Are adipokines related to COVID-19 and its severity? A systematic review and meta-analysis

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Abstract

Introduction. The relationship between several adipokines and COVID-19 severity has lately been evaluated, results being inconclusive. Therefore, we aimed to assess the association between adipokines in COVID-19 and its severity.

Methods. A search was performed in PubMed, Scopus, and Embase using predefined keywords. The Newcastle of Ottawa Scale (NOS) was used for the quality assessment of included studies. The main summary outcome was the mean difference (MD) in adipokine levels.

Results. A total of 8 studies involving 473 individuals were included. A significant MD in serum adiponectin levels was demonstrated in mild vs. severe COVID-19 patients (-5.734 [95% CI -11.215 – -0.252]), with no significant MD in mild vs. moderate (-7.117 [95% CI -19.546 – 5.313]), or moderate vs. severe COVID-19 (-1.846 [95% CI -4.516 – 0.824]). Moreover, no significant MD was found in adiponectin and leptin levels when comparing COVID-19 patients vs. controls (-12.675 [95% CI -36.159 – 10.808]) and (8.034 [95% CI -10.403 – 26.471]), respectively.

Conclusion. Adiponectin levels were significantly increased in patients with severe compared to mild COVID-19. However, no significant MD was found in adiponectin levels in mild vs. moderate and moderate vs. severe COVID-19 patients, nor in adiponectin and leptin levels in COVID-19 patients vs. controls.

Keywords: COVID-19, SARS-CoV-2, adipokines, adiponectin, leptin, meta-analysis

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected over 200,000,000 people and caused death in over 4.3 million cases [1], leading to a serious challenge for intensive care facilities worldwide. The typical clinical picture of the associated disease, coronavirus disease 2019 (COVID-19), includes fever, cough, dyspnea, malaise, and fatigue [2,3]. Symptoms of mild disease usually resolve in day 10-12 after onset. However, in severe cases, infected patients progress to acute respiratory distress syndrome (ARDS) and usually require ventilation support [4-7].

Medical research strongly suggests that obesity is an independent risk factor for severe COVID-19, by increasing the risk of hospital admission, severe lung inflammation, admission in the intensive care unit (ICU), and mortality [8]. Several mechanisms like chronic hyperinflammatory state or adipose tissue acting as a viral reservoir could possibly elucidate the association between increased severity of COVID-19 patients and obesity [9-11].

Adipose tissue can exert autocrine, paracrine, and endocrine functions through producing peptides known as adipokines. These adipokines include adiponectin, leptin, visfatin, and adipsin [9]. Adiponectin plays several protective roles promoting insulin sensitivity and anti-atherogenic effects. Low serum

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adiponectin levels were associated with diabetes, obesity, metabolic syndrome, and inflammation [8]. Terminally ill COVID-19 patients admitted to the ICU with reduced adiponectin levels, also known as hypoadiponectinemia, were found to be associated with a worse prognosis [9,10].

Moreover, leptin was shown to promote inflammation by stimulating the proliferation of immune cells such as natural killer and helper T cells, leading to an increased release of tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-12 [12]. Since adipose tissue is an essential source of IL-6 secretion, which is increased in obese patients, a self-regulation inflammation loop is created, leading to a chronic hyperinflammatory state by stimulating immune cells like macrophages, T cells, and B cells. In this proinflammatory status, a cytokine storm, characterized by inappropriate and excessive release of cytokines, could be triggered by a viral infection. Leptin is secreted proportionally to the adipose tissue mass, possibly explaining the higher incidence of inflammatory cytokine storm in obese patients with severe forms of COVID-19 [13]. The consequences of a cytokine storm might lead to vascular hyperpermeability and multiorgan failure, as seen in a severe COVID-19 course [9].

Although several studies evaluated the relationship between adipokines and COVID-19, current evidence remains inconclusive with conflicting results, limiting our understanding of the role of adipokines in COVID-19 and its severity. Therefore, we conducted, to the best of our knowledge, the first systemic review and meta-analysis evaluating the association between adipokines including adiponectin and leptin, with COVID-19 and disease severity.

Methods

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist 2020 [14].

Data sources and search strategy

We searched for articles assessing adipokines levels in COVID-19 and the severity of the disease. A predefined search string was used to identify the current literature published in PubMed, Embase and Scopus. We used the following search strategy for Pubmed: ((“COVID-19”[Mesh]) OR (“COVID-19”[All Fields])) AND ((“Adipokines”[Mesh]) OR (“Adipokines”[All Fields]) OR (“Leptin”[Mesh]) OR (“Leptin”[All Fields]) OR (“Adiponectin”[Mesh]) OR (“Adiponectin”[All Fields]) OR (“Resistin”[Mesh]) OR (“Resistin”[All Fields]) OR (“Nicotinamide Phosphoribosyltransferase”[Mesh]) OR (“Nicotinamide Phosphoribosyltransferase”[All Fields]) OR (“Apelin”[Mesh]) OR (“Apelin”[All Fields]) OR (“SERPINA12 protein, human” [Supplementary Concept]) OR (“Vaspin”) OR (“ITLN1 protein, human” [Supplementary Concept]) OR (“omentin”)) and similar for Embase and Scopus, identifying original evidence published from inception till 23 August 2021. No search filters or restrictions to duration, country, or language were applied. We performed a manual search by sweeping the references of included articles for possible missing relevant publications.

Subsequently, titles and abstracts of the relevant studies were evaluated for eligibility. Eligible studies were further evaluated by reviewing the full text assessing for the inclusion and exclusion criteria. Two authors (L.B. and A.I.) evaluated studies for eligibility and extracted the data from the final included studies separately, while discrepancies between the two authors were settled by discussion. Extracted data included author names, publication year, country, study design, as well as study characteristics including total subjects, mean age, gender, COVID-19 diagnosis, COVID-19 percentage, adiponectin and leptin levels in serum, adiponectin/leptin ratio, in addition to the main study findings that were entered into tables, while final data were collected and presented in the manuscript text.

Eligibility criteria

Inclusion criteria of original articles were as follows: (1) studies with full-text articles of an observational cohort, cross-sectional, or case-control designs that assessed adipokine levels including adiponectin, leptin, resistin and adipsin; (2) diagnosis of COVID-19 according to each study criteria; (3) serum and plasma adipokines measured using enzyme-linked immunosorbent assay (ELISA) or Magnetic Luminex assay; (4) human studies only; and (5) studies published in English, German, French, or Romanian.

Exclusion criteria were as follows: (1) abstracts published without a full-text article, literature reviews, systemic reviews, meta-analyses, editorials, letters to the editor, conference abstracts, case reports, practice guidelines and commentaries; and (2) experimental studies.

