

CONUT score is associated with mortality in patients with COVID-19: a retrospective study in Wuhan

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Research article

Keywords: 2019 novel coronavirus disease (COVID-19), CONUT score, mortality

Posted Date: June 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-32889/v1>

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Abstract

Background

The coronavirus disease 2019 (COVID-19) pneumonia, outbreak in Wuhan, China, has led to a global pandemic. The high mortality of COVID-19 patients makes it significant to evaluate possible disease progression. This study was designed to explore the prognostic value of Controlling Nutritional Status (CONUT) score in patients with COVID-19.

Methods

Patients diagnosed with COVID-19 of a single center in Wuhan, China from January 2020 to February 2020 were enrolled in this study. Logistic regression analysis was performed to find independent risk factor of mortality. Receiver operating characteristics (ROC) curve was drawn to evaluate the prognostic value of CONUT score.

Results

Among 442 included patients, there were 79 non-survivors with mortality of 17.9%. Compared with survivors, the median age ($p < 0.001$) and male ratio ($p = 0.042$) were higher in non-survivors. Non-survivors had higher incidence of comorbidities including hypertension ($p < 0.001$), chronic lung disease ($p = 0.001$) and cardiovascular disease ($p = 0.005$). Complications such as respiratory failure ($p < 0.001$), acute kidney injury (AKI) ($p < 0.001$) occurred more frequently in non-survivors. Multivariate logistic regression analysis showed that CONUT ($p = 0.002$), lactate dehydrogenase (LDH) ($p < 0.001$), C-reactive protein (CRP) ($p = 0.020$) were risk factor of mortality in COVID-19 patients. Area under the ROC curve (AUC) of CONUT and Nutrition risk screening 2002 (NRS2002) score were 0.813 and 0.795, respectively. Comprised of CONUT, LDH, CRP, the constructed prognostic model had higher AUC of 0.923 ($Z = 3.5210$, $p < 0.001$).

Conclusion

CONUT is an independent risk factor of mortality in COVID-19 patients. Evaluating CONUT is beneficial for clinicians to predict the progression of COVID-19 patients and strengthen monitoring and management to improve prognosis.

Background

Initially outbreaked in Wuhan, China in December 2019, the Coronavirus disease 2019 (COVID-19) caused by SARS coronavirus 2 (SARS-CoV-2) has been declared as a global pandemic by the World Health Organization (WHO). Up to 27 May, 82995 people were diagnosed with COVID-19 in China and 4634

patients of them died [1]. Thanks to the strong administrative management and effective allocation of medical resources by the Chinese government, the growth trend of confirmed cases has been contained. However, the number of confirmed and dead cases increases abruptly in the United States and European country such as Italy and Spain. As of 27 May, 1634010 and 230555 patients were diagnosed with COVID-19 in United States and Italy, respectively [2]. Patients commonly manifest as fever, cough, fatigue, sputum, polypnea and myalgia. It was investigated that 23–26% hospitalized patients would be transferred to intensive care unit due to severe comorbidities including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), cardiac injury, liver dysfunction and shock [3–5]. These combined organ dysfunctions have been confirmed to increase the risk of unfavorable outcome in COVID-19 patients [4, 6–8]. The damage to various tissues including heart, lung, kidney and occurrence of multiple organ system failure may be attributable to the cytokine release syndrome (CRS), which is characterized as an excessive production of immune cells and cytokine [9, 10]. It has been verified that classic inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6) and neutrophil-to-lymphocyte ratio (NLR) were associated with disease severity and outcome in COVID-19 patients [3, 11–13]. Utilizing these indexes to estimate the possible trend of disease development may be beneficial to supply scarce medical resources to potential severe and critical patients. The Controlling Nutritional Status (CONUT) score, which is calculated from serum level of albumin, lymphocyte and cholesterol, actually reflects state of systemic inflammation, nutrition and immune responsiveness [14]. The prognostic value of CONUT has been confirmed in various clinical settings including cardiovascular disease, liver disease and cancer [15–19]. We designed this study to explore the correlation between CONUT and mortality of COVID-19 patients.

Materials And Methods

Subjects

Patients diagnosed with COVID-19 and admitted to Renmin Hospital of Wuhan University from January 30 to February 24, 2020 were enrolled in this study. Utilizing real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR), the diagnose was confirmed by positive result for COVID-19 RNA in nasopharyngeal swabs. According to “Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia version 7 (trial)”, patients were classified into four levels including mild, common, severe and critical. (1) Mild: mild clinical symptoms, no signs of pneumonia on imaging; (2) Common: fever, respiratory tract symptoms, and imaging findings of pneumonia; (3) Severe: meet any of the following criteria ☐ shortness of breath, respiratory rate (RR) $\geq 30/\text{min}$; ☐ mean oxygen saturation $\leq 93\%$ in resting state; ☐ partial pressure of arterial oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ≤ 300 mmHg (1 mmHg = 0.133 kPa). Patients whose pulmonary imaging showed that the lesions progressed more than 50% within 24–48 hours were managed as severe; (4) Critical: Meet any of the following criteria ☐ occurrence of respiratory failure and requirements of mechanical ventilation; ☐ occurrence of shock; ☐ combined with other organ failure and requirements of ICU monitoring and treatment. Finally, a total of 442 patients were included in this single-center study.

