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Title: BMI and pneumonia outcomes in critically ill COVID-19 patients: an international multicenter study.

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FP and MJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Study Importance

What is already known?

- Early evidence has linked the overall severity of COVID-19 with older age, male sex, and preexisting chronic conditions such as cancer, and chronic renal, liver, respiratory, and cardiovascular disease.
- Some studies also found an overall association of disease severity with obesity, and other metabolic risk factors, including diabetes, hypertension, and smoking.
- A wider geographic representation, across centers with variable prevalence of obesity, is needed.

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What does this study add?

- We showed a significant relation between BMI and invasive mechanical ventilation (IMV): adjusted OR 1.27 (95% CI, 1.12-1.45) in the whole cohort, and 1.65 (95% CI, 0.97-2.79) per 5 kg/m^2 in females under 50 years.
- Adjusted Cox regression model showed a significant association between BMI and 28-day all-cause mortality, which was only increased in obesity class III (≥40 kg/m^2) (adjusted HR 1.68 (95% CI 1.06-2.64).

How might these results change the focus of clinical practice?

- We observed a linear association between BMI and the need for IMV in ICU COVID-19 patients, across multiple countries, independent of other metabolic risk factors, and a non-linear association between BMI and mortality risk.
- These findings will help to determine the risk of severe COVID-19 pneumonia, in all BMI categories, in order to provide clear guidance for specific prevention, including vaccination in patients at highest risk.

Abstract

Background: Previous studies unveiled a relation between the severity of COVID-19 pneumonia and obesity. The aims of this multicenter retrospective cohort study were to disentangle the association of BMI and associated metabolic risk factors (diabetes,

hypertension, hyperlipidemia, current smoking) in critically ill patients with COVID-19. Methods: This multicenter retrospective cohort study enrolled patients admitted in intensive care for COVID-19, in 21 centers (Europe, Israel, USA) between 02/19/2020 and 05/19/2020. Primary and secondary outcomes were the need for invasive mechanical ventilation (IMV), and 28-day mortality. Results: A total of 1,461 patients were enrolled, median(IQR) age was 64 years (40.9-72.0); 73.2% males; BMI 28.1 kg/m^2 (25.4-32.3); 1,080 patients (73.9%) required IMV; the 28-day mortality estimate was 36.1% (95%CI, 33.0-39.5). Adjusted mixed logistic regression model showed a significant linear relation between BMI and IMV: OR 1.27 (95%CI, 1.12-1.45) per 5 kg/m^2. Adjusted Cox proportional hazards regression model showed a significant association between BMI and mortality, which was only increased in obesity class III (≥40 kg/m^2) (HR 1.68 (95%CI 1.06-2.64). Conclusion: In critically ill COVID-19 patients, we observed a linear association between BMI and the need for IMV, independent of other metabolic risk factors, and a non-linear association between BMI and mortality risk. (NCT04391738).

Introduction

Eighteen months after the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the coronavirus disease 2019 (COVID-19) pandemic has expanded globally, having already affected more than 150 million individuals worldwide and claimed more than 3 millions lives (1). Identifying risk factors of worse outcomes is essential for reducing the future overall burden of COVID-19 on health system and enforcing prevention efforts in populations at higher risk. Early evidence has linked the overall severity of COVID-19 with older age, male sex, and preexisting chronic conditions such as cancer, and chronic renal, liver, respiratory, and cardiovascular disease (2–4). Numerous studies also found an overall

association of disease severity with obesity (5–9), and other metabolic risk factors, including diabetes (10, 2, 5, 11), hypertension (3), and smoking (12). One distinct feature of COVID-19 is pneumonia and the frequent need for invasive mechanical ventilation (IMV), resulting in great strain on intensive care resources worldwide (13). Simonnet et al. (14) reported that the need for IMV gradually increased with body mass index (BMI) in COVID-19 patients admitted in intensive care units (ICU). The association between obesity and the need for IMV was also found statistically significantly in four independent studies (15–18), in contrast with other studies (19–21). Some reports suggested that the relation between BMI and COVID-19 severity might be restricted to younger patients (22–25). Based on existing data, public health agencies in Europe and the USA have issued guidelines that include obesity as an increased risk factor of severe COVID-19 (26–28). Likewise, the COVID-19 pandemic has already impacted people living with obesity in multiple ways, ranging from food shortages and insecurity, reduced physical activity during lockdown, anxiety from cancellation of care, and mental health issues compounded by isolation (29). More global data is therefore urgently needed to determine the risk of severe COVID-19 pneumonia, across all BMI categories, in order to provide clear guidance and inform patient care (30). A wider geographic representation, across centers and countries with variable prevalence of obesity, is also needed to ensure the validity and generalizability of the findings.

This multicenter international retrospective cohort study was designed to examine the relationship between BMI and COVID-19 pneumonia severity, as defined by the need for IMV (primary outcome) and the 28-day all-cause mortality rate (secondary outcome) among patients admitted in ICU. The study secondary objectives were to disentangle the influence of BMI from other metabolic risk factors, such as diabetes, hypertension, dyslipidemia, and current smoking, as well as to investigate the modifying effects of age and sex on this relationship.

