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CLINICAL RESEARCH

Malnutrition is associated with hyperinflammation and immunosuppression in COVID-19 patients: A prospective observational study

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Background: Coronavirus disease 2019 (COVID-19) is spreading globally and has caused many deaths. This study investigated, for the first time, COVID-19 patients' nutrition status and its effects on their inflammatory and immune responses.

Methods: Forty-seven COVID-19 patients were recruited for this prospective study. According to the subjective global assessment at admission, patients were divided into the normal nutrition (NN), risk of malnutrition (RMN), or MN group. Serum cytokines and whole blood T-cell subpopulations were measured to assess the inflammatory and immune responses in COVID-19 patients. Analysis of covariance and χ^2 tests were used.

Results: On admission, the incidences of MN and the RMN in COVID-19 patients were 17.0% and 38.3%, respectively. The MN group had a higher proportion with severe/critical COVID-19 and a longer hospitalization duration than the NN group. Serum interleukin (IL) 6 concentrations were elevated in 97.9% of the patients and were the highest in malnourished patients. The IL-4 and IL-10 levels were elevated in 46.8% and 48.9% of the patients, respectively. The proportion of CD8+ T cells was significantly lower in the MN group than in the NN group.

Conclusion: A high proportion of COVID-19 patients are malnourished or at risk of malnuourishment, especially those with severe disease. MN is associated with hyperinflammation and immunosuppression in COVID-19 patients, and it may contribute to disease progression.

KEYWORDS
coronavirus disease 2019, cytokines, immunosuppression, inflammation, malnutrition, nutrition status

INTRODUCTION

In December 2019, a cluster of cases of pneumonia of unknown etiology were identified in Wuhan, Hubei Province, China.[1] A novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated from a pneumonia patient and suspected of being the causative pathogen.[2,3] The disease caused by the virus was called coronavirus disease 2019 (COVID-19) by the World Health Organization.[4] The virus spread from Wuhan to all of China and had caused 89,905 cases of COVID-19, including 4710 deaths, as of August 17, 2020.[5] Because of the initiation of effective government interventions, the outbreak of COVID-19 is under control in mainland China.[6] However, there has been a steady increase in the daily total number of COVID-19 cases globally. To date, >21 million cases of COVID-19 have been confirmed in 183 countries/regions, and COVID-19 has become a major global health concern.[6]

Most COVID-19 patients have mild symptoms and a good prognosis.[7] However, some patients rapidly develop acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), leading to death.[7,8] Cytokine storms may play a crucial role in the progression of COVID-19 and are also a leading cause of ARDS and MOF.[9] In patients with severe COVID-19, controlling the cytokine storm increases their chance of survival.[9]

Nutrition status is an important factor that influences the host defense against pathogenic organisms.[10,11] Epidemiological and clinical data suggest that malnutrition (MN) plays a role in acute and chronic infections, possibly because of an underlying immunodeficiency, which substantially increases the incidence of disease as well as its severity.[10] Disease progression can in turn exacerbate malnutrition, leading to a vicious cycle. COVID-19 is a new, acute infectious disease, and the nutrition status of COVID-19 patients has not yet been examined. Additionally, the associations of nutrition status with the inflammatory and immune responses in COVID-19 patients needs to be elucidated.

We performed a prospective observational study to assess the nutrition status in COVID-19 patients and investigate its association with their immune responses.

MATERIALS AND METHODS

Patients

This prospective observational study was approved by The First Affiliated Hospital of Anhui Medical University Committee on Medical Ethics in compliance with the Chinese national regulations and standards for ethical research (Quick-J-2020-04-11). Patients enrolled in this study signed informed consent forms. All procedures were performed in accordance with the principles of the Declaration of Helsinki. We prospectively collected the records of inpatients with laboratory-confirmed COVID-19 from Cancer Center of Union Hospital Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China. The inclusion criteria were age ≥15 years and two positive results on real-time polymerase chain reaction assays (TaqMan One-Step real-time PCR Kits from Shanghai Huirui Biotechnology Co, Ltd or Shanghai BioGerm Medical Biotechnology Co, Ltd) for SARS-CoV-2 from nasopharyngeal swab specimens. The exclusion criteria were age <15 years, pregnancy, and inability to reliably assess the patient's nutrition (eg, comatose or confused patients).

