Abdominal Obesity Phenotype Predicts COVID-19 Chest X-Ray Severity Score better than General Obesity

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Abstract

Purpose

Chest x-ray (CXR) severity score and general obesity are predictive risk factors for COVID-19 hospital admission. However, the relationship between abdominal obesity and CXR severity score has not yet been fully explored.

Methods

This retrospective cohort study analyzed the association of different adiposity indexes, including waist circumference and body mass index (BMI), with CXR severity score in 215 hospitalized patients with COVID-19.

Results

Patients with abdominal obesity had significantly higher CXR severity scores and higher rates of these scores than those without abdominal obesity (P<0.001; P=0.001, respectively). While, there were no significant differences between BMI classes (P=0.104; P=0.271, respectively). Waist circumference and waist-to-height ratio (WHtR) correlated more closely with CXR severity score than BMI (r=0.43, P<0.001; r=0.41, P<0.001; r=0.17, P=0.012, respectively). The area under the curves (AUCs) for waist circumference and WHtR were significantly higher than those for BMI for distinguishing a high CXR severity score (≥8) (0.68 [0.60-0.75] and 0.67 [0.60-0.74] vs 0.58 [0.51-0.66], P=0.001). Multivariable analysis indicated abdominal obesity (risk ratio: 1.75, 95% CI: 1.25-2.45, P<0.001), bronchial asthma (risk ratio: 1.73, 95% CI: 1.07-2.81, P=0.026) and oxygen saturation at admission (risk ratio: 0.96, 95% CI: 0.94-0.97, P<0.001) as the only independent predictors of a high CXR severity score.

Conclusion

Abdominal obesity might predict a high CXR severity score better than general obesity in hospitalized patients with COVID-19. Therefore, when performing clinical hospital practices, waist circumference should be assessed, and patients with abdominal obesity should be monitored closely when hospitalized.

Introduction

Coronavirus 2019 (COVID-19), the infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a broad spectrum of varieties from asymptomatic infection to influenza-like symptoms all the way to severe pneumonia, leading then to acute respiratory distress syndrome (ARDS) [1]. Early identification of individual phenotypes is essential in patients who are particularly inclined to develop a severe COVID-19 disease and who may need hospital admission. Older patients and those with preexisting non-communicable diseases (NCDs) seem more vulnerable to severe forms of COVID-19 [2].

Obesity is a gateway to many NCDs, and people with general obesity seem to have a high risk of hospitalizations, serious illnesses, and mortality [3]. With the rising prevalence of obesity, awareness of its impact on communicable diseases has increased [4, 5]. During the 2009 influenza A H1N1 pandemic, obesity was identified as an independent risk factor for more severe disease and mortality in infected individuals [6]. Moreover patients with obesity were likley to develop higher frequency of both upper and lower respiratory tract infections [7] and even hypoventilation-associated to pneumonia [8, 9].

Evidence is now emerging that obesity is also a risk factor in the current SARS-CoV-2 pandemic [10, 11]. Recent analysis found that COVID-19 becomes more severe as the body mass index (BMI) increases and that hospitalized male patients with obesity have a higher mortality rate and are more likely to require mechanical ventilation [12, 13], with most patients with BMI > 35 requiring intubation [14, 15].

During the current SARS-CoV-2 pandemic, chest x-ray (CXR) played a very important role in the early diagnosis and treatment of patients with suspected or confirmed COVID-19 chest infections. It became the primary imaging modality for clinical management and severity stratification [16–18]. Although computed tomography (CT) is considered the most effective method for the detection of lung abnormalities, it is characterized by a lower specificity [19] and its routine use may be impractical especially when there is a large inflow of patients with suspected COVID-19 chest infections [16]. A high CXR severity score as well as a high BMI might be predictive risk factors for hospitalization and intubation in COVID-19 patients [17]. In addition, patients with obesity have a higher risk of CXR severity due to COVID-19 pneumonia than normal weight patients [20].

However, BMI is not always the best indicator of obesity because it does not account for the amount and distribution of body fat, which can vary markedly among people with different ranges of BMI [21]. Location is the key when it comes to body fat.

People with obesity appear to present systemic low-grade inflammation, higher proneness to infections due to a reduced immune response, and higher morbidity and mortality associated with infections [22–24]. The excess of abdominal visceral fat is considered the main culprit in inflammatory diseases of obesity and is an indicator of increased ectopic fat that could increase atherosclerosis and raise cardiometabolic risks [25]. It has been recently suggested that excessive visceral adiposity may be related to the outcome of severe COVID-19 [26–30]. Patients in a large population-based cohort, with central obesity assessed by their waist circumference or waist-to-hip ratio (WHR), were also reported to be more likely to develop severe COVID-19 [31].

Detailed phenotyping of patients with COVID-19 pneumonia is essential to identify individuals or subgroups that are at increased levels of risk, and to forecast illness progressions and outcomes better. However, further investigation is still needed on the putative role of the abdominal distribution of adiposity in COVID-19 development and progression.

Therefore, the aim of this study was to find out whether abdominal obesity could better predict CXR severity scores rather than general obesity in COVID-19 hospitalized patients.

Methods

Study setting

During the early stages of the COVID-19 pandemic, the Lombardy Health Care Service decided to employ some hospitals in Milan city and the hinterland exclusively for the admission and care of COVID-19-positive patients. As the number of cases grew, our hospital, the IRCCS Policlinico San Donato, reacted swiftly by increasing the number of beds in the intensive care units (ICUs), and was then converted entirely into a COVID-19 hub with all medical wards dedicated to COVID-19 patients.

Study design

This was a retrospective single-centered cohort study and approved by the local ethics committee, protocol code 37/int/2020. Due to the retrospective nature of this analysis, informed consent was considered not to be necessary and waived. The patients' confidentiality was protected by assigning anonymous identification codes. The study was partially supported by Italian Ministry of Health, to IRCCS Policlinico San Donato.

Study population

Through a review of the clinical and imaging database of the IRCCS Policlinico San Donato in San Donato Milanese, Italy, from March 9 to April 27, 2020 we have identified data of 221 hospitalized patients with confirmed COVID-19 (by positive nasopharyngeal swab for RT-PCR) who underwent a CXR at the site of the emergency room isolation within a maximum time interval of 12 hours and to whom anthropometric measurements (weight, height and waist circumference) were taken within the internal medicine and endocrinological-metabolic ward (Fig. 1). Patients with a poor-quality image due to artifacts (n = 6) were being excluded. Finally, a total of 215 patients affected by COVID-19 with optimal CXR image were included in this study. For patients with multiple CXR examination, the CXR with the shortest time interval between imaging and symptom onset was used for this analysis.

Data collection

At admission to our ward, each patient's demographic, anthropometric and clinical history was collected into the hospital's electronic clinical database, and all clinical data was updated daily during the entire hospital stay. We extracted the following data for the present study: gender, age, race, height, weight, waist circumference, preexisting comorbidities and clinical outcomes. Values of inflammatory biochemical data of interleukin 6 (IL-6), oxygen saturation at admission (SpO_2) and oxygen therapy which were closest in time to the CXR were also collected. Patients were then classified according to waist circumference thresholds, as with abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females) or without abdominal obesity (waist circumference < 102 cm for males, < 88 cm for females) [32]. According to the CDC definition [33], patients were also classified on the basis of their BMI as: with underweight (less than 18.5 kg/m^2), with normal weight (18 to < 25 kg/m^2), with overweight (25 to < 30 kg/m^2) and with general obesity (≥ 30 kg/m^2).

