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Original article

Influence of nutritional status on clinical outcomes among hospitalized patients with COVID-19

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S U M M A R Y

Background and aims: Several factors that worsen the prognosis of the new coronavirus SARS-CoV-2 have been identified, such as obesity or diabetes. However, despite that nutrition may change in a lockdown situation, little is known about the influence of malnutrition among subjects hospitalized due to COVID-19. Our study aimed to assess whether the presence of malnutrition among patients admitted due to COVID-19 had any impact on clinical outcomes compared with patients with the same condition but well nourished.
Methods: 75 patients admitted to hospital due to COVID-19 were analyzed cross-sectionally. Subjective Global Assessment (SGA) was completed by phone interview. Clinical parameters included were extracted from the electronic medical record.
Results: According to the SGA, 27 admitted due to a COVID-19 infection had malnutrition. Patients not well nourished were older than patients with a SGA grade A (65 ± 14.1 vs 49 ± 15.1 years; $p < 0.0001$). Length of hospital stay among poorly nourished patients was significantly higher (18.4 ± 15.6 vs 8.5 ± 7.7 days; $p = 0.001$). Mortality rates and admission to ICU were greater among subjects with any degree of malnutrition compared with well-nourished patients (7.4% vs 0%; $p = 0.05$ and 44.4% vs 6.3%; $p < 0.0001$). CRP (120.9 ± 106.2 vs 60.8 ± 62.9 mg/l; $p = 0.03$), D-dimer (1516.9 ± 1466.9 vs 461.1 ± 353.7 ng/mL; $p < 0.0001$) and ferritin (847.8 ± 741.1 vs 617.8 ± 598.7mcg/l; $p = 0.03$) were higher in the group with malnutrition. Haemoglobin (11.6 ± 2.1 vs 13.6 ± 1.5 g/dl; $p < 0.0001$) and albumin 3.2 ± 0.7 vs 4.1 ± 0.5 g/dl; $p < 0.0001$) were lower in patients with any degree of malnutrition.
Conclusions: The presence of a poor nutritional status is related to a longer stay in hospital, a greater admission in the ICU and a higher mortality.

1. Introduction

COVID-19 is a disease caused by the coronavirus SARS-CoV-2 that has reached a pandemic status. In fact, by October 2020, the WHO has reported 44.351.506 confirmed cases of COVID-19, including 1.171.255 deaths [1]. Spain has been one of the countries more affected by this infectious disease, with more than one million confirmed cases and up to 35.000 deceased people [1–4].

Several factors that worsen the prognosis of this infection have been identified, such as age, the presence of comorbidities (cardiovascular disease, hypertension, diabetes, obesity and chronic obstructive pulmonary disease) and also nutritional status [5–7]. Moreover, the mortality rate of COVID-19 varies significantly not only by country or race, but for socioeconomic status [8]. Actually, a poor socioeconomic status and/or a weak immunity appear to increase vulnerability to this disease [9,10]. In fact, a proper nutritional status is mandatory for the maintenance of an adequate immune response against infections [11].

Malnutrition among hospitalized patients is very frequent. In fact, several studies have demonstrated that up to 60% of older patients in acute care settings are malnourished [12], and these prevalence rates are even greater when the patients have

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associated comorbidities [13,14]. A poor nutritional status in this setting adversely affects clinical outcomes, such as complications, length of stay and mortality [15]. Actually, underweight adults with other respiratory viral diseases, such as influenza, para influenza or rhinovirus, exhibited greater rates of hospitalization compared to their normal-weight counterparts [12].

On the other hand, in this pandemic situation, there have been numerous factors that could make a proper nutrition difficult. The lockdown, especially among elderly or frailty people, make difficult the access to fresh products, such as vegetables or fruits, and they are changed to non-perishable items. Also, many people have received fewer incomes during this period, which may turn to cheaper food items of lower nutritional value [16].

Therefore, nutritional status should be evaluated in all infected patients with COVID-19 after hospital admission. However, not only the isolation of these patients, but also the shortage of professional staff to cope the sudden and massive patient demands that makes more difficult a proper nutritional evaluation.

Even though this complicated setting, it is imperative that nutritional screening is not lost, using adequate validated tools [17,18]. Actually, a group has proposed an empirical early nutritional supplementation protocol to implement in all hospitalized patients present at admission [19]. Their purpose is to identify and treat promptly nutritional deficiencies, as malnutrition could be a modifiable risk factor of poor prognosis among these patients with a SARS-CoV-2 infection [19].

