



**HAL**  
open science

## Visceral fat is associated to the severity of COVID-19

Guillaume Favre, Kevin Legueult, Christian Pradier, Charles Raffaelli, Carole Ichai, Antonio Iannelli, Alban Redheuil, Olivier Lucidarme, Vincent Esnault

► **To cite this version:**

Guillaume Favre, Kevin Legueult, Christian Pradier, Charles Raffaelli, Carole Ichai, et al.. Visceral fat is associated to the severity of COVID-19. *Metabolism*, 2021, 115, pp.154440 -. 10.1016/j.metabol.2020.154440 . hal-03493584

**HAL Id: hal-03493584**

**<https://hal.science/hal-03493584v1>**

Submitted on 15 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**Title** : visceral fat is associated to the severity of COVID-19

**Short title** : visceral fat and COVID-19

**Authors**: Guillaume Favre, MD, PhD <sup>1</sup> \*; Kevin Legueult, MD <sup>2</sup> ; Christian Pradier, MD, PhD <sup>2</sup> ; Charles Raffaelli, MD <sup>3</sup> ; Carole Ichai, MD, PhD <sup>4</sup> ; Antonio Iannelli, MD, PhD <sup>5</sup> ; Alban Redheuil, MD, PhD <sup>6</sup> ; Olivier Lucidarme, MD, PhD <sup>7</sup> ; Vincent Esnault, MD, PhD <sup>1</sup>

<sup>1</sup> University of Côte d'Azur, CNRS-UMR 7073 (LP2M), Department of Nephrology-Dialysis-Transplantation, Pasteur University Hospital, F-06002 CD1, Nice, France

<sup>2</sup> University of Côte d'Azur, Department of public health, Archet University Hospital, F-06202, Nice, France

<sup>3</sup> Radiology Department, Pasteur University Hospital, F-06002, Nice, France

<sup>4</sup> University of Côte d'Azur, Intensive Care Unit, Pasteur University Hospital, Nice, F-06002, France

<sup>5</sup> University of Côte d'Azur, INSERM-U1065, Digestive Surgery and Liver Transplantation Unit, Archet University Hospital, F-06202, Nice, France

<sup>6</sup> Sorbonne University, Pitié-Salpêtrière Hospital (AP-HP), ICT Cardiothoracic Imaging Unit & Radiology Department, LIB Biomedical imaging laboratory INSERM, CNRS, ICAN Institute of Cardiometabolism and Nutrition, Paris, France

<sup>7</sup> Sorbonne University, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, APHP, Pitié-Salpêtrière hospital, F-750013, Paris, France

**\* Corresponding author**: Dr. Guillaume Favre, Service de Néphrologie-Dialyse-

Transplantation, CHU Pasteur, 30 voie Romaine, 06002 CD1, Nice, France,

favre.g@chu-nice.fr , Phone number (0033) 492038428, Fax number (0033)

492038495.

## Abstract

**Background:** Excess visceral fat (VF) or high body mass index (BMI) are risk factors for severe COVID-19. The receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is expressed at higher levels in the VF than in the subcutaneous fat (SCF) of obese patients.

**Aim:** To show that visceral fat accumulation better predicts severity of COVID-19 outcome compared to either SCF amounts or BMI.

**Methods:** We selected patients with symptomatic COVID-19 and a computed tomography (CT) scan. Severe COVID-19 was defined as requirement for mechanical ventilation or death. Fat depots were quantified on abdominal CT scan slices and the measurements were correlated with the clinical outcomes. ACE 2 mRNA levels were quantified in fat depots of a separate group of non-COVID-19 subjects using RT-qPCR.