Data Collection

We collected demographic data and clinical data of patients including age, sex, history of underlying diseases, initial symptoms, vital signs, laboratory findings and complications. Laboratory findings were acquired by testing the first blood sample on admission. All these data were recorded from electronic medical record system (EMRS) of Renmin Hospital of Wuhan University. Nutrition risk screening (NRS 2002) was evaluated on admission. The CONUT score was calculated according to peripheral lymphocyte counts, serum albumin and cholesterol levels. ☐ Lymphocyte counts: ≥ 1.600 , 1.200–1.599, 0.800–1.199, $< 0.800 \times 10^9/L$ were scored as 0, 1, 2, 3, respectively; ☐ Serum albumin: ≥ 3.5 , 3.0–3.49, 2.5–2.99, < 2.5 g/dL were scored as 0, 2, 4, 6, respectively; ☐ Serum cholesterol: ≥ 180 , 140–179, 100–139, < 100 mg/dL were scored as 0, 1, 2, 3, respectively. The CONUT score was obtained by summing the separate score of above three parts. The primary outcome was in-hospital mortality which was obtained by following up from admission to discharge. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of West China hospital of Sichuan University and Renmin Hospital of Wuhan University. Informed consent of all included patients were obtained by us from patients or their legal representatives.

Statistical analysis

Normally distributed and non-normally distributed variables were presented as the form of mean \pm standard deviation and median (interquartile range), respectively. Kolmogorov-Smirnov test was performed to analyze the normality of variables. Categorical variables were presented as numbers (percentage). Independent Student's t-test and Mann-Whitney U test were respectively used to compare group difference of normally distributed and non-normally distributed variables. And we used Chi-square test to examine the difference of categorical variables. Then, univariate and multivariate logistic regression were sequentially performed to find risk factors of mortality in COVID-19 patients. Correlation between CONUT and other variables were examined by Spearman correlation analysis. Receiver operating characteristic (ROC) curves were drawn and area under the ROC curves (AUC) were calculated to evaluate the predictive value of CONUT and prognostic model.

A P value < 0.05 was considered to be statistically significant. SPSS 22.0 Windows software (SPSS, Inc, Chicago, IL) and GraphPad Prism 5 were used for all statistical analysis and figure drawing.

Results

Baseline characteristics of survivors and non-survivors

A total of 442 patients diagnosed with COVID-19 was included in this study. And 79 patients had poor outcomes with mortality rate of 17.9% (Table 1.). The median age of non-survivors was 63, which was higher than that of survivors (63 vs 38, $p < 0.001$). And non-survivors had higher male ratio than survivors (57.0% vs 44.4%, $p = 0.042$). Compared with survivors, non-survivors had significantly higher incidence of

complicated underlying diseases including hypertension ($p < 0.001$), chronic lung disease ($p = 0.001$) and cardiovascular disease ($p = 0.005$). Hypertension was the most common comorbidity in the total cohort with incidence of 19.7%. Considering signs and symptoms on admission, we found that non-survivors were more likely to be manifested as fever ($p = 0.047$) and dyspnea ($p < 0.001$). In addition, the heart rate and respiratory rate were both higher in non-survivors than survivors (88 vs 83, $p = 0.01$; 22 vs 20, $p < 0.001$). Blood routine and blood biochemistry showed that non-survivors had higher level of white blood cell (WBC), neutrophil, total bilirubin, glutamic oxaloacetic transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP). However, the level of lymphocyte, platelet, albumin and cholesterol was significantly lower in non-survivors. Moreover, surviving patients had higher level of PNI (43.95 vs 36.95, $p < 0.001$) but lower CONUT score (3 vs 6, $p < 0.001$). Coagulation test indicated that the value of PT, INR, APTT, D-dimer was higher in group of non-survivors ($p < 0.001$). The NRS score of non-survivors was significantly higher than that of survivors (4 vs 0, $p < 0.001$). In this study, there were 160 severe patients and 151 critical patients which accounted for the majority of enrolled participants. The distribution of disease severity was statistically different between two groups ($p < 0.001$). Critical and severe type accounted for 48.1% and 46.8% of the total non-survivors, respectively. However, among survivors, common, severe and critical type had comparable proportions, accounting for 30.9%, 33.9% and 31.1% respectively. Complications including respiratory failure, AKI, metabolic acidosis, liver dysfunction and shock were more frequently observed in non-survivors than survivors ($p < 0.001$).

