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Dyslipidemia, obesity and coronavirus disease (Covid-19)

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Dyslipidemia, obesity and coronavirus disease 2019 (Covid-19)

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Editorial: Dyslipidemia, obesity and coronavirus disease 2019 (COVID-19)

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Editorial on the Research Topic
Dyslipidemia, obesity and coronavirus disease 2019 (COVID-19)

Almost 3 years after its emergence in December 2019, coronavirus disease 2019 (COVID-19) still causes a significant burden on health, economic, and social aspects of life (1). While some SARS-CoV-2 infections appear as mild upper respiratory symptoms and may be self-limiting, there is still a notable number of patients who require hospitalizations and intensive treatment following progression into more severe cases, varying from simple lower respiratory tract infections to acute respiratory distress syndrome (ARDS) or multi-organ failure (MOF). Identification of risk factors for severe disease and special populations at risk are important to help mitigate the pandemic, reducing the morbidity and mortality from COVID-19 (2). Among the comorbidities which are associated with severe COVID-19, dyslipidemia and obesity may become important as these two have often been under-looked. Moreover, the role of drugs commonly used in patients with dyslipidemia and obesity has gathered a lot of attention because they may potentially alter the course of COVID-19. This Research Topic, focused on the role of dyslipidemia, obesity, and their related disorders in the course of COVID-19, consists of a set of eight papers—three original research articles, two brief research reports, two mini-reviews, and one review article.

Countries around the world have implemented strategies to control the COVID-19 pandemic, such as social distancing, lockdown, isolation, quarantine, and so on. However, these measures are increasingly impacting all classes of people with sheer frustration, especially university students, with far-reaching effects on their mental, physical, and social lives. A cross-sectional study conducted in Bangladesh has revealed that during the COVID-19 lockdown, there is an increased prevalence of overweight/obesity among university students due to changes in eating behaviors and reduction in physical activities (Hossain et al.). This is concerning because studies

have shown that obesity may increase the risk of mortality and severe COVID-19 complications, including ICU admission and intubation. People with higher body mass index (BMI) also tend to be more vulnerable to SARS-CoV-2 infections (Vassilopoulou et al.). Not only BMI, but also the percentage of body fat (%BF) and visceral fat (%VF) were significantly associated with poor outcomes from COVID-19 (Stevanovic et al.). Therefore, measurement of BMI, %BF, and %VF through bioelectrical impedance analysis (BIA) may serve as a potential tool to predict which patients are at high risk of developing poor COVID-19 outcomes.

People with obesity are suggested to focus on lowering their body weight to achieve a normal BMI target. One of the non-pharmacological treatments which can be offered is dietary changes. Among several available dietary patterns, the ketogenic diet may give benefit not only for healthy subjects but also patients with respiratory diseases, including SARS-CoV-2 infection (Gangitano et al.). This beneficial effect has been attributed to the anti-inflammatory, anti-viral, and weight-reducing effects of a ketogenic diet, which therefore may be considered in obese patients as a preventive measure for COVID-19.

The management of obesity should not only focus on BMI. Several vitamin and mineral concentrations may be altered in people with obesity. The presence of obesity and higher visceral fat content is related to a higher incidence of vitamin D deficiency, probably because of vitamin D sequestration into adipose tissue. A higher proportion of patients with obesity have low vitamin D levels ($<$20 ng/ml or $<$50 nmol/L). Both low vitamin D levels and vitamin D deficiency ($\leq$12 ng/ml or $<$30 nmol/L) are associated with higher mortality from COVID-19 independent of BMI, partly mediated by the effect of vitamin D on markers of disease severity, such as D-dimer and ultrasensitive cardiac troponins (Vanegas-Cedillo et al.). Besides vitamin D, magnesium may also be associated with obesity. Magnesium is known to have roles in glucose, insulin, and energy homeostasis through its activity on pancreatic beta-cells, increasing glucose uptake from peripheral tissue, and modulation of the inflammatory process. Magnesium deficiency is frequently observed in obese people. A cross-sectional study in Iran has shown that high magnesium intake in COVID-19 patients was associated with lower levels of several inflammatory biomarkers, such as C-reactive proteins (CRP) and erythrocyte sedimentation rate (ESR; Nouri-Majd et al.). Patients with higher dietary magnesium intake may also have lower odds of developing severe COVID-19 conditions compared to those with low magnesium intake. We can conclude from these studies that vitamin D and magnesium supplementation should be considered to reduce the burden of COVID-19 in those who are deficient, especially people with obesity.

When treating people with obesity, we must also consider its related disorders such as dyslipidemia. Dyslipidemia has been repeatedly shown to be associated with the risk and severity of COVID-19, and one of the mainstay therapies in patients with dyslipidemia is a statin. Studies have shown that statins are generally safe for COVID-19 patients and may even offer therapeutical benefits, owing to their antiviral, immunomodulatory, anti-thrombosis, and anti-oxidative effects (Liu et al.). The use of statins should therefore not be discontinued during COVID-19, especially in those who have dyslipidemia where the benefit from statins will be more prominent. Besides statins, studies have shown that L-carnitine has a key role in fatty acid metabolism and could function as an additional agent to improve dyslipidemia. Using the Mendelian randomization method, it has been demonstrated that carnitine might have a protective role on COVID-19, and carnitine might be a therapy that is worth further exploration in clinical trials (Li et al.).

We hope that the studies under our Research Topic collection may give us a better understanding of COVID-19 and its relationship with both obesity and dyslipidemia. Their results enable better risk stratification, earlier detection, and a more holistic approach for these populations. These publications also show how this field is in an emergent phase and how much research is needed in this area of knowledge.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Carnitine and COVID-19 Susceptibility and Severity: A Mendelian Randomization Study

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Background: Carnitine, a potential substitute or supplementation for dexamethasone, might protect against COVID-19 based on its molecular functions. However, the correlation between carnitine and COVID-19 has not been explored yet, and whether there exists causation is unknown.

Methods: A two-sample Mendelian randomization (MR) analysis was conducted to explore the causal relationship between carnitine level and COVID-19. Significant single nucleotide polymorphisms from genome-wide association study on carnitine ($N = 7,824$) were utilized as exposure instruments, and summary statistics of the susceptibility ($N = 1,467,264$), severity ($N = 714,592$) and hospitalization ($N = 1,887,658$) of COVID-19 were utilized as the outcome. The causal relationship was evaluated by multiplicative random effects inverse variance weighted (IVW) method, and further verified by another three MR methods including MR Egger, weighted median, and weighted mode, as well as extensive sensitivity analyses.

Results: Genetically determined one standard deviation increase in carnitine amount was associated with lower susceptibility (OR: 0.38, 95% CI: 0.19–0.74, *P*: 4.77E−03) of COVID-19. Carnitine amount was also associated with lower severity and hospitalization of COVID-19 using another three MR methods, though the association was not significant using the IVW method but showed the same direction of effect. The results were robust under all sensitivity analyses.

Conclusions: A genetic predisposition to high carnitine levels might reduce the susceptibility and severity of COVID-19. These results provide better understandings on the role of carnitine in the COVID-19 pathogenesis, and facilitate novel therapeutic targets for COVID-19 in future clinical trials.

Keywords: carnitine, COVID-19, protective, Mendelian randomization (MR), causation

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world and led to substantial morbidity and mortality (1). Global efforts have been invested in treatment options concerning the pandemic, but no effective therapy has been found so far. Although a

number of drugs have been put in clinical trials, evidence from a large living systematic review and network meta-analysis suggested that only glucocorticoids, such as dexamethasone, probably reduce mortality and mechanical ventilation in patients with severe COVID-19 (2). Coincidentally, L-carnitine, a potentially promising substitute for dexamethasone, has been found to mimic some of the biological activities of glucocorticoids, especially immunomodulation, while with less side effect (3). L-Carnitine was shown to have antiviral and anti-inflammatory effects in HCV and HIV infections (4, 5). Meanwhile, L-carnitine is an essential nutrient with a major role in cellular energy production (6), while abnormal lipid metabolism is a common symptom of COIVD-19 (7). Furthermore, earlier investigations have suggested that L-carnitine might be a supportive and therapeutic option to prevent the harm caused by COVID-19 based on its molecular functions (8, 9). However, the correlation between carnitine and COVID-19 has not been explored yet, and whether there exists causation is still unknown.

Here, to evaluate the correlation between carnitine level in the body and risk of COVID-19, we employed the two-sample Mendelian randomization (MR) approach to explore the causal role of carnitine on COVID-19 (10, 11). As a result, we found that higher carnitine level was causally associated with decreased susceptibility and severity of COVID-19.

METHODS

Datasets

We obtained summary statistics for carnitine from a previous genome-wide association study (GWAS) on human metabolic traits (12). This study analyzed the genetic influences on human blood metabolites using the GWAS method in 7,824 European-ancestry participants. The study design like the collection of samples, quality control procedures and imputation methods have been described in the original publication. Single nucleotide polymorphisms (SNP) that passed the generally accepted genome-wide significance threshold ($P < 5E{-}08$) for carnitine were chosen as instrument variants. None of the significant SNPs for carnitine was suggestively associated with body mass index (BMI) searched in GWAS Catalog (13) ($P < 1E{-}05$). Then we clumped instrument variables based on 1,000 Genomes Project linkage disequilibrium (LD) structure, and kept index SNPs ($R^2 < 0.001$ with any other associated SNP within 10 Mb) with the lowest *P*-value. The final summary information for each instrument was shown in **Supplementary Tables 1–3**.

Summary statistics of COVID-19 susceptibility and severity for the selected instrument variables were obtained from the COVID-19 Host Genetics Initiative (14) (https://www.covid19hg.org/, Release 5). GWAS on COVID-19 susceptibility involved 42,557 patients with COVID-19 and 1,424,707 population controls, while GWAS on COVID-19 severity involved 5,582 very severe respiratory confirmed patients with COVID-19 and 709,010 population controls. Meanwhile, we also analyzed GWAS on COVID-19 hospitalization involving 9,986 hospitalized patients with COVID-19 and 1,877,672 population controls, since hospitalized patients with COVID-19 were mostly with severe symptoms. Harmonization was undertaken to rule out strand mismatches and ensure alignment of SNP effect sizes. The final summary information was shown in **Supplementary Tables 1–3**.

The current study only utilized publicly available summarized results from published genome-wide association studies. No individual-level data were involved.

Mendelian Randomization Analysis

We hypothesized that carnitine level as a protective factor could causally decrease the risk of COVID-19, and the following assumptions were satisfied: the genetic variants used as instrumental variables are associated with carnitine level; the genetic variants are not associated with any confounders; the genetic variants are associated with COVID-19 through carnitine level (namely horizontal pleiotropy should not be present).

To comprehensively evaluate the causative effect of carnitine on COVID-19, we performed the two-sample MR analysis using the random effects inverse variance weighted (IVW) method, which is most widely used in MR studies and could provide robust causal estimates under the absence of directional pleiotropy. Meanwhile, we verified the results using another three MR methods, namely Mendelian randomization Egger regression, weighted median and weighted mode. To evaluate potential violations of the model assumptions in the MR analysis, we further conducted comprehensive sensitivity analyses. Cochran's Q test was computed to check heterogeneity across the individual causal effects. Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis was conducted to detect outlier instrument (15). MR-Egger regression was performed to evaluate the directional pleiotropy of instruments (16). To evaluate the strength of each instrument variable, we computed the F-statistic of each SNP as described by a previous study (17). Leave-one-out analysis was conducted with the inverse variance weighted method to assess the influence of individual variants on the observed association. And reverse causal inference was conducted to explore whether COVID-19 susceptibility and severity have a causal impact on carnitine level with Steiger analysis (18). The statistical power calculated at http://cnsgenomics.com/shiny/mRnd/ is sufficient (1.00) assuming the true causal OR of carnitine on COVID-19 is 0.8, given the involved sample size and the significance level α as 0.05 (19). The main statistical analyses were conducted using the R package TwoSampleMR 0.5.5 (20).

RESULTS

We analyzed the role of carnitine on COVID-19 using the two-sample MR approach. Results showed that each one standard deviation (1-SD) increase in carnitine amount was associated with a lower risk of COVID-19 (OR: 0.38, 95% CI:

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MR, Mendelian randomization; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; LD, linkage disequilibrium; SD, standard deviation; IVW, inverse variance weighted.

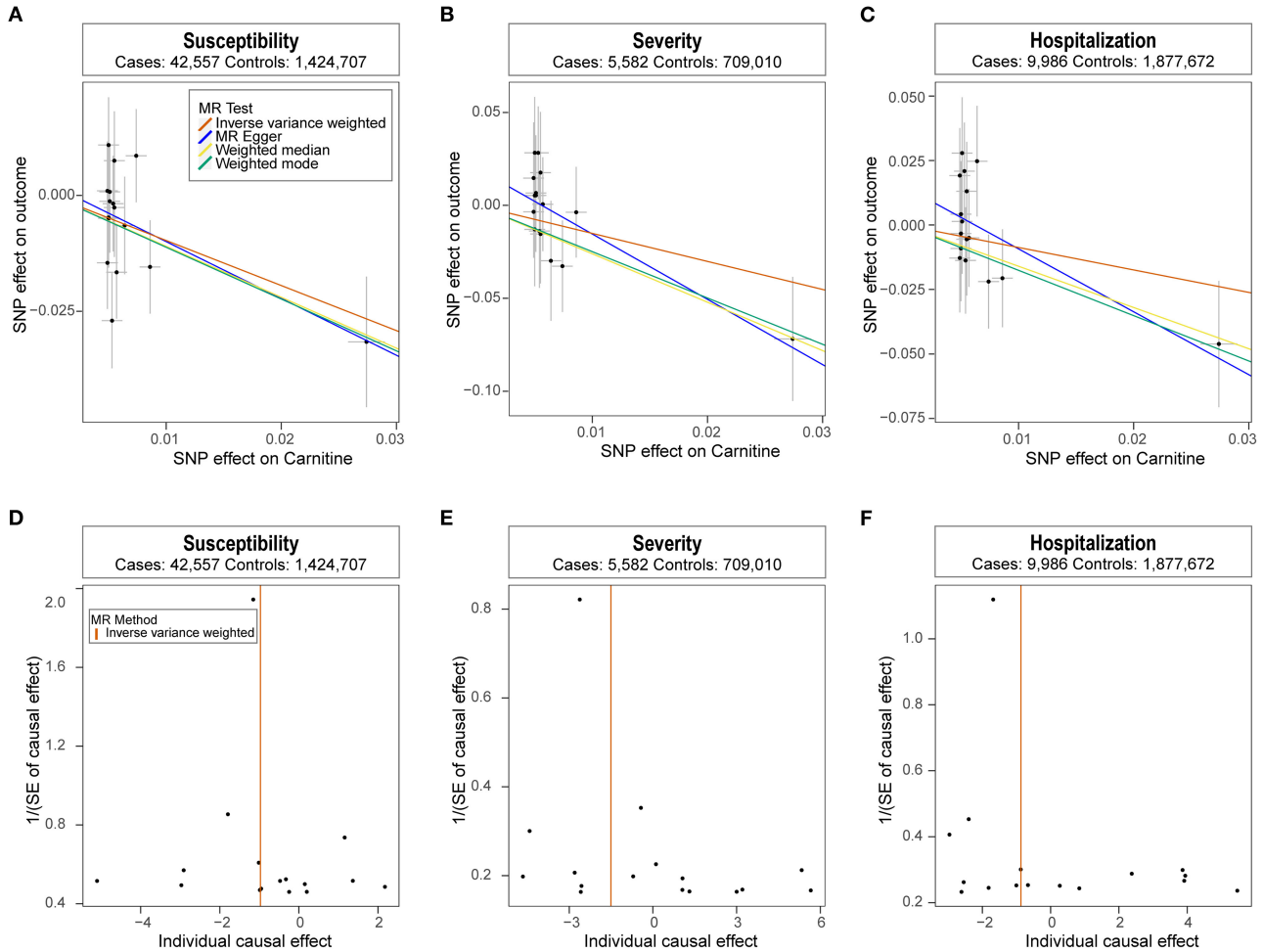

FIGURE 1 | Mendelian randomization analysis results. **(A-C)** Scatter plot of single nucleotide polymorphism (SNP) potential effects on carnitine level vs. COVID-19. The 95% CI for the effect size on COVID-19 is shown as vertical lines, while the 95% CI for the effect size on carnitine level is shown as horizontal lines. The slope of fitted lines represents the estimated Mendelian randomization (MR) effect per method. **(D-F)** Forest plot showing results from the Mendelian randomization analysis to evaluate potential causal associations between carnitine and COVID-19. Estimates are per 1 standard deviation (SD) increase in the trait.

TABLE 1 | Heterogeneity and horizontal pleiotropy analyses results.

Outcome	Heterogeneity			Horizontal pleiotropy		
	IVW Q	IVW Q df	IVW *P* value	Egger intercept	SE	*P*
COVID-19 susceptibility	14.49	15	0.49	0.0023	0.01	0.65
COVID-19 severity	7.80	15	0.93	0.020	0.01	0.14
COVID-19 hospitalization	11.27	15	0.73	0.015	0.01	0.11

IVW, inverse variance weighted; Q, Cochran's Q test estimate; df, Cochran's Q test degrees of freedom; SE, standard error.

0.19∼0.74, P: 4.77E−03), and the results were verified using the weighed median and weighted mode methods (**Figure 1A**). Meanwhile, higher carnitine amount was associated with lower severity and hospitalization of COVID-19 using three MR methods, though such association was not significant using the IVW method (**Figures 1B,C**). The funnel plot displays symmetric pattern of effect size variation around the point estimate (**Figures 1D–F**).

Next, we performed extensive sensitivity analyses to validate the causal association between carnitine and COVID-19. No heterogeneity of effects was detected using Cochran's Q test (**Table 1**). The F statistics of all the instrument variables were above 10 (ranging from 29 to 293), indicating the absence of weakness in the selected instruments. The intercept of MR-Egger is not significantly deviated from zero, suggesting no apparent horizontal pleiotropy (**Table 1**). Directionality examination by

Steiger analysis did not suggest a violation of the causality either. The MR-PRESSO analysis detected no potential instrumental outlier at the nominal significance level of 0.05. The leave-one-out results suggest that the causal effect was not driven by single instrumental variable (**Supplementary Figures 1**, **2**).

DISCUSSION

Recent studies have proposed the potential role of carnitine as therapy options for COVID-19, but whether there is any correlation between them has not been explored yet. Meanwhile, unmeasured confounding factors in clinical studies can potentially bias the association evidence, as is a common criticism inherent to observational studies. Here, based on results from comprehensive two-sample MR analyses, we demonstrated that higher carnitine level was causally associated with decreased susceptibility and severity of COVID-19.

Carnitine occurs in two forms known as D-carnitine and L-carnitine, and only L-carnitine is biologically active in the body (21). L-carnitine is an essential carrier for long-chain fatty acids from the cytosol through the inner mitochondrial membrane into the matrix, where β-oxidation takes place (22). Although no studies have investigated the correlation between carnitine and COVID-19, previous research on carnitine might provide some insights from molecular aspects of why L-carnitine might protect against COVID-19. L-carnitine plays an important role in fatty acid metabolism and could act as an adjuvant agent in the improvement of dyslipidemia (23). L-carnitine was previously found to increase high-density lipoprotein and lower triglyceride, total cholesterol and low-density cholesterol (23), while dyslipidemia has been shown to be associated with the risk and severity of COVID-19 repeatedly (7, 24). In addition, as an effective antioxidant, L-carnitine was involved in modulating the mechanisms of the immune system and the nervous system (8), and could inhibit the expression of inflammatory factors (25, 26). Antioxidants supplementation has been recommended in therapeutic strategies against COVID-19 (27), since antioxidant therapy could improve oxygenation rates, glutathione levels and strengthen the immune response (28). Meanwhile, anti-inflammatory drugs were suggested to potentially inhibit a key enzyme in the replication and transcription of SARS-CoV-2 (29), and anti-inflammatory agents have also been proposed as potential therapies for COVID-19 due to their prevention of cardiovascular events. Furthermore, L-carnitine plays a critical role in energy production, as it transports long-chain fatty acids into the mitochondria so they can be oxidized to produce energy (30). More energy for the immune system means more immune cells can be produced to protect against infection from virus. Lastly, current evidence showed that severely ill patients with COVID-19 tend to have a high concentration of pro-inflammatory cytokines, such as IL-6, compared to those who are moderately ill, and the high level of cytokines also indicates a poor prognosis in COVID-19 (31). L-carnitine could suppress the production of pro-inflammatory cytokines by preventing the hyperosmolarity-induced oxidative stress (32), and thus might help prevent patients with COVID-19 from cytokine storm. Taken together, so many biological functions make L-carnitine a potential therapeutic option to protect against COVID-19. Unfortunately, no clinical or epidemiological studies have investigated the correlation between them. Here, using the MR approach, we clarified the protective role of carnitine on COVID-19 susceptibility and severity from a genetic perspective. Future clinical or functional studies could put importance to this, and further explore the role of carnitine in protecting against COVID-19.

Based on the Mendelian randomization results obtained from large-scale GWAS summary data, we demonstrated that carnitine might have a protective role on COVID-19, and carnitine might be a therapy which is worth further exploration in clinical trials. These results help better understand the role of carnitine on COVID-19, and will facilitate therapeutic drugs in future clinical trials.

STRENGTHS AND WEAKNESSES

The strength of our work is the Mendelian randomization method which could avoid confounding factors. And comprehensive sensitivity analyses guaranteed the reliability of the association. Meanwhile, current results have very important clinical implications. Up till now, global efforts were still invested in finding effective drugs for COVID-19. Our findings provided some guidance and new direction for future clinical trials. There were also some limitations to the current study. Though we identified a protective role of carnitine against COVID-19, the biological mechanism of this protection was still unclear. Further clinical and functional studies were necessary to clarify the effect of carnitine on COVID-19.

DATA AVAILABILITY STATEMENT

Summary statistics of carnitine could be found in http://mips.helmholtz-muenchen.de/proj/GWAS/gwas/index.php (ID: M15500). Summary statistics of COVID-19 could be downloaded from the COVID-19 Host Genetics Initiative (https://www.covid19hg.org/, release 5). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Code or algorithm used to generate results in this study are available from the corresponding authors on reasonable request.

AUTHOR CONTRIBUTIONS

CL and HS conceived the study. CL performed the statistical analyses and prepared the drafted manuscript. RO, QW, and HS contributed to writing and editing of the manuscript. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.780205/full#supplementary-material

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Ketogenic Diet for Obese COVID-19 Patients: Is Respiratory Disease a Contraindication? A Narrative Review of the Literature on Ketogenic Diet and Respiratory Function

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Morbid obese people are more likely to contract SARS-CoV-2 infection and its most severe complications, as need for mechanical ventilation. Ketogenic Diet (KD) is able to induce a fast weight loss preserving lean mass and is particularly interesting as a preventive measure in obese patients. Moreover, KD has anti-inflammatory and immune-modulating properties, which may help in preventing the cytokine storm in infected patients. Respiratory failure is actually considered a contraindication for VLCKD, a very-low calorie form of KD, but in the literature there are some data reporting beneficial effects on respiratory parameters from ketogenic and low-carbohydrate high-fat diets. KD may be helpful in reducing ventilatory requirements in respiratory patients, so it should be considered in specifically addressed clinical trials as an adjuvant therapy for obese patients infected with SARS-CoV-2.

Keywords: SARS-CoV-2, COVID-19, ketogenic diet, low-carbohydrate high-fat diet, obesity, VLCKD, respiratory disease, respiratory failure

INTRODUCTION

Obesity and COVID-19: An Emergency in the Emergency

The pandemic of SARS-CoV-2 infection has been challenging the world for over a year. Many risk factors for the development of Coronavirus 2019 disease (COVID-19) have been identified, and among these, metabolic diseases play a major role. Severe obesity is associated with a greater risk of severe COVID-19 (1, 2), ICU admission (1) and need for invasive mechanical ventilation (2, 3). Moreover, obesity may be a risk factor for developing COVID-19 at a younger age (4).

The current pandemic, with lockdown imposed to reduce the spread of the virus, is being leading to social distancing and long times at homes. The reduced possibility of exercising outdoor and the reduced spontaneous outdoor activity, the closure of the gyms and the swimming pools, together with the increase of stress-related disorders, may lead lots of people to a worsening of the weight excess and related comorbidities.

In the real-world setting, health professionals face many practical difficulties in treating obese patients. The excess of adipose tissue hinders the diagnosis with pulmonary ultrasound, delaying the intervention in advanced stages, with consequent higher mortality (5). In addition, the facilities for severely obese patients in the wards and intensive care units are lacking, so that interventional procedures as intubation may be slow and exert a negative impact on the prognosis of the patients (5). Moreover, obese people develop a reduced response to vaccinations (6) and central obesity has been recently associated with lower antibody titres in response to COVID-19 mRNA vaccine (7). Therefore, strategies aimed to reduce weight excess are mandatory.

Ketogenic Diet

Ketogenic diet is a dietary approach characterized by the consumption of a very low amount of carbohydrates, <50 g/day, with consequent development of ketosis. Fat is used as a primary source of energy, through the beta-oxidation of fatty acids. There are different kinds of ketogenic diets, defined on the basis of the macronutrient composition.

The low-carbohydrate high-fat ketogenic diet (LCHF) is characterized by the absence of a limit for calorie intake and fat intake, which is around 80–90% of total day energy. The low-calorie diet (LCD) provides among 800–1,200 Kcal/day and the very low-calorie diet (VLCD) is characterized by an even more strict calorie restriction (<800 Kcal/day), but they do not necessary lead to ketosis. The very-low calorie ketogenic diet (VLCKD) is characterized by a similar caloric restriction, but is always associated to ketosis, and is particularly interesting for the treatment of obesity and its comorbidities. In 2019 the Italian Society of Endocrinology released a consensus statement on the administration of VLCKD for the management of metabolic diseases (8), and respiratory failure was counted among the absolute contraindications. Anyhow, the use of KDs is recently spreading in new proposed fields of application, and some pathological features which are currently considered contraindications may benefit from its tailored use on the single patient, by experienced physicians (9).

The prescription of KD is currently under consideration in other pathologies than obesity, as headache (10), polycystic ovary syndrome (11), cancer (12), and neurodegenerative diseases (13, 14).

Ketogenic Diet and COVID-19

KD may be helpful in fighting COVID-19 through many mechanisms (see **Figure 1**). Severe SARS-CoV-2 infection determines a large innate immune response and ineffective adaptive immune response, that in some patients are associated with a cytokine storm and acute respiratory distress syndrome (15, 16). In fact, a virus infection with cytokine storm leads to an increase of reactive oxygen species and nitrogen species, which downregulate or inactivate many metabolic enzymes. Therefore, B and T cell proliferation is impaired, and cytokine production and cell death increase. These features of severe infections are related to reduced energy metabolism, altered redox state, oxidative damage and cell death, and may be at least partially dammed by KD. Ketone bodies have anti-inflammatory properties, since they are able to inhibit the NLRP3 inflammasome (17–19) and histone deacetylases (20), and consequently KD may reduce the risk of developing the cytokine storm, which is counted among the worst pathological features of COVID-19 (16, 21).

KD may be able to reduce viral replication and assembly (23), because many viruses, as varicella-zoster virus (24), hepatitis C (25) and cytomegalovirus (26), are dependent on fatty acid metabolism pathway for their replication cycle, and fatty acid synthesis is usually reduced in KD, thanks to the metabolic switch induced by the diet. The metabolic switch in the liver consists in passing from the glucogenic/glycolytic pathway (fed state) to the ketogenic pathway (fast state) (23).

Thanks to these antiviral and anti-inflammatory properties, Soliman et al. proposed the use of KD and intermittent fasting as a prophylactic and adjuvant therapy for SARS-CoV-2 infection (23). KD administration has also been hypothesized as a preventive measure in obese patients, in order to achieve a fast weight loss preserving lean mass, and a supportive care for obese COVID-19 patients (22, 27).

A recent animal model study with aged mice infected with a natural murine beta coronavirus observed that the ketogenesis led to an expansion of tissue protective γδ T cells, deactivation of NLRP3 inflammasome and remodeling of inflammatory monocytes in the lungs (28).

KD administration during lockdown may rise some concerns regarding the monitoring of patients. Anyway, KD has been administered to young patients and the studies showed good results in terms of safety and maintenance of ketosis. HFKD or modified Atkins diet (MAD; macronutrient ratio fat/carbohydrates+proteins usually of 1:1, and carbohydrates limited to 10–20 g/day) have been administered to children and young patients with uncontrolled seizures, and the authors nor the members of the International Ketogenic Diet Study Group, pediatric consensus group, reported any issues (34). Patients were followed with a mixed approach of in person meetings and telemedicine visits. Similarly, another study reported no major issues using teleassistance for the maintenance of patients on KD (34). Most parents of drug-resistant epilepsy pediatric patients were satisfied of the telemedicine approach (35, 36) and would recommend it regardless of the pandemic (36).

The administration of KD in infected patients is under evaluation in ongoing clinical trials, and the effects on respiratory function have not been clearly evaluated yet. A retrospective study showed a possible beneficial effect of an eucaloric ketogenic diet (carbohydrates < 30 g/day) in COVID-19 patients admitted to hospital, studying a sample of 34 patients compared with 68 patients receiving an isocaloric standard diet, but the authors did not assess respiratory function, except for the need for CPAP (Continuous Positive Airway Pressure), which did not differ among groups (37).

The aim of our study is to review the literature on ketogenic diets in respiratory patients, to consider the possibility of their safe use, from a respiratory point of view, in COVID-19 obese patients.

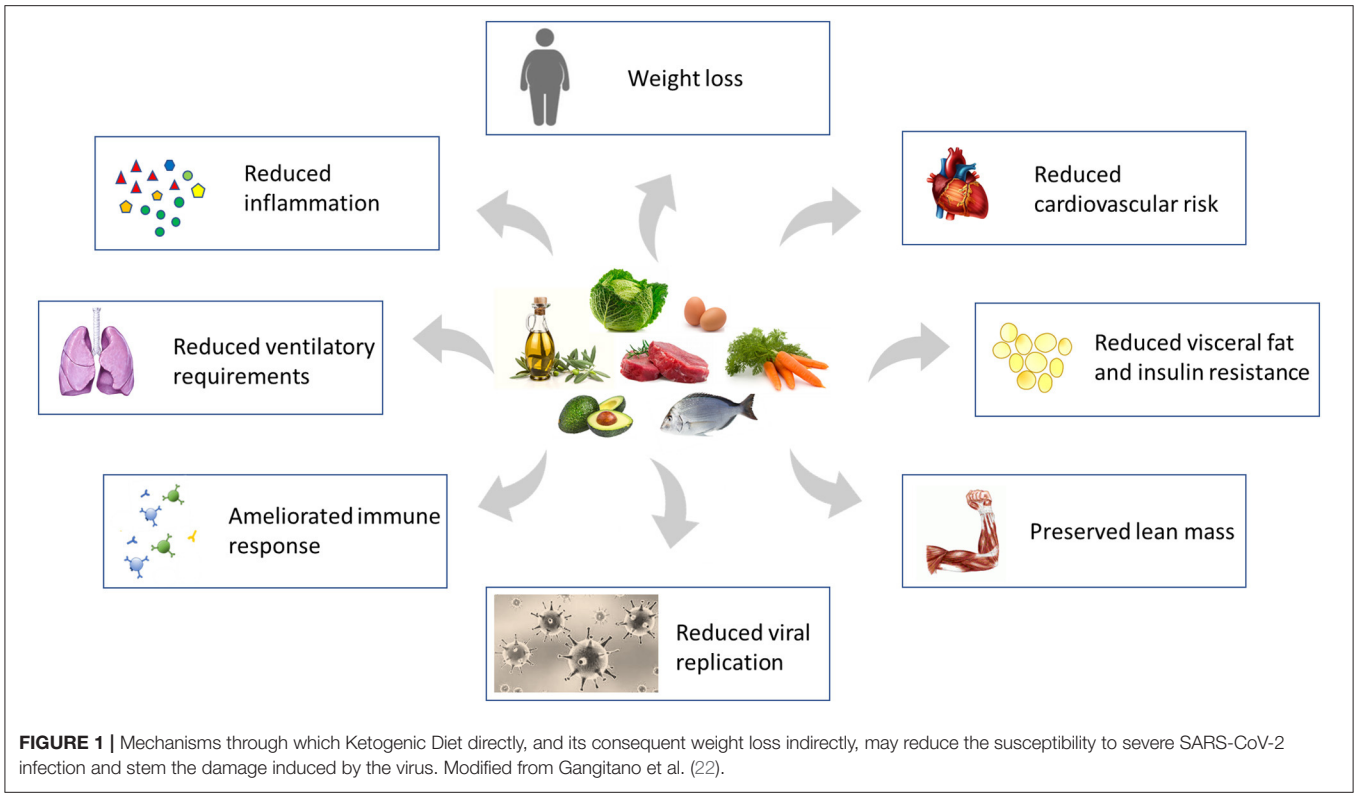

FIGURE 1 | Mechanisms through which Ketogenic Diet directly, and its consequent weight loss indirectly, may reduce the susceptibility to severe SARS-CoV-2 infection and stem the damage induced by the virus. Modified from Gangitano et al. (22).

LOW-CARBOHYDRATE HIGH-FAT DIETS AND RESPIRATORY FUNCTION IN HEALTHY SUBJECTS

On a pathophysiological basis, fat oxidation produces less carbon dioxide (CO_2) per amount of oxygen consumed compared to carbohydrates (CHO) (38), resulting in reduced ventilatory requirements. Therefore, ketogenic diet decreases metabolic carbon dioxide production for a given oxygen consumption, and may theoretically lead to a reduction in arterial carbon dioxide partial pressure ($PETCO_2$), pulmonary ventilation, and CO_2 body stores (29, 30).

Carbohydrates loads have been reported to precipitate respiratory failure in patients with lung compromise (39–42) since they may worse respiratory acidosis in patients unable to improve ventilation as a compensatory mechanism to excrete more CO_2 (39, 43).

Over time, some authors investigated the effects of low-carbohydrate high-fat diets or supplements on respiratory parameters in healthy subjects, and most of them reported beneficial effects (see **Table 1**). In the majority of studies we report below, patients were administered an amount of CHO that could possibly lead to ketosis, but the development of ketosis wasn't verified.

Rubini et al. (29) observed that a ketogenic diet (CHO < 30 g/day) administered for 20 days reduced $PETCO_2$ in 32 healthy subjects, without modifications in oxygen uptake, carbon dioxide production nor expired total ventilation, which may be related to a reduction in CO_2 body stores. Therefore, it may be beneficial for patients with high carbon dioxide arterial partial pressure due to respiratory insufficiency, because it lowers CO_2 levels without increasing respiratory muscle fatigue, with the consequent risk of respiratory failure on mechanical basis. Interestingly, the reduction of $PETCO_2$ was maintained even after the end of the diets, suggesting a long-term effect.

Similarly, Kwan et al. (30) observed that a ketogenic diet (50 g CHO/day) administered for 1 week to 6 healthy female subjects reduced arterial carbon dioxide tension, while resting ventilation and breathing frequency remained unchanged. Interestingly, pulmonary function tests showed an increase in peak expiratory flow rate and functional residual capacity respect to the baseline, respectively, by 5 and 10%.

Sue et al. (44) studied the effects of altering the composition of dietary fat and carbohydrate content on gas exchange, at rest and during exercise, on 8 healthy volunteers. At rest, the mean oxygen uptake did not differ, as did not the minute ventilation, while mean CO_2 output was significantly less on the low-carbohydrate high-fat diet (10% of calories from CHO), compared to the high-carbohydrate diet (70% of calories from CHO). This differences was smaller during exercise, probably because of the preferential use of glycogen stores from the muscle (44).

On the other hand, one study reported negative effects of a ketogenic diet. The administration of a low-carbohydrate high-fat ketogenic diet, providing 2,400 Kcal/day for 4 weeks in 17 healthy women (<25 g of CHO/day), was associated with an earlier muscle fatigue at higher intensities and during daily

TABLE 1 | Summary table of the interventional studies on the effects of low-carbohydrate dietary interventions (minimum 5 days of intervention) on ventilatory parameters and pulmonary function in spontaneously breathing patients.

References	Patients	Diet composition	Length of the dietary intervention	Ketosis	Effect on ventilatory and pulmonary function parameters
Rubini et al. (29)	32 healthy subjects	ketogenic diet (<30 g CHO/day, 848 Kcal) with phytoextracts, followed by low-carbohydrate no-ketogenic diet (80 g CHO/day, 938 Kcal) with phytoextracts, followed by Mediterranean diet (210 g CHO/day, 1,400 Kcal)	20 days of ketogenic diet, 20 days of low-carbohydrate non-ketogenic diet, 2 months of Mediterranean diet	Yes	- Reduced carbon dioxide end-tidal partial pressure - No significant change in oxygen uptake, carbon dioxide production, nor expired total ventilation
Kwan et al. (30)	6 healthy female subjects	low-carbohydrate diet (<50 g CHO/day), isoenergetic with the usual diet of each subject	1 week	Yes	- Reduced pressure of expired carbon dioxide; trend for reduction in carbon dioxide production - Peak expiratory flow rate and functional residual capacity increased respect to the baseline - No change in resting ventilation and breathing frequency
Angelillo et al. (31)	14 patients with COPD and chronic hypercapnia	liquid diets; low-carbohydrate high-fat (28% calories from CHO, 55% from fat), moderate-carbohydrate moderate-fat (53% calories from CHO and 30% from fat) and high-carbohydrate low-fat (74% calories from CHO, 9.4% from fat); caloric intake tailored on each patient's requirement	5 days for each diet, sequence of diets assigned randomly	No	- Lower CO_2 production and lower arterial pCO_2 with the low-carbohydrate diet - No differences in oxygen consumption - Amelioration of forced vital capacity and forced expiratory volume in 1 second (FEV_1) observed at the end of the administration of all diets - No change in respiratory frequency; trend for reduction in minute ventilation with the low-CHO diet
Tirlapur et al. (32)	8 clinically stable COPD patients with chronic hypercapnic respiratory failure; six obese and twi non-obese	Low-calorie low-carbohydrate diet (30 g CHO/day, 600 Kcal/day)	2–8 weeks	Not specifically evaluated	- Increased arterial oxygen tension and oxygen saturation - Reduced arterial carbon dioxide tension - Increased one-second forced expiratory volume and forced vital capacity - Reduction of nocturnal hypoxemic dips and apnoeic episodes
Kwan et al. (33)	8 clinically stable COPD patients with chronic hypercapnic respiratory failure; non-obese	2 diets isocaloric to the patients' usual diet (about 2,100 Kcal/day), and each containing 200 or 50 g of CHO/day; control diet with CHO intake around 280 g/day	1 week for each diet	No	- Both diets increased arterial oxygen tension and decreased arterial carbon dioxide tension respect to the control diet - The 50 g CHO diet compared to the 200 g CHO diet further reduced the arterial carbon dioxide tension - Carbon dioxide production and oxygen consumption did not change - No significant changes in pulmonary function tests - Amelioration of dyspnoea during the 50 g CHO diet

KD, Ketogenic Diet; CHO, carbohydrates; COPD, Chronic Obstructive Pulmonary Disease; CO_2, carbon dioxide.

life activities, probably because of the reduced glycogen stores in the muscle (45). However, a study on 7 well-trained male cyclists consuming a low-carbohydrate high-fat diet (15–82 g of CHO/day), for a long-time (at least the previous 8 months), showed that these athletes had a similar gluconeogenesis rate and reduced glycogenolysis respect to the 7 athletes fed with a mixed diet (46). These findings suggest that after a long-term adaptation to a low-carbohydrate high-fat diet, liver glycogen contributes to endogenous glucose production during exercise, and that glucose may be preferentially obtained from glycerol derived from lipolysis of intramuscular triglycerides (47), configuring an hypothetical difference among about subjects accustomed to a low-carbohydrate high-fat diet and "newbies."