**Results:** Among 165 patients with a mean BMI of  $26.1 \pm 5.4$  kg/m<sup>2</sup>, VF was associated with severe COVID-19 ( $p=0.022$ ) and SCF was not ( $p=0.640$ ). Subcutaneous fat was not different in patients with mild or severe COVID-19 and the SCF/VF ratio was lower in patients with severe COVID-19 ( $p=0.010$ ). The best predictive value for severe COVID-19 was found for a VF area  $\geq 128.5$  cm<sup>2</sup> (ROC curve), which was independently associated with COVID-19 severity ( $p<0.001$ ). In an exploratory analysis, ACE 2 mRNA positively correlated with BMI in VF but not in SCF of non-COVID-19 patients ( $r^2=0.27$  vs  $0.0008$ ).

**Conclusion:** Severe forms of COVID-19 are associated with high visceral adiposity in European adults. On the basis of an exploratory analysis ACE 2 in the visceral fat may be a trigger for the cytokine storm, and this needs to be clarified by future studies.

**Keywords:** coronavirus disease 19, obesity, visceral fat, subcutaneous fat, severe acute respiratory syndrome coronavirus 2, angiotensin-converting enzyme.

**Abbreviations:** body mass index (BMI); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 19 (COVID-19); real-time quantitative polymerase chain reactions (RTq-PCR); white adipose tissue (WAT); angiotensin-converting enzyme (ACE); computed tomography (CT); renin-angiotensin-aldosterone system (RAAS); visceral fat (VF); subcutaneous fat (SCF).

## 1. Introduction

Obesity is a risk factor for hospitalisation during COVID-19 [1] and requirement for invasive mechanical ventilation [2] as recently confirmed in a large metanalysis [3]. More precisely, depots of visceral fat (VF) and ectopic fat are linked to the severity of COVID-19 in non-obese Asian people [4-7] and metabolic syndrome is frequent among patients with severe COVID-19 [8]. The angiotensin-converting enzyme (ACE) 2 is the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [9] and belongs to the renin-angiotensin-aldosterone system (RAAS). It is expressed in many tissues, including white adipose tissue (WAT). Since VF show a higher expression of ACE 2 than SCF in patients with severe or morbid obesity [10], we looked for its expression in non-COVID-19 adults, and hypothesised that the amount of VF may predict the COVID-19 outcome better than SCF or than BMI in French patients.

## 2. Methods

We first selected 46 consecutive patients in Nice and we confirmed our results in 119 consecutive patients in Paris (Table 1) with symptomatic COVID-19 and a computed tomography (CT) scan. We then combined the two cohorts (Table 2) for multivariate analyses. Since our patients were not obese, we compared mRNA expression for ACE 2 both in VF and in SCF. To that aim, we measured ACE 2 with real-time quantitative polymerase chain reactions (RTq-PCR) in a historical cohort without COVID-19 and plotted the results against BMI (Table 3 and Figures 3). Severe COVID-19 was defined as requirement for mechanical ventilation or death. All out-clinic COVID-19 patients were paucisymptomatic. Visceral and subcutaneous fat depots were quantified on a CT scan slice located between the 3<sup>rd</sup> and the 4<sup>th</sup> lumbar vertebrae by a radiologist blinded to the severity of the disease [11]. We correlated anthropometric measurements with clinical outcome. Our study followed the principles outlined in the Declaration of

Helsinki. Data were analysed using R version 4.0.1 and RStudio version 1.3.959. For inference statistics, the linear model ANOVA was used for continuous data and the chi-square test was used for categorical data. Univariate and multivariate regression analyses were performed. Logistic regression was used to determine the odds ratio for several explanatory variables in five different models. A receiver operating characteristics (ROC) curve was used to look for the best predictive cutoff value of VF for severe COVID-19. The level of statistical significance was set at 0.05.

### 3. Results

In the combined cohort (patients from Paris and Nice), the mean age was  $64 \pm 17$  years, the mean SCF was  $152.8 \pm 103.4 \text{ cm}^2$ , the mean VF was  $131.7 \pm 101.3 \text{ cm}^2$  and the mean BMI was  $26.1 \pm 5.4 \text{ kg/m}^2$ . Subcutaneous fat was not different in patients with mild or severe COVID-19 and the SCF/VF ratio was lower in patients with severe COVID-19 ( $p=0.010$ ). The best predictive value for severe COVID-19 was found for a VF area  $\geq 128.5 \text{ cm}^2$  according to the ROC curve.