Anthropometric measures

Anthropometric measures were taken at admission in the internal medicine and endocrinological-metabolic ward, with light indoor clothing and no shoes. The standing height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg using a scale with a stadiometer. The waist circumference was measured at the umbilicus three times using an extensible tape measure and the average of the three was recorded. Waist-to-height ratio (WHtR) was calculated as the waist circumference divided by the height, in centimeters. BMI was calculated as weight (kilograms) divided by height (meters) squared.

CXR examination

All CXR were taken at bedside in the emergency department (ED) isolation rooms, using one of two different CXR systems (Digital GM85, Samsung Healthcare, Seoul, South Korea; Digital FDR Go PLUS, Fujifilm, Tokyo, Japan). Two radiologists (F.S. and S.S., with respectively 15 and 7 years of experience in chest imaging) independently and blindly reviewed all anonymized CXR. In case of discordance, agreement was reached on how to rate the

pulmonary parenchyma. The interobserver agreement of the CXR severity scores between the reviews of the two radiologists was excellent (ICC 0.995).

CXR severity score

The readers rated pulmonary parenchymal involvement using a semi-quantitative severity score, dividing each lung into three zones (Fig. 2). The upper zone (from the lung apex to the aortic arch profile), the middle zone (lung hilum, from the aortic arch profile to the lower margin of the lower pulmonary vein), and the lower zone (from the lower margin of the lower pulmonary vein to the diaphragm). CXR was classified with a severity scale expressed as a continuous variable. For each zone a score of 0–3 in 1-point increments was assigned: 0, normal lung parenchyma; 1, interstitial involvement only; 2, radiopacity for less than 50% of the visible lung parenchyma; 3, radiopacity for 50% or more of the visible lung parenchyma (Fig. 3). In our population, CXR severity scores ranged from 0 to 17.

High CXR severity score

A CXR severity score of 8 or more was associated with the involvement of at least four out of six lung segments, so we established a cutoff of 8 to indicate a high CXR severity score. This enabled the clinical staff to stratify the patient's risk very quickly.

Oxygen therapy

The need and invasiveness of oxygen therapy, within 12 hours after hospitalization, were rated as follows: mild, when the patient did not require O_2; moderate when the patient required O_2; severe when the patient required non-invasive ventilator support (continuous positive airway pressure, CPAP) but was not intubated; critical when the patient required intubation.

Preexisting comorbidities

Preexisting comorbidities, such as hypertension, diabetes mellitus, ischemic cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney failure, bronchial asthma, or chronic heart failure were recorded from the patient’s clinical history and electronic medical records.

Statistical analysis

Categorical variables were described as frequency and percentages, and continuous variables as mean ± SD or median and interquartile range (IQR), as appropriate. Means for continuous variables were compared using independent group t-tests when the data were normally distributed; or else the Mann-Whitney test was applied. Categorical variables were compared using the χ^2 test or Fisher’s exact test. Correlations between continuous variables were evaluated according to Spearman Rho. To evaluate the accuracy of waist circumference, the WHtR and BMI in relation to a high CXR severity score, receiver operating characteristic (ROC) curves were used. The area under the curve (AUC) was taken as the summary discrimination measure. The AUCs were compared with the method of DeLong et al. [34].

We used Poisson regression models with a robust error variance [35] to identify the clinical determinants (with univariate $p < 0.1$ and forcing age into the model), independently associated with a high CXR severity score (≥ 8), using risk ratios (RR) and 95% confidence intervals (CI). The analyses included continuous variables (age, IL-6 and SpO_2) and categorical variables (gender, race, smoking, abdominal obesity, general obesity, and comorbidities).

All statistical tests were two-sided. $p < 0.05$ was considered significant. All analyses were made with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics of patients, based on different adiposity indexes

We phenotyped our study population according to different adiposity indexes, adopting waist circumference as an indicator of abdominal fat distribution and BMI as an indicator of general fatness. The clinical characteristics of patients with and without abdominal obesity or with normal weight, with overweight and with general obesity are shown in Table 1. No patient was underweight and only 6.5% (n = 14) had a BMI between 35 and 40 kg/m^2, while 1.4% (n = 3) had a BMI over 40 kg/m^2. In the overall population CXR severity scores ranged from 0 to 17 and 48% (n = 103) of patients had high CXR severity score (≥ 8). Patients with abdominal obesity had significantly higher CXR severity scores (Fig. 4A) and higher rates of CXR severity scores (≥ 8) than those without abdominal obesity ($P < 0.001$; $P = 0.001$, respectively) (Table 1), while there were no significant differences between patients with normal weight, with overweight and with general obesity ($P = 0.104$; $P = 0.271$, respectively), (Table 1, Fig. 4B).

Table 1
Clinical characteristics of patients with COVID-19 based on adiposity indexes

	Total	Abdominal obesity			BMI classes			
	(215)	No 102 (47%)	Yes 113 (53%)	p-value	Normal weight n = 74, (34%)	Overweight n = 87, (41%)	General Obesity n = 54, (25%)	p-value
Demographic information								
Age, years[a], no. **(%)**	62.7 ± 14.05	61.6 ± 15.0	63.7 ± 13.1	0.275	63.6 ± 14.8	63.9 ± 13.7	59.6 ± 13.4	0.169
< 40	12 (6)	9 (9)	3 (3)		5 (7)	5 (6)	2 (4)	
(40–50]	26 (12)	13 (13)	13 (11)		8 (11)	7 (8)	11 (20)	
(50–60]	57 (26)	25 (24)	32 (28)		15 (20)	22 (25)	20 (37)	
(60–70]	49 (23)	22 (22)	27 (24)		20 (27)	22 (25)	7 (13)	
> 70	71 (33)	33 (32)	38 (34)		26 (35)	31 (36)	14 (26)	
Gender, no. **(%)**				0.129				**0.001**
Male	145 (67)	74 (73)	71 (63)		38 (51)	65 (75)	42 (78)	
Female	70 (33)	28 (27)	42 (37)		36 (49)	22 (25)	12 (22)	
Race, no. **(%)**				0.132*				0.909*
Caucasian	191 (89)	92 (90)	99 (88)		66 (89)	77 (89)	48 (89)	
Latin-American	12 (6)	4 (4)	8 (7)		3 (4)	5 (6)	4 (7)	
African	4 (2)	0 (0)	4 (3)		1 (1)	2 (2)	1 (2)	
Asian	4 (2)	3 (3)	1 (1)		3 (4)	1 (1)	0 (0)	

No abdominal obesity (Waist circumference < 102 cm for males, < 88 cm for females); Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m^2); Overweight (BMI from 25 to < 30 kg/m^2); General Obesity (BMI ≥ 30 kg/m^2). Not available (NA); Body Mass Index (BMI); Waist-to-height ratio (WHtR); Chest x-ray (CXR); Interleukin 6 normal value < 10 pg/mL; Oxygen saturation at admission (SpO_2).

Categorical variables presented as number (percentage), and continuous variables as mean (± SD)[a] or median (interquartile range)[b]. To compare variables between different groups, the $\chi 2$ test or *Fisher's exact test was used for categorical variables.

