





The effect of nutritional scores on mortality in COVID-19 patients

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SUMMARY

OBJECTIVES: While studies on the treatment for the coronavirus disease 2019 (COVID-19) pandemic continue all over the world, factors that increase the risk of severe disease have also been the subject of research. Malnutrition has been considered an independent risk factor. Therefore, we aimed to investigate the clinical effect of dietary habits and evaluate the prognostic value of the Controlling Nutritional Status score in the COVID-19 patients we followed up.

METHODS: A total of 2760 patients hospitalized for COVID-19 were examined. Patients were retrospectively screened from three different centers between September 1 and November 30, 2020. A total of 1488 (53.9%) patients who met the criteria were included in the study. Risk classifications were made according to the calculation methods of prognostic nutritional index and Controlling Nutritional Status scores and total scores. The primary outcome of the study was in-hospital mortality.

RESULTS: The groups with severe Controlling Nutritional Status and prognostic nutritional index scores had a significantly higher mortality rate than those with mild scores. In the multivariable regression analysis performed to determine in-hospital mortality, the parameters, such as age (OR 1.04; 95%CI 1.02–1.06, $p < 0.001$), admission oxygen saturation value (SaO₂) (OR 0.85; 95%CI 0.83–0.87, $p < 0.001$), and Controlling Nutritional Status score (OR 1.34; 95%CI 1.23–1.45, $p < 0.001$), were independent predictors. The patient groups with a low Controlling Nutritional Status score had a higher rate of discharge with recovery ($p < 0.001$).

CONCLUSIONS: Higher Controlling Nutritional Status scores may be effective in determining in-hospital mortality in patients with COVID-19. Nutrition scores can be used as a useful and effective parameter to determine prognosis in patients with COVID-19.

KEYWORDS: Malnutrition. Prognostic nutritional index. COVID-19. Nutrition status. Pandemic.

INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which emerged in Wuhan, China, in December 2019, was defined as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2020^{1,2}. The SARS-CoV-2 infection can present with a variety of clinical manifestations from asymptomatic to mild upper respiratory tract disease, but it can also cause respiratory failure due to viral pneumonia³. This has caused COVID-19 to become an important public health issue worldwide. While studies on the treatment for the coronavirus pandemic continue all over the world, factors that increase the risk of having a severe disease have been the subject of research. Since the nutritional status of the host plays a crucial role in the defense system against infection, individuals with malnutrition are more susceptible to a number of infectious diseases that can lead to harmful consequences^{4,5}. Malnutrition has been considered an independent risk factor⁶. Especially, the dietary habits of elderly patients with

chronic diseases are often poor, which makes them a risk group for a possible infection³. Therefore, nutritional assessment is important to determine the prognosis of patients. The Controlling Nutritional Status (CONUT) score is a new and comprehensive index calculated using lymphocyte count, total cholesterol, and serum albumin levels⁷. The prognostic nutritional index (PNI), calculated from serum albumin concentration and total lymphocyte count, was used to estimate the risk of complications after gastrointestinal surgery. The CONUT and PNI scores, a simple, cost-effective, and efficient screening tool to determine the nutritional status of inpatients, have been used for assessing the prognosis of many tumors⁸⁻¹⁰. Recently, the CONUT and PNI scores have been reported to be independently associated with poor prognosis in many cardiovascular diseases¹¹⁻¹³.

Therefore, whether there is a relationship between the CONUT and PNI scores with COVID-19 should be investigated. Many studies on COVID-19 have focused on the epidemiology of COVID-19 patients, their clinical characteristics, and secondary events that develop during the follow-up period. However, the number of

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studies to evaluate the nutritional status of these patients is limited. Therefore, we aimed to investigate the clinical effect of dietary habits and evaluate the prognostic value of the CONUT and PNI scores in COVID-19 patients we followed up.

METHODS

A total of 2760 patients hospitalized for COVID-19 were examined. Patients were retrospectively screened from three different centers between September 1 and November 30, 2020. All patients with positive PCR test results of combined oral and nasopharyngeal swab samples were included in the study. A total of 850 patients whose computed tomography (CT) and clinical findings were compatible with COVID-19, but whose two PCR tests performed on two consecutive days were negative, were excluded from the study. Moreover, hematological diseases, chronic liver diseases, and malign cancers were excluded. In addition, patients with missing albumin, lymphocyte, and total cholesterol data were excluded from the study. A total of 1488 patients who met these criteria were included in the study.