Table 1
Baseline characteristics of survivors and non-survivors in COVID-19 patients

	Total (N = 442)	Survivors (n = 363, 82.1%)	Non-survivors (n = 79, 17.9%)	p
Age (years)	58 (41–70)	38 (54–67)	63 (71–79)	< 0.001
Male	206 (46.6%)	161 (44.4%)	45 (57.0%)	0.042
Comorbidity				
Hypertension	87 (19.7%)	55 (15.2%)	32 (40.5%)	< 0.001
Diabetes mellitus	26 (5.9%)	19 (5.2%)	7 (8.9%)	0.238
Chronic lung disease	30 (6.8%)	17 (4.7%)	13 (16.5%)	0.001
Cardiovascular disease	14 (3.2%)	7 (1.9%)	7 (8.9%)	0.005
Chronic liver disease	19 (4.3%)	13 (3.6%)	6 (7.6%)	0.125
Malignancy	7 (1.6%)	4 (1.1%)	3 (3.8%)	0.112
Signs and symptoms				
Fever	345 (78.1%)	277 (76.3%)	68 (86.1%)	0.047
Cough	247 (55.9%)	200 (55.1%)	47 (59.5%)	0.474
Dyspnea	167 (37.8%)	117 (32.2%)	50 (63.3%)	< 0.001
Fatigue	149 (33.7%)	123 (33.9%)	26 (32.9%)	0.868
Diarrhea	39 (8.8%)	31 (8.5%)	8 (10.1%)	0.658
MAP (mmHg)	86.33 (93.33–97.75)	93.33 (86.67–97.33)	93.00 (84.33–101.67)	0.644
Heart rate (bps)	78 (84–93)	83 (77–92)	88 (78–104)	0.01
Respiratory rate (min ⁻¹)	18 (20–21)	20 (18–20)	22 (18–28)	< 0.001
Body temperature (°C)	36.5 (36.7–37)	36.7 (36.5–37)	36.7 (36.5–37)	0.692
Laboratory results				
WBC (× 10 ⁹ /L)	5.77 (4.31–7.94)	5.42 (4.11–7.24)	8.88 (6.51–12.46)	< 0.001
Neutrophil (× 10 ⁹ /L)	3.94 (2.63–6.35)	3.44 (2.48–5.09)	7.4 (4.97–11.27)	< 0.001

	Total (N = 442)	Survivors (n = 363, 82.1%)	Non-survivors (n = 79, 17.9%)	p
Lymphocyte ($\times 10^9/L$)	1.12 (0.77–1.54)	1.2 (0.9–1.6)	0.7 (0.4–0.92)	< 0.001
Monocyte ($\times 10^9/L$)	0.43 (0.3–0.59)	0.44 (0.31–0.59)	0.39 (0.26–0.63)	0.160
Platelet ($\times 10^9/L$)	212 (156–271)	220 (165–281.5)	172 (118–223)	< 0.001
Hemoglobin (g/L)	127 (115–138)	126 (115–137)	131 (117–140)	0.132
Albumin (g/L)	37.1 (33.4–40.2)	37.9 (34.6–41)	33.3 (31.2–35.8)	< 0.001
Globulin (g/L)	24.1 (21.7–27.8)	24 (21.7–27.6)	24.9 (21.9–29)	0.175
Cholesterol (mg/dL)	145.40 (127.61–166.76)	146.56 (129.54–171.69)	138.05 (121.81–155.45)	0.006
CONUT	4 (2–5)	3 (2–5)	6 (4–7)	< 0.001
Total bilirubin (umol/L)	10.7 (8.13–15.28)	10.15 (7.9–14.1)	14.55 (9.78–19.7)	< 0.001
ALT (U/L)	25 (16–39)	24 (16–39)	26 (19–45)	0.072
AST (U/L)	27 (20–41)	24 (19–36)	42 (30–63)	< 0.001
ALP (U/L)	61 (50–79)	60 (49–74)	73 (52–99)	0.004
LDH (U/L)	246 (190–313)	229 (186–288.75)	538 (367–706)	< 0.001
Serum creatinine (umol/L)	60 (50–74)	58 (49–71)	70 (53–87)	0.001
BUN (mmol/L)	4.72 (3.7–6.78)	4.38 (3.62–5.9)	7.80 (5.18–12.33)	< 0.001
Uric acid (uumol/L)	257 (199–336)	257 (208–333)	245 (165–366)	0.324
CRP (mg/L)	22.9 (5–70.8)	11.4 (5–50.6)	89.45 (51.7–167.35)	< 0.001
PCT (ng/L)	1.15 (0.12–4.40)	2.50 (0.11–4.40)	0.46 (0.17–3.39)	0.876
PT (s)	12 (11.4–12.7)	12 (11.3–12.6)	12.7 (12–13.8)	< 0.001

