (13%)	.563
Hypertension	115 (28%)	94 (27%)	21 (31%)	.485
Cardiovascular diseases	44 (11%)	35 (10%)	9 (13%)	.421
Pulmonary diseases	16 (4%)	11 (3%)	5 (8%)	.188
Cancer	27 (7%)	19 (6%)	8 (12%)	.092
Chronic renal diseases	9 (2%)	5 (1%)	4 (6%)	.062
History of operation	85 (21%)	69 (20%)	16 (24%)	.465
Drug allergy	36 (9%)	29 (8%)	7 (10%)	.583
Signs and symptoms				
Fever	340 (82%)	289 (84%)	51 (76%)	.146
Cough	313 (76%)	260 (75%)	53 (79%)	.489
Myalgia or fatigue	107 (26%)	88 (25%)	19 (28%)	.617
Sputum production	145 (35%)	114 (33%)	31 (46%)	.037
Headache	46 (11%)	42 (12%)	4 (6%)	.142
Dyspnea	170 (41%)	141 (41%)	29 (43%)	.700
Gastrointestinal disorder	107 (26%)	92 (27%)	15 (22%)	.472
Impaired appetite	246 (60%)	204 (59%)	42 (63%)	.569
Medication				
Antibacterial agents	318 (77%)	257 (74%)	61 (91%)	.003
Antiviral agents	413 (100%)	346 (100%)	67 (100%)	-
Glucocorticoids	136 (33%)	91 (26%)	45 (67%)	<.001
Human serum albumin	106 (26%)	66 (19%)	40 (60%)	<.001
Immunoglobulin	55 (13%)	36 (10%)	19 (28%)	<.001
Respiratory support	383 (93%)	319 (92%)	64 (96%)	.482
Nasal cannula or face mask	338 (88%)	311 (97%)	27 (42%)	<.001
High-flow nasal cannula or noninvasive mechanical ventilation	42 (11%)	8 (3%)	34 (53%)	
Invasive mechanical ventilation	3 (1%)	0	3 (5%)	

BMI, body mass index; bpm, beats per minute.
[a]Continuous variables were presented as mean ± SD (n); categorical variables are shown as n (%). Medication and respiratory support information was recorded during entire hospital stay; other information was recorded at admission.
[b]*P*-values were from *t*-test for continuous data and from χ^2 test for categorical data.

and glucocorticoids (136 of 413; 33%) during the entire hospital stay. In addition, 106 (of 413; 26%) and 55 (of 413; 13%) patients were given human serum albumin and immunoglobulin, respectively. Of the patients, 383 (of 413; 93%) received respiratory support. Furthermore, the proportion of nasal cannula or face mask use in the severe illness group was significantly higher than that in the critically ill group, whereas critically ill patients were more likely to receive high-flow nasal cannula, noninvasive mechanical ventilation, or invasive mechanical ventilation ($P < .001$). The comparisons of treatment and medication between the 2 groups are shown in Table 1.

Table 2. Laboratory Characteristics on Admission for Severely and Critically Ill Patients With Coronavirus Disease 2019[a].