Venous blood samples were obtained from all patients on admission due to COVID-19. The CONUT and PNI scores were calculated after the diagnosis of COVID-19 from on-admission blood samples. Information on the drugs used by patients was obtained from the database of the Ministry of Health of the Republic of Turkey. Demographic characteristics, laboratory results, physical examination, and follow-up data of patients were obtained from the hospital database. The treatment and follow-up of patients diagnosed with COVID-19 infection were performed in line with the COVID-19 guideline recommendations of the Ministry of Health of the Republic of Turkey. The diagnosis of acute respiratory distress syndrome (ARDS) was based on the WHO interim guidelines. The primary endpoint of the study was in-hospital mortality. ARDS, intensive care follow-up, ventilator support, and discharge with recovery were the secondary endpoint. The data of this study were obtained from three different centers operating as a third-level health institution (university hospital, training, and research hospital) in Turkey. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. Our clinical study received ethics committee approval on June, 11, 2021 from the Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital/Turkey, with number 781.

Definitions

The CONUT score is calculated based on three parameters, namely, serum albumin level, total cholesterol level, and total lymphocyte count. After the CONUT score was calculated, those with a score of <2 in the normal group without malnutrition,

those with a score between 2 and 4 in the mild malnutrition group, those with a score between 5 and 8 in the moderate malnutrition group, and those with a score of ≥ 9 in the severe malnutrition group were included.

The PNI was calculated using the following formula; $10 \times$ serum albumin value (g/dL) + $0.005 \times$ total lymphocyte count in peripheral blood (per mm^3). After calculating the PNI score, those with a score of <35 in the severe malnutrition group, those with a score between 35 and 38 in the moderate malnutrition group, and those with a score of >38 in the normal group without malnutrition were included.

Nutrition scores are not routinely used in clinical practice in the institutions where the data were obtained.

Statistical analysis

The IBM SPSS version 24.0 software package was used for analyses. Normal distribution of data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were expressed as percentages (%) and were compared using the chi-square test or Fisher's exact test. Continuous variables with normal distribution were expressed as mean \pm standard deviation (SD) and were compared using the Student's t-test. Continuous variables with non-normal distribution were expressed as median (25–75th percentile) and were compared using the Mann-Whitney U test. Logarithmic transformation was used as blood parameters and showed abnormally wide distributions for CRP, D-dimer, and ferritin. The Kaplan-Meier analysis with log-rank test was performed according to their CONUT scores to determine a 60-day survival. Receiver operating characteristic (ROC) analysis was used to evaluate the sensitivity and specificity of CONUT and PNI scores in predicting mortality in COVID-19 patients. To determine confounding independent predictors of mortality in patients with COVID-19, univariate and multivariate logistic regression analyses were performed. The variables resulting from the univariate model with a p-value <0.05 were entered as covariates in the multivariate model. All values were given as odds ratio (OR) and 95% confidence interval (CI), both in univariate and multivariate logistic regression models. A p-value <0.05 was considered statistically significant for all tests.

RESULTS

A total of 1488 patients, 814 women (54.7%) and 674 men (45.3%), were included in the study. The patients were divided into four groups according to the CONUT score. Risk classifications were made according to the calculation methods and total scores of PNI and CONUT scores. Patients were compared in Table 1 in terms of primary outcome according

Table 1. Demographic, clinical, laboratory characteristics of groups, and predictive power of controlling nutritional status and prognostic nutritional index scores for mortality.

