Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 3227–3235

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Metabolic characteristics in patients with COVID-19 and no-COVID-19 interstitial pneumonia with mild-to-moderate symptoms and similar radiological severity

Stefano Rizza [a,*], Alessandro Nucera [a], Marcello Chiocchi [b], Alfonso Bellia [a], Daniele Mereu [a], Gianluigi Ferrazza [a], Marta Ballanti [a], Francesca Davato [a], Giovanni Di Cola [a], Claudio O. Buonomo [c], Luca Coppeta [b], Gianluca Vanni [c], Romualdo Gervasi [a], Marina Cardellini [a], Davide Lauro [a], Massimo Federici [a]

[a] Department of Systems Medicine, University of Rome Tor Vergata, Italy
[b] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy
[c] Department of Surgical Science, University of Rome Tor Vergata, Italy

Received 26 April 2021; received in revised form 10 August 2021; accepted 11 August 2021
Handling Editor: G.P. Fadini
Available online 18 August 2021

KEYWORDS
SARS-CoV-2;
COVID-19;
Pneumonia;
Diabetes;
Glycated hemoglobin

Abstract *Background and aims:* It is known that the highest COVID-19 mortality rates are among patients who develop severe COVID-19 pneumonia. However, despite the high sensitivity of chest CT scans for diagnosing COVID-19 in a screening population, the appearance of a chest CT is thought to have low diagnostic specificity. The aim of this retrospective case–control study is based on evaluation of clinical and radiological characteristics in patients with COVID-19 ($n = 41$) and no-COVID-19 interstitial pneumonia ($n = 48$) with mild-to-moderate symptoms.
Methods and results: To this purpose we compared radiological, clinical, biochemical, inflammatory, and metabolic characteristics, as well as clinical outcomes, between the two groups. Notably, we found similar radiological severity of pneumonia, which we quantified using a disease score based on a high-resolution computed tomography scan (COVID-19 = 18.6 ± 14.5 vs n-COVID-19 = 23.2 ± 15.2, $p = 0.289$), and comparable biochemical and inflammatory characteristics. However, among patients without diabetes, we observed that COVID-19 patients had significantly higher levels of HbA1c than n-COVID-19 patients (COVID-19 = 41.5 ± 2.6 vs n-COVID-19 = 38.4 ± 5.1, $p = 0.012$). After adjusting for age, sex, and BMI, we found that HbA1c levels were significantly associated with the risk of COVID-19 pneumonia (odds ratio = 1.234 [95% CI = 1.051–1.449], $p = 0.010$).
Conclusions: In this retrospective case–control study, we found similar radiological and clinical characteristics in patients with COVID-19 and n-COVID-19 pneumonia with mild-to-moderate symptoms. However, among patients without diabetes HbA1c levels were higher in COVID-19 patients than in no-COVID-19 individuals. Future studies should assess whether reducing transient hyperglycemia in individuals without overt diabetes may lower the risk of SARS-CoV-2 infection.

* Corresponding author. Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133, Rome, Italy.
E-mail address: stefano.rizza@uniroma2.it (S. Rizza).

https://doi.org/10.1016/j.numecd.2021.08.035
0939-4753/

Introduction

From its discovery until December 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused approximately 73 million confirmed cases of coronavirus disease 2019 (COVID-19), resulting in more than 1.6 million deaths globally. This constitutes an unprecedented public health emergency in the 21st century [1,2].

The symptoms of COVID-19 range in severity from very mild to critical; severe cases of viral infection can rapidly progress to acute respiratory distress syndrome, septic shock, and multiple organ dysfunction syndrome [3]. Elderly individuals and individuals with pre-existing conditions, including hypertension, cancer, cardiovascular diseases, severe renal impairment, obesity and diabetes, have a demonstrated higher risk for developing more severe cases of COVID-19 and for COVID-19-associated mortality [4–7].

Although the interaction between the SARS-CoV-2 virus and the immune system of an individual may result in a diverse, multi-organ, potentially lethal disease, the main manifestation of COVID-19 is an interstitial pneumonia, called novel coronavirus-infected pneumonia (COVID-19 pneumonia) [3]. A diagnosis of COVID-19 pneumonia is usually determined via computed tomography (CT) [8]. However, despite the high sensitivity of chest CT scans for diagnosing COVID-19 in a screening population, some studies have still reported a low specificity for this test [9–11]. In fact, it remains difficult to distinguish COVID-19 pneumonia from other viral pneumonia on a chest CT [9].

Individuals with diabetes have been reported to have an especially high risk of severe or critical illness if they acquire COVID-19 [12,13]. A recent large meta-analysis showed that overt diabetes patients with COVID-19 pneumonia had an approximately two-fold higher risk of requiring admission to an intensive care unit and a three-fold higher risk of in-hospital mortality [14]. The three main pathophysiological pathways described in the literature linking diabetes and COVID-19 are the angiotensin-converting enzyme 2 (ACE2) system, liver dysfunction, and chronic inflammation [15–17]. However, there is limited evidence on the physiological processes underlying these connections. In addition, it is still unclear how severely hyperglycemia or prediabetes increases the risk of complicated illness or mortality in patients with COVID-19 pneumonia [18].

We conducted a retrospective case–control study to describe the radiological, clinical, biochemical, inflammatory, and metabolic characteristics of a group of consecutive inpatients hospitalized for CT-confirmed pneumonia with suspected COVID-19 etiology and with mild-to-moderate symptoms. To identify unique characteristics of COVID-19, we compared patients with COVID-19 pneumonia, diagnosed based on a positive result from polymerase chain reaction testing of a nasopharyngeal sample, to patients with non-COVID-19 pneumonia.

