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How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? Results from a single Italian centre.

Short running title: obesity and COVID-19

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Abstract

Objective

Specific comorbidities and old age create a greater vulnerability to severe Coronavirus Disease 19 (COVID-19). While obesity seems to aggravate the course of disease, the actual impact of the body mass index (BMI) and the cutoff which increases illness severity are still under investigation. The aim of the study was to analyze whether the BMI represented a risk factor f qor respiratory failure, admission to the intensive care unit (ICU) and death.

Research Design and Methods

A retrospective cohort study of 482 consecutive COVID-19 patients hospitalised between March 1 and April 20, 2020. Logistic regression analysis and Cox proportion Hazard models including demographic characteristics and comorbidities were carried out to predict the endpoints within 30 days from the onset of symptoms.

Results

Of 482 patients, 104 (21.6%) had a BMI $\geq$ 30 kg/m^2. At logistic regression analysis, a BMI between 30 and 34.9 kg/m^2 significantly increased the risk of respiratory failure (OR: 2.32; 95% CI: 1.31-4.09, p=0.004), and admission to the ICU (OR: 4.96; 95% CI: 2.53-9.74, p<0.001). A significantly higher risk of death was observed in patients with a BMI $\geq$ 35 kg/m^2 (OR: 12.1; 95% CI: 3.25-45.1, p<0.001).

Conclusions

Obesity is a strong, independent risk factor for respiratory failure, admission to the ICU and death among COVID-19 patients. Whereas a BMI ≥ 30 kg/m^2 identifies a population of patients at high risk for severe illness, a BMI ≥ 35 kg/m^2 dramatically increases the risk of death.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been identified as the cause of Coronavirus disease 19 (COVID-19) which was initially reported in December 2019 in China and has since rapidly spread worldwide (1,2). The World Health Organization (WHO) reported over 6 million cases of COVID-19 and over 382,000 related deaths in the world as of June 4, 2020 (3). Italy was the first Western country to be hit, and the one to witness the quickest increase in mortality among COVID-19 patients. To date, 233,836 confirmed cases and 33,601 deaths were reported in Italy (3). Although the disease is believed to have a favorable prognosis in the majority of cases, a significant proportion of patients require hospitalization and intensive medical support (4-7).

Older age and the presence of specific comorbidities, such as type 2 diabetes, hypertension and cardiovascular disease, have been shown to strongly relate to a higher risk of severe disease (8–10). Whether this was partially driven by the risk posed by obesity (which, in turn, drives metabolic and cardiovascular diseases)(11) was assessed either in a limited set of patients or in substantially different populations (12-19).

Thus, taking into account that a correlation between obesity and mortality after viral infections has been shown in the past (20, 21), there is an unmet need for more complete data regarding the effect of obesity on the outcomes of COVID-19 (22).

The aim of the present study was therefore to analyze the correlation between the body mass index (BMI) and the main outcomes of COVID-19, including respiratory failure, admission to the intensive care (ICU), and death.

Methods

Study design and participants

This was a retrospective cohort study involving 516 adult (≥ 18 years) patients. The patients were admitted to the hospital between March 1 and April 20, 2020. The last follow-up date was April 27, 2020. Inclusion criteria: patients who had a confirmed COVID-19 diagnosis using a positive RT-PCR (Reverse transcription polymerase chain reaction) test on nasopharyngeal swabs. Exclusion criteria: patients without an available BMI (34 patients). After the application of the exclusion criteria, 482 patients were analyzed. Normal weight, overweight and obesity classes were defined as for the WHO guidelines (23).

All patients were included in the study regardless of the outcome of the hospitalisation (discharge, still in the hospital or death).

The database incorporated the list of the major comorbidities (hypertension, type 2 diabetes, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), moderate to severe renal disease, previous cancer), and history of smoking.

Data collection

The dataset utilised for patient identification was created for the ongoing PREDI-CO multicentric study (Trial Registration NCT04316949). However, in our study, only patients who were hospitalised in Sant'Orsola Hospital in Bologna, Italy were included in order to respect the strict privacy regulations regarding the access of de-anonymised data which was necessary to contact the patients. In fact, since the BMI was not reported in a notable proportion of cases, and it was not clear whether the weight was that at the time of admission or before the onset of symptoms, all patients (or their next of kin) were contacted by telephone to review the clinical notes

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(including height and weight) in order to reduce the bias associated with the patient case-mix and to exclude re-admission in another hospital or death after discharge.

Study outcomes

The endpoints selected were the onset of respiratory failure, admission to the ICU and mortality within 30 days from the onset of symptoms. Respiratory failure was defined by the presence of two of the following criteria: a) $pO_2 < 60$ mmHg or an oxygen blood saturation <90%; b) $pCO_2 > 50$ mmHg with $pH < 7.35$ c) signs of acute respiratory distress.

The study was approved by the Ethical Committee.

Statistical analysis

The continuous variables were expressed as mean ± standard deviation (SD) while the categorical variables were presented as number (%).

The differences in the categorical and the continuous variables by BMI class were initially evaluated using the chi-squared test and the t-test, respectively. The potential independent predictors of respiratory failure, admission to the ICU and death were then evaluated using both Cox proportional hazards analysis and logistic regression (using the data censored at 30 days of follow-up). No multivariable analysis was attempted to predict mechanical ventilation due to the scarce sample.

BMI was treated as either dichotomous, continuous or categorical, and the association between outcomes and several BMI cutoffs were explored. The differences between intermediate categories of overweight (e.g., BMI 27.5-30) and normal weight (BMI<25) were not significant in all models; thus, normal and overweight were grouped together in the main analyses. In fact, Kaplan-Meier estimates of time to respiratory failure, time to admission to the ICU, and time to death were computed using dichotomic BMI (obesity vs. normal and overweight). To evaluate the shape of the association between BMI and the three main outcomes, however, we categorized BMI in eight, commonly used categories of BMI (<20; 20-22.4; 22.5-24.9; 25-27.4; 27.5-29.9; 30-32.4; 32.5-35; >=35) (24), and computed the adjusted odds ratios of each BMI class versus a reference category (BMI 22.5-24.9).

