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ORIGINAL CONTRIBUTION

Effects of Bariatric Surgery on COVID-19: a Multicentric Study from a High Incidence Area

Federico Marchesi[1,2] · Marina Valente[1] · Matteo Riccò[3] · Matteo Rottoli[4,5] · Edoardo Baldini[6] · Fouzia Mecheri[7] · Stefano Bonilauri[8] · Sergio Boschi[9] · Paolo Bernante[4,5] · Andrea Sciannamea[4] · Jessica Rolla[10] · Alice Francescato[7] · Ruggero Bollino[8] · Concetto Cartelli[8] · Andrea Lanaia[8] · Francesca Anzolin[11] · Paolo Del Rio[1] · Diletta Fabbi[12] · Gabriele Luciano Petracca[1] · Francesco Tartamella[1] · Giorgio Dalmonte[1]

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Abstract

Introduction The favorable effects of bariatric surgery (BS) on overall pulmonary function and obesity-related comorbidities could influence SARS-CoV-2 clinical expression. This has been investigated comparing COVID-19 incidence and clinical course between a cohort of patients submitted to BS and a cohort of candidates for BS during the spring outbreak in Italy.

Materials and Methods From April to August 2020, 594 patients from 6 major bariatric centers in Emilia-Romagna were administered an 87-item telephonic questionnaire. Demographics, COVID-19 incidence, suggestive symptoms, and clinical outcome parameters of operated patients and candidates to BS were compared. The incidence of symptomatic COVID-19 was assessed including the clinical definition of probable case, according to World Health Organization criteria.

Results Three hundred fifty-three operated patients (Op) and 169 candidates for BS (C) were finally included in the statistical analysis. While COVID-19 incidence confirmed by laboratory tests was similar in the two groups (5.7% vs 5.9%), lower incidence of most of COVID-19-related symptoms, such as anosmia (*p: 0.046*), dysgeusia (*p: 0.049*), fever with rapid onset (*p: 0.046*) were recorded among Op patients, resulting in a lower rate of probable cases (14.4% vs 23.7%; *p: 0.009*). Hospitalization was more frequent in C patients (2.4% vs 0.3%, *p: 0.02)*. One death in each group was reported (0.3% vs 0.6%). Previous pneumonia and malignancies resulted to be associated with symptomatic COVID-19 at univariate and multivariate analysis.

Conclusion Patients submitted to BS seem to develop less severe SARS-CoV-2 infection than subjects suffering from obesity.

Keywords Obesity · COVID-19 · SARS-CoV-2 · Bariatric surgery

✉ Federico Marchesi
federico.marchesi@unipr.it

1 Unit of General Surgery, Parma University Hospital, Parma, Italy

2 Università degli Studi di Parma, Via Gramsci, 14-43126 Parma, Italy

3 Dipartimento di Sanità Pubblica/Public Health, AUSL-IRCCS Tecnologie Avanzate e Modelli Assistenziali in Oncologia di Reggio Emilia, Reggio Emilia, Italy

4 Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna, Italy

5 Centre for the Study and Research of Treatment for Morbid Obesity, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

6 Department of Surgery, Ospedale "Guglielmo da Saliceto", Piacenza, Italy

7 Division of General, Emergency Surgery and New Technologies, OCSAE (Ospedale Civile Sant'Agostino Estense), Baggiovara, Modena, Italy

8 General and Emergency Surgery Unit, Arcispedale Santa Maria Nuova di Reggio Emilia, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy

9 Programma Dipartimentale Chirurgia Malassorbitiva AUSL di Bologna, Bologna, Italy

10 Department of Medicine, Ospedale "Guglielmo da Saliceto", Piacenza, Italy

11 Medical Department, Clinical Nutrition Unit, Maggiore-Bentivoglio Hospital, Ausl Bologna, Bologna, Italy

12 Department of Medicine and Surgery, University of Parma, Parma, Italy

Introduction

The role of bariatric surgery (BS) in weight reduction is undisputed [1]. Surgery in patients suffering from severe obesity leads to successful long-term weight loss and improvement of the main obesity-related comorbidities, such as diabetes, hypertension, obstructive sleep apnea, and hyperlipidemia [2–4]. Furthermore, surgically induced weight loss markedly improves the overall pulmonary function in patients with obesity [5], leading to significant reduction in both respiratory impairment and systemic inflammation related to obesity [6].

In the light of the above, a protective role of BS versus respiratory infective disease is conceivable. Indeed, during the 2009 influenza pandemic, obesity was recognized as an independent risk factor for severe H1N1 pulmonary infection [7] as well as for the development of influenza-related systemic complications [8].

In December 2019, a new coronavirus causing a severe acute respiratory syndrome emerged in Wuhan, China [9]. The novel coronavirus 2 (SARS-CoV-2) and subsequent SARS-CoV-2-induced coronavirus disease 2019 (COVID-19) spread very rapidly worldwide and were classified as a pandemic by the World Health Organization (WHO) on March 11, 2020.

Between late February and April, Italy faced a massive outbreak of COVID-19, with more than 200,000 confirmed infected patients by the end of April. Furthermore, northern Italy had one of the highest clinical burdens in the world, with data showing a tremendously high case fatality rate (CFR), up to 15–18% in high incidence areas [10]. The clinical manifestations of COVID-19 run from asymptomatic disease to severe acute respiratory infection requiring hospitalization, with oxygen support or intensive care and invasive ventilation [11]. Old age and the presence of comorbidities have been reported as risk factors for more severe disease and death [12]. The pathways that underlie inter-individual variability and that can thus be predictors of worse clinical presentation are not yet fully clear.

It is plausible that severe obesity, per se and due to its associated comorbidities, may impact on the clinical course of infected patients.

The aim of this study was to assess whether BS may influence the clinical course of COVID-19 by investigating possible discrepancies in clinical presentation and outcomes between patients undergone BS and a cohort of patients with obesity candidates for BS, particularly in the exceptional scenario of the epidemic that overburdened Northern Italy National Healthcare System.

