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Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding

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Original Article

ABSTRACT

Introduction: On the last three months the new SARS-COV-2 coronavirus has created a pandemic, rapidly spreading all around the world. The aim of the study is to investigate whether obesity impacts on COVID-19 morbidity.

Methods: One hundred consecutive patients with COVID-19 pneumonia admitted in our Medical Unit were evaluated. Anthropometric parameters and past medical history were registered. Nasopharyngeal swab samples and biochemical analysis were obtained at admission and during hospital stay.

Results: Patients with (OB, 29) and without obesity (N-OB, 71) were similar in age, gender and comorbidities, with the exception of hypertension that was more frequent in OB group. At admission, inflammatory markers were higher in OB than N-OB group. OB group showed a worse pulmonary clinical picture, with lower PaO2 (57 ± 15 vs. 68 ± 14 mmHg, p = 0.042), and SaO2 (88 ± 6 vs. 92 ± 5%, p = 0.049) at admission consequently requiring higher volumes of oxygen (FiO2: 38 ± 15 vs. 29 ± 19%, p = 0.047) and a longer period to achieve oxygen weaning (10 ± 6 vs. 15 ± 7 days, p = 0.03). OB group also had positive swabs for longer time (19 ± 8 vs. 13 ± 7, days, p = 0.002), and required longer hospital stay (21 ± 8 vs. 13 ± 8, days, p = 0.0008). Partial least square regression analysis showed that BMI, age and CRP at admission were related to longer length of hospital stay, and time for negative swab. On the contrary, in this cohort, obesity did not predict higher mortality.

Conclusions: Subjects with obesity affected by COVID-19 require longer hospitalization, more intensive and longer oxygen treatment, and they may have longer SARS-COV-2 shedding.

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Introduction

Obesity is an increasingly important mortality risk factor, partially because it increase the risk of several non-communicable diseases [1–4]. Pathogenetic mechanisms underlying these diseases appear to be related, at least in part, to a chronic, low-level inflammatory exposure which often accompanies adipose tissue accumulation and promotes the development of metabolic and cardiovascular complications. Furthermore, the thromboembolic risk is known to be higher in patients with obesity than in the general population [5].

Although increased body mass index (BMI) has been associated with a higher susceptibility to and more severe presentation of infections [6] (such as H1N1 influenza virus), data remain conflicting. Indeed, several reports have suggested that patients with obesity might have a lower mortality rate during severe sepsis than normal-weight patients [7–12]. This phenomenon seems to be in line with some studies reporting a paradoxical association between overweight and class I obesity and reduced mortality in patients with chronic heart failure [13,14].

On the last three months, the new SARS-COV-2 infection has rapidly spread around the world. Even though the outbreak started in China, the pandemic quickly moved to Europe and America, leading to a crisis of several National Health Systems.

Compared to China, in these westernized societies the population is older, and there is a much higher prevalence of obesity.

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These features might aggravate the severity of the disease, given the greater frailty of the population and the well-established mechanical restrictive pattern imposed by high body weight to the respiratory system dynamic. Furthermore, in obese patients there is an increased prevalence of respiratory diseases, including chronic obstructive pulmonary disease (COPD) and sleep apnea. These factors might explain the greater severity, hospitalization and mortality from H1N1 virus infection observed in obese compared to non-obese patients [15].

Recent studies have suggested that BMI represents a risk factor for severe complications in patients with COVID-19 [16,17].

Epidemiological data of the Italian Health Institute (Epicentro) have shown that in people died with positive SARS-COV-2 swab the prevalence of obesity was 11% [18]. This data reflects the prevalence of obesity in Italian population reported by the Italian Barometer Diabetes Observatory Foundation in the 2019 [19].

In the present study, we wished to investigate whether in our cohort of COVID-19 subjects, obesity was predicting a worse outcome, in terms of mortality, or of other factors that could be related to a worse clinical picture.