To reduce over-fitting, all models were fit including only significant variables (with the exception of age, gender, hypertension and type 2 diabetes that were included a priori), and cerebrovascular disease and moderate/severe renal disease which were also included in all models as they were significant predictors of one of the outcomes. Standard diagnostic procedures were adopted to check the validity of all the models: (a) in logistic models, influential observation analysis (Dbeta, change in Pearson chi-square), the Hosmer-Lemeshow test for the goodness of fit and C statistic (area under the Receiving Operator Curve) and (b) in Cox models, the Schoenfeld's test to check the validity of proportional hazards assumption, and Nelson-Aalen cumulative hazard estimates to check the validity of constant incidence ratios during the follow-up (25). Missing data were <5% in all primary analyses; thus, no missing imputation technique was adopted. Statistical significance was defined as a two-sided p-value<0.05, and all analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2014).

Results

Of the 482 patients included in the study, 202 (41.9%) had a BMI < 25 kg/m^2, 176 (36.5%) had a BMI between 25 and 29.9 kg/m^2, and 104 (21.6%) were obese (BMI ≥ 30 kg/m^2). In the group with obesity, 20 patients (4.1%) had a BMI ≥ 35 kg/m^2. A total of 18 patients (3.7%) had a BMI < 20 kg/m^2.

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Table 1 shows the demographic characteristics, the prevalence of comorbidities, the rate of respiratory failure, admission to the ICU and death in the overall population, and the comparison of the variables among patients grouped by classes of BMI. Hypertension and type 2 diabetes were reported in 76 (72.8%) and 27 (26%) patients with a BMI ≥ 30 kg/m^2, respectively. Among patients with obesity, 54 (51.9%) experienced respiratory failure, 38 (36.4%) were admitted to the ICU, 26 (25%) required mechanical ventilation, and 31 (29.8%) died within 30 days from the onset of symptoms.

Table 2 reports the results of the logistic regression predicting the outcomes (Supplementary Table 1 reports the same analysis with the unadjusted odds ratios). A BMI ≥ 30 kg/m^2 significantly increased the risk of respiratory failure (Odds ratio [OR]: 2.48; 95% confidence interval [CI]: 1.46-4.21, p=0.001), admission to the ICU (OR: 5.28; 95% CI: 2.81-9.91, p<0.001), and death (OR: 2.35; 95% CI: 1.17-4.75, p=0.017). The risk of respiratory failure and ICU admission was significantly higher both in patients with a BMI between 30 and 34.9 kg/m^2 (OR: 2.32; 95% CI: 1.31-4.09, p=0.004, and OR: 4.96; 95% CI: 2.53-9.74, p<0.001, respectively) and in patients with a BMI ≥ 35 kg/m^2 (OR: 3.24; 95% CI: 1.21-8.68, p=0.019, and OR: 6.58; 95% CI: 2.31-18.7, p<0.001, respectively). The risk of death was significantly higher among patients with a BMI ≥ 35 kg/m^2 (OR: 12.1; 95% CI: 3.25-45.1, p<0.001).

Although 1-unit increase in BMI was significantly associated with all outcomes, overweight (BMI 25-29.9), as compared with normal weight, did not show a significant increase in the risk of any outcome, in any model, using any categorization (e.g. 27-29.9, or 28-29.9). In fact, in all models, the BMI cutoff determining an increase of risk was 30.

Respiratory failure was also associated with cerebrovascular disease (OR: 2.22; 95% CI: 1.07-4.60, p=0.032); ICU admission was also correlated with moderate/severe renal disease (OR: 4.80; 95% CI: 1.83-12.6, p=0.001), and death was associated with male gender (OR: 2.36; 95% CI: 1.26-4.43, p=0.007), and cerebrovascular disease (OR: 3.41; 95% CI: 1.61-7.26, p<0.001). Age > 60 was significantly associated with a progressively higher risk of respiratory failure and death, but not with admission to the ICU.

A total of 68 patients (14.1%) were still in hospital at the time of the analysis. Since the study population was not a closed cohort in which every patient had either died or been discharged, the analyses were repeated using a time-to-event model (Cox proportion hazards regression), which substantially confirmed the results of the logistic regression analysis as shown in Table 3. Figure 1 shows the Kaplan-Meier estimates of respiratory failure (A), admission to the ICU (B), and death (C) during follow-up.

Supplementary Figure 1 shows the adjusted odds ratios of various categories of BMI versus a reference category (BMI 22.5-24.9) for the risk of respiratory failure (A), admission to the ICU (B), and death (C), during follow-up. Figure 2C, in particular, shows that the risk of death was significantly higher also in patients with a BMI < 20 kg/m^2, however, no further analysis was performed given the low number of patients in this group.

Discussion

The present study showed that obesity was significantly associated with respiratory failure (OR: 2.48; 95% CI: 1.46-4.21, p=0.001), ICU admission (OR: 5.28; 95% CI:

2.81-9.91, $p<0.001$) and death (OR: 2.35; 95% CI: 1.17-4.75, $p=0.017$) in hospitalised COVID-19 patients.

Other recent studies showed a higher risk of severe illness among severely obese patients. In a large series involving COVID-19 patients under 60 years of age admitted to hospital in New York City, Lighter et al. (13) found that a BMI between 30 and 34.9 and a BMI ≥ 35 kg/m^2 increased the risk of admission to critical care 1.8 and 3.6 fold, respectively, as compared to patients with a BMI < 30. In their study, which included 124 patients, Simonnet et al. (12) found that patients with a BMI between 30 and 34.9, and those with a BMI ≥35 kg/m2 were 3.45 and 7.36 fold more likely to require intensive mechanical ventilation, respectively, as compared to those with a BMI < 25 kg/m2. Petrilli et al. recently reported the outcomes of 5279 patients who tested positive for COVID-19 in New York City, USA (16), and found that a BMI > 40 kg/m^2 was associated with a higher risk of hospital admission (OR 2.5) and critical illness (OR 1.5). Similar findings were reported by Palaiodimos et al., who showed that BMI higher than 35 kg/m^2 was significantly associated with the need for mechanical ventilation and death, in their series of 200 patients admitted to a New York hospital (19). Cai et al. analyzed the outcomes of 383 patients who were hospitalised in Shenzhen, China, and reported that patients with obesity had increased risk of progressing to severe COVID-19 (18). The association between obesity and severe outcomes was analyzed also in patients affected by specific comorbidities. Zheng et al. showed that the risk of severe COVID-19 illness in patients affected by metabolic associated fatty liver disease was 5.77 fold greater among obese patients (15), and the CORONADO study found that the BMI was independently associated with a higher risk of tracheal intubation and death within 7 days (17).