In each cohort of patients, high VF amount  $\geq 128.5 \text{ cm}^2$  was significantly associated with the severity of COVID-19. In the combined cohort, VF considered as a continuous variable or as a binary variable was associated to the severity of COVID-19 (Table 1).

In multivariate analysis, VF considered as a continuous variable was not linked to the severity of COVID-19 (models 1 to 4), whereas VF considered as a binary variable (models 5 and 6) was strongly associated with the severity of COVID-19 ( $p=0.001$ ).

The relationship between high VF amount and the severity of COVID-19 was stronger than the relationship between the severity of COVID-19 and BMI ( $p=0.022$ ) or sex ( $p=0.010$ ) (Table 2).

In a small exploratory analysis, we found a positive correlation between the expression of the mRNA of ACE 2 and the BMI in VF, but not in SCF; the patients from the

historical non-COVID-19 cohort were not statistically different from the COVID-19 patients in Nice (Table 3 and Figures 3).

#### 4. Discussion

High VF amount was a stronger predictor of severe forms of COVID-19 in non-obese Caucasian patients than BMI. Low VF was not protective, and therefore there was not a linear correlation over the full spectrum of VF amounts. Subcutaneous fat was not related to COVID-19 severity, and consequently, the visceral over subcutaneous fat ratio is not relevant either. In multivariate analysis, only high VF was related to COVID-19 severity but not age and sex. Given that adults and men have more visceral fat than children and women [12], is it likely that the relationship between severity of disease, age and sex is accounted for by the amount of VF. Indeed, men or elderly patients die more frequently from COVID-19 than women or young patients.

Visceral fat and the severity of COVID-19 are related in three other cohorts of patients [4, 5, 7]. We here show that a certain amount of VF is necessary to observe severe forms of COVID-19 (Table 2). White adipose tissue has a limited expansion capability following excess dietary intake [13]. Beyond a threshold, WAT accommodates excess calories by the production of pro-inflammatory adipocytokines in the VF and by ectopic fat storage leading to insulin resistance [14]. Accordingly, fatty liver, high epicardial adipose tissue [6] or increased intramuscular fat [4] are associated with severe COVID-19. Hypertension, type 2 diabetes and ischaemic cardiomyopathy are the most common comorbidities found in patients with severe COVID-19 [15]. The lack of relationship between VF as a continuous variable and COVID-19 severity might also partly depend on the uneven distribution of VF in our combined cohort. Indeed, the patients from Nice have twice as much VF than the patients from Paris (Table 1). Of note, the VF from Chinese patients tend to be smaller than those from our French patients (90.5 versus

119.7 cm<sup>2</sup> for good outcomes and 131.9 versus 158.0 cm<sup>2</sup> for bad outcomes, respectively). This is in accordance with the lower threshold for being overweight in Asian people, compared with European people [16]. Consistent with its harmless role regarding metabolic health, SCF was not linked to the severity of COVID-19 (Table 1). RAAS intrinsic to WAT modulates inflammation, oxidative stress and immune status of both visceral and ectopic fat depots [17]. For example, angiotensin-II (Ang-II) produced by the WAT contributes to the recruitment of macrophages [18, 19] and to their polarisation into a pro-inflammatory M1-phenotype [20]. We, and others, propose that RAAS imbalance could trigger the cytokine storm of severe COVID-19 [21, 22]. The virus would enter VF through the digestive tract because the intestinal cells highly express ACE 2 [23, 24] and are more often infected by SARS-CoV-2 in patients with severe COVID-19 [25, 26]. The engagement of SARS-CoV-2 on ACE 2 in the VF would impair the enzymatic activity of ACE 2 and increase the production of Ang-II, thereby enhancing the production of inflammatory cytokines and their release into the systemic circulation. In support of this hypothesis, in a small exploratory analysis in non-COVID-19 patients, ACE 2 mRNA expression in VF positively correlated with BMI (Table 3 and Figures 3). Such a relationship was not observed for SCF. In addition, ACE 2 protein is higher in VF as compared to SCF of patients with severe or morbid obesity [10]. It is rather unlikely that VF would serve as a reservoir for SARS-CoV-2 in non-severe COVID-19 because the viral genome is not present in the VF depots of four patients with mild COVID-19 undergoing emergent abdominal surgery [27]. Mechanisms other than RAAS imbalance intrinsic to the WAT may play a role in the severity of COVID-19 because the use of ACE inhibitor or angiotensin receptor blockers for the purpose of treating hypertension in patients with COVID-19 does not lower the likelihood of severe COVID-19 [28]. As an alternate mechanism, the