Methods

Study Design and Setting

This is a multicentric retrospective observational cross sectional study, involving 6 major centers of bariatric surgery in Emilia Romagna, Northern Italy. Clinical data regarding patients that had already undergone a bariatric procedure were compared with those of patients waiting for BS in the above-mentioned hospitals. Inclusion criteria were age above 18 years and ability to give a valid informed consent. We excluded from the analysis (a) subjects who resided outside the Emilia Romagna, Lombardy, Veneto, Liguria and Marche regions from February 24 and August 31, 2020; (b) subjects that underwent a bariatric procedure other than adjustable gastric band (AGB), sleeve gastrectomy (SG), Roux-en-Y Gastric By-pass (RYGB), and One Anastomosis Gastric By-pass (OAGB); and (c) subjects that had undergone the intervention less than 12 months before the interview. The subjects were enrolled from June to August 2020.

All the subjects had been interviewed by phone by medical members of the bariatric teams. If a patient was unable to answer the survey (e.g., death), information was gathered from relatives. Data regarding hospital diagnosis, admission, and outcomes were confirmed consulting hospital registries.

Ethics and Consent Form

Ethical approvals of the study protocol were obtained by each center from the relevant Ethics Committee and informed consent obtained from all subjects. All data were handled and stored in accordance with the European Union General Data Protection Regulation (EU GDPR) 2016/679 [13].

Data Collection and Variables

All patients defined as eligible to undergo bariatric surgery met the 2020 EAES Clinical Practice Guidelines on bariatric surgery [14]. The bariatric procedures considered (AGB, SG, RYGB, and OAGB) account for 96.8% of all bariatric procedures performed worldwide, being also representative of the Italian recent trend in BS [15]. Patients submitted to procedures for which the study center had no certified expertise (at least 10 procedures) were not included. Among operated patients, only subjects that had undergone the procedure more than 12 months before the interview were considered for the analysis. This is normally the minimum time to weight loss stabilization and remission of comorbidities [16, 17].

Each patient was administered a questionnaire consisting of 87 questions, mostly closed-ended, divided into 11 sections including geographic data, demographic data, bariatric surgery history, comorbidities, vaccination history, clinical evaluation, diagnostic assessment, and outcome parameters.

Demographic variables included anthropometric characteristics. COPD, obstructive sleep apnea syndrome (OSAS), hypertension, diabetes, the use of insulin, hypertriglyceridemia, hypercholesterolemia, smoking habit, concomitant pneumonia, autoimmune diseases, immunodeficiencies, and malignancies were considered as comorbidities able to influence the clinical course.

Chronic use of ACE inhibitors, hydroxychloroquine, or steroids was also recorded for its supposed relation with COVID-19 [18–20]. Vaccination history (seasonal influenza, pneumococcus, BCG) was collected as well, because of the supposed role of vaccinations in mitigating the infection severity [21–24].

In the clinical evaluation section, the following symptoms reported from February 24 were considered: fever (> 37.5 °C), fever at rapid onset, shivering, cough, productive cough, anosmia, ageusia, asthenia, myalgia, headache, sore throat, running nose, nausea or vomit, diarrhea, and conjunctivitis.

In the diagnostic section, we recorded nasopharyngeal swabs, serologic tests, chest x-rays, or chest CT scans. Any hospital admission, length of hospital stay, need of oxygen supplemental therapy, non-invasive ventilation (NIV), ICU admission, and death were considered as indicators of the severity of COVID-19.

In agreement with the latest definitions given by the WHO, patients with a laboratory confirmation (nasopharyngeal swab or serologic test) for SARS-Cov 2 were considered as confirmed COVID-19 cases (CC). During the epidemic peak, the shortage of diagnostic tools led to a high rate of undiagnosed patients [25]; therefore, we mainly focused on the group of probable COVID-19 cases (PC), including, in addition to CC patients, subjects meeting the WHO clinical criteria for "probable cases." Specifically, we included patients residing in regions considered as very high risk of transmission who had experienced since February 24, 2020, an episode of anosmia/dysgeusia or had a chest imaging suggestive of COVID-19 or the association of rapid onset fever (self-measured temperature ≥ 37.5 °C) and cough or the association of any three or more of the following signs and symptoms: fever, cough, general weakness, headache, myalgia, sore throat, nose discharge/swelling, nausea/vomiting, or diarrhea [26].

For the above reasons, patients residing in medium or low incidence regions were excluded.

Factors influencing the incidence of symptomatic forms (PC) and outcome parameters (hospitalization) were investigated through univariate and multivariate analysis.

Statistical Analysis

Continuous variables were described as mean ± standard deviation. Categorical variables were considered in a numerical manner and as holding percentages. At the beginning, continuous variables were analyzed with D'Agostino-Pearson test, in order to verify distribution, assuming normal distribution as the one identified by a corresponding p value > 0.100.

Continuous variables were compared with Student's t test in the case of normal distribution, or with Mann-Whitney, if normal distribution was rejected. The distribution of dichotomous variables related to the outcomes "probable case" vs "non-probable case"; "COVID-19 positive" vs "COVID-19 negative"; "hospitalization" vs "non-hospitalization" was initially assessed by means of chi-squared test, estimating the corresponding p value. All variables associated with a p value < 0.2 were included in a model of multivariate analysis through binary logistic regression, estimating corresponding odds ratio (OR) values with their 95% confidence interval (CI95%).

Assuming a point prevalence of 2.8% for SARS-CoV-2 IgG positivity [27], a probability of falsely rejecting a true null hypothesis (α) = 0.05, with $Z\alpha = 1.96$ a minimum sample size of 42 participants from every center, (i.e., minimum sample size of 210 participants) was calculated.

Results

Out of the 594 patients interviewed, 25 were excluded due to epidemiological criteria and 47 were excluded because they met other exclusion criteria.