Characteristics	All cases (n = 409)	Severe cases (n = 343)	Critical illness cases (n = 66)	*P*-value[b]
Blood routine				
White blood cell count, 10^9/L	5.8 (4.4–7.4)	5.6 (4.3–7.2)	8.1 (5.0–10.9)	<.001
<3.5	45 (11%)	38 (11%)	7 (11%)	<.001
3.5∼9.5	311 (76%)	277 (81%)	34 (51%)	
>9.5	53 (13%)	28 (8%)	25 (38%)	
Neutrophil count, 10^9/L	4.0 (2.9–5.9)	3.9 (2.8–5.3)	7.1 (3.6–10.1)	<.001
Lymphocyte count, 10^9/L	1.0 (0.7–1.4)	1.1 (0.8–1.4)	0.7 (0.4–0.9)	<.001
<1.1	245 (60%)	186 (54%)	59 (89%)	<.001
≥1.1	164 (40%)	157 (46%)	7 (11%)	
Platelet count, 10^9/L	224.0 (160.0–294.0)	232.0 (170.0–307.0)	169.0 (107.5–235.3)	<.001
Hemoglobin, g/L	126.0 (115.0–136.0)	126.0 (115.0–135.0)	124.5 (114.8–136.5)	.840
Coagulation function				
D-dimer, mg/L	0.6 (0.3–1.7)	0.6 (0.2–1.5)	1.7 (0.4–8.0)	<.001
Prothrombin time, s	13.2 (12.6–14.0)	13.1 (12.6–13.9)	13.5 (12.8–15.1)	.001
Activated partial thromboplastin time, s	35.8 (32.6–39.9)	35.4 (32.1–38.6)	38.9 (34.3–44.5)	<.001
Inflammatory markers				
Procalcitonin, ng/mL	0.07 (0.05–0.14)	0.06 (0.04–0.11)	0.23 (0.12–0.45)	<.001
<0.05	93/293 (32%)	91/239 (38%)	2/54 (4%)	<.001
0.05∼0.1	92/293 (31%)	84/239 (35%)	8/54 (15%)	
>0.1	108/293 (37%)	64/239 (27%)	44/54 (81%)	
C-reactive protein, mg/L	22.7 (4.7–63.5)	16.1 (3.9–50.9)	69.0 (33.2–118.4)	<.001
≤8	129/396 (33%)	125/331 (38%)	4/65 (6%)	<.001
>8	267/396 (67%)	206/331 (62%)	61/65 (94%)	
IL-2, pg/mL	2.7 (2.3–3.7)	2.7 (2.3–3.7)	2.8 (2.4–3.5)	.404
IL-4, pg/mL	2.4 (1.6–3.7)	2.4 (1.6–3.8)	2.3 (1.6–3.7)	.775
IL-6, pg/mL	6.4 (4.2–12.4)	6.1 (4.0–9.9)	14.8 (6.2–46.6)	<.001
IL-10, pg/mL	3.9 (2.8–5.3)	3.8 (2.7–5.2)	4.5 (3.5–7.4)	.005
TNF-α, pg/mL	2.3 (1.7–3.2)	2.3 (1.7–3.2)	2.5 (1.9–3.2)	.401
IFN-γ, pg/mL	2.1 (1.6–3.5)	2.1 (1.6–3.5)	2.4 (1.7–3.8)	.423
Nutrition-related markers				
Total protein, g/L	62.4 (59.0–66.1)	62.6 (59.2–66.3)	61.5 (58.3–64.5)	.036
Serum albumin level, g/L	30.7 (27.7–34.0)	31.1 (28.3–34.2)	28.4 (25.0–31.6)	<.001
Globulin, g/L	31.1 (28.5–34.8)	31.0 (28.4–34.7)	31.6 (29.2–37.2)	.123
Serum albumin:globulin	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	<.001
<1.5	394 (96%)	328 (96%)	66 (100%)	.144
≥1.5	15 (4%)	15 (4%)	0	
Prealbumin, mg/L	142.7 (96.9–203.3)	148.3 (104.7–213.9)	100.0 (69.2–141.5)	<.001
Serum urea nitrogen, mmol/L	4.7 (3.6–6.6)	4.4 (3.4–5.9)	7.0 (4.4–10.3)	<.001
Creatinine, μmol/L	68.8 (57.2–82.1)	67.5 (57.1–81.6)	74.6 (59.7–94.7)	.043
Glucose, mmol/L	6.1 (5.4–7.9)	5.9 (5.3–7.5)	7.7 (6.4–11.7)	<.001
≤6.1	198 (48%)	184 (54%)	14 (21%)	<.001
>6.1	211 (52%)	159 (46%)	52 (79%)	
Total bilirubin, μmol/L	10.7 (8.1–14.3)	10.4 (7.8–14.0)	12.1 (9.2–18.0)	.004
Total cholesterol, mmol/L	4.0 (3.4–4.6)	4.1 (3.4–4.5)	3.9 (3.2–4.8)	.982
Triglyceride, mmol/L	1.3 (1.0–1.8)	1.3 (1.0–1.8)	1.5 (1.1–1.9)	.341
High-density lipoprotein cholesterol, mmol/L	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	.526
Low-density lipoprotein cholesterol, mmol/L	2.4 (1.8–2.9)	2.4 (1.9–2.9)	2.3 (1.5–3.1)	.684

IFN-γ, interferon γ; IL, interleukin; TNF-α, tumor necrosis factor α.

[a]Continuous variables were presented as median (interquartile range); categorical variables are shown as n (%).

