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Original article

The coexistence of low albumin levels and obesity worsens clinical outcomes among subjects admitted for sars-cov-2 infection

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Background and aims: The clinical spectrum of the SARS-CoV-2 infection is very broad, ranging from asymptomatic infection to severe pneumonia. However, the majority of fatalities related to COVID-19 have involved old, frail and patients with comorbidities, such as obesity, groups that also have high rates of a poor nutritional status. To assess the impact on clinical outcomes of the coexistence of any degree of obesity and low albumin levels on admission among patients with COVID-19.
Methods: This is a sub-analysis of a former study where 75 patients admitted due to COVID-19 were evaluated cross-sectionally. In this analysis, patients were divided in two groups, according to the presence of obesity and albumin levels on admission lower than 3.5 g/dl.
Results: 11 out 75 patients evaluated (14.7%) had obesity and albumin levels lower than 3.5 g/dl. Patients with obesity and hypoalbuminemia were older than patients without these two conditions (65.3 ± 7.7 vs 54.2 ± 17 years; $p = 0.01$). CRP (141.4 ± 47.9 vs 70.1 ± 60.6 mg/l; $p = 0.002$), D-dimer (2677.3 ± 2358.3 vs 521.7 ± 480.3 ng/ml; $p = 0.001$), fibrinogen (765.9 ± 123.9 vs 613.5 ± 158gr/L; $p = 0.007$) ferritin levels (903.1 ± 493 vs 531.4 ± 418.9 mcg/l; $p = 0.01$) and procalcitonin (3.5 ± 0.6 vs 1.1 ± 0.7 ng/ml; $p = 0.009$) were significantly higher in the group with obesity and hypoalbuminemia. Among patients with low albumin and obesity, length of hospital was higher (21.9 ± 18.7 vs 10.5 ± 9.5 days; $p = 0.004$) and the proportion of subjects admitted to ICU was greater (81.8% vs 11.5%; $p < 0.0001$). However, mortality rates were comparable between the two groups (3.8% vs 0%; $p = 0.5$).
Conclusions: The combination of obesity and hypoalbuminemia may worsen the prognosis of patients with a SARS-CoV-2 infection. Therefore, prompt identification and amelioration of nutritional status could be beneficial.

1. Introduction

Since the first case reported in December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) has been responsible for numerous human and economic losses. In this sense, Spain has been one of the most countries affected worldwide, with more than 81,000 million deaths and 4.22 million affected people [1,2]. The clinical spectrum of the SARS-CoV-2 infection is very broad, ranging from asymptomatic infection to severe pneumonia requiring admission to the ICU and mechanical ventilation [3–6].

However, the majority of fatalities related to SarS-CoV-2 infection have involved old, frail and patients with comorbidities, such as cardiovascular disease, hypertension, diabetes or obesity, groups that also have high rates of a poor nutritional status [3–5].

Since the beginning of this pandemic, efforts have focused on detecting markers of poor prognosis, not only clinical but also biochemical. In this sense, although its mechanism is not well defined, low albumin levels have been shown to predict poor clinical outcomes among patients admitted due to a SarS-CoV-2 infection [7–13]. However, the majority of these studies have been carried out in the Asian population, without knowing the real effect in the Caucasian population. In fact, albumin is a non-specific biomarker of illness severity that has been shown to be diminished among elderly subjects, and in several diseases, both acute and chronic, including

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inflammatory states such as obesity and malnutrition. Besides, low albumin levels have been associated with critically ill patients and increased mortality in numerous clinical settings [9,14]. Previously, low albumin levels on admission predicted the need of intensive respiratory support in adult subjects with influenza A (H1N1) infection [15]. Also, hypoalbuminemia, together with lymphopenia and elevated CPR, were predictive factors for worsening pneumonia in patients with MERS-CoV infection [16].

Actually, although it may seem otherwise, subjects with obesity have nutritional deficits frequently. In fact, in the recent years, the term sarcopenic obesity has become particularly important and it has been associated with greater morbidity and mortality as well as impaired quality of life [17]. It is well known that obesity is an important public health problem that mainly affects Western countries, with this metabolic disease being less prevalent among the Chinese population [18].