Risk of bias assessment in individual studies

We used the Newcastle-Ottawa Scale (NOS) quality assessment tool to evaluate the included studies [15]. We applied two tools for cross-sectional and cohort studies. In order to assess the quality of the included studies, a “star system” was used. The stars were obtained by evaluating the comparability, study selection, and outcome of interest. The NOS uses a scoring system ranged from 0 to 9 stars. Studies ranked with a score from 0-2 were considered of poor quality, while a score greater than 7 was considered of high quality. The bias assessment was evaluated by two authors (L.B. and N.A.) independently, while in case of disagreement, a consensus was achieved through discussion.

Summary measures and synthesis of results

The mean difference (MD) of adipokine levels, including adiponectin and leptin was the principal summary outcome. The analyzed data of the systematic review and meta-analysis were performed using R with Metafor package (OpenMeta [Analyst]) [16,17]. We used $\chi 2$ based Q-test and I^2 to evaluate between-study heterogeneity. In

studies that reported medians and interquartile ranges, we calculated the mean and standard deviation (SD), as well as combined groups when necessary. Furthermore, we used the random-effects model and MD for the analysis of the estimated total effect size. According to the extracted data present in the included studies, we conducted subgroup analyses including adipokine levels according to COVID-19 severity, in addition to COVID-19 patients vs. controls. Statistical significance was considered as a p value < 0.05. The data from each study were described as the estimated MD with 95% CI.

Results

General results

The primary search yielded 220 articles (PubMed = 68 articles, Embase = 149 articles, Scopus Library = 3 articles) as illustrated in figure 1. A total of 60 studies were detected as duplicates and withdrawn. Subsequently, we retained 182 articles that were evaluated according to the inclusion and exclusion criteria by the screening of titles and abstracts for eligibility. Screening identified the following results: (1) letters/editorials (n = 20), (2) conference abstracts (n = 8), (3) studies conducted on animals (n = 8), (4) reviews (n = 49), (5) irrelevant studies (n = 64), (6) case report (n = 1). A total of 10 articles were sought for retrieval, out of which 1 full-text article was not retrieved (the authors were contacted by email, but no feedback was received), while the other was excluded as it evaluated adipokine receptor expression rather than adipokine serum or plasma levels [18]. Moreover, in order to perform a comprehensive meta-analysis including the data from currently published literature, authors of studies assessing adipokines in COVID-19 patients but who did not report their levels were contacted by email. However, we did not receive the requested values from contacted authors. The total number of articles included in our qualitative synthesis was 8, while 5 were included in our quantitative analysis [4,11,19-24].

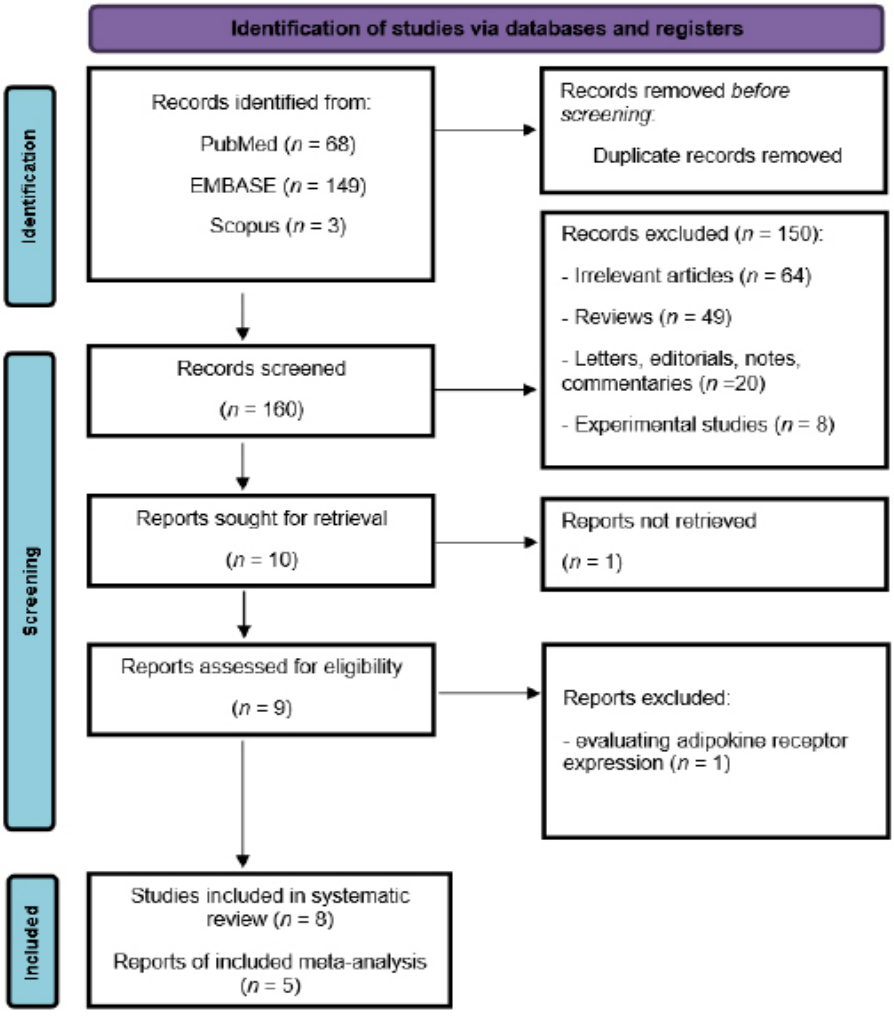

Figure 1. PRISMA flow diagram 2020 outlining the identification, screening, and inclusion phases of our syst.

Study characteristics

A summary of the main characteristics of included studies is shown in table I. This systematic review and meta-analysis included a total number of 473 individuals. Seven out of eight studies reported sex distribution involving a total of 434 subjects, where females counted for 155 participants (35.71%), and males were 279 participants (64.28%). However, one study did not report the gender distribution [24]. Moreover, a total of 322 COVID-19 patients (68.08%) were included.

All included studies were of observational study design. Four studies were undertaken in Europe (Italy – *n* = 2, France – *n* = 1, Netherlands – *n* = 1), one study in Asia (China – *n* = 1), and three studies in the USA (*n* = 3).

Table I. Studies evaluating adipokines in COVID-19.