Methods and material

Study design and patients

Consecutive patients admitted to the COVID-19 unit of Cisanello Hospital, at the “Azienda Ospedaliero Universitaria Pisana–AOUP” (Pisa, Italy), between March 16th and April 15th, 2020 were enrolled in this single-centre, retrospective, observational cohort study. This retrospective observational study was based on medical records, in strict agreement with local Ethical statement of AOUP. Patient confidentiality was protected by assigning an anonymous identification code, and the electronic data were stored in a locked, password-protected computer. All patients were diagnosed with COVID-19 pneumonia according to World Health Organization interim guidance [20] with SARS symptoms characterized by dyspnea, increased respiratory frequency, decreased blood oxygen saturation, and need for oxygen support therapy. Two nose and pharyngeal swab samples were obtained from all patients at admission and, at different times depending on the clinical evolution of the disease, during the hospital stay. The presence of the SARS-COV-2 genome was detected using real-time reverse transcriptase-polymerase chain reaction assays [21]. Demographic, anthropometric and clinical parameters, including sex, age, body mass index (BMI), blood pressure, heart and respiratory rate, oxygen saturation, body temperature, oxygen requirements were recorded at the admission. Vital signs were regularly collected during hospitalization to monitor clinical conditions. Arterial blood gases and venous blood samples (for standard biochemistry and circulating levels of inflammatory markers) were collected at the admission and, depending on the patient clinical conditions, during the hospital stay. Cytokines were measured by Quantikine ELISA assay kits (R&D system).

Detailed medical history was recorded from all patients, with a specific focus on the following diseases: hypertension, cardiovascular disease, diabetes, dyslipidemia, chronic respiratory disease, chronic obstructive pulmonary disease (COPD).

Statistical analysis

Quantitative data were expressed as mean ± SD or median [interquartile range], for variables with normal or skewed distribution, respectively. Continuous variables with a normal distribution were compared by the Student t test, while the variables with a skewed distribution by the Mann Whitney U test. Categorical data, expressed as percentage, were analysed with X2 test.

In order to identify the variables, at admission, maximally contributing to the duration for obtaining a negative oropharyngeal or nasal swab, and the length of hospital stay, respectively, two partial least square (PLS) regressions [22] were generated. Variables with Variable Importance in Projection (VIP, expressing a measure of a variable’s relevance in the model) greater than 1.50 were considered significant for association with the dependent variable (duration for a negative swab, or length of hospital stay). The same method has been used in order to identify the variables maximally contributing to group separation of subjects between survivors and dead.

A p value <0.05 was considered to be significant; when necessary correction for multiple testing was applied. Statistical analysis was performed by R and IBM-SPSS packages for Mac Os X.

Results

Characteristics of the study participants at hospital admission by BMI groups

A total of 100 consecutive patients admitted in our Covid-Medical Unit were enrolled in the present study. Patients were grouped by BMI (≥30 kg/m2 or <30 kg/m2) as patients with obesity (OB, 29) and patients without obesity (N-OB, 71). The OB group was mainly constituted by class I obesity subjects, with only 4 patients with BMI ranging between 35 and 40 kg/m2.

The anthropometric and biochemical characteristics of the study participants at admission are shown in Table 1. Age and sex distribution were similar between the two groups, as well as the main comorbidities, except for hypertension that was more frequent in the OB group (OB vs. N-OB: 69% vs. 46%, p = 0.04).

There were no differences in total blood count, fasting plasma glucose, indexes of cytolysis, renal and liver function between the two groups. Among inflammatory markers, ferritin, C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) levels were higher in the OB group than N-OB subjects (Table 2). No differences