LOW-CARBOHYDRATE HIGH-FAT DIETS AND RESPIRATORY FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

Many Chronic Obstructive Pulmonary Disease (COPD) patients experience hypercapnia and hypoxemia, therefore a nutritional approach that decreases carbon dioxide production, and consequently respiratory muscles work, is extremely interesting.

Some authors observed an improvement of ventilatory measurements in COPD hypercapnic patients after a low-carbohydrate high-fat diet. In a small sample of 14 patients

with chronic hypercapnia and COPD the administration of a low-carbohydrate diet (28% CHO) for 5 days, determined a trend of lower CO_2 production, lower arterial pCO_2, respect to moderate-carbohydrate moderate-fat diet and high-carbohydrate low-fat diet. An amelioration of forced vital capacity and forced expiratory volume in 1 s (FEV_1) were observed for all diets, which may reflect an increase in muscle strength (31). However, some recent papers observed that a KD did not improve muscle strength in healthy women (45) and in trained athletes (48, 49), so we may hypothesize that the amelioration in FEV_1, which was observed for all diets, was to be ascribed to the beneficial effects of the nutritional support rather than its composition. Also, we may speculate that the effect of the diet on muscle strength would be more evident in non-trained patients than in trained athletes.

Some authors studied the short-term alterations following the administration of a particular meal or supplement. Akrabawi et al. (38) enrolled 36 outpatients with COPD and administered a high-fat meal (55% calories from fat, 25 g of CHO) or a moderate fat meal (41% calories from fat, 35 g of CHO) and observed a higher CO_2 production and O_2 consumption in patients fed the moderate-fat meal in the early post-prandial time, probably reflecting the earlier absorption of the meal, and no difference for pulmonary function. A recent study on 60 low-body weight patients with COPD and elevated arterial carbon dioxide tension observed that the group administered a low-carbohydrate high-fat evening supplement with 50–75 g of CHO daily for 3 weeks had an overall improvement in ventilatory status, with decrease in VCO_2, $PaCO_2$, VO_2 and minute ventilation, and an increase of PaO_2 and FEV_1, respect to the group administered a traditional high-carbohydrate diet (60–70% CHO) (50). This confirms the importance of nutritional therapy in malnourished COPD patients, since it has a strong impact on respiratory muscle weakness, and the importance of its macronutrient composition.

Many studies on the effects of carbohydrate loads on respiratory parameters and physical performance in chronic obstructive lung disease patients report a detrimental effect of CHO. High-carbohydrate diets may result in increased CO_2 production and O_2 consumption in clinically stable COPD patients (39). Kuo et al. (39) studied 12 clinically stable COPD patients and 12 healthy controls after administering an isocaloric high-fat (55.2% fat and 28.1% CHO) or high-carbohydrate (31.5% fat and 54.5% CHO) liquid meal, and found that the high-fat diet had a small effect on gas exchange parameters and ventilation, while the high-carbohydrates diet resulted in a great increase of CO_2 production, O_2 consumption and minute ventilation in COPD patients. Efthimiou et al. (40) studied a small sample of 10 clinically stable patients with the 6 min walking test. They observed that the group administered CHO-rich drink experienced a reduced physical performance correlated to the increased CO_2 production and a perceived effort to breathe. Similar detrimental effects of CHO on walking and exercise performance were obtained in 18 patients with chronic airflow obstruction (41, 42). Increased CO_2 production and increased minute ventilation after a high-carbohydrate formula, administered for nighttime enteral feeding, were observed in 10 young adult patients with cystic fibrosis with moderate to advanced lung disease (51). On the contrary, a small study with 13 patients affected by stable airways disease fed a high-carbohydrate meal (480 ml of grape juice and three-fourths cup of sucrose) showed that 7 patients who retained carbon dioxide had an increase in PaO_2, probably reflecting the increased alveolar ventilation, and had not a significant increase in $PaCO_2$, therefore the authors conclude that most patients with chronic airways disease are able to tolerate the increased endogenous carbon dioxide load resulting from a meal high in carbohydrates (52).

LOW-CARBOHYDRATE HIGH-FAT DIETS, RESPIRATORY FAILURE AND MECHANICAL VENTILATION

Most patients with COPD and acute respiratory failure have marked reduction of body protein stores (53) and lower muscle concentrations of adenosine triphosphate and creatinine phosphate, and these factors may be an important determinant of respiratory failure (54). Moreover, critically ill patients are more responsive to changes in dietary composition than less critical ones (55).

Some authors suggest that a low-carbohydrate diet may be an effective tool to ameliorate respiratory failure (30, 32, 33).

A study on 8 clinically stable chronic hypercapnic respiratory failure patients with congestive heart failure showed that a very low-calorie ketogenic diet (600 Kcal/day, 30 g of CHO/day), administered for on average 1 month, was effective in ameliorating arterial oxygen tension and oxygen saturation, reducing arterial carbon dioxide tension, and ameliorating electrocardiographic abnormalities associated with hypoxiemia (32). These results were probably to be ascribed to the combined effect of diet composition and weight loss, and even two non-obese patients had beneficial effects from the diet.

Another study on 8 chronic hypercapnic respiratory failure patients administered 200 or 50 g of CHO daily for a week within an isocaloric diet, observed that the reduction in the CHO intake on both diets improved the general well-being of the patients, increased arterial oxygen tension and decreased arterial carbon dioxide tension. The 50 g CHO diet compared to the 200 g CHO diet further reduced the arterial carbon dioxide tension, suggesting that such a diet may be used in patients with intractable respiratory failure (33).

Regarding mechanically ventilated patients, in the literature there are some evidences of a beneficial effect of a low-carbohydrate high-fat diet (55–57). A study on 20 clinically stable ventilated patients showed that low-carbohydrate high-fat enteral feeding (55.2% fat, 28.1% carbohydrate) is able to reduce $PaCO_2$ levels and the time of mechanical ventilation (55). A recent study on 100 patients with type II respiratory failure, secondary to pulmonary disease requiring mechanical ventilation, showed a great improvement in arterial carbon dioxide tension and minute volume at weaning with the low-carbohydrate high-fat feeding (55.2% fat, 28.1% carbohydrate) (56). Interestingly, similarly to Al-Saady (55), this was highly significantly associated with less time spent on mechanical ventilation (56). On the other hand, a study on 32 patients requiring mechanical ventilation

reported no beneficial effects of a similar low-carbohydrate high-fat enteral nutrition (55.2% fat, 28.1% carbohydrate) in $PaCO_2$ levels during weaning from the ventilator, respect to a standard enteral nutrition (30% fat, 53.3% carbohydrate) (58). Another recent study on 51 critically ill ventilated children with pulmonary disease observed that the low-carbohydrate high-fat diet (30% carbohydrate, 50% fat) was effective in reducing carbon dioxide tension but did not reduce the duration or level of ventilatory support (59).

Similarly to healthy subjects and respiratory patients in outpatients conditions, the acute carbohydrate loading has detrimental effects on patients with acute respiratory distress (60, 61) and acute respiratory failure (43, 62, 63), acting as a precipitating factor.

Acute respiratory failure was reported in 3 patients under ventilatory support within hours after the beginning of total parenteral nutrition, probably due its high carbohydrate content. The substantial increase of the carbon dioxide production in these patients unable to increase their ventilatory response, led to development of hypercapnia and respiratory acidosis (43).

CONCLUSION AND FUTURE PERSPECTIVE

Ketogenic diet should be considered in severely obese people as a preventive measure for SARS-CoV-2 infection, in order to achieve a fast weight loss preserving lean mass. In addition, KD use may be hypothesized as an adjuvant therapy in obese infected patients.

Data obtained in respiratory patients, mainly lean, are indicative of the safety of low-carbohydrate high-fat diets in respiratory compromised patients, and some beneficial effects on respiratory parameters were recorded. KD administration may be helpful for obese patients with chronic hypercapnia, thanks to the reduced CO_2 production induced by the diet. Many respiratory patients are malnourished, and obese patients themselves are frequently sarcopenic, therefore an adequate protein supplementation is mandatory, since malnutrition may worsen the general prognosis. Many supplements for malnourished patients are rich in carbohydrates, and this is detrimental for their respiratory function, as extensively seen above. KD may be useful for obtaining an adequate protein intake, reducing the ventilatory requirements, the dyspnea and the risk of muscle fatigue. Anyhow, the studies are pretty old, diet administration quite short, samples relatively small, and ketosis not always addressed. In addition, we focused on chronic respiratory diseases, and not on acute infective respiratory illnesses, which may present other issues. Also active infections, in fact, are considered among the contraindications for VLCKD.

Anyway, KD has anti-inflammatory effects and may reduce the risk of cytokine storm, thanks to the anti-inflammatory effects of ketone bodies, and may have a direct anti-viral effect. Therefore, ketogenic diet may be an effective adjuvant therapy in obese non-critically ill COVID-19 patients, and may even be considered in respiratory lean patients. New focused clinical trials with adequate sample sizes, led by a multidisciplinary experienced team of pneumologists, endocrinologists and nutritionists, are needed to confirm the safety and the beneficial effects on ventilatory parameters of such approach in respiratory patients.

AUTHOR CONTRIBUTIONS

EG, LG, and CL: conceptualization. EG and RT: writing—original draft preparation. SM, AL, LG, and CL: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Serum Vitamin D Levels Are Associated With Increased COVID-19 Severity and Mortality Independent of Whole-Body and Visceral Adiposity

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Introduction: Coronavirus disease (COVID-19) is a global pandemic. Vitamin D deficiency has been associated with susceptibility to infectious disease. In this study, the association between COVID-19 outcomes and vitamin D levels in patients attending a COVID-19 reference center in Mexico City are examined.

Methods: Consecutive patients with confirmed COVID-19 were evaluated. All patients underwent clinical evaluation and follow-up, laboratory measurements and a thoracic computerized tomography, including the measurement of epicardial fat thickness. Low vitamin D was defined as levels <20 ng/ml (<50nmol/L) and deficient Vitamin D as a level ≤12 ng/ml (<30 nmol/L).

Results: Of the 551 patients included, low vitamin D levels were present in 45.6% and deficient levels in 10.9%. Deficient Vitamin D levels were associated with mortality (HR 2.11, 95%CI 1.24–3.58, $p = 0.006$) but not with critical COVID-19, adjusted for age, sex, body-mass index and epicardial fat. Using model-based causal mediation analyses the increased risk of COVID-19 mortality conferred by low vitamin D levels was partly mediated by its effect on D-dimer and cardiac ultrasensitive troponins. Notably, increased risk of COVID-19 mortality conferred by low vitamin D levels was independent of BMI and epicardial fat.

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Conclusion: Vitamin D deficiency (≤12 ng/ml or <30 nmol/L), is independently associated with COVID-19 mortality after adjustment for visceral fat (epicardial fat thickness). Low vitamin D may contribute to a pro-inflammatory and pro-thrombotic state, increasing the risk for adverse COVID-19 outcomes.

Keywords: Vitamin D, COVID-19, adipose tissue, severe COVID-19, SARS-CoV-2

INTRODUCTION

Coronavirus Disease (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused significant burden in healthcare systems world-wide. In Mexico, COVID-19 has caused a large number of deaths, primarily due to the large prevalence of cardio-metabolic diseases linked to adverse outcomes and additionally due to the impact of socio-demographic factors which impact healthcare access and quality of care across Mexico (1–4). SARS-CoV-2 spreads primarily by close contact with respiratory droplets from infected individuals and contaminated surfaces (5, 6). SARS-CoV-2 infects cells using the angiotensin converting enzyme-2 (ACE-2) receptor; infection can produce an interstitial pneumonia that may progress to acute respiratory distress syndrome (ARDS) and death (7, 8). COVID-19 severity has been shown to be modified by the presence of cardio-metabolic comorbidities as well as inflammatory markers which may reflect vascular or respiratory deterioration (9–12).

Vitamin D is a steroid hormone involved in essential physiological roles including preserving bone integrity, immunomodulation by stimulating innate immunity and tempering adaptive immunity, infectious disease prevention and cardiovascular health (13, 14). It also acts on the renin angiotensin aldosterone (RAAS) system, inhibiting the angiotensin converting enzyme [ACE (7)]. Several factors are known to influence vitamin D levels; lower levels are associated with ethnicity, variation in sun exposure due to higher latitudes, season, time of day, clothing, sunscreen use and skin pigmentation, age, lower sun exposure, obesity and chronic illnesses (15). Low levels of vitamin D have been associated with increased susceptibility to infectious disease, particularly respiratory tract infections. Several studies have explored the relationship between COVID-19 and vitamin D levels (16, 17); however, concerns regarding residual confounding and the lack of mechanistic interpretations for the association of low Vitamin D levels with adverse COVID-19 outcomes requires further studies. Overall, pooled evidence suggests that high Vitamin D levels have been associated with reduced risk of adverse COVID-19 outcomes, which may suggest a beneficial role for Vitamin D in COVID-19 (18). Nevertheless, evidence from randomized controlled trials have not shown benefit from Vitamin D supplementation in COVID-19 or other infections due to the high heterogeneity across studies and its systematic use requires further evaluation (19, 20).

The presence of obesity results in decreased bioavailability of vitamin D, which is probably related to sequestration into adipose tissue. Furthermore, higher visceral fat content has been shown to be related to a higher incidence of vitamin D deficiency (21, 22). Obesity and ethnicity are important risk factors for severe disease and are also known to modulate vitamin D levels. This may be particularly relevant in Mexico, where high rates of diabetes and obesity have been associated with an increased risk of severe COVID-19 (9). Here, we evaluated the association between COVID-19 outcomes and Vitamin D levels in patients attending a COVID-19 reference center in Mexico City. We aimed to identify determinants of Vitamin D levels in COVID-19 patients and develop causal-mediation models to propose mechanisms by which Vitamin D may lead to increased COVID-19 mortality.

METHODS

Study Population

This study included consecutive patients evaluated at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a COVID-19 reference center in Mexico City between 17th March and 31st May 2020 with complete vitamin D measurements at admission (10). Subjects were initially assessed at triage and required either ambulatory or in-hospital care for COVID-19 (confirmed with computerized tomography (CT) and/or via RT-qPCR test from nasopharyngeal swabs. At the time of this writing, the INCMNSZ was a reference center for COVID-19 patients, which attended primarily severe and critical cases of COVID-19 from Mexico City. All patients had moderate to severe disease as defined by National Institute of Health criteria (*Moderate Illness:* Evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on air. *Severe Illness:* SpO_2 <94% on air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%). Subjects underwent a chest CT, and a radiologist determined the degree of pulmonary parenchymal disease and assessed epicardial fat thickness as a proxy for visceral fat. In addition, a medical history, anthropometric measurements, and laboratory tests were obtained, including 25 hydroxy-vitamin D. The electronic files of each patient were reviewed to document the outcomes during hospitalization. All proceedings were approved by the research and ethics committee of the INCMNZ (Ref 3383) and informed consent was waived due to the nature of the study.

Laboratory and Clinical Measurements

Clinical variables and laboratory measures were obtained at the time of initial evaluation. Physical examination included:

weight, height, body mass index (BMI, calculated as weight in kilograms divided by squared height in meters), pulse oximeter saturation (SpO_2), respiratory rate (RR), temperature and arterial blood pressure (BP). Laboratory measurements included: full blood count and chemistry panel including liver function tests, C-reactive protein (CRP), fibrinogen, D-dimer, ferritin, troponin I (TPNI), erythrocyte sedimentation rate (ESR) and procalcitonin levels. The blood samples were processed in the central laboratory of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vitamin D (25-hydroxivitamin D) was measured by chemiluminescence using the Abbott Architect I2000 equipment. Low levels of vitamin D were defined as <20 ng/ml (<50 nmol/L) and deficient as a levels <12 ng/ml (<30 nmol/L) (6–9).

Epicardial Fat Measurements

All patients underwent unenhanced CT scans including low-dose CT and two ultra-low-dose CT protocols with commonly reported imaging features of COVID-19 pneumonia. The thoracic CT was performed using a 64-slice scanner (GE MEDICAL SYSTEMS Revolution EVO). Epicardial adipose tissue (EAT) thickness was measured at three points (right atrioventricular fossa, left atrioventricular fossa, and anterior interventricular fossa) in the reformatted 4-chamber view using the multiplanar reconstruction (MPR) tool on the workstation (23–26). The maximum thickness of the EAT was determined from the surface of the myocardium to the pericardium (measured perpendicular to the pericardium). The measurements were made on two different occasions, obtaining a total of six measurements; the average of them was used for all statistical analyses. Pericardial adipose tissue (PAT) was quantified with the volume measurement tool with the Carestream system of the workstation. The thickness of the thoracic subcutaneous adipose tissue (TscAT) was measured from the anterior border of the sternum to the skin, at the level of the mitral valve in the axial plane of the tomography. The 80th gender-specific percentile of EAT thickness was obtained and used as the threshold to define increased EAT thickness. In addition, chest CT findings were recorded and used to evaluate severity of COVID infection (25).

COVID-19 Outcomes

Outcomes included mortality and critical disease (defined as the combination of mortality and need for mechanical ventilation /intubation). For time-to-event analyses, time from self-reported symptom onset prior to evaluation until last follow-up (censoring) or death, whichever occurred first was estimated.

Statistical Analyses

Cases with low and deficient vitamin D levels were analyzed using Student's *t*-test or Mann-Whitney U according to the variable distribution (parametric or non-parametric) for continuous variables. The chi-squared test was applied for categorical variables. Logarithmic, squared root and cubic root transformations were carried out to ensure variable symmetry prior to modeling. Missing data on predictors other than Vitamin D were multiply imputed using the *mice* R package under the assumption of data missing completely at random and combined using Rubin's rules. All statistical analyses were conducted using R software version 4.0.2.

Predictors of Vitamin D Levels

Linear regression analyses were fitted to identify predictors of log-transformed vitamin D levels in patients with COVID-19, and model selection was carried out using minimization of the Bayesian Information Criterion (BIC). Logistic regression models were also fitted using a dummy variable which defined low and deficient vitamin D to identify predictors for these categories and again model selection was conducted using BIC. Finally, model diagnostics for linear regression were conducted using residual analyses and the Hosmer-Lemeshow test for logistic regression analyses.

Prediction of Mortality and Severe COVID-19

Cox proportional risk regression analyses was used to investigate the association of vitamin D with mortality related to COVID-19. Univariate models and fully adjusted models were generated which included the following covariates: age, gender, BMI, C-reactive protein, D-dimer, ultrasensitive cardiac troponin, epicardial fat, T2D, CKD and oxygen saturation levels. An interaction effect was explored with BMI or BMI categories to rule out the differential impact of vitamin D adjusted for BMI. Model diagnostics were done using Schoenfeld residuals. Results are presented with Hazard Ratios (HR) and its corresponding 95% confidence intervals. Finally, the association of vitamin D with requirement for mechanical ventilation or the composite of critical COVID-19 was explored using logistic regression analyses adjusted for the covariates. Results are presented with Odds Ratios (OR) and its corresponding 95% confidence intervals.

Causal Mediation Models

Finally, to explore whether variables which are influenced by Vitamin D levels may act as a mediator of the risk conferred by Vitamin D on COVID-19 severity, model-based causal mediation analyses were developed: D-dimer and ultrasensitive cardiac troponins were proposed as mediators of the effect of Vitamin D on COVID-19 mortality. All mediation analyses were performed using the mediation R package; to permit inference to obtain a 95% confidence interval using bias-corrected accelerated non-parametric bootstrap. To demonstrate the sequential ignorability assumption, a sensitivity analysis was run to demonstrate residual confounding by varying the correlation between the residuals of both the outcome and the moderator models. Statistical analyses were performed using R software version 4.0.3. A $p < 0.05$ was considered statistically significant.

RESULTS

Study Population

This study included 551 patients with confirmed COVID-19 (with compatible computerized tomography findings and/or positive RT-qPCR test from nasopharyngeal swabs) and vitamin D measurements. The mean age of participants was 51.92 ± 13.74

years, with a male predominance ($n = 355$, 64.4%), and a mean BMI of 30.05 ± 5.72. Median follow-up was 15.0 days (IQR 10.0, 20.0) and 445 patients required hospitalization (81.1%). Overall, 93 patients received invasive mechanical ventilation (16.88%) and 116 in-hospital deaths (21.1%) were recorded. Type 2 diabetes (T2D) was present in 146 patients (26.9%), 219 patients had obesity (42.7%) and 217 were overweight (42.4%). Mean vitamin D levels were 21.78 ± 9.01 and vitamin D levels below 20 ng/ml were present in 251 subjects (45.6%) (**Table 1**). Extremely low vitamin D levels (≤12 ng/ml) were observed in 59 patients (10.7%).

Determinants of Vitamin D Levels Amongst Patients With COVID-19

The pathophysiological adaptations to COVID-19 may be predictive of low vitamin D levels. To this end, determinants of low vitamin D in COVID-19 were sought in an attempt to develop a mechanistic explanatory model for this relationship. Subjects with low vitamin D levels (<20 mmg/dl) were more likely to be female, have type 2 diabetes, higher HbA1c, D-dimer and ferritin levels and lower oxygen saturation, albumin and C-reactive protein. Using linear regression, a lower log-transformed vitamin D level was independently associated with female gender, higher log-transformed ultrasensitive cardiac troponin, higher log-transformed D-dimer, higher log-transformed epicardial fat area, and lower C-reactive protein levels (**Table 2**). When exploring a model to detect low vitamin D levels, there was a significantly higher odds for log-transformed D-dimer levels (OR 1.31, 95%CI 1.06, 1.63); lower odds were associated with male gender (OR 0.45, 95%CI 0.31, 0.65), higher oxygen saturation levels (OR 0.98, 95%CI 0.97, 0.99) and higher C-reactive protein values (OR 0.75, 95%CI 0.61, 0.92), adjusted for age, and log-transformed epicardial fat. There was no association between days from symptom onset and vitamin D levels at admission.

Vitamin D Levels and COVID-19 Mortality

Overall, vitamin D levels were significantly lower when comparing non-fatal to fatal COVID-19 cases (22.41 ± 9.34 vs. 19.44 ± 67.19, $p < 0.001$). When assessing risk related to the association between mortality and vitamin D levels using Cox regression, a 1-unit increase in vitamin D levels was associated with a decreased risk of COVID-19 mortality. Interestingly, when stratifying cases according to gender, the difference in vitamin D levels between fatal and non-fatal cases was greater in women compared to men and lower in cases with obesity (**Figure 1**). When the mortality models were adjusted for age, gender, BMI, and C-reactive protein, CKD and T2D the observed association between vitamin D levels and a decrease in COVID-19 mortality persisted (**Table 3**). There was no significant interaction with BMI, (as a continuous variable or categorized) in normal weight, overweight and obese with vitamin D levels. Using post-estimation simulation to predict risk associated with changes in vitamin D levels using the simPH R package, there was a steady decrease in risk attributable to increasing vitamin D concentrations using vitamin D <20 ng/ml and ≤12 ng/ml as thresholds (**Figure 2**).

TABLE 1 | Clinical characteristics, imaging findings and severity scores in patients with COVID-19, comparing cases with and without low vitamin D levels.

Parameter	Vitamin D [>20 ng/ml] ($n = 300$)	Vitamin D [≤20 ng/ml] ($n = 251$)	*P*-value
Age (years)	53.0 (±14.92)	51.0 (±12.60)	0.088
Male sex (%)	219 (73)	136 (54.2)	<0.001
Low-socioeconomic status (%)	203 (67.66)	172 (68.5)	0.902
Critical outcome (%)	85 (28.3)	81 (32.3)	0.363
Intubation (%)	53 (17.6)	40 (15.9)	0.670
Mortality (%)	57 (19)	59 (23.5)	0.23
Arterial hypertension (%)	83 (27.94)	89 (35.9)	0.058
Type 2 diabetes (%)	68 (22.9)	78 (31.6)	0.031
Time since diagnosis (years)	9.8 (±7.8)	9.20 (±7.5)	0.831
Obesity (%)	118 (39.9)	111 (44.9)	0.269
Smoking status (%)	15 (5.8)	12 (5.8)	0.789
CKD (%)	6 (2.0)	12 (4.9)	0.111
CVD (%)	6 (2.0)	10 (4.0)	0.258
Cirrhosis (%)	0 (0)	3 (1.21)	0.186
BMI (kg/m^2)	29.83 (±4.9)	30.3 (±6.6)	0.343
Respiratory rate (rpm)	28.5 (±12.4)	28.3 (±9.11)	0.821
Heart rate (bpm)	102.3 (±18.2)	101.9 (±18.5)	0.771
Systolic arterial pressure (mmHg)	120 (110–131)	123 (110–135)	0.264
Diastolic arterial pressure (mmHg)	76 (70–80)	74 (67–81)	0.322
Oxygen saturation (%)	82.65 (±11.4)	79.89 (±13.4)	0.010
C-reactive protein	14.9 (9.0–23.2)	13.6 (6.4–21.8)	0.052
Glucose levels (mg/dl)	149.7 (±85.7)	163.6 (±98.0)	0.081
HbA1c (%)	6.1 (5.8–7.1)	6.9 (6.0–9.6)	0.004
Triglycerides (mg/dl)	149 (114–192)	140 (110–179)	0.291
HDL-C (mg/dl)	32.7 (±15.3)	33.3 (±10.7)	0.911
LDL-C (mg/dl)	95.9 (±57.4)	75.1 (±34.7)	0.282
Total cholesterol (mg/dl)	159.5 (±60.9)	135.7 (±44.2)	0.266
Hemoglobin (%)	15.45 (1.9)	17.4 (23.0)	0.179
Platelet count (1,000 cells/ul)	231.0 (90.9)	236.5 (103.8)	0.509
Lymphocytes (1,000 cells/ul)	8.9 (4.4)	9.2 (4.9)	0.529
Neutrophils (cells/ul)	6435.0 (4699.1)	6336.8 (5227.2)	0.819
Serum creatinine (mg/dl)	0.9 (0.8–1.2)	0.9 (0.7–1.2)	0.645
Ferritin (mg/dl)	656.0 (323.3–1138.7)	553.3 (284.7–959.7)	0.062
D-dimer (ng/ml)	629 (401–1049)	821 (454–1376)	0.001
Protrombin time (seconds)	11.4 (10.8–12.4)	11.4 (10.6–12.5)	0.364
Fibrinogen (mg/dl)	697.0 (556.5–854.5)	672 (482–789)	0.014
BUN (mg/dl)	18.1 (11.6)	20.7 (17.7)	0.054
AST (U/L)	42.6 (30.5–62.5)	41.4 (30.1–64.7)	0.679
ALT (U/L)	35.9 (23.7–55.1)	33.50 (23.8–58.2)	0.632

(Continued)

TABLE 1 | Continued

Parameter	Vitamin D [>20 ng/ml] ($n = 300$)	Vitamin D [≤20 ng/ml] ($n = 251$)	*P*-value
Albumin (mg/dl)	3.8 (3.4–4.0)	3.6 (3.3–4.0)	0.002
Lactate dehydrogenase (U/L)	361 (291–466)	374 (278.5–498.5)	0.757
Creatinine kinase (U/L)	116 (64–236)	104.5 (55–225.3)	0.198
Procalcitonin (ng/ml)	0.3 (0.1–0.6)	0.3 (0.2–1.2)	0.299
Symptoms (number)	5 (3–5)	4 (3–5)	0.107
Comorbidities (number)	1 (0–1)	1 (0–2)	0.001
Time hospitalized (days)	6 (3–10)	6 (3–10)	0.995
CT findings			
Epicardial fat (%)	9.3 (7.3–11.7)	10 (8.2–12.2)	0.011
Pericardial fat (%)	185 (61.7)	145 (57.8)	0.407
Subthoracic fat (%)	15 (10–21)	17 (12–24)	0.010
Ground glass opacity (%)	297 (99)	248 (98)	0.710
Consolidations (%)	158 (53.6)	136 (54.2)	0.781
GGO + consolidations (%)	158 (53.6)	136 (54.2)	0.721
Lobules afected			
1 (%) 2 (%) 3 (%)	34 (11.3) 82 (32.7) 132 (52.6)	34 (11.3) 125 (41.7) 140 (46.6)	0.178
Hepatic steatosis (%)	99 (33)	90 (35.9)	0.539
Severity scores			
NEWS (points)	8 (6–9)	8 (7–9)	0.733
QSOFA (points)	1 (1)	1 (1)	0.329
CURB−65 (points)	1 (0–2)	1 (0–2)	0.347

Values are presented as mean (± standard deviation) or median (inter-quartile range), where appropriate. NEWS, National Early Warning Score; QSOFA, Quick Sequential Organ Failure Assessment Score; CURB-65, CURB-65 Score for Pneumonia Severity; GGO, Ground Glass Opacity; CT, Computed Tomography; CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; BUN, Blood Urea Nitrogen; BMI, Body mass index.

Vitamin D and Critical COVID-19

When assessing the impact of vitamin D on the risk of invasive mechanical ventilation there was no significant association even after adjustment for age, gender, BMI, C-reactive protein, CKD or T2D status (OR 0.986, 95%CI 0.957, 1.015, $p = 0.366$). However, when assessing the composite of critical COVID-19 using logistic regression models, lower vitamin D levels were associated with critical COVID-19 (OR 0.97, 95%CI 0.94, 0.99, $p = 0.042$, adjusting by age, gender, BMI, C-reactive protein, D-dimer, CKD, SpO_2 or T2D status).

Causal Mediation Models

Finally, model-based causal mediation models were developed to assess whether the effect of vitamin D (E) on increased mortality risk (Y) was mediated through changes in variables identified in **Table 2** (M), adjusted for age, gender, BMI and epicardial fat. The direct effect of vitamin D on increased mortality risk was significant ($\Delta_{E\rightarrow Y}$ −0.144, 95%CI −0.069, −0.010) and the indirect effect of vitamin D, mediated by increase D-dimer levels ($\Delta_{E\rightarrow MY}$ −0.035, 95%CI −0.164, −0.010), represented 19.3% (95%CI 9.5, 77.0%) of the overall association of vitamin D on mortality. A similar scenario was observed for cardiac troponins, whereby both the direct effect of vitamin D on mortality ($\Delta_{E\rightarrow Y}$ −0.133, 95%CI −0.150, −0.020) and the indirect effect mediated by ultrasensitive cardiac troponins ($\Delta_{E\rightarrow MY}$ −0.047, 95%CI −0.085, −0.020), were significant and represented 26.2% (95%CI 14.9, 73.0%) of the overall effect of vitamin D on mortality (**Figure 3**). Notably, there were no significant causal mediation models for either BMI or epicardial fat, here there was only a direct effect on mortality, independent of vitamin D levels (**Table 4**).

DISCUSSION

In this study, the association between vitamin D levels and severity of COVID-19 was explored in a Mexican population. Deficient levels of vitamin D (deficiency) showed a clear association with mortality, even after adjusting for confounders, including epicardial fat as a proxy of visceral fat and BMI. A vitamin D level <20 ng/ml (<50 nmol/L), showed a strong negative predictive value, suggesting that when levels are adequate, the probability of mortality is low. Furthermore, the increased risk of mortality from COVID-19 was partly mediated by the effect of vitamin D on markers of disease severity, such as D-dimer and ultrasensitive cardiac troponins, independent of BMI and epicardial fat (these showed effects on COVID-19 mortality independent of vitamin D levels). This suggests that vitamin D may be a marker of an impaired response to infection within the pulmonary epithelium, most notably in those with severe deficiency (27).

Several studies have explored the relationship between COVID-19 and vitamin D levels (18, 20, 27, 28). These include those examining vitamin D levels and risk of infection and those examining an association with severity of COVID-19. Higher levels of IL-6 were observed in vitamin D deficiency suggesting a greater inflammatory response in these patients (29, 30). A recent systematic review and meta-analysis reported that vitamin D deficiency was not associated with increased risk of infection, but severe cases presented with greater vitamin D deficiency compared with mild cases. Vitamin D deficiency has been associated to increased hospitalization and mortality risk from COVID-19 (16, 18). Physiological mechanisms by which vitamin D exerts a protective function include enhanced innate immunity including augmentation of physical barriers to infection and optimization of adaptive immunity (27). Vitamin D has also been proposed to exert a modulatory effect on the inflammatory response caused by COVID-19 by curbing adaptive immunity though inhibition og B cell proliferation, differentiation and production of antibodies and plays a role in regulation the T cell phenotype. Thus, there is a shift in the adaptive immune response from Th1 to a more regulatory Th2 response, characterized by an increase in expression of Th2 associated cytokines. This may attenuate the quantity of pro-inflammatory cytokines that are associated with severe infection (27). In addition, vitamin D induces ACE-2 expression, and suppresses the angiotensin-renin system, thus reducing

TABLE 2 | Multiple linear regression model to identify determinants of Vitamin D levels in patients with COVID-19.

Model	Parameter	β-coefficient	95%CI	*t*	*P*-value
Vitamin D	Intercept	3.515	3.177, 3.853	20.426	<0.001
$R^2 = 0.1091$	Male Sex	0.168	0.097, −0.238	4.668	<0.001
	Ultrasensitive troponin	−0.033	−0.063, −0.002	−2.124	0.034
	D-dimer	−0.060	−0.100, −0.020	−2.951	0.003
	C-reactive protein	0.065	0.026, 0.103	3.265	0.001
	Epicardial fat	−0.126	−0.222, −0.031	−2.599	0.010
	Type 2 diabetes	−0.072	−0.147, 0.004	−1.871	0.062

95%CI, 95% Confidence intervals.

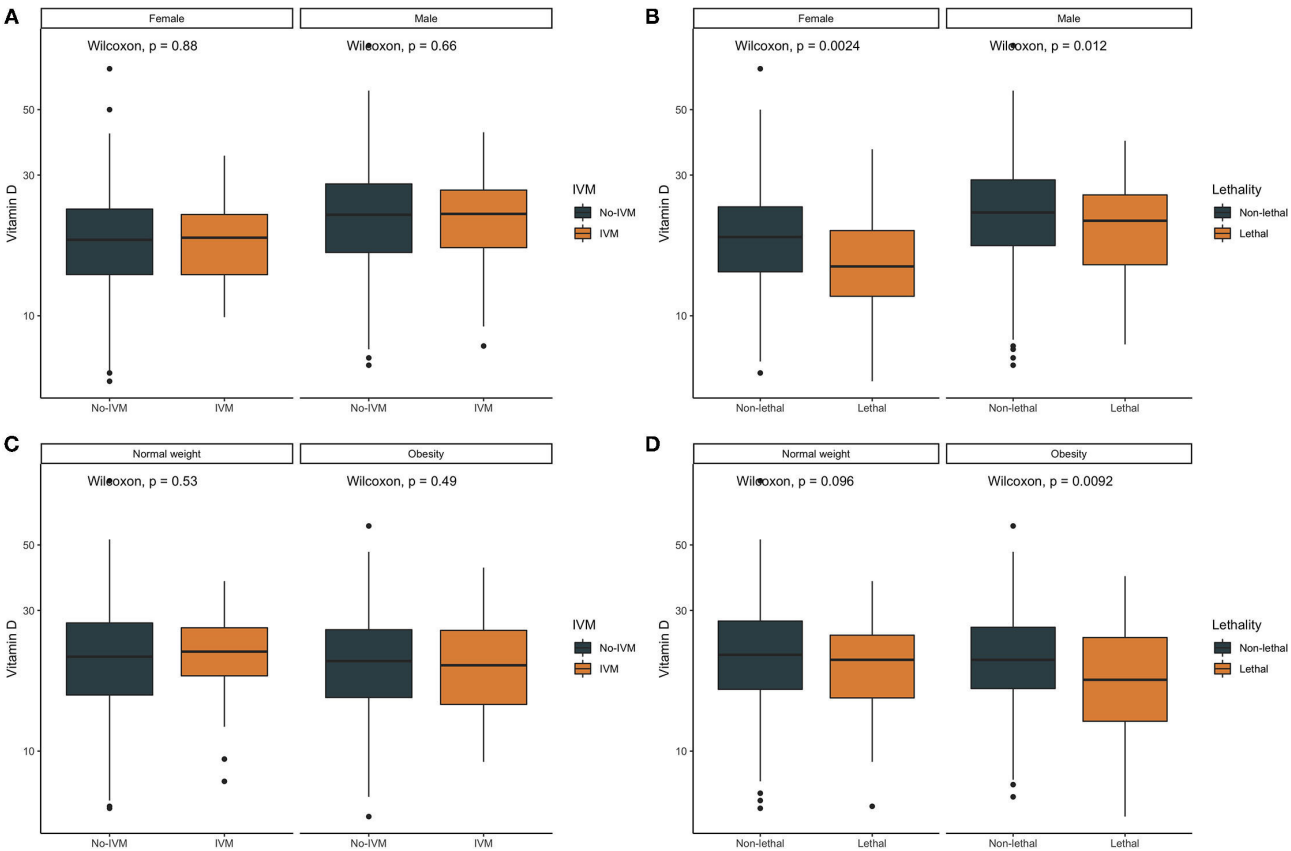

FIGURE 1 | Boxplots comparing Vitamin D levels according to the need for invasive mechanical ventilation (IVM) or lethal COVID-19 stratified by gender **(A,B)** and by body-mass index categories **(C,D)**.

levels of proinflammatory angiotensin II. Hence, vitamin D deficiency, could potentiate the cytokine storm perpetuating a pro-inflammatory state and worsening pulmonary outcomes (28, 29). Finally, thrombotic complications are common in such patients; vitamin D is also involved in the regulation of thrombotic pathways (31, 32). The mechanisms through which Vitamin D may influence pro-thrombotic pathways is closely related to its anti-inflammatory properties, which reduce endothelial activation and oxidative stress (33). In our study, low vitamin D levels in COVID-19 patients were related to inflammatory, pro-thrombotic and metabolic markers of severity, confirming observations from previous studies.