Up to date, there is little evidence about the impact of nutritional status on COVID-19 outcomes. Our study aimed to assess whether the presence of malnutrition among patients admitted due to a SARS-CoV-2 infection had any impact on clinical outcomes compared with patients with the same condition but well nourished.

2. Material and methods

2.1. Subjects

This cross-sectional study was performed in 75 patients admitted to the Internal Medicine Department of a tertiary hospital due to an infection caused by SARS-CoV-2 from April until June 2020. All patients were confirmed with COVID-19 by a PCR. Ineligibility criteria were as follows [1]: Patients who were unable to respond questions by phone autonomously [2]; patients with a previous diagnose of moderate to severe dementia [3]; patients who did not consent to participate in the study. This study was conducted according to the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee of the hospital. Informed consent was obtained from all subjects prior to study participation.

2.2. Clinical characteristics, laboratory values and anthropometric measures

Clinical parameters included were extracted from the electronic medical record. They included demographic characteristics, comorbidities; symptoms and treatment related to SARS-CoV-2 infection. Blood tests drawn the 24 h after admission were also extracted from the electronic system. Blood tests included blood count, coagulation, inflammatory parameters, glycemic values, lipid and renal parameters, thyroid and hepatic profiles. Height and pre-admission weight were self-reported by the patient. Body mass index (BMI) was calculated as weight divided by height squared.

3. Nutritional assessment

Questionnaire assessments were completed by a phone interview performed by a trained nutritionist. The Subjective Global Assessment (SGA) is often considered a gold standard in numerous hospital malnutrition studies. It was developed in 1987 by Destky et al. and since then it has been widely studied and validated in different types of patients, including inpatients [20]. It is based on a short medical history and a physical examination. The clinical history includes data regarding weight changes in the last 6 months, changes in intake, gastrointestinal symptoms that persist for more than 2 weeks and changes in functional capacity. Physical exam includes: loss of subcutaneous fat, muscle wear, ankle or sacral edema, and ascites. Due to the isolation situation of these patients, physical exam was not done by the nutritionist. However, the presence of edema was reported by the nurses/physicians and recorded in the electronic medical history. Patients are classified into 3 categories according to the predominance of symptoms: well nourished (A), suspicion of malnutrition or moderate malnutrition (B) (weight loss of 5–10%, reduced intake in recent weeks and loss of subcutaneous tissue) and severe malnutrition (C) (weight loss >10%, severe loss of muscle mass and subcutaneous tissue or presence of edema). To perform the statistical analysis, patients were classified into well nourished (SGA grade A) and not well nourished (SGA grade B and C) [21,22].

On the other hand, the evaluation of a proper adherence to a Mediterranean diet was performed by using the Spanish version of the “adherence to a Mediterranean diet questionnaire” [23].

3.1. Statistical analysis

Data are presented as means and standard deviations, medians and interquartile ranges, or numbers and percentages. Intergroup comparisons employed the independent-samples t-test or the Mann–Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. ROC curves of quantitative risk factors associated to Hospitalization in ICU were performed. The optimal cutoff values were determined by the maximum Youden index (J), defined as sensitivity + specificity −1. Binary logistic regression models were used to identify risk factors associated to UCI hospitalization. Analysis was performed using the stepwise backward method. A two-tailed p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

4. Results

According to the SGA, 27 admitted due to a SARS-CoV-2 infection had malnutrition, in other words, 36% of the sample had a B or C SGA. When taking into account the severity of malnutrition, 63% (17/27) had a SGA grade B, whereas the remaining 33.3% (9/27) has a SGA grade C.

Patients not well nourished were older than patients with a SGA grade A (65 ± 14.1 vs 49 ± 15.1 years; $p < 0.0001$). No differences between the two groups regarding gender, tobacco use or regular alcohol consumption were seen. Both groups were comparable when taking into account weight or BMI on admission (75.9 ± 17.5 vs 80.9 ± 18.6 kg and 29.5 ± 7.1 vs 28.5 ± 5.5 kg/m^2; $p = 0.4$ and $p = 0.8$, respectively).