Moreover, during lockdown the nutritional status of the general population could even have worsened. During this period, the quality of the food consumed could have been impaired for multiple reasons, such as the reduced availability of fresh products, the lockdown itself and reduced incomes. This could have led to a protein deficit and an increase in daily low-quality calories [19].

We aimed to assess the impact on clinical outcomes of the coexistence of any degree of obesity and low albumin levels on admission among patients with COVID-19.

2. Material and methods

2.1. Subjects

This is a sub-analysis of a former study where 75 patients admitted to the Internal Medicine Department of a tertiary hospital due to an infection caused by SARS-CoV-2 (confirmed by a PCR) from April until June 2020 were evaluated cross-sectionally. In this previous study we found that the presence of a poor nutritional status was related to a longer stay in hospital, a greater admission rate in the ICU and a higher mortality [20]. In this analysis, patients were divided in two groups, according to the presence of obesity and albumin levels on admission lower than 3.5 g/dl. 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 and 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. According to WHO, obesity is defined as a BMI equal or greater than 30 kg/m^2 [18].

3. Statistical analysis

Data are presented as means and standard deviations 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. 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

11 out 75 patients evaluated (14.7%) had obesity and albumin levels lower than 3.5 g/dl, whereas the remaining 64 subjects included (85.3%) did not meet those criteria.

Patients with obesity and hypoalbuminemia were older than patients without these two conditions (65.3 ± 7.7 vs 54.2 ± 17 years; $p = 0.01$). As expected, those patients with obesity had a greater BMI on admission (34.5 ± 5.8 vs 28 ± 5.5 kg/m^2; $p < 0.0001$). Despite the weight loss, the BMI at discharge was also greater among subjects with obesity and low albumin levels (31.2 ± 5.7 vs 26.4 ± 5.8 kg/m^2; $p < 0.03$). No differences between the two groups regarding gender, tobacco use or regular alcohol consumption were seen.

When taking into account cardiovascular risk factors, the proportion of patients with either type 2 diabetes or dyslipidemia was greater in the group with hypoalbuminemia and obesity on admission (63.6% vs 17.6% and 72.7% vs 36.5%; $p = 0.004$ and $p = 0.04$, respectively). No differences were seen between the two groups regarding the frequency of hypertension, ischemic disease or chronic pulmonary obstructive disease.

Moreover, length of hospital stay among obese patients and hypoalbuminemia was significantly higher compared to those without these two conditions (21.9 ± 18.7 vs 10.5 ± 9.5 days; $p = 0.004$). What is more, the proportion of subjects admitted to ICU was greater among the group with obesity and low albumin levels (81.8% vs 11.5%; $p < 0.0001$). Also, ICU stay was greater among those patients compared with patients without obesity (11.1 ± 7.2 vs 2.1 ± 1.2 days; $p < 0.0001$). However, mortality rates were comparable between the two groups (3.8% vs 0%; $p = 0.5$).

Regarding symptoms related to COVID-19, no differences were seen between the two groups. When we looked at the treatment prescribed against SARS-CoV-2 infection, the proportion of patients included in the group with obesity and hypoalbuminemia who were prescribed corticosteroids was significantly higher compared with the other group without these two conditions (72.7% vs 9.6%; $p < 0.0001$).

All these data are summarized in Table 1.

As shown in Table 2, some biochemical parameters were significantly different between both groups. CRP (141.4 ± 47.9 vs 70.1 ± 60.6 mg/l; $p = 0.002$), D-dimer (2677.3 ± 2358.3 vs 521.7 ± 480.3 ng/ml; $p = 0.001$), fibrinogen (765.9 ± 123.9 vs 613.5 ± 158gr/L; $p = 0.007$) ferritin levels (903.1 ± 493 vs 531.4 ± 418.9 mcg/l; $p = 0.01$) and procalcitonin (3.5 ± 0.6 vs 1.1 ± 0.7 ng/ml; $p = 0.009$) were significantly higher in the group with obesity and hypoalbuminemia compared with the group without these conditions. Furthermore, fasting plasma glucose levels were higher among subjects with obesity and hypoalbuminemia (201.9 ± 100.9 vs 112.6 ± 30.8 mg/dl; $p = 0.002$). Moreover, haemoglobin levels were lower in obese patients with low albumin levels compared with subjects with a good nutritional status (10.4 ± 1.7 vs 13.4 ± 1.8 g/dl; $p < 0.0001$). Subjects with obesity and hypoalbuminemia had calcium levers lower than the group without obesity (8.1 ± 0.5 vs 8.8 ± 0.7 mg/dl; $p = 0.002$). Furthermore, subjects with obesity and low albumin had greater both GOT (34.5 ± 11.7 vs 27.5 ± 19.6U/L; $p = 0.02$) and bilirubin plasma levels (0.7 ± 0.4 vs 0.5 ± 0.2 mg/dl; $p = 0.03$) compared with subjects without this condition.