	Total (N = 442)	Survivors (n = 363, 82.1%)	Non-survivors (n = 79, 17.9%)	p
INR	0.97 (1.04–1.09)	1.03 (0.96–1.08)	1.09 (1.03–1.19)	< 0.001
APTT (s)	28.2 (25.9–30.6)	27.85 (25.73–30.18)	29.60 (27.30–32.13)	< 0.001
TT (s)	17.8 (17–18.7)	17.7 (17–18.6)	17.9 (16.8–19.55)	0.113
D-dimer (mg/L)	0.80 (0.38–2.86)	0.64 (0.32–1.82)	4.83 (0.96–17.35)	< 0.001
FIB (g/L)	4.1 (3.04–5.12)	4.09 (3.08–4.97)	4.44 (2.77–5.70)	0.177
AT-III (ug/L)	87.6 (79.6–96.33)	89 (82.1–97.5)	79.60 (70.03–88.48)	< 0.001
NRS 2002	1 (0–3)	0 (0–3)	4 (3–5)	< 0.001
Disease severity				< 0.001
Mild	15 (3.4%)	15 (4.1%)	0 (0%)	
Common	116 (26.2%)	112 (30.9%)	4 (5.1%)	
Severe	160 (36.2%)	123 (33.9%)	37 46 (46.8%)	
Critical	151 (34.2%)	113 (31.1%)	38 (48.1%)	
Complications				
Respiratory failure	169 (38.2%)	103 (28.4%)	66 (83.5%)	< 0.001
AKI	28 (6.3%)	11 (3.0%)	17 (21.5%)	< 0.001
Metabolic acidosis	94 (21.3%)	45 (12.4%)	49 (62.0%)	< 0.001
Liver dysfunction	161 (36.4%)	112 (30.9%)	49 (62.0%)	< 0.001
Shock	119 (26.9%)	40 (11.0%)	79 (100.0%)	< 0.001
Days from illness onset to admission time (days)	10 (7–13)	10 (7–13)	11 (7–13)	0.578
Length of hospital stay (days)	9 (5–13)	9 (5–14)	6 (3–11)	< 0.001
Course of disease (days)	19 (15–26)	20 (15–27)	18 (13–23)	0.020

Total (N = 442)	Survivors (n = 363, 82.1%)	Non-survivors (n = 79, 17.9%)	p
<p><i>COVID-19</i> Corona Virus Disease 2019; <i>MAP</i> mean arterial pressure; <i>WBC</i> white blood cell; <i>CONUT</i> controlling nutritional status; <i>ALT</i> aspartate aminotransferase; <i>AST</i> alanine aminotransferase; <i>ALP</i> alkaline phosphatase; <i>LDH</i> lactate dehydrogenase; <i>BUN</i> blood urea nitrogen; <i>CRP</i> C-reactive protein; <i>PCT</i> procalcitonin; <i>PT</i> prothrombin time; <i>INR</i> international normalized ratio; <i>APTT</i> activated partial thromboplastin time; <i>TT</i> thrombin time; <i>FIB</i> fibrinogen; <i>AT-III</i> antithrombin III; <i>NRS2002</i> Nutrition risk screening 2002; <i>AKI</i> acute kidney injury.</p>			

Univariate And Multivariate Analysis Of Risk Factor For Mortality

We included clinical and laboratory variables which were statistically significant in baseline comparison into logistic regression analysis (Table 2.). Nearly all included variables were still statistically significant in univariate logistic regression analysis. However, results of multivariate logistic regression analysis showed that only CONUT (OR 1.457, p = 0.002), LDH (OR 1.005, p < 0.001) and CRP (OR 1.009, p = 0.020) were independently associated with mortality after adjusting confounders.

Table 2

Univariate and multivariate logistic regression analysis of risk factors for in-hospital mortality in COVID-19 patients

	Univariate analysis			Multivariate analysis		
	OR	95CI%	P	OR	95CI%	p
Age	1.071	1.050–1.092	< 0.001			
Male	1.661	1.016–2.714	0.043			
Hypertension	3.813	2.237–6.497	< 0.001			
Chronic lung disease	4.009	1.859–8.646	< 0.001			
Cardiovascular disease	4.944	1.683–14.528	0.004			
Heart rate	1.023	1.007–1.039	0.005			
Respiratory rate	1.122	1.075–1.171	< 0.001			
WBC	1.294	1.199–1.397	< 0.001			
Neutrophil	1.354	1.252–1.465	< 0.001			
Lymphocyte	0.064	0.031–0.133	< 0.001			
Platelet	0.992	0.988–0.995	< 0.001			
Albumin	0.793	0.742–0.849	< 0.001			
Cholesterol	0.987	0.979–0.995	0.002			
CONUT	1.752	1.524–2.015	< 0.001	1.457	1.144–1.856	0.002
Total bilirubin	1.057	1.027–1.087	< 0.001	1.017	0.974–1.061	0.455
AST	1.021	1.012–1.029	< 0.001			
ALP	1.009	1.004–1.015	0.001			
LDH	1.008	1.006–1.011	< 0.001	1.005	1.002–1.007	< 0.001