Length of hospital stay among poorly nourished patients was significantly higher compared to those without malnutrition (18.4 ± 15.6 vs 8.5 ± 7.7 days; $p = 0.001$). Besides, compared with well-nourished patients, more patients with some degree of malnutrition were admitted to ICU (44.4% vs 6.3%; $p < 0.0001$). Also, ICU stay was greater among poorly nourished patients

Table 1
Comparison of sociodemographic features, toxic habits and anthropometric variables among subjects hospitalized due to COVID-19 with criteria for malnutrition and individuals without it.

	Criteria for malnutrition (n = 27)	Well-nourished COVID-19 patients (n = 48)	*p*
Gender (male/female) (%)	54.5/45.5	46.7/53.3	0.5
Age (years)	65 ± 14.1	49 ± 15.1	<0.0001
Tobacco use (%)	36.4	15.9	0.1
Regular alcohol consumption (%)	59.1	51.1	0.5
Weight on admission (kg)	75.9 ± 17.5	80.9 ± 18.6	0.4
BMI on admission (kg/m^2)	28.5 ± 5.5	29.5 ± 7.1	0.3
Length of hospital stay (days)	18.4 ± 15.6	8.5 ± 7.7	0.001
ICU admission (%)	44.4	6.3	<0.0001
ICU stay (days)	6.4 ± 6	1.2 ± 1	<0.0001
Mortality (%)	7.4	0	0.05
HTA (%)	54.5	48.9	0.7
DM2 (%)	40.7	18.8	0.06
Dyslipidaemia (%)	45.5	33.3	0.3
Obesity (%)	36.4	40	0.8
Coronary disease (%)	13.6	8.9	0.6
Pulmonary obstructive disease (%)	36.4	24.4	0.3

Data are mean ± SD or %. BMI, body mass index. ICU, intensive care unit.

compared with patients without malnutrition (6.4 ± 6 vs 1.2 ± 1 days; $p < 0.0001$). Mortality rates were greater among subjects with any degree of malnutrition compared with well-nourished patients (7.4% vs 0%; $p = 0.05$). The causes of death in these patients were severe pneumonia and respiratory sepsis.

All these data are shown in Table 1.

Regarding symptoms related to COVID-19, patients with malnutrition referred more hyporexia compared with subjects with a good nutritional status (97.6% vs 80%; $p = 0.04$). No differences between the two groups were seen regarding any other symptoms of COVID-19 infection.

Furthermore, the proportion of patients with malnutrition who reported more than 150 min of exercise per week was lower than well-nourished subjects (12.5% vs 51.1%; $p = 0.002$). However, both groups were comparable when taking into account the proportion of subjects with a regular adherence to a Mediterranean diet (59.1% vs 80%; $p = 0.1$).

These data are shown in Table 2.

As shown in Table 3, some biochemical parameters were significantly different between patients with or without malnutrition. CRP (120.9 ± 106.2 vs 60.8 ± 62.9 mg/l; $p = 0.03$), D-dimer (1516.9 ± 1466.9 vs 461.1 ± 353.7 ng/mL; $p < 0.0001$), ferritin levels (847.8 ± 741.1 vs 617.8 ± 598.7mcg/l; $p = 0.03$) and procalcitonin (1.5 ± 1.1 vs 0.8 ± 0.2 ng/mL; $p = 0.005$) were significantly higher in the group with malnutrition compared with the well-nourished group. Also, fasting plasma glucose levels were higher among subjects with malnutrition (148.3 ± 68.5 vs 116.3 ± 49.7 mg/dl; $p = 0.02$). Beyond that, the level of haemoglobin (11.6 ± 2.1 vs 13.6 ± 1.5 g/dl; $p < 0.0001$) was significantly lower in patients with any degree of malnutrition compared with subjects with a good nutritional status. These data showed that COVID-19 patients with malnutrition are at higher risk of excessive uncontrolled inflammation responses and hypercoagulable state, which may contribute to a poorer prognosis of COVID-19. Besides, nutritional values were different between the two groups. Subjects with malnutrition had both albumin (3.2 ± 0.7 vs 4.1 ± 0.5 g/dl; $p < 0.0001$) and calcium (8.2 ± 0.7 vs 8.9 ± 0.7; $p = 0.001$ mg/dl) levels lower than well-nourished patients.

No differences between the two groups were seen regarding either comorbidities or any other symptoms of COVID-19. Both groups were comparable when taking into account the treatment prescribed against SARS-CoV-2 infection.