Methods

Patients

From 10 March to 28 May 2020, during the first wave of the COVID-19 pandemic, the Tor Vergata Polyclinic in Rome, Italy was transformed into a COVID-19 hospital. During this time, the hospital's emergency department (ED) admitted hundreds of patients with community-acquired pneumonia. After admission in ED, all individuals underwent a volumetric high-resolution CT (HRCT). Notably, according to ED policy no individuals with symptoms of pneumonia underwent thoracic US or RX scan. We retrospectively included consecutive 93 patients with radiological features suggesting COVID-19 infection (ground-glass opacity, crazy paving, consolidation with or without air bronchogram, peripheral, central or diffuse parenchymal distribution) and with symptoms that were clinically classifiable as mild to moderate (e.g., patients had no need for mechanical ventilation during hospitalization and required only passive oxygen therapy). This study was approved by the local ethics committee, and all patients provided written informed consent before their enrollment. All data was collected anonymously, and the study Fig. 1 provides a flowchart overviewing the study approach.

Clinical data and laboratory methods

For each patient, we collected data on clinical and demographic characteristics (age, sex, body mass index [BMI], and history of smoking) and the existence of comorbidities including hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, active and previous malignancy, and chronic kidney disease. Chronic kidney disease was defined as an estimated glomerular filtration rate equal to or lower than 60 ml min^{-1} (1.73 m^{-2}), according to the Chronic Kidney Disease Epidemiology Collaboration formula. We then measured each patient's fasting plasma glucose (FPG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, creatinine, urea, lactate dehydrogenase, ferritin, aminotransferases, gamma-glutamyltransferase, blood count (hemoglobin, leukocytes, lymphocytes, and platelets), D-dimer, and fibrinogen using standard immunoenzymatic methods. Insulin levels were measured using an immunochemiluminescence assay (ADVIA Centaur XP, Siemens Healthineers Diagnostics), the glycated hemoglobin (HbA1c) percentage was determined using high-performance liquid chromatography, high-sensitivity C-reactive protein (hsCRP) was measured via nephelometric immunoassay (Dimension Vista 1500, Siemens Healthineers Diagnostics), and interleukin-6 (IL-

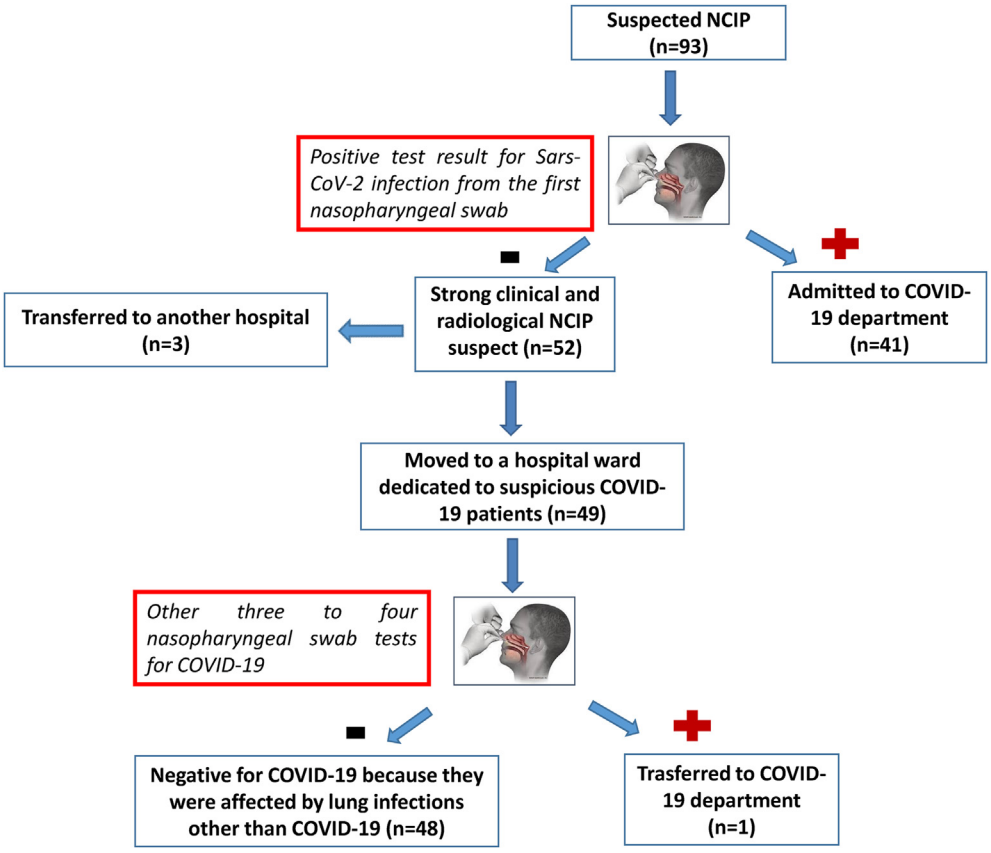

Figure 1 Flowchart overviewing the study approach.

6) levels were analyzed using a sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Real-time reverse transcription–polymerase chain reaction testing

Nasopharyngeal swabs were collected from each patient for SARS-CoV-2 real-time reverse transcription–polymerase chain reaction (RT-PCR) testing (AllpexTM 2019-nCOV Assay). Samples were tested within a few hours after collection without any cooling or freezing step. Estimates of the test sensitivity (74%; 95% confidence interval [CI], 68%–80%) and specificity (99.7%; 95% CI, 99.5%–99.9%) were obtained from our final sample of 49 healthy control patients without COVID-19 and 52 pneumonia patients with a PCR-confirmed COVID-19 diagnosis, as previously described [19].

Chest CT scan and imaging evaluation

Volumetric high-resolution CT (HRCT) scans of the lungs were performed without contrast medium using a 128-slice CT scanner (GE Revolution EVO 64 Slice CT Scanner, GE Medical Systems, Milwaukee, WI, USA). Patients were in the supine position for the scan and were breath-holding following inspiration. Scans were performed using the standard HRCT parameters (tube voltage: 120 kV; tube current modulation: 100–250 mAs; spiral pitch factor: 0.98; slice thickness: 1.25 μm).

