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SHORT COMMUNICATION

Obesity as a risk factor for hospitalization in COronaVirus Disease-19 (COVID-19) patients: Analysis of the Tuscany regional database

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Abstract *Background and aims:* Aim of the present study is to determine the role of obesity as a risk factor for COronaVirus Disease-19 (COVID-19) hospitalization.
Methods and results: This observational study was performed using Istituto Superiore di Sanità (ISS) Tuscany COVID-19 database by the Agenzia Regionale Sanità (ARS), including all COVID-19 cases registered until April 30th, 2020, with reported information on chronic diseases. The principal outcome was hospitalization. An age and gender-adjusted logistic regression model was used to assess the association of clinical and demographic characteristics with hospitalization. Further multivariate models were applied. Of 4481 included subjects (36.9% aged over 70 years), 1907 (42.6%) were admitted to hospital. Obesity was associated with hospitalization after adjusting for age and gender. The association of obesity with hospitalization retained statistical significance in a fully adjusted model, including possible confounders (OR: 2.99 [IC 95% 2.04 −4.37]). The effect of obesity was more evident in younger (<70 years) than in older (≥70 years) subjects.
Conclusions: The present data confirm that obesity is associated with an increased risk of hospitalization in patients with COVID-19. Interestingly, the association of obesity with hospitalization was greater in younger (<70 years) patients.
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Introduction

Several cohort study of hospitalized patients with COVID-19 have shown that obesity is associated with increased risk of Intensive Care Unit (ICU) admission and mortality in patients with COVID-19 [1–8]. The prognostic value of obesity seems to be greater in lower age groups [6].

Most available studies on the relationship between COVID19 and obesity have been performed on hospitalized patients. To our knowledge, only two surveys [9,10], both performed in New York City, explored the association between obesity and risk of hospitalization in COVID-19, both showing an increased risk in obese subjects.

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Patients referring to emergency departments are only a fraction of those diagnosed with COVID-19. In fact, a relevant number of individuals, at least in some areas, received diagnosis and treatment at home, or in nursing homes. Patients referring to emergency rooms are not representative of all those who received a diagnosis of COVID-19; obesity could have interfered with emergency room referral.

Aim of the present study is the assessment of the role of obesity as a possible risk factor for hospitalization in an unselected cohort of patients with COVID-19, exploring the effect of comorbidities as putative moderators.

Methods

This study was performed in Tuscany, a region of central Italy with approximately 3.73 million inhabitants, which was moderately affected by the first outbreak of COVID-19. The regional healthcare system provides universal free-of-charge coverage including hospitalization, emergency room admission, transportation to hospitals, outpatient and home care. During the COVID-19 outbreak, an effort was made to limit hospital admissions, providing support for home care and isolation in the majority of cases. The saturation of available hospital beds and ventilators was never reached during the outbreak, with hospitalized and ICU patients never surpassing the system's surge capacity. In addition, the regional healthcare system increased its testing capacity for Severe Acute Respiratory Syndrome-COronaVirus2 (SARS-Cov2) during the first weeks of the epidemic, reaching at the end of April an output of more than 100 daily tests for 100,000 inhabitants. The overall positive/total test ratio on April 30th (since the beginning of outbreak) was 6.6% (www.protezionecivile.gov.it).

This observational study was performed using the Tuscany section of the database of COVID-19 cases of the ISS (www.iss.it), managed by Agenzia Regionale Sanità (ARS). This database collects over 80% of registered cases and it includes the following parameters (obtained through a case report form): gender, age, comorbidities, and other concurrent conditions (identified by yes/no binary fields). Obesity was defined as BMI$\geq$30 kg/m^2, as reported in clinical records. All COVID-19 cases registered in the database as of April 30th, 2020, were included in the analysis, provided that they reported information on chronic diseases.

The primary outcome was hospitalization, and the secondary outcome was mortality. An age and gender-adjusted logistic regression model was used to assess the association of clinical and demographic characteristics with the risk of hospitalization. Further multivariate models were applied, adjusting for confounders. Separate analyses were performed for patients aged less than or over 70 years. Analyses were performed using the Stata/SE 14.2 software.