Methods

The BMI-SARS-CoV-2 study was a multicenter, international, retrospective cohort study designed to investigate the relationship between BMI and the need of IMV, among adult patients admitted in ICU for COVID-19 (ClinicalTrials.gov Identifier: NCT04391738, sponsored by the Lille University Hospital, France). The study complied with standard operating procedures in place, in accordance with the European Data Protection Directive (95/46/EC) and, upon its entry into force, Regulation (EU) 2016/679 (also referred to as the General Data Protection Regulation (GDPR)), and French CNIL frameworks n° MR004 regarding the processing of personal data in clinical studies. The institutional review board from other centers in USA and Israel approved the retrospective case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent. The study report followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data Sources

Centers that routinely registered BMI in patients admitted in ICU for COVID-19 during the study period were identified among a preexisting network of ICUs in France (French Network of Simulation in Intensive Care) or through the published literature. The Medline database (https://pubmed.ncbi.nlm.nih.gov) and the Clarivate Web of Science database (https://webofknowledge.com) were searched using the following keywords: intensive care, COVID-19, SARS-CoV-2, obesity, body mass index to identify cohort studies that reported BMI in patients admitted in ICU for COVID-19. Overall, 27 centers from seven countries (France, China, Belgium, USA, Israel, Italy, and Spain), were identified and contacted, and 21 agreed to participate as follows: France (13), Italy (3), USA (2), Israel (1), Belgium (1), and Spain (1). In order to minimize data input errors or possible bias, each participating center received a standardized template, based on the registered study design and accompanied by a glossary of required variables and a data entry support guide, in order to enforce the homogeneity and validity of the data and to lower the number of missing values. At each center, investigators extracted primary data from medical records from all consecutive patients admitted in ICU for COVID-19, between February19th 2020 and May 11th, 2020. Data cleaning involved repeated cycles of screening, diagnosing, treatment, and documentation of this process. Finally, each center removed all potential identifiers from the dataset, which was assembled in random order, protected with a password, prior to being sent

to the study sponsor, in accordance to the data transfer agreement. Individual data were eventually aggregated by the sponsor center, in random order, with an inclusion number corresponding to each center.

Study Patients and Covariates

Participants were patients admitted in ICU for confirmed COVID-19 related pneumonia with acute respiratory distress syndrome, as diagnosed on the basis of WHO guidance (31). SARS-CoV-2 infection was defined as a positive result on real-time reverse transcriptase–polymerase chain reaction assay of nasal or pharyngeal swab specimens, as previously described (32). All primary data were reviewed and collected by trained physicians. The variables collected at the time of admission included sex, age, height, and body weight, measured or estimated by a physician, as well as pre-specified metabolic risk factors such as current smoking status and history of diabetes, hypertension, and dyslipidemia. Other associated comorbidities included cardiovascular disease (including chronic heart disease, cerebrovascular disease, and peripheral arterial disease), chronic obstructive pulmonary disease, and immunodeficiency (including steroid use, pre-existing immunological condition, or current chemotherapy in individuals with cancer). Current or previous history of cancer and chronic kidney disease were also collected, as well as the use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and antidiabetic treatment, with or without insulin.

Exposure of Interest:

The exposure of interest was BMI, defined as the weight in kilograms divided by the square of height in meters, and measured at the time of admission in ICU. BMI was analyzed as a continuous variable, or classified in BMI categories as defined by the World Health Organization (33): underweight (under 18.5 kg/m^2); normal weight (18.5 to 24.9 kg/m^2); overweight (25 to 29.9 kg/m^2); obesity class I (30 to 34.9 kg/m^2); obesity class II (35 to 39.9 kg/m^2); and obesity class III (40 kg/m^2 and above). In some subgroup analyses, underweight and normal weight categories, on one hand, and obesity class I, II and III categories, on the other hand, were combined as lean (under 25 kg/m^2), and obesity (30 kg/m^2 and above), respectively, in order to gather sufficient numbers of patients.

Outcomes and Follow-up

The primary outcome was the need for IMV prior to, or after, ICU admission. The secondary outcome was all-cause mortality rate within 28 days following ICU admission. Data were collected from February 19th to May 19th, 2020. The following events were collected: the date of ICU admission, the number of days between admission and intubation (0 day means that IMV occurred the day of admission), and the number of days spent under IMV (1 day means that the patient was extubated after a day spent under IMV). When the patient was tracheotomized, the return to spontaneous ventilation with ambient air was considered as an extubation event. Patient status at last news (deceased, discharged from, or still hospitalized in ICU) and the number of days that elapsed since ICU admission was also collected.

Statistical Analysis

Having examined histograms, all quantitative variables were summarized by median and quartiles, and groups compared using the Mann-Whitney U-test. Categorical variables were expressed as numbers (percentage) and compared by Chi-square test with the use of Yates' continuity correction.