ROC curves and optimal cut off values were calculated for quantitative risk factors associated to ICU hospitalization (Fig. 1). As can be seen, D-dimer greater than 440 ng/mL had a sensitivity (Se) and a specificity (Sp) of 73.3% and 75.5%, respectively. The overall accuracy (A) was 75% for D-dimer > 440 ng/mL and it was lower than those for age higher than 65 years (A: 78.7%; Se:

Table 2
Comparison of symptoms related to COVID-19, adherence to a Mediterranean diet, regular diet and percentage of patients with corticosteroid treatment among subjects hospitalized due to COVID-19 with criteria for malnutrition and individuals without it.

	Criteria for malnutrition (n = 27)	Well-nourished COVID-19 patients (n = 48)	*p*
Fever (%)	77.3	75.6	0.8
Asthenia (%)	100	91.1	0.1
Dry cough (%)	63.6	66.7	0.8
Dyspnea (%)	86.4	88.9	0.8
Hyporexia (%)	97.6	80	0.04
Nausea (%)	63.6	48.9	0.3
Vomiting (%)	27.3	24.4	0.8
Dysgeusia (%)	59.1	51.1	0.5
Anosmia (%)	33.3	18.2	0.2
Diarrhea (%)	91.1	77.3	0.2
Less than 150 min of exercise per week (%)	12.5	51.1	0.002
Adherence to a Mediterranean diet (%)	59.1	80	0.1
Corticosteroid treatment (%)	33.3	14.6	0.08

Data are mean ± SD or %.

Table 3
Comparison of biochemical parameters among subjects hospitalized due to COVID-19 with criteria for malnutrition and well-nourished patients.

	Criteria for malnutrition (n = 27)	Well-nourished COVID-19 patients (n = 48)	*p*
Hemoglobin (g/dl)	11.6 ± 2.1	13.6 ± 1.5	<0.0001
Lymphocyte count (x10^9)	3.1 ± 2.9	2.3 ± 3.5	0.3
Platelet count (x10^9)	291.3 ± 107	264.2 ± 117.7	0.4
Prothrombin time (%)	70.9 ± 15.1	76.6 ± 11.1	0.08
Fibrinogen (g/L)	701 ± 171.1	607 ± 146.1	0.07
D dimer (ng/ml)	1516.9 ± 1466.9	461.1 ± 353.7	<0.0001
FPG (mg/dl)	148.3 ± 68.5	116.3 ± 49.7	0.02
Creatinine (mg/dl)	1.5 ± 1.2	1 ± 0.9	0.2
Calcium (mg/dl)	8.2 ± 0.7	8.9 ± 0.7	0.001
Albumin (g/l)	3.2 ± 0.7	4.1 ± 0.5	0.0001
Ferritin (mcg/l)	847.8 ± 741.1	617.8 ± 598.7	0.03
CRP (mg/l)	127.8 ± 115.6	59.2 ± 63.8	0.04
Procalcitonin (ng(ml)	1.5 ± 1.1	0.8 ± 0.2	0.005
GOT (U/l)	27.8 ± 18.5	29.5 ± 21.9	0.9
GPT (U/l)	30.9 ± 35.1	35.1 ± 33.9	0.4
GGT (U/l)	127.2 ± 60.1	58.2 ± 49.3	0.1
FA (U/l)	93 ± 63.9	77.1 ± 34.1	0.4

Data are mean ± SD or %. FPG, fasting plasma glucose. CRP, C-reactive protein.

73.3%; Sp: 80.0%) and for malnutrition (A: 76.0%; Se: 80%; Sp: 75%).

Univariate and multivariate logistic regression analysis were used to investigate factors associated to the ICU hospitalization. All previously listed factors ($p < 0.1$ in Tables 1–3) were included initially in the model before stepwise and backward elimination. Crude and adjusted Odds Ratio (adjusted by age) are shown in the table of Fig. 2. As can be seen in this table, hypoalbuminemia and malnutrition were the factors with the highest significant age-adjusted O.R. associated to ICU hospitalization. The best model of factors associated to ICU hospitalization was the one that included age >65 years and hypoalbuminemia. The AUC (95%CI) of this model was 0.906 (0.834–0.977) ($p < 0.001$). Nevertheless, another good model was obtained considering age older than 65 years, D-dimer levels greater than 440 ng/mL, and malnutrition as the risk factors associated to ICU hospitalization (Fig. 2b). The AUC (95%CI) was 0.897 (0.815–0.979) for this last model that include hospitalization (Fig. 2c, $p < 0.001$).

