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

Xiaobo Zhao, MS1,*; Yan Li, PhD2,*; Yanyan Ge, PhD2; Yuxin Shi, MS2; Ping Lv, MS2; Jianchu Zhang, PhD3; Gui Fu, MS1; Yanfen Zhou, MS1; Ke Jiang, PhD4; Nengxing Lin, PhD5; Tao Bai, PhD6; Running Jin, PhD4; Yuanjue Wu, PhD7; Xuefeng Yang, PhD2 and Xin Li, PhD1

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 $\geq 3$, 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. As of April 17, 2020, there were 2,000,000 confirmed cases and nearly 130,000 deaths globally. 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. COVID-19 patients also have some signs of malnutrition such as decreased serum albumin and prealbumin level and impaired liver and kidney function. Nutrition risk screening and nutrition support have been recommended for critically ill COVID-19 patients. 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. Patients were defined as severely ill if they met the following criteria: (1) respiratory distress (respiratory rate ≥ 30 breaths/min); (2) pulse oxygen saturation ≤ 93% on room air; (3) low arterial oxygenation ratio (PaO2/fraction of inspired oxygen ≤ 300). Patients were defined as critically ill if they 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). 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, China).

From the 1Department of Paediatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China; 2Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, MOE Key Laboratory of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P. R. China; 3Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China; 4Department of Thoracic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China; 5Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China; 6Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China; and the 7Department of Clinical Nutrition, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, P. R. China.

*Xiaobo Zhao and Yan Li contributed equally to this work.

Financial disclosure: None declared.

Conflicts of interest: None declared.

Received for publication April 28, 2020; accepted for publication June 23, 2020.

This article originally appeared online on July 20, 2020.

Corresponding Author:
Xuefeng Yang, Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, MOE Key Laboratory of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei 430030, P. R. China.
Email: xxyf@mails.tjmu.edu.cn

Xin Li, Department of Paediatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei Province 430030, P. R. China.
Email: doctorlixin@hotmail.com
China), interleukins were analyzed by BD FACSCanto II system (BD Biosciences, Franklin Lakes, NJ, USA), and other blood biochemical indicators were detected by LABOSPEKT008AS 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. 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 ≥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 χ² 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 ± 12.68 years, and 212 (of 413; 51%) of them were men. The average BMI of patients was 23.73 ± 2.26 kg/m². The most common symptoms at onset of illness were fever (340 of 413; 82%), cough (313 of 413; 76%), myalgia (237 of 413; 57%), and headache (230 of 413; 55%). 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. Comorbidities 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%)
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 1. Demographics, Characteristics, and Clinical Features of Severely and Critically Ill Patients With Coronavirus Disease 2019a.

| Characteristics                        | All cases (n = 413) | Severe cases (n = 346) | Critical illness cases (n = 67) | P-value |
|----------------------------------------|---------------------|------------------------|-------------------------------|---------|
| 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%)                        | 9.16    |
| 18.5–23.9                              | 197 (52%)           | 165 (53%)              | 30 (48%)                      | .916    |
| 24.0–27.9                              | 130 (35%)           | 108 (34%)              | 23 (38%)                      | .648    |
| ≥28.0                                  | 35 (9%)             | 27 (9%)                | 7 (11%)                       | .532    |
| 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 ± 18.16 (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    |
| 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%)               | 45 (67%)                      | <.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.

*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 χ² test for categorical data.
Table 2. Laboratory Characteristics on Admission for Severely and Critically Ill Patients With Coronavirus Disease 2019.

| 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%)          | 46/65 (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      |
| **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                                       | 11 (4%)             | 15 (4%)                |                                |           |
| 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)                 |           |
| 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.

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

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 χ² test for categorical data.
Table 3. Nutrition Risk in Severely and Critically Ill COVID-19 Patients.

| Variables                        | All cases | Severe cases | Critical illness cases | P-value<sup>+</sup> |
|----------------------------------|-----------|--------------|------------------------|--------------------|
| 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<sup>c</sup> |           |              |                        |                    |
| 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<sup>d</sup>            |           |              |                        |                    |
| 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.
<sup>a</sup>Data were presented as n (%).
<sup>b</sup>P-values were from $\chi^2$ test.
<sup>c</sup>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.
<sup>d</sup>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 ≥ 3) and 58 (of 371; 16%) with high nutrition risk (NRS score ≥ 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 $\geq 3$, 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 $\geq 3$.