[b]*P*-values were from *t*-test for normally distributed continuous data and from Mann-Whitney *U* test for abnormally distributed continuous data. *P*-values were from χ^2 test for categorical data.

Table 3. Nutrition Risk in Severely and Critically Ill COVID-19 Patients[a].

Variables	All cases	Severe cases	Critical illness cases	*P*-value[b]
NRS score	371	310	61	<.001
<3	29 (8%)	29 (9%)	0	
3–4	284 (76%)	261 (84%)	23 (38%)	
≥5	58 (16%)	20 (7%)	38 (62%)	
Severity of disease score[c]				
2	307 (83%)	307 (99%)	0	<.001
3	64 (17%)	3 (1%)	61 (100%)	
Impaired nutrition status score				
0	69 (19%)	65 (21%)	4 (7%)	.003
1	194 (52%)	161 (52%)	33 (54%)	
2	103 (28%)	82 (27%)	21 (34%)	
3	5 (1%)	2 (1%)	3 (5%)	
Age score[d]				
0	277 (75%)	235 (76%)	42 (69%)	.254
1	94 (25%)	75 (24%)	19 (31%)	

COVID-19, coronavirus disease 2019; NRS, Nutritional Risk Screening 2002.
[a]Data were presented as n (%).
[b]*P*-values were from χ^2 test.
[c]Severely ill COVID-19 patient was scored 2 points, critically ill COVID-19 patient was scored 3 points, and 3 severely ill patients (1%) received 3 points in consideration of their other disease condition, assessed by 2 specialists in practice.
[d]Patients received an extra point if they were 70 years or older.

Laboratory Parameters

Laboratory characteristics of 409 patients were collected and are presented in Table 2. On admission, white blood cell counts were below the reference range in 45 (of 409; 11%) patients and above the reference range in 53 (of 409; 13%) patients. White blood cell counts and neutrophil counts were lower in severely ill patients than in critically ill patients ($P < .001$ and $P < .001$, respectively). Most patients had remarkable lymphopenia, and critically ill patients demonstrated more severe lymphopenia and thrombocytopenia ($P < .001$ and $P < .001$, respectively). The levels of coagulation function indexes such as D-dimer, prothrombin time, and activated partial thromboplastin time on admission were higher in critically ill patients than in severely ill patients ($P < .001$, $P = .001$, and $P < .001$, respectively). Regarding the inflammatory markers, procalcitonin (PCT) and C-reactive protein (CRP) levels were above the reference range in most patients. Notably, elevated PCT and CRP levels were observed in 96% (52 of 54) and 94%(61 of 65) of critically ill patients, respectively. Similar results occurred in interleukins. Interleukin (IL)-6 and IL-10 levels were significantly higher in critically ill patients ($P < .001$ and $P = .005$, respectively). As for nutrition-related indicators, the total protein, serum albumin, and prealbumin levels of critically ill patients were significantly lower than those of severely ill patients ($P = .036$, $P < .001$, and $P < .001$, respectively). Moreover, the levels of serum urea nitrogen, creatinine, glucose, and total bilirubin were increased obviously in critically ill patients ($P < .001$, $P = .043$, $P < .001$, and $P = .004$, respectively). No significant differences in hemoglobin, total cholesterol, or uric acid were observed between the 2 groups. Other blood biochemistry results are presented in Table S2.

Nutrition Risk

In total, 371 patients underwent an assessment of NRS, which considered age, disease severity, and nutrition status. The assessment identified 342 (of 371; 92%) patients with nutrition risk (NRS score $\geq$ 3) and 58 (of 371; 16%) with high nutrition risk (NRS score $\geq$ 5). For critically ill patients, all of them were evaluated as at risk and 38 (of 61; 62%) as high risk. Compared with severely ill patients, critically ill patients had a significantly higher proportion of high NRS scores ($P < .001$). Among the 3 major parameters of NRS, critically ill patients tended to have higher scores of impaired nutrition status than severely ill patients did ($P = .005$). The results of the NRS are presented in Table 3.

Correlations Between Blood Parameters and NRS Score

Table S3 demonstrates the correlations between blood parameters and NRS score. Most proinflammatory cytokines had positive correlations with NRS score. Among them, the correlation coefficient between PCT and NRS score reached 0.501, which meant they were strongly and positively correlated. When it came to nutrition-related markers, the correlations between NRS score and total protein, serum albumin, and prealbumin levels were negative. Correlation

coefficients were −0.153, −0.351, and −0.386, respectively. Other nutrition-related markers, such as serum urea nitrogen and creatinine glucose, were positively correlated with NRS score.