Nutrition status assessment

This study evaluated nutrition status by using the subjective global assessment (SGA) at admission. The SGA was administered as described by Detsky and colleagues.[12] The SGA is a valid and reliable tool that assesses nutrition status on the basis of the features available in the medical history (weight change, dietary intake change, gastrointestinal symptoms that have persisted for >2 weeks, changes in functional capacity) and on physical examination (loss of subcutaneous fat, muscle wasting, ankle/sacral edema, and ascites). These features were combined subjectively into an overall or global assessment, and patients were rated as well nourished, suspected of being malnourished, or severely malnourished.[12] The SGA was administered for COVID-19 patients by a single dietitian who was very experienced with this assessment. According to the SGA, the patients were divided into three groups: the normal nutrition (NN) group, risk of malnutrition (RMN) group, and MN group.

Clinical treatment

According to the guidelines for COVID-19 (trial fifth edition) issued by the China National Health Commission, patients were divided into four groups: mild, moderate, severe, and critical disease.[13] Mild disease was characterized by mild clinical symptoms and no signs of pneumonia on imaging. Moderate disease was characterized by fever, respiratory tract symptoms, and signs of pneumonia on imaging. Patients were diagnosed with severe COVID-19 if they met any of the following criteria: (1) shortness of breath, with a respiratory rate (RR) >30 times/min; (2) a mean oxygen saturation ≤93% at rest; or (3) a partial

pressure of arterial oxygen/oxygen concentratio ≤30 mm Hg (1 mm Hg = 0.133 kPa), with evidence on pulmonary imaging that the lesions had progressed significantly within 24 to 48 h or involvement of >50% of the lung. Critical disease was defined as the presence of any of the following conditions: (1) respiratory failure necessitating mechanical ventilation, (2) shock, or (3) any organ failure necessitating monitoring and treatment in the intensive care unit (ICU).[13]

Routine therapies, such as bed rest, enhanced nutrition support, oxygen therapy, antiviral therapy, and monitoring, were used for patients with mild and moderate COVID-19. However, patients with severe and critical COVID-19 received more life-support therapies, such as mechanical ventilation, continuous renal replacement therapy, and extracorporeal membrane oxygenation.

Clinical data collection

Epidemiological, demographic, clinical, and outcome data were collected from the patients' medical records. Other nutrition parameters, such as the body mass index (BMI), white blood cell (WBC) count, hemoglobin (Hb) level, lymphocyte count (LYM), creatinine (Cr) level, hypersensitive C-reactive protein (hsCRP) level, serum albumin (ALB) level, and transferrin (TF) level, were also collected. Clinical outcomes were followed up to April 15, 2020. A nurse on our research team collected all the relevant data, which were independently rechecked by two other researchers.

Cytokine and T-cell subpopulation measurements

To assess changes in inflammatory and immune responses in COVID-19 patients, we examined a range of cytokines and T-cell subpopulations. Serum proinflammatory cytokines (interleukin [IL] 2, IL-6, tumor necrosis factor-α, and interferon-γ [IFN-γ]) and antiinflammatory cytokines (IL-4 and IL-10) were measured in all patients by using a Human Cytokine Standard 27-Plex Assay panel (Bio-Rad, Hercules, CA, USA) according to the manufacturer's instructions. The phenotypic analysis of lymphocytes ($CD3^+$, $CD4^+$, and $CD8^+$ T cells) in the peripheral blood was performed with a FACSCalibur CellSorting System (BD Bioscience, San Jose, CA, USA).

Statistical analysis

Continuous variables are presented as the means and SEs, and the significance of differences among groups was assessed with analysis of covariance, in which disease severity was used as a covariate. Categorical variables are presented as numbers (percents) and were compared with the χ^2 test or Fisher exact test. A two-sided $P < .05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 21.0, IBM).

