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1. Introduction

The novel coronavirus outbreak in Wuhan, China has resulted in a pandemic, leading to >1,000,000 infections and nearly 600,000 deaths [1]. The new coronavirus can affect many organs by binding to the angiotensin-converting enzyme 2 receptor [2–4], although the lungs are the most affected. Current epidemiological evidence shows that the critical illness incidence rate in patients with the 2019 novel coronavirus disease (COVID-19) infection is 5% [5], and that mortality rate in intensive care unit (ICU) patients is approximately 45–60% [6,7]. Presently, due to the absence of effective antiviral drugs and vaccines, the treatment of every severe patient is a significant challenge in clinical practice.

Wu et al. have shown that of 201 patients with COVID-19 pneumonia, 84 eventually developed adult respiratory distress syndrome (ARDS) [8]. Approximately 6–8% of patients with COVID-19 pneumonia need to be admitted to the ICU for intensive care [9]. Sang et al. have demonstrated that the mortality rate in ICU...
patients with COVID-19 was 60% and 40% in patients receiving invasive ventilator treatment [6]. Patients admitted to the ICU often had more organ dysfunction conditions and chronic basic diseases. A cytokine storm is manifested by uncontrolled production of inflammatory cytokines which are significantly higher in ICU patients than non-ICU patients hospitalized with COVID-19 [10]. These are significantly higher in ICU than in non-ICU patients hospitalized with COVID-19 [10]. Manjili et al. have described COVID-19 as an acute inflammatory disease [11]. Therapeutic strategies for the management of severe symptoms have been focused on the control of viremia and/or inflammation [11].

Systemic inflammatory response and organ dysfunction in critical patients can lead to energy intake and utilization disorders. The incidence of malnutrition in the ICU is 38–78% [12] and is independently related to poor prognosis. Wu et al. have also found that patients who developed ARDS had lower levels of low-density lipoprotein cholesterol (LDL-c), albumin (ALB), and prealbumin (PA) [8]. However, specific nutritional risk screening tools have not been widely used in clinical practice to identify COVID-19 patients with a higher malnutrition risk. The application of nutritional risk screening tools is an important part of nutritional assessment of severely ill COVID-19 patients and the first step in nutritional support therapy. Nutritional status appears to be a relevant factor influencing the outcome in COVID-19 patients. However, not much information has emerged so far on the impact of early nutritional support in pre-ICU COVID-19 patients [13]. The National Health Commission of the People's Republic of China and the National Administration of Traditional Chinese Medicine recommend implementing “strengthened supportive care to ensure sufficient energy intake” [14].

The Nutritional Risk Screening (NRS) 2002 score is a recommended tool for nutritional risk screening [15]. While established based on data from general patients, it has since been validated in ICU patients [16,17]. The Nutrition Risk in the Critically Ill (NUTRIC) score, while developed for ICU patients by Canadian researchers [18], does not contain nutritional data, and is calculated retrospectively based on severity scores. The American Society for parenteral and enteral nutrition (ASPEN) recommends to use both scores [19], while the European Society for Clinical nutrition (ESPEN), recommends only the NRS score [16]. However, the clinical evidence for the association between nutritional risk assessment tools and clinical outcomes in patients with COVID-19 is limited. Therefore, the present retrospective study was designed to analyze the risk of malnutrition in severe and critical COVID-19 patients. The main objective was to evaluate nutritional metabolism in COVID-19 patients upon admission and prognostic value of the NUTRIC and NRS score in COVID-19 patients in the ICU.

2. Methods

This is a multicenter retrospective observational study. The retrospective analysis was carried out at four designated hospitals for COVID-19, including two critical and two general designated hospitals. Severely and critically ill patients were defined according to the guidelines of National Health Commission of the People’s Republic of China [20]. Severely ill patients were included in the study if they met any of the following criteria: 1) respiratory distress and respiratory rate was ≥30 times/min; 2) oxygen saturation in a resting state was <93%; and 3) arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) was ≤300 mm Hg. Critically ill patients were included if they met any of the following criteria: 1) respiratory failure and need for mechanical ventilation; 2) shock; and 3) other organ failure requiring ICU monitoring. Positive results for real-time polymerase chain reaction testing of respiratory or blood samples were defined as confirmed cases [21].