Nutrition Support or Dietary Supplements for Severely and Critically Ill COVID-19 Patients

The nutrition support or dietary supplements for severely and critically ill patients according to their nutrition status are shown in Table 4. Among 371 patients, 91 (of 371; 25%) received nutrition support, including 55 (of 371; 15%) patients with EN, 44 (of 371; 12%) patients with PN, and 8 (of 371; 2%) patients with EN and PN. Moreover, 121 (of 371; 33%) patients and 45 (of 371; 12%) patients were given probiotics and dietary supplements, respectively. Compared with severely ill patients, critically ill patients had a significantly higher proportion of patients receiving nutrition support (46% vs 20%, $P < .001$), receiving PN (31% vs 8%, $P < .001$), or receiving EN and PN (8% vs 1%, $P = .002$). For patients with NRS score ≥3, the ratio of those receiving nutrition support, EN, PN, or EN+PN among critically ill patients was higher than that among severely ill patients. However, for the proportion of patients receiving nutrition support, there was no significant difference between the group with NRS score <3 and the group with NRS score ≥3.

The Clinical Outcomes of Severely and Critically Ill COVID-19 Patients

Until March 31, 2020, the clinical outcomes of 403 patients were collected, as displayed in Table 5. The mortality was 9%(37 of 413) in the whole population and up to 47% (30 of 64) in critically ill patients. The average hospital length of stay was 30.18 ± 11.06 days. Critically ill patients had significantly higher mortality and longer stay in hospital than severely ill patients did ($P < .001$ and $P < .001$, respectively). In addition, a great difference was found in clinical outcomes among the patients in 3 ranks of NRS score. Those with higher NRS scores had significant higher mortality and a longer stay in hospital ($P < .001$ and $P = .002$, respectively). These results were confirmed by Kaplan-Meier survival estimates, which showed a higher likelihood for mortality with increasing NRS scores (Figure 1). In logistic regression models, similar results were obtained after adjusting sex, age, comorbidity, and BMI, and a 1-unit increase in NRS score was associated with the risk of mortality increasing by 1.23 times (adjusted odds ratio, 2.23; 95% CI, 1.10–4.51; $P = .026$). As for hospital length of stay, those with higher NRS scores had a longer stay in hospital ($\beta = 1.23$; 95% CI, 0.37–2.10; $P = .005$) in the crude model. After adjusting covariates, this association disappeared (Table 6).

Table 4. Nutrition Support or Supplements for Severely and Critically Ill Patients With Coronavirus Disease 2019[a].

	All cases				NRS score <3			NRS score ≥3			
Supporting treatment	Total (n = 371)	Severe cases (n = 310)	Critical illness cases (n = 61)	*P*-value[b]	Total (n = 29)	Severe cases (n = 29)		Total (n = 342)	Severe cases (n = 281)	Critical illness cases (n = 61)	*P*-value[b]	*P*-value[c]
Nutrition support	91 (25%)	63 (20%)	28 (46%)	<.001	7 (24%)	7 (24%)		84 (25%)	56 (20%)	28 (46%)	<.001	.959
EN	55 (15%)	41 (13%)	14 (23%)	.051	6 (21%)	6 (21%)		49 (14%)	35 (13%)	14 (23%)	.034	.513
PN	44 (12%)	25 (8%)	19 (31%)	<.001	1 (3%)	1 (3%)		43 (13%)	24 (9%)	19 (31%)	<.001	.246
EN+PN	8 (2%)	3 (1%)	5 (8%)	.002	0	0		8 (2%)	3 (1%)	5 (8%)	.004	.867
Probiotics	121 (33%)	99 (32%)	22 (36%)	.529	5 (17%)	5 (17%)		116 (34%)	94 (34%)	22 (36%)	.696	.066
Dietary supplements	45 (12%)	39 (13%)	6 (10%)	.548	6 (21%)	6 (21%)		39 (11%)	33 (12%)	6 (10%)	.671	.240

EN, enteral nutrition; NRS, Nutritional Risk Screening 2002; PN, parenteral nutrition.
[a] Data were presented as n (%). Dietary supplements included vitamins (vitamin C, vitamin D, or vitamin E) or minerals (calcium, iron).
[b] *P*-values were from χ^2 test between severe and critical illness cases.
[c] *P*-values were from χ^2 test between NRS score <3 and NRS score ≥3.