353 patients operated (Op) and 169 candidates for BS (C) were finally included in the statistical analysis. Sleeve gastrectomy (SG) was the most common procedure performed (65.2%), followed by Roux- en-Y gastric bypass (RYGB) (31.6%), adjustable gastric banding (AGB) (2.3%) and One Anastomosis gastric bypass (OAGB) (1.1%), reflecting the Italian proportion according to SICOB (Italian society of obesity surgery) registry [28]. Op and C groups were similar for mean age and sex proportion (Table 1).

As predictable effect for BS, Op patients presented a significant lower BMI (30.7 vs 43.5, p<0.001) and lower incidence of main comorbidities, such as obstructive sleep apnea syndrome, hypertension, diabetes, hypertriglyceridemia and hypercholesterolemia (Table 2). No significant difference was found in smoking habits, previous pulmonary, autoimmune or neoplastic disease or immunodeficiency.

Vaccination history and chronic use of hydroxychloroquine or steroids was similar in the two groups too (Table 2).

The use of ACE inhibitors was lower in Op group, probably owing to hypertension improvement.

Among Op patients, we recorded a lower incidence of most COVID-19-related symptoms (Table 3), such as anosmia (*p:0.046*), ageusia/dysgeusia (*p: 0.049*), fever with rapid onset (*p: 0.046*), asthenia (*p: 0.034*), and particularly cough (*p: 0.001*) and productive cough (*p: 0.009*).

Probably as result of the above, a higher percentage of C patients was submitted to nasal swab (24.3 vs 11.6, *p: 0.001*) (Table 3).

The rate of probable cases was respectively 14.4% in Op patients and 23.7% in the C group, with a statistically significant difference (*p: 0.009*). We recorded a significantly

Table 1 Demographics

	Total N=522		Op N = 353		C N = 169		P value
Age (years; average ± SD)	47.8 ± 11.0		48.3 ± 11.2		46.5 ± 10.5		0.074
Age stratification (N; %)							0.226
< 30 years	37	7.1	23	6.5	14	8.3	
30–39 years	83	15.9	56	15.9	27	16.0	
40–49 years	149	28.5	97	27.5	52	30.8	
50–59 years	188	36.0	124	35.1	64	37.9	
60–69 years	59	11.3	48	13.6	11	6.5	
≥ 70 years	6	1.1	5	1.4	1	0.6	
Sex (male) (N; %)	117	22.4	71	20.1	46	27.2	0.069
Weight (kg; mean ± SD)	95.1 ± 26.7		83.4 ± 18.2		119.6 ± 25.0		< 0.001
Height (cm; mean ± SD)	164.9 ± 9.1		164.5 ± 8.9		165.5 ± 9.3		0.241
BMI (kg/m^2; mean ± SD)	34.9 ± 8.8		30.7 ± 5.7		43.5 ± 7.8		< 0.001
Type of surgery (N; %)							
AGB	8	1.5	8	2.3	–	–	
RYGB	111	21.3	111	31.6	–	–	
SG	230	44.1	230	65.2	–	–	
OAGB	4	0.8	4	1.1	–	–	
Waiting list	169	32.4	–		169	100	

Op Operated patients; *C* Candidates for surgery; *BMI* Body Mass Index; *AGB* Adjustable Gastric Banding; *RYGB* Roux-en-Y Gastric Bypass**;** *SG* Sleeve Gastrectomy; *OAGB* One Anastomosis Gastric Bypass

different distribution of PC among the provinces of Emilia Romagna region, with a decreasing rate going from northwest to southeast (41.6% in Piacenza, 4.6% in Bologna).

Considering only CC, incidence was respectively 5.7% in Op patients and 5.9% in the C group (*p:0.908*) (Table 3).

Hospitalization was more frequent in C patients (2.4% vs 0.3%, *p: 0.02)* as well as O2 therapy (2.4% vs 0.3%, *p:0.02*). No patient was admitted to the ICU. We had 1 death in Op patients (0.3%) and 1 in the C group (0.6%) (Table 3).

Univariate analysis indicated OSAS, hypertension, diabetes, pneumonia, autoimmune diseases, previous non-bariatric surgery, malignancy, the use of ACE-inhibitors as related to COVID-19 probable infection (Table 4). Surprisingly, 2019–2020 seasonal flu vaccination was associated with probable SARS-CoV-2 infection (i.e. 31.9% in probably infected patients vs 20.9% in probably not infected patients; p: 0.03). Considering only CC, solely autoimmune diseases showed a significant correlation (*p: 0.007*) (Table 5), confirmed also by the multivariate analysis.

Interestingly, the type of bariatric procedure seems also to correlate with COVID-19 probable infection, with a relatively higher frequency of RYGB among PC (Table 4).

Diabetes, hypertension, and the use of ACE-inhibitors resulted as predictive of hospital admission (Table 6).

At multivariate analysis, only previous pneumonia and malignancies confirmed to be associated with PC (OR: *3.536, 95%CI: 1.961; 7.040*, and *OR: 2.786, 95%CI: 1.255; 7.022, respectively)* (Table 7), while hypertension, diabetes, and the use of ACE inhibitors did not confirm to be associated with hospital admission (Table 7).

Discussion

The outbreak of the SARS-Cov-2 pandemic laid bare structural deficiency in healthcare systems along with individual frailties all over the world. Besides old age, the death toll of this "tsunami" has shown to be proportional to pulmonary and metabolic comorbidities and to the availability of dedicated healthcare facilities, especially at the peak of the epidemic curve [29]. From this point of view, patients suffering from obesity certainly represent a paradigmatic target.