The inclusion time was from January 2, 2020 to February 15, 2020 for discharged and dead patients. The severity of COVID-19 patients was determined using the analysis of electronic medical records, nursing records, and related examinations. All data review was performed by experienced ICU doctors. A total of 523 patients participated in the study, including 377 severe and 146 critically ill patients. Of these, 211 patients were admitted to the ICU, with hospital death and transfer to ICU considered as the end events. Due to the speed of COVID-19 spread and the risk of infection, exemption from written informed consent was obtained. This study complied with the Declaration of Helsinki and was approved by the ethics committee of Hubei Provincial Hospital of Traditional Chinese Medicine (HBZY2020-C14-01).

2.1. Data collection

Data for age, gender, history of chronic diseases (hypertension, coronary heart disease, and diabetes), vital signs, laboratory values, hospitalization time, chest imaging characteristics, and prognosis for COVID-19 patients were collected. In-hospital death or survival were defined as the prognosis in this study. In addition, the Glasgow Coma Scale, sequential organ failure assessment (SOFA), acute physiology and chronic health assessment II scores (APACHE II), PaO2 and lactate concentration, PaO2/FiO2, NRS score, and other indicators for subsequent analysis data were collected from the hospital’s electronic medical and nursing records. Except for the 43 patients who were transferred to the ICU with endotracheal intubation and were unable to provide the NRS score, the remaining patients completed the NRS score evaluation on the first day of admission to the ICU. The nutritional risk for each patient was assessed upon ICU admission using the modified NUTRIC (mNUTRIC) score. This score (0–9 points) was calculated based on the NUTRIC score by eliminating IL-6 values. It consisted of five variables: age, APACHE II score upon admission, SOFA score upon admission, number of comorbidities, and pre-ICU hospital length of stay [22]. A score of >5 indicated that a patient had a high nutritional risk.

2.2. Statistical analysis

Demographic and medical data meeting normal distribution requirements were represented as mean ± SD. Data with a skewed distribution were presented as median (IQR). Categorical variables were described as frequency rates and percentages. The differences between survivors and non-survivors were assessed using two-sample t test or Mann–Whitney test depending on normal or skewed distribution of data for continuous variables and Chi-squared test for categorical variables. Logistic regression was used to analyze the association between nutritional and metabolic factors with a death risk in the hospital or other clinical adverse outcomes. Survival curves for body mass index (BMI) and ALB groups were estimated according to the Kaplan–Meier method and compared using the log-rank test. We used multivariate Cox regression to examine the relationships between the mNUTRIC score and BMI with end points. All statistical analyses were performed using the SPSS 22.0 software (SPSS Inc, Chicago, Illinois) and P < 0.05 was considered to be statistically significant.

3. Results

In this study, the average age of 523 patients was 54.2 ± 15.9 years, of which 250 (47.9%) were men. A total of 115 (22.0%) deaths occurred in the course of the study. Among the 523 patients, 211 were admitted to the ICU for intensive care. Patients in the ICU were older and predominantly male. They also had chronic diseases,
higher fasting blood glucose (FBG) levels, and markers of renal function and inflammatory factors. Among the indicators reflecting nutritional status, patients admitted to the ICU had lower BMI and high-density lipoprotein cholesterol and plasma protein levels (Table 1). Of the 211 patients in the ICU, 95 (45.0%) eventually died. Similarly, patients who died in the ICU were older, had more chronic diseases, higher basal blood pressure, higher FBG levels, and worse renal and cardiac function indexes (Table 1). They also had lower plasma protein levels, absolute lymphocyte counts, and LDL-c levels. Although there was no difference in mean BMI between patients who died in the ICU and those who survived (22.1 ± 2.7 vs 21.6 ± 2.9, p = 0.208), the proportion of patients who died with BMI ≤ 20.5 was higher (Table 1).