**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 $\pm$ 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 $P < .001$, 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 ($\beta = 1.23; 95\% \text{ CI}, 0.37–2.10; P = .005$) in the crude model. After adjusting covariates, this association disappeared (Table 6).
Table 5. The Clinical Outcomes of Severely and Critically Ill Patients With Coronavirus Disease 2019\textsuperscript{a}.

| Nutrition risk | Total | Discharged | Died | P-value\textsuperscript{b} | Hospital length of stay, d | P-value\textsuperscript{c} |
|---------------|-------|------------|------|-----------------------------|-----------------------------|-----------------------------|
| 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     |       |            |       |                             |                             |                             |
| <3            | 28    | 28 (100%) | 0      |                             | 29.75 ± 9.32                |                             |
| 3–4           | 297   | 266 (96%) | 11 (4%) |                             | 29.72 ± 11.19               |                             |
| ≥5            | 56    | 32 (57%)  | 24 (43%) |                             | 36.97 ± 11.30               |                             |

NRS, Nutritional Risk Screening 2002.
\textsuperscript{a}Data were presented as n (%).
\textsuperscript{b}P-values were from \chi^2 test.
\textsuperscript{c}P-values were from analysis of variance or t-test.

Discussion

The World Health Organization (WHO) declared the COVID-19 a pandemic in March 11, 2020.\textsuperscript{6} The mortality of critically ill patients with COVID-19 is up to 61.5%, a considerable level.\textsuperscript{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.
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. Nonetheless, it could not be implemented in the present study, 90% (371 of 413) of the patients were considered to be at nutrition risk; 62% (38 of 61) of them were identified as "high risk." 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. 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. 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. 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. 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 the survival rate of critically ill patients was 25% (91 of 371) of the patients received nutrition support, especially for critically ill patients infected with SARS-CoV-2. Nonetheless, it could not be implemented in many designated hospitals. In this study, only about 25% (91 of 371) of the patients reached 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

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

| Model          | Mortality | Hospital length of stay, d |
|----------------|-----------|---------------------------|
|                | 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.

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.

Although there was limited supportive evidence that specific interventions, such as nutrition support, could decrease mortality in acute respiratory distress syndrome, 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. Considering the positive effects of nutrition support, some expert consensus also recommended nutrition support, especially for critically ill patients infected with SARS-CoV-2. 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 ≥ 3), the proportion was 25% (84 of 342) as well, though it should reach 92% (342 of 371).
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.  

Additionally, 33% (121 of 371) patients were given probiotics in the present study, as recommended by guidelines for the treatment of COVID-19. 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 drafted 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.

Acknowledgments

The authors sincerely acknowledge all participants who participated in this study for their cooperation. The authors also thank all members of this study group for their valuable contributions.

