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High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation.

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Abstract (180 words)

Objective: The Covid-19 pandemic is rapidly spreading worldwide, notably in Europe and North America, where obesity is highly prevalent. The relation between obesity and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has not been fully documented.

Methods: In this retrospective cohort study we analyzed the relationship between clinical characteristics, including body mass index (BMI), and the requirement for invasive mechanical ventilation (IMV) in 124 consecutive patients admitted in intensive care for SARS-CoV-2, in a single French center.

Results : Obesity (BMI >30 kg/m2) and severe obesity (BMI >35 kg/m2) were present in 47.6% and 28.2% of cases, respectively. Overall, 85 patients (68.6%) required IMV. The proportion of patients who required IMV increased with BMI categories ($p<0.01$, Chi square test for trend), and it was greatest in patients with BMI >35 kg/m^2 (85.7%). In multivariate logistic regression, the need for IMV was significantly associated with male sex ($p<0.05$) and BMI ($p<0.05$), independent of age, diabetes, and hypertension. The odds ratio for IMV in patients with BMI >35 kg/m^2 vs patients with BMI <25 kg/m^2 was 7.36 (1.63-33.14; $p=0.02$)

Conclusion: The present study showed a high frequency of obesity among patients admitted in intensive care for SARS-CoV-2. Disease severity increased with BMI. Obesity is a risk factor for SARS-CoV-2 severity requiring increased attention to preventive measures in susceptible individuals.

What is known

1. A novel coronavirus causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and has spread globally, creating a worldwide pandemic.
2. Obesity has been previsously recognized as an independent predisposition factor for severe H1N1 pulmonary infection
3. Information about the clinical characteristics of infected patients who require intensive care is limited and the relationship between obesity and SARS-CoV-2 is unclear.

What is new

1. Obesity was unexpectedly frequent in a cohort of patients admitted in intensive care for SARS-CoV-2
2. Disease severity was associated with increased body mass index categories, being maximal in patients with a BMI ≥35 kg/m2.
3. The need for invasive mechanical ventilation was associated with severe obesity and was independent of age sex , diabetes, and hypertension.

What will change

1. Patients with obesity should avoid any COVID-19 contamination by enforcing all prevention measures during the current pandemic.
2. Patients with severe obesity should be monitored more closely.
3. Future studies should explore the mechanisms behind the association of SARS-CoV-2 with obesity

Introduction

Patients at risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been characterized as having preexisting diseases such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, or cancer (1). Surprisingly, body mass index (BMI) was rarely mentioned among the significant clinical risk factors for SARS-CoV-2 reported in early clinical reports from China (2), Italy (3), or the United States (4). Obesity has been, however, described as an independent predisposition factor for severe H1N1 pulmonary infection (5). Moreover, abdominal obesity is associated with impaired ventilation of the base of the lungs, resulting in reduced oxygen saturation of blood (6). Furthermore, the abnormal secretion of adipokines and cytokines like TNF-alpha and interferon characterise a chronic low-grade inflammation characteristic of abdominal obesity, which may impair immune response (7) and have effects on the lung parenchyma and bronchi (8). Altogether, it appears likely that obesity *per se* may be an independent risk factor for SARS-CoV-2 (9). COVID-19 pandemic is now rapidly spreading worldwide, notably in Europe and North America, where obesity is highly prevalent (10). Exploring the relationship between obesity and the severity of the disease is therefore of major clinical importance. In this retrospective cohort we aimed to investigate the association between BMI and clinical characteristics and the need for invasive mechanical ventilation in patients admitted to intensive care for SARS-CoV-2.