In agreement with the above findings, the present study found that both patients with a BMI between 30-34.9 kg/m^2 and those with a BMI ≥ 35 kg/m^2 had a significantly higher risk of respiratory failure (2.60 and 3.66 fold higher, respectively) and admission to the ICU (6.23 and 7.91 fold higher, respectively). However, the risk of death significantly and dramatically increased in patients with a BMI ≥ 35 kg/m^2 (OR: 12.3; 95% CI: 3.36-44.7, p<0.001) as compared to patients having a BMI between 30 and 34.9 kg/m^2 (OR: 1.70; 95% C I: 0.81-3.55, p=0.2).

Compared to the above-mentioned reports, our study population differs in terms of ethnicity, being for the greater proportion of our patients represented by Caucasian patients, and of the rate of obesity among the general population. In the U.S.A., the age-adjusted prevalence of obesity among the adult population was 42.4% in the period from 2017 to 2018 (26), compared to 10.9% in Italy, in the period from 2015 to 2018 (27).

Nevertheless, this finding calls for prevention and treatment strategies to reduce the risk of infection and hospitalisation in patients with relevant degrees of obesity, supporting a revision of the BMI cutoff of 40 Kg/m^2, which was proposed as an independent risk factor for an adverse outcome of COVID-19 in the current U.S.A. Center for Disease Control recommendations and in the guidelines for social distancing in the United Kingdom (28, 29): it may be appropriate to include patients with BMI > 30 among those at higher-risk for COVID-19 severe progression.

Several studies have assessed the relevant role of comorbidities regarding serious adverse outcomes in patients with COVID-19, including in particular hypertension, diabetes and coronary heart disease (9, 30, 31). Obesity is a known risk factor for these major comorbidities (11). In the present series, not surprisingly, patients with obesity were more likely to be affected by hypertension and type 2 diabetes than

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patients who were overweight and those of normal weight. However, the present study showed that obesity, and mainly severe obesity, independently increased the risk for death, and that the risk was higher regardless of the presence of the obesity-related comorbidities.

Obesity has also been widely recognized as a factor associated with impaired immunological response and pathogen defense (20, 21). Several mechanisms have been hypothesized to explain these findings, including increased viral spread to the alveolar region of the lungs, alterations of the lung environment affecting the immune response, higher levels of circulating leptin and pro-inflammatory cytokines, reduced macrophage activation, and both T cell and B cell response associated with the obesity-related chronic inflammatory state (32, 33). Moreover, obese patients have been proven to have a higher viral load and a longer time of virus shedding as compared to non-obese patients (34).

The strengths of the present study included the relatively long follow-up, compared to other studies in the literature, and the analysis of the correlation between obesity and all the significant outcomes of COVID-19 (respiratory failure, ICU admission, and death). The study, however, had also some limitations. First, since the study was carried out during a medical emergency, which put great stress on the healthcare system, the dataset was compiled retrospectively, and the BMI was missing in a proportion of patients (6.6%). However, the rates of all outcomes of the patients with or without recorded BMI were not significantly different (data not shown). Secondly, 14.1% of the patients included were still in the hospital at the time of analysis; although the outcomes could be different over a longer time of observation, the time-to-event analysis confirmed the findings of the linear regression. Thirdly, this is a single centre study, and the great majority of patients are of Caucasian ethnicity.

In addition, our dataset did not allow to analyze the prevalence and the effects of prediabetes on the risk of severe outcomes among the patients affected by COVID-19. Prediabetes has been identified as a relevant risk factor for significant comorbidities regardless of the BMI, such as cardiovascular and renal disease, and its role on the outcome of COVID-19 has yet to be assessed (35). Similarly, it was not possible to discriminate between patients with metabolically healthy or unhealthy obesity (36). This distinction might have allowed to identify subpopulation of patients with obesity at different risks of severe outcomes. Future studies, including a greater number of patients and detailed information regarding the metabolic status, will be necessary to differentiate the intertwined role of obesity and its associated comorbidities as risk factors for adverse outcomes of COVID-19.

In conclusion, in a population of patients hospitalised for COVID-19, a BMI ≥ 30 kg/m^2 was associated with a significantly higher risk of respiratory failure, admission to the ICU and death. The current CDC BMI cutoff of 40 kg/m^2 should be reassessed in order to properly identify patients at higher risk, and avoid an underestimation of the potential impact of SARS-CoV-2 infection in a large proportion of the general population.

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The study was approved by the local Ethical Committee (Comitato Etico AVEC - Area Vasta Emilia Centro)

Conflicts of interest

The authors report no conflict of interest.

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Author contributions

MR designed the study, coordinated the acquisition of data, wrote the article; PB contributed to the discussion and reviewed/edited the manuscript; AB researched data, reviewed the manuscript; FB researched data, contributed to the review of the literature; SG researched data, reviewed the final draft; MG, AC, ST, SI, and ERDT researched data; TT, VMR, and GP contributed to the final review of the manuscript; UP contributed to design the study, revised it critically for important intellectual content, reviewed the manuscript; LM contributed to design the study, designed the statistical methods, interpreted the data, reviewed the manuscript; PV and MB coordinated the acquisition of data, reviewed the final draft of the manuscript.