RESULTS

Demographics and baseline characteristics

Eighty-two COVID-19 patients were screened, but 35 of them were excluded on the basis of the criteria. Finally, a total of 47 COVID-19 patients were recruited from February 14, 2020, to March 14, 2020. All patients were discharged from the hospital at the end of follow-up. The flowchart outlining patient selection is presented in Figure 1.

All of the recruited patients had lived in Wuhan for a long time, and none of them had a history of exposure to the local Huanan South China Seafood Market in Wuhan city. In total, 8 (17.0%) patients were part of familial clusters of cases. COVID-19 patients enrolled in the study (n = 47) were distributed unevenly among the nutrition categories (NN, n = 21; RMN, n = 18; and MN, n = 8), and the majority were males (51.1%). Patient ages ranged from 29 to 92 years, with a median of 68 years. The duration of disease (time from symptom onset to admission) ranged from 5 to 30 days, with a median of 15 days. Twenty-one (44.7%) of the COVID-19 patients were aged 66–75 years, and 8 (17.0%) were aged >75 years (Table 1). Of the 47 patients, 29 (61.7%) had chronic diseases, including cardiovascular disease (46.8%, 22 of 47), endocrine system disease (23.4%, 11 of 47), digestive system disease (17.0%, 8 of 47), respiratory system disease (4.3%, 2 of 47), and malignancy (8.5%, 4 of 47). Fever (76.6%, 36 of 47), dry cough (42.6%, 20 of 47), and respiratory distress (51.1%, 24 of 47) were the most common symptoms at the onset of illness (Table 1).

On admission, the incidences of MN and the RMN in COVID-19 patients were 17.0% (8 of 47, MN group) and 38.3% (18 of 47 RMN group), respectively. A total of 44.7% (21 of 47) of the patients had NN status (NN group) (Table 1). There were no significant differences in sex and mean age among the three groups. Additionally, the mean duration of disease was not significantly different among the three groups. Consistent with the nutrition status assessment, the BMI value was the lowest in the MN group (17.7 ± 1.3), followed by the RMN group (23.0 ± 0.7; all P values < .001). A total of 50.0% (4 of 8) of the patients in the MN group had a history of malignant tumors. The prevalence of endocrine system disease in the RMN group (44.4%, 8 of 18) was significantly higher than