Adverse COVID-19 outcomes have been linked to the ethnic origin of the population under study and its socio-economic characteristics; this has also been associated with the presence of vitamin D deficiency. Asians, African Americans, and ethnic minorities are at an increased risk of mortality from COVID-19 (34). This may partly be due to a decrease in the production of vitamin D dependent on UV rays. This is related to the skin levels of melanin present in

TABLE 3 | Cox proportional risk regression models to predict mortality related to COVID-19 using Vitamin D levels adjusted for covariates.

Model	Parameter	β-coefficient	HR (95%CI)	*P*-value
Model 1	Vitamin D	−0.036	0.965 (0.942, 0.988)	0.003
c-statistic = 0.566				
Model 2	Vitamin D	−0.043	0.938 (0.934, 0.983)	0.001
c-statistic = 0.694	Age	0.037	1.037 (1.022, 1.052)	<0.001
	Male gender	0.787	2.196 (1.373, 3.512)	0.001
	BMI	0.038	1.039 (1.005, 1.073)	0.024
	CRP	0.004	1.004 (1.002, 1.007)	<0.001
Model 3	Vitamin D	−0.039	0.962 (0.935, 0.989)	0.006
c-statistic = 0.702	CKD	0.301	0.749 (0.276, 2.030)	0.570
	T2D	0.325	1.384 (0.882, 2.170)	0.157
	Ultrasensitive cardiac troponin	0.170	1.185 (1.002, 1.403)	0.048
	D-dimer	0.003	1.003 (0.804, 1.252)	0.980
	Oxygen saturation	−0.026	0.975 (0.960, 0.990)	0.001
	Epicardial fat thickness	0.669	1.952 (0.501, 7.607)	0.335

Model 1: Unadjusted; Model 2: Adjusted for age, gender, body-mass index (BMI) and C-reactive protein (CRP); Model 3: Model 2 adjusted for chronic kidney disease (CKD), epicardial fat and type 2 diabetes (T2D). CKD, Chronic Kidney Disease; BMI, Body mass index; CRP, C-reactive protein; T2D, Type 2 diabetes mellitus; HR, Hazard Ratio; 95%CI, 95% Confidence Interval.

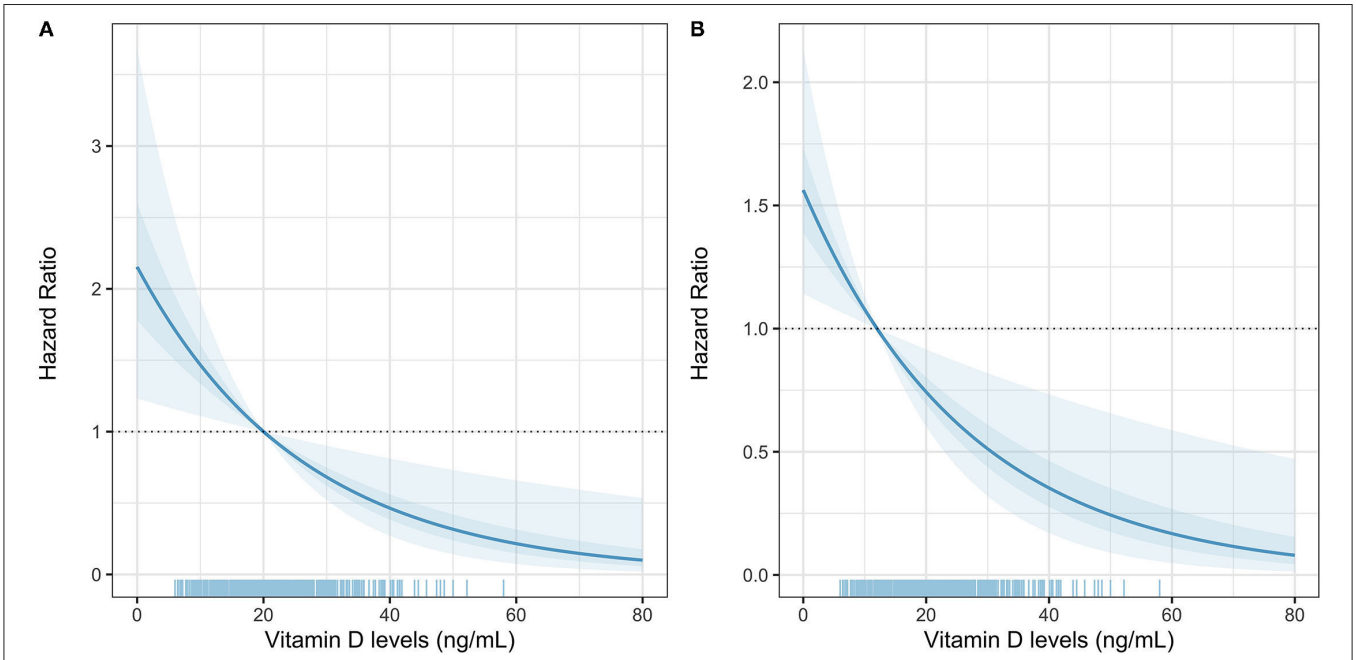

FIGURE 2 | Post-estimation simulation of Vitamin D levels to predict COVID-19 lethality, adjusted for age, sex, BMI, C-reactive protein, epicardial fat, D-dimer, oxygen saturation, T2D, and CKD using Vitamin D cut-offs of <20 ng/dl **(A)** and ≤12 ng/ml **(B)**.

these populations and on the unequal distribution of poverty and cardiometabolic disease rates across such ethnicities and populations. This finding is relevant and may explain lower vitamin D levels and severity of COVID-19 in México in previous studies (35–37). Previous reports in similar populations, including Hispanics, have shown higher risk of severe SARS-CoV-2 infection, compared to Caucasian population (38). This could be attributable to increased cardio-metabolic comorbidities in cases from Mexico, where vitamin D deficiency is more prevalent in type 2 diabetes and obesity primarily due to increased adiposity, as supported by our results (39). The relationship between vitamin D levels and sex may also underlie our finding of lower vitamin D levels in women, who have increased adiposity content compared to males (40). Low vitamin D levels may also occur in CKD, by reduced expression of 1-alpha hydroxylase; given a large, despite its

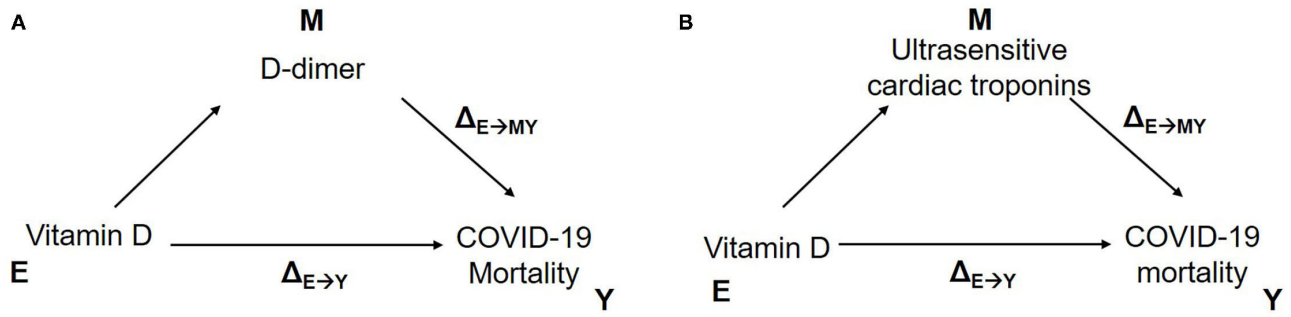

FIGURE 3 | Model-based causal mediation analyses to investigate the role of Vitamin D on COVID-19 mortality mediated by D-dimer **(A)**, ultrasensitive cardiac troponins **(B).**

TABLE 4 | Causal mediation analyses predicting the effect of Vitamin D levels (E) mediated by elevated D-dimer, ultrasensitive cardiac troponins or low SpO2 (M) on severe COVID-19 and mortality (Y), adjusted by gender, age, BMI and epicardial fat.

Outcome (Y)	Efector (E)	Mediator (M)	ACME (95%CI)	ADE (95%CI)	Total effect (95%CI)	Proportion mediated (95%CI)
COVID-19 mortality		D-dimer	−0.035 (−0.069,−0.010)	−0.144 (−0.164, −0.10)	−0.179 (−0.188,−0.050)	19.3% (9.5–77.0%)
	Vitamin D	Ultrasentivie cardiac troponins	−0.047 (−0.085, −0.020)	−0.133 (−0.150, −0.020)	−0.181 (−0.183, −0.060)	26.2% (15.0–73.0%)
		SpO_2	−0.037 (−0.066, −0.010)	−0.144 (−0.159, −0.030)	−0.181 (−0.186,−0.050)	20.3% (9.7–64.0%)

ACME, average causal mediation effects; ADE, average direct effects; SpO_2, Oxygen saturation levels.

influce on Vitamin D status, our study only included a reduced number of cases with CKD. Currently, routine vitamin D supplementation in hospitalized patients with COVID-19 is not recommended. A recent clinical trial study study showed that administration of a high dose of calcifediol or 25-hydroxyvitamin D, did not reduce length of hospital stay in patients COVID-19 (20). Ideally, additional large randomized controlled trials are needed to properly assess this claim and whether vitamin D supplementation can significantly impact risk of severe COVID-19.

This study has certain strengths and limitations. It included a large sample of patients with heterogenous risk profiles in whom a variety of disease severity parameters were measured. In addition, a series of statistical tests were carried out to ensure minimal possibility of residual confounding. Nevertheless, some limitations must be acknowledged to properly interpret this study. First, a chemiluminescence immunoassay was used to assess vitamin D levels, this may lead to inconsistent results compared to other techniques including competitive binding protein-CBP, radioimmunoassay-RIA liquid chromatography-LC, UV detection with liquid chromatography and liquid chromatography mass spectrometry LCMS or tandem mass spectrometry. Since most patients were attended in the institution for the first time for COVID-19, historic vitamin D values were not available to assess the effect of vitamin D dynamics on infection risk or outcomes. Furthermore, given the disease course of COVID-19, severity profiles are highly heterogeneous even amongst hospitalized patients, which may influence vitamin D values based on varying severity; control for this factor using propensity score matching was carried out, however, there remains a possibility for residual confounding. Finally, since this is a secondary analysis, *post-hoc* sample size calculation was not performed, and negative results should be interpreted with caution. Notably, these results are from a COVID-19 reference center in Mexico City, this could reduce the representativeness of the findings primarily to severe and critical forms of COVID-19 from the central region of Mexico. Further evidence in other regions of Mexico to confirm the role of vitamin D as a marker of disease severity and mortality in Mexicans with COVID-19 is needed.

CONCLUSIONS

Vitamin D levels ≤12 ng/ml (30 nmol/L) are independently associated with COVID-19 mortality, even after adjusting for confounders, including measures of visceral and total body fat. No association was confirmed between vitamin D levels and the need for intubation. Vitamin D deficiency is more prevalent in women and patients with type 2 diabetes mellitus. Vitamin D supplementation may be considered in deficient patients, but evidence of benefit is required from double blind randomized controlled trials.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://github.com/oyaxbell/covid_metabolism.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research and Ethics Committee of the INCMNZ (Ref 3383). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RM, OB-C, and CA-S: research idea and study design. RM, PV-C, NR-P, MJ-Á, CP, BR, JV-G, and CA-S: data acquisition. OB-C, RM, CA-S, NA-V, and AV-V: data analysis/interpretation. OB-C and NA-V: statistical analysis. RM, OB-C, NA-V, AV-V, and CA-S: manuscript drafting. RM, CA-S, AP, and JS-O: supervision or mentorship. All authors contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Higher Intake of Dietary Magnesium Is Inversely Associated With COVID-19 Severity and Symptoms in Hospitalized Patients: A Cross-Sectional Study

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Background and Aims: Magnesium is an anti-inflammatory mineral that plays a role in the innate immune system, and the relaxation of bronchial smooth muscle warrants additional attention in COVID-19. This study examined the association between magnesium intake and COVID-19 severity and related symptoms in hospitalized patients.

Methods: A cross-sectional study was done enrolling 250 COVID-19 patients aged 18 to 65 years. A validated 168-item online food frequency questionnaire (FFQ) was used to assess dietary magnesium intake. COVID-19 Treatment Guidelines were used to determine COVID-19 severity, and symptoms were evaluated using a standard questionnaire. Crude and adjusted analyses were performed (Model 1: age, sex, and energy intake; Model 2: Model 1 + physical activity, supplements, corticosteroids, and antiviral drugs; Model 3: Model 2 + body mass index).

Results: The mean age of participants was 44.1 ± 12.1 years, and 46% of them had severe COVID-19. Patients at the highest tertile of dietary magnesium intake had lower serum levels of inflammatory biomarkers, including CRP (11.8 ± 2.2 vs. 29.5 ± 2.1 mg/L, $p < 0.001$) and ESR (15.8 ± 2.4 vs. 34.7 ± 2.4 mm/hr, $p < 0.001$), than those at the lowest tertile. After controlling for potential confounders, we observed that a higher dietary magnesium intake was associated with a lower odds of severe COVID-19 (OR: 0.32; 95% CI: 0.15–0.70). Also, we found a significant inverse association between dietary magnesium intake and odds of COVID-19 symptoms.

Conclusion: We found that higher intake of dietary magnesium was inversely associated with COVID-19 severity and symptoms.

Keywords: COVID-19, COVID-19 severity, COVID-19 symptoms, magnesium, magnesium intake

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) outbreak rapidly became the most serious threat to global health (1, 2). More than 260 million people worldwide were infected in 2021, with over 5 million deaths (3). Prevention and proper treatment for COVID-19 and genetic variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain a concern (4). Along these lines, COVID-19 has imposed a significant financial burden on the global economy and health (5, 6).

Numerous studies have investigated potential interactions between nutrition and immune function (7, 8). Not surprisingly, more emphasis has been placed on the role of vitamins, minerals, and other functional nutrients against infectious-respiratory diseases, including the array of harmful effects of COVID-19 (9, 10). In this light, evoked potentials by micronutrient supplements, such as vitamin D, B12, vitamin C, zinc, and magnesium, have been tested in COVID-19 patients to boost immune function (11–17). However, further investigation is warranted to determine the effects of dietary intake of functional nutrients instead of greater focus on supplementation.

Among a plethora of nutrients thought to be candidates for immune system enhancement, magnesium stands out due to its recognized effects in reducing inflammation and oxidative stress, playing a role in the cytokine storm, lowering blood pressure, and relaxing airway smooth muscles, thus counteracting systemic and respiratory problems (15, 18–20). It is no wonder that recent studies show that hypomagnesemia is a poor prognostic marker of COVID-19 (21, 22). A cohort study of 83 hospitalized patients revealed a link between low serum magnesium levels and an increased risk of COVID-19 symptoms and mortality (21). In a cross-sectional analysis of 60 patients admitted to the intensive care unit with COVID-19 disease discovered that lower serum magnesium levels were associated with more severe disease (22). Another cross-sectional study found that a higher dietary magnesium intake was associated with improved lung function, airway hyperactivity, and wheezing (23). Additionally, a meta-analysis of cross-sectional studies involving 32,918 participants revealed an inverse relationship between dietary magnesium intake and serum CRP levels (24).

Indeed, the relationship between dietary intake of magnesium and COVID-19 must be better examined, however. To the best of our knowledge, there is no study to examine the relationship between dietary magnesium intake and COVID-19 severity and related complications. Therefore, employing a cross-sectional study, we investigated the association between dietary magnesium intake and COVID-19 symptoms and severity in hospitalized patients.

METHODS

A retrospective cross-sectional study was conducted from June to September 2021 at Shahid Beheshti Hospital in Kashan, Iran. The ethics committee of Kashan University of Medical Sciences approved the study protocol with the registration number of IR.KAUMS.MEDNT.REC.1400.048. All participants signed an informed consent form.

Participants

Using simple random sampling, 250 COVID-19 hospitalized patients aged 18–65 years were included in the study. Participants were selected from improved COVID-19 patients who had been firstly diagnosed for a maximum of 3 months last. Patients who met any of the following criteria were excluded: a history of chronic diseases such as heart disease, diabetes, etc.; the presence of diseases other than COVID-19 as well as diseases that affect the severity of COVID-19; pregnant or breastfeeding women; those who had adherence to a special diet; a body mass index (BMI) >40 kg/m^2; current smokers; taking drugs that affect respiratory function such as fluticasone, flunisolide, and so on; taking dietary supplements more than twice a week before the diagnosis of COVID-19, as well as a those with lack of necessary information in their medical records (**Figure 1**).

Assessment of Dietary Intakes

Patients' dietary information was collected over the past year before being infected by COVID-19 using a 168-item web-based online food frequency questionnaire (FFQ). As the participants in this study were hospitalized and their diets may have changed due to the disease and its complications, we used the FFQ to assess dietary intakes. Participants were able to report their food intake daily, monthly, or annual using this questionnaire. The food consumption was then converted to grams per day using "household measures" (25). Finally, the amounts of dietary micronutrients and macronutrients were determined using the Nutritionist 4 (N4) software.

Assessment of COVID-19 Severity

COVID-19 Treatment Guidelines (CTG), which were updated on October 19, 2021 (26), were used in this study to determine the severity of COVID-19. According to this tool, the severity of COVID-19 was classified into five levels. (1) Asymptomatic or presymptomatic infection: individuals who had a positive virologic test for SARS-CoV-2 (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but did not exhibit symptoms of COVID-19; (2) Mild illness: individuals who did not have dyspnea, shortness of breath, or abnormal chest imaging but had one or more of the COVID-19 signs or symptoms (e.g., sore throat, weakness, fever, headache, cough, muscle aches, loss of taste and smell, nausea, vomiting, and diarrhea); (3) Moderate illness: individuals who demonstrated evidence of lower respiratory disease during clinical evaluation or imaging and had a room air oxygen saturation (SpO_2) of 94 % at sea level; (4) Severe illness: individuals with a SpO2 <94% in room air at sea level, a PaO_2/FiO_2 ratio <300 mm Hg, a respiratory rate >30 breaths per minute, or lung infiltrates $>50\%$; (5) More severe illness: Individuals who suffered from septic shock, respiratory failure, and/or multiple organ dysfunction. Mild and moderate diseases were considered non-severe diseases in this study.

Assessment of COVID-19 Symptoms

COVID-19 symptoms were assessed using a standard questionnaire. In this questionnaire, participants were asked to report any of the common COVID-19 symptoms, including

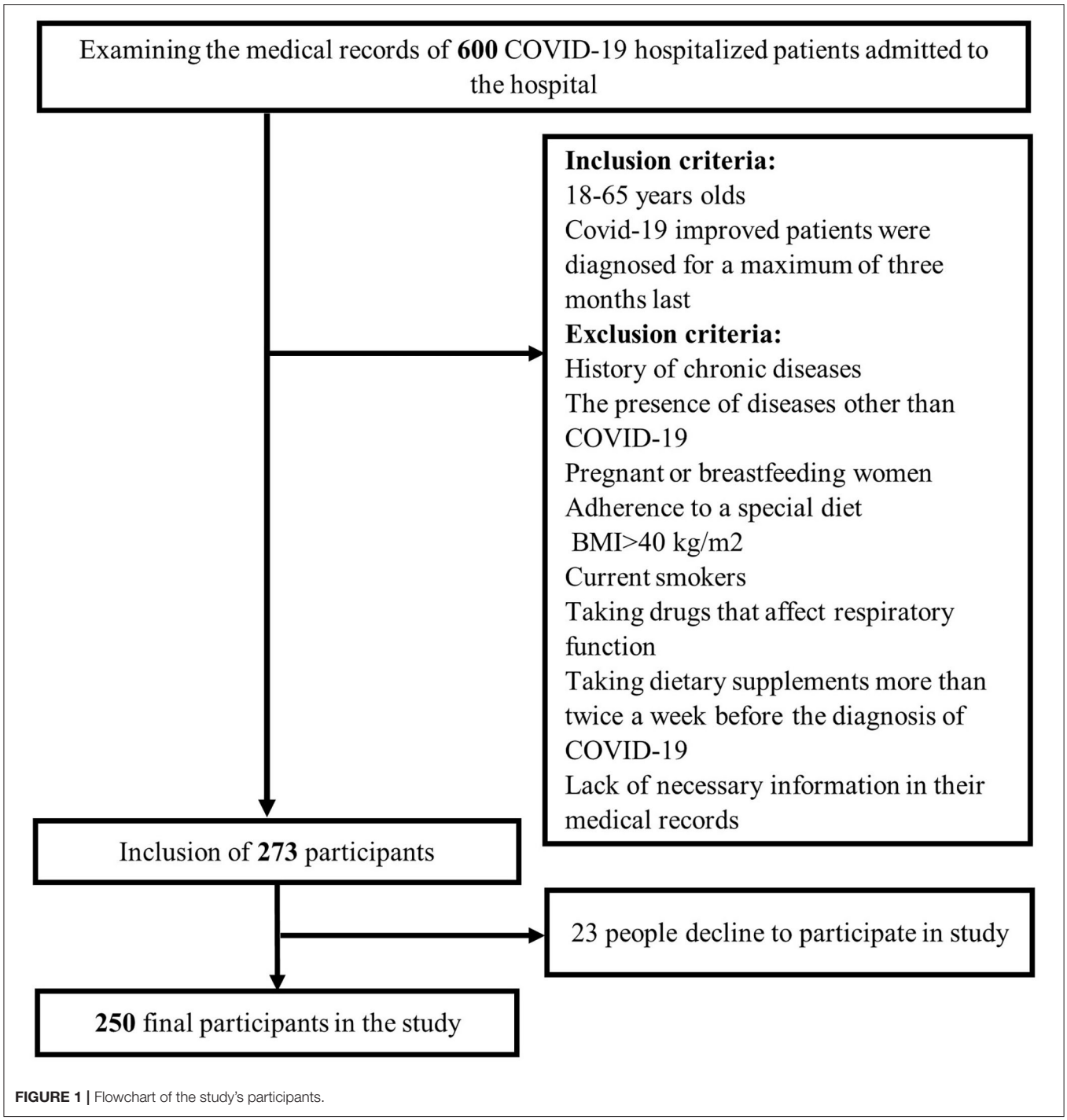

FIGURE 1 | Flowchart of the study's participants.

fever, chills, cough, sore throat, dyspnea, nausea, vomiting, weakness, and myalgia. These symptoms were confirmed by an infectious disease physician.

Assessment of Other Variables

A general questionnaire was used to collect data on the participants' demographic characteristics, convalescence duration, physical activity, supplement usage, corticosteroid use, and antiviral medication use, as well as their self-reported weight and height.

Assessment of Inflammatory Biomarkers

Serum levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured after the disease diagnosis was extracted from the medical records.

Statistical Analysis

The Kolmogorov-Smirnov test was used to determine whether data were normally distributed or not. We classified participants into tertiles according to their dietary magnesium intake. The general characteristics of study participants across dietary magnesium intake tertiles were compared using one-way ANOVA and chi-square analysis, respectively, for continuous and categorical variables. After adjusting for age, gender, BMI, and physical activity, we used ANCOVA to compare inflammatory biomarkers (CRP and ESR) between dietary magnesium intake tertiles. Binary logistic regression was used in several models to examine the association between dietary magnesium intake and COVID-19 severity and symptoms. Age (year), sex (male/female), and energy intake (kcal per day) were controlled in the first model. Physical activity (sedentary/moderate/intense), supplementation (yes/no), corticosteroid use (yes/no), and antiviral drug use (yes/no) were additionally controlled in the second model. Finally, BMI was added to the previous model's adjustments. All analyses were conducted using the Statistical Package for Social Sciences (SPSS Inc., version 21). Statistical significance was defined as P-values <0.05.

TABLE 1 | General characteristics of participants across tertiles of dietary magnesium intake.

	Tertiles of magnesium intake			
	T1 ***n = 83***	**T2** ***n = 84***	**T3** ***n = 83***	***P****
Age (years)	45.7 ± 11.5	44.2 ± 12.5	42.5 ± 12.3	0.23
Female (%)	59.0	51.2	47.0	0.29
BMI (kg/m^2)	27.8 ± 3.6	27.8 ± 4.2	25.3 ± 2.7	<0.001
Physical activity				0.50
Sedentary	14.5	15.5	7.2	
Moderate	78.3	77.4	86.7	
Intense	7.2	7.1	6.0	
Overweight or obese (%)	78.3	70.2	53.0	0.002
Supplements intake (%)	92.8	95.2	96.4	0.56
Corticosteroids use (%)	91.5	92.3	92.0	0.83
Antiviral Drugs use (%)	91.6	92.9	91.6	0.94
Duration of hospitalization (day)	7.2 ± 3.1	6.5 ± 3.09	5.9 ± 2.4	0.007
Convalescence duration (day)	10.1 ± 3.3	10.3 ± 4.5	8.0 ± 2.9	<0.001

Data were obtained from ANOVA or Chi-square test, when appropriate.

RESULTS

Table 1 shows the general characteristics of participants across tertiles of dietary magnesium intake. Compared with subjects in the lowest tertile of dietary magnesium intake, patients in the third tertile had a shorter duration of hospitalization (5.9 ± 2.4 vs. 7.2 ± 3.1 days, $p = 0.007$) and convalescence (8.0 ± 2.9 vs. 10.1 ± 3.3 days, $p < 0.001$). Moreover, they were less likely to have overweight or obesity (53.0% vs. 78.3%, $p = 0.002$).

Dietary intakes of study participants across tertiles of dietary magnesium intake are presented in **Table 2**. Individuals in the top tertile of dietary magnesium intake had higher intakes of energy, carbohydrate, fat, protein, dietary fiber, B vitamins, vitamin C, vitamin D, omega3, calcium, zinc, potassium, and magnesium when compared to those in the lowest tertile. Furthermore, those in the highest tertile of dietary magnesium intake consumed more refined grains, fruits, vegetables, processed meats, fish, poultry, legumes, nuts, high and low-fat dairy. Daily consumption of whole grains and red meat was not significantly different between tertiles of dietary magnesium intake.

Table 3 demonstrates the comparison of inflammatory biomarkers across dietary magnesium intake tertiles. Patients in the highest tertile of dietary magnesium intake had lower levels of CRP (11.8 ± 2.2 vs. 29.5 ± 2.1 mg/L, $p < 0.001$) and ESR (15.8 ± 2.4 vs. 34.7 ± 2.4 mm/hr, $p < 0.001$) than those in the lowest tertile. Moreover, patients in the second tertile of dietary magnesium intake had lower levels of CRP (17.7 ± 2.1 vs. 29.5 ± 2.1 mg/L, $p < 0.001$) and ESR (24.3 ± 2.3 vs. 34.7 ± 2.4 mm/hr, $p < 0.001$)compared to those in the lowest tertile.

The crude and multivariable-adjusted OR with 95% confidence intervals (CI) for severe disease according to tertiles of dietary magnesium intake are presented in **Table 4**. Higher tertiles of magnesium intake were associated with lower odds of severe illness from COVID-19 in both crude and adjusted models when compared to the lowest tertile. OR for tertile 2 and 3 were, respectively, as follows: 0.45 (0.24–0.83) and 0.24 (0.13–0.47) for crude analysis, 0.39 (0.20–0.76) and 0.21 (0.11–0.43) for model 1, 0.37 (0.18–0.75) and 0.20 (0.09–0.41) for model 2, and 0.41 (0.20–0.85) and 0.32 (0.15–0.70) for model 3.

Crude and multivariable-adjusted OR and 95% CIs for symptoms of COVID-19 according to tertiles of dietary magnesium intake are indicated in **Table 5**. Higher tertiles of magnesium intake were associated with lower odds of all COVID-19 symptoms assessed (dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat) in both crude and adjusted models when compared to the lowest tertile.

DISCUSSION

This current cross-sectional study found that higher dietary magnesium intake was associated with lower COVID-19 severity and related symptoms, including dyspnea, cough, fever, chills, weakness, myalgia, nausea and vomiting, and sore throat. More importantly, higher dietary magnesium intake was found to be inversely related to the length of hospitalization and convalescence. Noteworthy, both the second (332 ± 11 mg/d) and the highest tertiles (382 ± 24 mg/d) of magnesium intake were associated with lower odds of severe illness from COVID-19 in both crude and adjusted models when compared to the lowest tertile (273 ± 42 mg/d), but the results were more expressive for the highest one. In this way, the subjects in the highest tertiles of magnesium had a 76, 79, 80, and 68% lowering likelihood of having severe COVID-19 for the crude analysis and adjusted models 1, 2, and 3, respectively, compared to the lowest tertile.

TABLE 2 | Selected food groups and nutrients intakes of participants across tertiles of dietary magnesium intake.

	Tertiles of magnesium intake			
	T1 ***n* = 83**	**T2** ***n* = 84**	**T3** ***n* = 83**	***P****
Nutrients				
Energy (Kcal/day)	2,554 ± 48.7	2,859 ± 48.4	2,827 ± 48.6	<0.001
Carbohydrate (g/d)	400.1 ± 4.4	412.8 ± 4.2	417.8 ± 4.3	0.01
Fat (g/day)	96.2 ± 2.2	107.8 ± 2.2	98.6 ± 2.2	0.001
Protein (g/day)	95.5 ± 1.1	108.0 ± 1.1	120.7 ± 1.1	<0.001
Dietary fiber (g/day)	19.1 ± 0.3	22.7 ± 0.3	27.7 ± 0.3	<0.001
Vitamin B1 (mg/d)	2.3 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	<0.001
Vitamin B2 (mg/d)	1.7 ± 0.3	1.9 ± 0.3	2.2 ± 0.3	<0.001
Vitamin B3 (mg/d)	26.2 ± 0.3	27.6 ± 0.3	28.5 ± 0.3	<0.001
Vitamin B6 (mg/day)	1.4 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	<0.001
Folate (μg/day)	337.6 ± 6.6	409.4 ± 6.5	501.5 ± 6.5	<0.001
Vitamin B12 (μg/day)	3.3 ± 0.1	4.1 ± 0.1	5.2 ± 0.1	<0.001
Vitamin C (mg/day)	110.7 ± 2.8	134.9 ± 2.7	171.7 ± 2.7	<0.001
Vitamin D (μg/day)	2.4 ± 0.8	2.1 ± 0.7	2.3 ± 0.7	0.01
Omega3 (mg/d)	0.27 ± 0.01	0.42 ± 0.01	0.52 ± 0.01	<0.001
Calcium (mg/day)	832.8 ± 10.1	883.0 ± 9.9	1013.0 ± 9.9	<0.001
Zinc (mg/day)	8.8 ± 0.1	10.4 ± 0.1	11.6 ± 0.1	<0.001
Potassium (mg/d)	3,172.9 ± 36.9	3,730.6 ± 36.0	4,253.6 ± 36.0	<0.001
Magnesium (mg/d)	278.5 ± 2.9	328.9 ± 2.8	379.3 ± 2.8	<0.001
Food groups (g/day)				
Refined grains	531.7 ± 16.3	489.4 ± 15.9	490.9 ± 15.9	0.01
Whole grains	72.3 ± 9.1	89.6 ± 8.8	85.1 ± 8.8	0.38
Fruits	278.2 ± 11.0	339.2 ± 10.7	448.7 ± 10.7	<0.001
Vegetables	202.9 ± 8.0	262.7 ± 7.8	367.6 ± 7.8	<0.001
Red meats	41.8 ± 2.2	41.1 ± 2.2	37.7 ± 2.2	0.98
Processed meats	12.5 ± 1.4	15.8 ± 1.4	5.4 ± 1.4	<0.001
Fish	12.5 ± 1.1	21.8 ± 1.1	34.8 ± 1.1	<0.001
Poultry	43.7 ± 2.1	52.1 ± 2.0	68.9 ± 2.0	<0.001
Legumes	103.7 ± 4.0	131.8 ± 3.9	166.7 ± 3.9	<0.001
Nuts	19.8 ± 1.2	33.1 ± 1.2	38.1 ± 1.2	<0.001
Low fat dairy	136.8 ± 7.6	146.2 ± 7.4	184.9 ± 7.3	<0.001
High fat dairy	148.3 ± 7.0	124.5 ± 6.7	126.5 ± 6.7	0.03

Data are presented as mean ± SE.
**All values were adjusted for age, sex and energy intake, except for dietary energy intake, which was only adjusted for age and sex using ANCOVA.*

TABLE 3 | Inflammatory biomarkers across tertiles of dietary magnesium intake.

	Tertiles of magnesium intake			
	T1 ***n* = 83**	**T2** ***n* = 84**	**T3** ***n* = 83**	***P****
CRP (mg/L)	29.5 ± 2.1	17.7 ± 2.1	11.8 ± 2.2	<0.001
ESR (mm/hr)	34.7 ± 2.4	24.3 ± 2.3	15.8 ± 2.4	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Data are presented as mean ± SE.
**Values were adjusted for age, sex, BMI, and physical activity using ANCOVA.*

TABLE 4 | Odds ratio (95% CI) of severe disease according to tertiles of dietary magnesium intake.

	Tertiles of magnesium intake			
	T1 ***n* = 83**	**T2** ***n* = 84**	**T3** ***n* = 83**	***P****
Crude	1	0.45 (0.24–0.83)	0.24 (0.13–0.47)	<0.001
Model 1	1	0.39 (0.20–0.76)	0.21 (0.11–0.43)	<0.001
Model 2	1	0.37 (0.18–0.75)	0.20 (0.09–0.41)	<0.001
Model 3	1	0.41 (0.20–0.85)	0.32 (0.15–0.70)	0.005

Model 1: Adjustments for age, sex, and energy intake.
Model 2: Model 1 + adjustments for physical activity and use of supplements, corticosteroids, and antiviral drugs.
Model 3: Model 2 + adjustment for BMI.
**Data obtained from Binary logistic regression.*

Although no previous studies have examined the relationship between dietary magnesium intake and the symptoms and severity of COVID-19 disease, we are aware that combining vitamin D, vitamin B12, and magnesium was associated with a significant reduction in the need for oxygen support or intensive care in elderly COVID-19 patients (16). Additionally, some studies have been conducted to determine serum magnesium concentrations in COVID-19 patients. For example, a cohort study ($n = 83$) conducted in Wuhan, China, discovered an inverse relationship between serum magnesium levels and COVID-19 symptoms and mortality (21). A cross-sectional study also found lower serum magnesium levels in adults with severe COVID-19 (22). Given that a lower magnesium intake results in lower serum magnesium concentrations (27), we conducted this study to add to the existing body of knowledge. In addition to our research, non-COVID studies support the association between lung function and magnesium intake. A cohort study of children found a relationship between low dietary magnesium intake and poor lung function (28), and a link between increased dietary magnesium intake and improved lung function, airway overreaction, and wheezing in adults was observed through a cross-sectional study (23). Thus, these results provide a biological rationale to our findings related to COVID-19 symptoms, mainly the inherent harmful effects in the respiratory system. Previous clinical trials suggest that magnesium-containing foods can improve the function of the immune system (29, 30). As nutritionally expected, we observed that the highest tertiles for magnesium intake were associated with higher intakes of fruits, vegetables, legumes, and nuts, which are recognized sources of magnesium and display an important role against low-grade inflammation thanks to the food matrix (31). To complement the principal findings of our study, we examined CRP and ESR levels to understand, in part, the inflammatory process, given that severe COVID-19 are associated with higher levels of both biomarkers (32, 33). Regarding CRP values, the difference between tertiles of dietary magnesium intake expresses great

TABLE 5 | Odds ratio (95% CI) for symptoms of COVID-19 according to tertiles of dietary magnesium intake.

	Tertiles of magnesium intake			
	T1 *n = 83*	**T2** *n = 84*	**T3** *n = 83*	***P****
Dyspnea				
Crude	1	0.51 (0.26–0.99)	0.29 (0.15–0.57)	<0.001
Model 1	1	0.41 (0.19–0.86)	0.23 (0.11–0.48)	<0.001
Model 2	1	0.35 (0.16–0.79)	0.20 (0.09–0.44)	<0.001
Model 3	1	0.38 (0.17–0.87)	0.28 (0.12–0.65)	0.004
Cough				
Crude	1	0.28 (0.14–0.54)	0.23 (0.12–0.46)	<0.001
Model 1	1	0.20 (0.09–0.42)	0.16 (0.08–0.35)	<0.001
Model 2	1	0.20 (0.09–0.42)	0.17 (0.08–0.37)	<0.001
Model 3	1	0.20 (0.09–0.45)	0.28 (0.12–0.63)	0.004
Fever				
Crude	1	0.24 (0.11–0.56)	0.30 (0.13–0.70)	0.007
Model 1	1	0.20 (0.08–0.48)	0.24 (0.10–0.59)	0.004
Model 2	1	0.19 (0.08–0.48)	0.25 (0.10–0.63)	0.007
Model 3	1	0.21 (0.08–0.52)	0.35 (0.13–0.93)	0.07
Chills				
Crude	1	0.21 (0.09–0.50)	0.26 (0.11–0.63)	0.004
Model 1	1	0.18 (0.07–0.45)	0.21 (0.09–0.55)	0.003
Model 2	1	0.17 (0.07–0.44)	0.22 (0.09–0.58)	0.005
Model 3	1	0.19 (0.07–0.48)	0.34 (0.13–0.92)	0.008
Weakness				
Crude	1	0.35 (0.18–0.67)	0.13 (0.06–0.28)	<0.001
Model 1	1	0.28 (0.14–0.57)	0.11 (0.05–0.25)	<0.001
Model 2	1	0.27 (0.13–0.56)	0.11 (0.05–0.26)	<0.001
Model 3	1	0.28 (0.14–0.59)	0.14 (0.06–0.34)	<0.001
Myalgia				
Crude	1	0.73 (0.40–1.35)	0.36 (0.19–0.68)	0.002
Model 1	1	0.70 (0.36–1.35)	0.35 (0.17–0.69)	0.002
Model 2	1	0.68 (0.35–1.32)	0.33 (0.17–0.67)	0.002
Model 3	1	0.74 (0.37–1.45)	0.45 (0.21–0.94)	0.03
Nausea and vomiting				
Crude	1	0.52 (0.24–1.16)	0.04 (0.005–0.29)	<0.001
Model 1	1	0.35 (0.15–0.83)	0.03 (0.003–0.20)	<0.001
Model 2	1	0.36 (0.15–0.86)	0.02 (0.003–0.19)	<0.001
Model 3	1	0.38 (0.16–0.91)	0.03 (0.004–0.24)	<0.001
Sore throat				
Crude	1	0.77 (0.41–1.42)	0.09 (0.04–0.23)	<0.001
Model 1	1	0.66 (0.34–1.27)	0.08 (0.03–0.21)	<0.001
Model 2	1	0.66 (0.34–1.28)	0.08 (0.03–0.21)	<0.001
Model 3	1	0.71 (0.36–1.38)	0.10 (0.04–0.29)	<0.001

Model 1: Adjustments for age, sex, and energy intake.
Model 2: Model 1 + adjustments for physical activity and use of supplements, corticosteroids, and antiviral drugs.
Model 3: Model 2 + adjustment for BMI.
**Data obtained from Binary logistic regression.*

clinical magnitude, given that almost three times higher CRP levels were noted in the lowest tertile compared to the highest one (29.5 ± 2.1 vs. 11.8 ± 2.2 mg/L, $p < 0.001$). In agreement with our findings, a 2014 meta-analysis consisting of seven cross-sectional studies ($n = \sim$33,000 participants) demonstrated that high magnesium intake was associated with lower serum CRP levels (24). However, this study was conducted prior to the COVID-19 pandemic, and no subsequent study has been conducted so far. Furthermore, another non-COVID-19 study, employing a cohort design, found that magnesium intake was inversely associated with high-sensitivity CRP, interleukin-6, and tumor necrosis factor-alpha concentrations in postmenopausal women (34).