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Figure legends

Figure 1. Kaplan-Meier estimates of the outcomes in patients with a BMI $<$ or ≥ 30 over the follow-up time

A) Risk of respiratory failure during follow-up

B) Risk of admission to the ICU during follow-up

C) Risk of death during follow-up

Supplementary Figure 1. Adjusted odds ratios of various categories of BMI versus a reference category (BMI 22.5-24.9)

A) Risk of respiratory failure during follow-up

B) Risk of admission to the ICU during follow-up

C) Risk of death during follow-up

Table 1. Characteristics and outcomes of the sample, overall and by Body Mass index (BMI).

	Overall	**BMI**				***P****
		<25	25-29.9	30-34.9	≥35	
n	482	202	176	84	20	
Mean age in years (SD)	66.2 (16.8)	67.7 (19.3)	64.5 (15.7)	68.1 (12.6)	58.9 (11.7)	C, F
Male gender, %	62.7	63.9	67.1	53.6	50.0	D
Current smoking **	22.5	20.8	22.0	28.1	21.4	
Comorbidities, %						
Hypertension	52.7	45.3	49.4	74.7	65.0	B, D
Type 2 diabetes	15.2	11.9	12.5	26.2	25.0	B, D
Ischemic heart disease	12.7	12.4	11.9	16.7	5.0	
Congestive heart failure	8.5	9.4	9.7	3.6	10.0	
Cerebrovascular disease	11.4	13.4	9.7	13.1	0.0	
COPD	13.1	14.4	9.7	15.5	20.0	
Moderate/severe renal disease	7.9	7.9	6.3	13.1	0.0	
Previous cancer	11.4	13.9	9.1	11.9	5.0	
Outcomes						
Respiratory failure	35.7	33.7	28.4	52.4	50.0	B, D, E
CU	13.9	5.0	11.9	33.3	40.0	A, B, C, D, E
Death	19.5	18.8	14.2	28.6	35.0	D, E
Mean follow-up in days (SD)						
Overall ***	37.8 (15.7)	36.8 (15.9)	39.2 (15.3)	37.5 (16.8)	35.5 (13.2)	
Time to respiratory failure	8.1 (5.5)	7.4 (5.8)	8.3 (5.2)	9.2 (5.6)	6.9 (4.4)	
n	172	68	50	44	10	
Time to ICU admission	9.6 (6.2)	14.8 (11.0)	8.3 (5.0)	9.4 (4.1)	7.4 (5.0)	A, B
n	67	10	21	28	8	
Time to death	14.2 (8.8)	12.1 (7.4)	12.4 (6.8)	17.2 (11.1)	21.9 (7.0)	B, C, E
n	94	38	25	24	7	

P-values<0.05 for the following comparisons: [A] BMI<25 versus BMI 25-29.9. [B] BMI<25 versus BMI 30-34.9. [C] BMI<25 versus BMI≥35; [D] BMI 25-29.9 versus BMI 30-34.9; [E] BMI 25-29.9 versus BMI≥35; [F] BMI 30-34.9 versus BMI≥35. ** Due to missing values: the overall sample was 378 (159, 141, 64 and 14 patients in each of the four groups, respectively). *** From symptoms to death or the end of follow-up (April 27, 2020). SD: standard deviation; COPD= Chronic obstructive pulmonary disease; ICU = Admission or transfer to the intensive care unit.

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Table 2. Logistic regression predicting respiratory failure, admission or transfer to the intensive care unit (ICU), and death, within 30 days after onset of symptoms.

Variables	**Respiratory failure**			**ICU**			**Death**		
	%	OR (95% CI)	*P*	%	OR (95% CI)	*P*	%	OR (95% CI)	*P*
Age class in years									
<60	18.0	1 (ref. cat.)	--	11.2	0.99 (0.88-1.11) [A]	0.8	3.4	1 (ref. cat.)	--
60-69.9	36.4	1.86 (0.98-3.50)	0.056	27.3	--	--	10.2	2.55 (0.67-9.67)	0.2
70-79.9	45.7	2.87 (1.53-5.41)	0.001	24.5	--	--	28.7	13.7 (4.35-43.5)	<0.001
≥80	53.3	5.02 (2.56-9.85)	<0.001	0.0	--	--	42.6	35.0 (10.8-113)	<0.001
Gender									
Female	35.6	1 (ref. cat.)	--	11.7	1 (ref. cat.)	--	16.1	1 (ref. cat.)	--
Male	35.8	1.24 (0.78-1.95)	0.4	15.2	1.54 (0.81-2.91)	0.2	21.5	2.36 (1.26-4.43)	0.007
Hypertension									
No	22.5	1 (ref. cat.)	--	9.2	1 (ref. cat.)	--	10.1	1 (ref. cat.)	--
Yes	47.4	1.43 (0.87-2.34)	0.2	17.8	1.61 (0.80-3.25)	0.2	27.7	1.09 (0.56-2.15)	0.8
Diabetes									
No	33.2	1 (ref. cat.)	--	11.7	1 (ref. cat.)	--	17.1	1 (ref. cat.)	--
Yes	49.3	1.10 (0.60-2.00)	0.8	26.0	1.55 (0.73-3.31)	0.3	32.9	1.00 (0.48-2.05)	0.9
Cerebrovascular disease									
No	32.1	1 (ref. cat.)	--	14.8	1 (ref. cat.)	--	15.2	1 (ref. cat.)	--
Yes	63.6	2.22(1.07-4.60)	0.032	7.3	0.52 (0.13-2.05)	0.3	52.7	3.41 (1.61-7.26)	0.001
Moderate/severe renal disease									
No	34.0	1 (ref. cat.)	--	12.4	1 (ref. cat.)	--	18.4	1 (ref. cat.)	--
Yes	51.3	1.84 (0.82-4.17)	0.14	31.6	4.80 (1.83-12.6)	0.001	33.3	2.35 (0.90-6.17)	0.082
BMI *									
Obesity (BMI≥30)									
No	31.2	1 (ref. cat.)	--	8.2	1 (ref. cat.)	--	16.7	1 (ref. cat.)	--
Yes	51.9	2.48 (1.46-4.21)	0.001	34.6	5.28 (2.81-9.91)	<0.001	29.8	2.35 (1.17-4.75)	0.017
BMI class									
<30	31.2	1 (ref. cat.)	--	8.2	1 (ref. cat.)	--	16.7	1 (ref. cat.)	--
30-35	52.4	2.32 (1.31-4.09)	0.004	33.3	4.96 (2.53-9.74)	<0.001	28.6	1.71 (0.80-3.64)	0.2
≥35	50.0	3.24 (1.21-8.68)	0.019	40.0	6.58 (2.31-18.7)	<0.001	35.0	12.1 (3.25-45.1)	<0.001
BMI, 1-unit increase	--	1.07 (1.02-1.13)	0.009	--	1.20 (1.12-1.28)	<0.001	--	1.09 (1.02-1.17)	0.012

