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Article type : Brief Cutting Edge Reports

Non-respiratory Complications and Obesity in Patients Dying with COVID-19 in Italy

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Word count: 1,182 words, 2 tables, 14 references

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What is already known?

- Obesity is associated with increased risk of respiratory complications in COVID-19
- This association appears stronger in young than in old adults

What are the new findings in your manuscript?

Obesity is associated with an increased probability of non-respiratory complications, particularly shock and acute renal failure.

- These associations seem stronger in young than in older adults.

How might your results change the direction of research or the focus of clinical practice?

Strategies should be put in place in COVID-19 patients with obesity to prevent non-respiratory complications.

ABSTRACT

Objective: to assess the impact of obesity on non-respiratory complications in patients dying with COVID-19.

Methods: medical charts of 3,694 patients dying with COVID-19 in Italy were reviewed to extract information on demographics, pre-existing comorbidities, and in-hospital complications leading to death. Multivariate logistic regressions were performed to assess the association of obesity with non-respiratory complications. These analyses were adjusted for age, gender and number of pre-existing comorbidities.

Results: obesity was present in 411/3,694 (11.1%) patients dying with COVID-19. Obesity was significantly associated with increased probability of experiencing acute renal failure (adjusted Odds Ratio: 1.33; 95% CI: 1.04-1.71) and shock (adjusted OR: 1.54; 95% CI: 1.19-1.99). The associations of obesity with acute renal failure and shock were stronger in patients aged < 60 years (adjusted OR: 2.00; 95% CI: 1.09-3.67 and OR: 2.37; 95% CI 1.29-4.36) than in those aged 60 years or older (adjusted OR: 1.20; 95% CI: 0.90-1.60 and OR: 1.22; 95% CI: 0.91-1.65).

Conclusions: In patients dying with COVID-19 in Italy, obesity is associated with an increased probability of non-respiratory complications, particularly shock and acute renal failure. These associations seem stronger in young than in older adults. Strategies should be put in place in COVID-19 *patients with obesity* to prevent these complications.

Introduction

Obesity has been shown to increase the risk of mortality and Intensive Care Unit admission in patients with COVID-19 and this association appears stronger in younger than in older adults (1-3). Obesity can increase severity of respiratory complications by restricting ventilation, impeding diaphragm excursion and reducing immune responses to viral infection (4).

In addition, obesity can increase inflammatory response and facilitate the onset of the cytokine storm syndrome, which appears to have a role in increasing risk of Acute Distress Respiratory Syndrome (4). This hyperinflammatory state can also be associated with the onset of non-respiratory complications, which are commonly observed in patients dying with COVID-19. For example, 22% of patients dying with COVID-19 in Italy experience acute renal failure, 20% shock, 13% superinfection and 11% myocardial infarction (5). For this reason, we assessed the impact of obesity on non-respiratory complications in patients dying with COVID-19.

Methods

At the outset of the COVID-19 outbreak, the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) launched an integrated national surveillance system to collect information on all individuals with COVID-19 throughout the country. Data on all confirmed COVID-19 cases were obtained from all 19 Italian Regions and the two autonomous provinces of Trento and Bozen (6,7). All deaths occurring in patients with confirmed COVID-19 were tracked by the surveillance system. COVID-19 related deaths were defined as those occurring in patients who tested positive for SARS-CoV-2 through Reverse Transcription Polymerase Chain Reaction, independently from preexisting diseases that may have caused or contributed to death. The system was unable to collect detailed clinical data. Thus, Regions and autonomous provinces were asked to send ISS the medical charts of COVID-19 patients who died in-hospital. These clinical charts were reviewed by a group of researchers of ISS to obtain more detailed information including demographics, pre-existing comorbidities and on complications leading to death. Data on the following COVID-19 related complications were collected: Acute Distress Respiratory Syndrome, acute renal failure, shock, superinfection and myocardial infarction. Information on pre-existing conditions diagnosed before hospital admission was collected based on anamnestic data reported in the chart.

As of July 9, 2020, 34,026 COVID-19 related deaths were reported in Italy (8) and 3,857 clinical charts were examined by ISS (11.3% of COVID-19 related deaths). These charts were selected to be representative of the regional distribution of COVID-19 related deaths.