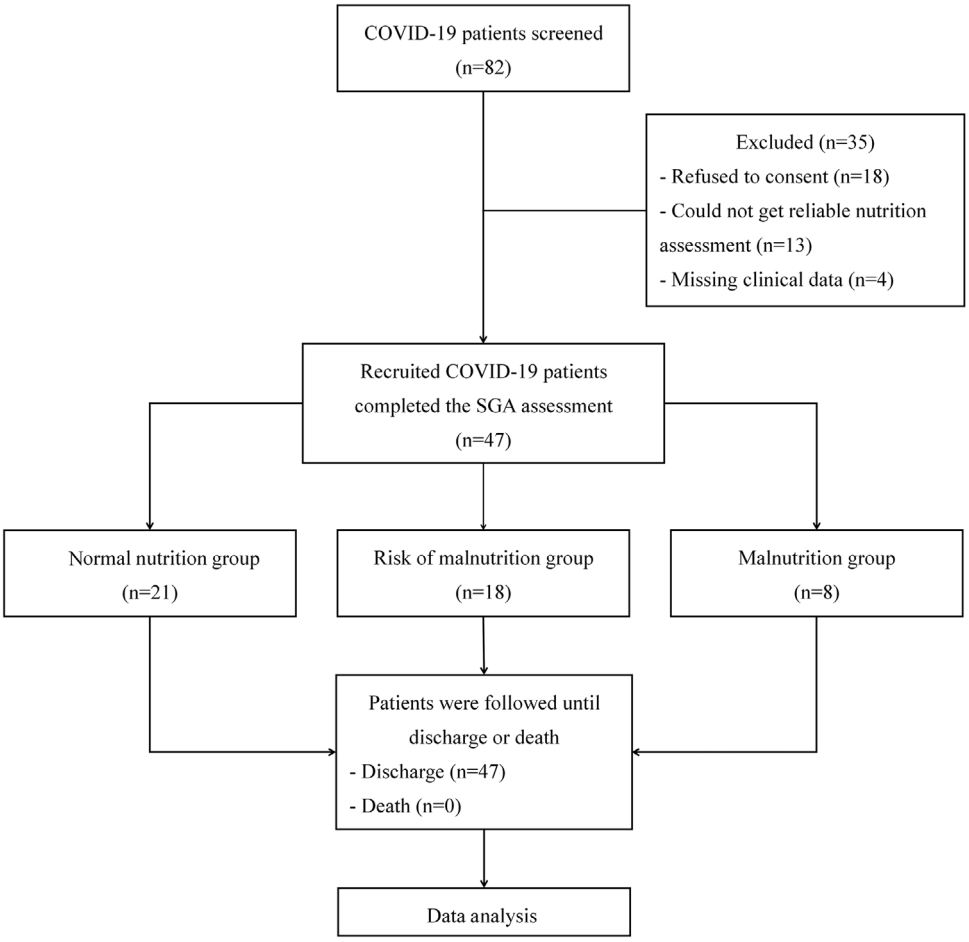

FIGURE 1 Flowchart outlining participant selection. COVID-19, coronavirus disease 2019; SGA, subjective global assessment

the prevalences in the other two groups. The prevalences of the remaining comorbidities, including cardiovascular diseases, digestive system diseases, and respiratory system diseases, were similar among the three groups.

Laboratory and clinical findings

The blood counts on admission showed lymphopenia (42.6%, 20 of 47), especially in the MN group ($P = .001$) (Table 2). The levels of both ALB and TF, which are inflammatory markers, were lower in the MN group than in the other two groups on admission (all $P < .05$). The proportion of patients with an increased level of hsCRP was higher in the MN group than in the other two groups. However, the mean level of hsCRP was not significantly different among the three groups. The three groups did not differ significantly in the WBC count or Hb level.

The proportion of patients with severe and critical disease was significantly higher in the MN group than in the NN group and RMN group ($P < .001$) (Table 2). Most of the COVID-19 patients (78.7%, 37 of 47) received antiviral treatment, and there were no differences among the three groups. Antibiotic treatment was more often administered in the NN group than in the other two groups (75.0%, 6 of 8; $P = .045$). Traditional Chinese medicine plays an important role in the treatment of COVID-19. The majority of patients received this treatment in the study, and no differences were found among the three groups. No patients died during hospitalization, and all patients were discharged at the end of follow-up. The mean length of stay in the MN group was significantly longer than that in the NN group (21.8 ± 7.3 days; $P = .028$).

Cytokines and T-cell subpopulation

The serum concentration of IL-6 in the MN group (30.7 ± 7.1 pg/ml) was higher than those in the other two groups ($P = .016$). The serum levels of TNF-α, IFN-γ, IL-4 and IL-10 were not significantly different among the three groups.

The distribution of the T-cell subpopulations differed among the three groups. In particular, the proportion of CD8+ T cells was significantly lower in the MN group than in the NN group ($P = .027$) (Table 3). The proportions of CD3+ and CD4+ T cells were similar among the three

TABLE 1 Nutrition status, demographics, and baseline characteristics of coronavirus disease 2019 patients at admission