OR: Odds Ratio; CI: Confidence Interval; BMI: body mass index. In all models, age, gender, hypertension and type 2 diabetes were included a priori. No variable other than those in the Table was significant at 0.10 cutoff. [A] Age was included as a continuous variable because no person aged ≥80 was admitted or transferred to the ICU; the OR refers to a 5-year increase. * All models were repeated, with the same covariates, including different categorisations of BMI (dichotomic, categorical or continuous). The differences between patients with a BMI 27.5-29.9 versus a BMI<27.5 or a BMI<25 were not significant in any model.

Table 3. Cox proportional hazards model predicting respiratory failure, admission or transfer to the intensive care unit (ICU), and death.

	Respiratory failure		**ICU**		**Death**	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age class in years						
- <60	1 (ref. cat.)	--	0.93 (0.85-1.02)[A]	0.14	1 (ref. cat.)	--
- 60-69.9	1.61 (0.96-2.68)	0.070	--	--	2.07 (0.71-6.08)	0.2
- 70-79.9	2.24 (1.37-3.64)	0.001	--	--	7.43 (2.96-18.6)	<0.001
- ≥80	2.68 (1.64-4.37)	<0.001	--	--	13.4 (5.39-33.5)	<0.001
Male gender	1.15 (0.84-1.59)	0.4	1.50 (0.89-2.55)	0.13	1.98 (1.26-3.10)	0.003
Hypertension	1.56 (1.08-2.25)	0.017	1.76 (0.98-3.17)	0.058	1.23 (0.74-2.04)	0.4
Diabetes	1.04 (0.71-1.53)	0.8	1.54 (0.87-2.73)	0.14	1.05 (0.64-1.74)	0.8
Stroke	1.88 (1.23-2.89)	0.004	0.54 (0.19-1.56)	0.3	2.12 (1.29-3.47)	0.003
Renal disease	1.29 (0.80-2.10)	0.3	2.83 (1.46-5.49)	0.002	1.53 (0.83-2.82)	0.2
BMI *						
Obesity (BMI≥30)	1.70 (1.20-2.42)	0.003	4.12 (2.48-6.83)	<0.001	2.18 (1.34-3.54)	0.002
BMI class						
<30	1 (ref. cat.)	--	1 (ref. cat.)	--	1 (ref. cat.)	--
30-35	1.10 (0.69-1.76)	0.7	3.81 (2.22-6.51)	<0.001	1.21 (0.64-2.27)	0.5
≥35	1.83 (1.24-2.70)	0.002	5.71 (2.53-12.9)	<0.001	1.72 (1.00-2.99)	0.051
BMI, 1-unit increase	1.04 (1.00-1.08)	0.042	1.15 (1.10-1.20)	<0.001	1.07 (1.02-1.13)	0.007

HR: Hazard Ratio; CI: Confidence Interval; BMI: body mass index. In all models, age, gender hypertension and type 2 diabetes were included a priori. No variable other than those in the Table was significant at 0.10 cutoff. [A] Age was included as a continuous variable because no person aged ≥80 was admitted or transferred to the ICU; the OR refers to a 5-year increase. * All models were repeated, with the same covariates, including different categorizations of BMI (dichotomic, categorical or continuous). The differences between patients with a BMI 27.5-29.9 versus a BMI<27.5 or a BMI<25 were not significant in any model.

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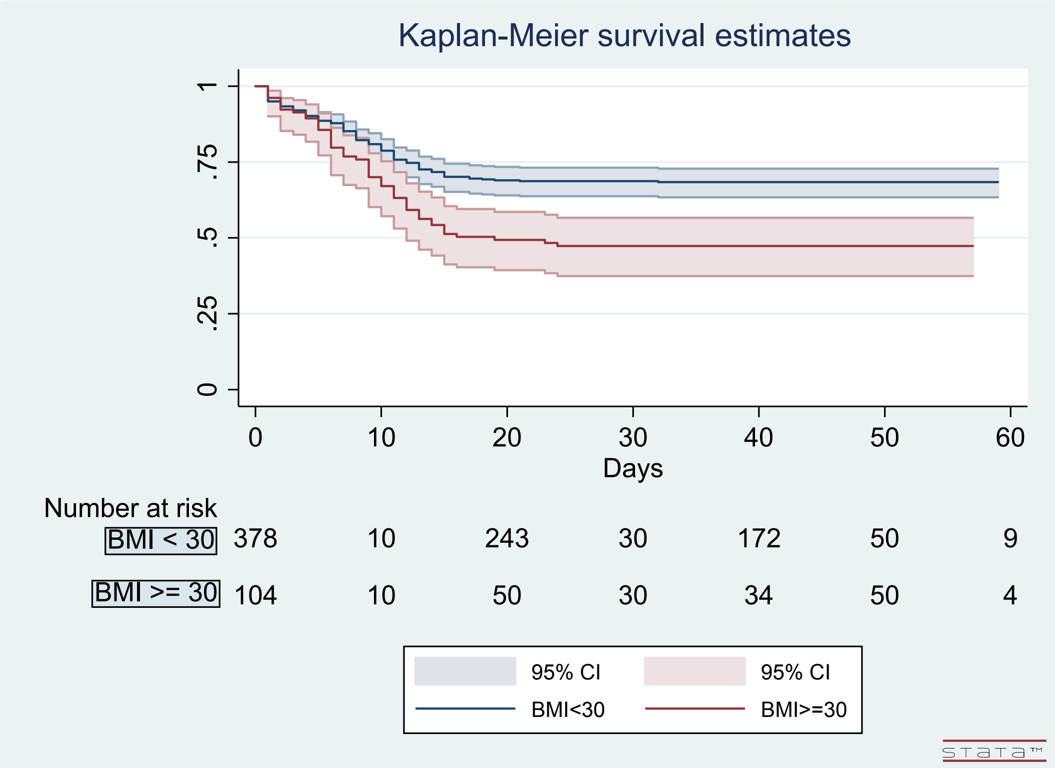