COVID-19 can affect multiple organ systems, including the gastrointestinal system, cardiovascular system, liver, kidneys, and respiratory system (20). Cytokine storm is the main cause of organ dysfunctions and death among COVID-19 patients, in which inflammatory cytokines such as interleukins, interferons, chemokines, and tumor necrosis factors are increasingly produced (20). Some mechanisms have been proposed to explain the link between magnesium intake and COVID-19 (**Figure 2**). Cytokine storm drains ATP in COVID-19, whose regeneration requires magnesium along with phosphate (35). Therefore, adequate magnesium body storage is crucial to avoid an aggressive magnesium deficiency in severe COVID-19 (36). Furthermore, magnesium plays an important role in the relaxation of bronchial smooth muscles, and thus its deficiency might result in respiratory dysfunction in COVID-19 patients (37). The innate immune system is the first line of defense in response to pathogens invasion, such as viral infections like COVID-19 (38). Finally, magnesium regulates the immune system in a variety of ways by orchestrating the activity of immune cells such as neutrophils and macrophages (39), activating T cells via MagT1 (40), and regulating vitamin D activity (41), hence improving the first line of defense in response to pathogens invasion and acting against viral infections like COVID-19 (38).

To the best of our knowledge, this is the first study examining the relationship between dietary magnesium intake and COVID-19 symptoms and severity. In addition to the severity and symptoms of COVID-19 disease, serum levels of inflammatory factors were investigated as predictive indices. Furthermore, many potential confounders were controlled for in this study. However, this study has some limitations that should be taken into account before interpreting the results. First, the cross-sectional design of this study does not allow for inferences about causation to be made. Second, even after adjusting for a variety of potential confounders, the possibility of residual confounding cannot be completely ruled out. Third, this was a single-center study. Although the study population included adults, it would be prudent to consider their sample size and the fact that they were all drawn from the same center when determining their generalizability to the general population. Fourth, despite an infectious disease physician's examination and confirmation of symptoms, we did not use a validated questionnaire to assess COVID-19 symptoms, which may introduce bias into reporting symptoms. Fifth, Using the FFQ to assess study participants' dietary intake could lead to a misclassification of their intake of magnesium. Sixths, serum magnesium levels were not determined to compare with dietary

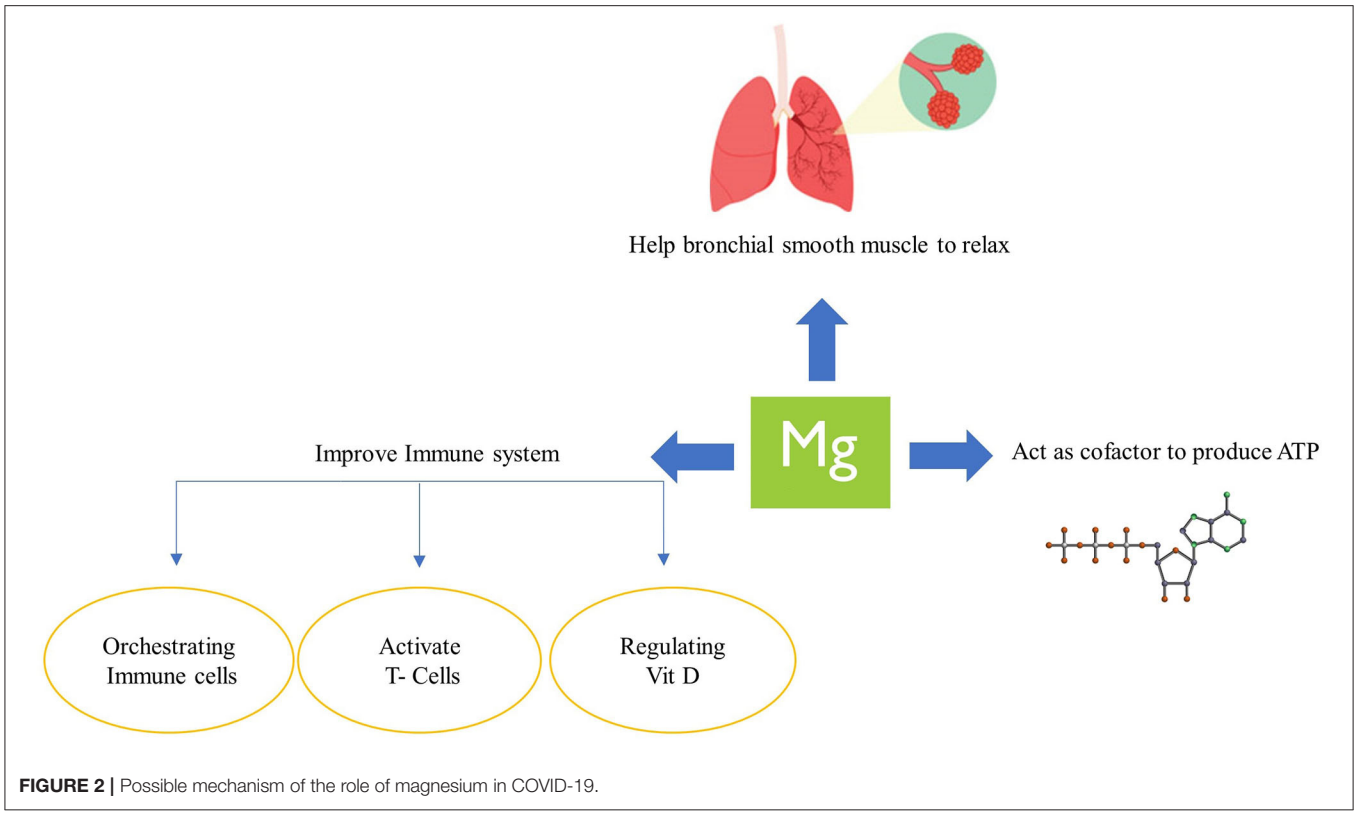

FIGURE 2 | Possible mechanism of the role of magnesium in COVID-19.

intake results. It would be suggested for future research to consider both the association of dietary magnesium intake and serum magnesium levels. Finally, we did not examine the socioeconomic status of participants, which may influence their dietary intake.

Although the current findings are encouraging, it should be noted that this is prognostic research based on habitual magnesium consumption and thus cannot be extrapolated as part of clinical recommendations. In some severe COVID-19 cases, as well as in other critical care cases, dietary magnesium intake may be insufficient to control serum and general body status; even oral magnesium supplementation may be inadequate in this scenario, and personalized parenteral administration may be required.

CONCLUSIONS

Magnesium is an anti-inflammatory mineral that plays a role in reducing inflammation and oxidative stress during cytokine storms and in relaxing airway smooth muscle. As a result of its role in systemic and respiratory problems in COVID-19, magnesium intake has gained more interest in this regard. While the association between serum magnesium levels and COVID-19 has been studied previously, little attention has been paid to the relationship between dietary magnesium intake as measured by the FFQ and COVID-19 severity and associated symptoms. We found that higher dietary magnesium intake was inversely associated with COVID-19 severity and symptoms in hospitalized patients. More precisely, higher magnesium intake was associated with a shorter duration of hospitalization and convalescence, as well as a lower chance of having COVID-19 symptoms, including dyspnea, cough, fever, chills, weakness, myalgia, nausea, vomiting, and sore throat. Additionally, a higher dietary magnesium intake was associated with lower inflammatory biomarker concentrations (CRP and ESR). We propose that future research examine additional nutrients and minerals that may be associated with COVID-19 severity and related symptoms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kashan University of Medical Sciences, IR.KAUMS.MEDNT.REC.1400.048. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SN-M and SM: conceptualization, formal analysis, writing—original draft, and writing—review and editing. AE, NZ, and

ME: data collection. AM and MT: supervision, conceptualization, methodology, investigation, funding acquisition, formal analysis, writing—original draft, and writing—review and editing. HS: writing—review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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BRIEF RESEARCH REPORT
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Impact of Prolonged COVID-19 Lockdown on Body Mass Index, Eating Habits, and Physical Activity of University Students in Bangladesh: A Web-Based Cross-Sectional Study

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Objectives: This current study aims to assess the prevalence and factors associated with body mass index (BMI), dietary patterns, and the extent of physical activities among university students following the prolonged coronavirus disease 2019 (COVID-19) lockdown in Bangladesh.

Methods: A cross-sectional web-based survey was conducted between July 10 to August 10, 2021, through a pre-designed Google Form to collect the data from Bangladeshi university students (age: ≥18 years). Informed consent was electronically obtained from each participant, and a simple snowball technique was employed during the sampling. Frequency and percentage distribution, paired *t*-test, chi-square [χ^2] test, and multinomial and binary logistic regression analyses were consecutively applied to analyze the collected data.

Results: Among the total participants ($n = 1{,}602$), 45.1% were female and 55.6% were 22–25 years' age group students. The BMI (mean ± standard deviation, SD) during the COVID-19 lockdown was 23.52 ± 7.68 kg/m^2, which was 22.77 ± 4.11 kg/m^2 during the pre-lockdown period (mean difference = 0.753; $p < 0.001$). The multinomial logistic regression analysis found a significant impact of gender [male vs. female: adjusted relative risk ratio (RRR) = 1.448; 95% confidence interval (CI) = 1.022, 2.053; $p = 0.037$], age (years) (<22 vs. >25: RRR =0.389, 95% CI = 0.213,0.710; $p = 0.002$, and 22–25 vs. >25: RRR = 0.473, 95% CI = 0.290, 0.772; $p = 0.003$), monthly family income (BDT) (<25,000 vs. >50,000: RRR = 0.525, 95% CI = 0.334,0.826; $p = 0.005$), university type (public vs. private: RRR = 0.540, 95% CI = 0.369, 0.791; $p = 0.002$), eating larger

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meals/snacks (increased vs. unchanged: RRR = 2.401, 95% CI = 1.597, 3.610; $p < 0.001$ and decreased vs. unchanged: RRR = 1.893, 95% CI = 1.218, 2.942; $p = 0.005$), and verbally or physically abuse (yes vs. no: RRR = 1.438, 95% CI = 0.977, 2.116; $p = 0.066$) on obesity during COVID-19 pandemic. Besides, the female students and those who have constant eating habits, were more likely to be underweight. Additionally, the binary logistic regression analysis found that the students from private universities [others vs. private: adjusted odds ratio (AOR) = 0.461, 95% CI = 0.313, 0.680; $p < 0.001$], urban areas (urban vs. rural: AOR = 1.451, 95% CI = 1.165, 1.806; $p = 0.001$), wealthier families (<25,000 BDT vs. >50,000 BDT: AOR = 0.727, 95% CI = 0.540, 0.979; $p = 0.036$), and who were taking larger meals/snacks (increased vs. unchanged: AOR = 2.806, 95% CI = 2.190, 3.596; $p < 0.001$) and had conflicts/arguments with others (no vs. yes: AOR = 0.524, 95% CI = 0.418, 0.657; $p < 0.001$), were significantly more physically inactive. Finally, the level of education and smoking habits significantly influenced the eating habits of university students during the extended strict lockdown in Bangladesh.

Conclusion: The current findings would be helpful tools and evidence for local and international public health experts and policymakers to reverse these worsening effects on students mediated by the prolonged lockdown. Several effective plans, programs, and combined attempts must be earnestly implemented to promote a smooth academic and daily life.

Keywords: obesity, overweight, eating behaviors, physical inactivity, cross-sectional web-based study, Bangladeshi university students

INTRODUCTION

Since its inception back in December 2019, the novel coronavirus disease (COVID-19), caused by a deadly and pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been continuing to bring havoc to our civilization, impacting not only the individual lives but also the global systems ranging from trades to national policies (1). Considering the calamitous worldwide situation with a rapid surge of infections, mortality, and morbidity, the World Health Organization (WHO) declared this viral invasion a pandemic on March 11, 2020 (1, 2). Despite the concerted efforts of both the local governments and the international endeavors, the pandemic persists worldwide. On top of that, we are now facing newer challenges due to multiple variants of the virus and a worldwide vaccine shortage, and inequitable distribution. Meanwhile, the notion of "new-normal" trends, including several anti-epidemic strategies, such as social distancing, shutdown or lockdown, isolation, quarantine, and so on, were introduced to counteract the devastating effects and challenges of COVID-19. However, these anti-COVID measures are increasingly impacting all classes of people with sheer frustration, especially university students, with far-reaching effects on their mental, physical, and social lives (2–4).

Being one of the most densely populated countries globally, with around 165 million people, Bangladesh was at a higher risk of inciting the virus among its citizens more swiftly. Besides, the relatively poor health care facilities and institutional capacities have made Bangladesh vulnerable to the COVID-19 outbreak (4). Nevertheless, Bangladesh got the first COVID-19 cases on March 8, 2020, and from March 26, 2020, the Government of Bangladesh declared lockdowns with several restrictive measures and extended these declarations throughout different time slots, so far (5). A nationwide emergency was imposed, including the closure of all categories of educational institutions, in line with the WHO and other local health experts' recommendations, to curb the spread of the virus. However, these prolonged home confinements have negatively influenced socioeconomic status, including physical and mental health behaviors. Remarkably, the students from all grades were affected badly due to the closedown of educational institutions as part of the lockdown measures (6). Around 2.6 million tertiary level (college or university) students in Bangladesh are now suddenly facing an indefinite halt on their academic activities, delaying their graduation and, ultimately, their timely entrance into the job market (6).

The imposed COVID-19 lockdown and its irrefutable regulations significantly influenced human beings' daily routine and activities, including eating habits, dietary choices, and physical and body weight-related behaviors (7). Even though the direct influence of the COVID-19 pandemic on physical activity and body weight is still not clearly defined, a study in Italy found increased consumption of unhealthy food and decreased physical activity among participants during lockdown (8). Furthermore, school closures dramatically reduced exercise or physical activity and prolonged sleep and screen time among children and adolescents (9). Robinson et al. (10) disclosed several alarming results that 56% of UK adults reported more frequent snacks,

and 40% of the population exercised less frequently during the COVID-19 shutdown. Besides, the study also revealed that the people fought against numerous barriers to physical activity and healthy eating, where the difficulties in accessing healthy food, lack of motivation, and insufficient mental and social support were associated with higher BMI. According to another study, students from high schools, colleges, and graduate schools showed a significant increase in both BMI (21.8–22.6 kg/m^2) and obesity (10.5–12.9%; $p < 0.001$) due to the severe COVID-19 lockdown in China (11). Alfawaz et al. (12) reported that the people of Saudi Arabia walking four times/week reduced their walking during COVID-19 home quarantine compared to before COVID-19 (before vs. during = 30.5 vs. 29.1%). In contrast, the prevalence of taking snacks between meals increased significantly during quarantine (27.4 vs. 29.4%, $p < 0.001$). Another study demonstrated that 32% of Saudi Arabian gained higher BMI, whereas 22% lost their body weight during the COVID-19 lockdown. Though the extent of physical activity was reduced, the sleep time and calorie intake increased significantly ($p = 0.0001$) (13). A worldwide cohort study, conducted by Urzeala et al. (14) on participants from 67 countries, concluded that BMI increased significantly during the COVID-19 lockdown.

On the contrary, physical activity significantly decreased by 31.25 and 26.05% for the youth and young (18–35 years) and adults (35–65 years), respectively. In a systematic review, Bakaloudi et al. (15) summarized that 11.1–72.4% of the population over the age of 16 had a significant increase in their body weight, whereas the elderly population over the age of 60 showed a notable loss in body weight (7.2–51.4%) and signs of malnutrition.

Moreover, the COVID-19 outbreak has a diversified impact on smoking. Some people viewed the lockdown as an opportunity to quit smoking, whereas others relied on smoking to cope with stress and emotions (16). A UK study revealed around a 9% increase in smoking or relapsed smoking intensity during the COVID-19 outbreak. This was, however, evidently associated with elevated symptoms of psychological disorders, impaired sleeping, overweight, and reduced quality of life caused by prolonged lockdown (17, 18). The overweight population is more likely to smoke than normal-weight people, and then, again, cessation of smoking may increase body weight (19, 20). Therefore, prolonged lockdown can intensely affect the dynamics of body weight and smoking behavior.

To the best of our knowledge, no study reported the impact of COVID-19 lockdown on BMI, eating habits, and the extent of physical activities among the Bangladeshi population, including university students. However, it is imperative to take prompt measures to mitigate the impact of these lost school hours, learning losses, and, ultimately, the associated mental pressure and physical disturbances they had faced during the lockdowns. So, we examined several sociodemographic factors, including perceived mental health conditions (depression, anxiety, loneliness, and suicidal thoughts), sleep disturbances, physical disturbances, and interpersonal behaviors (conflict with others, physically or verbally abused) potentially associated with BMI, eating habits and physical activity. This, in turn, necessitates a comprehensive assessment of the changes in their lifestyle, if any, to address the issues in the post-lockdown period. Besides, there is strong evidence of changing patterns in their physical and habitual activities, body weight, and other related parameters. Therefore, the current study plans to point out perceived changes between "before" and "during" the COVID-19 lockdown from the viewpoint of BMI, eating habits, and the extent of physical activity among university students in Bangladesh. The study results can further be used by national and international academic professionals, epidemiologists, or policymakers associated with educational institutions to get an in-depth view of the status of their students. Accordingly, effective and targeted actions might be taken for the students to ease the impacts induced by the prolonged social lockdown and, thereby get them back to normal life.

METHODS

Study Design

A questionnaire-based Google Form was generated and designed for data collection to perform this cross-sectional study. The questionnaire set was drafted under four sections. Section A contained several questions regarding sociodemographic information like gender, age, education level, university type, current living area, monthly family income, and smoking habit. Section B consisted of information regarding BMI (body height and body weight "before COVID-19 lockdown" and "during COVID-19 lockdown" body weight), and section C contained physical activity and eating habit-related questions. Finally, section D had several further mental health-related (for example: sleep disturbance, feeling loneliness, feeling depressed, feeling anxious, and suicidal thoughts), interpersonal (for example conflict/arguments with others, verbally or physically abused), and weight management-related (for example, physical exercise) questions. However, while designing the questionnaire, we considered similar previous studies for adaptation of the questions and all the parameters about our research objectives (10, 21, 22), and several BMI-related parameters were further adjusted in the Bangladesh perspective according to WHO expert consultation (23). Accordingly, 21 questions were finalized and initially drafted in English, which was translated into the Bangla version for the convenience and better understanding of the participants. A professional way for a forward-backward translation process of the questionnaire was adopted with the help of a bilingual expert having good knowledge of medical terminology (24). Moreover, a total of 12 hypotheses have been synthesized to analyze the association between the present study's covariates and outcome variables based on the target group of this study (8–10, 25–29). The study hypothesis development section was described in the **Supplementary Material**. Besides, to better understand the current study objective and hypothesis, a tentative conceptual framework might be sketched in **Supplementary Figure 1**.

Data Collection and Sampling Technique

The students from the leading three categorized universities: public universities governed by the government, private universities conducted by various private organizations, and

other universities (various medical colleges or universities equivalent to the government or private colleges run by the government or private organizations) in Bangladesh were targeted for data collection. As we had no contact details of all university students, a simple web-based snowball sampling strategy has been employed to recruit the target samples in this current pandemic situation (2, 24, 30). The designed Google Form link was shared with them through various popular social media platforms (Facebook, Messenger, Instagram, IMO, WhatsApp, and so on) to collect data relevant to this study. The respondents were requested but not mandatorily to further share the link with other students who might meet the eligibility criteria for this survey. A widely used standard equation, $n = (Z_{\alpha/2})^2 \times [p(1\text{-}p)/(d)^2]$, was applied for estimating the size of the study sample, where n denotes the sample size, and p represents the proportion of the population (here 50% were expected; $p = 0.5$). The $Z_{\alpha/2}$ (1.96) means the normal distribution value at the 5% significance level, and d indicates the standard error at the 5% tolerated level (24). According to the formula, the calculated sample was 384. Hence a total of 1,718 participants participated voluntarily in the survey between July 10 to August 10, 2021, with no financial compensation. However, we had to eliminate 6.7% ($n = 116$) incomplete or partial responses, while cleaning the raw datasheet. Finally, we have analyzed a total of 1,602 participants, which might lead to more comprehensive and reliable study results.

Eligibility, Ethics, and Approval

University students of Bangladesh (age: 18 years or above), who have internet access who understood the purpose of this study and were willing to take part, were encouraged to respond to the survey. Additionally, the participants, who had clinical symptoms of dementia during participation in the study and had psychological disturbance before COVID-19 lockdown, were immensely requested to avoid responding to the survey. The questionnaire began with a brief introduction regarding the study's objectives, a declaration of respondents' anonymity, instructions on filling out the survey, and sharing the link with other eligible participants. Informed consent from each participant was also collected virtually before the participation. All the collected data were privately and confidentially preserved. Besides, all the guidelines and ethical protocols of the World Medical Declaration of Helsinki were strictly followed in this questionnaire-based survey. Furthermore, the Human Ethics Committee, State University of Bangladesh, has approved all the protocols and procedures of the study and provided an ethical approval number (2021-06-17/SUB/ERC/0004) after a critical revision and evaluation of the research details.

Independent Variables

In this current analysis, we included several sociodemographic factors, such as gender (male vs. female), age (18 to below 22 years, 22–25, and above 25 years), education level (lower grade-1st/2nd/3rd year vs. higher grade-4th/5th/Master's or above), current living area (urban vs. rural), monthly family income [below 25,000 BDT, 25,000–50,000 BDT, and above 50,000 BDT; 1 USD = 84.48 Bangladeshi Taka (BDT) as of August 22, 2021], university type (private, public, and others), smoking habits (yes vs. no), meal patterns, several physical and psychological parameters, and interpersonal behavioral manifestations. Physical activity, physical exercise, sleep disturbance, and meal patterns were subdivided into three options "increased," "deceased," and "unchanged." At the same time, the psychological parameters (depression, anxiety, loneliness, and suicidal thoughts) and interpersonal behaviors (conflicting with others and physically or verbally abused) were categorized as yes vs. no.

Assessment of BMI and Other Dependent Variables

In this survey, all the participated participants mandatorily filled their height and two weights of "before COVID-19 lockdown" and "during COVID-19 lockdown." BMI of each participant was measured from the very well-known ratio of weight (kg)/height (m^2), and the cut-off scores for Asia and South-Asian countries were adopted to define the underweight (BMI: <18.5 kg/m^2), normal weight (BMI: $\geq$18.5–23 kg/m^2), overweight (BMI: $\geq$23–27.5 kg/m^2), and obesity (BMI $>$ 27.5 kg/m^2) according to the WHO expert consultation (23). Besides, eating a larger amount of meals or snacks (increased, decreased, unchanged) and physical inactivity (increased, decreased, unchanged) were two other dependent variables of this current analysis.

Statistical Analysis

Descriptive statistics (frequency and percentage distribution) for sociodemographic characteristics of the eligible participants who answered the questionnaire entirely were assessed during univariate analysis. Besides, the mean and standard deviation (SD) were also measured for comparing the BMI of the participants "before" and "during" COVID-19 lockdown. Paired t-test was applied to observe whether BMI increased significantly in the "during" social lockdown period compared to the BMI "before" the COVID-19 lockdown. Association of BMI, eating large meals/snacks, and physical activity with different socioeconomic, demographic, psychological, and interpersonal behavior was evaluated using the chi-square (χ^2) test of association. Multinomial logistic regression was used to find the potential factors associated with various degrees of BMI. In contrast, binary logistic regression was applied to get the factors potentially related to eating larger meals/snacks and physical inactivity among university students in Bangladesh.

Software

We used software IBM SPSS version 20 to apply the above-mentioned models in our data. We also used software STATA version 15 and ggplot2 package from R version 4.0.5 for drawing graphs.

RESULTS

Sociodemographic Characteristics

A total of 1,602 students [average height (mean $\pm$ standard deviation, SD) = 164.5 $\pm$ 9.5 cm] responded to the questionnaire

TABLE 1 | Descriptive statistics of body mass index (BMI) before and during COVID-2019 lockdown by different socio-demographic characteristics (p-value obtained from paired t-test).

Variables	Options	Body mass index (BMI)				Mean difference	Paired *t*-test	*p*-value
		Current BMI		BMI before COVID-19				
		Mean	SD	Mean	SD			
Overall		23.526	7.680	22.772	4.111	0.753	4.42	**<0.001**
Gender	Male	23.993	9.5872	23.0896	3.9517	0.904	3.03	**0.002**
	Female	22.957	4.2842	22.3871	4.2691	0.570	5.33	**<0.001**
Age (years)	<22	23.076	4.4475	22.4844	4.3552	0.592	4.10	**<0.001**
	22–25	23.207	3.9613	22.6815	3.9179	0.525	7.59	**<0.001**
	>25	25.524	16.887	23.6462	4.2197	1.87	1.80	**0.036**
Education level	Lower grade	23.167	4.2921	22.5739	4.3104	0.593	6.07	**<0.001**
	Higher-grade	23.968	10.425	23.0182	3.8410	0.950	2.63	**0.004**
Current living area	Urban	23.435	4.0656	22.8462	4.0763	0.589	7.76	**<0.001**
	Rural	23.666	11.140	22.6609	4.1652	1.005	2.41	**0.007**
Monthly family income (BDT)	<25,000	23.446	11.244	22.2238	3.9703	1.22	2.85	**0.002**
	25,000–50,000	23.378	4.0317	22.8885	4.0317	0.490	6.28	**<0.001**
	>50,000	23.951	4.0939	23.5563	4.3725	0.394	3.37	**<0.001**
University type	Public	23.236	3.9505	22.4564	3.6152	0.780	7.10	**<0.001**
	Private	23.709	9.9152	22.9181	4.4151	0.791	2.49	**<0.001**
	Others	23.719	4.6756	23.2861	4.2356	0.433	2.59	**<0.001**
Smoking habit	Yes	23.823	3.7346	23.0941	3.8338	0.729	3.78	**<0.001**
	No	23.477	8.1505	22.7200	4.1543	0.757	3.86	**<0.001**

completely; among them, 51.7% ($n = 829$) and 38.9% ($n = 623$) were from private and public universities, respectively, and 54.95% ($n = 880$) of the total participants were male students (**Supplementary Table 1**). Most of the students belonged to the age group 22-25 (55.6%; $n = 890$) from the three age categories (18 to below 22 years, 22–25 years, and above 25 years), and around 60.5 % ($n = 969$) of the respondents were living in the urban area. More than half of the participants (55.2%, $n = 884$) were from the lower grade education level (level of schooling: 1st/2nd/3rd year), and most of the students' (40.1%, $n = 642$) monthly family income was between 25,000–50,000 BDT (Bangladeshi Taka; 1 USD = 84.48 BDT as of August 7, 2021). Besides, out of 1,602 Bangladeshi university students, 227 (14.2%) had regularly smoking habits. Likewise, all the demographic variables with their descriptive statistics are summarized in **Supplementary Table 1**.

About 35.1% of the participants took larger meals/snacks during the COVID-19 lockdown, while 56.4 and 45.1% of the students decreased their physical activity and physical exercise, respectively, compared to their normal days before the lockdown. Besides, 43.8% of the students faced sleep disturbance. Alarmingly, 68.5% of the students felt lonely, and more than 70% of the participants voted that they were suffering from depression and anxiety. More than half of the respondents had suicidal thoughts, while 28.7% ($n = 459$) of the participants were orally or physically abused (**Supplementary Table 1**).

Comparison of the Degree of BMI Between "Before" and "During" COVID-19 Lockdown

It is noted that 6.4% (during lockdown: 42.7% and before lockdown: 36.3%; **Supplementary Table 1**) and 2.1% (during lockdown: 13.8% and before lockdown: 11.7%; **Supplementary Table 1**) of the students gained overweight and obesity, respectively, due to over 1 year of home confinement and closure of educational institution in Bangladesh. On the other hand, due to the prolonged COVID-19 lockdown, significant changes appeared in the degree of BMI among the study participants with an increased mean difference of 0.753 ($p < 0.001$), which is described in **Table 1** with *p*-values obtained from paired *t*-test. Before lockdown, there were 39.9% ($n = 639$) of the participants with normal BMI, which has now decreased to 33.3% ($n = 533$). Besides, **Figure 1** delineated a significant increasing trend for both overweight and obese during COVID-19 lockdown; in contrast, there was a decreasing trend for both normal BMI and underweight participants.

The BMI increased significantly within the lockdown, with a mean difference of 0.904 ($p = 0.002$) in male participants. In contrast, the increase of BMI was soaring at the highest rate for the > 25 years age group among the three age groups with a mean difference of 1.87 ($p = 0.036$). Consequently, the upsurge of BMI during the lockdown was the highest rate among higher-grade (4th/5th/Master's or above) university students with a mean difference of 0.950 ($p = 0.004$), while the

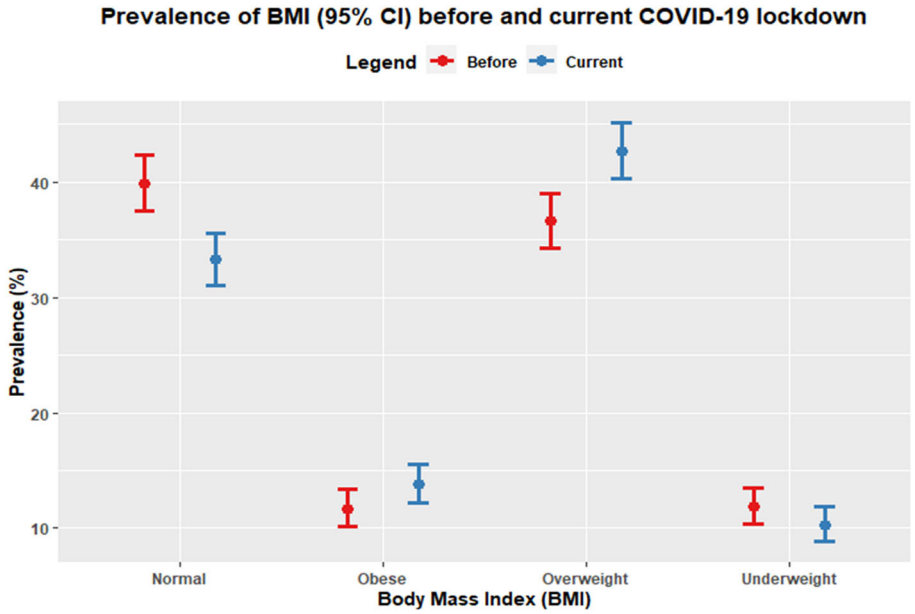

FIGURE 1 | The prevalence of body mass index (BMI) "before" and "current or during" the COVID-19 lockdown among the university students of Bangladesh.

private university students showed the most elevation of BMI following the prolonged lockdown (mean difference = 0.791, $p < 0.001$). Moreover, the rural and urban students exhibited higher BMI during lockdown than the before lockdown, with a mean difference of 1.005 (mean ± SD: 23.666 ± 11.14 vs. 22.6609 ± 4.1652; $p = 0.007$) and 0.589 (23.435 ± 4.0656 vs. 22.8462 ± 4.0763; $p < 0.001$), respectively**.** Furthermore, participants from three categories according to monthly family income (<25,000 BDT, 25,000–50,000 BDT, and >50,000 BDT) displayed increased BMI with mean difference 1.22 ($p = 0.002$), 0.490 ($p < 0.001$), and 0.394 ($p < 0.001$), respectively. Public and private university students showed elevated BMI with a unique mean difference of almost 0.8 ($p < 0.001$), whereas the students from other institutions (government colleges or various medical colleges) showed a small increased mean difference of 0.433 ($p < 0.001$). Finally, both smokers and non-smokers showed 0.729 ($p < 0.001$) and 0.757 ($p < 0.001$) mean differences in BMI, respectively, between before lockdown and during lockdown (**Table 1**). Besides, the prevalence of BMI among the students from various sociodemographic categories during the COVID-19 lockdown was illustrated in **Figure 2**.

Chi-Square (χ^2) Analysis

The Degree of BMI and Associated Potential Factors

The χ^2 analysis was performed to investigate the association of different sociodemographic, physical, psychological, and interpersonal behavioral factors with the degree of BMI among Bangladeshi university students, and the findings were tabulated in **Table 2**. The χ^2 test identified a significant association with all the listed variables with the degree of BMI, except the current living area of the participants, physical activity, and mental disturbance parameters ($p > 0.05$).

Numerically, the male students showed 7.6% (46.1 vs. 38.5%; $p < 0.001$) and 2% (14.7 vs. 12.7%; $p < 0.001$) more likely to be overweight and obese, respectively, compared to the female students. The students with > 25 years exhibited significantly more overweight (53.8%) and obesity (17.8%) compared to the other two age groups of < 22 years (overweight = 36.8% and obese = 12.9%) and 22–25 years (overweight = 42.7% and obesity = 13.1%). Besides, higher grade students were 4.4% (45.1 vs. 40.7%; $p = 0.041$), and 1% (14.3 vs. 13.3%; $p = 0.041$) more overweight and obese, respectively, than the lower grade students.

Moreover, the students, who belonged to families with monthly income >50,000 BDT, significantly showed 1.8% (44.4 vs. 42.6%; $p = 0.042$), and 2.5% (44.4 vs. 41.9%; $p = 0.042$) more overweight and 6.8% (17.9 vs. 11.1%; $p = 0.042$), and 3.7% (17.9 vs. 14.2%; $p = 0.042$) more obese compared to the rest two counter groups (<25,000 and 25,000–50,000 BDT), respectively. Similarly public and private university students significantly showed 10.4% (36 vs. 46.4%; $p = 0.003$) and 5.1% (36 vs. 41.1%; $p = 0.003$) less overweight and 11.7 (10.3% vs. 22%; $p = 0.003$), and 7% (15 vs. 22%; $p = 0.003$) less obesity, respectively, compared to the other university students after the prolonged lockdown. Besides, participants taking larger meals or snacks were 7.6% (48 vs. 40.4%; $p < 0.001$) and 8.5% (48 vs. 39.5%; $p < 0.001$) more overweight and 2.7% (18.1 vs. 15.4%; $p < 0.001$) and 8.9% (18.1 vs. 9.2%; $p < 0.001$) more obese compared to the participants with decreased and unchanged food habit, respectively. The effect of smoking is also evident from the data with 7.2% (48.9 vs. 41.7%; $p = 0.091$) and 0.4% (14.1 vs. 13.7%; $p = 0.091$)

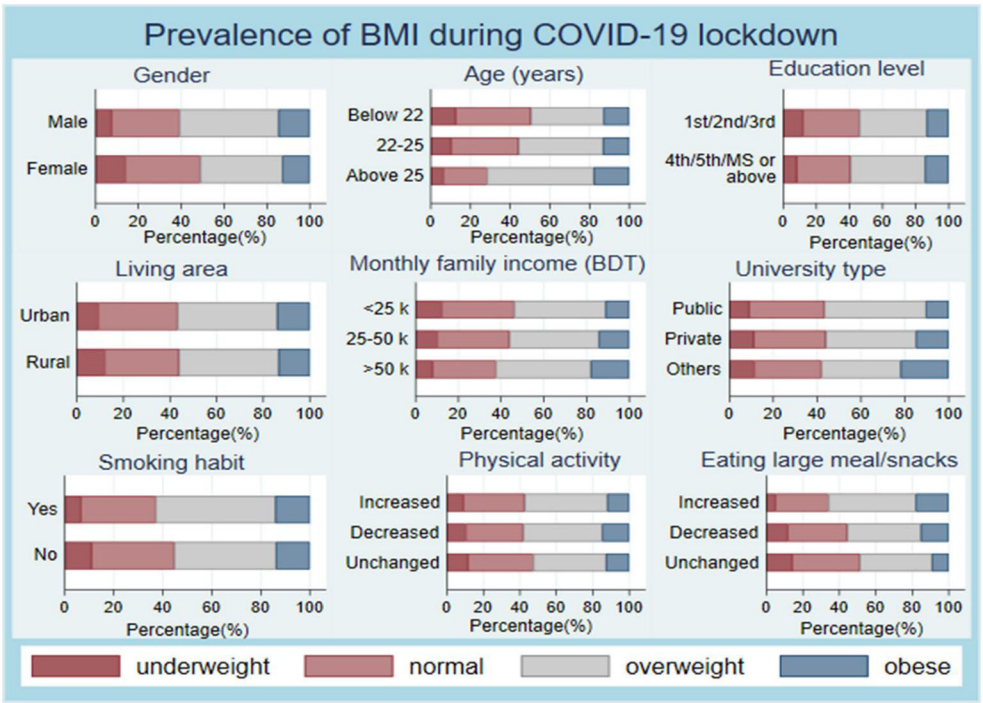

FIGURE 2 | The prevalence of BMI among several sociodemographic groups of university students in Bangladesh during the prolonged COVID-19 lockdown.

more overweight and obese participants in the smokers than the non-smoker participants. Besides, participants with suicidal thoughts showed significantly 7.5% (19.7 vs. 12.2%; $p = 0.002$) more obese. Finally, verbally or physically abused students were 6.9% (18.7 vs. 11.8%; $p = 0.004$) more obese than the other participants, and students who involved conflicting or arguments with others had 5.8% (16.5 vs. 10.7%; $p = 0.007$) more obesity than others.