5. Discussion

We found that the coexistence of low albumin levels and obesity among subjects admitted to hospital due to COVID-19 was related to more admissions at the ICU as well as a longer stay, both in the ICU and in a conventional ward.

Since this COVID-19 pandemic has reached this alarming situation in relation to the high number of infections despite the fact that a substantial number of people have already received a complete vaccination, the urgent need to find biomarkers that may predict the prognosis of these patients is essential. In this sense, Huang et al., were the first group to conclude that albumin levels lower than 35 g/l were associated with worse outcomes among patients with COVID-19. Furthermore, baseline hypoalbuminemia independently increased the risk of mortality by at least 6-fold [8]. In a meta-analysis of Chinese studies, Aziz and colleagues concluded that there was an association of hypoalbuminemia and severe COVID-19 [9]. Subsequently, other studies have shown that these findings also occur in the Caucasian population [7,10,11]. Specifically in Spain, Viana-Llamas and colleagues found that low albumin levels were an early predictor of mortality during hospitalization among 609 Spanish patients admitted due to COVID-19, independently of age, comorbidity and inflammatory markers [11]. Moreover, de la Rica et al., concluded that hypoalbuminemia was related to longer hospital length and greater mortality in 48 COVID-19 patients hospitalized in the Balearic Islands [10].

Albumin is a protein synthetized in the liver with a substantial number of physiological functions that include providing oncotic pressure, binding and transporting different plasmatic compounds and acting as an antioxidant, among other functions [21,22]. During an acute period in a critical illness, the synthesis of albumin decreases significantly in order to prioritize the production of acute inflammatory markers. Also, these acute phase reactants allow albumin to escape from the vessels to the extravascular space by increasing vascular permeability and, subsequently, aggravating hypoalbuminemia [23]. But not only acute illnesses have their negative impact on albumin levels, but also chronic diseases have been shown to diminish this protein, according to the magnitude of the inflammatory response they generate [24].

All these findings support the clinical usefulness of serum albumin determination in the initial stages of hospital admission, in order to stratify the risk among patients with COVID-19. However, a point to consider is that all these studies have a retrospective or cross-sectional and therefore, this design cannot make any definitive conclusions regarding a causal relationship between low albumin levels on admission and prognosis among patients with a SARS-CoV-2 infection. In this sense, Zhang et al. observed albumin levels longitudinally and they found a continuous decrease in albumin from the emergency room to ICU admission [25]. In fact, Vincent et al., showed in a meta-analysis that included 90 cohort studies with acute ill critical patients, that for every 1 g/dl diminish in plasmatic albumin levels, there was a significant rise in the odds of not only morbidity and longer hospital length, but also mortality [26]. Thus, serial determination of plasma albumin levels could be more useful as a predictor of poor prognosis in COVID-19 patients compared to an isolated determination.

On the other hand, obesity has been shown to be a risk factor for greater severity and worse prognosis in patients with COVID-19 [27–30]. Many mechanisms have been proposed by which this metabolic disease worsens the clinical outcomes of COVID-19. These would include a low-grade chronic inflammatory state with an increase in circulating pro-inflammatory cytokines, a hypercoagulability state and an impaired pulmonary function [27]. Likewise, obesity is associated with other cardiovascular risk factors that also worsen clinical outcomes among COVID-19 patients, such as type 2 diabetes, hypertension, atherosclerosis, etc. [27].