Images were obtained using both parenchymal (width 1500 Hounsfield Units [HU]; level 600 HU) and mediastinal (width 350 HU; level 40 HU) window settings and were transferred to a dedicated workstation (ADW-6,7, GE-Healthcare) for quantitative image analysis (Thoracic VCAR v13.1, GE Medical Systems). Each lung was automatically divided into three zones for analysis: upper, which included the parenchyma above the carina; middle, which included the parenchyma below the carina and above the inferior pulmonary vein; and lower, which included the parenchyma below the inferior pulmonary vein.

The volumetric and densitometric parenchymal analysis software that we used allowed us to automatically calculate the volume of each lung and of each of the six lung zones (upper, middle, and lower zones in each of the two lungs). We also used the color-coded ranges of parenchymal density to calculate the percentages of each zone (by volume) that were occupied by air (−1024/-977 HU, blue), normal parenchyma (−977/760 HU, black), ground-glass opacities (−760/-368 HU, pink), crazy paving (368/-135 HU, white), and consolidation (−135/-40 HU, red). The cumulative percentages of crazy paving and consolidation (white and red colors) in each lung and in

each of the six zones were then calculated as an index of the extent of parenchymal involvement. We lastly calculated the total lung volume and the total upper, middle, and lower lung volumes across both lungs, as well as percent attenuation values.

HRCT scans were independently evaluated by two radiologists with 6 and 12 years of experience, respectively, who were blind to the results of the software-based analysis described above. Notably, they were also blinded to COVID-19 tests results. Scans were scored on the axial images according to literature [20,21]. Each of the six zones was scored separately on two scales: a three-point scale for the presence of CT features (1 for normal attenuation, 2 for ground-glass opacity, and 3 for consolidation) and a four-point scale for the extent of the parenchymal distribution of ground-glass opacities or consolidation (0 for none, 1 for <25%, 2 for 25–50%, 3 for 50–75%, and 4 for >75%). The final scores for each zone were calculated by multiplying the two scores, and then a total score for each patient was calculated by summing the scores for each zone. Total scores ranged from 0 (absence of pathology) to 72 (maximum severity). In cases of a discrepancy between the two radiologists, final scores were determined by consensus.

Statistical analysis

The primary hypothesis of this study is based on equivalence of radiological characteristics evaluated by the HRCT score [19] between COVID-19 pneumonia and non-COVID-19 pneumonia individuals with symptoms clinically classifiable as mild to moderate. Quantitative data are expressed as mean ± standard deviation and categorical variables are expressed as number (percentage). Data were tested for skewness via visual inspection of Q–Q plots, stem and leaf plots, or box plots, as well as with the Shapiro–Wilk test for normal distributions. Creatinine, white blood cells (WBCs), lymphocytes, liver transaminases, gamma-glutamyltransferase, insulin, IL-6, D-dimer, lactate dehydrogenase, and hsCRP did not follow a normal distribution and were therefore logarithmically transformed for analysis. All other data are presented as raw values. An unpaired t-test was used to compare patients with and without COVID-19, and an analysis of covariance was used to correct the differences between the variables of interest for differences in sex, BMI, and age. Partial correlation was used to calculate bivariate correlations between variables after controlling for sex, BMI, and age. Significant differences in categorical predictors between groups were evaluated using the chi-square test or Fisher's exact test analysis. We lastly used simple and multiple linear regressions to explore significant associations between COVID-19 pneumonia and clinical variables that were significantly correlated with COVID-19 infection. All p-values are from two-tailed tests, and the significance level was defined at $p < 0.05$ before all analyses. Analyses were performed in SPSS version 19.0 for Windows.

Results

The clinical protocol for this study is presented as a flowchart in Fig. 1. All patients were tested for COVID-19 using a nasopharyngeal swab RT-PCR assay for SARS-CoV-2. Study cases (COVID-19, $n = 41$) were individuals with confirmed COVID-19 pneumonia, diagnosed based on a positive test result for SARS-CoV-2 infection from the first nasopharyngeal swab. Study controls (n-COVID-19, $n = 52$) were patients with a negative test result for COVID-19 from the first nasopharyngeal swab but with clinical, radiological, and laboratory results suspicious for SARS-CoV-2. Three of these control patients were transferred to another hospital, and the remaining 49 were moved to a hospital ward dedicated to suspicious COVID-19 patients. The latter 49 patients underwent another three to four nasopharyngeal swab tests for COVID-19. One patient subsequently received a positive COVID-19 diagnosis and was moved to a COVID-19 hospital ward, and the remaining patients ($n = 48$) were eventually declared negative for COVID-19 (n-COVID-19) because they were affected by lung infections other than COVID-19.

Table 1 displays the main characteristics of the study population, separated by SARS-CoV-2 test results (positive or negative). Interestingly, the radiological severity of pneumonia, assessed based on the HRCT scans, was similar between the two groups (COVID-19 = 18.6 ± 14.5 vs. n-COVID-19 = 23.2 ± 15.2, $p = 0.289$, Fig. 2). As a confirmation of this result, there were no significant differences in clinical outcomes between the two groups (Table 2), nonetheless this observation should be interpreted with extreme caution because of the small sample size. Moreover, we did not find any significant correlation between HRCT-score components and SARS-CoV-2 test results (positive or negative). COVID-19 patients were more frequently male ($p = 0.018$), had non-significantly higher levels of CRP, IL-6, and ferritin, and had significantly lower levels of WBCs (COVID-19 = 7.3 ± 5.7 vs. n-COVID-19 = 11.0 ± 8.7, $p = 0.028$) and lymphocytes (COVID-19 = 1.2 ± 0.7 vs n-COVID-19 = 1.7 ± 0.9, $p = 0.031$), after correcting for age, sex and BMI. Notably, inflammatory parameters, including WBCs and lymphocytes, did not correlate with glycated hemoglobin, glycemia, insulin and HOMA-IR. Moreover, there were no significant differences between COVID-19 infected and COVID-19 uninfected patients with respect to glycemia, insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR), glycated hemoglobin, and the prevalence of major clinical comorbidities, even after adjustment for age, sex, and BMI. Interestingly, when only patients without diabetes were analyzed, COVID-19 pneumonia patients were again more frequently male ($p = 0.012$) but had significantly higher levels of HbA1c than patients with non-COVID-19 pneumonia (COVID-19 = 41.5 ± 2.6 vs n-COVID-19 = 38.4 ± 5.1, $p = 0.012$, controlled for age, sex and BMI), with no other significant differences apart from a decrease in WBCs and lymphocytes (Table 3). After correcting for age, sex, and BMI, only elevated HbA1c levels were significantly associated with