Parameters	All patients(n=1488)	Survival(n=1163)	Death(n=325)	p-value
Age, years	64.5±14.4	62.3±14.4	72.3±11.4	<0.001
In-hospital stay, days	8 (6-12)	8 (6-11)	11 (7.5-16)	<0.001
Gender, female, n %	814 (54.7)	661 (56.8)	153 (47.1)	0.002
Body mass index, kg/m ² , mean (±SD)	26.1±3.3	26.2±3.2	25.8±3.5	0.106
Hypertension, n (%)	885 (59.5)	666 (57.3)	219 (67.4)	0.001
Coronary artery disease, n (%)	322 (21.6)	229 (19.7)	93 (28.6)	0.001
Heart failure, n (%)	84 (5.6)	60 (5.2)	24 (7.4)	0.124
Diabetes mellitus, n (%)	511 (34.3)	387 (33.3)	124 (38.2)	0.102
Chronic renal failure, n (%)	83 (5.6)	57 (4.9)	26 (8)	0.031
Chronic obstructive pulmonary disease, n (%)	109 (7.3)	74 (6.4)	35 (10.8)	0.007
Cerebrovascular disease, n (%)	84 (5.6)	56 (4.8)	28 (8.6)	0.009
Atrial fibrillation, n (%)	64 (4.3)	35 (3)	29 (8.9)	<0.001
Unilateral lesions, n (%)	57 (3.8)	54 (4.6)	3 (0.9)	0.002
Bilateral lesions, n (%)	1395 (93.8)	1077 (92.6)	318 (97.8)	0.001
Acute respiratory distress syndrome, n (%)	259 (17.4)	44 (3.8)	215 (66.2)	<0.001
Nasal O ₂ , n (%)	1007 (67.7)	764 (65.7)	243 (74.8)	0.002
Mechanical ventilator, n (%)	282 (19)	27 (2.3)	255 (78.5)	<0.001
High flow nasal oxygen, n (%)	125 (8.4)	45 (3.9)	80 (24.6)	<0.001
Admission SaO ₂ (oxygen saturation), %	89 (84-92)	90 (87-93)	80 (70.5-85)	<0.001
Systolic blood pressure, mmHg	120 (110-130)	120 (110-125)	120 (110-130)	<0.001
Diastolic blood pressure, mmHg	70 (60-80)	70 (65-80)	70 (60-80)	0.001
White blood cell, 10 ³ /μL	7.1 (5.3-9.9)	6.9 (5.2-9.1)	8.7 (5.8-12.4)	<0.001
Hemoglobin, g/dL	13.1 (11.9-14.3)	13.3 (12-14.4)	12.8 (11.4-14)	0.001
Neutrophile, 10 ⁹ /L	5.3 (3.7-7.9)	5 (3.6-7.1)	7.3 (4.5-10.7)	<0.001
Lymphocyte, 10 ⁹ /L	1.10 (0.78-1.51)	1.2 (0.87-1.6)	0.79 (0.58-1.1)	<0.001
Platelet, 10 ³ /μL	209 (169-265)	212 (171-266)	203 (159-260)	0.118
Glomerular filtration rate, mL/min	72 (46-89)	76 (54-90)	49 (31-73)	<0.001
Albumin, g/dL	3.3 (2.9-3.7)	3.4 (3.1-3.7)	2.9 (2.6-3.2)	<0.001
Total cholesterol, mg/dL	183 (156-213)	186 (157-216)	176 (147-200)	0.002
Ferritin, ng/mL	384 (192-729.5)	343 (173-653)	530 (291-1096)	<0.001
C-reactive protein, mg/dL	76 (32.6-125)	65.9 (27.9-109.5)	115 (67.9-167)	<0.001
Procalcitonin, ng/mL	0.11 (0.06-0.27)	0.09 (0.05-0.18)	0.32 (0.12-1.2)	<0.001
D-dimer, ng/mL	274 (178-477)	249 (168-402)	418 (258-892)	<0.001
CONUT, n (%)				
Normal	263 (17.7)	254 (21.8)	9 (2.8)	<0.001
Mild	641 (43.1)	565 (48.6)	76 (23.6)	
Moderate	511 (34.3)	317 (27.3)	194 (59.7)	
Severe	73 (4.9)	27 (2.3)	46 (14.2)	
PNI, n (%)				
Normal	771 (51.8)	730 (62.8)	41 (12.6)	<0.001
Moderate	282 (19)	208 (17.9)	74 (22.8)	
Severe	435 (29.2)	225 (19.3)	210 (64.6)	

CONUT: controlling nutritional status; PNI: prognostic nutritional index.

Bold values indicate statistical significance at the p<0.05 level.

to clinical and demographic characteristics and laboratory parameters. The mortality rate was significantly higher in the groups with severe CONUT and PNI scores than that in the mild groups ($p < 0.001$, Table 1). As the CONUT score increased, follow-up with noninvasive mechanical ventilator, mechanical ventilator, high-flow nasal oxygen, progression to ARDS, mortality rate, and intensive care follow-up period were found to be significantly higher. In the patient groups with low CONUT scores, the rate of cure and discharge was higher ($p < 0.001$, Appendix 1).