Besides, obesity does not always imply an optimal nutritional status. In fact, in recent years the term sarcopenic obesity has been gaining relevance. Although there are still some concerns relating its definition and diagnostic methods, sarcopenia could be defined as a pathological condition characterized by generalized loss of skeletal muscle mass and function. When this loss of function and/or muscle mass is associated with a conserved or even increased fat mass, sarcopenic obesity comes into play. The prevalence of sarcopenic obesity is estimated to be 2% for patients aged 60–69 years and increases to 10% for subjects aged over 80 years. However, to date, there are few studies in relation to sarcopenic obesity and its effects in subjects under 65 years of age. The pathogenesis is complex and multifactorial, with age, insulin resistance and inflammatory mediators playing a relevant role [17]. Therefore, a SARS-CoV-2 infection in an individual with sarcopenic obesity or hypoalbuminemia could have a worse prognostic by aggravating this inflammatory state.

However, to date, there are no studies that have studied whether the coexistence of obesity and low albumin levels might worsen the prognosis of patients admitted for COVID-19. Actually,

Table 1
Comparison of sociodemographic features, clinical and anthropometric variables among subjects hospitalized due to COVID-19 with obesity and hypoalbuminemia and individuals without it.

	Subjects with obesity and hypoalbuminemia (n = 11)	Well-nourished COVID-19 patients (n = 64)	*p*
Gender (male/female) (%)	27.3/72.7	51.9/48.1	0.2
Age (years)	65.3 ± 7.7	54.2 ± 17	0.01
Tobacco use (%)	9.1	19.6	0.7
Regular alcohol consumption (%)	36.4	50	0.5
BMI on admission (kg/m^2)	34.5 ± 5.8	28 ± 5.5	<0.0001
BMI at discharge	31.2 ± 5.7	26.4 ± 5.8	0.03
Length of hospital stay (days)	21.9 ± 18.7	10.5 ± 9.5	0.004
ICU admission (%)	81.8	11.5	<0.0001
ICU stay (days)	11.1 ± 7.2	2.1 ± 1.2	<0.0001
Mortality (%)	3.8	0	0.5
HTA (%)	72.7	48.1	0.2
DM2 (%)	63.6	17.6	0.004
Dyslipidaemia (%)	72.7	36.5	0.04
Coronary disease (%)	0	9.6	0.6
Pulmonary obstructive disease (%)	36.4	30.8	0.7
Corticosteroid treatment (%)	72.7	9.6	<0.0001

Data are mean ± SD or %. BMI, body mass index. ICU, intensive care unit. HTA, hypertension. DM2, type 2 diabetes.

Table 2
Comparison of biochemical parameters among subjects hospitalized due to COVID-19 with obesity and hypoalbuminemia and well-nourished patients.

	Subjects with obesity and hypoalbuminemia (n = 11)	Well-nourished COVID-19 patients (n = 64)	*p*
Hemoglobin (g/dl)	10.4 ± 1.7	13.4 ± 1.8	<0.0001
Lymphocyte count (x10^9)	3.2 ± 3.9	2.6 ± 2.7	0.4
Platelet count (x10^9)	307.8 ± 110.2	267.2 ± 124.2	0.2
Prothrombin time (%)	73.9 ± 11.6	75.3 ± 13.3	0.7
Fibrinogen (g/L)	765.9 ± 123.9	613.5 ± 158	0.007
D dimer (ng/ml)	2677.3 ± 2358.3	521.7 ± 480.3	0.001
FPG (mg/dl)	201.9 ± 100.9	112.6 ± 30.8	0.002
Creatinine (mg/dl)	1 ± 0.6	1 ± 0.2	0.7
Calcium (mg/dl)	8.1 ± 0.5	8.8 ± 0.7	0.002
Albumin (g/dl)	2.8 ± 0.5	3.9 ± 0.6	<0.0001
Ferritin (mcg/l)	903.1 ± 493	531.4 ± 418.9	0.01
CRP (mg/l)	141.4 ± 47.9	70.1 ± 60.6	0.002
Procalcitonin (ng/ml)	3.5 ± 0.6	1.1 ± 0.7	0.009
GOT (U/l)	34.5 ± 11.7	27.5 ± 19.6	0.02
GPT (U/l)	33.4 ± 22.2	31.4 ± 30.2	0.3
GGT (U/l)	82.4 ± 58.7	70.9 ± 60.5	0.2
FA (U/l)	82.1 ± 46.4	72.6 ± 42.9	0.3
Bilirubin (mg/dl)	0.7 ± 0.4	0.5 ± 0.2	0.03