	Total	Abdominal obesity			BMI classes			
Arabic	4 (2)	3 (3)	1 (1)		1(1)	2 (2)	1 (2)	
Smoke, no. **(%)**				0.648*				0.932*
Current smoker	28 (13)	12 (12)	16 (14)		9 (12)	14 (16)	5 (9)	
Former smoker	4 (2)	1 (1)	3 (3)		1 (1)	2 (2)	1 (1)	
Never smoked	147 (68)	71 (70)	76 (67)		51 (69)	61 (70)	35 (64)	
NA	36 (17)	18 (17)	18 (16)		13 (18)	10 (12)	13 (24)	
Anthropometric measures								
Weight (kg)[a]	79.6 ± 16.6	71.5 ± 12.7	86.9 ± 16.4	**< 0.001**	64.5 ± 9.5	80.7 ± 8.9	98.5 ± 13.4	**< 0.001**
Height (cm)[a]	170.0 ± 10.0	169 ± 10	170 ± 10	0.379	169 ± 10	171 ± 10	169 ± 10	0.335
Waist (cm)[a]	99.7 ± 13.4	89.4 ± 9.2	109.0 ± 9.1	**< 0.001**	88.2 ± 10.8	101.5 ± 8.4	112.4 ± 10.0	**< 0.001**
Waist male (cm)[a]	103.0 ± 12.1	93.3 ± 7.2	112.3 ± 7.6	**< 0.001**	91.7 ± 10.1	102 ± 7.3	113.3 ± 10.4	**< 0.001**
Waist female (cm)[a]	93.7 ± 14.2	79.1 ± 5.3	103.4 ± 8.9	**< 0.001**	84.5 ± 10.3	100.0 ± 11.2	109.4 ± 7.9	**< 0.001**
WHtR[a]	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	**< 0.001**	0.5 ± 0.06	0.6 ± 0.05	0.7 ± 0.1	**< 0.001**
BMI (kg/m^2) [a]	27.5 ± 4.9	24.9 ± 3.7	29.8 ± 4.7	**< 0.001**	22.6 ± 1.8	27.5 ± 1.3	34.0 ± 3.5	**< 0.001**
Adiposity status								
Abdominal obesity, no. (%)								**< 0.001**
Yes	113 (53)	-	-	-	17 (23)	49 (56)	47 (87)	

No abdominal obesity (Waist circumference < 102 cm for males, < 88 cm for females); Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m^2); Overweight (BMI from 25 to < 30 kg/m^2); General Obesity (BMI ≥ 30 kg/m^2). Not available (NA); Body Mass Index (BMI); Waist-to-height ratio (WHtR); Chest x-ray (CXR); Interleukin 6 normal value < 10 pg/mL; Oxygen saturation at admission (SpO_2).

Categorical variables presented as number (percentage), and continuous variables as mean (± SD)[a] or median (interquartile range)[b]. To compare variables between different groups, the $\chi 2$ test or *Fisher's exact test was used for categorical variables.

	Total	Abdominal obesity			BMI classes			
No	102 (47)	-	-	-	57 (77)	38 (44)	7 (13)	
BMI classes, no. (%)				**< 0.001**				
Normal weight	74 (34)	57 (56)	17 (15)		-	-	-	-
Overweight	87 (41)	38 (37)	49 (43)		-	-	-	-
General obesity	54 (25)	7 (7)	47 (42)		-	-	-	-
Comorbidities, no. **(%)**								
Hypertension	87 (41)	40 (39)	47 (42)	0.751	19 (26)	41 (47)	27 (50)	**0.001**
Diabetes mellitus	31 (14)	10 (10)	21 (19)	0.067	7 (9)	15 (17)	9 (17)	0.320
Ischemic cardiomyopathy	16 (7)	9 (9)	7 (6)	0.447	4 (5)	9 (10)	3 (5)	0.570
Atrial fibrillation	13 (6)	7 (7)	6 (5)	0.646	5 (7)	7 (8)	1 (2)	0.459*
Chronic Obstructive Pulmonary Disease	10 (5)	5 (5)	5 (4)	1.000*	4 (5)	4 (5)	2 (1)	0.9179*
Chronic Kidney Failure	8 (4)	5 (5)	3 (2)	0.478*	3 (4)	2 (2)	3 (5)	0.465*
Bronchial asthma	5 (2)	2 (2)	3 (2)	1.000*	1 (1)	4 (5)	0 (0.0)	0.295*
Chronic heart failure	5 (2)	1 (1)	4 (4)	0.372	0 (0.00)	4 (5)	1 (3)	0.195
Clinical features, no. **(%)**								
Chest x-ray								

No abdominal obesity (Waist circumference < 102 cm for males, < 88 cm for females); Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m^2); Overweight (BMI from 25 to < 30 kg/m^2); General Obesity (BMI ≥ 30 kg/m^2). Not available (NA); Body Mass Index (BMI); Waist-to-height ratio (WHtR); Chest x-ray (CXR); Interleukin 6 normal value < 10 pg/mL; Oxygen saturation at admission (SpO_2).

Categorical variables presented as number (percentage), and continuous variables as mean (± SD)[a] or median (interquartile range)[b]. To compare variables between different groups, the $\chi 2$ test or *Fisher's exact test was used for categorical variables.

	Total	Abdominal obesity			BMI classes			
CXR severity score[b]	7 (4–10)	6 (3–9)	9 (6–11)	**< 0.001**	7 (3–10)	7 (5–10)	9 (5–11)	0.104
High CXR severity score (≥ 8), no. (%)	103 (48)	36 (35)	67 (59)	**0.001**	33 (45)	39 (45)	31 (57)	0.271
Biochemical inflammation marker								
Interleukin 6 (pg/mL)[b]	87 (23–357)	32 (11–145)	150 (55–693)	**< 0.001**	44 (9-211)	80 (28–320)	181 (55–814)	**< 0.001**
SpO_2 at admission[b]	95% (91–96)	95% (92–96)	94% (89–95)	0.792	95% (92–97)	95%(91–96)	94% (92–96)	0.638
Oxygen therapy, no. (%)				0.249				0.215*
Mild, O_2 not necessary	37 (17)	23 (22)	14 (12)		16 (22)	14 (16)	7 (13)	
Moderate, O_2 necessary	124 (58)	57 (56)	67 (60)		41 (55)	53 (61)	30 (55)	
Severe, CPAP necessary	44 (20)	19 (19)	25 (22)		11 (15)	19 (22)	14 (26)	
Critical, needs intubation in ICU	10 (5)	3 (3)	7 (6)		6 (8)	1 (1)	3 (6)	
ICU, no. (%)	12 (6)	5 (5)	7 (6)	0.439	6 (8)	2 (2)	4 (7)	0.207*
Days of hospitalization[a]	21.3 ± 13.6	20.3 ± 11.1	21.5 ± 12.8	0.468	20.1 ± 13.5	20.6 ± 11	22.2 ± 11.2	0.601
Death, no. (%)	4 (2)	0 (0)	4 (4)	0.124*	1 (1)	1 (1)	2 (4)	0.540*

No abdominal obesity (Waist circumference < 102 cm for males, < 88 cm for females); Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m^2); Overweight (BMI from 25 to < 30 kg/m^2); General Obesity (BMI ≥ 30 kg/m^2). Not available (NA); Body Mass Index (BMI); Waist-to-height ratio (WHtR); Chest x-ray (CXR); Interleukin 6 normal value < 10 pg/mL; Oxygen saturation at admission (SpO_2).

Categorical variables presented as number (percentage), and continuous variables as mean (± SD)[a] or median (interquartile range)[b]. To compare variables between different groups, the χ2 test or *Fisher's exact test was used for categorical variables.

IL-6 values were significantly higher in patients with abdominal obesity than those without (P < 0.001) as well as in patients with overweight and with obesity compared to those with normal weight (P < 0.001) (Table 1, Fig. 4C, 4D).

There were no differences in age between patients with and without abdominal obesity or between BMI classes (P = 0.275; P = 0.169) (Table 1). No significant gender differences were found between patients with or without abdominal obesity (P = 0.129), although male gender was more prevalent in patients with overweight and with general obesity than in those with normal weight (P = 0.001) (Table 1).