	Total (N = 47)	NN group (n = 21)	RMN group (n = 18)	MN group (n = 8)	*P*-value
Gender					.319
Male	23 (48.9)	13 (61.9)	7 (38.9)	3 (37.5)	
Female	24 (51.1)	8 (38.1)	11 (61.1)	5 (62.5)	
Mean age, years		63.4 ± 2.9	65.4 ± 3.1	67.6 ± 5.9	.785
Mean duration of disease, days		19.1 ± 1.9	18.6 ± 2.0	19.9 ± 3.9	.634
BMI		25.5 ± .6[a]	23.0 ± .7[b]	17.7 ± 1.3[c]	<.001
Comorbidity	29 (61.7)				
Cardiovascular diseases	22 (46.8)	9 (42.9)	7 (38.9)	6 (75.0)	.250
Endocrine system disease	11 (23.4)	3 (14.3)	8 (44.4)	0	.025
Digestive system disease	8 (17.0)	6 (28.6)	1 (5.6)	1 (12.5)	.139
Respiratory system disease	2 (4.3)	1 (4.8)	1 (5.6)	0	1.000
Malignant tumor	4 (8.5)	0	0	4 (50.0)	<.001
Signs and symptoms					
Fever	36 (76.6)	19 (90.5)	11 (61.1)	6 (75.0)	.077
Dry cough	20 (42.6)	9 (42.9)	8 (44.4)	3 (37.5)	1.000
Expectoration	13 (27.7)	4 (19.0)	6 (33.3)	3 (37.5)	.512
Chest distress	24 (51.1)	13 (61.9)	7 (38.9)	4 (50.0)	.399
Fatigue	14 (29.8)	9 (42.9)	5 (27.7)	0	.091
Diarrhea	9 (19.2)	7 (33.3)	1 (5.6)	1 (12.5)	.080
Headache	4 (8.5)	2 (9.5)	2 (11.1)	0	1.000

Note: Values are mean ± SE or frequency (percent). [a-c]Labeled means in a row that do not share a common letter differ significantly ($P < .05$).
Abbreviations: BMI, body mass index; MN group, malnutrition group; NN group, normal nutrition group; RMN group, risk of MN group.

groups. The CD4 to CD8 ratio was significantly higher in the MN group than in the other two groups ($P = .015$).

DISCUSSION

As an emerging infectious disease, COVID-19 is currently spreading around the world and has caused hundreds of thousands of deaths.[14] The prevention, diagnosis, and treatment of COVID-19 are currently being studied by doctors and scientists around the world. It is well known that nutrition plays an important role in the occurrence and development of and recovery from diseases. However, to date, there have been no reports on the nutrition status of COVID-19 patients. This study was conducted to clarify the nutrition status of COVID-19 patients and its effects on their inflammatory and immune responses. This study had two important findings. First, 17.0% of the COVID-19 patients were malnourished, which was associated with more severe disease and a prolonged duration of hospitalization. Second, MN promotes hyperinflammation and immunosuppression in COVID-19 patients.

The basic epidemiological and clinical features were reported. In this study, 17.0% of the COVID-19 patients were part of a familial cluster of cases, with no significant difference between the sexes. Because of the high proportion of elderly patients, with 61.7% of patients older than 66 years, most of the patients had underlying diseases. Different durations of disease can influence the inflammatory and immune responses in COVID-19 patients.[15] There were no significant differences in disease duration among the three groups, which suggested that the inflammatory and immune responses should be comparable. Consistent with previous studies, fever and respiratory symptoms were the most common clinical manifestations in COVID-19 patients. Patients had differing levels of severity of gastrointestinal symptoms, such as diarrhea and a poor appetite, which could have led to changes in their nutrition status.

By administering a nutrition status assessment, we found that 51.1% of the COVID-19 patients were at RMN or were already undernourished at admission; this was especially true for elderly patients. The BMI value was related to the results of the SGA, confirming the accuracy of the nutrition assessment.

Laboratory tests showed that the LYM count was significantly lower in patients in the MN group than in patients in the NN group. Huang et al found that 85% of patients with COVID-19 treated in the ICU had lymphocytopenia,

TABLE 2 Nutrition status and clinical characteristics of coronavirus disease 2019 patients at admission