| Table 1 | Main anthropometric and biochemical features of study participants at admission. |
|---------|---------------------------------------------------------------------------------|
|         | OB (n = 29) | N-OB (n = 71) | p value |
| Baseline characteristics | | | |
| Age (years) | 70 ± 15 | 69 ± 17 | ns |
| BMI (kg/m2) | 33.0 ± 1.7 | 24.6 ± 2.5 | <0.0001 |
| Gender (M/F) | 12/17 | 40/31 | ns |
| Smoking habit | 6(21%) | 11(15%) | ns |
| Hypertension | 20(69%) | 33(46%) | 0.04 |
| Type-2-diabetes | 9(31%) | 16(23%) | ns |
| COPD | 5(17%) | 9(13%) | ns |
| Chronic heart failure | 7(25%) | 21(29%) | ns |
| Laboratory parameters | | | |
| RBC (1012/mm3) | 4.42 [4.07–4.78] | 4.39 [4.09–4.43] | ns |
| Hb (g/dL) | 13.0 ± 1.6 | 13.1 ± 1.7 | ns |
| Neutrophils (109/mm3) | 6.6 [4.1–11.4] | 5.3 [3.6–7.0] | ns |
| Lymphocytes (109/mm3) | 1.0 [0.68–1.42] | 1.1 [0.68–1.68] | ns |
| Monocytes (109/mm3) | 0.58 [0.34–0.82] | 0.61 [0.38–0.83] | ns |
| Platelets (109/mm3) | 208 [156–305] | 212 [153–268] | ns |
| Creatinine (mg/dL) | 1.1 ± 0.5 | 1.0 ± 0.4 | ns |
| Fasting glucose (mg/dL) | 133 ± 56 | 126 ± 78 | ns |
| Albumin (g/dL) | 3.7 [3.3–4.0] | 3.6 [3.2–3.9] | ns |
| AST (IU/L) | 32 [20–50] | 26 [20–36] | ns |
| ALT (IU/L) | 23 [18–48] | 20 [15–32] | ns |
| yGT (IU/L) | 37 [26–74] | 24 [18–46] | ns |
| LDH (IU/L) | 347 [256–498] | 273 [211–310] | ns |
| Creatine kinase (U/L) | 114 [74–275] | 82 [43–148] | ns |
| Myoglobin (µg/L) | 71 [38–132] | 48 [27–111] | ns |
| hs-Troponin (ng/mL) | 270 [115–457] | 190 [101–342] | ns |
| Cholinesterase (U/mL) | 5.2 [4.3–6.6] | 5.9 [4.9–6.8] | ns |
Table 2

Acute phase protein and cytokines at the hospital admission.

| Laboratory parameters | OB (n = 29) | N-OB (n = 71) | P value |
|------------------------|-------------|---------------|---------|
| Ferritin (ng/mL)       | 1379 [343–1712] | 624 [323–981] | 0.042 |
| Fibrinogen (mg/dL)     | 673 [579–768]  | 602 [424–730] | ns      |
| D-Dimer (ng/mL)        | 0.64 [0.42–1.54] | 0.55 [0.33–0.77] | ns      |
| CRP (mg/mL)            | 8.5 [5.4–16.3] | 7.9 [2.4–12.1] | 0.037 |
| IL-6 (pg/mL)           | 1.0 [0.12–0.45] | 0.11 [0.06–0.21] | ns      |
| IL-1 (pg/mL)           | 1.4 [1.0–2.3] | 1.3 [0.9–2.1] | ns      |
| IL-2 (pg/mL)           | 26.1 [7.1–65.1] | 14.2 [9.5–32.1] | ns      |
| TNF-α (pg/mL)          | 11.0 [4.5–20.5] | 5.9 [2.3–10.5] | 0.021 |

Fig. 1. Obese subjects had longer length of hospital stay (A), and longer length for having negative oropharyngeal and/or nasal swabs (B). In the box plots the top and bottom of the box represent the 75th and 25th percentile, respectively. The top and bottom bars (“whiskers”) represent the entire spread of the data points for length of hospital stay (or time period for having a negative swab) and each group, excluding “extreme” points, which are indicated with black circles. The lines inside the boxplots show the median values.

were found in any other cytokine parameters. OB patients tended to have a worse blood gas analysis compared to the N-OB subjects, with a lower value of arterial oxygen pressure (57 ± 15 vs. 68 ± 14 mmHg, p = 0.042) and worse oxygen saturation (88 ± 6 vs. 92 ± 5, %, p = 0.049), consequently requiring higher oxygen support (FiO2 via Venturi Mask 38 ± 15 vs. 29 ± 19%, p = 0.047).