Table 5. The Clinical Outcomes of Severely and Critically Ill Patients With Coronavirus Disease 2019[a].

Nutrition risk	Outcome			*P*-value[b]	Hospital length of stay, d	*P*-value[c]
	Total	Discharged	Died			
Total	403	366 (91%)	37 (9%)	<.001	30.18 ± 11.06	<.001
Severe cases	339	332 (98%)	7 (2%)		29.31 ± 10.69	
Critical illness cases	64	34 (53%)	30 (47%)		38.68 ± 11.15	
NRS score	361	326 (90%)	35 (10%)	<.001	30.43 ± 11.23	.002
<3	28	28 (100%)	0		29.75 ± 9.32	
3–4	277	266 (96%)	11 (4%)		29.72 ± 11.19	
≥5	56	32 (57%)	24 (43%)		36.97 ± 11.30	

NRS, Nutritional Risk Screening 2002.
[a]Data were presented as n (%).
[b]*P*-values were from χ^2 test.
[c]*P*-values were from analysis of variance or *t*-test .

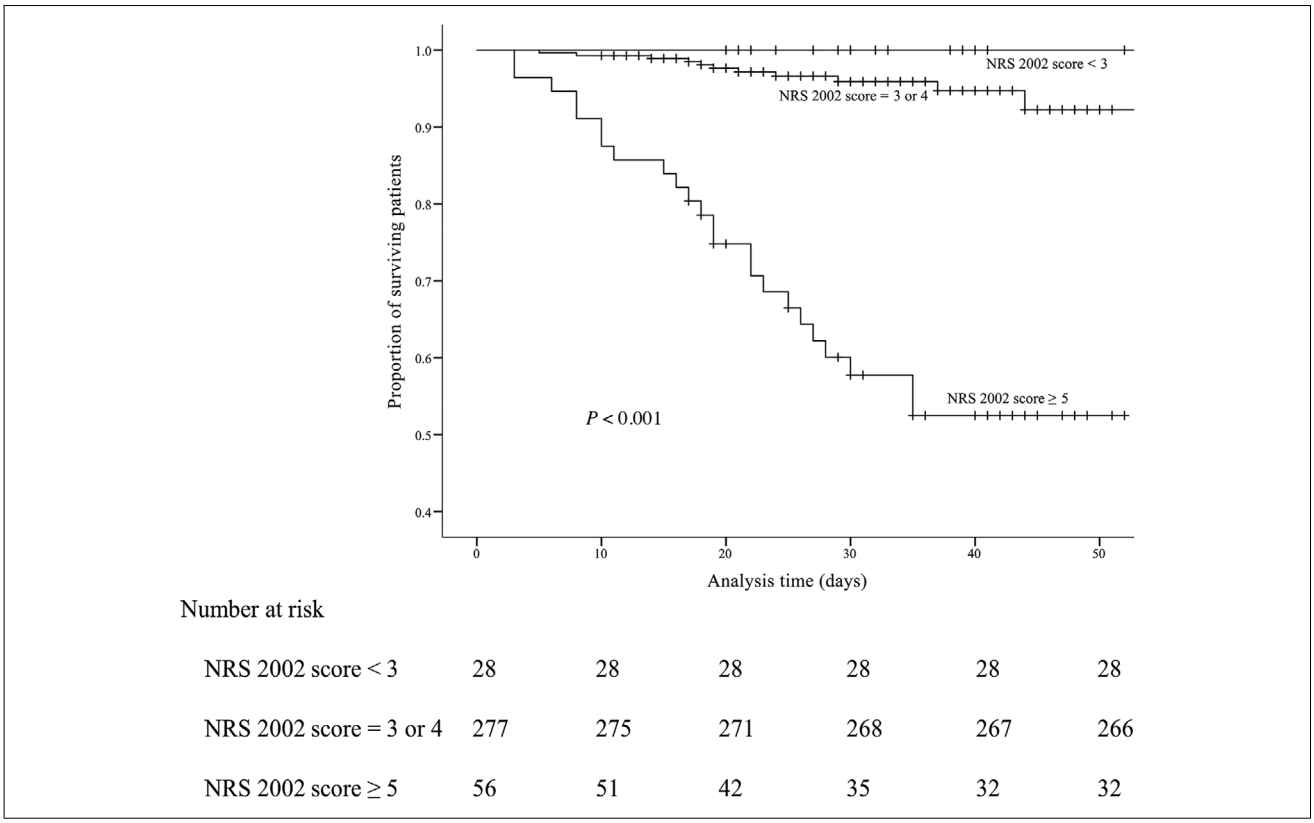

Figure 1. Survival of severely and critically ill patients with coronavirus disease 2019, stratified by the NRS score, over a period of 50 days ($P < .001$). NRS, Nutritional Risk Screening 2002.

Discussion

The World Health Organization (WHO) declared the COVID-19 a pandemic in March 11, 2020.[6] The mortality of critically ill patients with COVID-19 is up to 61.5%, a considerable level.[18] Therefore, giving appropriate treatment and reducing mortality of severe and critical illness caused by COVID-19 are of crucial importance. This study is the first to describe the clinical characteristics, especially the changes of nutrition metabolism, in severely and critically ill patients in detail and explore the relationship between nutrition risk and clinical outcomes. The findings will provide important evidence for revising the diagnosis and treatment scheme of critically ill patients to improve clinical outcomes.

Table 6. The Association Between NRS Score and Clinical Outcomes in All Patients With Coronavirus Disease 2019[a].

	Mortality		Hospital length of stay, d	
Model	OR (95% CI)	*P*-value	β (95% CI)	*P*-value
Model 1	3.39 (2.27–5.05)	<.001	1.23 (0.37–2.10)	.005
Model 2	2.95 (1.93–4.51)	<.001	0.90 (0.03–1.77)	.044
Model 3	2.23 (1.10–4.51)	.026	0.27 (−1.40 to 1.94)	.752

Model 1, crude model; Model 2, adjusted for sex, age, and comorbidity; Model 3, adjusted for model 2 + body mass index; NRS, Nutritional Risk Screening 2002; OR, odds ratio.
[a]Logistic regression models were used to analyze the association between NRS score and mortality, and linear regression models were used to analyze the association between NRS score and hospital length of stay. NRS score was treated as a continuous variable in regression models.

This study showed great alterations in clinical characteristics and laboratory findings, especially metabolic indexes related to nutrition, in severely and critically ill patients. The results showed that the infection led to a series of inflammatory reactions, indicated by an increase in PCT, CRP, and interleukin levels, again consistent with other studies.[8,19,20] The changes in metabolic nutrition-related indicators were noteworthy. The reduction of serum albumin, prealbumin, and total protein levels and the elevation of creatinine and serum urea nitrogen warned that critically ill patients were at tremendous nutrition risk.