translocation of microbial-associated molecular patterns into the VF following intestinal infection with SARS-CoV-2 might activate the TLR-receptors from M1-macrophages intrinsic to the WAT and trigger the cytokine storm [29].

The strengths of our study are the presence of two independent cohorts of Caucasian patients showing the same association between VF and COVID-19 severity, and the finding that ACE 2 parallels BMI in the VF of overweight patients. However, our work is limited by the fact that ACE 2 measurements were taken in fat from non-COVID-19 individuals in a small exploratory analysis, by the lack of data regarding traits of metabolic syndrome in our combined cohort and by the small number of patients.

Larger studies are needed to confirm our observations.

We conclude that severe forms of COVID-19 are more frequent in patients with high visceral adiposity, among European and Asian adults. Given that VF is central to metabolic syndrome, metabolic parameters should be carefully evaluated in every patient infected with SARS-CoV-2 [30], keeping in mind their diverse thresholds among Asian and Caucasian people. We also propose that the constitutive overexpression of ACE 2 – the receptor of SARS-CoV-2 – in VF may contribute to the cytokine storm, and we await further work regarding the underlying mechanisms.

### **Acknowledgements**

#### **Author Contributions**

Drs Favre, Esnault and Pradier had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Esnault, Favre, Pradier.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Favre, Esnault.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Legueult, Pradier.

Administrative, technical, or material support: Legueult, Pradier, Ichai, Iannelli, Lucidarme, Redheuil, Raffaelli, Favre.

Supervision: Favre.

We are indebted to Veli Yildirim for measurements of fat depots on CT-scans, to Svetlana Dariault for the data organisation of the Pitié Salpêtrière center and to Dr Jérôme Parra for the constitution of the cohort of non-COVID-patients.

Conflict of interest disclosure : none for any of the authors

Funding : This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## **References**

- [1] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020.
- [2] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)*. 2020.
- [3] Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. *Obes Rev*. 2020;21:e13128.
- [4] Yang Y, Ding L, Zou X, Shen Y, Hu D, Hu X, et al. Visceral Adiposity and High Intramuscular Fat Deposition Independently Predict Critical Illness in Patients with Sars-COV-2. *Obesity (Silver Spring)*. 2020.
- [5] Watanabe M, Caruso D, Tuccinardi D, Risi R, Zerunian M, Polici M, et al. Visceral fat shows the strongest association with the need of intensive Care in Patients with COVID-19. *Metabolism*. 2020:154319.
- [6] Deng M, Qi Y, Deng L, Wang H, Xu Y, Li Z, et al. Obesity as a Potential Predictor of Disease Severity in Young COVID-19 Patients: A Retrospective Study. *Obesity (Silver Spring)*. 2020.
- [7] Petersen A, Bressemer K, Albrecht J, Thiess HM, Vahldiek J, Hamm B, et al. The role of visceral adiposity in the severity of COVID-19: Highlights from a unicenter cross-sectional pilot study in Germany. *Metabolism*. 2020;110:154317.
- [8] Belanger MJ, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. Covid-19 and Disparities in Nutrition and Obesity. *N Engl J Med*. 2020;383:e69.
- [9] Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med*. 2020;382:1653-9.