Materials and Methods

Study design and patients

In this single center retrospective cohort study, we enrolled all consecutive patients admitted to intensive care for SARS-CoV-2, in Roger Salengro Hospital, at "Centre Hospitalier Universitaire de Lille" (CHU Lille, France), between February 27th and April 5th, 2020. CHU Lille is the tertiary referral center for 4.5 million inhabitants from two French departments (Nord and Pas de Calais). All patients were diagnosed with COVID-19 pneumonia according to World Health Organization interim guidance (11) with SARS symptoms characterized by dyspnea, increased respiratory frequency, decreased blood oxygen saturation, and need for oxygen support therapy for at least 6 L/min. Throat swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase–polymerase chain reaction assays as previously described to identify SARS-CoV-2 infection (12). The study participants were also compared with a historical control group composed of 306 patients admitted to intensive care at our institution for a non SARS-CoV-2 related, severe acute respiratory disease, during the year 2019.

Data collection

A trained team of physicians reviewed and collected epidemiological data, past medical history, treatments, clinical data, and outcomes for all consecutive patients from their admission to April 6th, 2020. This observational study was based on medical records, in strict compliance with the French reference methodology MR-004, established by French National Commission on Informatics and Liberties (CNIL), and approved by the Institutional data protection authority of CHU Lille. Patient confidentiality was protected by assigning an anonymous identification code, and the electronic data were stored in a locked, password-protected computer.

Study outcomes

The primary outcome of this study was the prevalence of patients receiving invasive mechanical ventilation (IMV) following admission to intensive care. The use of IMV was determined when oxygen therapy (≥ 10 L/min) with target spO2 (90-94%) was ineffective, and when respiratory rate was above 25/min, with signs of acute respiratory failure, despite maximal oxygen therapy. The following patient characteristics were analyzed: sex, age, weight, height, body mass index (BMI), past history of diabetes, hypertension, and dyslipidemia. Patients were classified according to their BMI in four categories as lean (from 18.5 to < 25 kg/m2), overweight (from 25 to < 30 kg/m2), moderate obesity (from 30 to < 35 kg/m2) and severe obesity (≥ 35 kg/m2).

Statistical analysis

All results were expressed as median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. Continuous variables were compared between groups with the Student t-test or Mann-Whitney U-test according to their distribution. Categorical variables were compared with the chi squared (or fisher's exact test). The association between BMI and the need for IMV, as well as that of predefined patient characteristics including age, sex, history of diabetes, hypertension on the need for IMV, was first assessed by univariate logistic regressions analysis. All variables were then included in multivariable logistic regression analysis to control the association of BMI with IMV for well-known predictors. A p-value level < 0.05 was considered significant. All statistical analyses were performed with SAS Studio Statistics (version 3.71) and Prism Graphpad (version 8.1.2).

Results

A total of 124 patients were admitted in intensive care for SARS-CoV-2 during the study period, and were all enrolled in the present study. At the time of analysis (April 6th), 60 patients (48%) had been discharged alive from intensive care, 18 (15%) had died and 46 remained hospitalized in intensive care. SARS-CoV-2 study participants were predominantly males (73%), and their median (IQR) age was 60 (51 to 70) years. Other clinical characteristics are detailed in Table 1. As illustrated in Fig.1 the distribution of BMI categories in SARS-CoV-2 participants differed markedly from the historical control group of patients admitted to intensive care for a non SARS-CoV-2 severe acute respiratory disease (Fig.1a) ($p<0.001$; Fisher exact test for trend). Obesity (BMI>30 kg/m^2) and severe obesity (BMI>35 kg/m^2) were significantly more frequent among SARS-CoV-2 participants than in these non SARS-CoV-2 controls: 47.6% vs 25.2% and 28.2% vs 10.8%, respectively. The median (IQR) BMI in SARS-CoV-2 participants was higher than in non SARS-CoV-2 controls; 29.6 (26.4 to 36.5) kg/m2 vs 24.0 (18.9 to 29.3) kg/m2, respectively ($p<0.0001$, t-test). In contrast, sex distribution and age were not significantly different from participants in non SARS-CoV-2 controls (63.5% males, $p=0.08$ vs SARS-CoV-2 subjects, Fisher exact test; 63 (51-71) years, $p=0.97$ vs SARS-CoV-2 subjects, t-test).