	Univariate analysis			Multivariate analysis		
Serum creatinine	1.007	1.003–1.011	0.002			
BUN	1.133	1.079–1.189	< 0.001			
CRP	1.018	1.014–1.023	< 0.001	1.009	1.002–1.018	0.020
PT	1.645	1.298–2.085	< 0.001			
INR	1.245	0.806–1.922	0.323			
APTT	1.138	1.057–1.225	0.001			
D-dimer	1.039	1.020–1.058	< 0.001			
AT-III	0.943	0.922–0.965	< 0.001			
NRS-2002	1.601	1.417–1.810	< 0.001			
<i>WBC</i> white blood cell; <i>AST</i> alanine aminotransferase; <i>ALP</i> alkaline phosphatase; <i>LDH</i> lactate dehydrogenase; <i>BUN</i> blood urea nitrogen; <i>CRP</i> C-reactive protein; <i>PT</i> prothrombin time; <i>INR</i> international normalized ratio; <i>APTT</i> activated partial thromboplastin time; <i>AT-III</i> antithrombin III; <i>NRS2002</i> Nutrition risk screening 2002.						

Correlation Between CONUT And Other Variables

Spearman correlation analysis was performed to explore relationship between CONUT and other established prognostic factors (Table 3.). The correlation coefficient between CONUT and age, CRP, LDH, D-dimer was 0.423 ($p < 0.001$), 0.588 ($p < 0.001$), 0.459 ($p < 0.001$) and 0.470 ($p < 0.001$), respectively (Fig. 1.), which meant CONUT was moderately associated with these indicators.

Table 3
The correlation between CONUT and other significant variables

	r	p
Age	0.423	< 0.001
Sex	0.209	< 0.001
CRP	0.588	< 0.001
PCT	0.042	0.439
WBC	0.140	0.003
LDH	0.459	< 0.001
D-dimer	0.470	< 0.001
Severity	0.283	< 0.001

CRP C-reactive protein; *PCT* procalcitonin; *WBC* white blood cell; *LDH* lactate dehydrogenase.

Predictive Value Of NRS 2002, CONUT And Prognostic Model

Logistic regression analysis was conducted to construct prognostic model incorporating CONUT, LDH and CRP. We draw ROC curves and calculated corresponding AUC value of NRS, CONUT and the prognostic model (Fig. 2.). The AUC value of CONUT was 0.813, which was higher than 0.795 of NRS score though without statistical significance ($Z = 0.519, p > 0.05$). The AUC value of the prognostic model was 0.923, which was higher than that of CONUT, 0.813 ($Z = 3.521, p < 0.05$) (Table 4.).

Table 4
Predictive value of NRS2002, CONUT and prognostic model

	AUC	95%CI	Sensitivity	Specificity
NRS-2002	0.795	0.746–0.845	0.785	0.689
CONUT	0.813	0.767–0.860	0.747	0.741
Prognostic model	0.923	0.884–0.961	0.929	0.788

AUC area under the receiver operating characteristics curve; *CI* confidence interval
The prognostic model is consisted of CONUT, LDH and CRP.

Discussion

It has been reported that the mortality of hospitalized COVID-19 patients ranged from 4.3–28.3% [3, 20, 21]. And group of severe and critical patients had highest mortality rate up to 61.5% [22]. The mortality of included patients in our study was 17.9% which was comparable with previous studies. Increased age and comorbidities have been acknowledged as independent risk factors of mortality in COVID-19 patients [23, 24]. Our results showed that the incidence of complicated underlying diseases including hypertension, chronic lung disease and cardiovascular disease was higher in non-survivor group. In this study, the most common symptoms sequentially were fever, cough, dyspnea and fatigue, which was consistent with other studies [3]. Compared with survivors, non-survivors were more likely to suffer organ dysfunction such as respiratory failure, AKI and liver dysfunction. These serious complications could result in the progression to unfavorable outcome.