[8,21] It is worth mentioning that prealbumin, a protein also known as transthyretin, has attracted much attention in nutrition status assessment in recent years. Because of the high sensitivity to inflammation, its ability to evaluate risk of malnutrition is often hampered.[22,23] Nevertheless, an increasing body of evidence suggests that it is a good marker for prognosis associated with malnutrition and is even better for monitoring refeeding efficacy despite inflammation.[24-26] Consistently, the serum prealbumin level decreased tremendously in both severely and critically ill patients and negatively correlated with NRS in the present study, indicating that this protein might be a good marker for nutrition risk.

Some expert consensus proposed that nutrition risk screening should be conducted in admitted COVID-19 patients.[9,15] In the present study, 90% (371 of 413) of the patients underwent nutrition risk screening within 48 hours of admission, using the NRS score. Among them, 92% (342 of 371) of the patients were considered to be at nutrition risk; meanwhile, all of the critically ill patients were at risk, and 62% (38 of 61) of them were identified as "high risk." The NRS score was determined by 3 parameters: impaired nutrition status, severity of disease, and age. Obesity has been considered as a risk factor to the severity of COVID-19.[27] It was also observed that 44% (163 of 376) of the patients had overweight or obesity in the present study, but BMI did not significantly affect the association between NRS and mortality in the logistic regression analysis. Only a few patients had lost weight prior to admission or had low BMI, indicating that they were not chronically malnourished. There exist 3 main reasons why COVID-19 patients have nutrition risk. First, hypercatabolic status and endocrine disorders caused by acute severe infection such as inflammatory stress, hypoxia, and bed rest result in increased gluconeogenesis, enhanced proteolysis, and accelerated fat oxidation. Second, loss of appetite and reduced dietary intake (as seen in 60% [246 of 413] patients in this study) also exacerbate the nutrient deficiency. Finally, interventions such as mechanical ventilation and use of broad-spectrum antibiotics triggered severe hypoproteinemia and damaged the digestive system function, which delay or prevent recovery from illness and even aggravate the inflammatory stress of the body.[28-32] Those abnormalities of indicators above could further aggravate the course of the disease in return. Consistent with the results of previous studies, we found that an elevated nutrition risk, which was positively correlated with inflammatory and nutrition-related markers, was associated with adverse clinical outcomes.[33-36] Thus, it is crucial to reduce nutrition risk in alleviating COVID-19 and improving clinical outcomes, especially for the patients with high nutrition risk (NSR 2002 score $\geq$ 5).