Eating Habits and Associated Potential Factors

The results from the χ^2 test (**Table 3**) demonstrated that age, education level, and smoking habit significantly influenced the outcome variable, which is "eating large meals/snacks," among the university students following the prolonged COVID-19 lockdown in Bangladesh. Students from the age group above 25 years exerted 11.1% (40.1 vs. 29%, $p = 0.014$) and 3.1% (40.1 vs. 37%, $p = 0.014$) more increased eating of larger meals/snacks than the other two age groups (>22 and 22–25 years, respectively), whereas 1% (25.2 vs. 24.2%, $p = 0.014$) and 4.1% (25.2 vs. 21.1%, $p = 0.014$) of students from below 22 years age group showed more decreased eating of larger meals/snacks than the other two age groups (22–25 and >25 years, respectively). Besides, 2.1% (24.9 vs. 22.8%, $p < 0.001$) of students in lower grade levels and 13.5% (46.7 vs. 33.2%, $p < 0.001$) of smokers decrease their consumption of larger meals/snacks compared to their counter groups, respectively, during the COVID-19 lockdown in Bangladesh.

Physical Activity and Associated Potential Factors

It is clear from **Table 3** that all the variables, except age, education level, and smoking habit, were significantly associated with the university students' physical activity during the COVID-19 lockdown in Bangladesh. Male students showed 4.9% (19.3 vs. 14.4%, $p = 0.018$) more increased physical activity than the female students. Contrary, female students exhibited 5.8% more decreased physical activity than male students. Similarly, rural participants showed 3.6% (19.3 vs. 15.7%, $p < 0.001$) more increased physical activity compared to the urban participants, whereas urban participants exerted 10.9% (60.7 vs. 49.8%, $p < 0.001$) more decreased physical activity compared to the rural participants. Besides, monthly family income and university type have significantly influenced the status of physical activity of the current university students. Notably, the participants involved in conflict/argument with others and abused verbally or physically were more likely to have decreased physical activity by 17.3% (64.4 vs. 47.1%, $p < 0.001$) and 1.6% (57.5 vs. 55.9%, $p = 0.057$), respectively, than their counter groups. Besides, the larger meals/snacks takers manifested 25.7% (69.8 vs. 44.1%, $p < 0.001$) more decreased physical activity than the group of unchanged amount meals/snacks takers.

Regression Analysis

Multinomial Regression for the Degree of BMI

Multinomial logistic regression analysis was carried out to assess the significant association of factors with underweight, overweight, and obese respondents compared to with normal

TABLE 2 | Chi-square (χ^2) test for finding potential association of sociodemographic and several physical, psychological, and interpersonal behavioral factors with the degree of body mass index (BMI) among university students following prolonged COVID-19 lockdown in Bangladesh ($N = 1,602$).

Variables	Categories	Current BMI after prolonged COVID 19 lockdown								*p*-value
		Underweight		Normal		Overweight		Obese		
		N	%	*N*	%	*N*	%	*N*	%	
Gender	Male	66	7.5	279	31.7	406	46.1	129	14.7	**<0.001**
	Female	98	13.6	254	35.2	278	38.5	92	12.7	
Age (years)	<22	58	12.5	176	37.8	171	36.8	60	12.9	**<0.001**
	22–25	91	10.2	302	33.9	380	42.7	117	13.1	
	>25	15	6.1	55	22.3	133	53.8	44	17.8	
Education level (level of schooling)	Lower grade	106	12.0	300	33.9	360	40.7	118	13.3	**0.041**
	Higher-grade	58	8.1	233	32.5	324	45.1	103	14.3	
Current living area	Urban	89	9.2	331	34.2	413	42.6	136	14.0	0.342
	Rural	75	11.8	202	31.9	271	42.8	85	13.4	
Monthly family income (BDT)	<25,000	74	11.9	213	34.4	264	42.6	69	11.1	**0.042**
	25,000–50,000	63	9.8	219	34.1	269	41.9	91	14.2	
	>50,000	27	7.9	101	29.7	151	44.4	61	17.9	
University type	Public	56	9.0	214	34.3	289	46.4	64	10.3	**0.003**
	Private	91	11.0	273	32.9	341	41.1	124	15.0	
	Others	17	11.3	46	30.7	54	36.0	33	22.0	
Smoking habit	Yes	15	6.6	69	30.4	111	48.9	32	14.1	**0.091**
	No	149	10.8	464	33.7	573	41.7	189	13.7	
Eating large meals or snacks	Increased	28	5.0	163	29.0	270	48.0	102	18.1	**<0.001**
	Decreased	45	11.7	125	32.6	155	40.4	59	15.4	
	Unchanged	91	13.9	245	37.4	259	39.5	60	9.2	
Physical exercise	Increased	20	6.5	102	33.1	154	50.0	32	10.4	**<0.001**
	Decreased	66	9.1	218	30.2	323	44.7	116	16.0	
	Unchanged	78	13.7	213	37.3	207	36.3	73	12.8	
Physical activity	Increased	24	8.8	93	33.9	124	45.3	33	12.0	0.479
	Decreased	92	10.2	287	31.8	390	43.2	134	14.8	
	Unchanged	48	11.3	153	36.0	170	40.0	54	12.7	
Sleep disturbance	Increased	73	10.4	232	33.1	296	42.2	100	14.3	0.927
	Decreased	40	10.4	126	32.6	162	42.0	58	15.0	
	Unchanged	51	9.9	175	34.0	226	43.9	63	12.2	
Feeling lonely	Yes	116	10.6	354	32.2	470	42.8	158	14.4	0.497
	No	48	9.5	179	35.5	214	42.5	63	12.5	
Feeling depressed	Yes	124	10.8	371	32.3	493	42.9	161	14.0	0.461
	No	40	8.8	162	35.8	191	42.2	60	13.2	
Feeling anxious	Yes	124	10.7	374	32.2	499	43.0	164	14.1	0.451
	No	40	9.1	159	36.1	185	42.0	57	12.9	
Suicidal thoughts	Yes	35	10.3	113	33.2	125	36.8	67	19.7	**0.002**
	No	129	10.2	420	33.3	559	44.3	154	12.2	
Conflict/argument with others	Yes	79	9.2	281	32.9	354	41.4	141	16.5	**0.007**
	No	85	11.4	252	33.7	330	44.2	80	10.7	
Verbally or physically abused	Yes	41	8.9	146	31.8	186	40.5	86	18.7	**0.004**
	No	123	10.8	387	33.9	498	43.6	135	11.8	

weight after adjusting for other factors, and the outcomes were abridged in **Table 4**.

The female students were significantly more likely to be risky of being underweight than male students [male vs. female: RRR = 0.590, 95% confidence interval (CI): 0.400, 0.869; $p = 0.008$]. In contrast, the male students were around 1.5 times more likely to be risky for being obese compared to the female students (male vs. female: RRR = 1.448, 95% CI: 1.022, 2.053; $p = 0.037$), respectively. The higher age category (>25 years) was significantly more likely to be risky for being both overweight

TABLE 3 | Chi-square (χ^2) test for finding the potential association of sociodemographic factors impacting eating larger meals/snacks and physical activity among university students following prolonged lockdown in Bangladesh ($N = 1,602$).

Variables	Categories	Eating larger meals or snacks							Physical activity						
		Increased		Decreased		Unchanged		*p*-value	Increased		Decreased		Unchanged		*p*-value
		N	%	*N*	%	*N*	%		*N*	%	*N*	%	*N*	%	
Gender	Male	304	34.5	209	23.8	367	41.7	0.757	170	19.3	473	53.8	237	26.9	**0.018**
	Female	259	35.9	175	24.2	288	39.9		104	14.4	430	59.6	188	26.0	
Age (years)	<22	135	29.0	117	25.2	213	45.8	**0.014**	79	17.0	257	55.3	129	27.7	0.598
	22–25	329	37.0	215	24.2	346	38.9		149	16.7	516	58.0	225	25.3	
	>25	99	40.1	52	21.1	96	38.9		46	18.6	130	52.6	71	28.7	
Education level	Lower grade	268	30.3	220	24.9	396	44.8	**<0.001**	152	17.2	499	56.4	233	26.4	0.983
	Higher-grade	295	41.1	164	22.8	259	36.1		122	17.0	404	56.3	192	26.7	
Current living area	Urban	331	34.2	237	24.5	401	41.4	0.586	152	15.7	588	60.7	229	23.6	**<0.001**
	Rural	232	36.7	147	23.2	254	40.1		122	19.3	315	49.8	196	31.0	
Monthly family income (BDT)	<25,000	209	33.7	145	23.4	266	42.9	0.107	109	17.6	301	48.5	210	33.9	**<0.001**
	25,000–50,000	248	38.6	154	24.0	240	37.4		107	16.7	394	61.4	141	22.0	
	>50,000	106	31.2	85	25.0	149	43.8		58	17.1	208	61.2	74	21.8	
University type	Public	241	38.7	142	22.8	240	38.5	0.127	109	17.5	363	58.3	151	24.2	**<0.001**
	Private	266	32.1	208	25.1	355	42.8		135	16.3	482	58.1	212	25.6	
	Others	56	37.3	34	22.7	60	40.0		30	20.0	58	38.7	62	41.3	
Smoking habits	Yes	106	46.7	50	22.0	71	31.3	**<0.001**	35	15.4	127	55.9	65	28.6	0.641
	No	457	33.2	334	24.3	584	42.5		239	17.4	776	56.4	360	26.2	
Conflict/arguments	Yes								140	16.4	551	64.4	164	19.2	**<0.001**
	No								134	17.9	352	47.1	261	34.9	
Verbally/physically abused	Yes								90	19.6	264	57.5	105	22.9	**0.057**
	No								184	16.1	639	55.9	320	28.0	
Large meals/snacks	Increased								89	15.8	393	69.8	81	14.4	**<0.001**
	Decreased								89	23.2	221	57.6	74	19.3	
	Unchanged								96	14.7	289	44.1	270	41.2	

TABLE 4 | Adjusted relative risk ratio (RRR) from multinomial logistic regression analysis for underweight, overweight, and obese respondents in comparison with normal weight respondents of university students following prolonged COVID-19 lockdown in Bangladesh.

Covariates	Categories	Underweight				Overweight				Obesity			
		RRR	*p*-value	95% CI		RRR	*p*-value	95% CI		RRR	*p*-value	95% CI	
				Lower	Upper			Lower	Upper			Lower	upper
Gender	Male	0.590	**0.008**	0.400	0.869	1.225	0.110	0.955	1.571	1.448	**0.037**	1.022	2.053
	Female[R]												
Age (years)	<22	0.732	0.413	0.348	1.543	0.352	**<0.001**	0.224	0.552	0.389	**0.002**	0.213	0.710
	22–25	0.900	0.752	0.470	1.724	0.470	**<0.001**	0.324	0.681	0.473	**0.003**	0.290	0.772
	>25[R]												
Education level	Lower grade	1.430	0.103	0.931	2.197	1.240	0.123	0.943	1.631	1.228	0.294	0.837	1.803
	Higher-grade[R]												
Monthly family income (BDT)	<25,000	1.486	0.142	0.876	2.520	0.889	0.488	0.638	1.239	0.525	**0.005**	0.334	0.826
	25,000–50,000	1.138	0.623	0.678	1.911	0.810	0.193	0.589	1.112	0.688	**0.079**	0.454	1.044
	>50,000[R]												
University type	Public	0.821	0.341	0.548	1.231	0.993	0.959	0.769	1.283	0.540	**0.002**	0.369	0.791
	Others	1.106	0.758	0.583	2.100	0.882	0.585	0.563	1.383	1.470	0.160	0.859	2.517
	Private[R]												
Smoking status	Yes	0.924	0.804	0.494	1.726	1.104	0.577	0.779	1.564	0.836	0.475	0.513	1.365
	No[R]												
Eating larger meals or snacks	Increased	0.495	**0.005**	0.302	0.813	1.476	**0.007**	1.112	1.959	2.401	**<0.001**	1.597	3.610
	Decreased	1.034	0.881	0.668	1.601	1.111	0.502	0.817	1.511	1.893	**0.005**	1.218	2.942
	Unchanged[R]												
Physical exercise	Increased	0.637	0.117	0.362	1.120	1.474	**0.021**	1.059	2.050	0.702	0.166	0.425	1.159
	Decreased	0.998	0.992	0.666	1.495	1.451	**0.008**	1.102	1.911	1.174	0.406	0.804	1.716
	Unchanged[R]												
Suicidal thoughts	Yes	1.066	0.787	0.669	1.700	0.767	0.094	0.563	1.047	1.296	0.197	0.874	1.920
	No[R]												
Conflict/arguments with others	Yes	0.910	0.635	0.615	1.345	0.922	0.531	0.716	1.188	1.226	0.271	0.853	1.763
	No[R]												
Verbally or physically abused	Yes	0.953	0.840	0.601	1.512	0.968	0.828	0.722	1.297	1.438	**0.066**	0.977	2.116
	No[R]												

[R]*Reference category.*

TABLE 5 | Logistic regression analysis for finding the potential associated factors with "conflict/arguments with others" and "physically or verbally abused by others" following prolonged COVID-19 lockdown among Bangladeshi university students.

Covariates	Categories	Increased eating larger meals/snacks				Increased physical inactivity			
		AOR	*p*-value	95% CI		AOR	*p*-value	95% CI	
				Lower	Upper			Lower	Upper
Gender	Male					0.924	0.467	0.746	1.144
	Female[R]								
Age (years)	<22	0.889	0.542	0.608	1.299				
	22–25	1.054	0.735	0.777	1.430				
	>25[R]								
Education level	Lower grade	0.675	**0.001**	0.530	0.860				
	Higher-grade[R]								
Current living area	Urban					1.451	**0.001**	1.165	1.806
	Rural[R]								
Monthly family income (BDT)	<25,000					0.727	**0.036**	0.540	0.979
	25,000–50,000					1.034	0.816	0.777	1.377
	>50,000[R]								
University type	Public					0.961	0.740	0.762	1.212
	Others					0.461	**<0.001**	0.313	0.680
	Private[R]								
Smoking status	Yes	1.673	**<0.001**	1.255	2.229				
	No[R]								
Eating larger meals or snacks	Increased					2.806	**<0.001**	2.190	3.596
	Decreased					1.638	**<0.001**	1.261	2.129
	Unchanged[R]								
Conflict/arguments with others	No					0.524	**<0.001**	0.418	0.657
	Yes[R]								
Verbally or physically abused	No					1.167	0.236	0.904	1.507
	Yes[R]								
Constant		0.621	**<0.001**			1.009	0.963		

and obese than the lower age categories (<22 years and 22–25 years). Notably, the students came from the families with monthly income < 25,000 BDT and 25,000–50,000 BDT were 48% (RRR = 0.525, 95% CI: 0.334, 0.826; $p = 0.005$) and 32% (RRR = 0.688, 95% CI: 0.454, 1.044; $p = 0.079$) less risky for being obese than the students from the families with monthly income more than 50,000 BDT. Besides, the public university students reported that they were 46% (95% CI: 0.369, 0.791; $p = 0.002$) less likely to have a chance obese than the private university students. Finally, verbally or physically abused students showed 1.4 (95% CI: 0.977, 2.116; $p = 0.066$) times higher risk for inclination toward obesity than the students with no abuse. Similarly, physical exercise and suicidal thoughts were significantly associated with overweight risk in multinomial regression analysis among university students in Bangladesh (**Table 4**).

Binomial Regression for Eating Larger Meals/Snacks and Physical Inactivity

A binomial logistic regression analysis was conducted during multivariate analysis to assess the significant association of potential factors with increased eating larger meals or snacks and physical inactivity after adjusting for other factors. These findings are listed in **Table 5**.

Students in higher grade levels were around 33% (95% CI: 0.530, 0.860; $p = 0.001$) less likely to have larger meals/snacks than the lower grade students, and students with smoking habits showed to significantly have larger meals/snacks than the non-smokers (AOR = 1.673, 95% CI: 1.255, 2.229; $p < 0.001$). Urban students were consistently more physically inactive than rural students (AOR = 1.451, 95% CI: 1.165, 1.806; $p = 0.001$), and notably, students from lower monthly income families (<25,000 BDT) were 30% less likely to be inactive than those from higher monthly income families (>50,000 BDT) (95% CI: 0.540, 0.979; $p = 0.036$). Besides, respondents from other universities reported being less engaged in physical inactivities than respondents from private universities (Others university vs. Private: AOR =0.461, 95% CI: 0.313, 0.680; $p < 0.001$). Furthermore, students with increased eating of larger meals/snacks reported being 2.8 (95% CI: 2.190, 3.596; $p < 0.001$) more likely to be engaged in physical inactivity than the students who did not change their eating habits. Finally, students with conflicting or arguments with others showed 48% (95% CI: 0.418, 0.657; $p < 0.001$) less likely

to be engaged in inactivity than the other students with no conflicting arguments.

DISCUSSIONS

The current study, to the best of our searching experience, aims for the first time to assess the changes in BMI among the university students "before" and "during" the COVID-19 lockdown, as well as to determine the relationship of various sociodemographic, psychological, and interpersonal behaviors with BMI changes. In addition, the research also focused on understanding if there was a link between different sociodemographic characteristics with eating habits and physical activity during the COVID-19 lockdown. The present study revealed that underweight, overweight, and obesity prevalence were 11.9, 36.6, and 11.7%, respectively, before the COVID-19 lockdown, which was enumerated as 10.2, 42.7, and 13.8%, respectively, following prolonged COVID-19 strict lockdown. Besides, the current data exhibited a clear perception of dietary patterns and prevalence of physical inactivity and several significantly influencing factors. However, direct comparisons of these findings may be difficult in the prevailing context due to limited evidence or lack of study on Bangladeshi university students in similar settings.

Determinants of Overweight, Obesity, and Underweight

The current study findings demonstrated a significant rise (during vs. before = 23.526 ± 7.680 vs. 22.772 ± 4.111; $p < 0.001$) in BMI among the university students following more than a year of educational institution closure and home confinement during COVID-19 lockdown in Bangladesh, which is consistent with earlier reported outcomes in several parts of the world (9, 31, 32). The BMI of all sociodemographic subgroups of the participants increased significantly. However, the BMI of male individuals increased substantially more than that of female participants. A similar study of 368 obese people found that women had lower BMI values than men (28.57 ± 3.89 vs. 30.64 ± 2.87) (33). In terms of risk categorized BMI, the male students were 7.6 and 2% more likely to be overweight and obese than the female students, which is also in line with some previous evidence (33, 34). Besides, the current data showed that students from the older age groups (>25 years) were likely to be more at risk for being overweight and obese than those in the younger age groups (22 years and 22–25 years). This finding was supported by the studies conducted on Bangladeshi (35) and Nepalese women (36), where the lower age group subjects were at a lower risk of being overweight or obese than women in the higher age group. In contrast, according to a study conducted in China, BMI and prevalence of overweight and obesity varied significantly across educational levels, with high-school students (age = 17.5 ± 1.2 years) having the highest BMI (22.7 ± 6.7 kg/m^2) and the highest prevalence of overweight (26.7%) and obesity (16.1%) than the undergrad (age = 20.6 ± 1.8 years) and graduate (age = 24.6 ± 3.5 years) students (33).

Moreover, the current analyses endorsed that the students from families with higher income (>50,000 BDT) were substantially more at risk of being obese than students from the other two counter groups (<25,000 BDT and 25,000–50,000 BDT). This outcome for the wealth-obesity relationship was consistent with the previous studies (35–41) that the richest were more likely to be obese than the poor. Furthermore, it is evident from the multinomial regression analysis that private university students had more risk of obesity during the prolonged lockdown. It is a widespread belief that most private university students come from wealthier families, and they might have a sedentary lifestyle, more access to energy-dense and processed food, and escape from physical work, which might be primarily responsible for higher BMI (40, 41).

The study also revealed that the students taking larger meals or snacks were likely to be 1.5 and 2.4 times more at risk of being overweight and obese, respectively, compared to those with unchanged food habits. Increased eating can be justified by the feeling of boredom, which may arise from staying home for an extended period (42, 43). Huber et al. reported that the increased amount of food consumption during lockdown was significantly mediated by higher BMI compared to the students with normal BMI (OR = 1.427; 95% CI = 1.032–1.974; $p = 0.032$) (21). Similarly, another study reported an increase in overeating during the lockdown in subjects with a higher BMI (10).

According to χ^2 analysis, physical activity exerted no significant relationship with overweight or obesity; nevertheless, physical exercise had a significant association with the likelihood of being overweight. Besides, the regression analysis found that the students who reduced their physical activity during the lockdown had a higher risk ratio to be overweight than the students who had unchanged physical activity. In line with several prior studies, higher BMI was associated with lower diet quality and decreased physical labor and exercise during physical mobility restrictions (10, 44, 45). On the other hand, the current data claimed that another group of students also gained a higher risk of being overweight upon increased physical exercise compared to the students with unchanged physical exercise. In those cases, there might occur a sudden weight gain with physical exercise for increased lean muscle mass and muscle fuel, as well as several mental complications that mediate emotional/stress-related overeating, prone to taking snacks after dinner during the pandemic situation (46–48). However, there might be some knowledge gap about the involvement of several drivers of the obesity epidemic during the current lockdown period, such as leisure-time exercise or physical activity.

Additionally, the current data also demonstrated that the students who were physically or verbally abused by others were likely to be 1.4 times more at risk of being obese than their peers. Several studies reported the drastic increase in physical or verbal abuse, sexual harassment, conflict, and overall social stigma, including domestic or social violence, during the COVID-19 period in Bangladesh (49, 50). This interpersonal distress, indirect effects of social networking or social destruction, and stigmatization significantly impact the behaviors and psychosocial stress that might strongly associate overall lifestyle and obesity/weight gain promotors (25, 51, 52).

In terms of being underweight, gender and diet/food consumption patterns are the major influencing factors in the study. The current regression analysis traced that the female students were almost 40% more at risk of being underweight than males. Besides, the students who increased their food consumption were significantly less at risk of being underweight than the students who unchanged their food pattern. The prevalence of underweight among women is higher than among men in South-East Asia and the Pacific regions reported in various previous studies due to biological, environmental, and economic factors that might be triggered in the COVID-19 lockdown period and associated with up to the severe level of malnutrition (36, 53).

Although we found a significant association between smoking habits with alterations in BMI during the χ^2 analysis of the samples, the regression identified no significant relationship between smoking with overweight/obesity. However, our findings exhibited that both smokers and non-smokers increased BMI due to home confinement. In contrast, smokers had a larger likelihood of being overweight or obese than non-smokers. A previous study conducted on USA college students reported that smoking significantly influenced obesity-enhancing behaviors, such as eating high calories dietary and food consumption while watching television (54).

Moreover, we investigated several psychological parameters like depression, anxiety, loneliness, and sleep disturbance with various degrees of BMI as these mental disorders were drastically increased among university students during the closure of educational institutions (24, 26). Although around 70% of the participants were suffering from these mental complications (sleep disturbance: 43.8%), the current data found no significant association of these parameters with underweight, overweight, or obesity. However, the students who had suicidal thoughts were 7.5% more obese than those who did not have suicidal thoughts during the χ^2 analysis. However, this factor was not significantly related to overweight/obesity in the multinomial regression analysis. Similarly, a study on UK adults found no significant relationship between mental health decline and higher BMI (10). On the contrary, a study discovered that participants who reported changes in their BMI status were more likely to suffer from depression and anxiety, but not suicidality (32).

Determinants of Consumption of Larger Meals/Snacks

This lockdown condition makes it difficult to eat a balanced and diversified diet. Limited access to daily grocery shopping, and convenience in online shopping, for example, may lead to a shift away from fresh foods like fruits, vegetables, and seafood to highly processed meals like convenience foods, junk foods, snacks, etc. Furthermore, psychological and emotional reactions to the COVID-19 outbreak enhanced the chance of developing imbalanced eating habits (32). The current study demonstrated that the higher-grade students were more likely to take larger meals/snacks during the lockdown than lower-grade university students. Various studies on Bangladeshi university students reported that higher-grade students suffered more from mental depression than lower-grade students (26). Academic and lockdown-induced psychological stress might affect the eating behaviors among university students (55).

Furthermore, the current evidence exerted that the university students who were regular smokers had a considerably higher tendency (1.7 times) to consume larger meals/snacks than non-smokers. Similarly, Huber et al. (21) reported that the university students who had smoking habits were 11.5% (42 vs. 30.5%; $p = 0.012$) more prone to taking larger meals/snacks than the non-smokers during the COVID-19 lockdown. Though the current study found a significant association between age and eating behaviors, the regression analysis found no significant association between age groups with increased eating larger meals. This prediction was also consistent with some of the previous study's findings (10, 21).

Determinants of Physical Inactivity

The COVID-19 restrictions have massively impacted physical activities since the early phase of the pandemic and prohibited people from reaching the threshold level of recommended physical movement for being healthy. The current data reported that around half of the students sharply minimized their physical activity and physical exercise. Consistently, Islam et al. (56) reported that 55.3% of the university students in Bangladesh were not engaged in regular physical exercise. In a systematic review of 66 studies, Stockwell et al. (57) disclosed that the participants from 64 studies reduced their physical activity and increased their sedentary manners during the COVID-19 lockdown.

Here, the present regression analysis enumerated almost 1.5 times higher engagement with physical inactivity among the urban students than rural students. Similarly, Rahman et al. (58) previously disseminated that urban people of Bangladesh showed 2.2 times (95% CI = 1.8–2.8; $p < 0.001$) higher physical inactivity and 2.9 times (95% CI = 2.2–3.7; $p < 0.001$) higher sedentary behaviors compared to the village people. Physical and social contextual elements that influence access, availability, and behaviors have a significant role in physical activity participation. The urban regions in Bangladesh are densely inhabited, and the number of COVID-19 cases was relatively higher (59–61). Besides, several factors such as fear of COVID-19 infection, the strict shutdown of almost every place (except emergency needs), including playgrounds and gymnasium, lack of companions to exercise with, loss of willingness to pursue physical activities, and so on, might demotivate the university students to be active in physical labors during the social lockdown (58). Furthermore, the students from higher-income families were significantly more physically inactive compared to the students from lower-income families, which was also consistent with the previous report (participants from upper-class families were three times (95% CI = 2.3–4.0, $p < 0.001$) more likely to be physically inactive than the lower-class participants) (58). The current analysis also found that the students from private universities were substantially more physically inactive during the lockdown than those from "others" category institutions. It is well-known that the students from highly reputed private universities come from wealthier families and their lifestyles are flexible, having more sedentary behaviors than the students from more impoverished families

or various colleges under the National University of Bangladesh (24). Besides, Trinh et al. (62) disclosed that the household wealth index significantly influenced physical inactivity (highest vs. lowest household wealth index: OR = 1.86, 95% CI = 1.29–2.66).

Moreover, there was a significant link between eating habits and physical inactivity. The students who increased the larger meals/snacks were 2.8 times more likely to be physically inactive than those who did not change their eating habits. Similarly, several previous studies examined the significant increase in taking larger meals/snacks during COVID-19 home confinement (21, 63), which might be a primary mediating factor for showing more sedentary acts and subsequent physical inactivation (58, 64). The study also observed that the students who decreased their eating amounts were significantly and more physically inactive than those who kept their dietary consumption unchanged. Similarly, Huber et al. (21) stated that the young adults who increased their sports activity decreased their food consumption by 1.9 times than the subjects who kept their food habits constant. A potential explanation might be that many students have passed most of their time on the electronic device screen for gaming, social media chatting, or gossiping with other friends during home confinement; these behaviors might be associated with being more physically inactive (25, 58). Besides, the present analysis found that the students having conflict/arguments with others were more physically inactive than their peers. Social isolation and loneliness increased hostility and extreme anger among young adults, thus, provoking psychoticism (65–67). The abnormal mental status might attribute the current university students embroiled in contradictory debates/conflicts and social violence. Although Robinson et al. (10) reported that many participants increased their social arguments/conflict, the authors did not find any significant association of the factor with physical inactivity.

PRACTICAL IMPLICATIONS

According to the best of our knowledge and searching experience, this unique investigation is the first ever to assess the correlations of several diverse sociodemographic factors with the degree of BMI, eating larger meals/snacks, and physical inactivity of the university students under the context of prolonged lockdown in Bangladesh. The results must be required for government agencies, educational institutions, and epidemiologists to address the BMI-related physiological and behavioral issues among the target students. Besides, the current study pointed out the risk factors of COVID-19 associated with obesity or overweight owing to prolonged confinement in the home followed by physical inactivity. These results obtained from this research can also be employed to understand the BMI status, eating habits, and the extent of physical activities among university students of other countries with identical demographic and socioeconomic conditions. Finally, the observations of this study can have implications in future policymaking involving the university students who would be facing a tough time in the aftermath of a pandemic due to the academic hours that they have lost due to lockdowns.

STUDY LIMITATIONS

The current analysis is not a flawless investigation with some drawbacks. The most noticeable limitation of this cross-sectional web-based survey is the absence of means to cross-check the quality of the self-reported data provided by the respondents. It was impossible on our part to assess whether the respondents had adequate thoughts before filling the google form unbiasedly. Besides, it is highly likely that students from rural or remote areas with no proper internet connectivity could not participate in the survey, which made the data comparatively less representative of the whole country. The study was conducted inside Bangladesh only; therefore, adequate cautions might be required while interpreting the results for other regions, particularly for the countries with irreconcilable demographic and socioeconomic characteristics. Furthermore, the study did not measure the pre-lockdown weight management behaviors that might be crucial for understanding the weight gain due to movement restrictions. Lastly, the participants had to answer their pre-lockdown weights that might be subject to recall bias. Also, height was collected only during the survey, which may somewhat affect the rigorous inventory of BMI with the time variation.

FUTURE RESEARCH

Some prospective studies might be designed to focus on comparing the significant changes in BMI of students amid the COVID-19 lockdown with other age groups of people. Besides, there are several scopes for the current research to advance and explore novel dynamics between all the recommended weight management behaviors and health concerns, including obesity among university students. The ongoing pandemic may further impose lockdown measures from time to time, and, thus, the findings of the current research can be explored in the long term to assess the impact on university students. The analysis can also be expanded by incorporating more participants of diversified demographic features to establish more reproducible research findings. Notably, the current research for policy reinforcement must be emphasized and intensified to vigorously assess the obesity influencing factors that might have a significant association with physical activities and regular dietary patterns among all the vulnerable groups, especially women and students.

CONCLUSION

The current analysis identified that the extended COVID-19 lockdown has profoundly impacted the eating behaviors and the extent of physical activities and BMI of university students in Bangladesh. The study inferred that the prevalence of overweight/obesity and underweight has disproportionately risen, and the degree of BMI has been substantially influenced by several demographic and socioeconomic factors, including eating habits and physical activity. Besides, the closure of educational institutions and stringent movement restrictions significantly increased food consumption and physical inactivity.

In the light of the current findings and evidence, several concerted attempts, plans, and programs must be warranted by epidemiologists, institutional administration, and government policymakers to employ weight management behaviors, balanced diets, and appropriate physical activities, including physical exercise in the context of home confinement measures. Apart from professional counseling to promote awareness for avoiding sedentary behaviors, smooth academic activities need to be secured to minimize the study gap due to the extended shutdowns.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Informed consent from each participant was also collected virtually before the participation. All the collected data were preserved private and confidential. Besides, all the guidelines and ethical protocols of the World Medical Declaration of Helsinki were strictly followed in this questionnaire-based survey. Furthermore, the Human Ethics Committee, State University of Bangladesh, has approved all the protocols and procedures of the study and provided an ethical approval number (2021-06-17/SUB/ERC/0004) after a critical revision and evaluation of the research details.

AUTHOR CONTRIBUTIONS

MH developed the idea of the work. MH and FA designed the study. MH, FA, SH, MR, MI, SM, TE, FI, and MA collected the data. MH and FA cured and analyzed the raw data. MH and FA interpreted the analyzed data. MH, MK, and PR searched the literature and drafted the original manuscript. MH, MS, and IM have made funding acquisitions. MH, MS, TE, and INM critically revised and improved the manuscript. All authors reviewed and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Biological Actions, Implications, and Cautions of Statins Therapy in COVID-19

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The Coronavirus Disease 2019 (COVID-19) showed worse prognosis and higher mortality in individuals with obesity. Dyslipidemia is a major link between obesity and COVID-19 severity. Statins as the most common lipid regulating drugs have shown favorable effects in various pathophysiological states. Importantly, accumulating observational studies have suggested that statin use is associated with reduced risk of progressing to severe illness and in-hospital death in COVID-19 patients. Possible explanations underlie these protective impacts include their abilities of reducing cholesterol, suppressing viral entry and replication, anti-inflammation and immunomodulatory effects, as well as anti-thrombosis and anti-oxidative properties. Despite these benefits, statin therapies have side effects that should be considered, such as elevated creatinine kinase, liver enzyme and serum glucose levels, which are already elevated in severe COVID-19. Concerns are also raised whether statins interfere with the efficacy of COVID-19 vaccines. Randomized controlled trials are being conducted worldwide to confirm the values of statin use for COVID-19 treatment. Generally, the results suggest no necessity to discontinue statin use, and no evidence suggesting interference between statins and COVID-19 vaccines. However, concomitant administration of statins and COVID-19 antiviral drug Paxlovid may increase statin exposure and the risk of adverse effects, because most statins are metabolized mainly through CYP3A4 which is potently inhibited by ritonavir, a major component of Paxlovid. Therefore, more clinical/preclinical studies are still warranted to understand the benefits, harms and mechanisms of statin use in the context of COVID-19.

Keywords: SARS-CoV-2, COVID-19, statins, obesity, dyslipidemia, inflammation, immune response, thrombosis

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INTRODUCTION

Obese individuals are more vulnerable to the SARS-CoV-2 caused Coronavirus Disease 2019 (COVID-19) (1–3). Obese people have ∼46% higher risk for SARS-CoV-2 positive, ∼74% increased odds for intense care unit (ICU) admission and ∼48% increased risk in deaths (4). Severe obesity [body mass index (BMI) ≥35] was significantly associated with the

need for invasive mechanical ventilation (IMV) (5), and was an independent predictor for intubation outcome (6). Moreover, with hyperlipidemia as a major link, obese individuals are prone to cardiovascular disease, hypertension, diabetes, myocardial infarction and stroke, which are among recognized risk factors for adverse COVID-19 outcomes (7–12) (**Figure 1**).

Prevalence of dyslipidemia was 18–39.7% as a comorbid condition in hospitalized COVID-19 patients (13–15). A population-based analysis on 61.4 million adult patients suggested that patients with hyperlipidemic state had 70% increased odds for catching COVID-19 (16). Moreover, COVID-19 patients may develop dyslipidemia that leads to life-threatening metabolic diseases and thrombotic complications (17–19), lipid-regulating agents are thus considered for possible therapeutic effects against COVID-19.

Statins are the most commonly used lipid-regulating drugs, 145.8 million people used statins in 2018 (20). Statins are HMG-CoA reductase inhibitors that can reduce serum total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, and have other pleiotropic effects such as modulating immune response and alleviating inflammation (21–23). Structurally, statins are classified as lipophilic (atorvastatin, lovastatin, simvastatin, and fluvastatin) and hydrophilic (pravastatin and pitavastatin), while rosuvastatin has an intermediate behavior (24). Statin prescription is majorly under consideration for primary preventions of cardiovascular disease, and other pathologies such as thrombosis (25, 26). Rational use of different types of statins are recommended according to LDL-C lowering need, pre-existing cardiovascular events or related risk factors including dyslipidemia, diabetes, hypertension, and age (25, 26).

Observational studies have suggested protective effects of statins in COVID-19 patients. Statin use was associated with a 55% decreased risk for IMV (27), 22–30% reduced risk of ICU admission (28), and 30–47% lower risk for death (28–33) (**Table 1**). Moreover, statin use prior to admission was associated with 71% reduction in the odds of developing severe COVID-19 (34) and 73% for death (31). High-intensity statin use reduced the risk of death by 49% in COVID-19 patients with coronary artery disease patients (32) (**Table 1**). Possible explanations for these benefits of statins include their recognized cholesterol-reducing, anti-inflammatory and immunomodulatory capacities (21, 23, 49), and also their anti-viral, anti-thrombosis and anti-oxidative abilities (50–53) (**Figure 1**). However, possible side effects of statin should be considered, such as elevated creatine kinase (CK) and serum glucose levels, which are already elevated in severe COVID-19 (19, 54–56). Currently, clinical trials are being conducted worldwide to confirm the safety and benefits of statin use for COVID-19 patients, with criteria including mortality, thrombosis formation, need for ECMO or IMV, viral load etc. (**Table 1**).

Different SARS-CoV-2 variants cause resurges of infections (57–60). Vaccines and antiviral therapies are powerful tools against COVID-19 (61, 62), yet data regarding the responses of obese individuals or statin users to these agents remain limited. It has been hypothesized that vaccines would offer reduced protection in obese individuals, based on evidence of immune cell dysregulation and alterations in inflammatory signaling pathways (4, 63). Given the immunomodulatory effects of statins, concerns have also been raised regarding possible interferences with COVID-19 vaccines. Moreover, cautions should be take that drug interactions between statins and some agents used in COVID-19 treatment, may lead to adverse effects (64–66).

Here, we provide a comprehensive update of the values, possible mechanisms, and noteworthy cautions regarding statin use in COVID-19. This review was conducted by consulting resources from peer-reviewed articles and/or official websites like WHO. Common search terms included "COVID-19 OR SARS-CoV-2" AND "statin OR lipid lowering", etc.

VALUES AND MECHANISMS OF STATINS IN COVID-19

As effective drugs for reducing cholesterol, statins can prevent cardiovascular events which are key risk factors for COVID-19 infection and poor prognosis (9, 67–69). Cholesterol reduction allows statins to affect cell membrane structure and function, particularly lipid rafts that play important roles in viral entry and cellular processes like signal transduction (70–72). Moreover, by

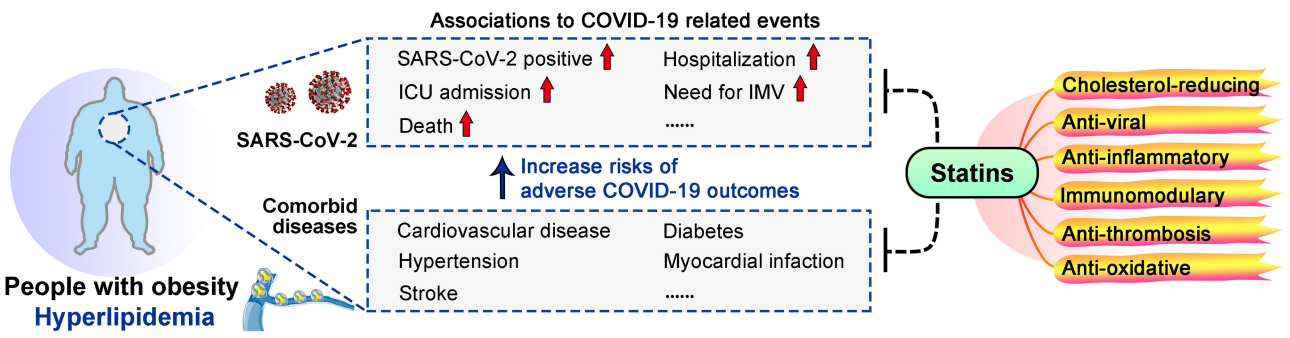

FIGURE 1 | Links between obesity, COVID-19 and statins. Obesity increased the risks of adverse COVID-19 outcomes, and dyslipidemia is a major link between obesity and COVID-19 severity. Statins may benefit COVID-19 patients, especially those with obesity and dyslipidemia, due to their multiple effects.