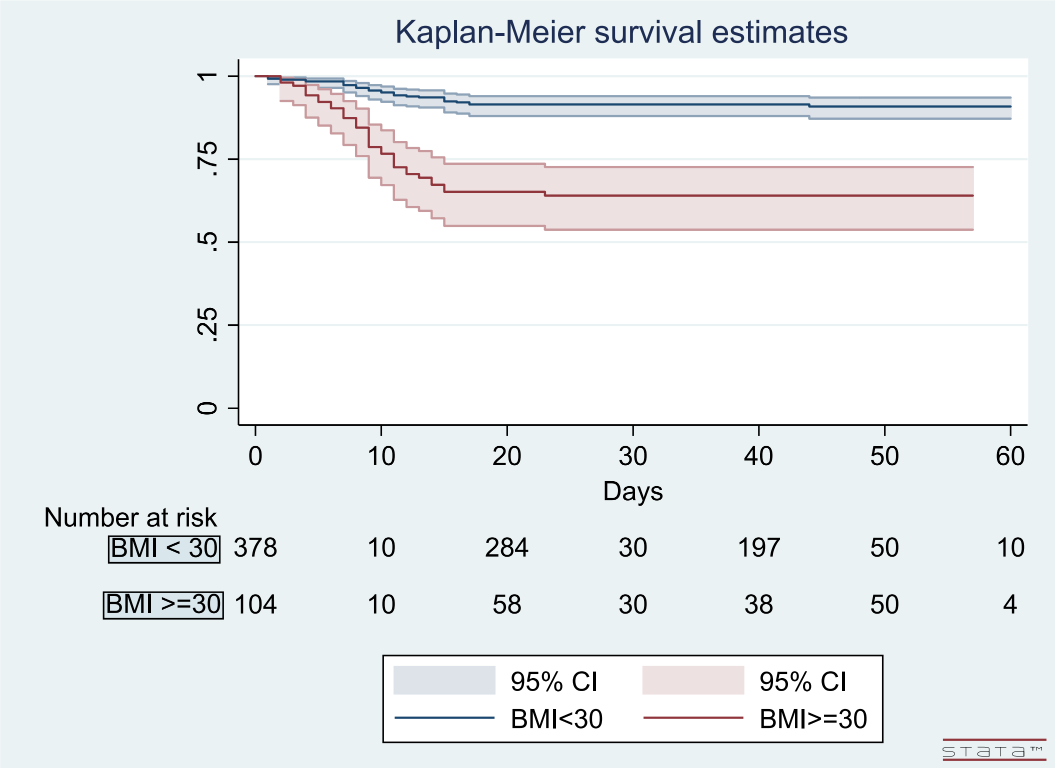
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Days
Number at risk
BMI < 30 378 10 284 30 197 50 10
BMI >=30 104 10 58 30 38 50 4
95% CI
BMI<30
95% CI
BMI>=30

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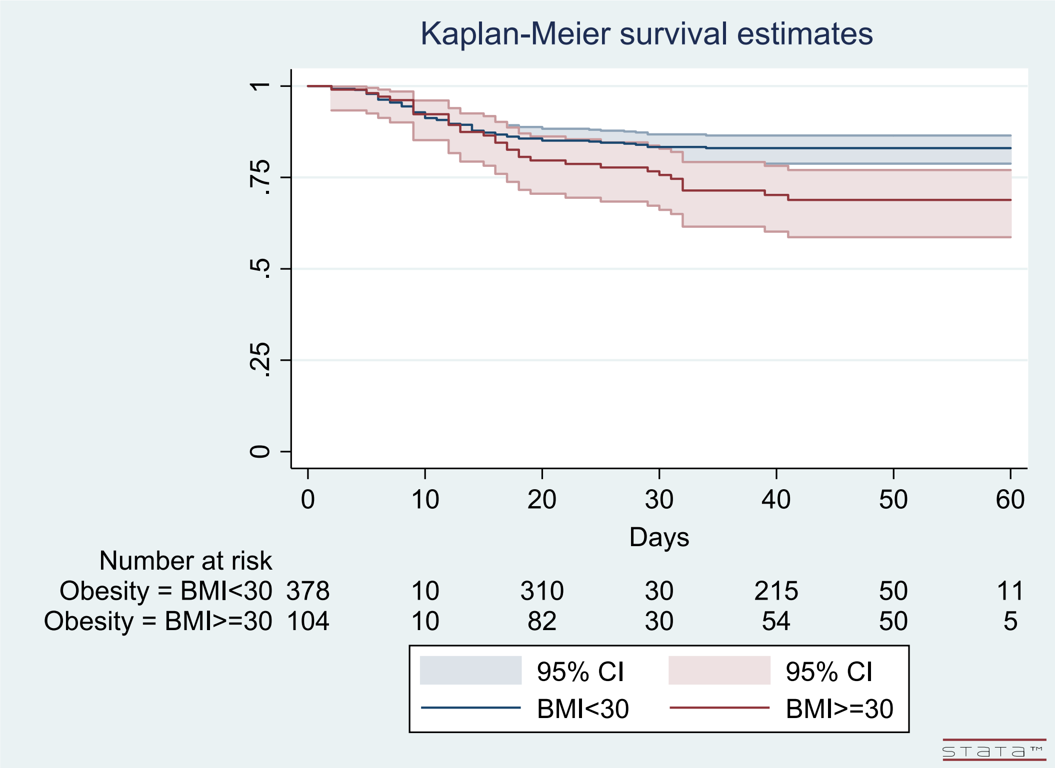

Supplementary Table 1. Unadjusted odds ratios (OR) of respiratory failure, admission or transfer to the intensive care unit (ICU), and death, within 30 days after onset of symptoms.