Table 1 Main characteristics of the study population, separated by SARS-CoV-2 test results.

	No COVID-19 pneumonia ($n = 48$)	% of missing values	COVID-19 pneumonia ($n = 41$)	% of missing values	p	p^*
Age (y)	69.0 ± 16.1	0	63.7 ± 17.2	0	0.139	n.a.
Female/male (n)	26/23	0	11/29	0	0.018	n.a.
Current/previous or never smokers (n)	11/38	0	12/28	0	0.285	0.367
BMI (kg/m^2)	26.3 ± 4.7	0	25.0 ± 3.7	0	0.166	n.a.
Total cholesterol (mg/dl)	160.6 ± 42.0	2	154.1 ± 39.7	2	0.499	0.277
HDL cholesterol (mg/dl)	36.2 ± 15.0	2	34.7 ± 17.4	2	0.682	0.439
Triglycerides (mg/dl)	135.6 ± 69.4	2	121.3 ± 58.5	2	0.343	0.299
HRCT score	23.2 ± 15.2	0	18.6 ± 14.5	0	0.289	0.186
Influenza viruses (IgM and/or IgG) (yes/no)	2/47	2	2/38	4	0.611	0.772
Hemoglobin (g/dl)	11.6 ± 1.9	2	12.4 ± 2.3	4	0.098	0.127
White blood cells (x1000/μl)	11.0 ± 8.7	2	7.3 ± 5.7	4	0.020	0.028
Lymphocytes (n°/mm^3)	1.7 ± 0.9	2	1.2 ± 0.7	4	0.020	0.031
Fasting glucose (mg/dl)	98.1 ± 28.5	0	97.6 ± 27.8	0	0.938	0.982
Fasting insulin (mU/L)	10.6 ± 13.9	2	9.4 ± 5.8	2	0.726	0.882
HOMA-IR	2.96 ± 4.66	2	2.45 ± 2.34	2	0.660	0.671
HbA1c (mmol/mol)	42.7 ± 16.1	0	45.9 ± 11.1	0	0.314	0.309
AST (UI/L)	35.2 ± 47.4	0	35.1 ± 23.4	0	0.995	0.962
ALT (UI/L)	29.9 ± 36.9	0	44.8 ± 76.8	0	0.245	0.331
Gamma-GT (UI/L)	57.6 ± 72.7	0	40.4 ± 42.2	0	0.222	0.239
e-GFR (<60 ml/min/≥60 ml/min)	15/33	0	13/28	0	0.963	**0.922**
IL-6 (ng/ml)	38.4 ± 51.3	4	74.7 ± 113.5	2	0.092	0.099
hs-CRP (mg/dl)	83.5 ± 82.2	2	141.7 ± 431.9	2	0.450	0.462
D-dimer (ng/ml)	1917.1 ± 2443.8	2	1324.8 ± 1358.0	2	0.164	0.277
CPK (UI/L)	123.6 ± 117.6	2	98.4 ± 73.9	0	0.256	0.421
Ferritin (ng/ml)	605.5 ± 717.2	0	694.9 ± 747.7	0	0.629	0.633
LDH (U/L)	259.8 ± 108.0	2	259.2 ± 93.8	0	0.979	0.904
Vitamin D (ng/ml)	15.3 ± 12.0	4	15.9 ± 10.0	2	0.787	0.633
PTH (pg/ml)	137.5 ± 231.9	4	107.1 ± 111.1	4	0.461	0.449
Coexisting disorders (n)						
Any (yes/no)	39/10	0	26/14	0	0.082	n.p.
Hypertension (yes/no)	32/17	0	20/20	0	0.188	n.p.
Diabetes (yes/no)	13/36	0	11/29	0	0.999	n.p.
Coronary artery disease (yes/no)	21/28	0	12/28	0	0.269	n.p.
Cerebrovascular disease (yes/no)	6/43	0	3/37	0	0.502	n.p.
COPD (yes/no)	14/35	0	7/33	0	0.316	n.p.
Chronic renal disease*	11/38	0	3/37	0	0.079	n.p.
Active malignancy	1/48	0	0/40	0	0.889	n.p.
Previous malignancy	14/35	0	5/35	0	0.075	n.p.

Footnotes: NCIP = Novel coronavirus-infected pneumonia; BMI = Body mass index; HDL = High-density lipoprotein; HRCT = High-resolution computed tomography; HbA1c = Glycated hemoglobin; HOMA-IR = Homeostatic model assessment of insulin resistance; AST = Aspartate aminotransferase; ALT = Alanine transaminase; e-GFR = Estimated glomerular filtration rate; hs-CRP = High-sensitivity C-reactive protein; CPK = Creatine phosphokinase; LDH = Lactate dehydrogenase; PTH = Parathyroid hormone; COPD = Chronic obstructive pulmonary disease. *e-GFR equals to or lower than 60 ml min^{-1} (1.73 m^{-2}). p = significance for t-test or chi-squared when appropriate; p^* = significance controlled for sex, BMI and age; n.a. = not applicable; n.p. = not performed.

the risk of COVID-19 pneumonia (odds ratio = 1.234, 95% CI = 1.051–1.449, $p = 0.010$, Table 4). Of note, compared to COVID-19 subjects, individuals with n-COVID-19 interstitial pneumonia showed an higher HRCT score, although not significantly different after adjustment for sex, BMI and age.