The association of BMI with the need of IMV in patients with COVID-19 admitted in intensive care was assessed by using a mixed logistic regression model, including center as random effect. BMI was analyzed as a categorical variable using modified WHO classification (see exposure description) and as a continuous variable. Odds ratio (OR) was calculated using the lean category (BMI < 25 kg/m^2) as reference, or per 5 kg/m^2 increase in BMI. The log-linearity assumption was examined using restricted cubic spline functions.

A multivariable analysis using a mixed logistic regression model was performed to adjust the association between BMI and IMV on predefined confounding variables, including age, sex, and the presence of pre-specified metabolic risk factors (diabetes, hypertension, dyslipidemia, and current smoking). Finally, in a secondary and exploratory analysis, we investigated the heterogeneity in the association of BMI and IMV into the mixed logistic regression models according to sex (male vs. female) and age subgroups (< 50 years, 50 to 74.9 years and ≥ 75 years).

The association between BMI and 28-day all-cause mortality was assessed by using a Cox proportional hazard regression models with a random center effect (frailty model) with and without predefined confounding variables. Similarly, to previous analyses, BMI was analyzed as a categorical variable using modified WHO classification (see exposure description) and

continuous variable. Since the log-linearity assumption was not satisfied, only results for BMI treated as categorical variable were reported. Hazard Ratio (HR) were calculated using the lean category (BMI < 25 kg/m^2) as reference.

Primary analyses for both outcomes were done after handling missing values by multiple imputations. Imputation procedure was performed using a regression switching approach (chained equations with m=10 imputations) under missing at random assumption using all patient characteristics with a predictive mean matching method for quantitative variables and a logistic regression model (binary, ordinal, or multinomial) for categorical variables. Regression estimates obtained in the different imputed datasets were combined using Rubin's rules. An available-case sensitivity analysis was also performed. Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of Study Population

A total of 1,461 individuals admitted in ICU with confirmed COVID-19 - in 21 institutions from 6 countries: France (13), Italy (3), USA (2), Israel (1), Belgium (1), and Spain (1), were included in this study (See study flow chart, **Figure S1**). **Table 1** details the characteristics of the participants who required IMV, and those who did not, as well as the prevalence of pre-existing chronic conditions and treatments at the time of admission. Overall, study participants were predominantly males (73.2%), with an age varying from 19 to 93 years, and a median (IQR) of 64 (56-73) years. The median (IQR) BMI was 28.1 (25.4-32.3) kg/m^2, with an overall prevalence of obesity (BMI above 30 kg/m^2) of 37.5%. The study participants had markedly higher BMI than those observed, after adjustment for sex and age, in the general population of the corresponding country (**Figure S2**).

Half of participants had hypertension (51.5%), while the prevalence of diabetes and dyslipidemia were 29.2% and 29.0%, respectively. Overall, 1,080 (73.9%) participants required IMV, after a median (IQR) time of 0 days (0-1) following ICU admission. As expected, patients who required IMV had a higher initial severity score than those who did not require IMV. The patients who required IMV were also predominantly males (76.3%), had a higher BMI, and were more frequently current smokers (**Table 1**). Patient characteristics and data collected in each of the 21 centers are detailed in **Figure S3**.

At the time of analysis (May 19th, 2020), 903 (61.8%) patients had been discharged alive, 385 (26.4%) had died following a median (IQR) 11 days (6-18) in the ICU, and 173 (11.8%) were still hospitalized in ICU. The median (IQR) follow-up period of observation following ICU admission was 13 days (7-26) in the overall population, and 15 days (7-29) among survivors. Among 1,080 patients who required IMV, 633 (58.6%) patients had been extubated alive at the time of analysis, after a median (IQR) duration of IMV of 14 days (8-22).

Association between BMI and the Need for IMV

In a multivariable mixed logistic regression model adjusted on center and/or age, sex, and pre-specified metabolic risk factors (diabetes, hypertension, dyslipidemia, and current smoking), BMI was statistically significantly associated with the need for IMV (**Table 2**). Moreover, the relation between BMI and the risk of the need for IMV was linear, as illustrated by the

gradual increase of OR with each BMI category, reaching 3.06 (1.53 to 6.10) in patients with class III obesity (BMI ≥ 40 kg/m^2) (**Figure 1a**). The relation between BMI and the need for IMV was further confirmed in a sensitivity analysis limited to available cases (**Table S1**). In addition, we observed that older age and male sex were independent predictors of the need for IMV, in contrast to diabetes, hypertension, dyslipidemia, and current smoking (**Table 3** and **Table S2**).

The heterogeneity of the association between BMI and IMV with age was studied in key subgroups exploratory analysis, on the overall study population and on the complete cases population (**Figure 2**). As illustrated, the association of BMI with IMV was more pronounced in females under 50 years, with an adjusted OR of 1.65 (95%CI, 0.97 to 2.79) in primary analysis and 1.86 (95%CI, 1.67 to 3.22) in sensitivity analysis.

Association of BMI with 28-day Mortality.