Laboratory results	Total (N = 47)	NN group (n = 21)	RMN group (n = 18)	MN group (n = 8)	*P*-value
WBC (whole blood), $\times 10^9$/L		5.0 ± .6	6.0 ± .5	6.5 ± 1.0	.466
<3.50	3 (6.4)	0	3 (16.7)	0	.197
3.50–10.00	41 (87.2)	21 (100.0)	13 (72.2)	7 (87.5)	
>10.00	3 (6.4)	0	2 (11.1)	1 (12.5)	
Hb (whole blood), g/L		121.9 ± 2.6	115.9 ± 2.8	122.2 ± 5.4	.241
<120.00	28 (59.6)	11 (52.4)	12 (66.7)	5 (62.5)	.533
≥120.00	19 (40.4)	10 (47.6)	6 (33.3)	3 (37.5)	
LYM (whole blood), $\times 10^9$/L		1.4 ± .1[a]	1.3 ± .1[a]	.7 ± .2[b]	.025
<1.100	20 (42.6)	5 (23.8)	7 (38.9)	8 (100.0)	.001
≥1.100	27 (57.4)	16 (76.2)	11 (61.1)	0	
ALB (serum) level, g/L		36.6 ± 1.0[a]	35.0 ± 1.0[a]	31.9 ± 2.2[b]	.019
<35.00	21 (44.7)	6 (28.6)	9 (50.0)	6 (75.0)	.066
≥35.00	26 (55.3)	15 (71.4)	9 (50.0)	2 (25.0)	
TF (serum), g/L		2.4 ± .1[a]	2.3 ± .1[a]	1.9 ± .2[b]	.011
<2.00	8 (17.0)	1 (4.8)	2 (11.1)	5 (62.5)	.001
≥2.00	39 (83.0)	20 (95.5)	16 (88.9)	3 (37.5)	
hsCRP (serum), mg/L		7.0 ± 5.0	11.4 ± 5.2	26.8 ± 10.1	.259
≤4.00	26 (55.3)	16 (76.2)	7 (38.9)	3 (37.5)	.039
>4.00	21 (44.7)	5 (23.8)	11 (61.1)	5 (62.5)	
Patient types					<.001
Mild and moderate types	36 (76.6)	19 (90.5)	16 (88.9)	1 (12.5)	
Severe and critical types	11 (23.4)	2 (9.5)	2 (11.1)	7 (87.5)	
Treatment					
Antiviral treatment	37 (78.7)	16 (76.2)	15 (83.3)	6 (75.0)	.107
Antibiotic treatment	19 (40.4)	6 (28.6)	7 (38.9)	6 (75.0)	.045
Traditional Chinese medical treatment	32 (68.1)	15 (71.4)	12 (66.7)	5 (62.5)	.208
Length of stay, days		13.5 ± 5.5[b]	18.3 ± 4.3[b]	21.8 ± 7.3[a]	.028

Note: Values are mean ± SE or frequency (percent). [a,b]Labeled means in a row that do not share a common letter differ significantly, $P < .05$.
Abbreviations: ALB, albumin; Hb, hemoglobin; hsCRP, hypersensitive C-reactive protein; LYM, lymphocyte; MN group, malnutrition group; NN group, normal nutrition group; RMN group, risk of MN group; TF, transferrin; WBC, white blood cell.

TABLE 3 Cytokines and T-cell subpopulation in coronavirus disease 2019 patients at admission

Cytokines	NN group (n = 21)	RMN group (n = 18)	MN group (n = 8)	*P*-value
IL-2 (serum), pg/ml	3.3 ± .2	3.9 ± .3	3.4 ± .5	.213
IL-6 (serum), pg/ml	9.8 ± 3.4[b]	12.8 ± 3.7[b]	30.7 ± 7.1[a]	.016
TNF-α (serum), pg/ml	3.7 ± .3	3.3 ± .3	3.2 ± .5	.525
IFN-γ (serum), pg/ml	2.6 ± .3	3.2 ± .3	4.0 ± .6	.121
IL-4 (serum), pg/ml	2.7 ± .3	3.4 ± .3	2.6 ± .6	.137
IL-10 (serum), pg/ml	4.3 ± .3	4.8 ± .4	4.6 ± .7	.597
T-cell subpopulation (whole blood)				
$CD3^+$, %	68.0 ± 2.2	70.1 ± 2.4	72.6 ± 4.6	.637
$CD4^+$, %	42.3 ± 1.7	42.9 ± 1.8	51.7 ± 3.4	.230
$CD8^+$, %	23.2 ± 1.5[a]	24.0 ± 1.5[a]	15.9 ± 2.9[b]	.027
CD4/CD8	2.0 ± .3[b]	1.9 ± .3[b]	4.2 ± .6[a]	.015