Discussion

In this retrospective case–control study, we found that COVID-19 and non-COVID-19 in-patients with pneumonia clinically classifiable as mild to moderate and similar HRCT image severity, as determined by HRCT scan score, had similar metabolic and clinical characteristics. There were also no differences in inflammatory burden or clinical outcomes between COVID-19 and non-COVID-19 individuals, though patients with non-COVID-19 pneumonia had higher leukocytes counts possibly due to bacterial infection. These results are particularly unexpected. One possible explanation is that it remains difficult to distinguish COVID-19 from other causes of viral pneumonia. Although chest HRCT has been reported to have a high sensitivity for COVID-19 diagnosis, this method still has low specificity. For example, influenza and COVID-19 both

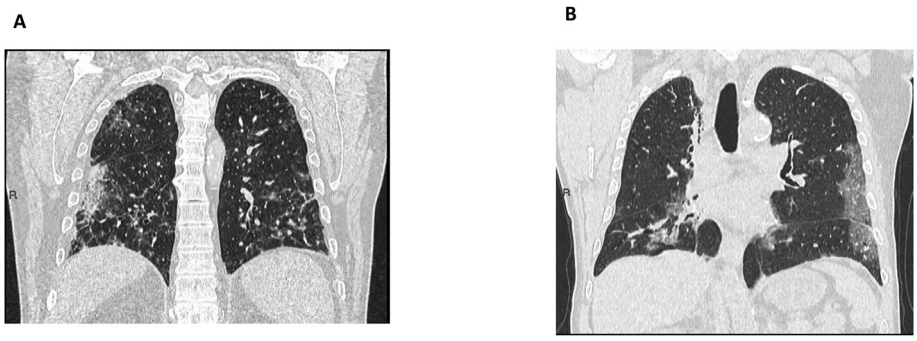

Figure 2 Volumetric high-resolution thoracic CT (HRCT) scans of a no-COVID-19 patients (A) and COVID-19 patient (B).

present with ground glass opacities and consolidation on a chest CT [16], making it complicated to perform a differential diagnosis.

Notably, pneumonia patients with and without COVID-19 also had similar circulating levels of IL-6. The induction of IL-6 production by interleukin-1, the primordial proinflammatory cytokine, instigates the well-known amplification loop that contributes to the cascade of cytokine overproduction that characterizes a "cytokine storm" [22]. However, even though IL-6 overload is a fundamental part of the cytokine storm and plays a crucial role in the pathophysiology of severe COVID-19, cytokine storm remains ill-defined, particularly when compared to cytokine levels in patients with bacterial sepsis or other critical illnesses [23]. Overall, our findings are surprising given that the COVID-19 pandemic is a public health emergency of global concern, has generated considerable public awareness, and has caused a major worldwide sanitary crisis [24].

Moreover, we found similar rates of comorbidities, including diabetes, between the two study groups in our study population. Diabetes is one of the most frequent diseases associated with COVID-19 infection [25], as COVID-19 pneumonia is more severe in diabetic than in patients without diabetes [26], COVID-19 patients with diabetes are at higher risk of excessive uncontrolled inflammatory responses and hypercoagulation [27] and newly-diagnosed diabetes and admission hyperglycemia are powerful predictors of COVID-19 severity due to rapid respiratory deterioration [28]. Recent evidence has focused on the vascular nature of COVID-19 [29], and diabetes is a well-known risk factor for vascular diseases [30]. However, we report, for the first time, a slight increase of glycated hemoglobin levels in subjects without diabetes and with COVID-19 pneumonia compared to non-diabetic patients with non-COVID-19 pneumonia. Although this difference was subtle, it was significant, and it was not affected by patient age or adiposity. This finding should not be underestimated because hyperglycemia, even in patients without diabetes, may lead to additional immune suppression and further complications [31]. Furthermore, our data might suggest that chronic hyperglycemia may increase the risk of symptomatic mild-to-moderate pneumonia following SARS-CoV-2 infection.

Interestingly, it has been reported that high and aberrantly glycosylated ACE2 levels in the lung tissue in patients with uncontrolled hyperglycemia could facilitate the cellular intrusion of SARS-CoV-2, thus leading to a higher susceptibility to COVID-19 infection and increased disease severity [32]. Although we adopted a cross-sectional design and were therefore unable to establish causality, our findings does not exclude that mild chronic hyperglycemia may increase the risk of SARS-CoV-2 infection. In fact, transient hyperglycemia has also been observed in patients with severe acute respiratory syndrome (SARS), and it has been reported that the virus that causes SARS also causes a transient impairment of pancreatic islet cell function [33]. In addition, the closely-related Middle Eastern respiratory syndrome coronavirus (MERS-CoV) [34], as well as the human coronavirus EMC [35], anchor to host cells via dipeptidyl peptidase 4 (DPP-4), which is physiologically implicated in the modulation of insulin action and in the degradation of incretins such as glucagon-like peptide 1.

The observation that mildly increased HbA1c in individuals without known diabetes might have broader clinical implications is certainly not new. HbA1c is known to be a reliable risk factor for both all-cause and cardiovascular mortality, even in individuals without diabetes [36]. Similarly, HbA1c levels are independently associated with the presence and severity of coronary artery atherosclerosis in subjects without diabetes, even when LDL-C levels are tightly controlled [37]. Furthermore, the near−linear association between HbA1c levels and the risk of several cancers supports the hypothesis that HbA1c

Table 2 Clinical outcomes, separated by SARS-CoV-2 test results.