The overall estimate of 28-day mortality was 36.1% (95%CI, 33.0 to 39.5%). As shown in table 2, we found a non-linear relationship between BMI categories and 28-day mortality, with an increased mortality risk only for patients with severe or class III obesity (≥ 40 kg/m^2) (Figure 1b). The non-linearity of the relation between BMI and 28-day mortality was further confirmed in a sensitivity analysis (**Table S1**).

In data driven model, considering BMI as binary variable (≥ 40 kg/m^2 vs. < 40 kg/m^2), obesity class III remained an independent predictor of mortality (HR=1.84; 95% CI 1.23 to 2.75) in addition to age (HR per 10-year increase, 1.74; 95% CI 1.54 to 1.95) (**Table 4**). These results were further confirmed in a sensitivity analysis (**Table S3**).

Discussion

To our knowledge, this multicenter cohort study represents the first international collaborative effort to explore the association of BMI with the outcomes of pneumonia among Covid-19 patients admitted in ICU. Our main finding was a linear correlation between BMI and the need for IMV, after adjustment on center, age, sex, and other pre-specified metabolic risk factors. Of note, we observed in age-sex subgroups analyses that the relation between BMI and the need for IMV, was more pronounced in females than in males under 50 years (**Figure 2**). An influence of age on the relation between obesity and COVID-19 severity has been previously suggested, (22–24), but one that existed regardless of sex. A milder severity of COVID-19 has been previously reported in pre-menopausal women (34). In line with our findings, obesity was also the variable most associated with COVID-19 disease severity in pregnant women in a recent report (35). Of note estrogen are classically playing a protective role in women (36), and Estradiol levels decreased with overweight and/or obesity in pre-menopausal women (36, 37). However, the observational nature of our study cannot address the complexity of this question. As expected, we also observed an overall association of the need for IMV with older age and male sex (11-19). However, we did not unveil any independent relation between the need of IMV and current smoking, nor with any other pre-specified metabolic risk factors. A distinct association of diabetes with the overall severity of COVID-19 had been suggested in previous reports (4, 16, 38). However, one study did not include BMI among the variables analyzed (38), while, in the two others, obesity was the main driver of the association between diabetes and the need for IMV (4, 16).

The second original finding of our study was the non-linear relation observed between BMI and the 28-day all-cause mortality rate in patients admitted in ICU. When fully adjusted on center, age, sex and pre-specified metabolic risk factors, obesity class III (BMI $\geq$ 40 kg/m^2) was associated with a 68% increase in mortality, as compared with lean patients (BMI <25 kg/m^2). On the other hand, mortality risk was not increased in patients with overweight or obesity class I and II (BMI between 25 kg/m^2 and 39.9 kg/m^2). This seemingly paradoxical relationship between mortality and BMI categories has not yet been reported in COVID-19 patients (5, 6), but echoes the "obesity survival paradox," generally observed in critically ill patients (39), with overweight and moderate obesity being protective as compared with lean BMI or normal BMI or more severe obesity (40) ici . Further research should focus on

identifying the underlying pathophysiologic mechanisms of the "obesity survival paradox" in COVID-19.

As expected, the all-cause mortality was also closely linked with age, with a 74% increase per ten-years. Of note, male sex and diabetes were only marginally associated with mortality in the present study, which enrolled only patients admitted in ICU, in contrast to other multicenter studies conducted in hospitalized patients (6, 38, 41) or in the general population (5).

Strengths

The main strength of the present study was the large number of participants, across all BMI categories, and both sexes, which allowed us to perform, all planned analyses, with BMI as exposure, and association with pre-specified metabolic risk factors. Second was the choice of IMV as the study primary outcome. As opposed to other less specific endpoints like hospital or ICU admission, all-cause mortality, or composite severity end points (6, 10, 20), IMV allowed us to specifically explore the association between BMI and severity of pneumonia in COVID-19. Finally, the wide geographic representation of participating centers provides insight related to the generalizability of effect across regions and countries with variable prevalence of obesity, thus improving the validity of our findings and enhancing their general relevance.

Limitations

The main limitation of our study lies in its retrospective nature. Standard clinical care may have varied between centers, and participants received various treatments which were not considered in our analyses. Second, the data from patients who remained hospitalized at the final study date (11.8%) were censored, and they may have led to an underestimation of the outcomes. This risk appears limited, however, since 98.7% of patients requiring IMV did so within 7 days from admission, and since, at the time of analysis, 95.8% of patients had been already discharged alive or had been hospitalized for more than 28 days. Third, the multicenter design of this international study creates a complex confounding structure. Results were not adjusted for other potential confounders, including race, ethnicity, socio-economic status indicators, and comorbidities such as chronic kidney, cardiovascular, and respiratory diseases. Finally, we did not enrolled participants from Africa, South America, or Asia, in whom different BMI cut points may have been more relevant. This may limit the generalizability of our findings which remain to be confirmed more globally.