From February 24, 2020 Italy experienced a rapid spread of COVID-19 becoming, on March 9, 2020, the country with the second highest total number of COVID-19 cases [30]. According to the Italian National Institute of Health (ISS), by May 4 in Italy, there were 209,254 cases of COVID-19 and 26,892 associated deaths (https://www.epicentro.iss.it/en/coronavirus/bollettino/Infografica_4maggio ENG.pdf). Geographical spread was heterogeneous: at its highest in the Northern regions and at its lowest in the Southern regions and in the main Islands [31, 32]. As a consequence, 91% of the excess mortality recorded in March 2020 was concentrated in the Northern Italy regions and in the Marche central Italy region. Due to this peculiar epidemic distribution, the Italian

Table 2 Comorbidities, therapy, and vaccinations

	Total *N* = 522		Op *N* = 353		C *N* = 169		*P* value
	N	%	N	%	N	%	
Comorbidities							
COPD	35	6.7	21	5.9	14	8.3	0.318
OSAS	105	20.1	57	16.1	48	28.4	0.001
B-PAP/C-PAP	35	6.7	23	6.5	12	7.1	0.803
Hypertension	166	31.8	97	27.5	69	40.8	0.002
Diabetes/oral hypoglycemic	62	11.9	34	9.6	28	16.6	0.022
Diabetes/insulin	11	2.1	1	0.3	10	5.9	<0.001
Hypertriglyceridemia	64	12.3	32	9.1	32	18.9	0.001
Hypercholesterolemia	127	24.3	71	20.1	56	33.1	0.001
Smoking	147	28.2	96	27.2	51	30.2	0.478
Surgery (non-bariatric)	376	72.0	243	68.8	133	78.7	0.019
Previous pneumonia	57	10.9	34	9.6	23	13.6	0.173
Autoimmune diseases	39	7.5	23	6.5	16	9.5	0.230
Malignancies	30	5.7	20	5.7	10	5.9	0.908
Immune deficiencies	15	2.9	9	2.5	6	3.6	0.522
Therapy							
ACE-inhibitors	75	14.4	44	12.5	31	18.3	0.073
Colchicine	2	0.4	1	0.3	1	0.6	0.594
Hydroxychloroquine	2	0.4	1	0.3	1	0.6	0.594
Steroids	19	3.6	14	4.0	5	3.0	0.565
Vaccine							
Seasonal Flu, 2019–2020	119	22.8	77	21.8	42	24.9	0.439
Seasonal Flu, any	170	32.6	116	32.9	54	32.0	0.836
BCG	78	14.9	57	16.1	21	12.4	0.264
Pneumonia, any	44	8.4	28	7.9	16	9.5	0.555

Op Operated patients; *C* Candidates for surgery; *COPD* Chronic Obstructive Pulmonary Disease; *OSAS* Obstructive Sleep Apnea Syndrome; *BCG* Bacillus Calmette–Guérin

Government deployed several preventive measures to curb the spread of the syndrome, banning travels between regions from the beginning of the pandemic, and finally with a lockdown of the entire territory on March 11, 2020. The specific demographic structure (old age and comorbidities) has been put forward, among other factors, to justify the stunning Italian CFR compared, for example, with the Chinese trend. Nevertheless, during the epidemic peak, due to the shortage of diagnostic tools, SARS-CoV-2 infection prevalence was most likely underestimated, affecting the reliability of many parameters, such as CFR. Indeed, only severely symptomatic patients were tested during the peak and the real proportion of mild symptomatic or asymptomatic population was not deeply investigated. In fact, only one study conducted in a small area of the north east [33] screened the entire population, revealing a rate of 41.1% of asymptomatic confirmed SARS-CoV-2 infections at the beginning of the outbreak.

Any attempt to assess a reliable incidence rate during the outbreak peak was therefore inconclusive. For these reasons, the "clinical" prevalence of COVID-19 (i.e., clinical manifestations, hospitalization, deaths) rather than its tested prevalence has been taken into account in this study.

According to the Italian Obesity Barometer Report 2019 [34], over 1 out of 3 Italians is overweight, and, more notably, 1 out of 10 suffers from obesity. It goes without saying that obesity, per se and due to its comorbidities, has been considered as a risk factor for increased susceptibility to infections and sepsis-related mortality [35]. In this regard, a predisposing role of obesity towards severe clinical course of COVID-19 could be reasonably assumed.

In our series, we recorded a significantly lower incidence of COVID-19 symptoms among patients who had previously undergone a bariatric procedure for severe obesity. Some of the collected symptoms are typical of pathogenetic human coronaviruses, with fever and cough reported most commonly [36], while others (anosmia and dysgeusia) have been recently reported as pathognomonic of SARS-CoV-2 infection [37]. With the definition of the PC category we aimed at improving

Table 3 Covid-19 related symptoms, tests, and outcomes

	Total *N* = 522		**Op** *N* = 353		**C** *N* = 169		***P* value**
	N	%	N	%	N	%	
Symptoms							
Any	161	30.8	93	26.3	68	40.2	0.001
Fever (> 37.5 °C)	65	12.5	38	10.7	27	16.0	0.092
Fever rapid onset	41	7.9	22	6.2	19	11.2	0.046
Shivering	44	8.4	24	6.8	20	11.8	0.053
Cough	39	7.5	17	4.8	22	13.0	0.001
Productive cough	16	3.1	6	1.7	10	5.9	0.009
Anosmia	21	4.0	10	2.8	11	6.5	0.046
Ageusia/dysgeusia	26	5.0	13	3.7	13	7.7	0.049
Asthenia	53	10.2	29	8.2	24	14.2	0.034
Myalgia	60	11.5	37	10.5	23	13.6	0.294
Headache	65	12.5	38	10.8	27	16.0	0.092
Sore throat	47	9.0	28	7.9	19	11.2	0.216
Running nose	55	10.5	31	8.8	24	14.2	0.059
Nausea/Vomiting	26	5.0	14	4.0	12	7.1	0.123
Diarrhea	34	6.5	23	6.5	11	6.5	0.998
Conjunctivitis	16	3.1	10	2.8	6	3.6	0.656
Length of fever (days; average ± SD)	6.8 ± 8.8		6.6 ± 8.4		7.2 ± 9.7		0.800
Length of symptoms (days; average ± SD)	8.8 ± 11.7		7.9 ± 8.7		9.8 ± 14.7		0.399
Diagnosis							
Nasal swab	82	15.7	41	11.6	41	24.3	< 0.001
Of them, positive	13	15.9	6	14.6	7	17.1	0.762
Serological tests	55	10.5	36	10.2	19	11.2	0.716
Of them, positive	25	45.5	18	50.0	7	36.8	0.351
Chest X-rays	17	3.3	8	2.3	9	5.3	0.065
Of them, positive	5	29.4	2	25.0	3	33.3	0.707
Chest CT Scan	8	1.5	6	1.7	2	1.2	0.653
Of them, positive	2	25.0	1	16.7	1	50.0	0.346
Confirmed cases	30	5.7	20	5.7	10	5.9	0.908
Probable cases	91	17.4	51	14.4	40	23.7	0.009
Outcomes							
Hospital admission	5	1	1	0.3	4	2.4	0.022
O_2 therapy	5	1	1	0.3	4	2.4	0.022
NIV	1	0.2	0	–	1	0.6	0.148
ICU	0	–	0	–	0	–	–
Death	2	0.4	1	0.3	1	0.6	0.581
Hospital stay (days; average ± SD)	15.2 ± 21.5		4.0		17.4 ± 23.3		0.672