Note: Values are mean ± SE. [a,b]Labeled means in a row that do not share a common letter differ significantly, $P < .05$.
Abbreviation: CD, cluster of differentiation; IFN-γ, interferon-γ; IL, interleukin; MN group, malnutrition group; NN group, normal nutrition group; RMN group, risk of MN group; TNF-α, tumor necrosis factor-α.

but only 54% of patients not treated in the ICU had lymphocytopenia.[8] A later large-sample study also showed that patients with severe disease had more prominent lymphocytopenia than those with nonsevere disease.[7] These results suggest that lymphocytopenia may be related to the severity of COVID-19. The proportion of patients with severe and critical COVID-19 was significantly higher than the proportion with mild and moderate COVID-19 in the MN group. Regarding treatment, there were no significant differences in the administration of antiviral treatment and traditional Chinese medicine treatment among the groups. However, the proportion of patients who received antibiotic treatment in the MN group was significantly higher than in the other two groups, which may be related to the susceptibility to bacterial coinfections in patients in the MN group. In a retrospective study of 1099 COVID-19 patients, similar results were obtained; up to 80.3% of the patients with severe disease needed antibiotic treatment.[7] In terms of the final clinical outcome, the mean length of stay in the MN group was also significantly longer than that in the NN group. The above results show that MN is not only a consequence of COVID-19 but also may contribute to disease progression. A study in pneumococcal pneumonia patients found that elderly patients had lower levels of serum ALB, which was associated with disease progression and a prolonged length of stay.[16] A randomized control trial also showed that nutrition intervention programs for malnourished elderly adults with pneumonia significantly improved their nutrition status and reduced the readmission rate.[17]

In the host response to infection with SARS-CoV-2, the nonspecific immune response is activated first, and immune cells produce cytokines to destroy the virus. Then, the specific immune response is activated, and the appropriate T cells or B cells are selected.[18] Early studies showed that increased levels of proinflammatory cytokines (eg, IL-1B, IL-6, IL-12 and IFN-γ) were associated with pulmonary inflammation and extensive lung damage in SARS patients.[19] Middle East respiratory syndrome coronavirus (MERS-CoV) infection was also reported to induce increases in the concentrations of proinflammatory cytokines (IFN-γ, TNF-α, IL-15, and IL-17).[20] We also observed that the levels of the proinflammatory cytokine IL-6 were increased in COVID-19 patients. Previous studies showed increased levels of IL-6 in 52.0% of COVID-19 patients.[21,22] Moreover, patients treated in the ICU had higher levels of granulocyte colony stimulating factor, IP10, monocyte chemotactic protein 1 (MCP1), active macrophage inflammatory protein 1-α, and TNF-α than those not treated in the ICU, suggesting that cytokine levels were associated with disease severity.[8,18] We found that the concentration of IL-6 was the highest in the MN group among the three groups, with a mean concentration that was 3.1 times that in the NN group. Additionally, acute-phase serum ALB and TF levels were significantly lower in the MN group. Early studies showed that the elevation of the lipopolysaccharide (LPS)-induced IL-6 messenger RNA level occurred earlier and lasted longer in malnourished rats than in control rats. These results suggest that MN may exacerbate the acute-phase inflammatory response by inducing IL-6 expression in COVID-19 patients. A series of subsequent studies investigating diseases has also reported that MN is related to upregulated serum IL-6 levels and serves as a prognostic marker.[23–26] We also found a relatively higher proportion of MN group patients with increased levels of hsCRP induced by elevated IL-6 levels. However, the mean level of hsCRP was not different among the three groups. A recent retrospective, multicenter study showed that an elevated IL-6 level was a predictor of critical disease in COVID-19 patients, suggesting that mortality might be due to virally driven hyperinflammation.[27] The excessive release of the proinflammatory cytokine IL-6 plays a key role in cytokine storms.[28,29] A postoperative cytokine storm characterized by an exaggerated IL-6 response and suppressed IL-1 receptor antagonist was identified in malnourished colon cancer patients.[30] We also found that the levels of the antiinflammatory cytokines IL-4 and IL-10 were reduced in COVID-19 patients. Several previous articles have also reported that the serum concentrations of IL-4 and IL-10 were reduced in COVID-19 patients, which was consistent with our findings.[8,22] Elevated levels of IL-4 and IL-10 were found to help suppress overreactive inflammation in SARS patients, and they may play the same role in COVID-19 patients.[18,31] However, MN may attenuate the inhibitory effect of IL-4 and IL-10 on excessive inflammation, leading to an uncontrolled inflammatory response.[32,33] From these results, we can see that cytokine storms mediated by elevated IL-6 levels are more likely to occur in malnourished COVID-19 patients, leading to disease progression. Tocilizumab has been administered intravenously as an experimental treatment for COVID-19 in China and Italy, and the results have been encouraging.[34] In a recent descriptive study, COVID-19 patients had high levels of IL-1B, IFN-γ, IL-6, TNF-α, IP10 (CXCL-10), and MCP1.[8] In this study, the TNF-α and IFN-γ levels did not differ significantly among the three groups, and they may not be affected by the nutrition status of patients.