- [10] Zhang Y, Somers KR, Becari C, Polonis K, Pfeifer MA, Allen AM, et al. Comparative Expression of Renin-Angiotensin Pathway Proteins in Visceral Versus Subcutaneous Fat. *Front Physiol.* 2018;9:1370.
- [11] Grauer WO, Moss AA, Cann CE, Goldberg HI. Quantification of body fat distribution in the abdomen using computed tomography. *Am J Clin Nutr.* 1984;39:631-7.
- [12] Bjorntorp P. The regulation of adipose tissue distribution in humans. *Int J Obes Relat Metab Disord.* 1996;20:291-302.
- [13] Smith U. Abdominal obesity: a marker of ectopic fat accumulation. *J Clin Invest.* 2015;125:1790-2.
- [14] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112:1796-808.
- [15] Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. *Am J Respir Crit Care Med.* 2020;201:1372-9.
- [16] Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363:157-63.
- [17] Favre GA, Esnault VL, Van Obberghen E. Modulation of glucose metabolism by the renin-angiotensin-aldosterone system. *Am J Physiol Endocrinol Metab.* 2015;308:E435-49.
- [18] Lee MH, Song HK, Ko GJ, Kang YS, Han SY, Han KH, et al. Angiotensin receptor blockers improve insulin resistance in type 2 diabetic rats by modulating adipose tissue. *Kidney Int.* 2008;74:890-900.
- [19] Solinas G, Vilcu C, Neels JG, Bandyopadhyay GK, Luo JL, Naugler W, et al. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. *Cell metabolism.* 2007;6:386-97.
- [20] Ma LJ, Corsa BA, Zhou J, Yang H, Li H, Tang YW, et al. Angiotensin type 1 receptor modulates macrophage polarization and renal injury in obesity. *Am J Physiol Renal Physiol.* 2011;300:F1203-13.

- [21] Iannelli A, Favre G, Frey S, Esnault V, Gugenheim J, Bouam S, et al. Obesity and COVID-19: ACE 2, the Missing Tile. *Obes Surg.* 2020.
- [22] Lanza K, Perez LG, Costa LB, Cordeiro TM, Palmeira VA, Ribeiro VT, et al. Covid-19: the renin-angiotensin system imbalance hypothesis. *Clinical science.* 2020;134:1259-64.
- [23] Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res.* 2020;126:1456-74.
- [24] Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature.* 2012;487:477-81.
- [25] Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol.* 2020;5:335-7.
- [26] Wong MC, Huang J, Lai C, Ng R, Chan FKL, Chan PKS. Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: A meta-analysis. *J Infect.* 2020;81:e31-e8.
- [27] Safari S, Keyvani H, Alamdari NM, Dehghanian A, Hashemi MR, Honar BN, et al. Abdominal Surgery in Patients with COVID-19: Detection of SARS-CoV-2 in Abdominal and Adipose Tissues. *Ann Surg.* 2020.
- [28] Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med.* 2020;382:2441-8.
- [29] Uzzan M, Corcos O, Martin JC, Treton X, Bouhnik Y. Why is SARS-CoV-2 infection more severe in obese men? The gut lymphatics - Lung axis hypothesis. *Med Hypotheses.* 2020;144:110023.
- [30] Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol.* 2020;16:341-2.