There was no statistical difference in SpO_2 at admission between patients with and without abdominal obesity or between patients with normal weight, with overweight and with general obesity (P = 0.792 and P = 0.638 respectively), although a trend toward lower SpO2 on admission was observed in patients with abdominal obesity compared to those without,

(Table 1).

We observed a trend in the increased need and invasiveness of oxygen therapy, within the first few hours of hospital admission, in patients with abdominal obesity than those without, but not reaching statistical significance (P = 0.249), while this trend did not appear in the three BMI classes (P = 0.215) (Table 1).

There was no difference in the hospital stays (days) between patients with and without abdominal obesity or between patients with normal weight, with overweight and with general obesity (P = 0.468 and P = 0.601, respectively) (Table 1).

In our sample 2% (n = 4) of patients died from COVID-19 complications. All of them had abdominal obesity and 1% (n = 2) of them were affected also by general obesity (Table 1).

In our cohort, hypertension, diabetes, cardiovascular disease, chronic kidney failure and bronchial asthma were the most common comorbidities. Diabetes was more frequent in patients with abdominal obesity than in those without, but the difference was not significant (P = 0.067) (Table 1). Hypertension was significantly more common in patients with overweight and with general obesity than in those with normal weight (P = 0.001) (Table 1).

Adiposity indexes and clinical features

Waist circumference and WHtR showed a higher correlation with CXR severity score than BMI (r = 0.43 [0.30–0.55], P < 0.001; r = 0.41 [0.28–0.53], P < 0.001; r = 0.17 [0.04–0.29], P = 0.012, respectively).

IL-6 correlated more closely with both waist circumference and WHtR than BMI (r = 0.46 [0.33–0.58], P < 0.001; r = 0.45 [0.32–0.57], P < 0.001; r = 0.34 [0.21–0.46], P < 0.001, respectively).

SpO_2 at admission correlated negatively with both waist circumference and WHtR (r= -0.17 [-0.29 - -0.04], P = 0.025; r= -0.18 [-0.30 - -0.05], P = 0.017, respectively), while no significant correlation was found with BMI (r= -0.07 [-0.19-0.06], P = 0.389).

SpO_2 at admission and IL-6 significantly correlated with CXR severity scores (r= -0.45 [-0.57 - -0.32], P < 0.001; r = 0.48 [0.35–0.59], P < 0.001, respectively).

ROC analysis

ROC curves were used to assess the discriminatory ability of waist circumference, WHtR and BMI in relation to a high CXR severity score (≥ 8). The best cutoff for a high score (≥ 8) in waist circumference was 102 cm in men and 86 cm in women, 0.58 for WHtR and 27.7 for BMI. The AUCs for waist circumference and WHtR were

significantly higher than those for BMI to distinguish a high CXR severity score (≥ 8) (0.68 [0.60–0.75] and 0.67 [0.60–0.74] vs 0.58 [0.51–0.66], P = 0.001) (Fig. 5).

CXR severity scores and IL-6 among patients with different adiposity indexes

We examined CXR severity scores and IL-6 in the three categories of BMI in relation to the concomitant presence of abdominal obesity phenotype (Table 2). CXR severity scores were higher in patients with abdominal obesity than in patients without abdominal obesity among the subgroup of patients with overweight (P < 0.001) and those with general obesity (P = 0.043). Even in the subgroup of patients with normal-weight, there was a trend towards higher CXR severity scores in those with abdominal obesity, but not reaching statistical significance (P = 0.094).

Table 2
Chest x-ray severity score and IL-6 values among patients with different adiposity indexes

	Abdominal obesity		
	No	**Yes**	p-value
	n = 102 (47%)	**n = 113 (53%)**	
Normal weight n = 74 (34%)	**n = 57 (77%)**	**n = 17 (23%)**	
CXR severity score	6.0 (3.0–9.0)	9.0 (6.0–11.0)	0.094
IL-6 values	21.0 (8.0-100.0)	140.0 (70.0-724.0)	**< 0.001**
Overweight, n = 87 (41%)	**n = 38 (44%)**	**n = 49 (56%)**	
CXR severity score	7.0 (3.0–8.0)	8.0 (5.0–10.0)	**0.043**
IL-6 values	41.0 (19.0-178.0)	96.0 (45.0-328.0)	**0.046**
General obesity, n = 54 (25%)	**n = 7 (13%)**	**n = 47 (87%)**	
CXR severity score	2.0 (0.0–4.0)	10.0 (7.0–12.0)	**< 0.001**
IL-6 values	52.0 (27.0-169.0)	222.0 (80.0-889.0)	**0.047**
No abdominal obesity (Waist circumference < 102 cm for males, < 88 cm for females); Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m^2); Overweight (BMI from 25 to < 30 kg/m^2); General obesity (BMI ≥ 30 kg/m^2). Chest x-ray (CXR); Interleukin 6 (IL-6) normal value < 10 pg/mL.			
Continuous variables as median (interquartile range).			

IL-6 values were higher in patients with abdominal obesity phenotype than in patients without abdominal obesity among the subgroup of patients with normal weight (P < 0.001), with overweight (P = 0.046) and with general obesity (P = 0.047).

Risk factors associated with a CXR severity score ≥ 8

Poisson regression with a robust error variance analysis was done to identify the risk factors associated with a high CXR severity score (≥ 8) in COVID-19 hospitalized patients (Table 3). Univariable analysis showed that

abdominal obesity (RR: 1.68, 95% CI: 1.24–2.28, P < 0.001), bronchial asthma (RR: 1.65, 95% CI: 1.04–2.62, P = 0.035), general obesity (RR: 1.28, 95% CI: 0.96–1.71, P = 0.088), IL-6 values (RR: 1.03, 95% CI: 1.01–1.05, P = 0.002) and SpO_2 at admission (RR: 0.96, 95% CI 0.94–0.97, P < 0.001) were significantly associated with a CXR severity score ≥ *8*. On multivariable analysis, considering variables associated in univariable models with p < 0.1 and forcing age, abdominal obesity (RR: 1.75, 95% CI: 1.25–2.45, P = 0.001), bronchial asthma (RR: 1.73, 95% CI: 1.07–2.81, P = 0.026) and SpO_2 at admission (RR: 0.96, 95% CI: 0.94–0.97, P < 0.001) were still independent predictors of a high CXR severity score (≥ 8).

Table 3
Univariable and multivariable logistic regression for the evaluation of risk factors associated with high chest x-ray severity score (≥ 8)

	Univariable		**Multivariable**	
	RR (CI 95%)	**p-value**	**RR (CI 95%)**	**p-value**
Age	1.01 (0.99–1.02)	0.234	1.00 (0.99–1.01)	0.849
Race				
Caucasian vs Non-Caucasian	0.79 (0.55–1.16)	0.235	-	
Gender				
Male vs Female	1.35 (0.97–1.90)	0.072	1.35 (0.97–1.87)	0.078
Smoke	0.95 (0.62–1.46)	0.805	-	
Comorbidities				
Abdominal obesity	1.68 (1.24–2.28)	**< 0.001**	1.75 (1.25–2.45)	**0.001**
General Obesity	1.28 (0.96–1.71)	**0.088**	1.02 (0.74–1.39)	0.915
Hypertension	1.35 (0.99–1.83)	0.055	1.17 (0.84–1.65)	0.355
Diabetes Mellitus	1.24 (0.88–1.75)	0.227	-	
Ischemic cardiopathy	1.03 (0.61–1.72)	0.924	-	
Chronic heart failure	1.23 (0.59–2.57)	0.571	-	
Atrial fibrillation	0.94 (0.51–1.73)	0.843	-	
Chronic Obstructive Pulmonary Disease	0.81 (0.38–1.77)	0.604	-	
Bronchial asthma	1.65 (1.04–2.62)	**0.035**	1.73 (1.07–2.81)	**0.026**
Chronic Kidney Failure	0.76 (0.31–1.88)	0.551	-	
IL-6 (pg/ml)	1.03 (1.01–1.05)	**0.002**	1.00 (0.99–1.03)	0.313
SpO_2 at admission	0.96 (0.94–0.97)	**< 0.001**	0.96 (0.94–0.97)	**< 0.001**

Abdominal obesity (waist circumference ≥ 102 cm for males, ≥ 88 cm for females); Normal weight (BMI from 18.5 to < 25 kg/m2); Overweight (BMI from 25 to < 30 kg/m2); General obesity (BMI ≥ 30 kg/m^2); Interleukin-6 (IL-6); Oxygen saturation at admission (SpO_2); Risk ratio (RR); Confidence Interval (CI).