The use of the ISS Tuscany COVID-19 database by ARS is allowed by current regulations without the need for specific ethical approval.

Results

Out of 7540 patients with COVID-19 at April 30th, 2020, 3059 were excluded because of missing data. Excluded and included cases did not differ for age, gender, geographic distribution within the Region, and hospitalization (data not shown).

Of the 4481 included subjects, 49.5 and 50.5% were women and men, respectively. Patients aged over 60 and 70 years were 2377 (53.1%) and 1655 (36.9%), respectively; those admitted to hospital were 1907 (42.6%).

Obesity was associated with a higher risk of hospitalization (relative risk [95% confidence interval]: 1.74 [1.56–1.97]). Obesity, rheumatic diseases, active malignancies, chronic kidney disease, CVD, and diabetes were all associated with hospitalization after adjusting for age and gender (Table 1). The association of obesity with

Table 1 OR of hospitalization for individual chronic diseases, after adjusting for age and gender.

Pathology	N (%)		OR	Inf.	Sup.
	Hospitalization	No Hospitalization			
Obesity (BMI > 30 Kg/m2)	113 (5,93)	44 (1,71)	2.99	2.04	4.37
Chronic rheumatic diseases	29 (1,52)	12 (0,47)	4.03	1.95	8.30
Active tumors	177 (9,28)	68 (2,64)	2.46	1.80	3.35
Kidney diseases	169 (8,86)	58 (2,25)	2.24	1.62	3.11
Cardiovascular diseases	873 (45,78)	451 (17,52)	1.86	1.59	2.18
Diabetes	312 (16,36)	148 (5,75)	1.76	1.41	2.19
Other metabolic diseases	141 (7,39)	95 (3,69)	1.44	1.08	1.93
Hypertension	142 (7,45)	108 (4,20)	1.30	0.99	1.72
Hypothyroidism	36 (1,89)	46 (1,79)	1.60	0.98	2.60
Chronic respiratory diseases	256 (13,42)	179 (6,95)	1.16	0.93	1.45
HIV	35 (1,84)	33 (1,28)	1.30	0.77	2.19
Dementia	47 (2,46)	24 (0,93)	1.23	0.74	2.07
Chronic neurological diseases	92 (4,82)	70 (2,72)	1.00	0.71	1.40
Liver diseases	14 (0,73)	9 (0,35)	1.48	0.61	3.63
Mental disorders	21 (1,10)	22 (0,85)	1.05	0.55	2.00
Chronic inflammatory bowel diseases	4 (0,21)	4 (0,16)	1.90	0.43	8.49

OR: Odds ratio; *BMI: Body Mass Index, HIV: Human immunodeficiency virus.*

hospitalization retained statistical significance in a fully adjusted model, considering all factors associated with hospitalization at univariate analysis as possible confounders (Fig. 1, panel A). When analyzing separately patients < and ≥70 years, the effect of obesity was more evident in younger than in older subjects (Fig. 1, panel B–C). The association of obesity and risk of hospitalization remained statistically significant even after excluding deceased patients not previously hospitalized (Table 2).

In an alternative model, in which the interaction term obesity x age <70 was added, both obesity (BMI≥30 kg/m^2) and the interaction term, were significantly associated with hospitalization (OR 1.82 [1.07–3.10] and 3.10 [1.50–6.43] respectively). In a further model with obesity x gender as interaction term, the outcome was associated with obesity but not with the interaction term (OR 2.85 [1.66–4.91] and 1.68 [0.82–3.45], respectively).