Op Operated patients; *C* Candidates for surgery; *CT* Computed Tomography; *ICU* Intensive Care Unit; *NIV* Non-Invasive Ventilation

symptoms specificity and assessing a more reliable parameter of symptomatic COVID-19 incidence. Based on PC rates, we can state that Op patients are less predisposed to symptomatic COVID-19 (14.4% vs 23.7% p:0.009); on the other hand, we can suppose that SARS-CoV-2 real incidence in the population of the study was probably higher than the one estimated based on the regional data during the outbreak [27, 33, 38].

It is not reasonable to ascribe this trend to a different rate of infection among Op, C patients and normal population, there being no evident social or behavioral difference able to modify the exposure to the virus. Conversely, as for other infections, it is more likely that obesity could mainly promote the clinical expression of the virus. In fact, the literature gives clear evidence that one of the typical features of severe obesity

Table 4 Univariate analysis: characteristics by status (COVID-19 probable vs. not probable)

	Total *N*=522		**Probable** *N* = 91		**Not probable** *N* = 431		***P* value**
	N	%	N	%	N	%	
≥ 60 years	253	48.5	51	56.0	202	46.9	0.111
Sex (male)	117	22.4	21	23.1	96	22.3	0.867
BMI ≥ 30 kg/m^2	341	65.3	63	69.2	278	64.5	0.389
BMI ≥ 35 kg/m^2	234	44.8	48	52.7	186	42.2	0.095
Type of surgery							0.012
AGB	8	1.5	1	1.1	7	1.6	
RYGB	111	21.3	24	26.4	87	20.2	
SG	230	44.1	26	28.6	204	47.3	
OAGB	4	0.8	0	–	4	0.9	
Waiting list	169	32.4	40	44	129	29.9	
Comorbidities							
COPD	35	6.7	8	8.8	27	6.3	0.381
OSAS	105	20.1	30	33.0	75	17.4	0.001
B-PAP/C-PAP	35	6.7	9	9.9	26	6.0	0.269
Hypertension	166	31.8	45	49.5	121	28.1	<0.001
Diabetes (any)	65	12.5	18	19.8	47	10.9	0.020
Diabetes/Oral hypoglycemic	62	11.9	17	18.7	45	10.4	0.027
Diabetes/ Insulin	11	2.1	2	2.2	9	2.1	0.947
Hypertriglyceridemia	64	12.3	16	17.6	48	11.1	0.088
Hypercholesterolemia	127	24.3	29	31.9	98	22.7	0.065
Smoking	147	28.2	30	33.0	117	27.1	0.262
Surgery (non-bariatric)	376	72	74	81.3	302	70.1	0.030
Previous pneumonia	57	10.9	22	24.2	35	8.1	<0.001
Autoimmune diseases	39	7.5	12	13.2	27	6.3	0.022
Malignancies	30	5.7	11	12.1	19	4.4	0.004
Immune deficiencies	15	2.9	3	3.3	12	2.8	0.790
Therapy							
ACE-inhibitors	75	14.4	25	27.5	50	11.6	<0.001
Colchicine	2	0.4	0	–	2	0.5	0.515
Hydroxychloroquine	2	0.4	0	–	2	0.5	0.515
Steroids	19	3.6	4	4.4	15	3.5	0.672
Vaccine							
Seasonal Flu, 2019–2020	119	22.8	29	31.9	90	20.9	0.023
Seasonal Flu, any	170	32.6	36	39.6	134	31.1	0.117
BCG	78	14.9	17	18.7	61	14.2	0.271
Pneumonia, any	44	8.4	10	11.0	34	7.9	0.333

BMI Body Mass Index; *AGB* Adjustable Gastric Banding; *RYGB* Roux-en-Y Gastric Bypass; *SG* Sleeve Gastrectomy; *OAGB* One Anastomosis

Gastric Bypass; *COPD* Chronic Obstructive Pulmonary Disease; *OSAS* Obstructive Sleep Apnea Syndrome; *BCG* Bacillus Calmette–Guérin

is persistent hyperleptinemia produced by a state of leptin resistance. Leptin has been recognized as a key link between nutritional status and immune response, and it is an important mediator of pulmonary immunity [39, 40]. Furthermore, adipose tissue inflammation is a hallmark of obesity: macrophage accumulation in adipose tissue provides a mechanism for adipocyte production of the proinflammatory cytokines, thus leading to chronic low-grade inflammation, which may impair immune response and have detrimental effects on the lung parenchyma and bronchi [41]. Substantiating this, the Centers for Disease Control and Prevention considers patients with BMI ≥ 40 kg/m2 at risk for flu complications [42–44].