Conclusion

Taken together, the data of this international multicenter cohort study provide direct evidence of the independent association between obesity and the severity of pneumonia in COVID-19. We first observed a overall linear relation of BMI with the need of IMV, which was most pronounced in females under the age of 50. Second, we observed a non-linear relation of BMI with 28-day all-cause mortality, which was increased in patients with severe obesity (BMI ≥ 40 kg/m^2). With the ongoing pandemic and the obesity epidemic feeding each other (42), this close association between BMI and the severity of COVID-19 pneumonia should foster more drastic measures to limit the risk of COVID-19 infections in patients with obesity.

The evidence presented here may also inform physio-pathological research to elucidate the relation between obesity and severe lung damage in COVID-19.

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The sponsors were represented by the corresponding authors, Francois Pattou and Merce Jourdain. The sponsors had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and review and approval to submit the manuscript for publication. The sponsors did not have the right to veto submission to any particular journal, but did participate in the writing group's discussion when selecting an appropriate journal for submission. The corresponding authors had the final say in submitting the manuscript for publication.

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Tables

Table 1. Characteristics at baseline of patients admitted in ICU, in the whole cohort (n=1461) and in patients who did (n=1080) or did not require invasive mechanical ventilation (n=381)

	N	All patients (n=1461)	Non IMV (n=381)	IMV (n=1080)	P-value[a]
Characteristics at admission					
Male sex, No. (%)	1461	1070 (73.2)	246 (64.6)	824 (76.3)	< 0.001
Age, median (IQR), y	1461	64 (56-73)	62 (53-75)	65 (56-72)	0.48
Age by classes, No. (%)	1461				< 0.001
< 50 y		210 (14.4)	74 (19.4)	136 (12.6)	
50 to 75 y		968 (66.3)	211 (55.4)	757 (70.1)	
≥ 75 y		283 (19.4)	96 (25.2)	187 (17.3)	
BMI, median (IQR), kg/m^2	1375	28.1 (25.4-32.3)	27.7 (24.7-31.2)	28.4 (25.4-32.6)	0.001
BMI, by WHO classes, No. (%)	1375				0.005[b]
< 18.5 kg/m^2		8 (0.6)	4 (1.1)	4 (0.4)	
18.5 to 24.9 kg/m^2		296 (21.5)	93 (25.7)	203(20.0)	
25 to 29.9 kg/m^2		557 (40.5)	147 (40.6)	410 (40.5)	
30 to 34.9 kg/m^2		301 (21.9)	71 (19.6)	230 (22.7)	
35 to 39.9 kg/m^2		134 (9.8)	32 (8.8)	102 (10.1)	
≥ 40 kg/m^2		79 (5.8)	15 (4.1)	64 (6.3)	
Pre-existing conditions					
Diabetes, No. (%)	1461	426 (29.2)	99 (26)	327 (30.3)	0.11
Hypertension, No. (%)	1461	752 (51.5)	193 (50.7)	559 (51.8)	0.71
Hyperlipidemia, No. (%)	1461	423 (29)	99 (26)	324 (30)	0.14
Current smoker, No. (%)	1275	83 (6.5)	14 (4.1)	69 (7.4)	0.049
Cardiovascular disease, No. (%)	1461	373 (25.5)	111 (29.1)	262 (24.3)	0.06
Chronic kidney disease, No. (%)	1265	133 (10.5)	35 (10.8)	98 (10.4)	0.86
Chronic obstructive pulmonary disease, No. (%)	1461	146 (10)	45 (11.8)	101 (9.4)	0.17
Malignancy, No. (%)	1461	150 (10.3)	37 (9.7)	113 (10.5)	0.68
Immunosuppression, No. (%)	1275	88 (6.9)	19 (5.9)	69 (7.3)	0.39
Severity score					
SAPS-II	1135	39 (29-53)	29 (22-39)	43 (33-57)	< 0.001
Treatments					

Hypoglycemic treatment	1362				0.09 [b]
No treatment, No. (%)		990 (72.7)	282 (76.2)	708 (71.4)	
Yes, but no insulin, No. (%)		222 (16.3)	58 (15.7)	164 (16.5)	
Insulin, No. (%)		150 (11)	30 (8.1)	120 (12.1)	
Renin–angiotensin–aldosterone system inhibitors					
ARBs, No. (%)	1153	192 (16.7)	59 (18.1)	133 (16.1)	0.41
ACEi, No. (%)	1153	190 (16.5)	55 (16.9)	135 (16.3)	0.82

Abbreviation: N., number, IQR, interquartile range, y, years, BMI, body mass index, WHO, World Health Organization, SAPS-II, simplified acute physiology score, ARBs, angiotensin receptor blockers, ACEi, angiotensin converting enzyme inhibitors, IMV, invasive mechanical ventilation. SAPS: simplified acute physiology score.

[a] Mann-Whitney U test was used for continuous variables comparison, and $\chi 2$ test with Yates' continuity correction was used for categorical variables comparison if not specified.

[b] Cochran-Armitage Trend Test was used for comparison of ordinal BMI categories.