Discussion

In this study, we analyzed the impact of different adiposity indexes on CXR severity scores in a hospitalized cohort affected by COVID-19. We observed that abdominal obesity was an independent predictor of the risk of worse COVID-19-related lung abnormalities. Patients with abdominal obesity had significantly higher CXR severity scores and higher rates of high scores than those without abdominal obesity, while there were no significant differences between the BMI classes. The correlation of CXR severity scores with waist circumference and WHtR was higher than the one with BMI classes. Therefore, there was also a significant difference in the AUCs of waist circumference and WHtR compared to BMI when detecting high CXR severity scores. Moreover, among the subgroup of patients with overweight and with general obesity, those with concomitant presence of abdominal obesity phenotype had significant higher CXR severity scores. Even in the subgroup of patients with normal weight, there was a trend toward higher CXR severity scores in those with concomitant presence of abdominal obesity phenotype, but without reaching statistical significance probably due to the small sample size of this subgroup.

Recently, Stefan et al. [36] stressed that anthropometric indexes such as waist and hip circumferences are important to better estimate the risk of complications in patients with COVID-19, in addition to the standard hospital parameters including BMI. Although BMI is widely used to define general obesity, further phenotyping of patients by assessing fat distribution and abdominal obesity might be a more accurate measure to stratify patients [16, 31, 36, 37]. Therefore, waist circumference is widely used in clinical practice as a required criterion for the diagnosis of metabolic syndrome, which has recently been associated with a higher risk of serious illness with COVID-19 [37, 38].

Recent data found that patients with central obesity assessed by waist circumference threshold and WHR, had higher risk of severe COVID-19 [31]. Another study suggested that visceral adipose tissue and CT-derived upper abdominal waist circumference increase the likelihood of severe COVID-19 in overweight patients who do not meet the diagnostic criteria for general obesity [29].

Patients with obesity are predisposed to respiratory dysfunction, increased risk for severe asthma and to hypoventilation-associated pneumonia [8, 9, 39]. Toussie et al. [17] already demonstrated that both CXR severity scores and general obesity. were independent predictors for hospitalization and intubation in COVID-19 patients. However, in their study, anthropometric parameters of fat distribution (e.g. waist circumference) were not available, so that any prediction and comparison of potential outcomes was not possible [17]. In our study, we found that SpO_2 at admission correlated negatively with waist circumference and WHtR, while no significant correlation was found with BMI. In addition, when performing multivariable analysis, our results indicated that abdominal obesity and SpO_2 at admission were independent predictors of a high CXR severity score. A previous study reported that obesity was a strong independent contributor to low SpO_2, with a negative correlation between BMI and SpO_2, nevertheless the authors had not investigated a possible correlation with indicators of abdominal fat distribution [9]. In the present study we observed a slight trend in the increased need and invasiveness of the oxygen therapy in patients with abdominal obesity than in those without, but not reaching statistical significance. Whereas this trend did not appear in the three BMI classes. The inconsistent results may be due to the small size of each subgroup. A recent study reported that visceral fat deposition within the abdomen seems to have a stronger association with the need of ICU admission and intubation for COVID-19 than other parameters such as severity of interstitial pneumonia, markers of inflammation, age, gender or comorbidities [30]. This supports that upper trunk fat can

contribute to respiratory drive and gas exchange impairment [40]. Excessive fat in the chest walls and abdomen has a high mechanical impact on lung functionalities [8]. Abdominal obesity and excess visceral fat adversely affects the chest walls and lungs compliance due to the accumulation, increasing intra-abdominal pressure and mechanical compression of the diaphragm, lungs, and chest cavity [8].

Interestingly, ectopic fat depots have been highlighted as new markers of major COVID-19 complications [26, 30, 41, 42]. A recent study reported that in patients with SarsCoV-2, visceral adiposity and high intramuscular fat deposition were independent risk factors for critical illness [28]. However, they did not find differences in BMI [28]. In addition, Deng et al. [26] not only confirmed that obesity is a major and independent risk factor for COVID-19 complications in young adults [43], but also pointed out ectopic and visceral fat depots as new markers of that risk. The authors found that CT imaging showed significantly higher fatty liver and epicardial adipose tissue (EAT) in severely and critically ill patients with COVID-19 under 40 years old as compared with those with milder disease [43]. The higher risk for people with obesity to develop severe COVID-19 cardiac and pulmonary injuries can be attributed to multiple factors, such as the chronic inflammatory status, the delayed immune response, and possibly fat tissue serving as a reservoir for the virus [44]. However, ectopic and visceral fat accumulation is an additional mechanism that may not be immediately identified. We now face a different phenotype of the high-risk patient who is much younger and who certainly has obesity but with prominent visceral obesity [27]. The findings of Deng et al. [26] may provide new insights to untangle the intricate, and still unclear, physiopathologic pathways leading to COVID-19 organ damage. EAT has been recognized as highly inflammatory and dense with macrophage infiltrates that can cause upregulation and increase the release of pro-inflammatory cytokines such as IL-6 [45], which is overly expressed in COVID-19 patients [46]. The role of EAT in causing and worsening the COVID-19 cardiac complications recently emerged [47]. EAT and the myocardium share the same microcirculation [45, 47]. EAT inflammatory cytokines can reach out to the myocardium via vasa vasorum or paracrine pathways [45, 47]. Hence EAT is likely implicated in COVID-19 myocardial inflammation and cardiorespiratory failure. We recently reported that EAT inflammation was linked to more severe COVID-19 disease in hospitalized patients with abdominal obesity phenotype [42].

Abdominal obesity is associated with a chronic inflammatory state, which can be an important risk factor in disease progression [48,49], particularly for SARS-CoV-2 [46]. The present study showed that IL-6 values correlated more closely with both waist circumference and WHtR than BMI. We also found a significant correlation of IL-6 concentrations with CXR severity scores. Noteworthy, IL-6 values were higher in patients with abdominal obesity phenotype than in patients without abdominal obesity among the subgroup of patients with normal weight, with overweight, and with general obesity. The elevated inflammatory cytokine levels in patients with heavy abdominal visceral fat may be associated with increased morbidity in infectious disease [22]. IL-6 is a key inflammatory cytokine that plays a major role in the inflammatory storm, and patients with more severe COVID-19 had higher plasma IL-6 concentrations than patients with milder symptoms [46].