Statistical analyses

From the initial sample of 3,857 patients dying with COVID-19 we excluded 163 patients because of missing data on demographics or COVID-19 related complications, leading to a final sample of 3,694. To compare characteristics of patients according to presence of obesity, we used t-tests for continuous variables and Chi-square test for categorical variables. Multivariate logistic regression model was used to assess the association of obesity with non-respiratory complications. Age, gender, number of pre-existing comorbidities, myocardial infarction, acute renal failure, superinfection and shock were included in the multivariate model. To address whether the associations between obesity and non-respiratory complications were similar across gender and age groups, we performed multivariate logistic regression models after stratifying the study cohort by gender and age (young adults: < 60 years and older adults: ≥ 60 years).

Ethical issues

On February 27th, 2020, the Italian Presidency of the Council of Ministers authorized the collection and scientific dissemination of data related to COVID-19 by the ISS and other public health institutions (9).

Results

Obesity was present in 411/3,694 (11.1%) of patients dying with COVID-19. As shown in table 1, ***in*** the univariate analysis, patients with obesity were significantly younger than those without obesity and they had a significantly higher prevalence of acute renal failure, shock and superinfection. In the multivariate analysis, obesity was significantly associated with age (Odds Ratio: 0.95 per 1 year increment; 95% Confidence Interval: 0.94-0.96), female gender (OR: 1.32; 95% CI: 1.05-1.66), acute renal failure (OR: 1.33; 95% CI: 1.04-1.71) and shock (OR: 1.54; 95% CI: 1.19-1.99). As shown in table 2, when the multivariate analysis was stratified by age groups, that the associations of obesity with acute renal failure and shock were stronger in young (OR: 2.00; 95% CI: 1.09-3.67 and OR: 2.37; 95% CI 1.29-4.36) than in older adults (OR: 1.20; 95% CI: 0.90-1.60 and OR: 1.22; 95% CI: 0.91-1.65). In addition, the associations of obesity with acute renal failure and shock were stronger in men (OR: 1.36; 95% CI: 1.00-1.84 and OR: 1.70; 95% CI 1.24-2.34) than in women (OR: 1.24; 95% CI: 0.79-1.96 and OR: 1.13; 95% CI: 0.70-1.80).

Discussion

We showed that, obesity, in addition to the known effect on COVID-19 respiratory complications, is associated with an increase probability of non-respiratory deaths. Obesity is a known risk factor for increased susceptibility to infections, sepsis, and infection-related mortality and this increased risk has been attributed to the state of chronic, low-grade inflammation that characterizes this condition (10).

Chronic inflammation, which accompanies obesity, can contribute, in patients with COVID-19, to trigger the inflammatory cascade that characterizes acute kidney failure and shock (4). Previous studies have suggested that obesity is a risk factor for a decline of glomerular filtration rate, albuminuria, onset and progression of kidney disease and that this effect is mediated by inflammation (11). Similarly, shock is observed in about 6% of patients with COVID-19 and inflammatory status seems to play a relevant role in the onset of this condition (12).

We show that the association of obesity with non-respiratory complications, namely acute renal failure and shock, is stronger in younger than in older adults. This finding confirms previous observations that suggested an obesity paradox in older persons with COVID-19, where higher BMI is associated with better outcomes when SARS-CoV-2 infection occurs (1-3).

In adjusted analyses, obesity is associated with female gender in patients dying with COVID-19, but the association of obesity with acute renal failure and shock seems stronger in men than in women. These results were consistent after adjusting for potential confounders, which included age and pre-existing comorbidities. This finding is in line with a previous study showing that obesity represents a risk factor for severe COVID-19 outcomes in men but not in women (13). Men are more likely to present with a visceral adipose tissue distribution, which is associated with higher levels of inflammation, and, therefore, with an higher risk of COVID-19 complications (14).

Our findings should be interpreted in light of potential limitations. First, data are based on chart review and an underreporting of pre-existing conditions and obesity is possible. Second, we reviewed charts of patients dying with COVID-19 and data on patients surviving to the disease were not collected. This limits the possibility of identifying the impact of obesity on overall survival and non-respiratory complications development. Third, the generalizability of our findings might be limited as we provide data only on hospitalized patients in Italy. Finally, data on Body Mass Index were not available.

In conclusion, we show that in patients dying with COVID-19 in Italy, obesity is associated with an increased probability of non-respiratory complications, particularly shock and acute renal failure. This association is more pronounced in men and young adults. Strategies should be put in place in patients with these characteristics to prevent COVID-19 complications.