Table 5 Univariate analysis: characteristics by status (Covid-19 positive vs. negative)

	Total *N* = 522	Positive *N* = 30			Negative *N* = 492		P value
	N	%	N	%	N	%	
≥ 60 years	253	48.5	17	56.7	236	48.0	0.355
Sex (male)	117	22.4	6	20.0	111	22.6	0.744
BMI ≥ 30 kg/m2	341	65.3	16	53.3	325	66.1	0.155
BMI ≥ 35 kg/m2	234	44.8	10	33.3	224	45.5	0.192
Comorbidities							
COPD	35	6.7	2	6.7	33	6.7	0.993
OSAS	105	20.1	3	10.0	102	20.7	0.155
B-PAP/C-PAP	35	6.7	1	3.3	34	6.9	0.447
Hypertension	166	31.8	11	36.7	155	31.5	0.556
Diabetes (any)	65	12.5	5	16.7	60	12.2	0.471
Diabetes/Oral hypoglycemic	62	11.9	5	16.7	57	11.6	0.404
Diabetes/Insulin	11	2.1	0	–	11	2.2	0.408
Hypertriglyceridemia	64	12.3	6	20.0	58	11.8	0.183
Hypercholesterolemia	127	24.3	11	36.7	116	23.6	0.105
Smoking	147	28.2	8	26.7	139	28.3	0.851
Surgery (non-bariatric)	376	72.0	25	83.3	351	71.3	0.155
Previous pneumonia	57	10.9	6	20.0	51	10.4	0.100
Autoimmune diseases	39	7.5	6	20.0	33	6.7	0.007
Malignancies	30	5.7	1	3.3	29	5.9	0.558
Immune deficiencies	15	2.9	1	3.3	14	2.8	0.877
Therapy							
ACE-inhibitors	75	14.4	7	23.3	68	13.8	0.149
Hydroxychloroquine	2	0.4	0	–	2	0.5	0.726
Steroids	19	3.6	2	6.7	17	3.5	0.362
Vaccine							
Seasonal Flu, 2019–2020	119	22.8	6	20.0	113	23.0	0.707
Seasonal Flu, any	170	32.6	6	20.0	164	33.3	0.130
BCG	78	14.9	7	23.3	71	14.4	0.184
Pneumonia, any	44	8.4	3	10.0	41	8.3	0.750

BMI Body Mass Index; *COPD* Chronic Obstructive Pulmonary Disease; *OSAS* Obstructive Sleep Apnea Syndrome; *BCG* Bacillus Calmette–Guérin

Moving to the outcome parameters, we did report a statistically significant difference in the rates of hospitalization (0.3% vs 2.4%, *p*:0.02*)* as well as in the rate of O_2 therapy (*p*:0,02) among the Op and C groups. Severe obesity is in fact associated with impairment of total respiratory system compliance, leading to reduced functional residual capacity and decreased expiratory reserve volume [45, 46], which can be responsible for difficult ventilation and the need of oxygen support in these patients. In fact, it is undisputed that respiratory impairment was the main criteria for hospital and ICU admission (no cases in our series). The low number of deaths in our study does not allow any definitive conclusion to be drawn about the role of BS in reducing COVID-19 mortality: studies on larger population should assess whether, as expected, the outcome trend will be confirmed.

OSAS, hypertension, diabetes, previous pneumonia, autoimmune diseases, malignancies, and the use of ACE-inhibitors were found as predictive of SARS-CoV-2 probable infection at univariate analysis, whereas at multivariate analysis only previous pneumonia and malignancies were confirmed.

Our data are in line with the results of a recent meta-analysis on more than 75,000 patients, in which hypertension, cardiovascular disease, diabetes, and malignancies were the most prevalent pre-existing comorbidities in hospitalized patients for COVID-19 [29]. Moreover, a recent study [47] has

Table 6 Univariate analysis: characteristics by status (hospitalization vs. no hospitalization)

	Total *N*=522		Hospitalization *N*=5		No Hospitalization *N*=517		P value
	N	%	N	%	N	%	
≥ 60 years	253	48.5	3	60.0	250	48.4	0.604
Sex (male)	117	22.4	2	40.0	115	22.2	0.343
BMI ≥ 30 kg/m2	341	64.3	4	80.0	337	65.2	0.488
BMI ≥ 35 kg/m2	234	44.8	4	80.0	230	44.0	0.112
Comorbidities							
COPD	35	6.7	0	–	35	6.8	0.547
OSAS	105	20.1	1	20.0	104	20.1	0.995
B-PAP/C-PAP	35	6.7	0	–	35	6.8	0.547
Hypertension	166	31.8	4	80.0	162	31.3	0.020
Diabetes (any)	65	12.5	3	60.0	62	21.0	0.001
Diabetes/Oral hypoglycemic	62	11.9	3	60.0	59	11.4	0.001
Diabetes/Insulin	11	2.1	0	–	11	2.1	0.742
Hypertriglyceridemia	64	12.3	1	20.0	63	12.2	0.596
Hypercholesterolemia	127	24.3	1	20.0	126	24.4	0.821
Smoking	147	28.2	0	–	147	28.4	0.160
Surgery (non-bariatric)	376	72.0	4	80.0	372	73.0	0.690
Previous pneumonia	57	10.9	1	20.0	56	10.8	0.513
Autoimmune diseases	39	7.5	1	20.0	38	7.4	0.284
Malignancies	30	5.7	1	20.0	29	5.6	0.169
Immune deficiencies	15	2.9	0	–	15	2.0	0.699
Therapy							
ACE-inhibitors	75	14.4	3	60.0	72	13.9	0.003
Colchicine	2	0.4	0	–	2	0.5	0.889
Hydroxychloroquine	2	0.4	0	–	2	0.5	0.889
Steroids	19	3.6	0	–	19	3.7	0.662
Vaccine							
Seasonal Flu, 2019–2020	119	22.8	1	20.0	118	22.8	0.881
Seasonal Flu, any	170	32.6	1	20.0	169	32.7	0.547
BCG	78	14.9	1	20.0	77	14.9	0.750
Pneumonia, any	44	8.4	0	–	44	8.5	0.495

BMI Body Mass Index; *COPD* Chronic Obstructive Pulmonary Disease; *OSAS* Obstructive Sleep Apnea Syndrome; *BCG* Bacillus Calmette–Guérin

found an association of type 2 diabetes with COVID-19 likely event in a cohort of patients undergone BS at 12 months follow-up.