First Author / Year / Country	Study Design	Study Characteristics	Main Findings
Van der Voort P. et al./ 2020 / Netherlands	Cross-sectional study	• **Total Subjects:** 39 (COVID-19 – 31; Controls – 8) • **COVID-19:** 31 (79.49%) • **Mean age (years):** - • **COVID-19 diagnosis:** - • **Gender (males):** - • **BMI:** 31 (24.8-48.4) • **Adipokines**: Leptin • **Adipokines measurement method:** ELISA • **Serum Leptin levels (µg/mL**): COVID-19 21.2 (6.0; 85.2); Controls 5.6 (2.4; 8.2	The mean leptin level was 21.2 (6.0–85.2) vs 5.6 (2.4–8.2) ug/L for SARS-CoV-2 and controls respectively (p 1⁄4 0.0007) Leptin levels did differ between COVID-19 pat and the control group significantly. Leptin levels. SARS-CoV-2 patients with a similar BMI to control patients had higher levels of serum leptin.
Wang J. et al. / 2021/ China	Observational study	• **Total Subjects:** 43 (mild:21; Severe:10; Controls: 12) • **COVID-19:** 31 (72.09%) • **Mean age (years):** COVID-19: 52.3 ± 17.9; Controls: 48 ± 15.7 • **COVID-19 diagnosis:** RT-PCR • **Gender (males):** COVID-19 20; Controls: 6 • **BMI:** Healthy donor: 23.8 ± 2.9; COVID-19 patients: 24.1 ± 2.8; Mild: 23.69 ± 2.7; Severe: 25.3 ± 2.6 • **Adipokines**: Leptin • **Adipokines measurement method:** ELISA **Serum Leptin levels (µg/mL**): -	The study found that leptin levels were significantly increased in both mild and severe COVID-19 patients compared with those in healthy controls. Furthermore, these leptin levels in severe patients were significantly higher than those in mild patients
Meilzish M. et al. / 2021/ USA	Cross-sectional cohort study	• **Total Subjects:** 85 (COVID-19 – 49; Controls – 13; longitudinal cohort 23) • **COVID-19:** 49 (57.65%) • **Mean age (years):** COVID-19 ICU: 62 Non-ICU: 69; Controls 48; • **COVID-19 diagnosis:** PCR • **Gender (males):** 38 • **BMI:** Obesity BMI >30 kg/m^2: Non-ICU: 4 (44); ICU-transfer: 4 (57); ICU-admit: 3 (43) • **Adipokines**: Resistin, Adiponectin, • **Adipokines measurement method:** ELISA **Serum Restistin levels (µg/mL**): -	Among patients initially admitted to non-ICU units (non-ICU, ICU-Transfer), those with day 1 RETN levels above the median value were much more likely to later require ICU transfer. Moreover, patients with day 1 RETN levels above the median were significantly less likely to survive.
Kearns S. et al. /2021/ USA	Observational study	• **Total Subjects:** 29 (COVID-19 – 12; Controls – 17) • **COVID-19:** 12 (41.38%) • **Mean age (years):** COVID-19: 61.3; non-COVID-19: 61.4 • **COVID-19 diagnosis:** RealTime SARS- CoV- 2 assay (Abbott Molecular Inc.; Des Plaines, IL**)** • **Gender (males):** 18 (62.07%) • **BMI:** Healthy controls: 23.8 ± 2.9; COVID-19: 24.1 ± 2.8 • **Adipokines**: Adiponectin, adipsin, resistin • **Adipokines measurement method:** Milliplex Human Adipokine Magnetic Bead Panel 1 kit (Millipore Sigma; Burlington, Massachusetts) • **Plasma Adiponectin levels (geometric mean ratio):** 0: 2,87(2,58); 24: 0,09(0,75); 72: 4,41(3,73) • **Plasma Adipsin levels (geometric mean ratio):** 0: 1,08(1,81); 24: 0,84(1,44); 72: 1,15(1,82) • **Plasma Resistin levels (geometric mean ratio):** 0:1,94(1,84); 24: 1,05(0,98); 72: 0,81(0,76)	COVID-19 respiratory failure was associated with significantly reduced adiponectin levels. Alternatively, it could suggest that patients with low adiponectin levels are more prone to develop COVID-19 respiratory failure. Conversely, adiponectin levels were significantly lower in the COVID-19 cohort over the 72 hr of evaluation (p = 0.003), as well as being significantly lower at Hour 0 (p = 0.031) and Hour 72 (p = 0.004). Adiponectin levels remained significantly lower in those with COVID-19

Table I. Studies evaluating adipokines in COVID-19 (continuation).