At the time of analysis, 85 out of the 124 study participants (68.6%) had required IMV, including 62 at admission, 13 at day 1, 4 at day 2 and the remaining 6 within 7 days. Their median (IQR) BMI was 31.1 (27.3 to 37.5) kg/m2 as compared as 27.0 (25.3 to 30.8) kg/m^2 in the 39 (31.4%) patients who did not require IMV ($p<0.001$). At the time of writing, 85 out of the 124 study participants (68.6%) had required IMV. Their BMI was higher than in the 39 (31.4%) patients who did not require IMV: 31.1 (27.3-37.5) kg/m2 vs 27 (25.3-30.8) kg/m^2, respectively ($p<0.001$, t-test). As illustrated in Fig.1, the distribution of BMI categories differed markedly between the two subgroups ($p<0.01$; Fisher exact test for trend); obesity (BMI>30 kg/m^2) and severe obesity (BMI≥35 kg/m^2) being more frequent among patients who required IMV than among those who did not: 56.4% vs 28.2% and 35.3% vs 12.8%, respectively (Fig.1b).

In multivariate logistic regression analysis, the relation between male sex and BMI categories and the need for IMV remained significant after adjustment for age, diabetes, and hypertension (Table 2).

Discussion

Our main finding was the unexpected high frequency of obesity among patients admitted to intensive care for SARS-CoV-2. Overall, 47.5% presented with obesity (BMI ≥ 30 kg/m2), including class II obesity (BMI 35-39.9 kg/m2) in 13.7% and with class III obesity (BMI ≥40 kg/m2) in 14.5%. This distribution of BMI categories was markedly different than the distribution observed in control subjects admitted during the previous years in intensive care for severe acute pulmonary condition, in the same institution. In these non SARS-CoV-2 patients, the prevalence of obesity was only 25.8%, similar to the prevalence observed in the general population from Nord and Pas de Calais, when adjusted for age and sex (13). Importantly, we also showed that the need for IMV, a robust proxy for the severity of SARS-CoV-2, gradually increased with body mass categories, reaching nearly 90% in patients with a BMI > 35 kg/m2. The main strength of the present study is its cohort design and the enrollment of all consecutive patients admitted in intensive care for SARS-cov-2 during the study period. This single center study also has limitations such as its retrospective nature and the limited number of patients enrolled. The distinct role of other important predictors such as diabetes and hypertension (2, 3), which did not appear to be independent from obesity in our cohort, might become significant in future studies enrolling larger numbers of patients. We had only a few younger patients (less than 30 years) and very old patients (more than 80 years) in our sample. Furthermore, we could not analyze the effect of body mass index on the mortality rate, because too few events were observed. Of note, many patients were still hospitalized at the time of this analysis. Taken together, our data demonstrate a distinct relation of obesity with the severity of SARS-CoV-2. Obesity is generally recognized as a risk factor for severe infection (7), as illustrated by the more severe disease of longer duration observed in patients with obesity during the influenza A H1N1 epidemic (7, 14, 15). Pulmonary function studies have also demonstrated a restrictive pattern and reduced lung volumes in obese individuals (16, 17). Moreover, these pulmonary features evolve favorably in association with weight loss following bariatric surgery (18). Moreover, obesity and the metabolic syndrome are thought to increase type 2 inflammation, which may have effects on the lung parenchyma and bronchi (8). In addition, raised interleukin 6 (IL-6) levels are associated with obesity and/or metabolic syndrome (19). The abnormal secretion of adipokines and cytokines like TNF-a and interferon characterize a chronic low-grade inflammation in abdominal obesity and may induce an impaired immune-response (7). Determining the cause of the relation between obesity and SRAS-CoV-2 goes beyond the scope of the present study and should now be the aim of future translational studies.

In conclusion, this cohort study showed that obesity is a factor in disease severity of SARS-CoV-2, having greatest impact in patients with a BMI ≥35 kg/m2. Patients with obesity and especially those with severe obesity should take extra measures to avoid COVID-19 contamination by enforcing prevention during the current pandemic.