The CONUT score, composed of lymphocyte count, albumin and cholesterol level, was generally considered as a reflection of inflammation and immune status. The reduction of lymphocyte, albumin and cholesterol could lead to the increase of CONUT score, which was commonly associated with detrimental inflammatory status and unfavorable outcomes. The immune dysfunction and cytokine storm play an important role in the progression of COVID-19 patients [25, 26]. In addition, CONUT has been confirmed valuable in assessing nutritional status and hence associated with outcome in various patients [27–29]. Malnutrition is actually a potent predictor of mortality in some viral infection such as influenza A (H1N1) virus infection [30, 31]. Consequently, we designed this study to explore the predictive value of CONUT in COVID-19 patients. Our results showed that CONUT of non-survivors was significantly higher than that of survivors in COVID-19 patients. Moreover, the CONUT was a prognostic risk factor after adjusting cofounders by multivariate logistic regression analysis. Low count of lymphocyte, which is an important component of high CONUT score, is often observed in patients with viral infection including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [32]. Both recent researches of COVID-19 and this study confirmed the universal existence of lymphopenia in COVID-19 patients. Some studies have illustrated that lymphopenia is associated with disease severity and prognosis in COVID-19 patients [33]. Higher level of neutrophil-to-lymphocyte ratio (NLR), indicating lower lymphocyte, combined with older age could be utilized as an efficient tool to recognize potential severe to critical patients who requires intensive monitoring and supportive care [34]. The decrease of peripheral lymphocyte is mainly attributable to the decreased T cells, especially CD3⁺, CD4⁺, and CD8⁺T cells [35]. Decreased CD4⁺ and CD8⁺ T cells with excessive activation of themselves could cause the immunocompromise and disease progression in COVID-19 patients [25]. It has been testified the SARS-CoV could induce the reduction of T cell by antigen presenting cells (APC) dysfunction and excessive inflammation mediated apoptosis [36, 37]. However, it remains unclear that whether direct invasion of T cells or indirect pathway above mentioned is responsible for the lymphopenia in patients infected with SARS-CoV-2. It deserves further investigation to explore the underlying mechanism of lymphopenia in COVID-19 patients. Serum albumin level is another significant part of CONUT. Decreased albumin level, which correlates with higher CONUT score, is usually considered as a marker of malnutrition. In fact, hypoalbuminemia is a valuable marker of detrimental inflammation status and poor prognosis in various clinical settings including cancer, cardiovascular

diseases and pneumonia [38–41]. Recent studies also confirmed albumin level was an independent risk factor of outcome in COVID-19 patients [42]. Our study showed that albumin level was lower in non-survivors than survivors. Previous study demonstrated that synthesis of albumin by hepatocytes could be inhibited through the release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [43]. It is the cytokine storm, which means a great release of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), granulocyte colony stimulating factor (G-CSF), Interferon- γ (IFN- γ), inducible protein-10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1), lead to the severe immune damage to organs in COVID-19 patients [26, 44]. Therefore, the correlation between albumin and prognosis may be mediated by the liver dysfunction caused by cytokine storm. As an essential part of CONUT score, serum cholesterol level is another valuable indicator of malnutrition during the acute inflammatory response [45]. The relationship between hypocholesterolemia and mortality of critically ill surgical patients has been confirmed [46]. And constantly decreased cholesterol levels may indicate the aggravation of infection or progression of organ dysfunction in trauma patients [47]. Results of our study showed non-survivors had lower level of cholesterol than survivors. Actually, the metabolism of cholesterol could be disturbed by inflammatory cytokines such as IL-1 and TNF- α , which in turn lead to hypocholesterolemia [48]. Therefore, reduced cholesterol level, the same as reduced albumin level, reflects the severe extent of cytokine storm in COVID-19 patients.

Combined effects of lymphocyte, albumin and cholesterol, the CONUT score could indicate nutritional and immune status in COVID-19 patients more synthetically. Higher level of CONUT, which means more poor nutritional status, was associated with unfavorable outcome in COVID-19 patients. The cause of malnutrition in COVID-19 patients is multifactorial. Firstly, accompanied vomiting and diarrhea could decrease food intake and absorption efficiency [3]. Secondly, fever and respiratory distress could increase heat loss and mechanical work which means increased energy expenditure. Thirdly, prolonged bed rest and decreased physical activities lead to the reduction of muscle volume. It has been verified that low levels of micronutrients including vitamins A, B6, E, and Zn correlated with unfavorable outcomes in patients with viral infections [49]. Although no research has illustrated optimal nutritional management and effects of nutritional support in COVID-19 patients, suitable and diversified nutrition supplement including vitamin and microelement may be essential for COVID-19 patients to enhance immunity and promote recovery.

In the multivariate logistic regression analysis, only CONUT, CRP and LDH were still statistically significant. And we found CONUT was moderately associated with CRP and LDH. CRP, an indicator of inflammatory response, has been documented correlated with prognosis of influenza pneumonia, MERS, and community acquired pneumonia patients [50–52]. In this study, the obviously higher level of CRP in non-survivors demonstrated that excessive cytokine storm played an important role in the pathogenesis of COVID-19. In fact, CRP also takes part in the innate host defense by binding to pathogens and promoting their elimination by phagocytes [53]. Existed in all body cells, especially the myocardial and liver cells, LDH is beneficial to evaluate severity of tissue damage in early stage [54]. Increased LDH is also associated with immunosuppression by promoting the production of lactate which in turn strengthen the immunosuppressive cells and weaken the cytolytic cells [55]. Our prognostic model

comprised of CONUT, CRP, LDH may comprehensively reflect the nutritional, inflammatory and immune status, and is a valuable tool to predict outcome of COVID-19 patients.