First Author / Year / Country	Study Design	Study Characteristics	Main Findings
Blot M. et al. / 2021/ France	Prospective observational single-center study	• **Total Subjects:** 63 (COVID-19 –27; Controls – 36) • **COVID-19**:27 (57,14%) • **Median age IQR (years):** non-COVID-19: 67.5 (63-76.5); COVID-19: 64 (57-71) • **COVID-19 diagnosis:** RT-PCR • **Gender (males):** 46 (73.02%) • **BMI:** Non-COVID-19: 27 (25-33); COVID-19: 31 (27-34) • **Adipokines:** Adiponectin, Leptin; Adiponectin/Leptin Ratio • **Adipokines measurement method:** Magnetic Luminex assay • **Plasma Leptin levels (ng/mL):** COVID-19 15,0 ± 19,1; Controls 18,5 ± 27,5 • **Plasma Adiponectin levels (ng/mL): COVID**-19 4090 ± 2745; Controls 5338 ± 4024 • **Plasma Adiponectin/Leptin Ratio levels:** COVID-19 1.2 ±2 .9; Controls 1.5 ± 2.1	COVID-19 patients displayed similar plasma concentrations of leptin and adiponectin as compared to nonCOVID-19 patients. Adiponectin levels were inversely correlated with BMI. Plasma concentrations of leptin and Adiponectin were not significantly correlated with baseline severity.
Caterino M et al. / 2021/ Italy	Cohort study	• **Total Subjects:** 53 (COVID-19 – 53) • **COVID-19:** 53 (100%); mild – 20; moderate – 16; severe – 17 • **Median age (years):** 58 • **COVID-19 diagnosis:** - • **Gender (males):** 37 (70%) • **BMI:** - • **Adipokines:** • **Adipokines measurement method:** ELISA • **Serum Adiponectin Levels (µg/mL):** T0: mild COVID-19 17.2 ± 3.14; moderate COVID-19 19.3 ± 4.92; severe COVID-19 21.4 ± 2.67 T1: mild COVID-19 15.6 ± 1.38; moderate COVID-19 19.0 ± 0.57; severe COVID-19 19.8 ± 2.57	No significant correlation was found between Adiponectin values at addmision and after 7 days in COVID-19 patients, divided according to mild, moderate, and severe cases.
Filippo L et al. / 2021/ Italy	Prospective observational study	• **Total Subjects:** 60 (COVID-19 -60) mild -11; moderate • **COVID-19:** 60 (100%) mild - 11; moderate - 25; severe - 24 • **Mean age (years):** 59.3; mild – 46.3 (34.2; 51.3) moderate – 59.5 (52.1; 67.5); severe - 62.7 (57.7;70.3) • **COVID-19 diagnosis:** - • **Gender (males):** 41 (68,33%) • **BMI:** 27 (25.0-30.5) • **Adipokines:** Leptin; Adiponectin; Adpn/Lep ratio • **Adipokines measurement method:** ELISA • **Serum Adiponectin levels (µg/mL):** Mild -COVID-19 4.1(2.7; 14.7); moderate -COVID-19 24.3(3.4; 39.2); severe- COVID-19 20.8(3.5; 29.7) • **Serum Leptin levels (ng/mL):** Mild -COVID-19 6.7 (3.8; 7.9) moderate -COVID-19 5.2 (1.3;10.2); severe-COVID-19 5.6 (2.9;13.3) • **Serum Adiponectin/Leptin Ratio:** Mild -COVID-19 1.2 (0.5; 2.0); mild -COVID-19 5.0(1.6; 11.2); severe -Covid-19 2.1 (1.0;1.6)	Adiponectin and leptin levels did not differ across severity groups, but patients with moderate severity had the highest Adpn/Lep ratio. Leptin significantly correlated with BMI.
Reiterer M. et al. / 2021/ USA	Retrospective Cohort study	• **Total Subjects:** 101 (COVID-19 - 59; Controls – 42) • **COVID-19:** 59 (58,42%) C-A- n=23; C-A+ n=19; C+A+ n=59 • **Mean age (years):** 59 • **COVID-19 diagnosis:** RT-PCR • **Gender (male):** 73 • **BMI:** Obesity: Overall: 1,067 (24%); Non-ARDS patients: 772 (23%); ARDS patients: 295 (28%) • **Adipokines:** Adiponectin; Resistin; Leptin; Adipsin; PAI-1Adipokine; Adiponectin/ leptin Ratio • **Adipokines measurement method:** ELISA • **Plasma panel Adiponectin levels (pg/mL):** Adiponectin C-A- 42,554,215 (23,948,160; 65,120,377); C-A+ 48,762,329 (28,519,584; 75,307,999); C+A+19,876,250 (11,564,496; 33,947,040) • **Plasma panel Leptin levels (pg/mL):** Leptin C-A- 1,921 (430; 4,443); C-A+ 732 (489; 2,339); C+A+ 3,226 (1,186; 8,931) • **Plasma panel Resistin levels (pg/mL):** C-A- 76,852 (42,781; 198,669); C-A+ 160,149 (103,462; 214,909); C+A+56,684 (37,270; 0.073,109,979) • **Plasma panel Adiponectin/leptin Ratio levels:** C-A- 41,070 (31,77;58,728); C-A+ 45,221 (20,483;67,740); C+A+ 61,900 (41,035; 99,918)	Adiponectin was found to be decreased by 50-60% in the serum of patients suffering from severe COVID-19, compared to ICU controls with or without ARD. The adiponectin-leptin ratio, was severely depressed in COVID-19 patients by 10- 34 fold compared to ARDS+ and 6-fold compared to ARDS-control patients. Resistin did not differ between the three groups.

Adpn/Lep ratio – Adiponectin leptin ratio; C+A+ COVID-19 patient with ARDS; C-A- control patient without ARDS; C-A+ Control patient with ARDS; COVID-19 – Coronavirus disease of 2019;
T0 – At admission; T1 – After 7 days from admission; 0- at admission; 24- after 24 hours; 72- after 72 hours.

Adiponectin levels according to COVID-19 disease severity

Adiponectin levels have been evaluated according to COVID-19 disease severity in several studies. Figure 2 summarizes the obtained meta-analysis results regarding adiponectin levels in mild vs. moderate, mild vs. severe, and moderate vs. severe COVID-19.

Adiponectin: Mild vs. moderate COVID-19

Serum adiponectin levels were evaluated in a total of two studies comparing COVID-19 patients with a mild vs. moderate course of the disease [11,20]. The pooled analysis of included studies assessing serum adiponectin levels in mild vs. moderate COVID-19 showed an overall MD of -7.117 (95% CI -19.546 − 5.313). Substantial heterogeneity was reported with an I^2 = 74.62% and a p-value of 0.047.

Adiponectin: Mild vs. severe COVID-19

Serum adiponectin levels were evaluated in a total of two studies comparing COVID-19 patients with a mild vs. severe course of the disease [11,19,20]. The pooled analysis of included studies found that the mean adiponectin levels were higher in severe compared to mild cases, (MD mild – severe = -5.734 [95% CI -11.215 − -0.252]). Moderate heterogeneity was reported with an I^2 = 42.1% and a p-value of 0.189.

Adiponectin: Moderate vs. severe COVID-19

Serum adiponectin levels were evaluated in a total of two studies comparing COVID-19 patients with a moderate vs. severe course of the disease [11,19,20]. The pooled analysis of the studies found that the mean adiponectin levels were higher in severe compared to moderate cases, (MD moderate – severe = -1.846 [95% CI -4.516 − 0.824]). Non-significant heterogeneity was reported with an I^2 = 0% and p-value of 0.356.