Table 2. Association of BMI categories with the need of invasive mechanical ventilation requirement and 28-day all-cause mortality

	BMI categories, kg/m²					P-value [a / b]
	< 25 (n=319)	25 to 29.9 (n=591)	30 to 34.9 (n=323)	35 to 39.9 (n=143)	≥ 40 (n=85)	
IMV						
No. (%)	219 (68.5)	436 (73.8)	248 (76.7)	109 (76.0)	69 (81.4)	
Center-adjusted OR (95% CI)	1.00 (ref.)	1.20 (0.86 to 1.66)	1.46 (0.98 to 2.15)	1.53 (0.93 to 2.52)	2.35 (1.21 to 4.52)	0.07 / 0.004
Fully-adjusted OR (95% CI)[c]	1.00 (ref.)	1.16 (0.82 to 1.61)	1.63 (1.09 to 2.44)	1.72 (1.02 to 2.88)	3.06 (1.53 to 6.10)	0.008 / < 0.001
Death						
No. (%[d])	84 (40.3)	134 (33.6)	72 (33.3)	34 (36.4)	31 (47.2)	
Unadjusted HR (95% CI)	1.00 (ref.)	0.79 (0.59 to 1.06)	0.75 (0.53 to 1.06)	0.73 (0.48 to 1.12)	1.21 (0.77 to 1.87)	0.10 / 0.81
Adjusted HR (95% CI)[c]	1.00 (ref.)	0.82 (0.61 to 1.10)	0.96 (0.68 to 1.36)	0.92 (0.60 to 1.42)	1.68 (1.06 to 2.64)	0.03 / 0.13

Values were calculated after handling missing values by multiple imputations.

Abbreviation: IMV, invasive mechanical ventilation, No., number, OR, odds ratio, CI, confidence interval, HR, hazard ratio, BMI, body mass index, ref., reference.

[a] p-value by treating BMI categories as categorical variable in regression model

[b] p-value for by treating BMI categories as ordinal variable in regression model.

[c] adjusted on center and pre-specified covariates (age, sex, diabetes, hypertension, hyperlipidemia and current smoking)

[d] Kaplan-Meier estimate at 28-days

Table 3. Association of continuous BMI with the need for invasive mechanical ventilation in multivariable analysis including age, sex and metabolic risk factors

	OR (95% CI)	P-value
BMI, per 5 kg/m^2 increase	1.27 (1.12 to 1.45)	< 0.001
Age, per 10-y increase	1.17 (1.05 to 1.31)	0.004
Male sex	1.82 (1.38 to 2.41)	< 0.001
Hypertension	0.97 (0.72 to 1.30)	0.84
Diabetes	1.21 (0.89 to 1.65)	0.21
Hyperlipidemia	1.08 (0.78 to 1.48)	0.64
Current smoking	1.25 (0.66 to 2.35)	0.48

OR were calculated using multivariable mixed logistic regression model by taking into account center as random effect and after handling missing values by multiple imputations.

Abbreviation: BMI, body mass index, y, year, OR, odds ratio, CI, confidence interval.

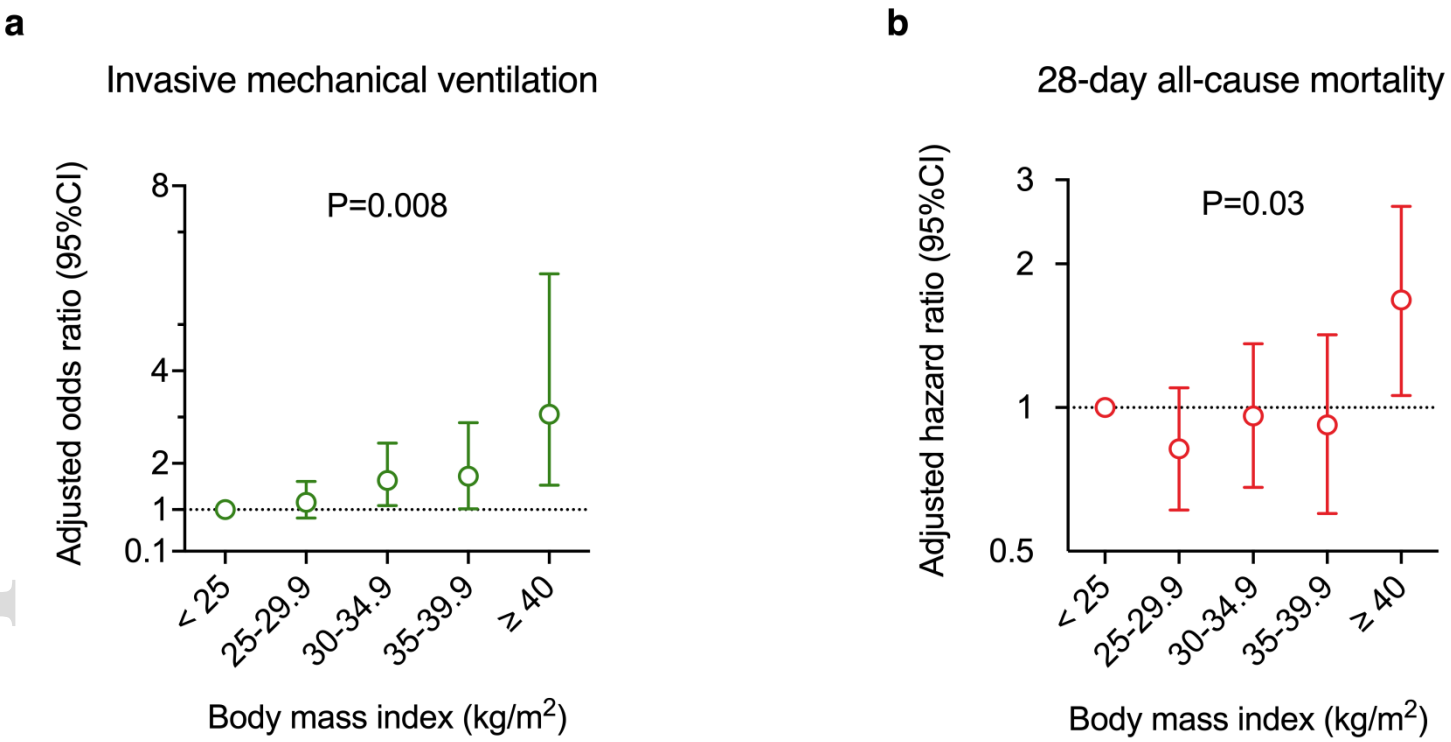
Table 4. Association of BMI ≥ 40 kg/m^2 with the 28-day all-cause mortality in multivariable analysis including age, sex and metabolic risk factors