TABLE 1 | Associations between statins and COVID-19 outcomes, and clinical trials regarding statin use in COVID-19.

References	Type of study	Study cohort	Key findings
Associations between statins and COVID-19 outcomes			
Song et al. (27)	Retrospective study	249 adult patients hospitalized with COVID-19 in Rhode Island, USA	After adjusting for age, sex, race, cardiovascular disease, chronic pulmonary disease, diabetes, and obesity, statin use was significantly associated with decreased risk for IMV [aOR = 0.45, (95% CI: 0.20–0.99)].
Vahedian-Azimi et al. (28)	Meta-analysis	32,715 patients in 24 studies	Statin use is associated with significant reductions in ICU admission (OR = 0.78, 95% CI: 0.58–1.06; $n = 10$; $I^2 = 58.5\%$) and death (OR = 0.70, 95% CI: 0.55–0.88; $n = 21$; $I^2 = 82.5\%$) outcomes, with no significant effect on tracheal intubation (OR = 0.79; 95% CI: 0.57–1.11; $n = 7$; $I^2 = 89.0\%$). Death was reduced further by in-hospital application of stains (OR = 0.40, 95% CI: 0.22–0.73, $n = 3$; $I^2 = 82.5\%$), compared with pre-hospital use (OR = 0.77, 95% CI: 0.60–0.98, $n = 18$; $I^2 = 81.8\%$).
Zhang et al. (29)	Retrospective study	13,981 cases of confirmed COVID-19 admitted in 21 hospitals from Hubei Province, China	The risk for 28-day all-cause mortality was 5.2 and 9.4% in the matched statin and non-statin groups, respectively, with an adjusted HR of 0.58; the use of statins in hospitalized subjects with COVID-19 was associated with a lower risk of all-cause mortality and a favorable recovery profile.
Lee et al. (30)	Nested case-control study	10,448 COVID-19 patients who were hospitalized in Korea	Statins were prescribed in 533 (5.1%) patients. After adjusting for age, sex, and comorbidities, Cox regression showed a significant decrease in hazard ratio associated with the use of statins [aHR, 0.637 (95% CI, 0.425–0.953); $P = 0.0283$]. Statin use is correlated with lower mortality in COVID-19 patients.
Memel et al. (31)	Cohort study	1,179 patients, 676 (57%) were male, 443 (37%) were >65 years old, and 493 (46%) had a BMI ≥30	Inpatient statin use reduced the hazard of death (HR, 0.566; $P = 0.008$). This association held among patients who did and those did not use statins before hospitalization [HR, 0.270 ($P = 0.003$) and 0.493 ($P = 0.04$), respectively]. Statin use was associated with improved time to death for patients aged >65 years but not for those ≤65 years old. Statin use during hospitalization for SARS-CoV-2 infection was associated with reduced 28-day mortality rates.
Choi et al. (32)	Retrospective study	5,375 COVID-19 patients admitted to Mount Sinai Health System hospitals in New York	Compared to non-statin users, both low-to-moderate-intensity (aHR 0.62, 95% CI 0.51–0.76) and high-intensity statin users (aHR 0.53, 95% CI 0.43–0.65) had a reduced risk of death. Subgroup analysis of 723 coronary artery disease patients showed decreased mortality among high-intensity statin users compared to non-users (aHR 0.51, 95% CI 0.36–0.71). Statin use in patients hospitalized with COVID-19 was associated with a reduced in-hospital mortality. The protective effect of statin was greater in those with coronary artery disease.
Rodriguez-Nava et al. (33)	Retrospective cohort study	87 adult patients with COVID-19 admitted to community hospital ICU in Evanston, IL, USA	In the multivariable Cox proportional hazards regression model, atorvastatin non-users had a 73% chance of faster progression to death compared with atorvastatin users (when probability = HR/HR + 1).
Daniels et al. (34)	Retrospective single-center study	170 hospitalized patients with COVID-19 and 5,281 COVID-negative subjects at University of California San Diego Health	Statin use prior to admission was associated with reduced risk of severe COVID-19 (aOR 0.29, 95% CI 0.11–0.71, $P < 0.01$) and faster time to recovery among those without severe disease (aHR for recovery 2.69, 95% CI 1.36–5.33, $P < 0.01$). The association between statin use and severe disease was smaller in the COVID-negative cohort (P for interaction = 0.07).
Rossi et al. (35)	Follow-up study	71 consecutive patients with a pre-existing chronic cardiovascular disease, who become ill from COVID-19	Among 42 statin users, 16/42 (38.1%) took a hydrophilic statin (rosuvastatin in 14 patients and pravastatin in 2), while 26/42 (61.9%) a lipophilic statin (atorvastatin in 22 patients, and simvastatin in 4). The group of lipophilic statins demonstrated a significant reduction in mortality respect both patients who do not take statins, and patients who assumed hydrophilic statins.
Saeed et al. (36)	Observational study	4,252 patients (65 ± 16 years old; 47% female) were admitted with COVID-19, 37% ($n = 1,570$) were Hispanic	Patients with diabetes mellitus on a statin ($n = 983$) reduced cumulative in-hospital mortality (24 vs. 39%; $P < 0.01$) than those not on a statin ($n = 1,283$). Statin use in people with diabetes was associated with a reduced risk of in-hospital mortality during COVID-19. No difference in hospital mortality was noted in patients without diabetes mellitus on or off statin (20 vs. 21%; $P = 0.82$).

(Continued)

TABLE 1 | Continued

References	Type of study	Study cohort	Key findings
De Spiegeleer et al. (37)	Retrospective study	154 COVID-19 diagnosed residents aged 86 ± 7 years in 2 Belgian nursing homes	Statin intake is associated with the absence of symptoms during COVID-19 (OR 2.91; 95% CI 1.27–6.71), which remained statistically significant after adjusting for covariates (aOR 2.65; 95% CI 1.13–6.68). In conclusion, statin intake in older, frail adults could be associated with a considerable beneficial effect on COVID-19 clinical symptoms.
Lala et al. (38)	Retrospective study	2,736 patients with COVID-19 admitted to 1 of 5 Mount Sinai Health System hospitals in New York City	Statins have a protective effect and were associated with improved survival (HR 0.57, 95% CI 0.47–0.69).
Gupta et al. (39)	Retrospective study	2,626 patients admitted with COVID-19, of whom 951 (36.2%) were antecedent statin users.	Among 1,296 patients (648 statin users, 648 non-statin users) identified with 1:1 propensity-score matching, statin use is significantly associated with lower odds of in-hospital mortality within 30 days in the propensity-matched cohort (OR 0.47, 95% CI 0.36–0.62, $P < 0.001$).
Byttebier et al. (40)	Retrospective observational case-control study	959 COVID-19 patients admitted consecutively to four Belgian hospitals	Treatment with statins and ACEIs/ARBs reduced 28-day mortality in hospitalized COVID-19 patients. Moreover, combination treatment with these drugs resulted in a 3-fold reduction in the odds of hospital mortality (OR = 0.33; 95% CI 0.17–0.69). In-hospital treatment with statins, ACEIs/ARBs, and especially their combination saves lives.
Ayeh et al. (41)	Retrospective study	4,447 patients hospitalized at the Johns Hopkins Hospital and affiliated hospitals with COVID-19, 594 (13.4%) were exposed to statins on admission.	The average treatment effect of statin use on COVID-19-related mortality was RR = 1.00 (95% CI: 0.99–1.01, $P = 0.928$), while its effect on severe COVID-19 infection was RR = 1.18 (95% CI: 1.11–1.27, $P < 0.001$).
			Statin use was not associated with altered mortality, but with an 18% increased risk of severe COVID-19 infection.
Kollias et al. (42)	Meta-analysis	41,807 patients, 14% with statin use	Statin therapy was associated with an about 35% decrease in the adjusted risk of mortality in hospitalized COVID-19 patients.
Lee et al. (43)	Two independent population-based nationwide cohort studies	214,207 patients older than 20 years who underwent tests for SARS-CoV-2 infection in South Korea	Statin users were associated with a decreased likelihood of severe clinical outcomes [statin users, 3.98% (32/804); non-users, 5.40% (85/1,573); aRR 0.62; 95% CI 0.41–0.91] and length of hospital stay (statin users, 23.8 days; non-users, 26.3 days; adjusted mean difference −2.87; 95% CI −5.68 to −0.93) than non-users.
			Prior statin use is related to a decreased risk of worsening clinical outcomes of COVID-19 and length of hospital stay but not to that of SARS-CoV-2 infection.
Kow et al. (44)	Meta-analysis	8,990 COVID-19 patients in 4 studies	The pooled analysis revealed a significantly reduced hazard for fatal or severe disease with the use of statins (Pooled HR = 0.70; 95% CI 0.53–0.94) compared to non-use of statins in COVID-19 patients.
Tan et al. (45)	Retrospective study	717 patients admitted to a tertiary center in Singapore for COVID-19 infection.	156 (21.8%) patients had dyslipidaemia and 97% of these were on statins. Logistic treatment models showed a lower chance of ICU admission for statin users when compared to non-statin users (Average treatment effect on statin (ATET): Coeff (risk difference): −0.12 (−0.23, −0.01); $P = 0.028$). Statin use was independently associated with lower ICU admission.

Study Title	Status	Locations	Summary	Key results
COVID-19 related clinical trials of statins				
Intermediate-dose vs. standard prophylactic anticoagulation and statin vs. placebo in ICU patients with COVID-19 (NCT04486508)	Completed	Masih Daneshvari Hospital, Tehran, Iran, Islamic Republic of Iran	This study investigates the safety and efficacy of two pharmacological regimens on outcomes of critically-ill patients (Actual Enrollment: 600 participants) with COVID-19 using a 2 × 2 factorial design.	In adults with COVID-19 admitted to the ICU, atorvastatin was not associated with a significant reduction in the composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality compared with placebo. The treatment was safe (46)

(Continued)

TABLE 1 | Continued

Study Title	Status	Locations	Summary	Key results
Effectiveness and safety of medical treatment for SARS-CoV-2 (COVID-19) in Colombia (NCT04359095)	Completed	6 hospitals in Colombia including Clinica santa Maria del lago, Clínica Reina Sofía, Fundacion Cardio Infantil, etc.	The study assesses the effectiveness and safety of rosuvastatin plus colchicine, emtricitabine/tenofovir, and their combined use in these patients. Six hundred and forty-nine patients agreed to participate and were enrolled in this study; among them, 633 (97.5%) were included in the analysis. The primary endpoint was 28-day all-cause mortality.	The combined use of emtricitabine with tenofovir disoproxil plus colchicine and rosuvastatin reduces the risk of 28-day mortality and the need for IMV in hospitalized patients with COVID-19 (47).
The impact of statin therapy in the COVID-19 patients (NCT05238402)	Completed	Deniz Demirci Antalya, Turkey	The study is retrospective single-center review of covid-19 patients (actual Enrollment: 707 participants). The study population was divided into patients who received a statin vs. those who did not receive a statin before the hospitalization. The primary outcome was in-hospital mortality during the follow-up period.	No results posted
Statin therapy and COVID-19 infection (NCT04407273)	Completed	Facultat de Medicina i Ciències de la Salut de Reus, Reus, Tarragona, Spain	This is a retrospective observational multicenter study. The SARS-CoV-2 severity of 2,159 COVID-19-infected patients with statin therapy was classified into 9 grades. Primary outcome is the WHO SARS-CoV-2 scale of severity (9 grades) achieved by COVID-19 patients, admitted in the hospital, with and without background statin therapy comparable in age and gender distribution.	No results posted
Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (NCT02735707)	Recruiting	322 hospitals worldwide	The purpose of this study is to evaluate the effect of about 50 interventions, including statin use, to improve outcome of patients admitted to ICU with community-acquired pneumonia including COVID-19.	No results posted
Colchicine/statins for the prevention of COVID-19 complications (COLSTAT) trial (NCT04472611)	Recruiting	4 hospitals in United States including Bridgeport Hospital, Greenwich Hospital, Yale New Haven Hosptial System, Lawrence and Memorial Hospital	This is a randomized open-label study of the safety and efficacy of the combination of colchicine and Rosuvastatin in addition to standard of care (SOC) compared to SOC alone in hospitalized patients with SARS-CoV-2 (Estimated Enrollment: 466 participants). The primary endpoint is the 30-day composite of progression to severe COVID-19 disease.	No results posted
Managing endothelial dysfunction in critically ill COVID-19 patients at LAUMCRH (NCT04813471)	Recruiting	LAUMCRH Beirut, Lebanon	The study seeks to target endothelial dysfunction in critically ill patients with COVID-19 by giving them an endothelial protocol (L-arginine, Folic Acid, Statin, Nicorandil, Vitamin B complex) and monitor clinical outcome in those patients.	No results posted
Atorvastatin as adjunctive therapy in COVID-19 (NCT04380402)	Recruiting	Mount Auburn Hospital Cambridge, Massachusetts, United States	This study assesses whether adjunctive therapy of COVID-19 with atorvastatin reduces the deterioration in hospitalized patients and improves clinical outcome.	No results posted

(Continued)

TABLE 1 | Continued

Study Title	Status	Locations	Summary	Key results
Helping alleviate the longer-term consequences of COVID-19 (HEAL-COVID) (NCT04801940)	Recruiting	Addenbrookes Hospital, Cambridge, United Kingdom	HEAL-COVID aims to evaluate the impact of treatments on longer-term morbidity, mortality, re-hospitalization, symptom burden and quality of life associated with COVID-19. The first two treatment arms are Apixaban and Atorvastatin.	No results posted
Combination therapies to reduce carriage of SARS-CoV-2 and improve outcome of COVID-19 in ivory coast: a phase randomized IIb trial (NCT04466241)	Recruiting	2 hospitals in Côte D'Ivoire including Service des Maladies Infectieuses et Tropicales, Centre Hospitalier et Universitaire (CHU) and Treichville Abidjan, Côte D'Ivoire Center de Traitement des Maladies Infectieuses (CTMI)	This study proposes to study whether the combination of two drugs (These drugs include the LPV/r already in use in Côte d'Ivoire as well as an antihypertensive drug—telmisartan, and atorvastatin) is more effective than taking a single drug on reducing the viral load in the respiratory tract but also on reducing inflammation.	No results posted
Statin treatment for COVID-19 to optimize neurological recovery (NCT04904536)	Not yet recruiting	The George Institute for Global Health Sydney, New South Wales, Australia	This trial was designed to study whether atorvastatin treatment (40 mg/day) over 18 months can improve neurocognitive function in adults with long COVID neurological symptoms.	No results posted
A study of anticoagulation treatment patterns and outcomes of participants hospitalized with coronavirus disease 2019 (COVID-19) in Japan (NCT04828772)	Active, not recruiting	Medical Data Vision, Tokyo, Japan	This study plans to assess the benefits and harms of anticoagulants (including statins) vs. active comparator, placebo or no intervention in people hospitalized with COVID-19.	Compared with no treatment, anticoagulants may reduce all-cause mortality but the evidence comes from non-randomized studies and is very uncertain (48).
Managing endothelial dysfunction in COVID-19: a randomized controlled trial at LAUMC (NCT04631536)	Active, not recruiting	LAUMCRH Beirut, Lebanon	This trial will examine the potential therapeutic effect of a regiment composed of several medications including atorvastatin as adjunct to mainstream management, to further knowledge in treating COVID-19.	No results posted
Atorvastatin for reduction of 28-day mortality in COVID-19: RCT (NCT04952350)	Active, not recruiting	Mansoura University Hospitals Mansoura, Aldakahlia, Egypt	This randomized placebo-controlled double-blinded clinical trial aims to test the efficacy of administering atorvastatin 40 mg to hospitalized COVID-19 patients for 28 days on the all-cause 28-day mortality.	No results posted
Study of ruxolitinib plus simvastatin in the prevention and treatment of respiratory failure of COVID-19 (NCT04348695)	Unknown	Hospital Universitario Madrid Sanchinarro, Madrid, Spain	This project examines whether the combined use of ruxolitinib with simvastatin show a synergistic effect in the inhibition of viral entry and in the anti-inflammatory effect.	No results posted
Preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy: a randomized controlled trial (NCT04333407)	Unknown	Charing Cross Hospital, London, United Kingdom	The trial plans to assess all-cause mortality 30 days after admission in COVID-19 patients (Estimated Enrollment: 3,170 participants) treated with different cardioprotective drugs, including Aspirin 75 mg, Clopidogrel 75 mg, Rivaroxaban 2.5 MG, Atorvastatin 40 mg, Omeprazole 20 mg.	No results posted
Coronavirus response—active support for hospitalized COVID-19 patients (NCT04343001)	Withdrawn	University College Hospital Ibadan, Oyo, Nigeria, and Shifa Tameer-e-Millat University, Rawalpindi, Pakistan	This project aims to evaluate the effect of aspirin (150 mg once daily), losartan (100 mg once daily), and simvastatin (80 mg once daily) in patients with COVID-19 infection.	No results posted

Data was acquired as of April 16, 2022. aHR, adjusted hazard ratio (HR); aOR, adjusted odds ratio (OR); BMI, body mass index; CI, confidence interval; ICU, intense care unit; IMV, invasive mechanical ventilation; I^2, I-squared statistics indicating between-study heterogeneity; RR, risk ratio.

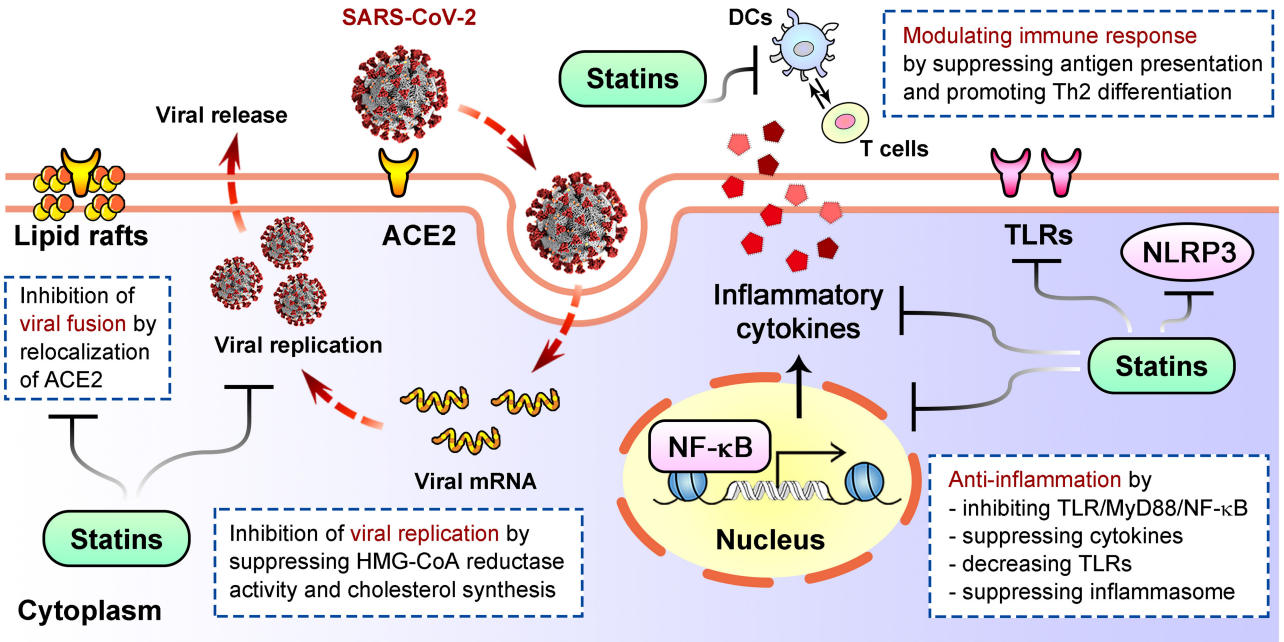

FIGURE 2 | Well established mechanisms of how statins inhibit viral life cycle, alleviate inflammation and modulate immune response after infection. DCs, dendritic cells; TLRs, Toll-like receptors.

reducing intermediate products of cholesterol biosynthesis, statins downregulate protein isoprenylation to regulate numerous signaling pathways including immune responses (73). Hyperactivation of immune responses, elevated systematic inflammation, increased oxidative stress, and thrombosis events have been observed in severe COVID-19, especially among those with obesity or cardiovascular diseases, while statins have shown suppressive effects against these processes (**Figure 1**).

Antiviral Effects

SARS-CoV-2 infection initiates from cell entry by attaching to its receptor ACE2 (70, 71). The cholesterol-rich membrane lipid rafts is crucial for this process. By reducing cholesterol, disrupting lipid raft composition, altering membrane receptor assembly and localization, statins interfere with virus fusion and entry in HIV models (51, 74). Potential mechanism is that statins-mediated blockade of HMG-CoA reductase leads to inhibition of Rho guanosine triphosphatase, a key contributor to clustering of lipid raft-associated receptors (74, 75). Statins may increase ACE2 levels under disease situations with unknown clinical relevance (76), and simvastatin significantly affected SARS-CoV-2 cell entry through displacing ACE2 on lipid rafts (77) (**Figure 2**). Simvastatin can also reduce SARS-CoV-2 replication (77). Viral infection increases HMG-CoA reductase activity and cholesterol synthesis to assist viral replication, which explains the negative impact of statins on viral replication (78, 79) (**Figure 2**). Viral assembly and release following replication can be suppressed by statins through inhibiting mevalonate synthesis and intracellular cholesterol levels (80, 81). Whether statins similarly affect the assembly and release of SARS-CoV-2 remain unknown.

Although multiple statins have showed antiviral effects against different viruses, a study suggested higher efficacy for lipophilic statins against Zika viral replication, possibly because they can enter cells *via* passive transport to reach higher intracellular concentrations (82). Moreover, comparison between the survival curves of patients with a pre-existing chronic cardiovascular disease indicated a significant reduction in mortality in lipophilic statin users vs. hydrophilic group and non-users group (35). Therefore, it will be critical to understand whether and how the type, dose and duration of statin therapy affect antiviral effects and subsequently the outcome of SARS-CoV-2 infection.

Anti-inflammatory and Immunomodulatory Effects

Exacerbated inflammation is a pathological hallmark of COVID-19 (83). During severe COVID-19, a generalized inflammatory state is caused by cytokine storm due to hyperactivation of host immune system, leading to lesions in multiple organs and even death (84). Upon SARS-CoV-2 invasion, antigen-presenting cells recognize the pathogen *via* Toll-like receptors (TLRs) and activates two main downstream pathways, MyD88- and TRIF-dependent pathways, both leading to NF-κB activation (85–88). NF-κB initiates the first stage of inflammasome activation and induces the production of pro-inflammatory factors, including interleukin-6 (IL-6), a key cytokine associated with COVID-19 severity and mortality (89–91). Activation of NLRP3 inflammasome involves in response to infection of

RNA viruses including SARS-CoV-2 (92–95). Patients with a reduced immune fitness and pre-existing systemic inflammatory state, such as obesity or cardiovascular diseases, are prone to demonstrate dysregulated NLRP3 inflammasome activity and pro-inflammatory cytokines expression, resulting in severe COVID-19 (92, 96, 97).

Statins are known for anti-inflammatory and immunomodulatory effects (**Figure 2**). Statins can decrease TLRs expression, suppress MYD88-NF-κB pathway and the levels of pro-inflammatory cytokines like IL-6, IL-8, TNF-α and MCP-1, thereby altering inflammatory pathway to reduce cell damage (21, 98–100). Statins directly regulate NLRP3 inflammasome (101), or suppress TLR4-MyD88-NF-κB pathway to inhibit its activation (102), thus downregulate cytokines including IL-18 and IL-1β (103, 104). Immunomodulatory actions also underlie statins' beneficial effects in pathologic status. For examples, statins block mevalonate generation required for T cell proliferation (105), repress MHC-II molecules that are critical for presenting antigen to T cells (23, 106), and suppress maturation of dendritic cells (107), therefore may alleviate hyperactivation of immune response. Rosuvastatin promotes the differentiation of peripheral blood monocytes into anti-inflammatory M2 macrophages (49, 108); atorvastatin suppresses proliferation of naïve Th0 cells and secretion of Th1 pro-inflammatory cytokines, while enhances secretion of Th2 anti-inflammatory cytokines (109).

Clinical studies indicate that statins decrease serum CRP levels (110), an inflammatory biomarker and risk factor for adverse COVID-19 outcomes (111). Importantly, in-hospital statin use is significantly associated with ameliorated inflammatory responses, as reflected by lower levels of circulating CRP, IL-6 and neutrophil counts in statin users (29). Correspondingly, simvastatin downregulated SARS-CoV-2-infection-triggered inflammation in human neutrophils, peripheral blood monocytes, and lung epithelial Calu-3 cells, showing its anti-inflammatory effect both at the site of viral infection and systemically (77). Statin-mediated CRP reduction can be achieved by lowering LDL-C, suppressing Rac-1 activation and increasing apolipoprotein A-I, all of which alleviate inflammation and subsequent CRP generation (112). Notably, for PCSK9 inhibitors, another class of lipid-lowering drugs that significantly decreases LDL-C but not inflammatory markers like CRP (113, 114), evidence is lacked so far regarding their possible benefits on COVID-19 outcomes, while deeper investigation is needed. Since COVID-19 patients with obesity are prone to immune cell dysregulation and elevated inflammations, further studies are warranted to explore whether and how statins may protect them from COVID-19.

Anti-thrombosis Effects

Thrombosis are among the most frequent complications in COVID-19 patients, especially in critically ill cases (115–117), and elevated D-dimer levels show prognostic significance for poor outcomes (7, 116, 118). Therefore, prevention/alleviation of thrombosis is a key to COVID-19 treatment, especially for obese patients who are prone to ICU admission and thromboembolic events.

Statins can reduce the occurrence of deep vein thrombosis and pulmonary embolism (52, 119–122), common thrombotic events in COVID-19 cases (123, 124). The anti-thrombosis impact of statins not only relates to its cholesterol-lowering effects and to plaque stabilization (125), but also involves lipid-lowering independent inhibitory effect on platelets activation and coagulation cascade, major pathways for thrombosis formation (18, 52, 126). Statins exert antiplatelet effect *via* downregulating prothrombotic factors including platelet thromboxane A2, NOX2 (the catalytic subunit of NADPH oxidase), oxidized low-density lipoprotein (oxLDL) and its receptor CD36 (127–129), and *via* promoting endothelial nitric oxide synthase (eNOS) which improves production of platelet nitric oxide (NO), a potent inhibitor of platelet activation and aggregation (130, 131).

Statins also interfere with clotting system and coagulation cascade. Statins downregulate the expression and activity of tissue factor which initiates the extrinsic pathway of coagulation (132–136), and reduce the serum level of plasminogen activator inhibitor (137); meanwhile, statins upregulate KLF2 that has anticoagulant and atheroprotective effects (138, 139), promote thrombomodulin expression and fibrinolytic activity (140–143). Since a mutual relationship exists between immune activation and thrombus formation (144), the anti-inflammatory actions of statins may also contribute to thrombosis suppression (18).

The anti-thrombosis effect of statins has been widely investigated in patients at risk for cardiovascular disease or those with established atherosclerosis, and varies from different statins (145, 146), but their impacts on COVID-19-related thrombosis remain largely unknown. A clinical trial in ICU admitted COVID-19 patients observed lower rate of thrombosis event in atorvastatin group, although without significant association, suggesting possible anti-thrombosis role of atorvastatin in COVID-19 cases; assessment of outcomes after long-time follow-up is ongoing (46).

Anti-oxidative Effects

Excessive reactive oxygen species (ROS) is associated with high neutrophil to lymphocyte ratio in critically ill COVID-19 (147). In monocytes and macrophages, SARS-CoV-2 infection triggers mitochondrial ROS production, induces HIF1α stabilization and consequently promotes glycolysis which facilitates viral replication (148). Overwhelming oxidative stress also causes local or systemic damages, induces thrombosis, contributing to COVID-19 severity (149).

Statins exerts anti-oxidative effect by attenuating NF-κB activation, reducing circulating oxLDL and their uptake by macrophages, inhibiting oxidant enzymes such as NADPH oxidase and myeloperoxidase, and upregulating the activity of antioxidant enzymes like catalase and paraoxonase (53, 150). Additionally, statins downregulate NOX2-derived oxidative stress, ultimately exerting antiplatelet effects (128, 151–153). Despite these anti-oxidative effects which possibly benefits COVID-19 treatment, statins may induce ROS production, mediate redox imbalance and consequent cellular oxidative damage, especially under excessive or long-term statin use (154).

CLINICAL TRIALS REGARDING STATIN USE AND COVID-19

Currently, among clinical trials regarding statin use and COVID-19, two have published results, while the others remain uncompleted or have not posted results (**Table 1**). In INSPIRATION/INSPIRATION-S study (NCT04486508) conducted in Iran ICU admitted COVID-19 patients, atorvastatin (20 mg/day) was not associated with a significant reduction in the composite of thrombosis, ECMO treatment, or all-cause mortality; however, atorvastatin treatment was safe, and may have clinical importance with lower overall event rates (46). Another study (NCT04359095) was conducted in Colombia (47), emtricitabine with tenofovir disoproxil (200/300 mg/day for 10 days) plus colchicine and rosuvastatin (0.5 mg and 40 mg/day for 14 days) combination reduced the risk of 28-day all-cause mortality by 22%, and lowered the need for IMV (47). These findings indicated safety and potential benefits of statins for COVID-19 treatment, yet the therapeutic effect varies from cohort and medications. More randomized controlled trials are therefore warranted to assess the effect of statin administration alone or in combination with regards of medication dose and duration, and to evaluate the influence of chronic statin use on COVID-19-related in-hospital events or long-term complications.

CAUTIONS ABOUT STATINS USE IN COVID-19

Although statins are generally well-tolerated, for COVID-19 patients especially those with obese or chronic statin use, cautions are required for potential risks of statins-associated muscle symptoms, liver injury, new-onset diabetes, renal injury, and neurological and neurocognitive disorders, which may also result from severe COVID-19 (68, 84, 126, 155, 156) (**Figure 3**).

Statin-associated muscular symptoms (SAMS) are principal cause of poor patient compliance that contribute to adverse outcomes (157, 158). SAMS include fatigue, weakness and pain, possibly accompanied by elevated serum CK levels and activity (54), while similar symptoms also present at early onset of COVID-19 (159). Therefore, for COVID-19 patients who use statins, careful monitoring muscle symptoms and CK levels are necessary; when muscle symptoms occur, assessment and approaches for statin intolerance may be considered (68, 160).

Statins-associated hepatotoxicity may add to COVID-19 related liver injury that potentially caused by psychological stress, systemic inflammation, etc., especially among obese individuals at higher risk of liver dysfunction (161–163). It has been suggested to avoid statin use in the case of severe liver damages, liver failure, and decompensated cirrhosis (24).

COVID-19 may induce or accelerate type 2 diabetes mellitus (T2DM) development as one of its acute and suspected long-term complications (19, 56), while statin may increase incidence of new-onset T2DM, which appears to be more common in obese patients (55, 164, 165). Despite the risk of T2DM, the cardiovascular benefits of statins should not be masked (166). Therefore, statin therapy can be continued in such patients with glucose monitoring, to achieve better glycemic control and avoid developing metabolic disorders after SARS-CoV-2 infection.

Clinicians should also be cautious when treating statin users with COVID-19 who show renal or neurological symptoms and relevant laboratory abnormalities. Renal dysfunction can be caused by SARS-CoV-2 infection and is associated with COVID-19 poor prognosis (167–169); whether statin-associated renal toxicity (170, 171) exacerbates COVID-19-related renal dysfunction remains unclear. There are also concerns regarding whether use of statin (especially lipophilic ones that can cross the blood-brain barrier) may worsen clinical manifestations of nervous system in COVID-19 patients, given their side effects of causing neurological disorders (171, 172).

Caution is also necessary for drug interaction during COVID-19 management. Most statins are predominantly metabolized by CYP450 enzymes, mainly through CYP3A4 (64). Therefore, concomitant administration of CYP3A4 inhibitors, such as some macrolides (clarithromycin/telithromycin/erythromycin) and antiretroviral drugs (lopinavir/ritonavir), with statins can increase the risk of adverse events (68, 173). For severe COVID-19 patients treated with IL-6 receptor blocker tocilizumab, rosuvastatin is recommended (68). Additionally, decreased LDL-C was observed in some severe COVID-19 cases (174, 175). Such finding may due to a more intensive lipid-lowering treatment in patients with high cardiovascular risk who are more vulnerable to COVID-19 (176), and deeper analysis is warranted to better prescribe appropriate intensity statin therapy.

STATINS AND COVID-19 VACCINES

The impact of statins on vaccine efficacy remain controversy. Take influenza vaccine for example, a clinical trial suggested immunosuppressive effect of chronic statin medication may weaken the immune response to vaccine (177), whereas another study indicated that statin did not modify influenza vaccine effectiveness (178). Presently, multiple COVID-19 vaccines have been approved, notably, vaccination participants with BMI $\geq$ 30 had a smaller infection risk reduction than those with BMI $<$ 30 (179), and central obesity (higher waist circumference) is associated with lower neutralizing antibody titers following vaccination (180). Presently, no evidence suggests statin may affect COVID-19 vaccine effectiveness.

STATINS AND COVID-19 ANTIVIRALS

SARS-CoV-2 variants may have substantial immune evasiveness that weakens vaccine protection due to spike protein mutations (57–60). Small molecular antivirals have reduced hospitalization rate and mortality in patients with promising safety (181, 182), among which Paxlovid stands out by reducing the risk of COVID-19-related hospital admission or death by 89% (183, 184). Paxlovid consists of a SARS-CoV-2 main protease inhibitor PF-07321332, and an anti-HIV drug ritonavir that boosts the effectiveness of protease inhibitors (184). However, co-administration of statins and Paxlovid may increase statin

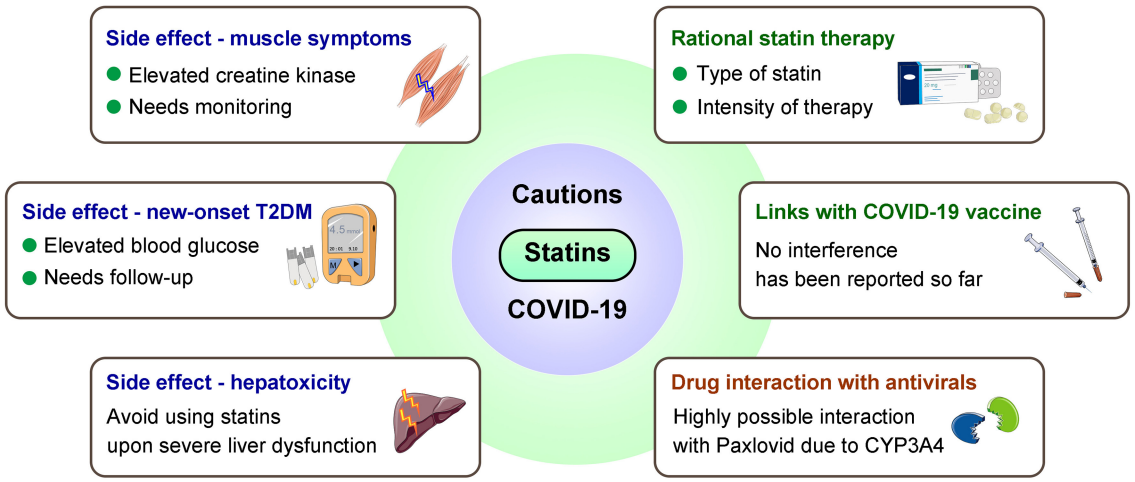

FIGURE 3 | Major cautions for statin use in COVID-19 patients. Considerations are needed from aspects including side effects, interferences with COVID-19 vaccines/antivirals, and proper statin therapy. T2DM, type 2 diabetes mellitus.

exposure and the risk of adverse effects including muscle symptoms and liver toxicity, because ritonavir potently inhibits CYP3A4 through which lipophilic statins are predominantly metabolized (64–66). Therefore, when such concomitant use is needed, it is possible to continue rosuvastatin therapy starting a low dose and titrating up (68, 156). More studies are needed to clarify the possible risks regarding co-administration of statins and antivirals, to find a proper regimen, and to explore whether obesity and dyslipidemia may interfere the efficacy of antivirals.

CONCLUSION AND FUTURE PERSPECTIVES

Current data suggest that statins are safe for COVID-19 patients and may exert therapeutical benefits. Generally, there is no necessity to discontinue statin use, and no evidence suggesting interference between statins and COVID-19 vaccines. However, cautions should be taken to achieve proper medication for statin users with COVID-19, considering possible side effects and drug interaction (**Figure 3**). Two major cautions are: *Proper type of statin.* Compared to hydrophilic statins, lipophilic statins enter cells *via* passive transport to reach higher intracellular concentrations, and have a larger distribution volume, thus may be more protective in respect of anti-viral ability. *Intensity of statin therapy.* Hypolipidemia is harmful. Decreased LDL-C is observed in some COVID-19 patients and associated with COVID-19 severity (174, 175), yet such findings may due to a more intensive lipid-lowering treatment in patients with high cardiovascular risk who are more vulnerable to COVID-19 (176). Low-, moderate-, high-intensity statin therapy should be applied according to specific LDL-C lowering needs. Importantly, careful monitoring of LDL-C, CK, blood glucose and liver function is recommended in context of COVID-19.

Currently known impacts of statins in COVID-19 are mostly based on observational studies and may vary due to heterogenicity in different trials/cohorts. To address the effect of statins in COVID-19 patients, especially in those with obesity or dyslipidemia-related diseases, randomized controlled trials with proper patient stratification are warranted. Moreover, experimental evidence of how different statins act in COVID-19 models are rare, highlighting the importance of related studies.

AUTHOR CONTRIBUTIONS

CL, WY, YC, and KH: conceptualization. CL, WY, YC, and JS: writing—original draft preparation. CL, YC, SW, AP, and KH: writing—review and editing. All authors have read and agreed to the final version of the manuscript.

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The Role of Bioelectrical Impedance Analysis in Predicting COVID-19 Outcome

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Background: Published data regarding the impact of obesity on COVID-19 outcomes are inconsistent. However, in most studies, body composition was assessed using body mass index (BMI) alone, thus neglecting the presence and distribution of adipose tissue. Therefore, we aimed to investigate the impact of body and visceral fat on COVID-19 outcomes.