In the univariable analysis, age, gender, chronic renal failure, hypertension, hemoglobin, neutrophil, C-reactive protein, D-dimer, ferritin, admission oxygen saturation, systolic blood pressure, and CONUT scores were found to be significantly more effective on in-hospital mortality. In multivariable regression analysis, advanced age, admission oxygen saturation, and CONUT scores were independent predictors of in-hospital mortality (Table 2).

In ROC analysis, the CONUT score predicted mortality with 75% sensitivity and 91% specificity. The area under the ROC curve was 0.786 (95%CI 0.758–0.814, $p < 0.001$). The PNI score predicted mortality with 64% sensitivity and 97% specificity. The area under the ROC curve was 0.806 (95%CI 0.779–0.833, $p < 0.001$).

In the Kaplan-Meier analysis, as the CONUT score increased, the in-hospital follow-up time and mortality increased. At the end of the 60-day follow-up, the number of patients in the patient group with a normal CONUT score increased from 263 to 254, from 641 to 565 in the mild group, and from 511 to 317 in the middle group; in the severe patient group, the number of patients decreased from 73–27 (Figure 1).

In the classification made according to the CONUT score, the effect of the groups on mortality was examined. Mortality rate was significantly higher in groups with high CONUT scores than in groups with low CONUT scores ($p < 0.001$, Figure 1).

Table 2. Univariable and multivariable regression analysis for determine predictor of in-hospital mortality: Effect of controlling nutritional status score on clinical prognosis in patients with COVID-19.

Parameters	Univariable analysis		Multivariable analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.06 (1.04–1.07)	<0.001	1.04 (1.02–1.06)	<0.001
Gender, male	0.67 (0.52–0.86)	0.002	0.72 (0.49–1.04)	0.084
Body mass index	0.96 (0.93–1.00)	0.107	*	
Heart failure	1.4 (0.89–2.39)	0.126	*	
Cerebrovascular disease	0.53 (0.33–0.86)	0.010	1.04 (0.53–2.03)	0.904
Chronic renal failure	0.59 (0.36–0.95)	0.033	0.57 (0.29–1.12)	0.105
Hypertension	1.54 (1.19–1.99)	0.001	1.09 (0.73–1.61)	0.658
Chronic obstructive pulmonary disease	0.56 (0.36–0.85)	0.008	1.30 (0.71–2.36)	0.384
Diabetes mellitus	0.80 (0.62–1.04)	0.102	*	
Coronary artery disease	0.61 (0.46–0.81)	0.001	0.90 (0.60–1.35)	0.620
Hemoglobin	0.88 (0.83–0.94)	<0.001	0.96 (0.87–1.06)	0.446
Neutrophil	1.12 (1.09–1.16)	<0.001	1.01 (0.97–1.05)	0.418
Procalcitonin	1.02 (1.00–1.03)	0.007	0.99 (0.98–1.01)	0.677
C-reactive protein	4.48 (3.18–6.33)	<0.001	0.91 (0.58–1.43)	0.699
D-dimer	4.14 (3.09–5.56)	<0.001	1.04 (0.68–1.59)	0.833
Ferritin	3.32 (2.42–4.55)	<0.001	1.65 (1.03–2.64)	0.034
Admission SaO ₂	0.82 (0.80–0.84)	<0.001	0.85 (0.83–0.87)	<0.001
Systolic blood pressure	1.01 (1.005–1.021)	<0.001	1.00 (0.98–1.01)	0.959
CONUT	1.58 (1.49–1.68)	<0.001	1.34 (1.23–1.45)	<0.001

CONUT: controlling nutritional status.

Bold values indicate statistical significance at the $p < 0.05$ level.