	Respiratory failure OR (95% CI)	**p**	**ICU** OR (95% CI)	**p**	**Death** OR (95% CI)	**p**
Age class in years						
- <60	1 (Ref. cat)		1 (Ref. cat)		1 (Ref. cat)	
- 60-69.9	2.61 (1.45-4.69)	0.001	2.83 (1.44-5.53)	0.002	3.14 (0.86-11.4)	0.083
- 70-79.9	4.06 (2.30-7.19)	<0.001	3.21 (1.63-6.32)	0.001	17.5 (5.89-52.1)	<0.001
- ≥80	7.00 (4.01-12.2)	<0.001	-- (-)*	--	39.5 (13.6-115)	<0.001
Male gender, %	0.95 (0.64-1.42)	0.8	1.25 (0.71-2.20)	0.4	1.36 (0.82-2.27)	0.2
Current smoking **	1.61 (0.96-2.71)	0.070	0.72 (0.32-1.63)	0.4	1.91 (1.05-3.46)	0.033
Comorbidities, %						
- Hypertension	3.14 (2.09-4.72)	<0.001	2.65 (1.51-4.68)	0.001	3.55 (2.08-6.05)	<0.001
- Type 2 diabetes	2.10 (1.24-3.56)	0.006	3.01 (1.57-5.76)	0.001	2.16 (1.21-3.87)	0.009
- Ischemic heart disease	1.73 (0.95-3.14)	0.073	1.27 (0.56-2.92)	0.6	2.78 (1.51-5.13)	0.001
- Congestive heart failure	1.85 (0.90-3.81)	0.096	0.76 (0.22-2.67)	0.7	2.04 (0.92-4.51)	0.078
- Cerebrovascular disease	4.47 (2.32-8.61)	<0.001	1.04 (0.34-3.17)	0.9	8.29 (4.35-15.8)	<0.001
- COPD	3.28 (1.83-5.89)	<0.001	1.85 (0.85-4.04)	0.12	3.24 (1.80-5.86)	<0.001
- Moderate/severe renal disease	2.58 (1.25-5.33)	0.011	5.03 (2.18-11.6)	<0.001	2.91 (1.38-6.11)	0.005
- Previous cancer	0.63 (0.34-1.20)	0.2	0.34 (0.10-1.13)	0.077	1.16 (0.57-2.37)	0.7
BMI						
Obesity (BMI≥30)	2.33 (1.47-3.68)	<0.001	5.75 (3.26-10.2)	<0.001	1.51 (0.89-2.57)	0.13
BMI class						
- <30	1 (Ref. cat)		1 (Ref. cat)		1 (Ref. cat)	
- 30-35	2.46 (1.49-4.05)	<0.001	5.64 (3.07-10.4)	<0.001	1.41 (0.79-2.54)	0.2
- ≥35	1.90 (0.77-4.69)	0.2	6.16 (2.30-16.5)	<0.001	1.91 (0.71-5.18)	0.2
- BMI, 1-unit increase	1.05 (1.00-1.10)	0.032	1.20 (1.12-1.27)	<0.001	1.01 (0.96-1.07)	0.7

* Omitted because no subject aged ≥80 years was admitted to ICU. ** Due to missing values: the overall sample was 378. CI = Confidence Interval; COPD= Chronic obstructive pulmonary disease; ICU = Admission or transfer to the intensive care unit.

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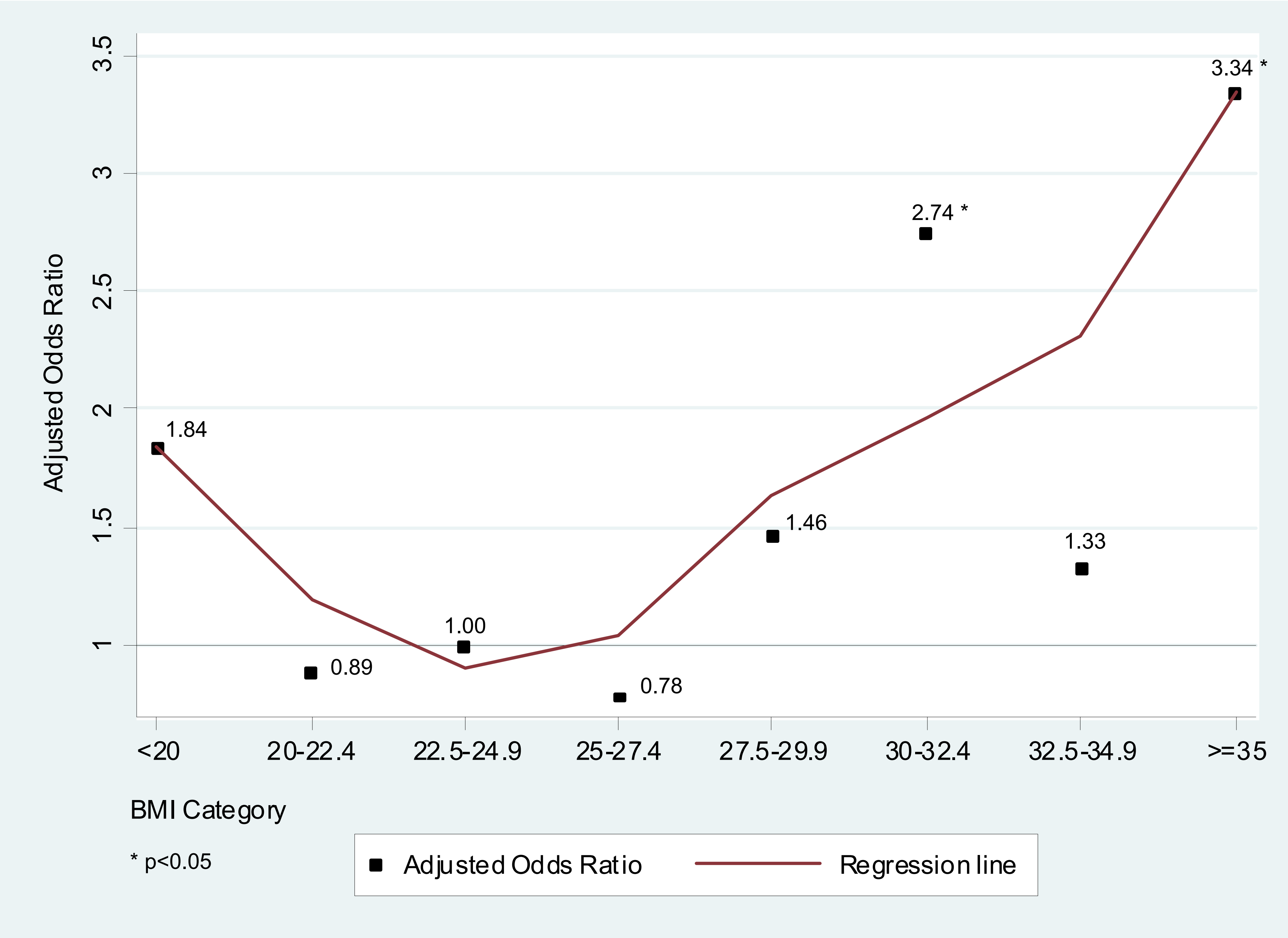