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Data sharing statement

The data sets generated during and/or analyzed during the current study are not publicly available, since they are subject to national data protection laws and restrictions imposed by the Institutional data protection authority of CHU Lille to ensure data privacy of the study participants.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1 : Baseline characteristics of 124 patients admitted in intensive care for SARS-CoV-2, who required invasive mechanical ventilation (n=85) and those who did not (n=39).

	All patients n=124	Invasive mechanical ventilation n=85	No invasive mechanical ventilation n=39
Male	90 (73)	64 (75)	26 (67)
Age (years)	60 (51-70)	60 (51-69)	60 (50-72)
Height (cm)	172 (166-178)	172 (166-178)	172 (165-180)
Weight (kg)	88 (80-108)	95 (81-112)	81 (75-94)
Body mass index (kg/m^2)	29.6 (26.4-36.4)	31.1 (27.3-37.5)	27 (25.3-30.8)
Diabetes	28 (23)	23 (27)	5 (13)
Hypertension	60 (49)	48 (56)	12 (32)
Dyslipidemia	34 (28)	24 (28)	10 (26)

Footnote: Results are expressed as median (IQR) for continuous variables and as frequency (percentage) for categorical variables.

Table 2: Univariate and multivariate logistic regression analysis of the association between patient clinical characteristics and the need for invasive mechanical ventilation.

	Univariate		Multivariate	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Age (years)	1.00 (0.97-1.02)	0.73	1.00 (0.97-1.04)	0.87
Male	1.52 (0.67-3.49)	0.32	2.83 (1.02-7.85)	0.046
Diabetes vs. no	2.45 (0.85-7.03)	0.10	1.60 (0.44-5.83)	0.48
Hypertension vs. no	2.81 (1.25-6.3)	0.012	2.29 (0.89-5.84)	0.08
Dyslipidemia vs. no	1.10 (0.47-2.61)	0.83	0.68 (0.24-1.97)	0.48
Body mass index categories		0.023		0.049
25-30 kg/m2 vs. <25 kg/m2	1.72 (0.56-5.23)	0.22	1.69 (0.52-5.48)	0.22
30-35 kg/m2 vs. <25 kg/m2	3.38 (0.9-12.72)	0.45	3.45 (0.83-14.31)	0.48
≥35 kg/m2 vs. <25 kg/m2	6.75 (1.76-25.85)	0.015	7.36 (1.63-33.14)	0.021

Footnote: Multivariate logistic regression analysis included all variables.

Figure Legend

Figure 1: (a) Distribution of body mass index categories in patients admitted during the study period in intensive care for SARS-CoV-2 (n=124) and in patients admitted during the previous year in intensive care for a non COVID-19 related severe pulmonary condition (n=306) (Chi square test for trend); (b) Distribution of body mass index categories in patients who required mechanical ventilation (n=85) and those who did not (n=39) (t test); (c) Proportions of patients requiring mechanical ventilation during their stay in intensive care, according to body mass index categories (Chi square test for trend).