Methods: Observational, prospective cohort study included 216 consecutive COVID-19 patients hospitalized at University Clinical Center Kragujevac (Serbia) from October to December 2021. Body composition was assessed using the BMI, body fat percentage (%BF), and visceral fat (VF) *via* bioelectrical impedance analysis (BIA). In addition to anthropometric measurements, variables in the research were socio-demographic and medical history data, as well as admission inflammatory biomarkers. Primary end-points were fatal outcomes and intensive care unit (ICU) admission.

Results: The overall prevalence of obesity was 39.3% according to BMI and 50.9% according to % BF, while 38.4% of patients had very high VF levels. After adjusting odds ratio values for cofounding variables and obesity-related conditions, all three anthropometric parameters were significant predictors of primary end-points. However, we note that % BF and VF, compared to BMI, were stronger predictors of both mortality (aOR 3.353, aOR 3.05, and aOR 2.387, respectively) and ICU admission [adjusted odds ratio (aOR) 7.141, aOR 3.424, and aOR 3.133, respectively].

Conclusion: Obesity is linked with COVID-19 mortality and ICU admission, with BIA measurements being stronger predictors of outcome compared to BMI use alone.

Keywords: body fat percentage, body mass index, COVID-19, obesity, visceral fat

INTRODUCTION

Although most published studies refer to obesity as one of the independent predictors of disease severity and worse outcome in hospitalized COVID-19 patients (1–4), the results regarding mortality are still inconsistent. While some meta-analysis authors observed no significant relationship between obesity and COVID-19 mortality (5, 6), others emphasize such a relationship exists only in younger patients and those with fewer comorbidities (7, 8).

Potential mechanisms by which obesity adversely affects the course of SARS-CoV-2 infection are chronic inflammation and immune response dysregulation, endothelial dysfunction, increased thrombogenic potential, endocrine dysfunction, and the simultaneous presence of other known risk factors (such as cardiovascular disease, metabolic syndrome, and diabetes mellitus) (2, 4, 9).

Given that most of these pathophysiological mechanisms are the effect of adipose tissue (dominantly visceral), the main limitation of published studies is that body composition was assessed solely based on body mass index (BMI), without insight into the presence and distribution of adipose tissue. Moreover, several studies in which abdominal adipose tissue had been assessed using CT scan emphasized the importance of visceral adipose tissue, rather than subcutaneous, on COVID-19 severity and worse outcome (10).

For the reasons stated, it is valuable to examine the impact of body and visceral fat on the course and outcome of the novel coronavirus infection and their correlation with other significant predictors of disease severity, primarily inflammatory biomarkers. In addition, bioelectrical impedance analysis (BIA) measurements could be more precise than BMI in predicting the risk of mortality and worse outcome in hospitalized COVID-19 patients. To the best of the authors' knowledge, this is the first study regarding BIA measurements and COVID-19 outcomes.

MATERIALS AND METHODS

Study Population

The study was a part of the "COVID-19 admission PREDICTors of OUTCOME" (*COVID-19 PREDICT OUTCOME*) Registry, which was approved by the university's Clinical Center Kragujevac (Serbia) Ethical Committee.

An observational, prospective cohort study included 216 consecutive COVID-19 patients hospitalized at University Clinical Center Kragujevac (Serbia) from October to December 2021. The patients were followed during the time of hospitalization. Inclusion criteria were adult age (>18 years old) and confirmed SARS-CoV-2 infection. Exclusion criteria were as follows: initial hospitalization at our Center for non-COVID pathology; pregnancy and the early postpartum period; impossibility to perform anthropometric measurements (i.e., poor general condition and severe deformities). In addition, for the reason that only one patient was underweight according to BMI and body fat percentage (%BF), that patient was excluded from further analysis.

Data Collection

The socio-demographic and medical history data were obtained using the patient's medical record (Health Informational System, ComTrade, Serbia). Patients were tracked during the hospitalization period, and primary end points were the following: (I) in-hospital mortality, (II) ICU admission, and (III) primary end-point (implying fatal outcome and/or ICU admission) (11).

Within 24 h of admission, a routine laboratory was sampled from peripheral venous blood (complete blood count, biomarkers of inflammation, coagulation parameters, and cardiac biomarkers).

Anthropometric measurements were obtained *via* the BIA method. Using the TANITA BC-543 apparatus (Tanita Corporation, Tokyo, Japan), patients were measured within the first 72 h of hospitalization, according to the manufacturer's instructions (barefoot, in light clothing, after the morning toilette, and before eating or drinking).

Anthropometric parameters of interest were:

(A) BMI, calculated using the formula: BMI [kg/m^2] = BM [kg]/BH [m^2], where BM is body mass expressed in kilograms (with0.1-kg precision), and BH is body height expressed in meters (with0.01 m precision). According to BMI values, patients were categorized as follows: (12). (I) underweight < 18.5 kg/m^2; (II) normal weight 18.6–24.9 kg/m^2; (III) overweight 25–29.9 kg/m^2; (IV) Class 1 obesity 30–34.9 kg/m^2; (V) Class 2 obesity 35–39.9 kg/m^2; (VI) Class 3 obesity > 40 kg/m^2.

(B) % BF, expressed as a percentage of the total mass (with0.1% precision). According to % BF values, regarding age and sex, patients were categorized as follows (13): (I) Low % BF; (II) Normal % BF; (III) High % BF, (IV) Very high % BF (age and sex adjusted cut-off values are presented in **Table 1**).

(C) Visceral fat (VF) levels, according to which patients were categorized as follows (14): (I) Normal (1–9); (II) High (10–14); (III) Very high (≥15)

Statistical Analysis

Statistical analysis was performed using the IBM SPSS statistical package version 23 (IBM Corporation, Armonk, NY, United States). The relationship between continuous variables was tested using Spearman's correlation. Cohen's kappa coefficient was used in order to measure the level of agreement between different anthropometric measurements in terms of defining obesity. Univariate analysis separately compared anthropometric parameters and other variables with primary end-points. Categorical variables were compared using the χ^2-test and continuous variables using the Mann-Whitney U test. After identifying the variables associated with end-points, uni- and multivariable binary logistic regression was performed. The strength of the relationship between examined variables and outcome was expressed as odds ratio (OR) belonging to 95% CI for univariate, and as adjusted OR (aOR) belonging to 95% CI for multivariate analysis. *P*-values < 0.05 were considered significant.

TABLE 1 | Age and sex adjuster cut-off values for body fat percentage (%BF) categories.

Sex	Age (years)	%BF categories			
		Low	Normal	High (overweight)	Very high (obesity)
Female	20–39	<21%	21–33%	33–39.5%	>39.5%
	40–59	<23%	23–34%	34–40%	>40%
	≥60	24%	24–36%	36–41.5%	>41.5%
Male	20–39	<7%	7–20%	20–25%	>25%
	40–59	<10.5%	10.5–22%	22–27.5%	>27.5%
	≥60	<12%	12–25%	25–30%	>30%

%BF, Body fat percentage.

RESULTS

Cohort Characteristics

Our cohort consisted of 216 adult patients with COVID-19 hospitalized at University Clinical Center Kragujevac (Serbia) from October to December 2021. The patient's characteristics are presented in **Table 2**. The median age was 67 years, and the most frequent comorbidities were arterial hypertension, diabetes mellitus, and chronic kidney disease. In our cohort, 16.7% of patients had a fatal outcome, 33.8% required ICU admission, and 35.6% had experienced primary end-point (implying fatal outcome and/or ICU admission).

Anthropometric Measurements

In our cohort, 39.3% of patients were obese according to BMI, 50.9% had a very high level of % VF, and 57.9% had an excessive level of VF (**Figure 1**). We noted that older patients had significantly higher values of VF compared to those younger than 65 years, although older patients were less frequently obese according to both BMI and % BF. Regarding sex differences, we observe that women were more frequently obese according to BMI and % BF, whereas men had higher VF levels.

When comparing an agreement between BMI and % BF in terms of defining obesity, we found moderate agreement (*kappa coefficient* 0.543; $p = 0.045$) for three anthropometric categories (eutrophic/overweight/obesity) and good agreement (*kappa coefficient* 0.733; $p = 0.045$) when comparing two groups (obesity/no obesity). However, despite a good agreement between BMI and % BF in defining obesity, 24.5% ($n = 27$) of patients with very high % BF values were categorized as normal-/overweight according to BMI. It is important to point out the high incidence of mortality and ICU admission in this group of patients (24.8 and 55.6%, respectively).

Obesity and Inflammatory Biomarkers

Upon interpreting associations between predictive laboratory biomarkers on admission [including C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6), ferritin, lactate-dehydrogenase (LDH), and fibrinogen] and anthropometric parameters, no significant relationship was found regarding BMI. However, patients obese according to BF % had significantly higher serum levels of LDH (median values: 793.5 and 701, respectively; $p = 0.024$) compared to non-obese (including normal and overweight). More interestingly, patients with very high VF levels had significantly higher serum values of CRP (median values: 116.2 and 88.8, respectively; $p = 0.014$) and IL-6 (median values: 88 and 50.4, respectively; $p = 0.028$) compared to those with normal/high VF levels. Statistical significance for other biomarkers was not found (**Supplementary Table 1**).

Body Composition and Primary End-Points

Table 3 shows crude and adjusted OR for different anthropometric measurements in regard to predicting primary end-points. Initially, % BF and VF levels were significant predictors of mortality, while BMI, although borderline, lacked statistical significance. However, after adjusting OR for age, sex, days from symptom onset, and obesity-related comorbidities (diabetes mellitus), all three anthropometric measurements were statistically significant predictors of mortality, with % BF and VF being stronger predictors compared to BMI.

In predicting ICU admission and the development of either primary end-point, all three anthropometric measurements were significant predictors before and after adjustment. Similar

TABLE 2 | Cohort characteristics regarding socio-demographic data, comorbidities, and data concerning disease course and outcome.

Cohort characteristics		Percentage (frequency) or median value (with interquartile range)
Sex	Male	63% (136)
	Female	37% (80)
Age (years)		Median: 67.0 (IQR 17.75)
COMORBIDITIES		
Arterial hypertension		67.6% (146)
Diabetes mellitus		25.9% (56)
Chronic kidney disease (grade III-V) *		14.4% (31)
Atrial fibrillation		6.9% (15)
Malignancy		6.0% (13)
Previous myocardial infarction		4.2% (9)
Obstructive lung disease **		3.2% (7)
Neurological condition ***		3.2% (7)
Charlson comorbidity index		Median: 3.0 (IQR 2)
DISEASE COURSE AND OUTCOME		
Duration between disease onset and hospital admission (days)		Median: 8.0 (IQR 5.0)
Hospital stay (days)		Median: 16.0 (IQR 12.0)
Oxygen support requirement		91.9% (214)
Mortality		16.7% (36)
ICU admission		33.8% (73)
Either primary end-point ****		35.6% (77)

**Chronic kidney disease, estimated glomerular filtration rate below 60 ml/min according to the Cocroft-Gault formula.*

***Obstructive lung disease, either chronic obstructive lung disease or bronchial asthma.*

****Neurological condition: history of stroke, brain tumor or malformation, vascular disease, dementia of any etiology, etc.*

*****Either primary end-point—fatal outcome and/or ICU admission.*

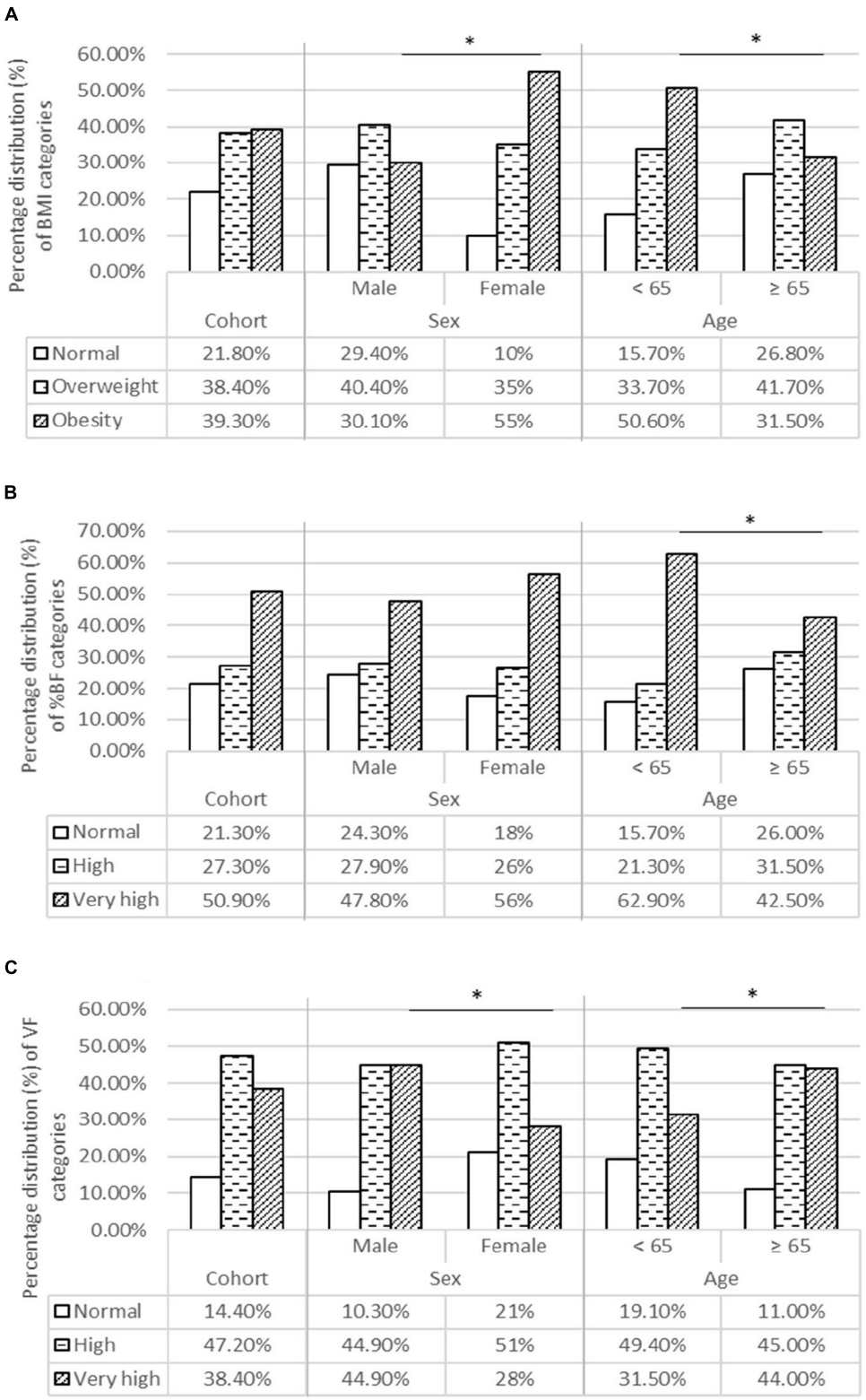

FIGURE 1 | Body composition categories for BMI **(A)**, BF% **(B)**, and VF **(C)** in the entire cohort and for age and sex categories. **(A)** Percentage distribution of BMI categories. **(B)** Percentage distribution of % BF categories. **(C)** Percentage distribution of VF categories. BF %, Body fat percentage; BMI, Body mass index; VF, Visceral fat. *Statistical significance level is taken for "*p*" values below 0,05, using the χ^2-test.

TABLE 3 | Crude and adjusted OR (with 95% CI and "*p*" values) for different somatometric measurement methods in regard to primary end-points occurrence (mortality, ICU admission, and either primary end-point).

Somatometric measurement method	Body composition categories	End-point occurrence (%)	Crude OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
Mortality						
BMI	Non-obese	13%	1		1	
	Obese	22.4%	1.930 (0.939–3.971)	0.075	**2.387** (1.067–5.337)	0.034
BF%	Non-obese	10.4%	1		1	
	Obese	22.7%	**2.540** (1.179–5.470)	0.017	**3.353** (1.471–6.642)	0.004
VF	Normal/High	10.5%	1		1	
	Very high	22.6%	**3.066** (1.466–6.411)	0.003	**3.050** (1.407–6.609)	0.005
Critical form						
BMI	Non-obese	22.1%	1		1	
	Obese	51.8%	**3.775** (2.087–6.827)	0.001	**3.113** (1.663–5.825)	0.001
BF%	Non-obese	13.2%	1		1	
	Obese	53.6%	**7.602** (3.868–14.960)	0.001	**7.141** (3.538–14.413)	0.001
VF	Normal/High	26.3%	1		1	
	Very high	56.8%	**2.364** (1.325–4.219)	0.004	**3.424** (1.781–6.581)	0.001
Composite outcome						
BMI	Non-obese	25.2%	1		1	
	Obese	51.8%	**3.187** (1.784–5.693)	0.001	**2.769** (1.495–5.125)	0.001
BF%	Non-obese	16%	1		1	
	Obese	54.5%	**6.282** (3.312–11.918)	0.001	**6.085** (3.121–11.862)	0.001
VF	Normal/High	27.8%	1		1	
	Very high	48.2%	**2.414** (1.360–4.284)	0.003	**3.208** (1.705–6.035)	0.001

% BF, Body fat percentage; BMI, Body mass index; CI, Confidence interval; ICU, Intensive care unit; OR, odds ratio; VF, Visceral fat.
OR values with a statistical significance level of <0.05 are presented in bold.
**OR was adjusted for age, sex, days from disease onset, and diabetes mellitus.*

to mortality prediction, % BF and VF had higher aOR compared to BMI.

The impact of socio-demographic characteristics and comorbidities on primary end-point occurrences are presented in **Supplementary Table 2**.

DISCUSSION

The research was conducted on 216 patients with COVID-19 consecutively hospitalized at our Center between October and December 2021, in a period of the presumed predominance of SARS-CoV-2 delta variant in our country. The majority of hospitalized COVID-19 patients in our cohort had disturbed body composition, with only two out of ten hospitalized patients having normal BMI and % BF, and 14.4% of patients having normal VF levels. The shown disturbances of body composition in hospitalized COVID-19 patients are not unexpected. First, obesity is a globally raging pandemic whose consequences are also noticeable in Serbia. According to a WHO report from 2013, 58.6% of the adult population in Serbia were overweight or obese, and, according to a model at the time, the predicament was that the obesity prevalence in 2020 would be 44% in adult men and 31% in adult women (15). Second, several studies have demonstrated that obesity is a significant risk factor for hospital admission (3, 6, 16), therefore it is somewhat expected to have a high prevalence of obesity among hospitalized COVID-19 patients. We must note that only one patient (man, 70 years old) was underweight according to BMI and % BF; therefore, he was neglected in further analysis. Although some studies have shown an increased risk for death and the need for mechanical ventilation in underweight patients (17).

Regarding age categories, patients younger than 65 years had a higher prevalence of obesity according to BMI and % BF measurements. In contrast, older patients had significantly higher VF levels. We accentuate that the high VF levels are associated with numerous health disorders and general mortality (18, 19), along with worse outcomes and death in patients with COVID-19 (10, 20–23). Therefore, excessive VF levels could be one of the links associated with increased mortality and severity in older patients with COVID-19, among others (7, 16, 24, 25). Moreover, some studies advocate obesity as a risk factor for COVID-19 mortality and severity dominantly for younger patients, with weaker or no impact at all in older patients (5, 26, 27). Perhaps this could be a misconclusion, for cited studies have used BMI

alone as a tool for accessing obesity, neglecting the significance of VF (7, 16, 24, 25).

In the initial analysis, only % BF and VF level were significant predictors of mortality, while BMI, although borderline, lacked statistical significance (**Table 3**). However, after adjusting OR for age, sex, days from disease onset, and obesity-related comorbidities (diabetes mellitus), all three anthropometric methods were significant predictors of mortality, with both % BF and VF having higher aOR values compared to BMI (aOR 3.353, aOR 3.05, and aOR 2.387, respectively). Results regarding ICU admission and experiencing either primary end-point were more concordant, where all three anthropometric measurement methods had significant predictive importance, with % BF (aOR 7.411 and 6.085, respectively) and VF (aOR 3.424 and 3.208, respectively) again having higher aOR values compared to BMI (aOR 3.113 and 2.769, respectively).

We must note that comorbidities selection for OR adjustment was arbitrary, and diabetes mellitus was chosen as a known obesity-related condition. Furthermore, a different selection of "adjusting" variables in a model (in addition to age and gender) did not significantly alter the aOR and "p" values of either anthropometric measurement. In a sensitivity analysis (**Supplementary Table 3**), conducted by implementing all socio-demographic and medical history data in a model, all three anthropometric measurements remained significant predictors of primary end-points, with % BF having an increase of aOR at the expense of a wider confidence interval range. In addition to anthropometric parameters, the model showed a significant predictive value of the Charlson comorbidity index for mortality and female sex for ICU admission.

Literature data agree that obesity, defined by BMI, is a significant predictor of disease severity (OR 1.47–5.47) (3–6, 28, 29), need for intensive care unit (OR 1.29–5.49) (3, 5, 6), and invasive mechanical ventilation (OR 1.2–6.01) (3, 5, 6, 17). However, the results regarding mortality are still inconsistent. Although some studies advocate obesity, defined by BMI, as a significant predictor of mortality, with OR ranging from 1.04 to 4.4, or even higher (1, 3, 4, 26, 30–32), others failed to show statistical significance or even showed negative predictive values (3, 5, 6, 16, 33, 34).

A relatively wide range of OR values in these studies, as well as lack of statistical significance for mortality, could be explained by different BMI cut-offs, sample size, diversity of study population (regarding diverse socio-demographic and comorbidity characteristics of the cohort, as well as different COVID-19 severity among patients), the predominance of different SARS-CoV-2 mutation variants, and other. Also, it is important to point out that all cited studies used BMI as the only measurement for defining obesity, possibly leading to misinterpretation of body composition by neglecting total body and visceral fat, especially in older and more comorbid patients (2). This is important because the majority of mechanisms by which obesity adversely affects the course of SARS-CoV-2 infection (chronic inflammation and immune response dysregulation, endothelial dysfunction and increased thrombogenic potential, endocrine dysfunction, etc.) are mostly effects of the adipose tissue (2, 4, 9). In addition, several studies in which abdominal adipose tissue had been evaluated using CT scan emphasized the importance of visceral adipose tissue on COVID-19 severity and mortality (10, 20–23). One of the pathophysiological explanations of this phenomenon lies in the fact that visceral adipose tissue, compared to subcutaneous, secretes 2–3 times higher concentrations of interleukin 6 (35), which is associated with the development of severe forms and fatal outcomes for patients with COVID-19 (1, 7). In our cohort, patients with excessive VF had significantly higher serum levels of CRP (p = 0.014) and IL-6 (p = 0.028) on admission compared to those with normal VF levels, possibly suggesting higher inflammation grade. We also note that patients with very high % BF had significantly higher values of LDH (p = 0.024), another notable COVID-19 predictor (1, 7), while no statistically significant relationship was found between BMI and any proinflammatory marker on admission. Finally, despite a good agreement between BMI and % BF in defining obesity, 24.5% of patients with very high % BF values were categorized as non-obese according to BMI. We accentuate the high incidence of mortality and ICU admission in this group of patients (24.8 and 55.6%, respectively).

All stated mechanisms could explain, at least partially, why BMI lacked statistical significance in terms of predicting mortality of patients with COVID-19 in cited studies. Also, stated mechanisms could explain why BIA measurements, both % BF and VF, had higher OR in predicting each primary end-point compared to BMI. Due to the relatively small sample size and other study limitations, perhaps the exact OR values for anthropometric measurements could not be generalized, particularly in terms of mortality. However, the results are suggestive of a link between obesity and COVID-19 severity and mortality.

CONCLUSION

Obesity is a globally raging pandemic that is, in addition to many other comorbidities and all-cause mortality, a significant predictor of COVID-19 severity and death. For that reason, intensive obesity prevention campaigns and programs should be one of the main focuses of healthcare systems worldwide.

Bioelectrical impedance analysis measurements could be a helpful tool in predicting COVID-19 severity and mortality on admission.

By having insight into the total body and visceral fat distribution, BIA measurements (both % BF and VF) were stronger predictors of each primary end-point (mortality and ICU admission) compared to BMI.

STUDY LIMITATIONS

Our study had several limitations. First, COVID-19, like infection and inflammation, can impact body composition. To minimize that effect, we have measured patients in the initial days of hospitalization. Second, a substantial number of patients were excluded from the study, because of their inability to undergo

BIA assessment (such as poor general condition, dementia, and lack of limbs). Third, we have included a relatively small number of patients for the generalization of the results.

Finally, although BIA measurements have satisfactory insight into total body fat and fat-free mass and are widely used for body composition assessment in the general population, this method has difficulty distinguishing visceral from abdominal fat, for which CT and MRI remain the gold standard (36, 37). Due to stated study limitations and presented results, the authors suggest and encourage continuing research on this issue.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Clinical Center Kragujevac, Kragujevac, Serbia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DS, VZ, MiP, VM, and IC contributed to conception and design of the study. VZ, MaP, IC, and VM ensured quality of the research and performed final review of the manuscript. DS and MiP organized the database. SM and NZ performed the statistical analysis and contributed to presentation of results. DT, AD, MM, DB, AA, and AJ contributed to data collection and helped in writing chapters of the manuscript. DS and MiP wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.906659/full#supplementary-material

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REVIEW
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Obesity and Infection: What Have We Learned From the COVID-19 Pandemic

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Objective: The critical role played by the nutritional status in the complications, duration of hospitalization and mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) has emerged from several research studies in diverse populations. Obesity has been associated with an increased risk of serious complications, as the adipose tissue appears to have significant effects on the immune response. The aim of this narrative review was to investigate the relationship between COVID-19 and obesity.

Methods: We performed a review of papers in the English language derived from PubMed, Science Direct, and Web of Science. The primary outcomes investigated were the severity of the disease, admission to the intensive care unit (ICU), need for intubation, and mortality.

Results and Conclusion: Review of 44 eligible studies from 18 countries around the world revealed evidence that obesity increases the risk of severe COVID-19 complications, ICU admission, intubation and mortality. Patients with a higher body mass index (BMI) appear to be more vulnerable to SARS-CoV-2 infection, with more severe illness requiring admission to ICU and intubation, and to have higher mortality. A healthy body weight should be targeted as a long-term prevention measure against acute complications of infection, and in the event of COVID-19, overweight and obese patients should be monitored closely.

Keywords: adipose tissue, COVID-19, obesity, mortality, infection, severity

INTRODUCTION

On 31 December 2019 the World Health Organization (WHO) was informed by Chinese officials of dozens of cases of pneumonia of unknown etiology in Wuhan, China.

On 11 March 2020 the WHO announced that the whole world was living under the threat of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic (COVID-19). The response from the scientific community was to produce anti-SARS-CoV-2 vaccines, and rapid immunization of the population was instituted, aimed at halting the spread of the virus.

By April 2022 the WHO reported approximately 504 million confirmed cases of COVD-19, and 6.2 million deaths (1). At this stage, ∼59% of the world population had received one dose of COVID-19 vaccine (2). The SARS-CoV-2 has mutated over time, resulting in genetic variations in the population of circulating viral strains over the course of the COVID-19 pandemic (3), and changing health effects, in terms of contagiousness, severity and symptoms (4).

The critical role of the nutritional status on the complications, length of hospitalization and mortality from SARS-CoV-2 viral infection has emerged from several research studies conducted from different perspectives. Weight status is indicated as a significant factor, with obesity being associated with an increased risk of serious complications (5), as the adipose tissue appears to have significant effects on the immune response (6).

Efforts made by the research community to interpret the mechanisms that lead to an exaggerated inflammatory response focus primarily on the role of adipose tissue in the function of white blood cells (WBCs). Specifically, the main mechanisms reported are the following:

Expression of Angiotensin 2 Enzyme in Adipose Tissue

SARS-CoV-2 has been reported to penetrate human cells by direct binding to ACE2 receptors on the cell surface. The concentration of ACE2 is higher in adipose tissue than in lung, thus suggesting that adipose tissue may be more vulnerable to COVID-19 infection. The obese population has more adipose tissue and higher levels of ACE2, which implies an increased susceptibility to infection due to exaggeration of the inflammatory response (7).

Metabolic Dysfunction

Human adipose tissue is known for its basic functions in helping to maintain the body's homeostasis, which include energy storage in the form of fat, and supply of energy in prolonged conditions of reduced food intake (8), thermal insulation of the body (9), absorption of environmental vibrations, and mechanical facilitation of the movement of the skin on the underlying tissues (10). In addition, adipose tissue is known to be actively involved in inflammation and immunity (11). Specifically, white fat cells produce numerous endocrine, paracrine and neuroendocrine signals through the production of adipokines. As described above, SARS-CoV-2 penetrates human cells by direct binding to ACE2 receptors on the cell surface (12). Because of the high concentration of ACE2 in adipose tissue, obese individuals may be more vulnerable to COVID-19 infection (13).

Tumor necrosis factor-α (TNF-α) is a multifunctional cytokine involved in many different pathways in human homeostasis and pathophysiology. In animal models, TNF-α is expressed in adipose tissue and affects insulin-induced signaling, inhibiting expression of glucose transporter type 4 (GLUT-4), resulting in raised levels of free fatty acids (FFA), and finally increasing insulin resistance (IR) (14). This promotes the activation of NF-kB, a transcriptional activator that controls proinflammatory cytokine synthesis and cell survival, inducing the pathway to cell death (15).

Excess FFAs, in turn, activate immune pathways of inflammation, through various signaling pathways that promote increase of TNF-α, interleukin-6 (IL-6), leptin, and resistin (16), which act directly on the differentiation of monocytes into activated M1 macrophages. M1 macrophages produce inflammatory cytokines, active oxygen radicals and nitric oxide (NO), affecting the endogenous immune response to pathogens (16). Obesity therefore leads to an inflammatory response characterized by increased cell aggregation and higher production of cytokines.

Thymus Gland

The thymus gland is an organ characterized by T-cell growth, and any thymus defect or impairment of the production of thymocytes, can lead to profound primary T-cell immunodeficiency (17). Defects affecting both T-cell and B-cell lines result in severe combined immunodeficiency syndrome (SCIDs) (17). Obesity causes a decrease in T-cell receptors (18).

In addition, the peripheral immune response to obesity reduces the migration of antigen-presenting cells (APCs) to peripheral lymph nodes, and lowers the number of T cells, resulting in a reduced immune response against infectious agents (19).

Adipocyte Function

Obesity, due to the direct evolutionary relationship of metabolic and immune pathways, causes major changes in the number, phenotype and tissue distribution of adipose tissue adipocytes, and in the attraction of various different immune cell populations (20, 21). Thus, about half of the adipose tissue cells in obese individuals are macrophages, characterized by the inflammatory phenotype of classically activated macrophages (M1), while in lean individuals, the macrophage phenotype of adipose tissue is that of anti-inflammatory alternatively activated macrophages (M2) (22). M1-macrophages produce a number of inflammatory agents, including TNF-α, IL-6, IL-1β, chemokine ligand-2 (CCL2), and macrophage inhibitory factor (MIF), resulting in the development of local inflammation (23). Strong experimental evidence suggests that other myelogenous immune cells (dendritic and squamous cells, granulocytes, and granulocytes) contribute significantly to the severe disruption of the network of immune mechanisms in the adipose tissue of obese subjects (24).

The aim of this narrative review was to investigate the association of obesity with the severity and complications of COVID-19 infection, admission to the intensive care unit (ICU), need for intubation, and mortality.

MATERIALS AND METHODS

A literature review was carried out, based on a search in PubMed, Science Direct and Web of Science to identify peer-reviewed studies, published between January 2020 and April 2022, using the following keyword combinations: Obesity OR visceral fat OR adipose tissue OR Body Mass Index AND

COVID-19 (SARS-CoV-2) severity OR COVID-19 (SARS-CoV-2) complications OR COVID-19 (SARS-CoV-2) intubation OR COVID-19 (SARS-CoV-2) mortality. Additional articles were identified through reference lists of the retrieved articles.

The search was completed on January 10th 2022 and updated on April 15th 2022.

Inclusion criteria were clinical studies that: (1) were quantitative (25) empirical human studies (26); (2) reported obesity prevalence and outcomes in patients with COVID-19; (3) were published in English in peer-reviewed journals. The exclusion criteria were (1) intervention studies with food supplements; (2) reports of patients with other comorbidities (e.g., cancer, cardiovascular disease); (3) studies focusing on other co-factors associated with complications, such as smoking, alcohol; (4) qualitative studies; (5) limited access; (6) reviews, systematic reviews, opinion articles, editorials.

Titles and abstracts were reviewed independently by two researchers (EV, RSB), and discrepancies were resolved through discussion or involvement of the other three researchers (AKP, AP, DB). The data extracted for review included first author's name, country where the study was performed, study type, patient characteristics, weight status and clinical outcomes, including disease severity and complications, admission to the ICU, intubation and mortality. The literature review was conducted with the RAYYAN online tool for systematic reviews (27).

Figure 1 shows the flow chart of the selection of studies included in this review. After removal of duplicates, 1,949 papers were evaluated, of which 44 met the inclusion criteria, and were the subject of the review.

Quality Assessment

The 44 studies were read extensively and scored according to the Ottawa Scale for case series, cohort, cross-sectional and case-control studies, for each of the following quality markers: (1) the target population was defined clearly; (2) recruitment was complete, random or consecutive; (3) the confidence intervals (CI) or standard error (SE) were reported.

The primary aim of the review was investigation of the association of obesity in patients with COVID-19 with the disease outcome, specifically severity, complications, ICU admission, intubation and mortality.

RESULTS

The characteristics of the studies included in the review are presented in **Supplementary Table 1** and are discussed in detail below.

Obesity in Patients With COVID-19 and Admission to the ICU

Alkhatib et al. reported on the body mass index (BMI) in a sample of 158 African-American patients with COVID-19 admitted sequentially to a tertiary care center between March 12 and April 9 2020. The BMI was significantly higher in those patients who needed to be hospitalized in the ICU (36.5 vs. 31.9 kg/m^2, $p = 0.002$). The multiple regression (MR) model indicated that, after testing for all other variables in the model, BMI functions as an independent prognostic factor for ICU admission, with adjusted odds ratio (aOR): 1.115; 95% CI: 1.052–1.182, in African Americans. The predicted aOR indicated that for an increase in BMI by 5 and 10 kg m^2 (aOR: 1.72; 95% CI: 1.29–2.31 and aOR: 2.97; 95% CI 66–5.32, respectively), the relative probability of admission to the ICU increases by 1.7 and 3 times, respectively (28). Similarly, Palaiodimos et al. in a retrospective study of the first 200 patients with confirmed COVID-19 infection admitted *via* the emergency department (ED), showed that a BMI of 35 kg/m^2 or higher was independently related to in-hospital mortality (aOR: 3.78; 95% CI: 1.45–9.83; $p = 0.006$), increased oxygen demand (aOR: 3.09; 95% CI: 1.43–6.; $p = 0.004$) and intubation (aOR: 3.87; 95% CI: 1.47–10.18; $p = 0.006$) (29).

In the study of Kalligeros et al. which included all adult patients (≥18 years) with confirmed SARS-CoV-2 virus infection admitted to Rhodes Island General Hospital or Mirian Hospital in Rhodes Island, Greece from February to April 2020, class 2 obesity (BMI ≥ 35 kg/m^2) was associated with an increased risk of admission to the ICU (aOR: 5.39, 95% CI: 1.13–25.64) (30). Shuelter-Trevisol et al. reported that obesity was an independent prognostic factor (aOR: 6.83; 95% CI: 1.93–24.25) for admission to the ICU, in a sample of 211 patients who were diagnosed with COVID-19 infection between March and July 2020, and were admitted to hospital in the Tubarão area, Santa Catarina, Brazil (31). In the retrospective study of Busetto et al. of 92 patients admitted to a COVID-19 ward from March to April 2020 in Veneto, Italy, admission to ICU or semi-ICU was needed for 18.7% of patients in the normal weight group, 54.8% of overweight patients and 41.3% of patients with obesity ($p < 0.05$) (32).

Similar findings were reported by Argenzian et al. from retrospective study of the first 1,000 consecutive patients with SARS-CoV-2 acute respiratory distress syndrome (ARDS) presenting at the ED or admitted to hospital between March and April 2020 in New York. Specifically, patients admitted to the ICU had a higher rate of obesity than those not requiring intensive care (45.7 and 39.5%, respectively) (33).

In a retrospective cohort study with 14,625 patients in Turkey, Sahin et al. observed that hospitalization, ICU admission, intubation/ventilation, lung involvement and mortality were significantly higher in overweight and obese patients. On adjusted analysis, overweight (OR, 95% CI: 1.82, 1.04–3.21; $p = 0.037$) and obesity (OR, 95% CI: 2.69, 1.02–1.05; $p < 0.001$) were associated with a higher rate of intubation/mechanical ventilation, but only obesity was associated with increased mortality (OR, 95% CI: 2.56, 1.40–4.67; $p = 0.002$) (34).

In Germany, Dreher et al. compared the clinical features of the first 50 COVID-19 patients hospitalized with or without ARDS. Patients with ARDS were more commonly overweight or obese [83% (64, 93) vs. 42% (26, 61)] or had a history of respiratory diseases [58% (95% confidence interval: 39, 76) vs. 42% (26, 61)] (35).

A study from England with 6,910,695 patients conducted by Gao et al. showed a significant positive linear association between each unit of increase in the BMI and admission to the ICU due to COVID-19 (36).