After further analysis, it was evident that patients who died in the ICU had higher SOFA, APACHE II, NRS score and mNUTRIC score (Table 2). The median mNUTRIC score in 211 ICU patients was 5 (4, 6). Of these, there were 129 low-risk patients (0–4) and 82 high-risk patients (5–9). The median time from admission to ICU transfer was one day for patients who survived and two days for patients who died. Moreover, patients who survived had fewer complications. During respiratory treatment, non-survivors more often adapted to mechanical ventilation and invasive mode than survivors. There was no difference in the proportion of ALB support between non-survivors and survivors. However, the ratio of parenteral nutrition (PN) therapy in non-survivors was greater than that in survivors (62.1% vs 10.3%, p < 0.001), and the time until onset of nutrition therapy was longer than that in survivors (Table 2).

Binary logistic regression model was used to analyze the relationship between common nutrition metabolism indices and endpoint events, including ICU transfer and death. BMI, HDL-c, FBG, blood urea nitrogen, creatinine (Cr), uric acid, and plasma protein levels were significantly associated with the two endpoint events. Hemoglobin and total bilirubin levels were significantly related to ICU transfer, while total cholesterol and LDL-c levels were independently related to patient death (Table 3). However, among these indicators, only triacylglycerol level was not associated with death and ICU transfer (Table 3).

Multivariate Cox regression analysis showed that the mNUTRIC score was closely related to patient death and ICU stay. In stage...
with hospital mortality and ICU stay time. After adjusting for age, sex, BMI, liver and kidney function index, inflammatory factors, therapies, and other variables, the mNUTRIC score was able to independently predict the risk of death in the hospital (OR = 1.197, 95%CI: 1.091–1.445, p = 0.006) and duration of the ICU stay (β = 0.566, 95%CI: 0.068–1.064, p = 0.026, Table 4). For each one-point increase in the mNUTRIC score, the risk of death in the ICU increased by nearly 20%. After adjusting for age and sex, for each standard deviation increase in BMI, the risk of in-hospital death was reduced by 13% (HR = 0.871, 95%CI: 0.795–0.955, p = 0.003), while the risk of ICU transfer was reduced by 7% (HR = 0.932, 95%CI: 0.853–0.981, p = 0.007, Table 4).

ICU patients were divided into low- and high-risk groups according to the mNUTRIC score. The Cox proportional risk model showed that after adjusting for age, sex, and other variables, patients with high nutritional risk (5–9 points) had a significantly increased risk of in-hospital death compared to patients with low nutritional risk (OR = 1.877, 95%CI: 1.122–3.143, p = 0.017, Fig. 1a). Similarly, patients were divided into two groups according to the unadjusted variables, mNUTRIC scores were significantly correlated with hospital mortality and ICU stay time. After adjusting for age, sex, BMI, liver and kidney function index, inflammatory factors, therapies, and other variables, the mNUTRIC score was able to independently predict the risk of death in the hospital (OR = 1.197, 95%CI: 1.091–1.445, p = 0.006) and duration of the ICU stay (β = 0.566, 95%CI: 0.068–1.064, p = 0.026, Table 4). For each one-point increase in the mNUTRIC score, the risk of death in the ICU increased by nearly 20%. After adjusting for age and sex, for each standard deviation increase in BMI, the risk of in-hospital death was reduced by 13% (HR = 0.871, 95%CI: 0.795–0.955, p = 0.003), while the risk of ICU transfer was reduced by 7% (HR = 0.932, 95%CI: 0.853–0.981, p = 0.007, Table 4).

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Table 4  
Cox regression of NUTRIC score and BMI associated with clinical adverse outcomes.

| nNUTRIC scores | Death OR 95%CI p value | Hospitalization days of ICU β 95%CI p value |
|----------------|------------------------|------------------------------------------|
|                |                        |                                          |
| Unadjusted     | 1.343 1.170 0.001      | 1.534 1.143–1.926 <0.001                |
| Model 1a       | 1.219 1.040 0.014      | 1.090 0.592–1.587 <0.001                |
| Model 2        | 1.348 1.137–1.597 0.001| 1.029 0.530–1.528 <0.001                |
| Model 3a       | 1.197 1.091–1.445 0.006| 0.566 0.068–1.064 0.026                 |

| BMIDeath HR per SD 95%CI p value | Transfer to ICU HR per SD 95%CI p value |
|----------------------------------|------------------------------------------|
| Unadjusted                       | 0.822 0.761–0.888 <0.001                 |
| Model 1b                         | 0.925 0.879–0.972 0.002                  |
| Model 2                          | 0.932 0.885–0.981 0.007                  |
| Model 3b                         | 0.923 0.876–0.973 0.003                  |
| Model 3b                         | 0.956 0.900–1.106 0.146                  |