One study reported substantially reduced peripheral CD4+ and CD8+ T-cell counts in a COVID-19 patient; however, the cells that were present were hyperactivated.[35] Additionally, the CD8+ T cells were found to harbor high concentrations of cytotoxic granules.[35] These results imply that the overactivation of T cells and elevated cytotoxicity in CD8+ T cells accounted for the severe immune impairment in that COVID-19 patient.[34] The results of

our study also showed lower CD8+ T-cell counts in the MN group than in the other two groups. However, there was no difference in the proportions of CD4+ and CD3+ T cells among the three groups. COVID-19 patients had high levels of cytokines (IL-1B, IFN-γ, IL-6, TNF-α, IP10, and MCP1), probably leading to the activation of T-helper-1 (Th1) (CD4+) cell responses. Current evidence strongly suggests that the Th1-type response is key for the successful control of SARS-CoV and MERS-CoV; it is likely that the same is true for SARS-CoV-2.[36] CD8+ T cells play an important role in protecting against infections and reinfections with intracellular pathogens such as viruses.[37] Therefore, the reduced count of CD8+ T cells in the MN group of COVID-19 patients may damage the body's ability to clear SARS-CoV-2, leading to the progression of the disease. Animal experiments showed that MN inhibited the CD8+ T-cell response by altering the bone marrow microenvironment and reducing virus-specific CD8+ T cells.[38] MN may play an accessory role in the immune dysfunction in COVID-19 patients. Some immune enhancers, such as thymosin, may be used in patients with severe and critical COVID-19 with immune dysfunction.

Limitations of this study should be mentioned. Although this was a prospective study, the patients were evaluated by the SGA only on admission, and their nutrition status might have changed as the disease developed; therefore, a single evaluation might not adequately reflect their nutrition status. Because of the small sample size of this study, confounding is also a factor to be considered in the analysis, and the results need to be verified by a study with a larger sample size. Furthermore, all patients were from the same center; the homogeneity of the study population and therapeutic environment may have precluded the identification of certain factors affecting the COVID-19 treatment outcome. However, among the studied variables, no other variable was identified that improved the predictive model. A prospective study in multiple centers assessing many time points is needed to confirm and refine our findings.

CONCLUSIONS

Our findings reveal that a high proportion of COVID-19 patients are malnourished or at RMN, especially those with severe disease. MN promotes hyperinflammation and immunosuppression in COVID-19 patients, which ultimately may lead to disease progression. Therefore, a timely and effective assessment of the nutrition status of COVID-19 patients and active nutrition interventions for those at RMN may contribute to improved outcomes.

CONFLICT OF INTEREST

None declared.

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None declared.

AUTHOR CONTRIBUTIONS

Heng Liu and Hong Zhang equally contributed to the conception and design of the research; Liang Zhou and Hugen Wang contributed to the design of the research; Guangbo Qu contributed to the acquisition and analysis of the data; Xiaobo Wang and Jing Cai contributed to the interpretation of the data; and Heng Liu 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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