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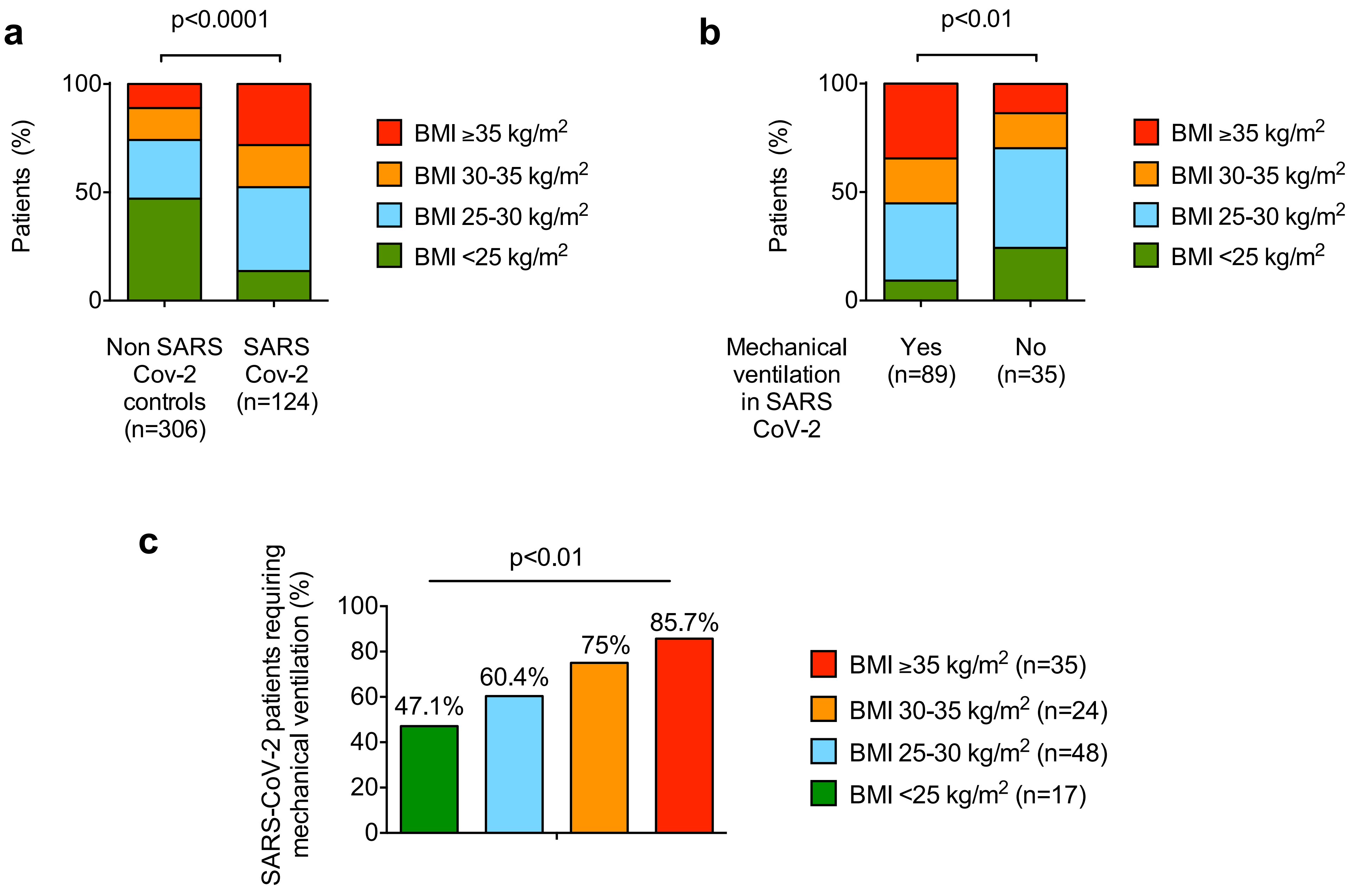
Fig.1


a
p<0.0001
Patients (%)
100
50
0
Non SARS Cov-2 controls (n=306)
SARS Cov-2 (n=124)
BMI ≥35 kg/m2
BMI 30-35 kg/m2
BMI 25-30 kg/m2
BMI <25 kg/m2
b
p<0.01
Patients (%)
100
50
0
Mechanical ventilation in SARS CoV-2
Yes (n=89)
No (n=35)
BMI ≥35 kg/m2
BMI 30-35 kg/m2
BMI 25-30 kg/m2
BMI <25 kg/m2
c
p<0.01
SARS-CoV-2 patients requiring mechanical ventilation (%)
100
80
60
40
20
0
47.1%
60.4%
75%
85.7%
BMI ≥35 kg/m2 (n=35)
BMI 30-35 kg/m2 (n=24)
BMI 25-30 kg/m2 (n=48)
BMI <25 kg/m2 (n=17)