Model 1a: adjusted for age, gender and BMI.
Model 2: Model 1a + Hypertension, Diabetes mellitus and Coronary artery disease.
Model 3a: Model 2 + Initial nutrition therapy mode, Oxygen therapy mode, Duration of start nutrition therapy.
Model 1 b: adjusted for age, gender.
Model 2: Model 1 b + Hypertension, Diabetes mellitus and Coronary artery disease.
Model 3 b: Model 2 + Cr, PCT, ALC, cTnI, hs-CRP, LDL-c and FBG.

Fig. 1. Cumulative hospitalization mortality between the different groups of NUTRIC score and nutrition therapy timing.
Nutritional support is an important part of the ARDS treatment [23]. In addition to affecting the lungs and inducing ARDS, coronavirus can also cause dysfunction in other organs, such as sepsis and myocardial damage [3,24]. The large amount of virus replication and amplification in vivo also leads to a dramatic increase in metabolism. Patients admitted to the ICU or those who died may have a higher nutritional risk and metabolic level due to a high viral load or extremely strong immune response in vivo. Some patients also have gastrointestinal symptoms [25], which further aggravate the nutritional risk. Nutritional support therapy can meet the patient needs for macronutrients, prevent the adverse effects of metabolism on diseases, reduce cell oxidative damage, and regulate the immune response [26]. The treatment of critical COVID-19 patients is a long process. Nutritional support is an important part of treatment and requires more attention.

The clinical characteristics of patients admitted to the ICU were further analyzed. Similar to other studies, the ICU patients had higher APACHE II and SOFA scores [6,21]. Most ICU patients received ALB support therapy. The European guidelines recommend that all hospitalized patients in the ICU consider medical

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**Fig. 2.** Kaplan–Meier curves stratified according to BMI and albumin.

**Fig. 3.** Kaplan–Meier analysis and Cox proportional risk model comparing elevated and low NRS scores.
nutrition treatment and that all patients who stay in the ICU for >48 h should receive early nutrition treatment [16]. Low-calorie nutrition (no more than 70% of energy consumption) should be used in the early stages of the acute disease [16]. If critical patients can eat normally, oral nutrition support (ONS) is better than enteral nutrition (EN) and PN. In the present study, only 6.2% of patients selected ONS as the initial nutrition support method. Most of them still preferred EN and PN. It is recommended that nutrition therapy be started within 48 h. However, many patients started nutrition therapy after >48 h. In the present study, although there was no difference in the risk of in-hospital death between patients who received early and delayed nutrition therapy, early nutrition therapy was still necessary.

BMI is widely used in cardiovascular, nutrition, and metabolic risk assessment [27,28]. The present study found that low BMI was significantly associated with an increased risk of death and ICU admission. The hospital survival time in patients with BMI <20.5 was significantly lower than that in patients with BMI >20.5. NRS recommends BMI of <20.5 to be an indicator for initial risk screening [15]. Obesity and morbid obesity are associated with lower mortality in patients with ARDS [29]. It is also considered important to maintain a certain weight during the COVID–19 outbreak.

It is necessary to use specific tools to screen for nutritional risk in ICU patients. The NUTRIC score was first proposed by Heyland et al., in 2011 and is also suitable for critically bedridden patients [18]. APACHE II and SOFA scores are the most widely used critical scales in the ICU. Based on the APACHE II and SOFA scores, the NUTRIC score added several simple indicators, such as age, number of complications, and time from hospital admission to ICU admission. Heyland et al. prospectively observed 597 patients in the ICU and found that the NUTRIC score was related to the mechanical ventilation time, 28-day mortality, and other prognostic indicators [18]. When the NUTRIC score was compared to traditional screening tools, a large variability was observed [16]. A limitation to this score is that no nutritional parameters are included. Furthermore, mortality is not the best outcome to assess the efficacy of a nutritional intervention considering the numerous factors influencing ICU mortality [16]. Viana et al. demonstrated that high NRS scores may identify patients at highest risk of poor outcome when exposed to underfeeding [17].