The tendency of people with visceral obesity to develop more serious complications if exposed to a virus, even severe COVID-19 related pulmonary and cardiac injuries, might be explained by various multiple factors, such as their chronic inflammatory status and a delayed and ineffective immune response [11, 22-24]. SARS-CoV-2 binds with the angiotensin-converting enzyme 2 (ACE2) receptor for intracellular invasion, and the mechanism for acute lung injury during infection has been postulated to be mediated through activation of the renin-angiotensin system (RAS) [50]. ACE2 is expressed in several human organs including the lung and adipose tissue [51]. Activation of the whole ACE/angiotensin II/type 1 angiotensin 2 receptor RAS axis is important in the

pathophysiology of obesity and visceral adiposity-related cardiac and acute lung injury risk [52, 53]. The interaction between the ACE2-RAS, adipose tissue, bronchial epithelium and COVID-19 might at least partially explain the higher morbidity and mortality risk for COVID-19 patients with obesity [51, 52]. However, the role of ACE2-RAS in COVID-19 remains to be clarified [51-53].

Strength and limits

As far as we know, this is the first study that has investigated the relations between abdominal obesity phenotype and CXR severity scores in COVID-19 hospitalized patients. There are several limitations of our study. First, it was a retrospective, single- center study with a small sample group. Most patients were of Caucasian ethnicity so the applicability of the waist circumference threshold to other ethnic groups requires further investigation. Second, waist circumference assessment is subject to operator variability and this could have led to some bias. Third, we extracted the information on comorbidities from the patients' records, assuming there was no comorbidity if none was mentioned. Finally, we did not use CT or MRI as a direct method for the detection of abdominal visceral fat. However, in daily clinical practice, it is not always possible to use these techniques and therefore indirect measures such as waist circumference are possibly useful in the first examination of hospitalized COVID-19 patients. Nevertheless, our study offered new insights on detailed phenotyping of hospitalized patients with COVID-19, adopting threshold values of waist circumference asindicators for abdominal obesity, which could predict the severity of lung abnormalities better than BMI.

What is already known on this subject?

The literature supports that CXR severity score and general obesity are independent predictors for hospitalization of COVID-19 patients. It has been shown that abdominal visceral obesity increases the risk of complications in COVID-19 patients; however, evidence is limited and the extent of these associations is not fully understood.

What your study adds?

The study shows that abdominal obesity rather than general obesity phenotype is an independent risk factor for a high CXR severity score in hospitalized COVID-19 patients. Moreover, abdominal fat distribution defined by waist circumference could be better than BMI to indicate a high CXR severity score. In hospital clinical practice the waist circumference should be assessed and patients with abdominal obesity phenotype should be monitored closely.

Conclusions

This study showed that abdominal obesity could be a better predictive factor for a high CXR severity score than general obesity in hospitalized COVID-19 patients. Therefore, in hospital clinical practice patients with abdominal obesity should be monitored closely when hospitalized.

Declarations

Funding: The study was partially supported by Italian Ministry of Health, to IRCCS Policlinico San Donato.

Compliance with ethical standards

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethics approval: This research study was conducted retrospectively from data obtained for clinical purposes and it was approved by the local ethics committee, protocol code 37/int/2020. Patient's confidentiality was protected by assigning anonymous identification codes.

Consent to participate: Due to the retrospective nature of this analysis, informed consent was not necessary and waived.

Availability of data and material: The datasets generated and/or analyzed during the current study will be made available upon reasonable request to the corresponding author.

Code availability: Not applicable

Declaration: Not applicable for that section.

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Figures

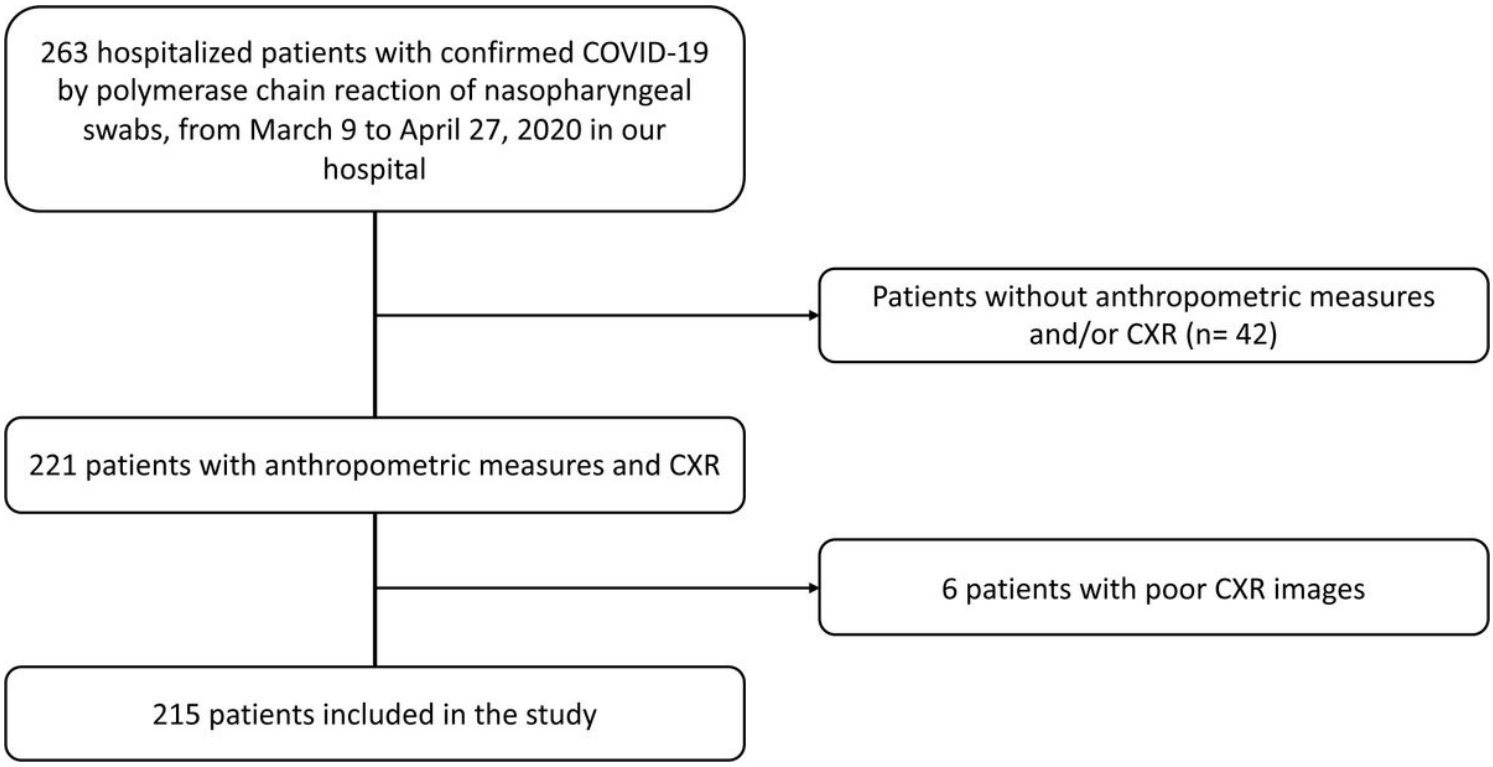

Figure 1

Flowchart for inclusion and exclusion criteria of our cohort. Chest x-ray (CXR). The figure was created by an author (S.B.) using the program Microsoft Power Point