Reducing the analysis to confirmed positive cases only, autoimmune diseases alone showed a significant positive correlation, both in univariate and multivariate analysis. However to date, available records in the literature are still not conclusive on this aspect [48, 49].

Along with BMI, the use of ACE inhibitors and diabetes were found predictive of hospital admission for COVID-19. It is demonstrated that the SARS-CoV-2 moves across species through spike glycoprotein S1, which binds to angiotensin converting enzyme 2 (ACE2) receptor present on host cells. However, many studies have been conducted to analyze this association, but the results are still not consistent [18, 50–52]. Conversely, the role of diabetes in the impairment of immune response and in the influence on COVID-19 prognosis has been widely confirmed [53, 54]. However no one of the aforementioned factors was confirmed at the multivariate analysis in our study.

Age, whose role in worsening COVID-19 clinical course has been clearly demonstrated [42], did not show any significant correlation with the symptomatic course (probable infection) or hospitalization rate in our series, probably owing to the restricted age interval of BS patients (usually 18–65 yo, according to International Guidelines).

Table 7 Multivariate analysis: characteristics by status (COVID-19 "probable" vs. "not probable"; positive vs. negative; hospitalized vs. not hospitalized)

	Probable vs. Not Probable		Positive vs. Negative		Hospitalized vs. not Hospitalized	
	aOR	**95%CI**	**aOR**	**95%CI**	**aOR**	**95%CI**
OSAS	1.526	0.863; 2.698	–	–	–	–
Hypertension	1.849	0.993; 3.443	–	–	2.774	0.148; 52.096
ACE-inhibitors	1.751	0.869; 3.528	–	–	3.707	0.381; 36.089
Diabetes (any)	1.364	0.688; 2.704	–	–	6.511	0.861; 49.231
Surgery (non-bariatric)	1.422	0.767; 2.635	–	–	–	–
Pneumonia	3.715	1.961; 7.040	–	–	–	–
Autoimmune diseases	1.832	0.846; 3.967	3.404	1.293; 8.960	–	–
Malignancies	2.969	1.255; 7.022	–	–	–	–
Seasonal Influenza 2019–2020	1.385	0.787; 2.439	–	–	–	–

Osas Obstructive Sleep Apnea Syndrome. Multivariate analysis through binary logistic regression; the model included all factors that in respective univariate analysis were associated with "probable" status with $p < 0.05$

Finally, recent studies suggested a protective role against COVID-19 of anti-influenza and anti- pneumococcal vaccines, and a role of influenza vaccination in mitigating the severity of the infection [21–23]. Nevertheless, in our series, neither in univariate nor in multivariate analysis did we observe any correlation. Interestingly, we noted an important difference in PC among our centers, which was not clearly predictable when we designed the study.

Along with the retrospective observational design of the study and the limited age range of the sample, the inter-center variability of COVID incidence represents a bias of the study. In fact, the analysis of those data that were not equally distributed among the centers (type of BS procedure, proportion of Op and C recruited) could have been affected. In particular, resizing the analysis on a smaller and more homogenous population, the relatively higher frequency of RYGB among PC was not confirmed and some of the clinical differences between Op and C group lost significance. However, in this latter case, the trend remained and the loss of significance could be ascribed to a lower statistical power given the smaller population.

Conclusions

Despite the aforementioned limits of the study and the reduced diagnostic accuracy in an exceptional epidemic setting, patients submitted to BS seem to develop less severe SARS-CoV-2 infection than subjects with obesity. This is probably due to the improvement in obesity related comorbidities after BS, as well as to weight loss and its effects on respiratory mechanics. Further studies on larger populations could confirm the role of BS on some crucial COVID-19 outcome parameters, such as ICU admission and deaths, which were poorly represented in our series.

Authors' Contributions Mario Bondi, Luigi Conti, Barbara Marchionni, Clelia Miloro, Alessandro Rampulia, Marta Ribolla, Patrizia Federica Toschi, and Giovanna Rosati contributed equally to this work.

Compliance with Ethical Standards

Conflict of Interest Federico Marchesi, Marina Valente, Matteo Riccò, Matteo Rottoli, Edoardo Baldini, Fouzia Mecheri, Stefano Bonilauri, Sergio Boschi, Paolo Bernante, Andrea Sciannamea, Jessica Rolla, Alice Francescato, Ruggero Bollino, Concetto Cartelli, Andrea Lanaia, Francesca Anzolin, Paolo Del Rio, Diletta Fabbi, Gabriele Luciano Petracca, Francesco Tartamella, and Giorgio Dalmonte have no conflicts of interest or financial ties to disclose.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. J Am Med Assoc. 2004;292:1724–37.
2. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307:56–65.
3. Sjöström L. Review of the key results from the Swedish obese subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273:219–34.
4. Sarkhosh K, Switzer NJ, El-Hadi M, et al. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. Obes Surg. 2013;23:414–23.
5. Alsumali A, Al-Hawag A, Bairdain S, et al. The impact of bariatric surgery on pulmonary function: a meta-analysis. Surg Obes Relat Dis. 2018;14:225–36.