5. Discussion

Our study found that the prevalence of malnutrition among patients admitted to hospital due to an infection caused by the novel coronavirus SARS-CoV-2 was relevant. What is more, the presence of a poor nutritional status was related to a longer stay in hospital, a greater admission in the ICU and a higher mortality.

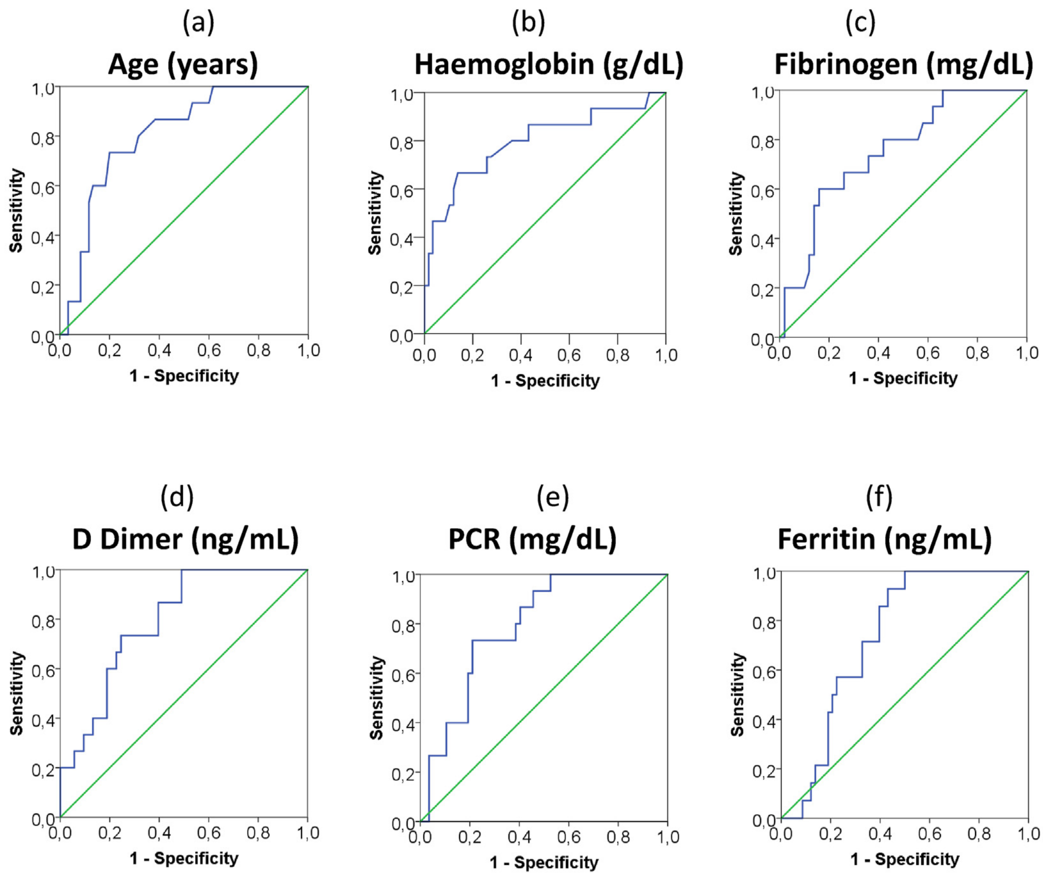
Actually, the prevalence of malnutrition among subjects admitted to hospital is high, especially among the elderly. Kayser et al. studied the prevalence of malnutrition among older adults, including 12 countries. They found that the overall incidence of malnutrition among the elderly was about 23%, with a 50.5% greater incidence in rehabilitation institutions and a 38.7% incidence among hospitalized patients [24]. Moreover, in a cross-sectional study, Li et al. evaluated the nutritional status of elderly inpatients with COVID-19 using the Mini Nutritional Assessment (MNA). They found that of a total of 182 patients included, 52.7% had criteria for malnutrition and up to 27.2% were at risk for malnutrition [25]. Also, Im et al. evaluated nutrient levels of 50 patients hospitalized due to a COVID-19 infection. In their sample, at least one missing nutrient, mainly 25-hydroxivitamin D3 and selenium, was present in 82% of the patients included. Furthermore, 11 out 12 patients who developed a respiratory distress were deficient in at least one nutrient [9].