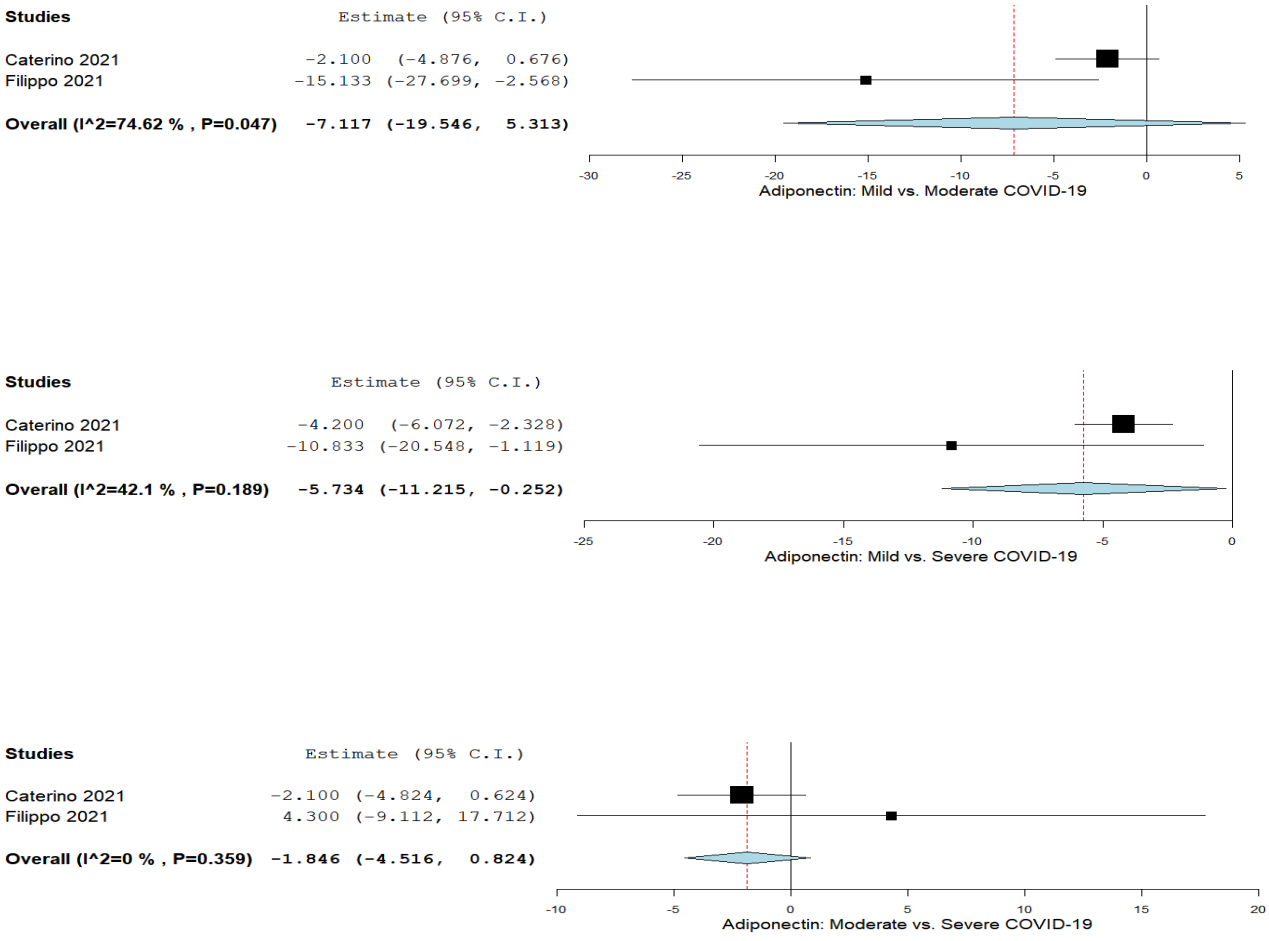

Figure 2. Serum adiponectin levels according to COVID-19 disease severity.

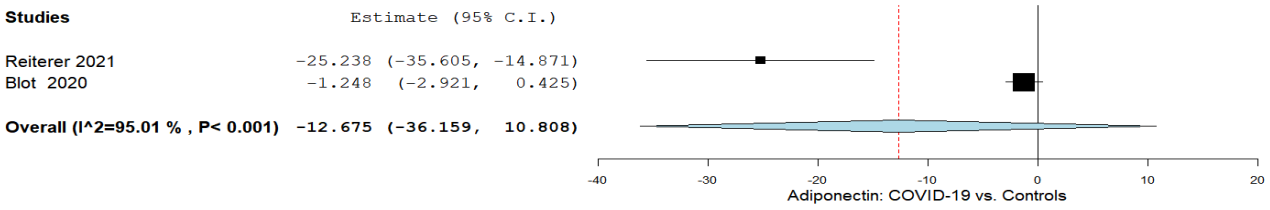

Figure 3. Serum adiponectin levels in COVID-19 patients vs. controls.

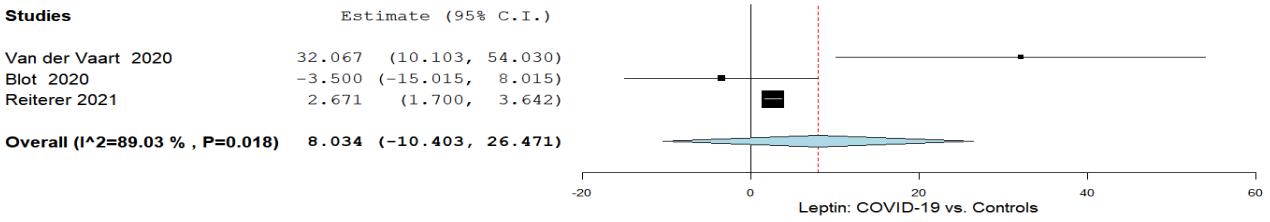

Figure 4. Serum leptin levels in COVID-19 patients vs. controls.

Adiponectin COVID-19 vs. Controls

Serum adiponectin levels were evaluated in a total of two studies comparing COVID-19 patients vs. controls, as outlined in figure 3 [19,21]. The pooled analysis found that the mean adiponectin levels were higher in controls compared to COVID-19 cases, (MD controls - COVID-19 =-12.675 [95% CI -36.159 − 10.808]). Considerable heterogeneity was reported with an I^2 = 95.01% and p-value of 0.001.

Leptin COVID-19 vs. Controls

Serum leptin levels were evaluated in a total of 3 studies comparing COVID-19 patients vs. controls, as presented in figure 4 [4,19,21]. The pooled analysis found that the mean leptin levels were higher in COVID-19 cases compared to controls, (MD COVID-19 - controls =8.034 [95% CI -10.403 − 26.471]). Considerable heterogeneity was reported with an I^2 = 89.03% and p-value of 0.018.

Quality assessment

The NOS was used to evaluate the methodological quality of the included eligible studies, as rendered in Supplementary Tables I and II. The NOS for cross-sectional studies was used in a total of 7 studies [4,11,19,21-24], while the NOS for cohort studies was used in 1 study [20,22]. We found several issues regarding the presence of bias in the evaluated studies. Overall, 6 studies received a score greater than 7 and a rating of "good quality" [4,11,21,22,24,25]. In total, all evaluated studies had a clearly formulated research question and objective. All studies used clearly defined measures of exposure that are considered reliable and valid besides 1 cohort study [20] and 2 cross-sectional studies [4,11]. All studies assessed the ascertainment of exposure in a satisfactory fashion [4,11,19-24].