6. Askarpour M, Khani D, Sheikhi A, et al. Effect of bariatric surgery on serum inflammatory factors of obese patients: a systematic review and meta-analysis. Obes Surg. 2019;29:2631–47.
7. van Kerkhove MD, Vandemaele KAH, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza a (H1N1) infection: a global pooled analysis. PLoS Med. 2011;
8. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza a(H1N1) infection in California. JAMA. 2009;302:1896–902.
9. CDC TNCPERETC. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronaviurs diseases. Vital Surveillances. 2020
10. Giangreco G. Case fatality rate analysis of Italian COVID-19 outbreak. J Med Virol. 2020;92:919–23.
11. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020
12. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;
13. European Union. Regulation 2016/679 of the European parliament and the Council of the European Union. Off J Eur Communities. 2016;
14. Di Lorenzo N, Antoniou SA, Batterham RL, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. Surg Endosc. 2020;
15. Welbourn R, Pournaras DJ, Dixon J, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Second IFSO Global Registry Report 2013–2015. Obes Surg. 2018;28:313–22.
16. Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the longitudinal assessment of bariatric surgery (LABS) study. JAMA Surg. 2018;153:427.
17. Maciejewski ML, Arterburn DE, Van Scoyoc L, et al. Bariatric surgery and long-term durability of weight loss. JAMA Surg. 2016;151:1046–55.
18. Patoulias D, Katsimardou A, Stavropoulos K, et al. Renin-angiotensin system inhibitors and COVID-19: a systematic review and meta-analysis. Evidence for Significant Geographical Disparities. Curr Hypertens Rep. 2020;22:90.
19. Li X, Wang Y, Agostinis P, et al. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis. 2020;
20. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med. 2020
21. Noale M, Trevisan C, Maggi S, et al. The association between influenza and pneumococcal vaccinations and sars-cov-2 infection: data from the epicovid19 web-based survey. Vaccines. 2020;8
22. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer AP, Daubenberger C, et al. Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil. medRxiv [Internet]. 2020;2020.06.29.20142505. Available from: http://medrxiv.org/content/early/2020/07/01/2020.06.29.20142505.abstract
23. Zanettini C, Omar M, Dinalankara W, Imada EL, Colantuoni E, Parmigiani G, et al. Influenza Vaccination and COVID19 Mortality in the USA. medRxiv Prepr Serv Heal Sci. 2020
24. Riccò M, Gualerzi G, Ranzieri S, et al. Stop playing with data: there is no sound evidence that bacille calmette-guérin may avoid SARS-CoV-2 infection for now. Acta Biomed. 2020;
25. Odone A, Delmonte D, Scognamiglio T, et al. COVID-19 deaths in Lombardy, Italy: data in context. Lancet Public Health. 2020;5:e310.
26. World Health Organization. Public Health Surveillance for COVID-19: Interim guidance. World Heal Organ. 2020.
27. Indagine sieroprevalenza virus Sars-Cov-2-primi-risultati [Internet]. Available from: https://statistica.regione.emilia-romagna.it/notizie/2020/indagine-sieroprevalenza-virus-sars-cov-2-primi-risultati
28. Registro Nazionale SICOb [Internet]. Available from: https://www.sicob.org/registro_obesi/
29. Emami A, Javanmardi F, Pirbonyeh N, et al. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med. 2020;
30. World Health Organization. Coronavirus disease (COVID-19) Situation Report – 162. A A Pract. 2020.
31. Rivieccio BA, Luconi E, Boracchi P, et al. Heterogeneity of covid-19 outbreak in Italy. Acta Biomed. 2020;
32. Prezioso C, Marcocci ME, Palamara AT, et al. The “Three Italy” of the COVID-19 epidemic and the possible involvement of SARS-CoV-2 in triggering complications other than pneumonia. J Neurovirol. 2020;26:311–23.
33. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo. Nature. 2020;584:425–9.
34. 1st Italian Obesity Barometer Report. 2019.
35. Frydrych LM, Bian G, O’Lone DE, et al. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. J Leukoc Biol. 2018;104:525–34.
36. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
37. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020;71:889–90.
38. Regione Emilia-Romagna_Report_Coronavirus_13/10/2020.
39. Ubags NDJ, Stapleton RD, Vernooy JHJ, et al. Hyperleptinemia is associated with impaired pulmonary host defense. JCI Insight. 2016;1
40. Jain M, Budinger GRS, Lo A, et al. Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferator-activated receptor-γ. Am J Respir Crit Care Med. 2011;183:1490–8.
41. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796–808.
42. Neidich SD, Green WD, Rebeles J, et al. Increased risk of influenza among vaccinated adults who are obese. Int J Obes. 2017;41:1324–30.
43. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012;36:1072–7.
44. Centers for Disease Control and Prevention. People who are at higher risk for severe illness | CDC. Centers Dis Control Prev. 2020
45. Watson RA, Pride NB, Thomas EL, et al. Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes. J Appl Physiol. 2010;108:1605–12.
46. Jones RL, Nzekwu MMU. The effects of body mass index on lung volumes. Chest. 2006;130:827–33.
47. Bel Lassen P, Poitou C, Genser L, et al. COVID-19 and its severity in bariatric surgery operated patients. Obesity. 2020;
48. Gianfrancesco M, Hyrich KL, Hyrich KL, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79:859–66.
49. Ansarin K, Taghizadieh A, Safiri S, et al. COVID-19 outcomes in patients with systemic autoimmune diseases treated with immunomodulatory drugs. Ann Rheum Dis. 2020:annrheumdis-2020-218737.

50. Mancia G, Rea F, Ludergnani M, et al. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. N Engl J Med. 2020;382:2431–40.
51. Palazzuoli A, Mancone M, De Ferrari GM, et al. Antecedent Administration of Angiotensin Converting Enzyme Inhibitors or angiotensin II receptor antagonists and survival after hospitalization for SARS-CoV-2 (COVID-19). J Am Heart Assoc. 2020;9:e017364.
52. Flacco ME, Acuti Martellucci C, Bravi F, Parruti G, Cappadona R, Mascitelli A, et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart [Internet]. 2020;106:1519 LP – 1524. Available from: http://heart.bmj.com/content/106/19/1519.abstract
53. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36
54. Burgos-Morón, Abad-Jiménez, Marañón, et al. Relationship Between Oxidative Stress, ER Stress, and Inflammation in Type 2 Diabetes: The Battle Continues. J Clin Med. 2019;8