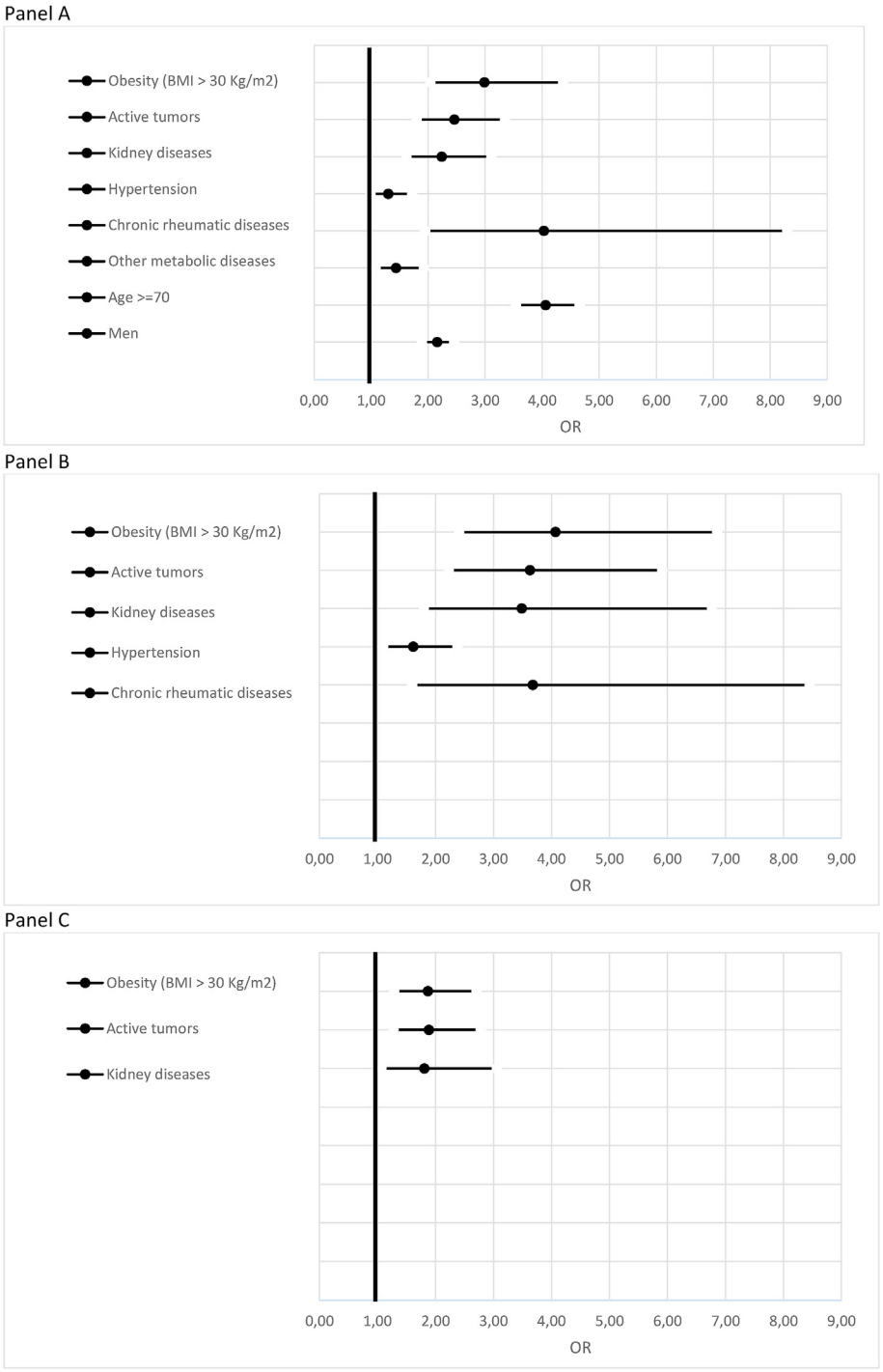

Figure 1 OR of hospitalization (multivariate model) Panel A - adjustment for age, gender and comorbidities; Panel B- in positive cases of SARS-Cov-2 <70 years; Panel C – in positive cases of SARS-Cov-2 >70 years.

Table 2 OR of hospitalization for individual chronic diseases, after adjusting for age and gender, excluding deceased patients not previously hospitalized (N = 76).