Discussion

Since the SARS-CoV-2 outbreak in 2019, humanity is trying to minimize its impact on the healthcare systems worldwide [25]. In this review, we attempted to evaluate one of the possible mechanisms of the disease. As several studies demonstrated that obesity could be associated with a worse COVID-19 prognosis and disease severity, the association between several adipokines and COVID-19 has also been assessed lately [19,24,26]. A better understanding of such mechanisms and pathways can help us develop noninvasive markers to predict disease severity and prognosis, as well as identify potential targeted therapeutic strategies. Therefore, we conducted the first systematic review and meta-analysis, to the best of our knowledge, evaluating the effects of several adipokines such as adiponectin, leptin, resistin, and adipsin in COVID-19. Sufficient studies were found to perform a quantitative assessment for adiponectin (COVID-19 vs. controls and disease severity) and leptin (COVID-19 vs. controls). We have showed that patients

with severe COVID-19 present significantly higher adiponectin levels compared with mild COVID-19. However, no significant mean differences were found in adiponectin levels between mild vs. moderate COVID-19 patients, COVID-19 patients vs. controls, and leptin levels in COVID-19 patients vs. controls.

In this review, we included 8 observational studies in our qualitative synthesis, out of which 5 were included in our quantitative synthesis, with a total population of 473 participants. Similar gender distribution was found among our included studies, possibly due to gender matching of subjects in several included studies. COVID-19 patients were almost 68% of the studied population. This can be explained by the fact that several studies included only COVID-19 patients and assessed adipokine levels according to disease severity without involving a control group or including a small control group. Studies were conducted in several continents, including Asia, Europe, and the Americas. However, some races and ethnicities have not been studied yet, limiting the generalizability of our results. This can be attributed to differences in adipokine levels that were reported according to race and ethnicity [27]. Future studies involving different racial and ethnic groups are necessary in order to confirm our obtained results.

Despite the current literature including several assessed adipokines in COVID-19 patients, including adiponectin, leptin, resistin, and adipsin, due to limited available data, we were unable to evaluate all of the mentioned adipokines in our quantitative synthesis. We found sufficient data to perform a quantitative analysis only in adiponectin and leptin. Moreover, subgroup analysis evaluating adipokine levels according to COVID-19 severity was only possible for adiponectin. However, due to the limited number of published studies, we were able to assess only two or three studies for each association. Thus, we recommend further studies evaluating more adipokines in COVID-19 patients vs. controls, as well as in COVID-19 severity.

Several adipokines have been demonstrated to be associated with obesity [28]. Nevertheless, we were not able to conduct a subgroup analysis, evaluating adipokine levels in COVID-19 patients according to BMI, due to the very limited published data. Blot et al. showed that while there was no statistically significant difference between patients with severe COVID-19 pneumonia and immunocompetent patients with severe pneumonia who were not infected with COVID-19, plasma concentrations of leptin and adiponectin were, respectively, positively and negatively correlated with BMI and glucose metabolism [19]. Leptin levels were significantly associated with BMI in COVID-19 subjects, according to Filippo et al., but there was no apparent disparity related to obesity between COVID-19 patients with mild, moderate, and severe disease [11]. This was also noted by Meizlish et al., who found no significant difference in obesity between ICU and non-ICU COVID-19 patients [22]. Furthermore, Kearns et al. observed that the BMI of severe COVID-19 patients was significantly higher than that of the total COVID-19 group, even though there was no statistically significant difference between the total COVID-19 group and the mild COVID-19 group [24]. However, Reiterer et al. showed that obesity was linked to a higher risk of developing ARDS [21]. According to Wang et al., there was no discernible difference in BMI between the COVID-19 total group and the mild COVID-19 group, while the severe COVID-19 group had a considerably higher BMI [23]. Intriguingly, Van der Voort et al. found that SARS-CoV-2 patients had greater serum leptin levels than control patients while having similar BMIs [4]. In a recently conducted study by Flikweert et al., visfatin levels were higher in COVID-19 critical patients compared to mild, severe, and non-COVID-19 ICU patients [29]. Moreover, adiponectin levels were reduced, but resistin levels were increased in critical and severe patients compared with patients who did not need to be hospitalized.

The current literature describes the alleged correlation between a hyperinflammatory state and the severe course of a COVID-19 infection in obese patients [4]. Adipose tissue, especially visceral fat, is known to be a pro-inflammatory factor by influencing the angiotensin 2 system [30], while secreting adipokines such as adiponectin and leptin [4,31,32]. In a mechanistic sense, the SARS-CoV-2 virus causes inflammation, potentially through signaling from molecules associated with cellular damage and an excessive release of immune signaling molecules known as cytokines, resulting in insulin resistance and a phenomenon called the adiponectin paradox [33]. This paradox links metabolic dysfunction to chronic diseases. Therefore, inhibiting the inflammatory signaling associated with adiponectin may be beneficial in preventing the adiponectin paradox. A more comprehensive understanding of this process could lead to the development of new therapies for both SARS-CoV-2 and its associated chronic disorders.

Leptin plays a role in angiogenesis, hematopoiesis, adaptive and innate immunity [4,31], it also influences gastric motility [34], the olfactory epithelium [35] and hunger sensation [23]. All these systems seem to be affected in severe COVID-19 infections [4]. In our meta-analysis, we could not support this allegation, as we did not find a significant relation between leptin levels in COVID-19 patients versus control groups. However, these results are to be considered with caution due to the limited number of published studies that were included in our meta-analysis. We were not able to perform subgroup analysis assessing leptin levels according to COVID-19

severity. Further research is needed to evaluate this potential association.

Adiponectin, on the other hand, seems to be an anti-inflammatory and insulin-sensitizing peptide hormone, which is reduced in obese patients [11,36] and could explain the hyperinflammatory state in overweight patients with COVID-19. However, interestingly, we found a significant increase in adiponectin levels in severe COVID-19 patients, compared to the mild form of the disease. However, we did not find a significant mean difference in adiponectin levels in mild vs. moderate, moderate vs. severe COVID-19 forms, or COVID-19 vs. control subjects.

As the COVID-19 pandemic continues, various variants of the SARS-CoV-2 have emerged worldwide. Among these variants, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) have gained widespread attention due to their potential to increase the transmissibility of the virus, severity of infection, and ability to evade vaccine-generated antibodies. Studies have shown that the Beta variant is associated with a 2.16 (95% CI: 1.19–3.14) times higher risk of hospitalization, 2.23 (95% CI: 1.31–3.15) times higher risk of severe illness, and a 1.50 (95% CI: 1.26–1.74) times higher risk of mortality compared to the wild-type virus [37]. Similarly, the Delta variant is associated with a 2.08 (95% CI: 1.77–2.39) times higher risk of hospitalization, 3.35 (95% CI: 2.5–4.2) times higher risk of severe illness, and a 2.33 (95% CI: 1.45–3.21) times higher risk of mortality compared to the wild-type virus [37].