	Discharge	Mechanical ventilation/ deaths	p^a	p^b
COVID-19 negative ($n = 48$)	44	4	0.333	0.219
COVID-19 positive ($n = 41$)	34	7		

[a] Significance for Fisher's exact test analysis.
[b] Significance after adjustment for age, sex, BMI, diabetes, hypertension, CVD and CKD.

Table 3 Study characteristics of patients without diabetes, separated by SARS-CoV-2 test results.

	No COVID-19 pneumonia (n = 36)	% of missing values	COVID-19 pneumonia (n = 29)	% of missing values	p	p^*
Age (y)	66.5 ± 17.4	0	60.9 ± 16.3	0	0.185	n.a.
Female/male	21/15	0	8/21	0	0.012	n.a
Current/previous or never smokers	8/28	0	8/21	0	0.382	0.348
BMI (kg/m^2)	25.7 ± 4.6	0	24.7 ± 3.7	0	0.352	n.a.
Total cholesterol (mg/dl)	159.9 ± 42.4	2	152.1 ± 39.8	0	0.473	0.566
HDL cholesterol (mg/dl)	36.8 ± 14.3	2	34.8 ± 16.0	0	0.611	0.633
Triglycerides (mg/dl)	137.9 ± 77.4	4	117.6 ± 60.4	0	0.277	0.218
HRCT score	24.0 ± 16.7	0	15.7 ± 13.3	0	0.033	0.076
Influenza viruses (IgM and/or IgG) (yes/no)	2/34	2	1/28	2	0.993	0.991
Hemoglobin (gr/dl)	11.9 ± 2.0	2	12.8 ± 1.9	2	0.093	0.097
White blood cells (x1000/μl)	11.7 ± 9.6	2	6.9 ± 6.2	2	0.035	0.039
Lymphocytes (n°/mm^3)	1.8 ± 1.0	2	1.3 ± 0.5	2	0.010	0.011
Fasting glucose (mg/dl)	91.4 ± 25.8	0	89.2 ± 14.4	0	0.702	0.799
Fasting insulin (mU/L)	9.0 ± 13.1	0	8.1 ± 4.0	0	0.811	0.922
HOMA-IR	2.03 ± 3.51	0	1.78 ± 3.09	0	0.428	0.419
HbA1c (mmol/mol)	38.4 ± 5.1	0	41.5 ± 2.6	0	0.013	0.012
AST (UI/L)	38.9 ± 55.0	0	36.7 ± 23.5	0	0.854	0.867
ALT (UI/L)	33.7 ± 41.8	0	49.2 ± 84.7	0	0.348	0.358
Gamma-GT (UI/L)	60.7 ± 81.9	0	40.0 ± 43.4	0	0.252	0.432
e-GFR (<60 ml/min/≥60 ml/min)	8/28	0	8/21	0	0.249	0.287
IL-6 (ng/ml)	36.7 ± 54.5	2	98.4 ± 112.5	2	0.208	0.287
hs-CRP (mg/dl)	78.8 ± 71.8	2	147.9 ± 495.6	2	0.412	0.348
D-dimer (ng/ml)	1662.0 ± 1972.3	2	1150.4 ± 1244.7	2	0.256	0.302
CPK (UI/L)	121.6 ± 90.5	2	90.9 ± 74.7	0	0.173	0.237
Ferritin (ng/ml)	626.7 ± 796.0	0	581.4 ± 582.3	0	0.832	0.894
LDH (U/L)	264.7 ± 118.9	2	262.2 ± 103.0	0	0.932	0.954
Vitamin D (ng/ml)	15.4 ± 13.3	2	18.0 ± 9.9	0	0.415	0.481
PTH (pg/ml)	149.5 ± 269.0	2	81.0 ± 43.9	2	0.351	0.342

Acronym definitions are the same as in Table 1.

could be used as an independent metabolic biomarker for cancer risk in individuals without diabetes [38]. In contrast, FPG levels have been shown to be significantly associated with the risk of death in COVID-19 patients, even in patients with normal FPG and HbA1c levels [39,40]. Even though our main finding is merely observational, it is intriguing to speculate that the mild increase in Hb1Ac in COVID-19 pneumonia patients might also reflect a systemic metabolic reaction to improve tolerance for COVID-19-induced inflammation [41]. In fact, it has been shown that an hyperglycemic response is protective from lethality of viral infections since provides adaptation to and survival from anti-viral inflammation and activation of stress-mediated apoptotic pathways [42].Nevertheless, we cannot exclude that infection per se may induce a transient dysmetabolic state causing mild insulin resistance and/or hyperglycemia leading to a temporal change in HbA1c.

Table 4 Logistic regression analysis for COVID-19 pneumonia risk in patients without diabetes (Nagelkerke R^2 = 0.31, p = 0.008).

	Odd ratio (OR)	95% CI for OR	p
Age	0.977	0.933–1.023	0.315
Sex (male)	3.694	0.990–13.778	0.052
BMI	0.876	0.721–1.065	0.183
HbA1c	1.234	1.051–1.449	0.010

Further studies are needed to understand whether increased HbA1c, especially HbA1c levels in the prediabetes range, are associated with poorer outcomes in patients with acute viral infections.

Our work has several limitations. First, our study mainly used a cross-sectional approach, has an exploratory nature, and no prospective analysis has been performed to date. Second, although the number of participants was balanced between the two study groups, the overall sample size was relatively small and some results may be related to this point. Third, we were not able to determine an alternative diagnosis for pneumonia patients who tested negative for SARS-CoV-2 via nasopharyngeal swabs, though each patient was tested for SARS-CoV-2 up to four times. Moreover, we did not provide clinical data regarding vital signs and blood gas analysis because uncompleted collected and we did not perform a survival analysis, because information about the occurrence of events has been acquired by telephone contacts and our knowledge on the exact timing of events such as deaths or mechanical ventilation was limited. Finally, even if steroid treatment was started in hospital's ED, where appropriate, we did not have specific data to report. However, although the effect of hyperglycemia on COVID-19 outcome may be confounded by glucocorticoid therapy being used in patients with more severe forms of disease [40], in our

opinion the risk that few days of steroid therapy may influence the stability of HbA1c is very low.