Fig. 2. In linear regression analysis, C-Reactive protein at admission correlated positively with the length of hospital stay (A) and with length for having negative oropharyngeal and/or nasal swabs (B).

Obesity and COVID-19 outcomes

PLS detected the following variables strictly related (VIP > 1.50) to length of hospital stay: age, BMI, lymphocytes, hemoglobin and CRP at admission. Regarding the dependent variable “length of hospital stay”, the method identify: age, BMI and CRP at admission. According to these results, patients with obesity showed a longer duration for obtaining a negative oropharyngeal or nasal swab (19 ± 8 vs. 13 ± 7, days, p = 0.002), required a longer period to achieve oxygen weaning (9.8 ± 6.4 vs. 15.2 ± 7.1, days, p = 0.03) which results in a longer length of hospital stay (21 ± 8 vs. 13 ± 8, days, p = 0.0008) (Fig. 1A,B).

In any case, at discharge, no difference was found in CRP levels (0.8 [0.5–2.7] vs. 0.7 [0.1–3.5], OB vs. N-OB respectively, p = ns), while ferritin tended to remain higher in OB group (1379 [343–1712] vs. 624 [323–981], OB vs N-OB respectively, p = 0.06).

The CRP at admission was associated with a longer length of hospital stay and time for negative swab (Fig. 2).

In this relatively small sample size, we did not find any difference in the mortality rates between the two groups (16% vs. 19%, OB vs. N-OB, respectively, p = ns). Moreover, PLS regression aimed to detect the variables at admission related to “survivor/dead” provided the following results: age (67 ± 17 vs. 80 ± 7 yrs), lymphocytes (1304 ± 1034 vs. 784 ± 412, mm³) and creatinine (1.0 ± 0.4 vs. 1.4 ± 0.5, mg/dl) but not BMI and CRP.
Discussion

Our study shows that obesity is associated with a severer respiratory presentation of COVID-19 and severer elevation of inflammatory markers, likely leading to higher oxygen demands at admission, prolonged oxygen requirement during hospitalization, delayed viral clearance and extended hospital stay. These characteristics, however, did not translate into a higher risk of mortality in subjects with obesity compared to the patients without obesity.

In a retrospective study on 112 COVID-19 patients with cardiovascular disease admitted to the intensive care unit (ICU) in Wuhan, BMI has been reported to be associated with higher mortality[17,23]. Furthermore, Lighter et al. [16] found that in patients aged <60 years, class II obesity was associated with a doubled risk of ICU access, whereas in patients aged ≥60 years, body weight did not appear to be a predictive factor for hospital admission or access to ICU.

In another recent paper [24] it has also been described that of 124 patients admitted to ICU for COVID-19, almost half of them were affected by obesity, and a higher BMI was associated with an increased risk of mechanical ventilation. Nearly 90% subjects requiring invasive mechanical ventilation had class II or III obesity.

In our cohort of patients, the prevalence of obesity (28%) in COVID-19 patients is higher compared to that (11%) reported by Italian Health Institute (Epicentro) [18]. This difference could have multiple explanations; first of all, our cohort is relatively small; moreover, out patients were older and represented a selected population, with greater clinical impairment and need for hospitalization compared to the total SARS-CoV-2 confirmed cases in Italy.

In a preliminary report of 52 subjects, we have previously reported that obesity was associated with a longer length of hospital stay [25]. We now confirm this finding, expanding the population included in our cohort and providing potential explanations for these results. We now did not find any significant difference concerning previous comorbidities between OB and N-OB group. Furthermore, in LPS regression analysis, age, BMI and CRP at admission were related to the duration of the hospitalization.