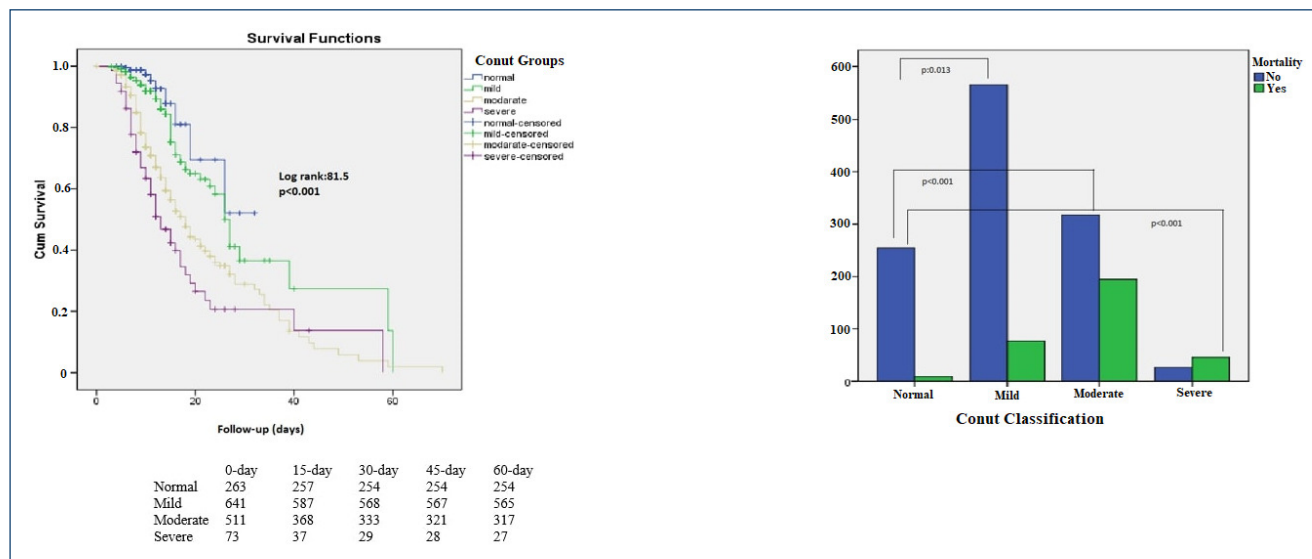


Figure 1. Correlation between controlling nutritional status score and 60-day survival by Kaplan-Meier analysis and comparison of mortality between controlling nutritional status groups.

DISCUSSION

Undernourished patients with COVID-19 infection had weaker immune functions, especially higher inflammatory responses. Nutritional status can influence viral genome mutations from a mildly pathogenic virus to a highly virulent virus and its spread to hosts⁵. Inflammation and malnutrition always exist concomitantly, as malnutrition can enhance the susceptibility to infections; meanwhile, infections further promote malnutrition via increased demand for nutrients and decreased appetite. Therefore, a thorough assessment of the nutritional status of patients helps clinicians determine the prognosis of the disease and treatment strategy. Virus invasion is able to result in the changes of white blood cells in peripheral blood, induce a cytokine storm, and thereby generate a series of immune response¹⁴. White blood cell and neutrophil counts were related to cytokine storms caused by viral invasion. 2019-nCoV infection can cause an exuberant inflammatory response, and uncontrolled pulmonary inflammation may be the major cause of fatality in COVID-19¹⁵. COVID-19 enters the cell via the ACE2 receptor. However, the virus may enter the bloodstream and accumulate in organs such as the gastrointestinal tract, heart, and kidneys, causing further damage. Serum protein is an important factor of the three standards of CONUT and is also a reliable systematic index of inflammation¹⁶. Pro-inflammatory cytokines, such as IL-6 and TNF- α , and CRP can also decrease the concentration of serum albumin and regulate albumin synthesis by liver cells¹⁷. Albumin is a good serum protein that determines the nutritional status of the patient. It makes up the majority of serum total protein and is mainly responsible for serum

osmotic pressure. In addition to its oncotic properties, albumin also has antioxidant and anti-inflammatory properties in scavenging reactive oxygen radicals and limiting their production. Lymphocytes are an important part of the immune system, and the prognostic role of lymphocyte count has been investigated in many studies in cardiovascular diseases. As these three indicators can comprehensively assess the general condition of patients, we used the CONUT score as an indicator to assess the nutritional status of patients. As expected in the beginning of the study, the groups with moderate and severe CONUT scores had significantly higher values of length of intensive care stay, progression to ARDS, mechanical ventilation support, and mortality rate. Therefore, malnutrition may cause an increased incidence of death in COVID-19 patients. Wei et al. showed that the CONUT score has a prognostic effect in patients with COVID-19 in a previous single-center study. They found that malnutrition was associated with a poor prognosis. This result supported the results of our study¹⁸.