Although there was limited supportive evidence that specific interventions, such as nutrition support, could decrease mortality in acute respiratory distress syndrome,[37] some studies on severe community-acquired pneumonia have shown that adequate and reasonable nutrition support was beneficial. It reduces nutrition risk by correcting inadequate energy intake and reducing oxidative damage and inflammatory response. These will enhance immunity, improve respiratory function, and thus improve the prognosis of disease.[31,38] Considering the positive effects of nutrition support, some expert consensus also recommended nutrition support, especially for critically ill patients infected with SARS-CoV-2.[10] Nonetheless, it could not be implemented in many designated hospitals. In this study, only about 25% (91 of 371) of the patients received nutrition support regardless of the nutrition risk; even in those who would benefit most from it with nutrition risk (NRS $\geq$ 3), the proportion was 25% (84 of 342) as well, though it should reach 92% (342 of 371). That means the implementation of nutrition support here was not based on the results of NRS. This situation of low proportion of nutrition support

was caused by several factors, including the limited attention to nutrition status and needs of patients in the emergency of COVID-19 outbreak and shortage of professional staff to cope with the sudden surge in patient demand. From the perspective of improving clinical outcomes (reducing mortality, shortening hospital length of stay, et al), more attention should be given to applying the information of NRS to directing nutrition support, and nutrition standard operating procedures should be implemented, which would reduce the enormous variability of practice.[39]

Additionally, 33% (121 of 371) patients were given probiotics in the present study, as recommended by guidelines for the treatment of COVID-19.[10,11] It has been mentioned that microecological preparation can be used to keep the equilibrium for intestinal microecology and prevent secondary bacterial infection as other treatments of COVID-19. However, further high-quality clinical trials are needed to conclusively prove the benefits of probiotics administration in COVID-19.

Our study is the first concerning nutrition risk and providing evidence to explore nutrition strategies in improving outcomes for severely and critically ill patients infected with SARS-CoV-2. However, this study has several limitations. First, the critically ill patients who had been admitted to the ICU were not enrolled in the present study, and the scores (such as Acute Physiology and Chronic Health Evaluation) that usually are used to evaluate the severity and predict the prognosis of the critically ill patients were not available. Therefore, there was selection bias in the inclusion of critically ill patients. Next, owing to the inconvenience of measurement in emergency, body height and weight data were self-reported by the patients. Thus, possible recall biases existed in the process of collecting data. Furthermore, retrospective design was used in this study. As a consequence, we only descriptively demonstrated the relationship between the nutrition risk and clinical outcomes. To further investigate the role of nutrition support in the prognosis of COVID-19 patients, more well-designed randomized controlled trials are needed.

In conclusion, most severely and critically ill patients infected with SARS-CoV-2 are at nutrition risk, and those who are at a higher nutrition risk tend to have worse outcomes. Adequate and reasonable nutrition support to patients with high nutrition risk could effectively improve the nutrition status and clinical outcomes of COVID-19 patients.

Statement of Authorship

X. Li and X. Yang equally contributed to the conception and design of the research; X. Li and X. Yang contributed to the design of the research; X. Zhao, Y. Li, Y. Ge, Y. Shi, P. Lv, J. Zhang, G. Fu, Y. Zhou, K. Jiang, N. Lin, T. Bai, R. Jin, and Y. Wu contributed to the acquisition and analysis of the data; Y. Li, Y. Ge, Y. Wu, and X. Zhao contributed to the interpretation of the data; and Y. Li and X. Zhao drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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