Several risk factors for COVID-19 infection have been studied. Data from the National Vital Statistics System indicate that age is the primary risk factor for severe outcomes related to COVID-19, with the risk of severe outcomes increasing with age. The COVID-19 pandemic has also highlighted disparities in COVID-19 illnesses, hospitalizations, and deaths based on race, ethnicity, and socioeconomic status. A study by Palaiodimos et al. including 200 hospitalized patients with COVID-19 found that a minority-predominant population, severe obesity, older age, and male sex were independently associated with higher in-hospital mortality and generally worse in-hospital outcomes [38]. In addition, the most significant genetic risk factor for severe COVID-19 is located on chromosome 3 and is inherited from Neanderthals [39]. This risk-associated DNA segment influences the expression of several chemokine receptors, including CCR5, a co-receptor for HIV that is down-regulated in carriers of the COVID-19 risk haplotype. Interestingly, carriers of the risk variant have a lower risk of HIV infection by approximately 27% [39].

Recent studies indicate that COVID-19 vaccines may have both protective and therapeutic effects against long COVID [40]. Meta-analytic results show that receiving at least one vaccine dose was associated with a protective effect against long COVID [41]. Protection against SARS-CoV-2 infection and symptomatic COVID-19 decreased over time but remained high against severe COVID-19 [42]. However, little is currently known about the relationship between adipokines and humoral immune responses after vaccination with SARS-CoV-2 vaccines. One study found that adipokines were associated with antibody immune responses in individuals younger than 60 years who received dual BNT162b2 vaccination [43]. Interestingly, individuals who had previously been infected with COVID-19 had higher levels of adiponectin and leptin, which were correlated with higher levels of IL-6 and IL-10 [43]. This may indicate polarization towards Th2 responses, which boost humoral immune responses and delay or prevent cellular immunity.

Our systematic review and meta-analysis has multiple limitations that need to be mentioned. Our qualitative and quantitative synthesis only includes a small number of studies, due to the limited published data. Small study numbers in some of the subgroup analyses in our review suggest underpowered analyses and less robust results, which should be taken into consideration. All included studies in our review are of observational design. Therefore, we cannot confirm or negate causality between the evaluated adipokines and COVID-19. We reported that several evaluated studies presented methodological flaws. Some studies did not clearly report the evaluation method used to confirm COVID-19 infection. If less accurate methods of diagnosing SARS-Cov-2, like rapid tests, then negative patients may be in fact positive, and if the negative patients are in the control group, then a directional classification bias would arise, diminishing the observed differences. Rapid tests have, however, high specificities, and thus their positive results are highly likely to really have the disease. The studies that did not select patients with negative results from the rapid tests are improbable to be impacted by the diagnosis method. Some studies did not correct for confounding factors, and this means more residual confounding is likely to be present in the results. Besides, there was reported heterogeneity among studies results, and also with respect to BMI, where adipose tissue may have a significant impact on adipokine levels, taking into consideration that obesity is a risk factor for COVID-19 and several patients included in the evaluated studies were obese [44]. Another problem is the timing. The moment when adipokines were sampled might influence the results:if the adipokines have a dynamic change during the COVID-19 progression; if the samples were taken at different moments for different subjects or groups in different studies, then this can modify the results in any direction. Therefore, results have to be interpreted with caution.

Nevertheless, our study has several important

strengths. The importance of this study results from the significant global impact of SARS-CoV-2 and the urgency to find novel noninvasive techniques to predict disease severity, establish therapeutic strategies, evaluate prognosis, and monitor disease progression. Therefore, we conducted this systemic review and meta-analysis evaluating adipokine levels in COVID-19. We believe that our review identifies several gaps in evidence that require further assessment in future studies while summarizing the current literature in a nonbiased manner. In addition, we conducted the search strategy in a comprehensive manner using several electronic databases, allowing us to properly evaluate the studied topic. To the best of our knowledge, we conducted the first systemic review and meta-analysis evaluating the effects of adipokines in COVID-19. In general, research indicates that adipokines may be involved in pneumonia, including COVID-19 pneumonia. However, further investigation is needed to fully comprehend their role in the disease and how they could be used as targets for therapeutic interventions.

Conclusions and future directions

Serum adiponectin levels were found to be significantly increased in severe COVID-19 patients compared to milder forms of the disease. However, no significant mean difference was found between adiponectin levels in mild vs. moderate COVID-19 or moderate vs. severe COVID-19, as well as serum adiponectin and leptin levels in COVID-19 vs. controls. Nevertheless, obtained results should be interpreted with caution due to the imperfect methodological quality of the included studies.

Future studies with larger sample sizes, more adipokines, and better methodological quality involving different races and ethnic groups remain necessary. Such associations, if found to be significant in future research, could allow the use of potential adipokines in evaluating the prognosis and severity of COVID-19 through a noninvasive manner, as well as help in developing targeted therapies for this disease.

References

1. Johns Hopkins University of Medicine. Coronavirus Research Center. Available at: https://coronavirus.jhu.edu/map.html.
2. da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, Farias de Oliveira T, Campos Alcântara R, Monteiro Arnozo G, et al. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr 2021;133:377-382.
3. Sattar N, Valabhji J. Obesity as a Risk Factor for Severe COVID-19: Summary of the Best Evidence and Implications for Health Care. Curr Obes Rep. 2021;10:282-289.
4. van der Voort PHJ, Moser J, Zandstra DF, Muller Kobold AC, Knoester M, Calkhoven CF, et al. Leptin levels in SARS-CoV-2 infection related respiratory failure: A cross-sectional study and a pathophysiological framework on the role of fat tissue. Heliyon 2020;6:e04696.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069.
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-481.
7. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020;382:2012-2022.
8. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care. 2003;26:2442-2450.
9. Aghili SMM, Ebrahimpur M, Arjmand B, Shadman Z, Pejman Sani M, Qorbani M, et al. Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis. Int J Obes (Lond). 2021;45:998-1016.
10. Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: Findings from the CORONADO study and other recent reports. Diabetes Metab. 2020;46:265-271.
11. Di Filippo L, De Lorenzo R, Sciorati C, Capobianco A, Lorè NI, Giustina A, et al. Adiponectin to leptin ratio reflects inflammatory burden and survival in COVID-19. Diabetes Metab. 2021;47:101268.
12. Fioravanti A, Porcelli B, Terzuoli L, Bacarelli MR, Tenti S, Cheleschi S. Tocilizumab, Adipokines and Severe Complications of COVID-19. Clin Drug Investig 2020;40:891-892.
13. Maurya R, Sebastian P, Namdeo M, Devender M, Gertler A. COVID-19 Severity in Obesity: Leptin and Inflammatory Cytokine Interplay in the Link Between High Morbidity and Mortality. Front Immunol. 2021;12:649359.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-605.
16. Made Tirta I, Anggraeni D. The development of web-based graphical user interface for unified modeling data with multi (correlated) responses. Journal of Physics: Conference Series. 2018;1008:012003.
17. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software,