Inflammation and malnutrition always coexist because malnutrition can increase susceptibility to infections. In the meantime, infections further increase malnutrition through increased demand for nutrients and decreased appetite¹⁹. A study by Eckart et al. on 2465 patients showed that a high serum CRP concentration was associated with low albumin levels, suggesting increased inflammatory parameters²⁰. Moreover, in their study on 416 patients with COVID-19, Shi et al. reported that 82 (19.7%) of them had a cardiac injury, with a higher in-hospital mortality rate compared to those without cardiac injury (51.2 vs. 4.5%)²¹. They stated that cardiac injury was

common among COVID-19 patients and was associated with a higher risk of mortality²¹.

While defense system cells play a central role in the effective host response against various pathogens, deficiency of immune cells disrupts immune homeostasis, causing pathological conditions. Recently, Qin et al. reported an association between the pathological process of COVID-19 disease and the immune system²². Patients with weaker immune functions were more likely to be infected with COVID-19³. Since there is a strong relationship between nutrition and immunity, malnutrition may result in weakened immune functions⁵. In clinical practice, the serum albumin level and lymphocyte count can be combined and used for PNI. The PNI was originally designed to assess immune nutritional status. This risk index has been widely used to assess surgical risk, particularly in patients with cancer, malnutrition, and systemic inflammation, and in gastrointestinal operations. Many studies have reported that a lower PNI score is associated with higher mortality in patients with cardiovascular diseases²³. A low PNI level may reflect the patient's malnutrition status, resulting in a deterioration in intravascular osmotic pressure, which is mainly generated by albumin. In addition, low PNI levels may indicate a decrease in the body's immune response to acute illness, manifested by disruption of intravascular osmotic pressure, when a systemic infection occurs. For these two reasons, mortality may be higher in patients with COVID-19 infection with a low PNI score. In our study, we found higher in-hospital mortality in patients with low PNI scores.

Study limitations

It was a retrospective study with a relatively small sample size. CONUT and PNI scores were not evaluated after hospital discharge. Therefore, the effect of changes in CONUT and PNI scores on clinical outcomes during the post-discharge follow-up

period could not be evaluated. Malnutrition was assessed using only the CONUT and PNI scores. Other nutritional indicators such as Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), and Geriatric Nutritional Risk Index (GNRI) were not used. In addition, the CONUT and PNI scores may be affected by hormonal changes such as serum catecholamine and cortisol, but we could not measure these hormone levels in our study. In addition, the CONUT and PNI scores may have yielded subjective results due to drugs or the presence of some undetected conditions.

CONCLUSIONS

Factors such as CONUT score, advanced age, and low admission oxygen saturation can be used as useful and effective parameters to predict the prognosis of COVID-19 patients. In particular, the CONUT score can help physicians pre-clarify patients with a poor prognosis and offer individualized treatment to improve their survival.

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AUTHORS' CONTRIBUTION

AA: Conceptualization, data curation, formal analysis, writing – original draft, and writing – review & editing. **TG:** Conceptualization, data curation, formal analysis, writing – original draft, and writing – review & editing. **MD:** Formal analysis and writing – original draft. **MÖ:** Conceptualization, data curation, and writing – original draft.

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Appendix 1. Effect of controlling nutritional status score on clinical prognosis in patients with COVID-19.

Clinical Prognosis	CONUT GROUPS					p-value
	Normal (n=263)	Mild (n=641)	Moderate (n=511)	Severe (n=73)	Total (n=1488)	
Discharge with recovery	250 (95)	546 (85.2)	338 (66.1)	31 (42.5)	1165 (78.3)	<0.001
Non-Invasive Mechanical Ventilator	16 (6)	76 (11.9)	140(27.4)	28 (38.4)	260 (17.5)	<0.001
Mechanical Ventilator	12 (4.5)	82 (12.8)	154(30.1)	34 (46.6)	282 (19)	<0.001
High Flow Nasal Oxygen	5 (1.9)	45 (7)	58(11.4)	17 (23.3)	125 (8.4)	<0.001
Acute Respiratory Distress Syndrome	12 (4.5)	75 (11.7)	148(29)	24 (32.9)	259 (17.4)	<0.001
Intensive Care Follow-Up	24 (9.1)	136 (21.2)	236(46.2)	52 (71.2)	448 (30.1)	<0.001
Mortality	9 (3.4)	76 (11.9)	194 (38)	46 (63)	325 (21.8)	<0.001