	HR (95% CI)	P-value
BMI ≥ 40 kg/m^2	1.84 (1.23 to 2.75)	-
Age, per 10-y increase	1.74 (1.54 to 1.95)	< 0.001
Male sex	1.24 (0.96 to 1.60)	0.10
Hypertension	0.93 (0.72 to 1.19)	0.56
Diabetes	1.25 (0.98 to 1.58)	0.07
Hyperlipidemia	1.00 (0.77 to 1.29)	0.97
Current smoking	1.00 (0.59 to 1.69)	0.99

HR were calculated using frailty model by taking into account center as random effect and after handling missing values by multiple imputations.

Abbreviation: BMI, body mass index, y, year, HR, hazard ratio

Figure 1. Linear association of BMI categories with the need of invasive mechanical ventilation requirement (Figure 1a) and non-linear association of BMI with 28-day all-cause mortality (Figure 1b)

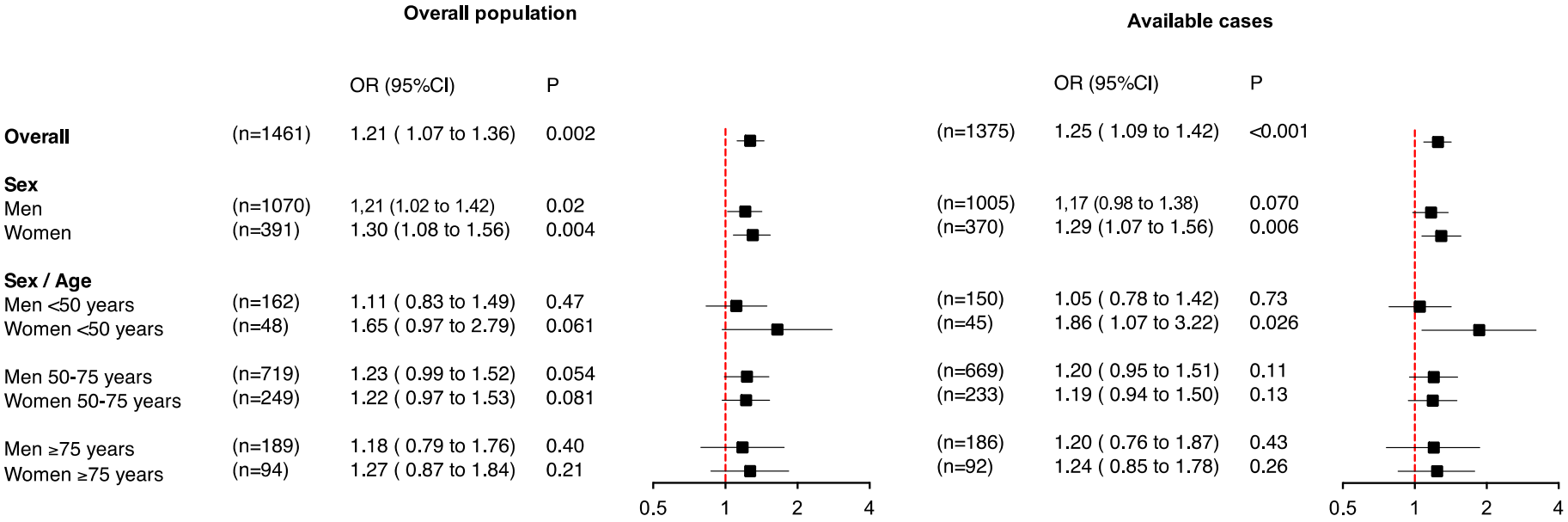


Odds and hazards ratio were calculated using the lean category (BMI < 25 kg/m^2) as reference and adjusted on center and pre-specified covariates (age, sex, diabetes, hypertension, hyperlipidemia and current smoking) after handling missing values by multiple imputations.