Pathology	N (%)		OR	Inf.	Sup.
	Hospitalization	No Hospitalization			
Obesity (BMI > 30 Kg/m2)	113 (5,93)	43 (1,70)	2.99	2.04	4.39
Chronic rheumatic diseases	29 (1,52)	12 (0,48)	3.96	1.91	8.19
Active tumors	177 (9,28)	64 (2,54)	2.53	1.84	3.48
Kidney diseases	169 (8,86)	54 (2,14)	2.28	1.62	3.19
Cardiovascular diseases	873 (45,78)	424 (16,81)	1.88	1.60	2.20
Diabetes	312 (16,36)	139 (5,51)	1.79	1.43	2.24
Other metabolic diseases	141 (7,39)	93 (3,69)	1.43	1.06	1.91
Hypertension	142 (7,45)	107 (4,24)	1.27	0.96	1.68
Hypothyroidism	36 (1,89)	46 (1,82)	1.58	0.97	2.57
Chronic respiratory diseases	256 (13,42)	167 (6,62)	1.21	0.96	1.51
HIV	35 (1,84)	33 (1,31)	1.26	0.75	2.13
Dementia	47 (2,46)	20 (0,79)	1.31	0.76	2.27
Chronic neurological diseases	92 (4,82)	58 (2,30)	1.18	0.82	1.69
Liver diseases	14 (0,73)	9 (0,36)	1.42	0.58	3.47
Mental disorders	21 (1,10)	22 (0,87)	0.99	0.52	1.90
Chronic inflammatory bowel diseases	4 (0,21)	4 (0,16)	1.87	0.42	8.39

OR: Odds ratio; *BMI: Body Mass Index, HIV: Human immunodeficiency virus.*

Obesity was also associated with a higher mortality rate among patients with COVID-19 (number of deaths: 329/3950 and 24/132 in non-obese and obese individuals, respectively; $\chi^2 = 12.76$, $p < 0.001$).

Discussion

The present data confirm that obesity is associated with an increased risk of hospitalization in patients with COVID-19, even adjusting for potential confounders, consistently with previously reported results [9,10]. Notably, this study was performed in an area with a moderate incidence of COVID-19, i.e., as of 30th April, 1.55 cases per 100,000 inhabitants. This allowed for a relatively efficient screening of oligosymptomatic cases, with a positive/total test ratio of 6.6%.

In addition, dedicated hospital bed capacity was not saturated by the epidemic surge; for this reason, hospitalization can be assumed as a reliable index of case severity, whereas in higher-incidence areas hospital admissions could have been limited by surge capacity.

Interestingly, the association of obesity with hospitalization was greater in younger (<70 years) patients [6,11]. It can be speculated that other known risk factors (i.e., comorbidities) were more frequent in older individuals, thus providing a greater contribution to disease severity.

The association of obesity with the risk of hospitalization is consistent with the reported increase in mortality and ICU admission in hospitalized obese patients with COVID-19 [5,12,13]. Several mechanisms could contribute to the increased severity of COVID-19 in obese patients. Excess weight is a risk factor for several conditions (e.g., diabetes, CVD, respiratory disease), which have been associated with poorer COVID-19 outcomes [14,15]. However, the association of obesity with hospitalization retains statistical significance even after adjusting for those conditions, suggesting different mechanisms. Among pathophysiological processes which could contribute to obesity-associated risk of severe COVID-19, obstructive sleep apnea [16] was not available among possible confounders in the present study. Other proposed mechanisms include changes in lung mechanics, low-grade systemic inflammation with interleukin 6 production, reduced expression of toll-like receptor 7, hyperexpression of angiotensin converting enzyme 2, and systemic endothelial dysfunction [17–20]. The present study does not allow a discrimination of potential pathogenetic mechanisms.

Some further limitations should be considered in interpreting the present results. It is possible that the diagnoses of comorbidities were inaccurate in some cases; furthermore, cases excluded from the analysis because of missing data are a potential source of bias. Anthropometric measures may have been inaccurate in an emergency setting. In addition, despite a relatively aggressive screening policy in Tuscany, a large number of asymptomatic or oligosymptomatic cases was probably missed. On the other hand, some strengths should be recognized: the survey was performed on the whole population, without barriers of access to healthcare. In addition, the analysis was performed in a Region in which the effectiveness of the diagnostic strategy was probably greater than in other parts of the Country, and in a condition in which hospitalization was accessible to all those in need.

In conclusion, obesity per se is a major risk factor for hospitalization in patients with COVID-19, particularly in younger individuals.

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