Even though there is lack of evidence concerning nutritional status and COVID-19 prognosis, previous research focused on other respiratory viruses has shown that an adequate nutritional support was positive. Actually, underweight adults with any respiratory viral infection have four times higher risk of hospitalization compared with normal weight adults. In fact, Altuna-Venegas et al. assessed the influence of sarcopenia on the incidence of community-acquired pneumonia among almost 2.000 older adults. They found that the risk of pneumonia was increased among patients with sarcopenia, especially when associated with malnutrition [18,26–28].

There are several reasons why these patients, especially when they are older, are at risk of malnutrition during this exceptional situation. It has been described that, during lockdown, people increased the consumption of junk food increased to the detriment of fresh and healthy products, due to emotional eating and/or low availability [29–31]. After hospitalization not only this poor nutritional status might persist but worsen. Firstly, there is a hypercatabolic situation with SARS-CoV-2 infection due to a severe inflammatory stress, resulting in increased gluconeogenesis, enhanced proteolysis and accelerated fat oxidation. In fact, the synthesis of acute-phase proteins, such as CRP and TNF-alfa, requires the consumption of albumin and even muscle protein. Secondly, the presence of non-respiratory symptoms, such as anosmia, dysgeusia, hyporexia or diarrhea, can promote the loss of appetite and reduce dietary intake, worsening the nutrient deficiency. Finally, mechanical ventilation or the use of broad-spectrum antibiotics can make oral intake even more difficult, aggravating this inflammatory state [18,32,33].

On the other hand, nutritional screening is complicated in this situation, not only by the isolation of the patient but by the lack of staff resources and/or knowledge. However, the use of validated tools should be encouraged in order to identify poorly nourished patients or at risk for malnutrition. Considering the deleterious consequences of malnutrition, the implementation of protocols for early intervention of nutritional supplementation among non-critically ill patients hospitalized for COVID should be encouraged. Moreover, nutritional therapy should continue after discharge, given some pre-existing risk factors that lead to a poor nutrition might persist and also some symptoms due to this infection that impair an adequate oral intake.

This study has several limitations that are worth noting. It was a study conducted in a single center with a relatively small number of

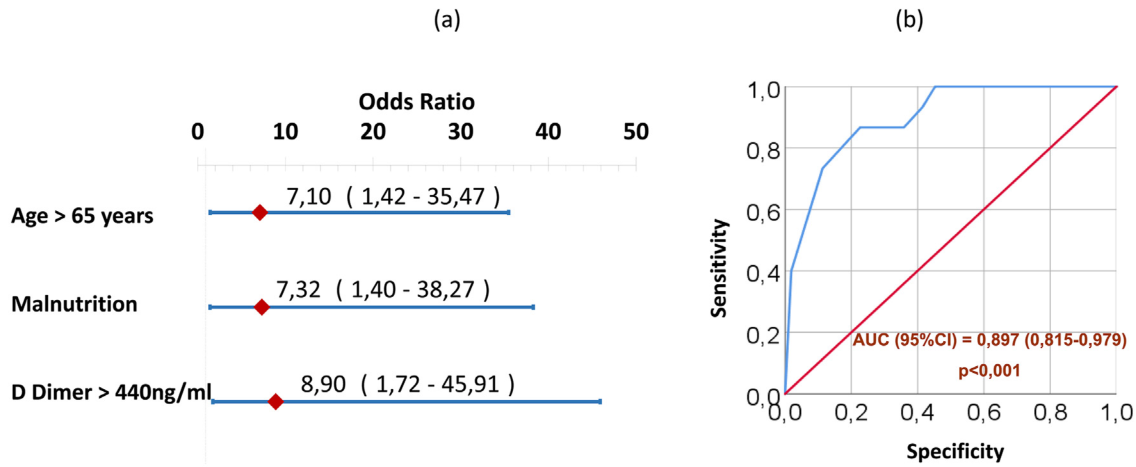


	AUC (95%CI)	Cut off value	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Age (years)	0,802 (0,692-0,913)	> 65	73,3	80,0	92,3	47,8
D Dimer (ng/mL)	0,794 (0,621-0,847)	> 440	73,3	75,5	90,9	45,8
Haemoglobin (g/dL)	0,800 (0,651-0,940)	< 11,7	66,7	84,5	90,7	52,6
Fibrinogen (mg/dL)	0,749 (0,617-0,882)	> 750	53,3	84,0	85,7	50,0
Ferritin (ng/mL)	0,734 (0,621-0,847)	> 400	78,6	60,3	92,1	32,4
PCR (mg/dL)	0,792 (0,683-0,847)	> 115	73,3	78,9	91,8	47,8