2010:36:48. doi: 10.18637/jss.v036.i03

18. Li XT, Zhang MW, Zhang ZZ, Cao YD, Liu XY, Miao R, et al. Abnormal apelin-ACE2 and SGLT2 signaling contribute to adverse cardiorenal injury in patients with COVID-19. Int J Cardiol. 2021;336:123-129.
19. Blot M, David Masson, Nguyen M, Bourredjem A; LYMPHONIE Study Group; Binquet C, et al. Are adipokines the missing link between obesity, immune response, and outcomes in severe COVID-19? Int J Obes (Lond). 2021;45:2126-2131.
20. Caterino M, Gelzo M, Sol S, Fedele R, Annunziata A, Calabrese C, et al. Dysregulation of lipid metabolism and pathological inflammation in patients with COVID-19. Sci Rep. 2021; 11:2941.
21. Reiterer M, Rajan M, Gómez-Banoy N, Lau JD, Gomez-Escobar LG, Gilani A, et al. Hyperglycemia in Acute COVID-19 is Characterized by Adipose Tissue Dysfunction and Insulin Resistance. medRxiv [Preprint]. 2021:2021.03.21.21254072.
22. Meizlish ML, Pine AB, Bishai JD, Goshua G, Nadelmann ER, Simonov M, et al. A neutrophil activation signature predicts critical illness and mortality in COVID-19. Blood Adv. 2021;5:1164-1177.
23. Wang J, Xu Y, Zhang X, Wang S, Peng Z, Guo J, et al. Leptin correlates with monocytes activation and severe condition in COVID-19 patients. J Leukoc Biol. 2021;110:9-20.
24. Kearns SM, Ahern KW, Patrie JT, Horton WB, Harris TE, Kadl A. Reduced adiponectin levels in patients with COVID-19 acute respiratory failure: A case-control study. Physiol Rep 2021;9:e14843.
25. Haileamlak A. The impact of COVID-19 on health and health systems. Ethiop J Health Sci. 2021;31:1073-1074.
26. Liu B, Qi Z. Authors' Reply to: Tocilizumab, Adipokines and Severe Complications of COVID-19. Clin Drug Investig. 2020;40:893-895.
27. Khan UI, Wang D, Sowers MR, Mancuso P, Everson-Rose SA, Scherer PE, et al. Race-ethnic differences in adipokine levels: the Study of Women's Health Across the Nation (SWAN). Metabolism. 2012;61:1261-1269.
28. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications. Int J Mol Sci. 2020;21:3570.
29. Flikweert AW, Kobold ACM, van der Sar-van der Brugge S, Heeringa P, Rodenhuis-Zybert IA, Bijzet J, et al. Circulating adipokine levels and COVID-19 severity in hospitalized patients. Int J Obes (Lond). 2023;47:126-137.
30. Yvan-Charvet L, Quignard-Boulangé A. Role of adipose tissue renin–angiotensin system in metabolic and inflammatory diseases associated with obesity. Kidney Int. 2011;79:162-168.
31. Alti D, Sambamurthy C, Kalangi SK. Emergence of Leptin in Infection and Immunity: Scope and Challenges in Vaccines Formulation. Front Cell Infect Microbiol. 2018;8:147.
32. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85-97.
33. Ho G, Ali A, Takamatsu Y, Wada R, Masliah E, Hashimoto M. Diabetes, inflammation, and the adiponectin paradox: Therapeutic targets in SARS-CoV-2. Drug Discov Today. 2021;26:2036-2044.
34. Yarandi SS, Hebbar G, Sauer CG, Cole CR, Ziegler TR. Diverse roles of leptin in the gastrointestinal tract: modulation of motility, absorption, growth, and inflammation. Nutrition. 2011;27:269-275.
35. Savigner A, Duchamp-Viret P, Grosmaitre X, Chaput M, Garcia S, Ma M, et al. Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. J Neurophysiol. 2009;101:2898-2906.
36. Nguyen TMD. Adiponectin: Role in Physiology and Pathophysiology. Int J Prev Med. 2020;11:136.
37. Lin L, Liu Y, Tang X, He D. The Disease Severity and Clinical Outcomes of the SARS-CoV-2 Variants of Concern. Front Public Health. 2021;9:775224.
38. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.
39. Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature. 2020;587:610-612.
40. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. BMJ Med. 2023;2:e000385.
41. Ceban F, Kulzhabayeva D, Rodrigues NB, Di Vincenzo JD, Gill H, Subramaniapillai M, et al. COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis. Brain Behav Immun. 2023;111:211-229.
42. Ssentongo P, Ssentongo AE, Voleti N, Groff D, Sun A, Ba DM, et al. SARS-CoV-2 vaccine effectiveness against infection, symptomatic and severe COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2022;22:439.
43. Pavel-Tanasa M, Constantinescu D, Cianga CM, Anisie E, Mereuta AI, Tuchilus CG, et al. Adipokines, and not vitamin D, associate with antibody immune responses following dual BNT162b2 vaccination within individuals younger than 60 years. Front Immunol. 2022;13:1000006.
44. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA Jr, Liang L. Association of obesity and its genetic predisposition with the risk of severe COVID-19: Analysis of population-based cohort data. Metabolism. 2020;112:154345.

Supplementary Tables

Supplementary Table I. The Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies.

Study	Selection				Comparability	Outcome			Score
	Representa-tiveness of the exposed (*)	Selection of non-Cohort (*)	Ascertainment of exposure (*)	Outcome of interest not presented at the start (*)	(**)	Assessment of outcome (*)	Was the follow-up long enough (*)	Adequacy of the follow-up (*)	
Caterino et al. 2021	-	*	*	*	-	*	-	*	5

Supplementary Table II. The Newcastle-Ottawa Scale (NOS) for assessing the quality of cross-sectional studies.

Study	Selection				Comparability	Outcome		Score
	Sample representativeness	Sample size	Non-Respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	
Van der Voort et al. 2020	*	*	*	*	-	**	*	7
Blot et al. 2021	-	-	*	**	-	**	*	6
Filippo et al. 2021	*	-	*	**	-	**	*	7
Kearns et al. 2021	*	*	*	**	**	**	*	10
Meizlish et al. 2021	*	*	*	**	*	**	*	9
Wang et al. 2021	-	*	*	**	*	**	*	8
Reiterer et al. 2021	*	-	*	**	**	**	*	9