P-value were calculated by treating BMI categories as categorical variable in regression model.

Abbreviation: CI, confidence interval.

Figure 2. Association of continuous body mass index (BMI) with the need for invasive mechanical ventilation, in the overall study population after handling missing values by multiple imputations and on the complete cases population (sensitivity analysis) according to sex, and sex/age subgroups. Odds ratios (OR) are expressed per 5 kg/m^2 increase, with 95% confidence intervals (CI) and calculated using mixed logistic regression models including center as random effect and adjustments for prespecified known risk factors (fixed effects) as diabetes, hypertension, hyperlipidemia and current smoking.



Tables and Figures titles

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Figure 1. Linear association of BMI categories with the need of invasive mechanical ventilation requirement (Figure 1a) and non-linear association of BMI with 28-day all-cause mortality (Figure 1b)

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Supplementary material

Table S1: Association of BMI categories with the need of invasive mechanical ventilation requirement and 28-day all-cause mortality in available case analysis.

Table S2: Association of continuous BMI with the need for invasive mechanical ventilation in multivariable analysis including age, sex and metabolic risk factors, in available case analysis.

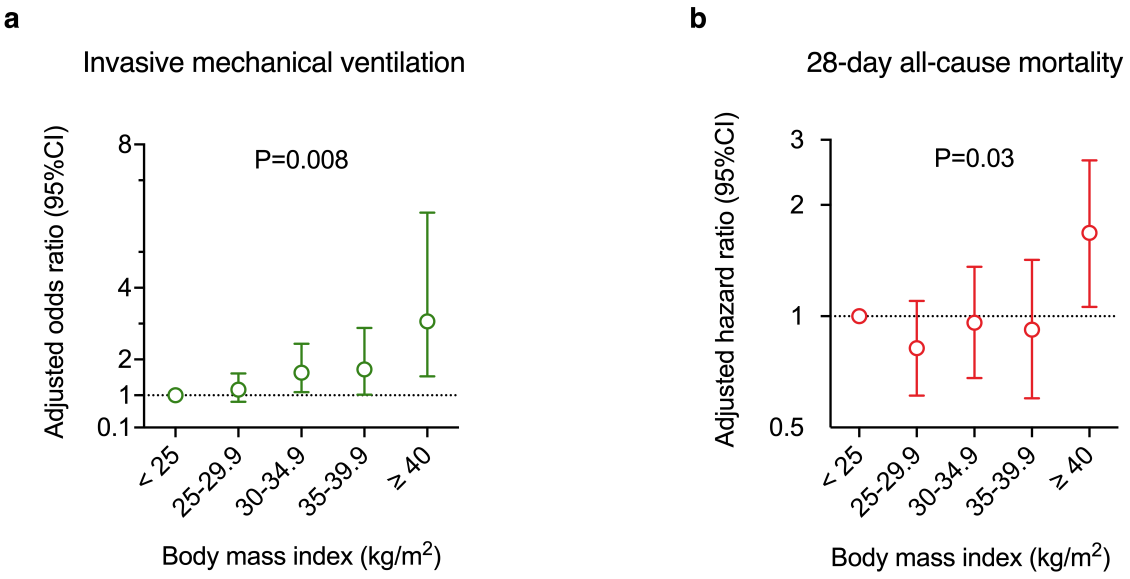
Table S3: Association of BMI $\geq$ 40 kg/m^2 with the 28-day all-cause mortality in multivariable analysis including age, sex and metabolic risk factors, in available case analysis.

Figure S1: Flow diagram of the 1461 study participants patients. A total of 28 centers in 8 countries (Belgium, Brazil, China, France, Israel, Italy, Spain, and USA,) were initially contacted to participate. Abbreviation: ICU, intensive care unit, RT-PCR, reverse transcription polymerase chain reaction.

Figure S2: Distribution of body mass index in the study population of critically ill patients with COVID-19, and in general population, adjusted for age and sex in each country.

Figure S3: Description of patients enrolled in each in 21 centers, by population size, male sex, age, body mass index and known metabolic risk factors. Patients are described for each center and plotted as a radial bar chart. Centers are sorted by population size (the largest at the outer edge of the circle). Proportion (%) of patients from the cohort (A); proportion (%) of male patient (B); mean age in years (C); mean body mass index in kg/m2 (D); proportion of patients (%) with diabetes (E), hypertension (F), hyperlipidemia (G), and current smoking (H)**.**

Study Groups and Collaborators



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