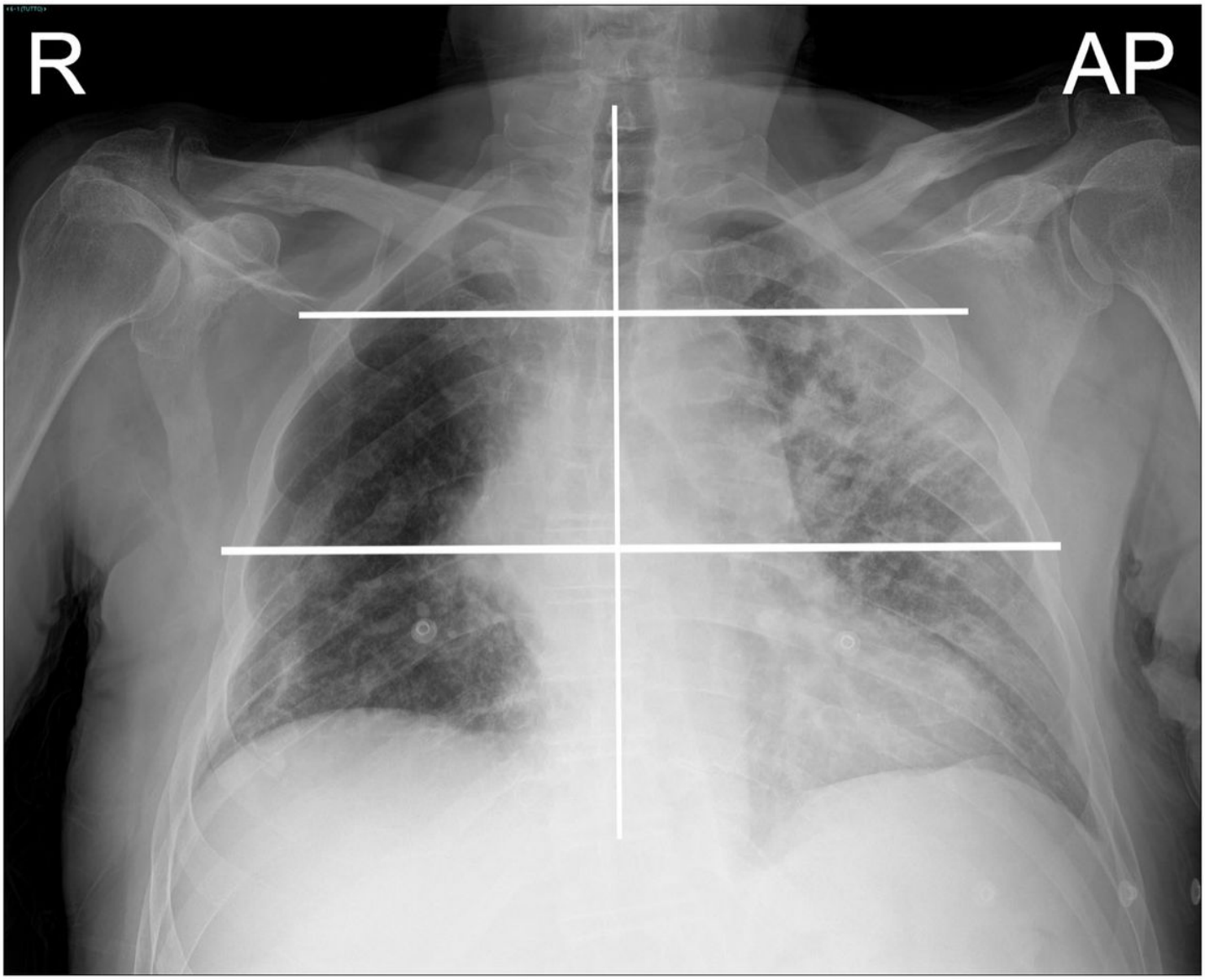

Figure 2

An example of a chest x-ray. Chest x-ray (CXR); Right (R); Antero-posterior (AP). Each CXR was divided into three parts for each lung: upper zone (from the lung apex to the aortic arch profile), middle zone (lung hilum, from the aortic arch profile to the inferior margin of the inferior pulmonary vein), and lower zone (from the inferior margin of the inferior pulmonary vein to the diaphragm).

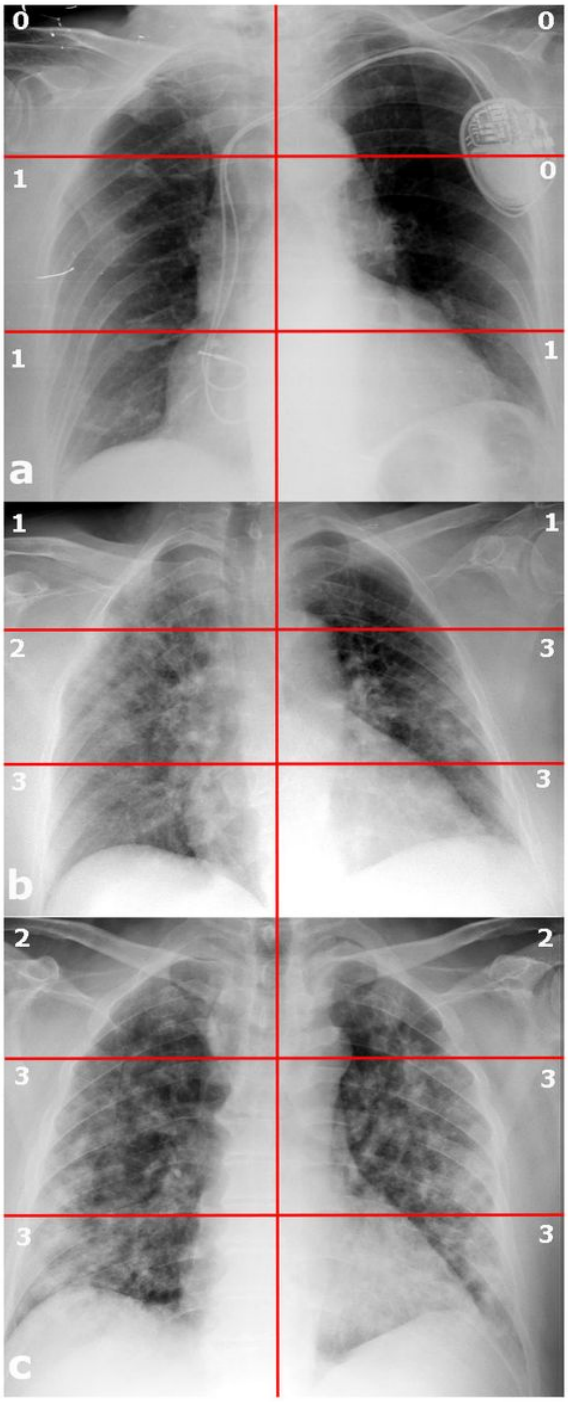

Figure 3

Three chest x-rays in COVID-19 patients with different lung parenchyma disease grades Chest x-ray (CXR). [a] CXR severity score 3; [b] CXR severity score 13; [c] CXR severity score 16.