Limitations

This study had several limitations. Firstly, this study was conducted in a single-center, so that the selection bias could not be avoided. The predictive value of our prognostic model should be verified in other medical centers. Secondly, some patients lacking the cholesterol level on admission were excluded from this study, which may also lead to the selective bias.

Conclusions

In summary, the CONUT score is an independent risk factor of mortality in patients with COVID-19. Incorporating CONUT into prognostic model could increase the predictive value. Evaluating CONUT early is beneficial for clinicians to estimate disease progression and allocate strained medical resources. As a marker of nutritional status, CONUT may be useful to guide clinicians to supply nutrients for patients so that enhancing their antiviral immunity and promoting their recovery.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of West China hospital of Sichuan University and Renmin Hospital of Wuhan University. All the patient data and used in the study was anonymized and de-identified.

Consent for publication

Not applicable.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

This research was supported by Project of Novel Coronavirus Pneumonia in West China Hospital. (Project number: HX2019nCoV027).

Authors' contributions

RRW and MH designed this study; MH carried out the study; ZXH and TZ communicated with patients' family and got their approval. DL and LB collected data; RRW performed statistical analyses and drafted the article; YK and JRY critically reviewed the paper; All authors read and approved the final version of this paper.

Acknowledgements

Thanks DL and LB for their contributions in collecting relevant data.

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Figures

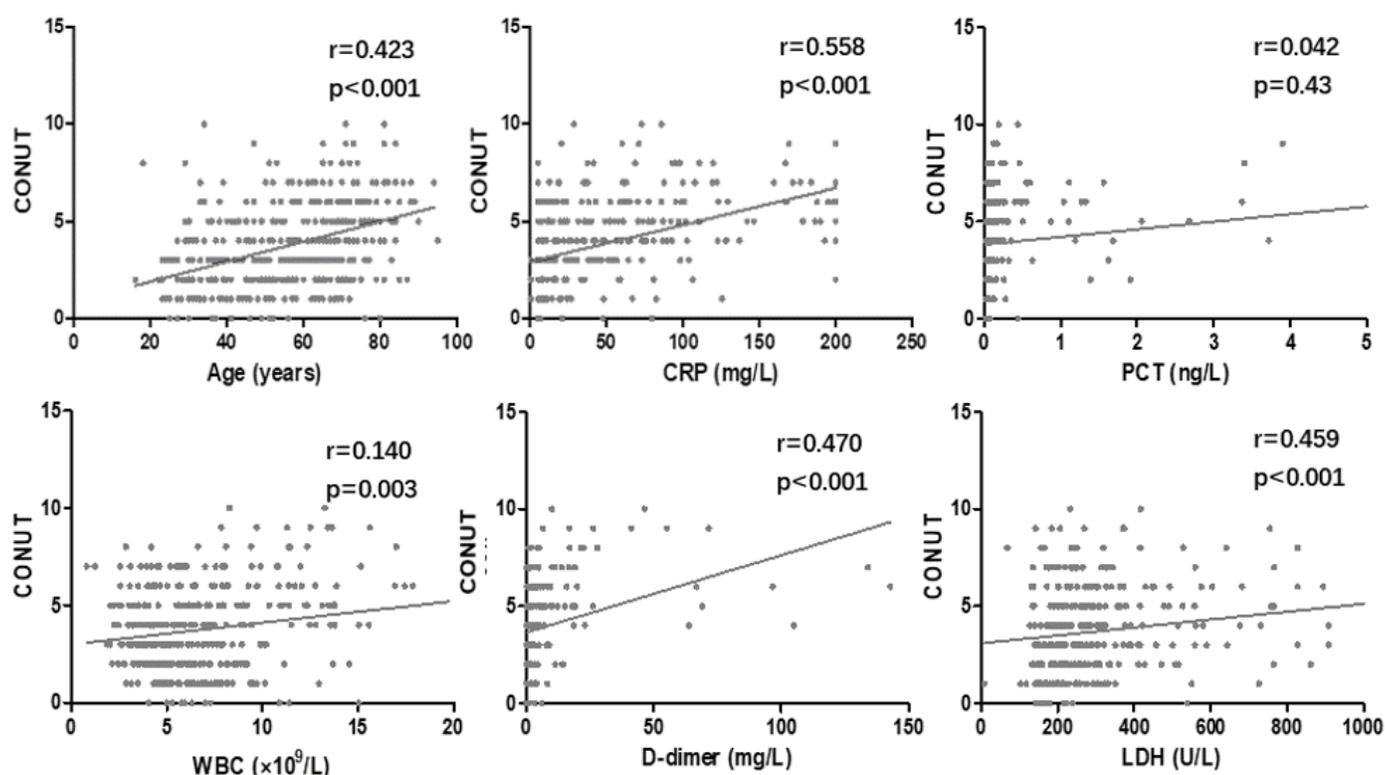


Figure 1

Spearman correlation analysis of CONUT with other significant variables.