A single-center retrospective study in Wuhan found that COVID-19 patients with a high nutritional risk had a higher probability of death at ICU 28-day than those with a low nutritional risk. The mortality of ICU 28-day was significantly higher in the high mNUTRIC score group than in the low mNUTRIC score group [30]. Zhao et al. found that critically COVID-19 patients and those with higher NRS score had a higher risk of mortality and longer stay in hospital. In their logistic regression models, 1-unit increase in NRS score was associated with the risk of mortality increasing by 1.23 times [31]. In the present study, we found that higher NUTRIC and NRS scores were associated with poor outcomes in patients with COVID-19. Therefore, we thought that NUTRIC score and NRS score are convenient, provides objectivity, and might be the suitable nutritional risk assessment tool for COVID-19 patients.

ALB and PA levels are two classical laboratory indexes in traditional nutrition assessment [32,33]. They cannot be used as the evaluation indexes of nutritional status alone. However, they can directly reflect the approximate nutritional status or disease severity in clinical practice. The ALB level can also provide a sensitive reflection of the condition and prognosis of critical patients with acute lung injury [34]. Serum PA level is a useful tool in the assessment of malnutrition in hospitalized patients [21]. In the present study population, the average ALB and PA levels upon admission already indicated a state of mild malnutrition. Therefore, the timing of nutritional support for COVID-19 patients may need to be further advanced.

5. Limitations

This study had some limitations. First, only a retrospective nutritional risk assessment was conducted in the ICU patients. Other patients not admitted to the ICU did not undergo a nutritional risk assessment. Whether early nutritional risk screening and early intervention in all in-hospital COVID-19 patients could reduce mortality and proportion of conversion to critical illness is worth further investigation. Second, due to the nature of the study, we were unable to accurately assess the daily energy needs of the ICU patients, which may have affected the prognosis judgment.

6. Conclusions

Severe and critical COVID-19 patients have a high risk of malnutrition. Low BMI and protein levels are significantly associated with adverse events, such as death and ICU transfer. The NUTRIC score and NRS score can be used to assess the nutritional risk of COVID–19 patients in the ICU. Early nutritional risk screening and therapy are necessary for COVID–19 patients.

Contributors

Drs G. Li, C. Zhou, Y. Wang and B. Shong contributed equally and share first authorship. Drs X. Cheng, Q. Dong, and S. You collected the epidemiological and clinical data. G. Li, C. Zhou, and Y. Wang summarized all data. G. Li, and L. Wang drafted the manuscript. G. Li and Y. Ba revised the final manuscript.

Conflict of Interest

We declare no competing interests.

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None.

Availability of data and materials

All data generated or analyzed in this study are included in this published article, and the datasets are available from the corresponding author within the limits imposed by ethical and legal dispositions.

Ethics approval and consent to participate

Exemption from the written informed consent was obtained. The study was approved by the ethics committee of Hubei Provincial Hospital of Traditional Chinese Medicine (HBZY2020-C14-01).

Consent for publication

Not applicable.

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Abbreviations

2019-nCoV 2019 novel coronavirus
Laviano A, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2
Manjili RH, Zarei M, Habibi M, Manjili MH. COVID-19 as an acute in
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References

SOFA Sequential Organ Failure Assessment

Alb albumin
APACHE II Acute Physiology and Chronic Health Evaluation II
ARDS acute respiratory distress syndrome
ASPEN American Society for Parenteral and Enteral Nutrition
BMI body mass index
COVID-19 Coronavirus Disease 2019
EN enteral nutrition
FGB fasting blood glucose
GCS Glasgow coma scale
ICU intensive care units
IL-6 Interleukin-6
LDL-c low-density lipoprotein cholesterol
NUTRIC modified Nutrition Risk in the Critically ill
NRS 2002 Nutritional Risk Screening 2002
PA prealbumin
PN parenteral nutrition
SARS severe acute respiratory syndrome
SOFa Sequential Organ Failure Assessment

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