Fig. 1. ROC curves and optimal cut off values calculated for quantitative risk factors associated to ICU hospitalization.

patients. Also, owing to the isolation situation of the patients, the information of body height and weight was self-reported by the patients. Besides, the presence of lower extremities edema was reported or recorded by physicians other than the nutritionist. Therefore, possible recall biases existed when collecting data. Another point to consider is that only patients who were capable of maintaining a conversation by phone were included. Moreover, as a cross-sectional study, we cannot make any definitive conclusions regarding a causal relationship between preadmission nutritional situation and prognosis among patients with a SARS-CoV-2 infection. However, to date, few studies have assessed the impact of nutritional status on clinical outcomes among patients admitted due to a COVID-19. To further investigate the role of routine screening of malnutrition and the implementation of protocols to cope a poor nutritional status in order to ameliorate the prognosis of patients admitted due to COVID-19, more well-designed randomized controlled trials are needed.

In conclusion, a poor nutritional status constitutes a modifiable risk factor of poor prognosis among hospitalized patients due to SARS-CoV-2 infection. Therefore, prevention, diagnosis and treatment of malnutrition should be included in the routine management of patients with a SARS-CoV-2 infection.



	Crude Odds Ratio (O.R.)	(95% C.I.for O.R)	p-value	Age-Adjusted O.R.	(95% C.I.for O.R)	p-value
Age > 65 years	11,00	(2,98 - 40,67)	<0,001			
Alcohol consumption	3,14	(0,90 - 10,99)	0,073	1,51	(0,36 - 6,35)	0,572
Type 2 diabetes	3,16	(0,97 - 10,36)	0,057	2,43	(0,64 - 9,28)	0,194
Dislipidemia	5,93	(1,67 - 21,07)	0,006	5,78	(1,40 - 23,8)	0,015
Malnutrition	12,00	(2,98 - 48,35)	<0,001	8,96	(2,09 - 38,39)	0,003
D-Dimer > 440 ng/mL	8,46	(2,30 - 31,18)	0,001	8,01	(1,85 - 34,61)	0,005
Haemoglobin<11,7 g/dL	10,90	(3,00 - 39,46)	<0,001	7,40	(1,83 - 29,96)	0,008
Fibrinogen > 750	6,00	(1,69 - 21,26)	0,006	4,35	(1,07 - 17,72)	0,040
CPR >115 mg/dL	10,31	(2,78 - 38,21)	<0,001	7,99	(1,95 - 32,80)	0,004
Ferritin > 400 ng/mL	5,96	(1,40 - 22,20)	0,015	7,90	(1,61 - 38,58)	0,011
Albumin < 3,5 g/dL	23,43	(5,24 - 104,76)	<0,001	15,5	(3,19 - 74,95)	0,001

Fig. 2. Univariate and multivariate logistic regression analysis used to investigate factors associated to the ICU hospitalization.

Statement of authorship

JN was responsible for designing the protocol, conducting the search, interpreting the results, writing the manuscript and approving the final version of the manuscript.

LA was responsible for designing the protocol, conducting the search, collecting the data, and approving the final version of the manuscript.

PS was responsible for the statistical analysis and the interpretation of the results.

JO was responsible for designing the protocol, collecting the data and approving the final version of the manuscript.

AS was responsible for collecting the data and approving the final version of the manuscript.

KD was responsible for collecting the data and approving the final version of the manuscript.

IR was responsible for designing the protocol, collecting the data and approving the final version of the manuscript.

LG was responsible for designing the protocol, collecting the data and approving the final version of the manuscript.

LM was responsible for designing the protocol and approving the final version of the manuscript.

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Declaration of competing interest

All authors declare no conflict of interest.

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