**Tables and figures****Table 1. Nice cohort, Paris cohort, combined cohort (univariate analysis)**

	Women	Men	Age (years)	BMI (Kg/m <sup>2</sup> )	SCF (cm <sup>2</sup> )	VF (cm <sup>2</sup> )	SCF/VF	High VF ≥ 128.5 cm <sup>2</sup>	Low VF < 128.5 cm <sup>2</sup>
Nice cohort (n=31)	16 (52%)	15 (48%)	66.8 (17.1)	25.9 (4.8)	230.3 (4.9)	175.8 (128.7)	2.1 (1.8)	17 (55%)	14 (45%)
Paris cohort (n=81)	28 (35%)	52 (65%)	62.4 (17.4)	25.4 (5.1)	119.5 (86.1)	97.6 (83.5)	1.6 (1.3)	15 (19%)	66 (81%)
Combined cohort (n=112)	44 (40%)	67 (60%)	63.6 (17.4)	25.5 (5.0)	150.2 (107.5)	119.7 (103.6)	1.8 (1.5)	32 (29%)	80 (71%)
Nice cohort (n=15)	2 (13%)	13 (87%)	70.1 (13.2)	26.4 (3.3)	219.4 (112.4)	239.9 (86.9)	1.0 (0.7)	13 (87%)	2 (13%)
Paris cohort (n=38)	8 (22%)	29 (78%)	64.1 (15.0)	27.6 (7.0)	134.2 (75.8)	125.6 (72.0)	1.3 (0.8)	19 (50%)	19 (50%)
Combined cohort (n=53)	10 (19%)	42 (81%)	65.8 (14.6)	27.2 (6.1)	158.3 (94.9)	158.0 (91.8)	1.2 (0.7)	32 (61%)	21 (40%)
P value (Nice cohort)	0.013 <sup>1</sup>		0.510 <sup>2</sup>	0.730 <sup>2</sup>	0.766 <sup>2</sup>	0.089 <sup>2</sup>	0.031 <sup>2</sup>	0.034 <sup>1</sup>	
P value (paris cohort)	0.145 <sup>1</sup>		0.612 <sup>2</sup>	0.073 <sup>2</sup>	0.372 <sup>2</sup>	0.078 <sup>2</sup>	0.116 <sup>2</sup>	< 0.001 <sup>1</sup>	
P value (combined cohort)	0.010 <sup>1</sup>		0.433 <sup>2</sup>	0.079 <sup>2</sup>	0.640 <sup>2</sup>	0.022 <sup>2</sup>	0.010 <sup>2</sup>	< 0.001 <sup>1</sup>	

Legend: Values are mean and standard deviation unless otherwise indicated; BMI : body mass index; SCF: subcutaneous fat; VF: visceral fat. Light grey : mild COVID-19; dark grey : severe COVID-19; statistics : Pearson's Chi-squared test <sup>1</sup> or Linear Model ANOVA <sup>2</sup>.

Table 2. Combined cohort with several multivariate analysis models

Explanatory variables for severe COVID-19	Odd ratio (univariate)	Odd ratio (multivariate)
<b>Model 1</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	0.82 (0.37-1.88, p=0.635)
Sex (men)	2.76 (1.29-6.33, p=0.012)	3.31 (1.39-8.76, p=0.010)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.02 (0.80-1.31, p=0.876)
BMI (kg/m <sup>2</sup> )	1.06 (0.99-1.14, p=0.085)	1.09 (1.02-1.18, p=0.022)
<b>Model 2</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	1.18 (0.49-2.92, p=0.717)
Sex (men)	2.76 (1.29-6.33, p=0.012)	3.11 (1.41-7.50, p=0.007)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.09 (0.87-1.36, p=0.471)
Subcutaneous fat (dm <sup>2</sup> )	1.08 (0.78-1.47, p=0.638)	1.28 (0.85-1.92, p=0.235)
<b>Model 3</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	1.26 (0.54-3.08, p=0.601)
Sex (men)	2.76 (1.29-6.33, p=0.012)	2.31 (1.05-5.45, p=0.044)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.02 (0.82-1.27, p=0.866)
Visceral fat (dm <sup>2</sup> )	1.44 (1.05-2.00, p=0.025)	1.39 (0.95-2.05, p=0.090)
<b>Model 4</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	1.33 (0.54-3.40, p=0.538)
Sex (men)	2.76 (1.29-6.33, p=0.012)	2.47 (1.05-6.31, p=0.046)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.03 (0.82-1.31, p=0.775)
Subcutaneous fat (dm <sup>2</sup> )	1.08 (0.78-1.47, p=0.638)	1.10 (0.68-1.75, p=0.702)
Visceral fat (dm <sup>2</sup> )	1.44 (1.05-2.00, p=0.025)	2.97 (0.86-2.09, p=0.200)
<b>Model 5</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	1.65 (0.71-4.03, p=0.256)
Sex (men)	2.76 (1.29-6.33, p=0.012)	2.06 (0.92-4.90, p=0.087)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.04 (0.83-1.31, p=0.730)
High visceral fat ( $\geq 128.5$ cm <sup>2</sup> )	2.57 (1.59-4.22, p<0.001)	2.73 (1.59-4.79, p<0.001)
<b>Model 6</b>		
Center (Paris)	0.97 (0.47-2.04, p=0.934)	1.50 (0.60-3.89, p=0.392)
Sex (men)	2.76 (1.29-6.33, p=0.012)	1.88 (0.80-4.72, p=0.160)
Age (decade)	1.08 (0.89-1.33, p=0.431)	1.02 (0.81-1.30, p=0.845)
Subcutaneous fat (dm <sup>2</sup> )	1.08 (0.78-1.47, p=0.638)	0.87 (0.53-1.41, p=0.574)
High visceral fat ( $\geq 128.5$ cm <sup>2</sup> )	2.57 (1.59-4.22, p<0.001)	2.97 (1.60-5.72, p=0.001)