Supplementary Information

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

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
2. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020;92(4):401-402.
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-473.
4. Wuhan Municipal Health Commission. Report of novel coronavirus-infected patients in China. 2020. http://wjw.wuhan.gov.cn/xwzx_28/gsgg/202004/20200430_1199593.shtml
5. Hui DS, Azhar EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-266. https://doi.org/10.1016/j.ijid.2020.01.009
6. World Health Organization. Coronavirus disease (COVID-19) pandemic. 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed March 11, 2020.
7. Uno C, Maeda K, Wakabayashi H, et al. Nutritional status change and activities of daily living in elderly pneumonia patients admitted to acute care hospital: a retrospective cohort study from the Japan Rehabilitation Nutrition Database. Nutrition. 2020;71:110613. https://doi.org/10.1016/j.nut.2019.110613
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
9. Chinese Medical Association. Recommendations from management experts on severe COVID-19. March 12, 2020. https://www.cma.org.cn/art/2020/3/12/art_2928_33535.html
10. National Health Commission of the People’s Republic of China. Diagnosis and treatment protocols of pneumonia caused by a novel coronavirus, trial version 7 [in Chinese]. 2020. http://www.nhc.gov.cn/yzygj/s7653p/202003/4ef9294a7dfe4cecf80d7f5912eb1989/files/cce3e6945832a438eae415350a8ce964.pdf. Accessed March 3, 2020.
11. National Health Commission of the People’s Republic of China, National Administration of Traditional Chinese Medicine of the People’s Republic of China. Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management. Beijing: People’s Medical Publishing House; 2020.
12. Kondrup J. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-336.
13. Chinese Medical Association. Clinical Practice Guidelines: Parenteral and Enteral Nutrition. Beijing: People’s Medical Publishing House; 2008.
14. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48-79.
15. Barazzoni R, Bischoff SC, Breda J, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020;39(6):1631-1638.
16. Hubei Province Hospital Association. Expert consensus on COVID-19 medical nutrition diagnosis and treatment in hubei province, trial version [in Chinese]. 2020. http://www.hbsyyxh.cn/upload/20200217/5e4a71f430b335.pdf. Accessed February 17, 2020.
17. Zhou BF, Cooperative Meta-analysis Group of Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci. 2002;15(s8):83-96.
18. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(6):616-628.
19. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
21. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. Nutrients. 2017;9(8):829.
22. Delliere S, Neveux N, De Bandt JP, Cynober L. Transthyretin for the routine assessment of malnutrition: a clinical dilemma highlighted by an international survey of experts in the field. Clin Nutr. 2018;37(6):2226-2229.
23. Sergi G, Coin A, Enzi G, et al. Role of visceral proteins in detecting malnutrition in the elderly. Eur J Clin Nutr. 2006;60(2):203-209.
24. Delliere S, Cynober L. Is transthyretin a good marker of nutritional status? Clin Nutr. 2017;36(2):364-370.
25. Berger MM, Pantet O, Jacquelin-Ravel N, et al. Supplemental parenteral nutrition improves immunity with unchanged carbohydrate and protein metabolism in critically ill patients: the SPN2 randomized tracer study. Clin Nutr. 2019;38(5):2408-2416.
26. Berger MM, Reintam-Blaser A, Calder PC, et al. Monitoring nutrition in the ICU. Clin Nutr. 2019;38(2):584-593.
27. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol. 2020;16(7):341-342.
28. Heighes PT, Doig GS, Sweetman EA, Simpson F. An overview of evidence from systematic reviews evaluating early enteral nutrition in critically ill patients: more convincing evidence is needed. Anaes Intens Care. 2010;38(1):167-174.
29. Tu GW, Ju MJ, Han Y, et al. Moderate-dose glucocorticoids as salvage therapy for severe pneumonia in renal transplant recipients: a single-center feasibility study. Ren Fail. 2014;36(2):202-209.
30. Sieske L, Janssen G, Babel N, Westhoff TH, Wirth R, Pourhassan M. Inflammation, appetite and food intake in older hospitalized patients. Nutrients. 2019;11(9):1986.
31. Liu Y, Zheng Y. Curative effect of enteral and parenteral nutrition support therapy in elderly patients with severe pneumonia [in Chinese]. Parenter Enteral Nutr. 2017;41(2):98-100. https://doi.org/10.1177/0149775216663272.
32. Brower RG. Consequences of Bed Rest. Crit Care Med. 2009;37(10 Supp):S422-S428.
33. Hersberger L, Bargetzi L, Bargetzi A, et al. Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes: secondary analysis of a prospective randomised trial. Clin Nutr. Accepted manuscript. Published online December 13, 2019. https://doi.org/10.1016/j.clnu.2019.11.041.
34. Yeo H, Byun KS, Han J, et al. Prognostic significance of malnutrition in critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Crit Care. 2020;24(11):1054-1062.
35. Zhu M, Wei J, Shen W, et al. Nutritional status at admission and discharge among Chinese hospitalized patients: a prospective, nationwide, multicenter study. J Am Coll Nutr. 2017;36(5):357-363.
36. Schols AM, Ferreira IM, Franssen FM, et al. Nutritional assessment and therapy in COPD: a European Respiratory Society statement. Eur Respir J. 2014;44(4):1504-1520.
37. Tonelli AR, Zein J, Adams J, Ioannidis JP. Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. Intens Care Med. 2014;40(6):769-787.
38. Yang PH, Lin MC, Liu YY, Lee CL, Chang NJ. Effect of nutritional intervention programs on nutritional status and readmission rate in malnourished older adults with pneumonia: a randomized control trial. Int J Environ Res Public Health. 2019;16(23):4758.
39. Hiesmayr M, Tarantino S, Moick S, et al. Hospital malnutrition, a call for political action: a public health and nutrition Day perspective. J Clin Med. 2019;8(12):2048.