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

obesity is rarely included as a significant comorbidity among studies performed in Chinese population due to its low prevalence. However, obesity has become a major health problem in the last decades across Western countries and, thus, it has a significant impact on prognosis among subjects with a SARS-CoV-2 infection [18]. Therefore, not all conclusions observed in a significant number of studies, mainly Chinese, can be extrapolated to our population.

What is more, we also found that subjects with obesity and low albumin levels were significantly older than their counterparts. In Spain, as in the majority of developed countries, the prevalence of obesity increases with age. Actually, in Spain, the age group with the highest prevalence of obesity is people over 55 years of age [18]. Besides, a suboptimal nutritional status is also more frequent among the elderly [31,32]. This situation could have worsened during the lockdown, due to the fear of going out and, therefore, replacing fresh products with processed food [19]. Also, emotional eating during this period of time could have increased the intake of high-dense caloric and palatable foods and thus, not only would increase weight but also diminish the nutritional quality of meals [33].

Our study showed that both acute phase reactants and procoagulant factors were greater among subjects with obesity and hypoalbuminemia. These results could be due to the increased production of proinflammatory cytokines during an acute illness aggravated by the low-grade inflammatory state present among individuals with obesity [34]. Therefore, these data show that COVID-19 patients with both obesity and low albumin levels are at higher risk of excessive uncontrolled inflammation responses and hypercoagulable state, which may contribute to a poorer prognosis of COVID-19.

We also found that GOT levels were higher among subjects with obesity and hypoalbuminemia. Actually, elevated transaminases have been frequently reported during the initial stages of the disease, with AST abnormalities found to be more frequent than GPT alteration [35–37]. Wagner and colleagues found that the presence of elevated AST, ALT o ALP on admission increased the risk of ICU admission among 65 patients with COVID-19 [13]. Actually, SARS-CoV-2 viral RNA has been isolated from human liver samples and, thus, it is probable that COVID-19 infects the liver [38]. However, as GPT is a more specific marker of hepatocyte injury rather than GOT, which is found in many other tissues. Therefore, the elevation of GOT could only represent a manifestation of systemic illness rather than liver injury itself.

Moreover, plasma glucose levels were significantly greater among subjects with obesity and low albumin levels. This could be either the increased prevalence of type 2 diabetes among subjects with obesity and hypoalbuminemia or an adverse effect of systemic glucocorticoid therapy, which was more frequently used among this group of patients. However, it has been shown that not only type 2 diabetes but hyperglycemia *per se* could worsen the clinical outcomes of these patients admitted for COVID-19 [39–41].

The strengths of this study include the combination of a clinical condition such as obesity and an easily obtained biochemical marker to stratify the severity of patients admitted for COVID-19. Also, our hospital works with institutional medical protocols that represent a real-life setting of COVID-19 clinical management. Besides, to our knowledge, this is the first study that combines obesity and hypoalbuminemia as prognostic factors for SARS-CoV-2 infection. Limitations include a relative small sample size in a single center. Also, its observational nature makes impossible to draw any conclusions on causality. Besides, we did not perform serial albumin measurements. It has been shown that this parameter decreases progressively from the early course of the disease and it does not regain its normal values until the recovery stage.

In conclusion, the coexistence of obesity and low albumin levels on admission is associated with a worse prognosis among patients admitted for SARS-CoV-2 infection. These findings could potentially lead to early recognition of severe disease with easy clinical and biochemical markers and improve the prognosis of these patients. Further research should focus on demonstrating if the correction of these low albumin levels on admission, through an individual nutritional therapy would improve outcomes for COVID-19 patients.

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.

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

AR 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.

AP 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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