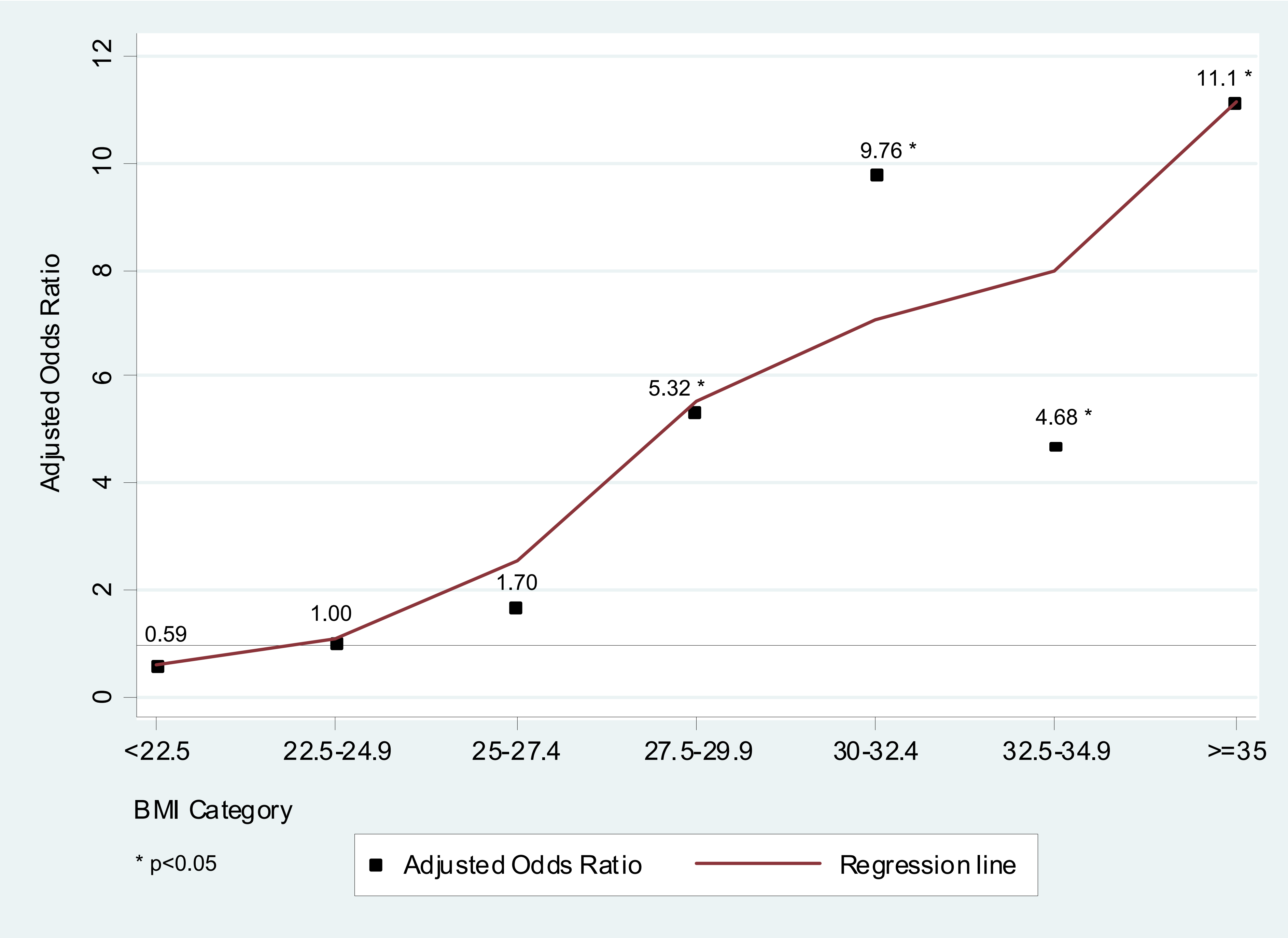
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22.5-24.9
25-27.4
27.5-29.9
30-32.4
32.5-34.9
>=35
BMI Category
* p<0.05
Adjusted Odds Ratio
Regression line

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