Even though the prevalence of COPD was not higher in the OB compared to the N-OB group, obesity in itself might impair the respiratory system dynamic, reducing lung compliance and increasing respiratory muscle reactivity, ultimately leading to an impaired gas exchange also in apparently healthy individuals [26]. It is know that subjects with obesity per se have an increased pro-inflammatory pattern [27]. For this reason, beyond the potential impact on the lung mechanics, obesity might influence the clinical presentation and evolution of SARS-CoV-2 infection through exacerbation of the immune-inflammatory response related to the disease, as confirmed by the increased levels of several inflammatory markers detected in the peripheral blood of patients with obesity in our population. Particularly, the abnormal secretion of adipokines and cytokines like TNF-alpha by the adipose tissue can sustain and amplify the inflammatory response to the SARS-CoV-2 infection, with potential consequences not only on the lung but also on the cardiovascular system [7,8]. Of note, Yende et al. have already documented that elevated pre-infection levels of systemic inflammatory markers predict a higher risk of hospitalization in patients with community-acquired pneumonia [28]. Collectively, these considerations might explain the later recovery, delayed weaning from O2 therapy and prolonged relapse from viral clearance of patients with obesity compared to the N-OB group observed in our study.

This hypothesis is in keeping with previous results showing a higher risk of invasive mechanical ventilation in subjects with higher BMI, independently of other comorbidities [19], as well as the prolonged viral shedding observed in people with >30 kg/m² BMI during influenza A infection [29].

It should be highlighted, however, that the estimated duration of the viral shedding calculated in our report might be inaccurate. Indeed, the days of viral shedding were counted starting from the date of the first positive swab performed upon admission to the Emergency Department. Information regarding the exact onset of the clinical symptoms was not systematically recorded. Another limitation of the present study is represented by the small number of patients included in our cohort, associated with a lack of a better characterization of adiposity. While in a routine clinical setting the most commonly used definition of obesity is based on the presence of a BMI >30 kg/m², it is well established that other measures such as waist-to-hip ratio might provide better information on the amount of visceral vs. subcutaneous adipose tissue; thus they might better reflect the presence of a pro-inflammatory environment related to fat accumulation. However, in the setting of an acute medical ward, with the huge burden of patients faced during phase 1 of the pandemic, collection of these measures was practically impossible. Finally, we did not have information on the severity of insulin resistance associated with obesity, which is known to have an impact on the risk of cardiac dysfunction and CVD-related mortality [30]. Phase 2 of the pandemic might represent an excellent opportunity for deepening our knowledge and acquiring further information regarding the potential influence of waist-to-hip ratio and the levels of insulin resistance on the association between obesity and severity of the SARS-CoV-2 infection.

In conclusion, our data show that subjects with obesity affected by COVID-19 required extended hospitalization and more intensive and prolonged oxygen treatment. Still, they did not have an increased risk of mortality as compared to the subjects without obesity. Our data also suggest that people affected by obesity might require more time to clear from SARS-CoV-2 shedding. If future studies will confirm this finding, clinical guidelines for the isolation period upon infection from SARS-CoV-2 should be personalized in case of individuals with obesity. Finally, subjects with obesity affected by COVID-19 have higher CRP and TNF-α levels, and future studies should clarify whether the pro-inflammatory state that is commonly observed in obesity could provide a mechanistic background for their severer clinical presentation and evolution in course of SARS-CoV-2 infection.

Author contributions statement

Diego Moriconi has made substantial contributions to conception, collection and interpretation of data and he has been involved in drafting the manuscript.

Stefano Masi, Eleni Rebelos, Salvatore De Marco have made substantial contributions to data collection and they have been involved in drafting the manuscript.

Maria Laura Manca, has been involved in statistical analysis.

Agostino Virdis, Stefano Taddei have been involved in revising it critically for important intellectual content.

Monica Nannipieri has made substantial contributions to conception and design of the study, data interpretation, and she has been involved in writing of the manuscript.

Conflict of interest

The authors received no funding and declare no conflict of interest.

Ethical statement

All retrospective data involving human participants were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained by the Local Ethics Committee.
I have read and have abided by the statement of ethical standards for manuscripts submitted to the Obesity Research & Clinical Practice.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.orcp.2020.05.009.

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