Legend: Values are Odds Ratios with their related confidence-intervals and p-values using multivariable binomial logistic regression models. Data are collected from 2 centers “Nice”, and “Paris” which is used as reference in the models. Subcutaneous fat

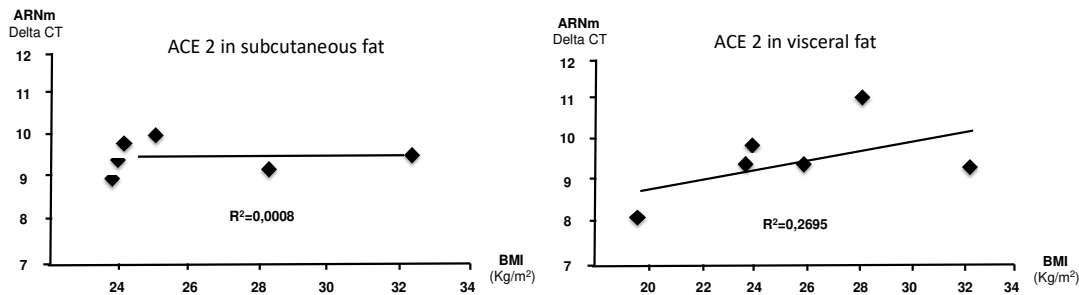
and visceral fat are expressed in  $\text{dm}^2$  and age in decade to increase the OR and to improve the reading. This does not change the p-values.



Table 3 and Figures 3. Exploratory analysis of ACE 2 mRNA expression.

COVID-19 (Nice) (n=46)	Non-COVID-19 (n=8)	Total (n=54)	p value	
Male sex – no. (%)	28 (60.9 %)	3 (37.5 %)	31 (57.4 %)	0.264 <sup>1</sup>
Age – years				0.893 <sup>2</sup>
Mean (SD)	67.9 (15.8)	72.0 (10.3)	68.5 (15.1)	
Range	26 – 88	56 – 90	26 – 90	
BMI, Mean (SD) – kg/m <sup>2</sup>	26.1 (4.4)	25.3 (3.7)	26.0 (4.2)	0.653 <sup>2</sup>

1. Fisher's exact test for Count Data
2. Wilcoxon rank sum test



Legend: Table 3 shows the comparison between COVID-19 patients from Nice and non-COVID-19 individuals from an historical cohort. Figures 3 show ACE 2 mRNA expression in fat subcutaneous or visceral fat depots from non-COVID-19 individuals.