Table 1. Factors associated with obesity in patients dying with COVID-19 in Italy

	Univariate analysis				Multivariate analysis
	Obesity n=411 n (%) or mean [SD]	**No obesity n=3,283 n (%) or mean [SD]**	***p-value***		**Odds Ratio (95% Confidence Interval)***
Demographics					
Age, mean [SD]	70.2 [12.0]	78.8 [11.4]	<0.001		0.95 (0.94-0.96)
Male gender	267 (65.0)	2,146 (65.4)	0.869		Ref.
Female gender	144 (35.0)	1,137 (34.6)			1.32 (1.05-1.66)
Pre-existing comorbidities					
Number of diseases					
0	24 (5.8)	151 (4.6)	0.120		Ref.
1	74 (18.0)	486 (14.8)			1.44 (0.85-2.44)
2	91 (22.1)	689 (21.0)			1.49 (0.89-2.51)
3 or more	222 (54.0)	1,957 (59.6)			1.57 (0.95-2.57)
Non-respiratory Complications					
Myocardial infarction	51 (12.4)	346 (10.5)	0.272		1.00 (0.72-1.40)
Acute renal failure	126 (30.7)	714 (21.7)	<0.001		1.33 (1.04-1.71)
Superinfection	98 (23.8)	470 (14.3)	<0.001		1.08 (0.82-1.43)
Shock	144 (35.0)	617 (18.8)	<0.001		1.54 (1.19-1.99)

* Results from multivariate logistic regression model. Age, gender, number of pre-existing comorbidities, acute renal failure, shock, superinfection and myocardial infarction were included in the model.

Table 2. Association of obesity with non-respiratory complications according to age groups and gender

	Univariate analysis				Multivariate analysis
	Age < 60 years (n=291)				
	Obesity n=81 n *(%)*	**No obesity n=210 n *(%)***	***p-value***		**Odds Ratio (95% Confidence Interval)***
Myocardial infarction	11 (13.6)	25 (11.9)	0.694		0.86 (0.37-1.96)
Acute renal failure	35 (43.2)	46 (21.9)	<0.001		2.00 (1.09-3.67)
Superinfection	33 (40.7)	64 (30.5)	0.099		1.05 (0.58-1.90)
Shock	52 (64.2)	82 (39.0)	<0.001		2.37 (1.29-4.36)
	Age ≥ 60 years (n=3,403)				
	Obesity n=330 n (%)	**No obesity n=3,073 n (%)**	**p-value**		**Odds Ratio (95% Confidence Interval)***
Myocardial infarction	40 (12.1)	321 (10.4)	0.347		1.00 (0.69-1.45)
Acute renal failure	91 (27.6)	668 (21.7)	0.018		1.20 (0.90-1.60)
Superinfection	65 (19.7)	406 (13.2)	0.002		1.05 (0.76-1.44)
Shock	92 (27.9)	535 (17.4)	<0.001		1.22 (0.91-1.65)
	Men (n=2,413)				
	Obesity n=267 n *(%)*	**No obesity n=2,146 n *(%)***	**p-value**		**Odds Ratio (95% Confidence Interval)¶**
Myocardial infarction	37 (13.9)	246 (11.5)	0.267		0.93 (0.62-1.39)
Acute renal failure	95 (35.6)	510 (23.8)	<0.001		1.36 (1.00-1.84)
Superinfection	71 (26.6)	299 (13.9)	<0.001		1.20 (0.79-1.58)
Shock	113 (42.3)	435 (20.3)	<0.001		1.70 (1.24-2.34)
	Women (n=1,281)				
	Obesity	**No obesity**	**p-value**		**Odds Ratio**

	n=144 n *(%)*	n=1,137 n *(%)*			(95% Confidence Interval) ¶
Myocardial infarction	14 (9.7)	100 (8.8)	0.713		1.12 (0.61-2.05)
Acute renal failure	31 (21.5)	204 (17.9)	0.304		1.24 (0.79-1.96)
Superinfection	27 (18.8)	171 (15.0)	0.270		0.98 (0.60-1.60)
Shock	31 (21.5)	182 (16.0)	0.097		1.13 (0.70-1.80)

* Results from multivariate logistic regression model. Age, gender, number of pre-existing comorbidities, acute renal failure, shock, superinfection and myocardial infarction were included in the model.

¶ Results from multivariate logistic regression model. Age, number of pre-existing comorbidities, acute renal failure, shock, superinfection and myocardial infarction were included in the model.

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Funding: none

Competing interests: no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.