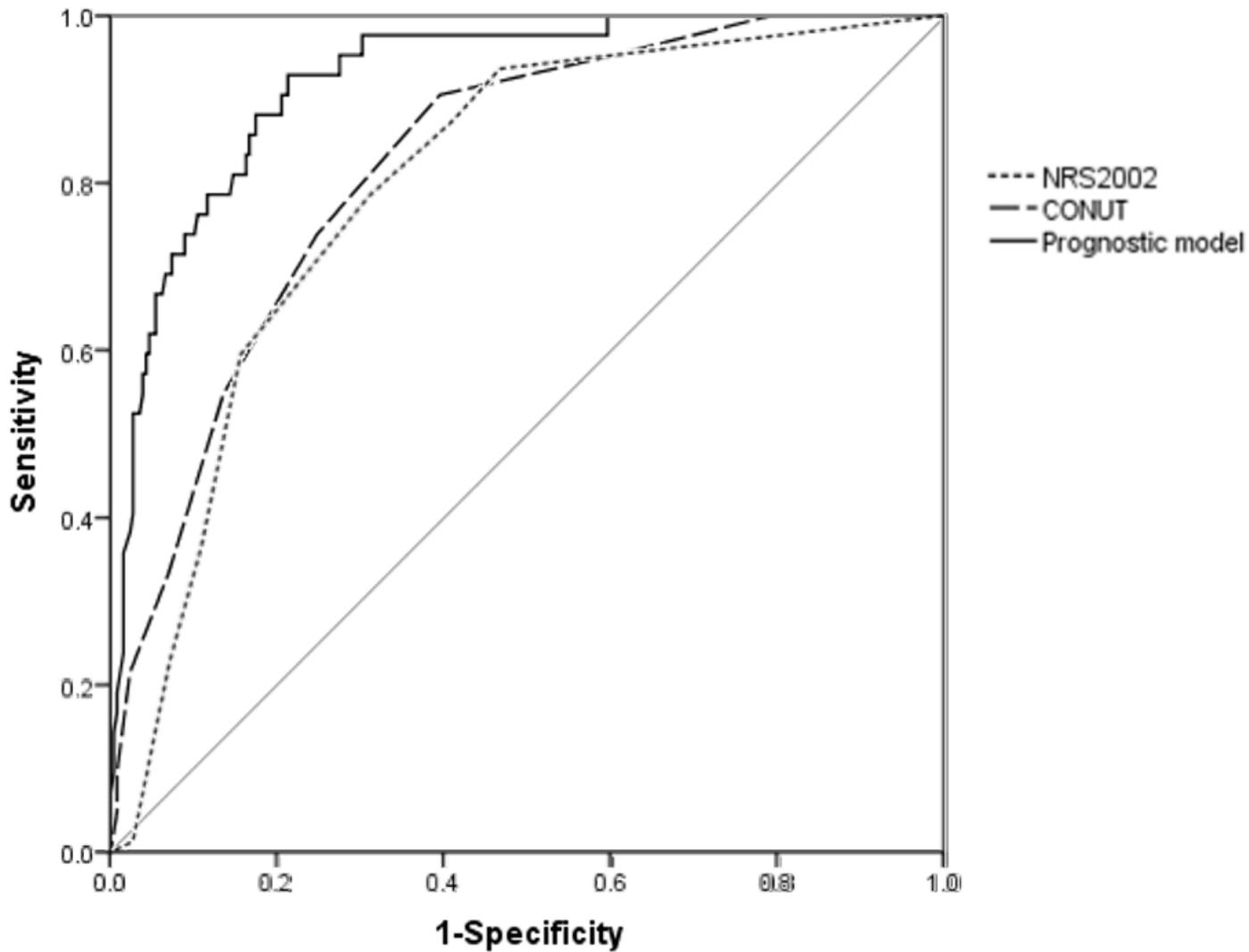


Figure 2

ROC curves of NRS2002, CONUT score and prognostic model for predicting mortality in COVID-19 patients. The prognostic model is consisted of CONUT, CRP and LDH. The AUC of NRS2002, CONUT and the prognostic model are 0.795 (0.746-0.845), 0.813 (0.767-0.860) and 0.923 (0.884-0.961), respectively.