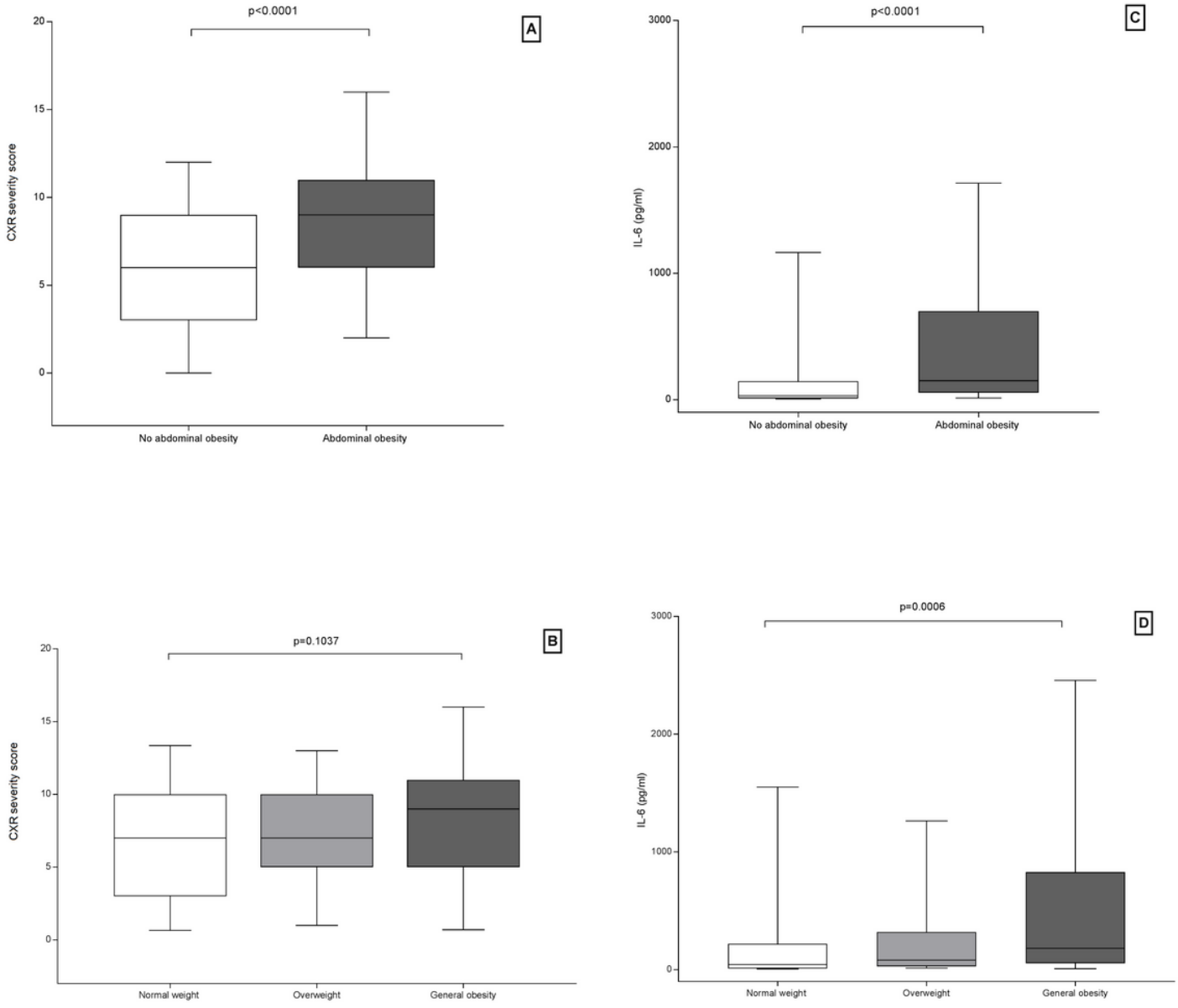

Figure 4

Chest x-ray severity scores of patients with and without abdominal obesity [A] and BMI classes [B], and IL-6 values of patients with and without abdominal obesity [C] and BMI classes [D] Chest x-ray (CXR); Interleukin-6 (IL-6); Body Mass Index (BMI). No abdominal obesity (Waist circumference <102 cm for males, <88 cm for females); Abdominal obesity (waist circumference ≥102 cm for males, ≥88 cm for females); Normal weight (BMI from 18.5 to <25 kg/m2); Overweight (BMI from 25 to <30 kg/m2); General obesity (BMI≥30 kg/m2); The figure was created by an author (V.M.) using the program GraphPad – Prism 7

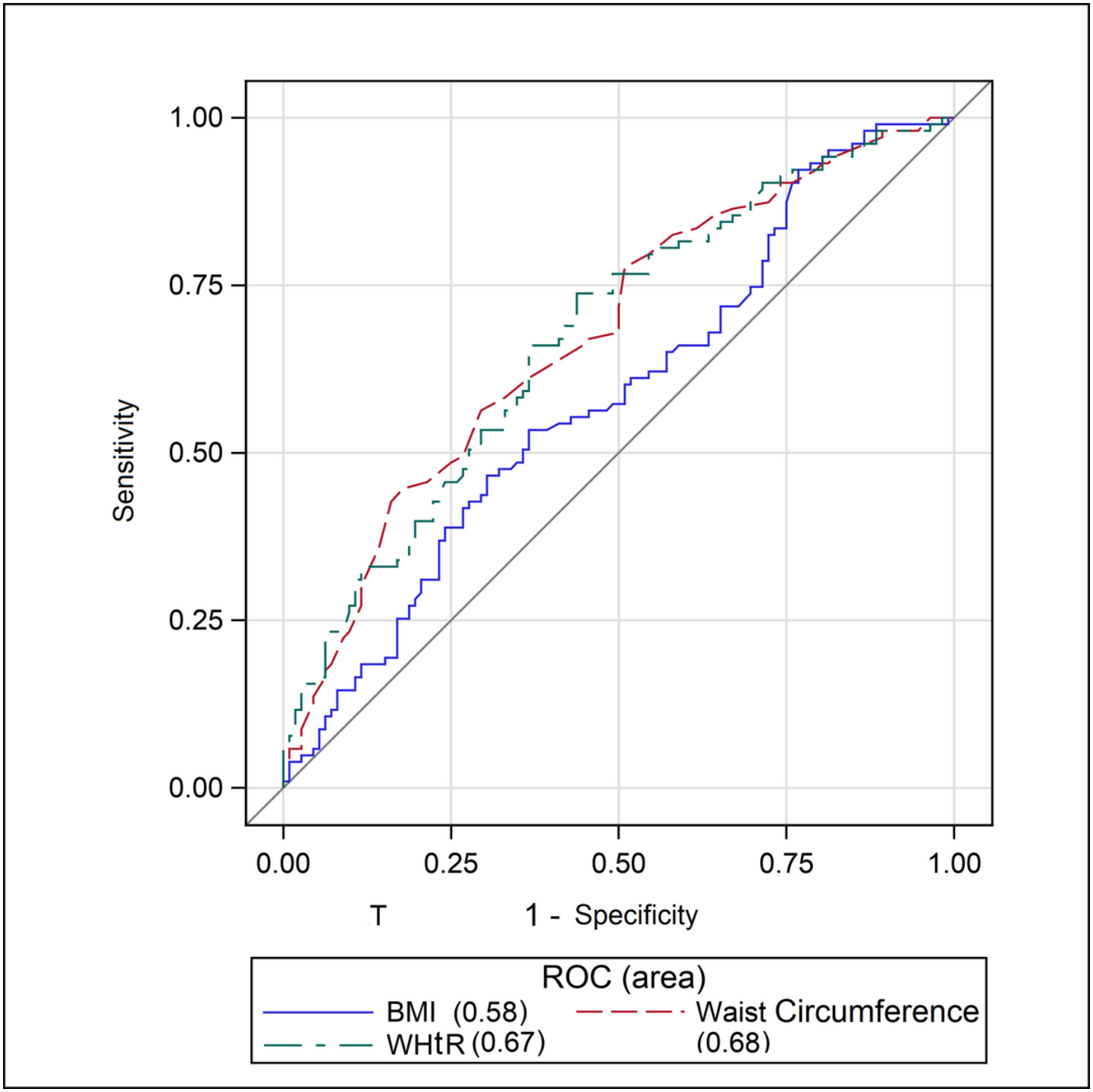

Figure 5

AUCs of waist circumference, waist-to-height-ratio and body mass index for establishing a high chest x-ray severity score Waist-to-height-ratio (WHtR) and Body Mass Index (BMI); Receiver Operating Characteristics (ROC). The figure was created by an author (V.M.) using the program SAS 9.4 (SAS Institute Inc., Cary, NC, USA).