Despite these limitations, the main finding of this study is noteworthy. To our knowledge, this is the first observation of increased glycated hemoglobin levels in individuals with COVID-19 pneumonia but without overt diabetes, relative to patients with non-COVID-19 pneumonia with similar clinical and radiological severity. Future studies should assess whether reducing transient hyperglycemia in individuals with COVID-19 pneumonia but without overt diabetes reduces the SARS-CoV-2 binding affinity for ACE2.

Ethical approval

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Source(s) of support

This manuscript was supported the following grants: Ministry of University (MIUR) Progetti di Ricerca di Interesse Nazionale (PRIN) [protocol number 2015MPESJS_004 and 2017FM74HK to MF] and by the “Bando per progetti di ricerca scientifica di Ateneo 2019 −BEYOND BORDERS-” n: E84I20000740005 to S.R.

Declaration of competing interest

All authors declare that they have no personal or financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.08.035.

References

[1] Johns Hopkins University. Coronavirus resource center. 2020. https://coronavirus.jhu.edu/map.html. [Accessed 28 July 2020].
[2] Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of hydroxychloroquine on clinical status at 14 Days in hospitalized patients with COVID-19: a randomized clinical trial. J Am Med Assoc 2020; Nov;9:e2022240. https://doi.org/10.1001/-jama.2020.22240. Epub ahead of print. PMID: 33165621; PMCID: PMC7653542.
[3] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727−33. https://doi.org/10.1056/NEJMoa2001017. PMID: 31978945. PMID: 31978945.
[4] Baden LR, Rubin EJ. Covid-19 - the search for effective therapy. N Engl J Med 2020; May 7;382(19):1851−2. https://doi.org/10.1056/-NEJMe2005477. Epub 2020 Mar 18. PMID: 32187463; PMCID: PMC7121446.
[5] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al., the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. J Am Med Assoc 2020; May 26;323(20):2052−9. https://doi.org/10.1001/jama.2020.6775. Erratum in: JAMA. 2020 May 26; 323(20):2098. PMID: 32320003; PMCID: PMC7177629.
[6] Solerte SB, D'Addio F, Trevisan R, Lovati E, Rossi A, Pastore I, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. Diabetes Care 2020;Dec;43(12):2999−3006. https://doi.org/10.2337/dc20-1521. Epub 2020 Sep 29. PMID: 32994187; PMCID: PMC7770266.
[7] Pontiroli AE, La Sala L, Chiumello D, Folli F. Is blood glucose or obesity responsible for the bad prognosis of COVID-19 in obesity - diabetes? Diabetes Res Clin Pract 2020 Sep;167:108342. https://doi.org/10.1016/j.diabres.2020.108342. Epub 2020 Jul 27. PMID: 32730788; PMCID: PMC7384403.
[8] Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-NCoV). Radiology 2020;295:202−7. https://doi.org/10.1148/radiol.2020200230. PMID: 32017661.
[9] Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RTPCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020;296(2):E32−40. https://doi.org/10.1148/radiol.2020200642. Published February 26, 2020, . [Accessed 1 March 2020].
[10] Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from non-COVID-19 viral pneumonia at chest CT. Radiology 2020; Aug; 296(2):E46−54. https://doi.org/10.1148/radiol.2020200823. Epub 2020 Mar 10. PMID: 32155105; PMCID: PMC7233414.
[11] Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020; Aug;296(2): E32−40. https://doi.org/10.1148/radiol.2020200642. Epub 2020 Feb 26. PMID: 32101510; PMCID: PMC7233399.
[12] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 2020; Sep;8(9):782−92. https://doi.org/10.1016/S2213-8587(20)30238-2. Epub 2020 Jul 17. Erratum in: Lancet Diabetes Endocrinol 2020 Oct;8(10):e5. PMID: 32687793; PMCID: PMC7367664.
[13] Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. Am J Physiol Metab 2020;2020. https://doi.org/10.1152/ajpendo.00124.2020.ajpendo.00124.
[14] Mantovani A, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies. Nutr Metabol Cardiovasc Dis 2020;30(8):1236−48. https://doi.org/10.1016/j.numecd.2020.05.014.
[15] Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis G-A, Vogiatzi G, Papaioannou S, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol 2019;14:50. https://doi.org/10.15420/ecr.2018.33.1.
[16] Zheng F, TangW, Li H, Huang Y-X, Xie Y-L, Zhou Z-G. Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in changsha. Eur Rev Med Pharmacol Sci 2020;24:3404e10. https://doi.org/10.26355/eurrev_202003_20711.
[17] Sattar N, Scherbakova O, Ford I, O'Reilly DSJ, Stanley A, Forrest E, et al. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of scotland coronary prevention study. Diabetes 2004;53:2855e60. https://doi.org/10.2337/diabetes.53.11.2855.
[18] Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, et al. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. J Med Virol 2020; Jun 26;93(1):409−15. https://doi.org/10.1002/jmv.26227. Epub ahead of print. PMID: 32589756; PMCID: PMC7361926.
[19] Rizza S, Coppeta L, Grelli S, Ferrazza G, Chiocchi M, Vanni G, et al. High body mass index and night shift work are associated with COVID-19 in health care workers. J Endocrinol Invest 2020; Aug 27;44(5):1−5. https://doi.org/10.1007/s40618-020-01397-0. Epub ahead of print. PMID: 32852704; PMCID: PMC7450678.
[20] Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PloS One 2020;15(3). https://doi.org/10.1371/journal.pone.0230548. PMID:32191764.
[21] Pugliese L, Sbordone FP, Grimaldi F, Ricci F, Di Tosto F, Spiritigliozzi L, et al. Chest computed tomography scoring in patients with novel coronavirus-infected pneumonia: correlation with clinical and

laboratory features and disease outcome. In Vivo 2020; Nov-Dec; 34(6):3735–46. https://doi.org/10.21873/invivo.12223. PMID: 33144492.
[22] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020; Sep 1;41(32):3038–44. https://doi.org/10.1093/eurheartj/ehaa623. PMID: 32882706; PMCID: PMC7470753.
[23] Kox M, Waalders NJB, Kooistra EJ, Gerretsen J, Pickkers P. Cytokine levels in critically ill patients with COVID-19 and other conditions. J Am Med Assoc 2020; Sep 3;324(15):1565–7. https://doi.org/10.1001/jama.2020.17052. Epub ahead of print. PMID: 32880615; PMCID: PMC7489366.
[24] Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing: the need for prevention and early intervention. JAMA Intern Med 2020; Jun 1;180(6):817–8. https://doi.org/10.1001/jamainternmed.2020.1562. PMID: 32275292.
[25] CDC. 2. National diabetes statistics report 2020. 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm#T1_down.
[26] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; Mar;31:e3319. https://doi.org/10.1002/dmrr.3319. Epub ahead of print. PMID: 32233013; PMCID: PMC7228407.
[27] Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metabol 2020; Jun 2; 31(6):1068–77. https://doi.org/10.1016/j.cmet.2020.04.021. e3 Epub 2020 May 1. PMID: 32369736; PMCID: PMC7252168.
[28] Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract 2020 Oct;168:108374. https://doi.org/10.1016/j.diabres.2020.108374. Epub 2020 Aug 15. PMID: 32805345; PMCID: PMC7428425.
[29] Siddiqi HK, Libby P, Ridker PM. COVID-19 - a vascular disease. Trends Cardiovasc Med 2020; Oct 14;31(1):1–5. https://doi.org/10.1016/j.tcm.2020.10.005. Epub ahead of print. PMID: 33068723; PMCID: PMC7556303.
[30] Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. J Am Med Assoc 2002; May 15;287(19):2570–81. https://doi.org/10.1001/jama.287.19.2570. PMID: 12020339.
[31] Polycarpou A, Howard M, Farrar CA, Greenlaw R, Fanelli G, Wallis R, et al. Rationale for targeting complement in COVID-19. EMBO Mol Med 2020; Aug 7;12(8):e12642. https://doi.org/10.15252/emmm.202012642. Epub 2020 Jul 12. PMID: 32559343; PMCID: PMC7323084.
[32] Brufsky A. Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic. J Med Virol 2020; Jul;92(7):770–5. https://doi.org/10.1002/jmv.25887. Epub 2020 Apr 27. PMID: 32293710; PMCID: PMC7262330.
[33] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010; Sep;47(3):193–9. https://doi.org/10.1007/s00592-009-0109-4. Epub 2009 Mar 31. PMID: 19333547; PMCID: PMC7088164.
[34] Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. MERS-CoV spike protein: a key target for antivirals. Expert Opin Ther Targets 2017; Feb;21(2): 131–43. https://doi.org/10.1080/14728222.2017.1271415. Epub 2016 Dec 21. PMID: 27936982; PMCID: PMC5457961.
[35] Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; Mar 14;495(7440):251–4. https://doi.org/10.1038/nature12005. PMID: 23486063; PMCID: PMC7095326.
[36] Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open 2017; Jul 31;7(7):e015949. https://doi.org/10.1136/bmjopen-2017-015949. PMID: 28760792; PMCID: PMC5642750.
[37] Wang WT, Hsu PF, Lin CC, Wang YJ, Ding YZ, Liou TL, et al. Hemoglobin A1C levels are independently associated with the risk of coronary atherosclerotic plaques in patients without diabetes: a cross-sectional study. J Atherosclerosis Thromb 2020; Aug 1;27(8): 789–800. https://doi.org/10.5551/jat.51425. Epub 2019 Dec 27. PMID: 31902804; PMCID: PMC7458793.
[38] de Beer JC, Liebenberg L. Does cancer risk increase with HbA1c, independent of diabetes? Br J Canc 2014; Apr 29;110(9):2361–8. https://doi.org/10.1038/bjc.2014.150. Epub 2014 Mar 27. PMID: 24675382; PMCID: PMC4007234.
[39] Huang Y, Guo H, Zhou Y, Guo J, Wang T, Zhao X, et al. The associations between fasting plasma glucose levels and mortality of COVID-19 in patients without diabetes. Diabetes Res Clin Pract 2020; Nov;169:108448. https://doi.org/10.1016/j.diabres.2020.108448. Epub 2020 Sep 16. PMID: 32946851; PMCID: PMC7492137.
[40] Daniele G, Guardado Mendoza R, Winnier D, Fiorentino TV, Pengou Z, Cornell J, et al. The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetol 2014 Feb;51(1):123–31. https://doi.org/10.1007/s00592-013-0543-1. Epub 2013 Dec 27. PMID: 24370923.
[41] Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD, et al. Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. Cell 2016; Sep 8;166(6):1512–25. https://doi.org/10.1016/j.cell.2016.07.026. e12 PMID: 27610573; PMCID: PMC5555589.
[42] Morieri ML, Fadini GP, Boscari F, Fioretto P, Maran A, Busetto L, et al. Hyperglycemia, glucocorticoid therapy, and outcome of COVID-19. Diabetes Res Clin Pract 2020; Oct;168:108449. https://doi.org/10.1016/j.diabres.2020.108449. Epub 2020 Sep 17. PMID: 32949651; PMCID: PMC7494492.