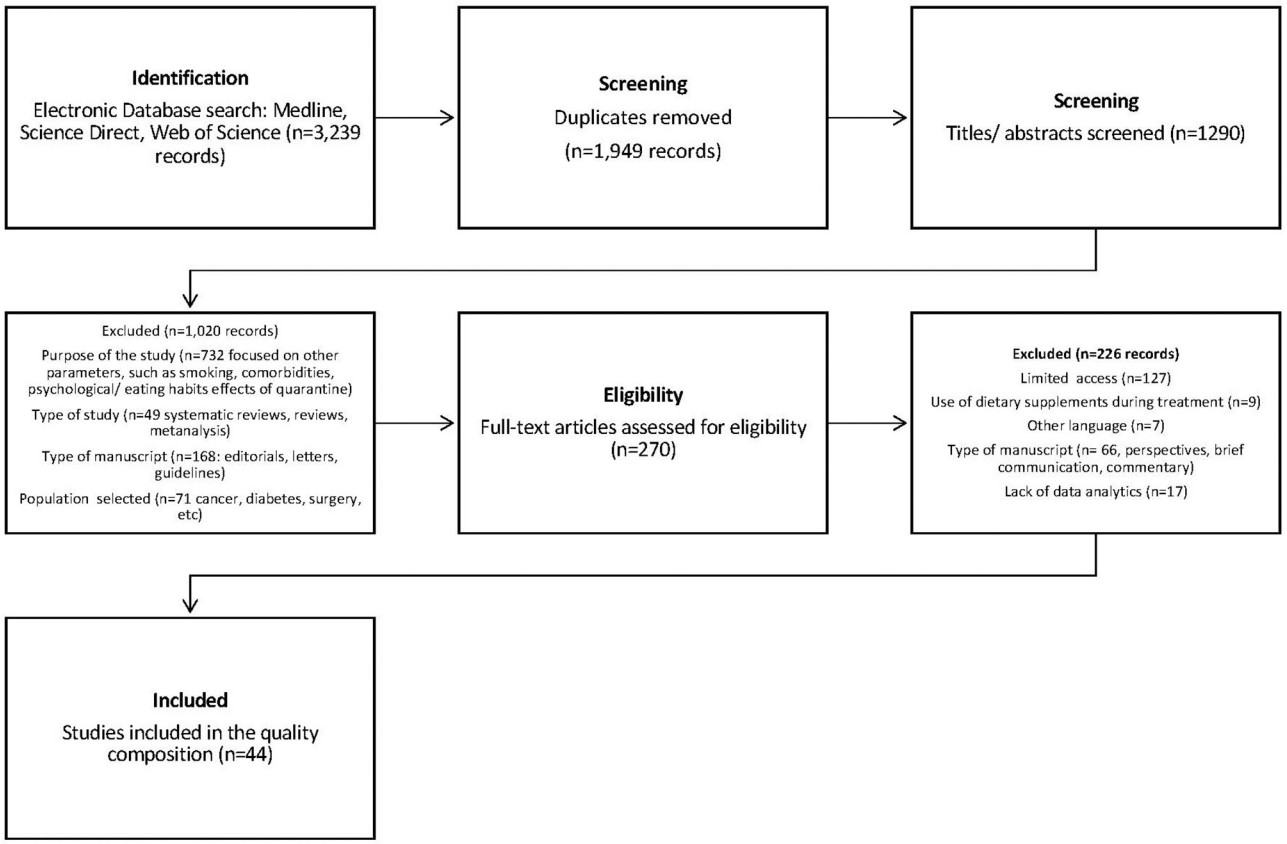

FIGURE 1 | Flow chart showing selection procedure for studies on obesity and COVID-19 infection.

Le Guen et al. retrospectively analyzed data on 600 patients, showing that obese patients had an increased rate of ICU admission ($p = 0.0215$) and increased duration of hospitalization ($p = 0.0004$) (37).

Al Sabah et al. reported that, in a retrospective cohort study of 1,158 patients, the median BMI of patients admitted to ICU was significantly higher than that of those who did not require ICU admission [median BMI: 27.5 kg/m^2, interquartile range (IQR) 25.3–31.4 kg/m^2 vs. 26 (23–29) kg/m^2, respectively, $p < 0.001$] (38).

In another retrospective study, Boudou et al. included 47,265 laboratory-confirmed cases of symptomatic COVID-19 infection from February to November 2020. They concluded that severe obesity, indicated by BMI $\geq$ 40, was a significant marker for ICU admission (OR 19.6), and a particularly significant predictor among patients with COVID-19 aged $<$ 41 years for ICU admission and $<$ 63 years for death (39).

Cordova et al. in a cohort study of 809 patients treated in 19 hospitals in Argentina, concluded that ICU admission was significantly correlated with male gender (OR 1.81; 95% CI 1.16–2.81), hypertension (OR 3.21; 95% CI 2.08–4.95), obesity (OR 2.38; 95% CI 1.51–3.7), and oxygen saturation $\leq$93% (OR 6.45; 95% CI 4.20–9.92) (40).

Yoshida et al. also in a retrospective study, conducted from February to July 2020 with 776 patients with COVID-19, demonstrated on multivariate analyses, an association between obesity and increased odds of intermittent mandatory ventilation (IMV) and ICU admission (41).

In the study of Wang et al. involving 297 patients with COVID-19 treated sequentially in 10 hospitals in China's Jiangsu Province from January to February 2020, the relationship between BMI level and probability of admission to ICU was not confirmed, as the percentage of patients admitted to ICU was similar in the three BMI groups (normal weight, overweight, obese) ($p = 0.087$). The mean number of days of hospitalization, however, differed between the 3 groups of patients ($p = 0.025$) (42).

Obesity in Patients With COVID-19 and Disease Severity/Complications

A retrospective study of Rao et al. of 240 patients with COVID-19 admitted to the Union Hospital in Wuhan, China between December 2019 and March 2020, led to the conclusion that patients with severe disease had significantly higher BMI and were more likely to be overweight [$n = 73$ (60.8%) vs. $n = 41$ (34.2%), $p < 0.001$]. In addition, overweight patients were more

likely to develop severe pneumonia than normal weight patients [$n = 73$ (64.0%) vs. $n = 47$ (37.3%), $p < 0.001$], and MR analysis indicated that being overweight [aOR: 3.075 (1.187–7.965), $p = 0.021$] is an independent prognostic factor for the development of severe pneumonia (43).

The retrospective study of Deng et al. in 96 patients hospitalized with SARS-CoV-2 infection at Dongguan People's Hospital, Nanfang Hospital and Xiamen University Collaborating Hospital in China in January and February 2020, reported that after treatment, the symptoms had improved or stabilized in 66/96 patients (44). The proportion of patients with a stable disease course with BMI < 24, 24–27.9 and ≥ 28 kg/m^2 were 74.2 19.7, and 6.1%, respectively, and these rates were significantly different from those of patients with other infections (63.3, 46.7, and 20.0%, respectively, $p = 0.001$) (44).

Negative findings for viral pneumonia on computerized tomography (CT) scan were reported in 85.7, 14.3, and 0%, respectively, of patients with BMI < 24, 24–27.9, and ≥ 28 kg/m^2, while pneumonia was diagnosed in 54.7, 32, and 13.3% of patients in the respective BMI groups ($p = 0.027$) (45). Obesity emerged as an important prognostic factor at admission for the development of severe COVID-19 disease. In the study of Denova-Gutiérrez et al. obesity was associated with a 1.43 times higher likelihood of developing severe disease (46). Wang et al. (42) showed that the disease severity was dependent on the weight status: severe disease developed in a higher proportion of overweight patients than in those who were normal weight (2.86%, $p = 0.006$), and in obese patients compared with those of normal weight (25 vs. 2.86%, $p < 0.001$). MR analysis indicated that overweight (aOR, 4,222; 95% DE: 1.322–13.476, $p = 0.015$) and obese patients (aOR, 9,216, 95% DE: 2,581–32,903, $p = 0.001$) had an increased chance of developing severe disease after controlling for the effect of the other variables on the model (42).

Hu et al. in a retrospective study of 323 patients with COVID-19 who were hospitalized from January to February 2020 at a reference hospital in Wuhan, observed that patients with BMI ≥ 30 kg/m^2 were more likely to have an adverse than a positive disease outcome (10.7% vs. 2.9%, $p = 0.029$) (47).

Likewise, Cai et al. (48) in a retrospective cohort study of 383 consecutive patients with COVID-19 admitted from January to February 2020 and monitored until March 2020 at Shenzhen 3rd People's Hospital (China) reported that overweight or obese patients were more likely to have severe disease; 19.2% in the normal weight group, 29.3% in the overweight group, and 39% in the obese group ($p \leq 0.001$). Overweight patients were 1.84 times more likely to develop severe COVID-19 (aOR: 1.84, 95% DE 0.99–3.43, $p < 0.05$), and those who were obese were 3.4 times more likely to develop severe disease than normal weight patients (aOR: 3.40, 95% DE: 1.40–2.86, $p = 0.007$) (45, 48).

Deng et al. in 65 patients with COVID-19 infection, aged 18–40 years and admitted consecutively from March to April 2020 to the Zhongnan Hospital of Wuhan University in China, observed that patients with severe disease were either overweight (33.3%) or obese (66.67%), and MR analysis showed that high BMI, and especially obesity, is a factor exacerbating the disease severity of COVID-19 infection in young people (44). Similarly, Ioannou et al. in a cohort study involving 101,301 U.S. veterans with SARS-CoV-2 infection, observed that being overweight (BMI 25–29.9 vs. 18.5–24.9 kg/m^2: aLE, 0.90; 95% DE, 0.77–1.06) or type I obese (BMI 30–34.99 vs. 18.5–24.9 kg/m^2: aLE, 0.84; 95% DE, 0.69–1.01) or type II obese (BMI$>$ 35 vs. 18.5–24.9 kg/m^2: aLE, 0.97; 95% DE, 0.77–1.21) was associated with an increased risk of adverse outcome (49).

Nachega et al. in a retrospective study of 766 patients treated for COVID-19 between 10 March 2020 and 31 July 2020 at seven hospitals in Kinshasa, Democratic Republic of the Congo, observed that obese patients were less likely to improve compared with non-obese patients (ASL = 0.27, 95% DE: 0.12–0.59) (50). Fresán et al. conducted a prospective cohort study in the period March to April 2020, in the Navarre region of Spain with 433,995 participants aged 25 to 79 years who had public health insurance. They concluded that those with severe obesity (BMI ≥ 40 kg/m^2) had a 2.3 times higher risk of developing severe COVID-19 disease [aQR: 2.30 95% CI: 1.20–4.40, $p = 0.012$), after adjusting for other confounding factors in the model (51).

In addition, Hendren et al. analyzed data from patients hospitalized with COVID-19 in 88 US hospitals enrolled in the American Heart Association (AHA) COVID-19 Cardiovascular Disease Registry. Data collected during July 2020 indicated that severe obesity (BMI ≥ 40 kg/m^2) was associated with an increased risk of in-hospital mortality only in those aged $\leq$50 years [hazard ratio, 1.36 (1.01–1.84)]. In the adjusted analysis, higher BMI was associated with venous thromboembolism and with dialysis initiation, but not with major cardiovascular events (52).

Pantea Stoian et al. investigating the link between mortality and comorbidities, gender, age and hospital pneumonia, showed that obesity is a negative marker for the severity of COVID-19 infection in adults aged $\leq$50 years ($p = 0.0001$) (53).

Terada et al. conducted a cohort study of 3,376 patients, categorizing them into two groups based on the severity of the infection at the time of admission: 2,199 cases (65.1%) were non-severe, and 1,181 cases (34.9%) were severe, and observed that obesity had a major effect on the severity of symptoms (OR 1.75; 95% CI 1.26–2.45, $p = 0.001$) (54).

Finally, Yanover in a cohort of 4,353 patients, studied the complications of COVID-19 in the presence of other comorbidities. Obesity was a risk factor for patients 18–50 years old (OR 11.09, 95% CI 4.15–32.67; $p \leq 0.001$), while for older patients (50–65 years) a risk factor was chronic kidney disease (OR 4.06, 95% CI 1.89–8.38; $p = 0.005$), while for patients $\geq$65 years was the neurological disorders (OR 2.65, 95% CI 1.69–4.17; $p = 0.001$) (55).

Obesity in Patients With COVID-19 and Likelihood of Intubation

Palaiodimos et al. reported that patients with severe obesity were more likely to undergo intubation (BMI < 25 kg/m^2: 18.4%, BMI 25–34 kg/m^2: 16.4%, BMI ≥ 35 kg/m^2: 34.8%, $p = 0.032$). Overall, 45% of the patients had increasing oxygen requirements during their hospital stay, but with no significant differences between BMI categories (56). Simmonet et al. in a monocentric retrospective study involving 124 patients who were admitted to the ICU with confirmed SARS-CoV-2 infection at Roger Salengro

Hospital at the "Center Hospitalier Universitaire de Lille" (CHU 27), concluded that the distribution of BMI categories differed significantly between those who needed mechanical ventilation and those who did not ($p < 0.01$, Fisher for trend accurate test). Obesity (BMI > 30 kg/m²) and severe obesity (BMI≥ 35 kg/m²) were more common in patients who needed mechanical ventilation than in those who did not (56.4 vs. 28.2% and 35.3 vs. 12.8%, respectively). MR analysis showed that being obese (BMI ≥ 35 kg/m² was an independent prognostic factor (aOR: 1.69, 95% DE: 0.52–5.48, compared to reference category BMI < 25 kg/m²) for the need for mechanical ventilation, after controlling for the other variables in the model (57).

The retrospective cohort study of Nakeshbandi et al. involved 504 patients screened for COVID-19 at SUNY Downstate Health Sciences University in New York, which was designated by Governor Andrew Cuomo as the COVID Reference Hospital for 10 March 2020 and 13 April 2020. They concluded that overweight patients (RR 2.0, 95% CI 1.2–3.3, $p = 0.01$) and obese patients (RR 2.4, 95% CI 1.5–4.0, $p = 0.001$) had an increased risk of intubation compared with the control category of normal weight (58). Cai et al. reported that the rates of BMI < 24, 24–27.9 and ≥ 28 kg/m² were 52, 24, and 24%, respectively in patients with ARDS, and differed significantly from the rates in those who did not develop ARDS (64.8, 29.6, and 5.6%, respectively, $p = 0.035$) (45). Busetto et al. reported that assisted ventilation (non-invasive and IMV ventilation), in addition to pure oxygen support, was used in 15.6% of normal weight patients, 54.8% of overweight patients, and 41.4% of obese patients with COVID-19, with the difference between the groups being statistically significant ($p < 0.01$) (32).

Klang et al. in a retrospective study of 3,406 patients with COVID-19, admitted to the University Hospital in New York during the period March to May 2020, concluded that the need for intubation and IMV was independently associated with BMI ≥ 40 kg/m², in both the younger (<50 years; aOR 4.1; 95% CI: 2.1–8.2) and the older age group (≥40 years; aOR 1.5; 95% CI: 1.1–2) (59).

In a retrospective study conducted by Deng et al. in 65 patients aged 18 to 40 years, consecutively admitted with COVID-19 infection to the Zhongnan Hospital of Wuhan University in China during March and April 2020, patients with severe COVID-19 disease were either overweight (33.3%) or obese (66.67%). Multiple regression analysis showed that high BMI, especially obesity, was a prognostic factor for severe disease in COVID-19 infection in young people (44).

Bartoletti et al. studied 1,265 inpatients diagnosed with COVID-19 in 11 Italian hospitals from February to April 2020. Multiple logistic regression analysis indicated that obesity was associated with severe respiratory failure, after adjustment for other variables (aQR 4.62; 95% CI 2.78–7.70) (60).

Mughal et al. in a retrospective study involving the first 129 patients with COVID-19 admitted to the Monmouth Medical Center (U.S.) from March to April 2020, concluded that among the patients who received IMV, a higher proportion was obese in comparison with those who did not require such intervention (36.7 vs. 10.1%, $p = 0.0334$) (61).

Sahin et al. reported that, in a total of 14,625 patients of median age 42years, presenting with COVID-19 between March and May 2020, mortality was significantly higher in obese or overweight patients. On adjusted analysis, overweight (OR, 95% CI: 1.82, 1.04–3.21; $p = 0.037$) and obesity (OR, 95% CI: 2.69, 1.02–1.05; $p < 0.001$) were associated with a higher rate of intubation/mechanical ventilation (34).

Similarly, Hendren et al. in a study of 7,606 patients with COVID-19, showed that overweight patients and obese (classes I to III) patients were at higher risk for mechanical ventilation [OR 1.28 (95% CI, 1.09–1.51), 1.54 (1.29–1.84), 1.88 (1.52–2.32), and 2.08 (1.68–2.58), respectively] (52).

Bailly et al. showed that IMV was necessary more frequently for obese in-patients with COVID-19 (aOR 1.9, 95% CI 1.8–2.0) (62). Yoshida et al. in a retrospective study of 776 patients, reported that obesity was a predictor of respiratory failure requiring IMV at a lower BMI class (> 35 kg/m²) in women (41). Conversely, Le Guen et al. in a retrospective cohort study that enrolled 600 obese patients who were positive for COVID-19, reported that the intubation rate ($p = 0.3705$) was not significantly higher in obesity (37).

Obesity in Patients With COVID-19 and Mortality

Palaiodimos et al. reported that 24% of 200 patients with COVID-19 in their retrospective study died during hospitalization, and that the mortality rate was higher in patients with severe obesity, specifically, BMI < 25 kg/m²: 31.6%, BMI 25–34 kg/m²: 17.2%, BMI ≥ 35 kg /m²: 34.8%, $p = 0.03$ (56). Similar results were reported by Van Halem et al. who studied 319 patients aged 16 years or older, hospitalized for at least 24 hours with confirmed COVID-19 infection by April 15 at a tertiary care center. They reported that 33.9% of patients who died were obese and that the percentage of obese people discharged was 20.11% ($p = 0.039$) (63).

Conversely, Busetto et al. reported that the mortality rate was significantly higher in the normal weight group (31.2%) than in overweight patients (no death) or in obese patients (6.9%) (p <0.001) (32).

In the study of Nakeshbandi et al. overweight (aOR 1.4, 95% CI 1.1–1.9, $p = 0.003$) and obese patients (aOR 1.3, 95% CI 1.0–1.7, $p = 0.04$) had an increased risk of mortality compared with those of normal BMI (58). Similarly, Klang et al. demonstrated on multiple regression analysis that in both the younger population (<50 years, $n = 572$) and the elderly population (> 50 years, $n = 2,834$), BMI ≥ 40 kg/m² was independently associated with mortality (aOR 5.1, 95 CI: 2.3–11.1 and aOR 1,6; 95% CI: 1.2–2.3, respectively) (59).

Czernichow et al. in a study of 5,795 patients with COVID-19 hospitalized in a Network Hospital Assistance Publique—Hôpitaux in Paris, concluded that mortality was significantly higher in obese individuals, specifically, BMI 30–35 kg/m², aOR 1.89; 95% CI: 1.45–2.47; BMI 35–40 kg/m², aOR 2.79; 95% DE: 1.95–3.97 and BMI > 40 kg/m², aOR 2.5; 95% CI: 1.62–3.95, compared with a control group of BMI 18.5–25 kg/m² (64).

In Mexico, also, a study conducted by Prado-Galbarro et al. which included all consecutive cases of COVID-19 treated by medical units and hospitals in Mexico between February and April 2020 ($n = 15,529$), demonstrated that obesity was associated with a higher risk of mortality from infection SARS-CoV-2 (in out-patients aOR: 1.55; 95% CI: 1.42–1.51), and in in-patients aOR: 12.84; 95% CI: 1.15–7.00) (65).

In the retrospective study of Chetboun et al. 1,461 patients were enrolled, with a median BMI of 28.1 kg/m^2 (IQ range 25.4–32.3 kg/m^2). An adjusted Cox proportional hazards regression model demonstrated a significant association between BMI and death, which was only increased in the class III obesity category [BMI $\geq$ 40 kg/m^2; hazard ratio = 1.68 (95% CI: 1.06–2.64)] (66).

The research findings of Sahin et al. were similar; they enrolled 14,625 patients with COVID-19 of median age 42 years of whom 57.4% were female, categorized into three groups, normal weight (34.7%), overweight (35.6%), and obese (29.7%). Obesity in this population was associated with increased mortality (OR, 95% CI: 2.56, 1.40–4.67; $p = 0.002$) (34).

Hendren et al. analyzed data from 7,606 patients hospitalized with COVID-19 at 88 US hospitals and concluded that classes I and II obesity were associated with a higher risk of in-hospital death [OR 1.28 (95% CI, 1.09–1.51), and 1.57 (1.29–1.91), respectively], and class III obesity was also associated with a higher risk of in-hospital death [hazard ratio, 1.26 (95% CI, 1.00–1.58)] (52).

Tartof et al. among 6,916 patients with COVID-19, compared patients with a BMI of 18.5 to 24 kg/m^2 with those with a BMI of 40–44 and $\geq$ 45 kg/m^2. In adjusted analysis, high BMI was strongly associated with a higher mortality risk, with a 4 times greater risk for the highest BMI classes. The adjusted mortality rate for the highest BMI classes was 7.08 per 100 patients (95% CI 3.58–14.00), equal to an attributable excess of 5.52 deaths per 100 patients (95% CI 0.63–10.42) when compared with those of BMI 18.5–24 kg/m^2 (67).

Azarkar et al. analyzed 364 cases of COVI-19, from February to September 2020, and reported that mortality showed a significant relationship with BMI ($p < 0.05$) (68).

In a retrospective cohort study conducted by Frank et al. a total of 305 patients were categorized by BMI: <25 kg/m^2, 54 patients (18%), $\geq$ 25–< 30 kg/m^2, 124 patients (41%), $\geq$ 30 kg/m^2–<35 kg/m^2, 58 patients (19%), and $\geq$35 kg/m^2, 69 patients (23%). In total, 128 patients (42%) had a severe disease course; 119 (39%) with intubation, and 9 (3%) died without intubation. Furthermore, 65 patients (51%) with BMI $\geq$ 30 kg/m^2 were intubated or died. Adjusted Cox models showed that BMI $\geq$ 30 kg/m^2 was associated with a 2.3-fold increased risk of intubation or death (95% CI, 1.2–4.3) compared with individuals with BMI <25 kg/m^2 (69).

Richardson et al. in a retrospective cohort study analyzed the records of 1,013 patients in March and April 2020. MR analysis revealed that obesity was an independent predictor of in-hospital 30-day mortality [adjusted hazard ratio (aHR) 2.71, 95% CI 1.28–5.73; $p = 0.002$] (70).

Smati et al. in the retrospective, multicenter, nationwide CORONADO study, assessed the relationship between BMI classes and early COVID-19 prognosis in 1,965 patients with type II diabetes mellitus (DM). MR analysis showed significant association between poor prognosis and overweight [OR 1.65 (1.05–2.59)], class I [OR 1.93 (1.19–3.14)], and class II/III obesity [OR 1.98 (1.11–3.52)] ($p = 0.0373$). An association was also found between IMV and overweight to class II/III obesity, but death was not associated with BMI status ($p = 0.9634$) (71).

Finally, a retrospective study of the COVID-19 ICU Group by Schmidt et al. in Switzerland involving all consecutive patients ($n = 4,643$) aged $\geq$16 years of age admitted to the ICU between February and May 2020, with laboratory-confirmed ARDS due to SARS-CoV-2 ($n = 4,244$) concluded that severe obesity, BMI $\geq$ 40 kg/m^2, is one of the foremost prognostic indicators of death during the 90 days, regardless of other variables in the model (aOR: 2.05; 95% CI 1.28–3.27) (72).

The relationship between obesity and mortality was not confirmed in the study of Le Guen et al. in which obese patients showed no differences in mortality ($p = 0.248$) (37).

Suresh et al. enrolled 1,983 patients of whom 1,031 (51.9%) were obese and 952 (48.9%) were not obese. The obese patients were younger than the patients of normal weight ($p < 0.001$). MR models adjusting for differences in sex, race, age, medical comorbidities and treatment modalities revealed no difference in 60-day mortality and 30-day readmission between the groups with and without obesity. The obese patients showed increased odds of ICU admission (aOR 1.37; 95% CI, 1.07–1.76; $p = 0.012$) and intubation (adjusted OR 1.37; 95% CI, 1.04–1.80; $p = 0.026$) (73).

DISCUSSION

Numerous studies in diverse populations from around the world have examined the role of body weight and body composition in relation to COVID-19 disease. Studies investigating the effects of BMI were thoroughly researched in the context of our review, yielding important conclusions. It appears that a high BMI is an indicator for the development of severe COVID-19 disease, as assessed by admission to the ICU, intubation, and even mortality. The results suggest the significance of maintaining a healthy body weight as a preventive measure against severe infection.

Basic research has shown that adipose tissue, and especially visceral fat, functions as an active gland, and is implicated in subclinical inflammation, *via* to the release of lipocytokines. The profile of lipocytokines changes in obesity, favoring inflammation, with activation of pro-inflammatory monocytes. The result is a vicious cycle of positive feedback, where inflammation and metabolic dysfunction reinforce each other (74). This mechanism is particularly important in COVID-19 disease, in which an exaggerated inflammatory response leads to severe disease (75).

This review had some limitations, mainly concerning the effect of the different virus strains that were responsible for the infection in the patients. Since the evolution of the pandemic different variants of SARS-CoV-2 revealed that were associated with one or more changes at the degree of global health significance, mainly affecting: transmissibility, changes in COVID epidemiology, increase in virulence or change in disease

presentation, decrease in effectiveness of public health and social measures or available diagnostics, vaccines and therapeutics. Unfortunately, during in the studies included in our review the specific information on the variants was not reported. Nevertheless, throughout the 2-year period that we revised, obesity was linked with increased complications, hospitalization and mortality rates, regardless the predominant variant reported in each sub-period. In addition, in the various studies reviewed, diverse populations were recruited and different factors were examined by different researchers, while in many cases the classification of BMI varied or subjects were classified only on the presence or absence of obesity. Finally, micronutrients' deficiencies, that contribute to the severity of COVID-19 symptoms in obese or inactive subjects were not investigated herein. For instance, vitamin D is a stakeholder for erasing inflammatory complications of COVID-19 (76, 77). Specifically in obese subjects with vitamin D deficiency (78), that more often occur during winter (79, 80) that COVIV-19 infection arose, increases the risk factors for COVID-19 mortality (81). For all the above reasons, we cannot draw definitive conclusions on the effect of the factors examined.

CONCLUSION

To conclude, despite the limitations of this review, it highlights the importance of body weight for the complications and prognosis of COVID-19 infection, and it should be taken into consideration in clinical practice. Obesity in patients with COVID-19 is independently associated with an increased risk of ICU admission, intubation and death. Recognizing that obesity impacts morbidity and mortality in this manner is crucial for appropriate management of patients with COVID-19 and probably expand the accumulated knowledge in the management of other infectious diseases.

In the future, animal studies or *in vitro* experiments on cells need to be performed to reveal the possible molecular mechanisms involved. Investigation is also needed on the effect of BMI on vaccination response/protection.

AUTHOR CONTRIBUTIONS

EV: conception and design of the work, data collection and interpretation, and drafting the article. AKP and ANP: data collection and interpretation. RB and DB: data collection and interpretation and critical revision of the article. All authors approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.931313/full#supplementary-material

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Associations of body mass index with severe outcomes of COVID-19 among critically ill elderly patients: A prospective study

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Background and Aim: Few studies assessed the associations of overweight and obesity with severe outcomes of coronavirus disease 2019 (COVID-19) among elderly patients. This study was conducted to assess overweight and obesity in relation to risk of mortality, delirium, invasive mechanical ventilation (IMV) requirement during treatment, re-hospitalization, prolonged hospitalization, and ICU admission among elderly patients with COVID-19.

Methods: This was a single-center prospective study that was done on 310 elderly patients with COVID-19 hospitalized in the intensive care unit (ICU). We collected data on demographic characteristics, laboratory parameters, nutritional status, blood pressure, comorbidities, medications, and types of mechanical ventilation at baseline. Patients were followed up during ICU admission and until 45days after the first visit, and data on delirium incidence, mortality, need for a form of mechanical ventilation, discharge day from ICU and hospital, and re-hospitalization were recorded for each patient.

Results: During the follow-up period, we recorded 190 deaths, 217 cases of delirium, and 35 patients who required IMV during treatment. After controlling for potential confounders, a significant association was found between obesity and delirium such that obese patients with COVID-19 had a 62% higher risk of delirium compared with normal-weight patients (HR: 1.62, 95% CI: 1.02–2.57). This association was not observed for overweight. In terms of other outcomes including ICU/45-day mortality, IMV therapy during treatment, re-hospitalization, prolonged hospitalization, and ICU admission, we found no significant association with overweight and obesity either before or after controlling for potential confounders.

Conclusion: We found that obesity may be a risk factor for delirium among critically ill elderly patients with COVID-19.

KEYWORDS

COVID-19, obesity, overweight, delirium, critically ill patients, elderly, Body Mass index

Introduction

Coronavirus disease 2019 (COVID-19) has been a pandemic disease that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). It has become a major threat to global public health during the last 2 years (1). COVID-19 is associated with a high variation in disease severity (2). Young patients usually experience mild-to-moderate symptoms, while elderly patients and those with comorbidities including diabetes (3, 4), cardiovascular diseases (CVDs), cancer, and pulmonary disease are at an increased risk of severe symptoms such as acute respiratory distress syndrome (ARDS) and even death due to COVID-19 pneumonia (2, 5). Therefore, detecting the factors involved in the high severity of disease among the elderly is urgently required.

To date, it has been shown that older age, smoking, taking immunosuppressive drugs such as glucocorticoids and benzodiazepine, and having comorbidities including diabetes, pulmonary diseases, and CVDs are associated with high severity of COVID-19 (6–8). Also, protein–energy malnutrition (PEM) and micronutrient deficiencies such as vitamin D deficiency are associated with a weakening immune system and therefore adversely affect COVID-19 outcomes. Moreover, elevated levels of inflammatory biomarkers may increase the risk of mortality and other severe outcomes in these patients. Recently, great attention has been paid to obesity (9–11). Some studies have shown that obese patients with COVID-19 are at a higher risk of requiring admission to the intensive care unit (ICU) and invasive mechanical ventilation (12, 13). Also, in ICU patients with or without COVID-19, overweight and obesity are associated with an increased risk of ARDS (14). By contrast, several studies indicated that overweight and obesity have a protective effect against mortality among critically ill patients in the ICU (15, 16). Therefore, a potential bidirectional relationship may exist between obesity and COVID-19. Studies have shown an increased SARS-CoV-2 susceptibility in individuals with overweight/obesity, more so in those with coexisting diabetes, as well as an increase in body mass index (BMI) following predominant mild and asymptomatic SARS-CoV-2 infection (17, 18). It has been suggested that a higher metabolic reserve in patients with obesity and differences in pulmonary mechanics and immunological aspects between patients with obesity and normal-weight patients are involved in the protective effect (19). The different effects of obesity on ICU patients are known as the "obesity paradox" (20).

This obesity paradox might be present in critically ill patients with COVID-19, and it is not clear how obesity affects the risk of mortality in these patients. However, the HOPE COVID-19-Registry showed no evidence of the obesity paradox and revealed that increasing BMI was not related to the mortality risk in patients with COVID-19 (21). Some studies have shown a significant association between obesity and mortality due to COVID-19 (22), while others revealed no significant association (23) or even an inverse association (24, 25). In a meta-analysis of 22 studies from seven countries, Zhang et al. (26) reported that obesity is associated with a more severe COVID-19 course but may not be associated with increased mortality. In another meta-analysis, Ho et al. (27) concluded that obesity increased the risk of severe complications, mortality, and infection among patients with COVID-19. In addition, the influence of obesity on other outcomes of critically ill patients with COVID-19 such as delirium and duration of ICU stay has not been studied. Delirium is the most common form of acute brain dysfunction affecting approximately 80% of ICU patients (28). Overall, given the aforementioned points, this study was conducted to assess the associations between obesity and severe outcomes of COVID-19 among critically ill patients.

Materials and methods

Study design and participants

This was a single-center prospective study that was conducted in the Khatam hospital, which was a government-designated referral hospital for patients with COVID-19. The location of this hospital was such that patients with COVID-19 from different socioeconomic levels could be admitted to it. This study was conducted from August 2021 to January 2022. We recruited critically ill older (≥65 years) patients with COVID-19 who were hospitalized in the intensive care unit (ICU). SARS-COV-2 infection was diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR) test and also chest CT scan lesions. Based on the classification of the Guidance for Coronavirus Disease 2019 (6th edition), published by the National Health Commission of China (29), we defined critically ill patients with COVID-19 according to the following criteria: (1) respiratory failure requiring a form of mechanical ventilation; (2) septic shock; and (3) having at least one organ failure necessitating monitoring and treatment in the intensive care unit (ICU). Other inclusion criteria were willingness to participate in the study and having an age of ≥65 years. We did not include patients with COVID-19 if (1) they were admitted to the ICU for the second time; (2) they had severe comorbidities including any brain damage and pre-existing end-stage liver disease, end-stage renal disease, and cancer; and (3) they had a history of pre-existing neurodegenerative disorders, mental illness, dementia, and cognitive disorders. Data from these disorders were obtained by evaluating medical records in the hospital. In addition, patients with COVID-19 who died or were discharged within the first 48 h of hospitalization were excluded because of the avoidance of bias in collecting information on complications and reviewing the effectiveness of treatments prescribed in the ICU. In total, 392 elderly patients with COVID-19 were included. We collected data on demographic characteristics, laboratory parameters, nutritional status, blood pressure, comorbidities, medications used for controlling the infection, and types of mechanical ventilation at baseline. Patients were followed up during the ICU admission and also until 45 days after the first visit to the ICU. During the follow-up period, we recorded data on delirium incidence, mortality, need for a form of mechanical ventilation, discharge day from the ICU and hospital, and re-hospitalization for each patient.

Ethics statement

We took written informed consent from each participant. If a patient was not conscious, the consent was taken from his/her first-degree relatives. Patients were reassured that data collected from medical records would be used for the current study in accordance with privacy laws. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.NNFTRI.REC.1400.071). We conducted this study based on

the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Sample size calculation

We calculated the required sample size using Power Analysis Software (PAS). By considering the type 1 error of 5%, study power of 80%, estimated hazard ratio (HR) of 1.2 for mortality, and mortality rate of 60% among critically ill patients with COVID-19, we needed a sample size of 272 elderly patients with COVID-19. However, we recruited 392 patients in the current study to increase study power and consider the probable drop-out.

Baseline assessment

During the first 24 h of ICU admission, data on demographic characteristics, laboratory parameters, nutritional status, blood pressure, comorbidities, medications used for controlling the infection, and types of mechanical ventilation were collected.

Demographic and clinical characteristics

We collected data on age (year), sex (male/female), weight (kg), height (m), marital status (single/married/divorced), having health insurance (yes/no), education (university educated/under-university educated), smoking (non-smokers/ex-smokers/current smokers), systolic and diastolic blood pressure (mmHg), and alcohol consumption (yes/no) by evaluating the hospital's electronic medical records or questionnaires and also by a direct interview with patients if needed. BMI was determined as weight in kilograms divided by height in meters squared. To collect data on weight, we used data from the medical records of patients. However, these records lacked data on height. Due to the inability of patients to move, the height was estimated by the length of the forearm's ulna bone. Based on this technique, the patient's arm was positioned on the shoulder by being bent across the chest to the opposite side. Then, we measured the distance between the conspicuous wrist bone and the elbow bone using a tape measure. The following formula, designed for critically ill patients, was used to estimate height based on gender and ulna bone length: Height (cm) = 153.492 − [7.97 × sex (male = 1, female = 2) + (0.974 × Ulna length (cm)] (30).

In addition, by reviewing the medical records at baseline, we obtained data on comorbidities (yes/no) including pulmonary diseases (i.e., acute pulmonary edema, asthma, bronchitis, chronic obstructive pulmonary disease, pleural effusion, pneumonia, pulmonary mass, pulmonary edema, respiratory tract infection, and sleep apnea syndrome), hyperlipidemia (total cholesterol levels of ≥4.7 mmol/L, triglyceride levels of ≥2.3 mmol/L, or LDL-C levels of ≥4.1 mmol/L), diabetes (2-h plasma glucose ≥200 mg/dL, HbA1c ≥ 6.5%, and fasting plasma glucose ≥126 mg/dL), hypertension (SBP ≥ 140 and DBP ≥ 90), CVDs (i.e., heart failure, left ventricular systolic dysfunction, right heart failure, dysrhythmia, ischemic heart disease, inflammatory heart disease or pericardium, non-ischemic cardiomyopathy, cardiogenic shock, cardiac arrest, and thrombotic disorders), chronic renal failure and liver disease (any type, based on data from medical records), incidence of organ failure from the time of entering in ICU, and ear and eye problems (any type, based on data from medical records). Organ failure was considered the failure of at least one organ to perform typical bodily tasks. This failure comprised at least one of the following: cardiovascular illness, lung failure, acute liver dysfunction, acute renal damage, a wide range of hematological abnormalities, and neurological diseases, as determined by a specialist. During the ICU admission, the incidence of acute kidney injury (AKI), caused by COVID-19 or medications (i.e., Remdesivir), was recorded by reviewing the medical records. AKI was defined as a rise in serum creatinine by 0.3 mg/dL (26.5 μmol/L) or more within 48 h (31). If data from medical records were incomplete for the diagnosis of mentioned diseases, we asked some questions to patients or their relatives to complete the aforementioned information.

The treatment protocols including medications and types of mechanical ventilation [invasive and non-invasive mechanical ventilation (IMV and NIMV), high-flow nasal cannula, and face mask] used for controlling COVID-19 and its symptoms were also recorded. We recorded the drugs that were currently used by patients. By using data on demographic (age), clinical (body temperature, mean arterial pressure, blood pH, heart rate, respiratory rate, oxygen partial pressure, and Glasgow coma scale), and laboratory variables (sodium, potassium, creatinine, hematocrit, and white blood cells), we calculated acute physiology and chronic health examination II (APACHE II) score for each patient. APACHE II scores range between zero and 71, with higher scores indicating a more severe condition. Details on the calculation of APACHE II were published elsewhere (32).

Laboratory parameters

On the first day of ICU admission, patients' medical records were assessed to obtain data on fasting blood sugar (FBS, mg/dL), serum levels of inflammatory biomarkers [C-reactive protein (CRP, mg/L) and interleukin-6 (IL-6, pg./mL)], albumin (g/dL), creatinine (mg/dL), urea (mg/dL), bilirubin (mg/dL), and 25-hydroxy vitamin D3 [25(OH)D3, ng/mL]. Serum levels of electrolytes including magnesium (mEq/L), phosphorous (mg/dL), calcium (mg/dL), sodium (mEq/L), and potassium (mEq/L) were also assessed. We also collected data on hematological factors including white blood cells (neutrophil and lymphocyte, 10^3/μL), hematocrit (%), and platelet (10^3/μL).

Follow-up

The incidence of delirium and the need for a form of mechanical ventilation (yes/no), particularly invasive ventilation, were recorded during the ICU admission. Delirium was diagnosed based on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (33). Accordingly, delirium has four features: (1) acute onset of changes or fluctuations in the course of mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness (other than alert). Patients were delirious if they had features 1 and 2 plus either feature 3 or 4. In the present study, delirium was evaluated every day using the CAM-ICU by an experienced ICU physician. To facilitate the assessment of acute onset or fluctuation of mental status changes, patients were followed up daily with the Glasgow coma scale. In addition to delirium, we recorded the occurrence of mortality (yes/no) during the ICU admission. After the ICU discharge, patients were admitted to the other wards of the hospital. Therefore, we followed patients in the hospital until they were discharged. Furthermore, the length of ICU and hospital stays was recorded for each patient. After

the hospital discharge, we had phone contact with patients or their relatives every week, until 45 days after the baseline, to record probable death and re-hospitalization. ICU admission ≥7 days was considered a prolonged stay in ICU and hospitalization ≥14 days was a prolonged stay in the hospital.

Statistical analysis

We first categorized elderly patients with COVID-19 based on BMI [normal-weight (BMI < 25), overweight (25 ≤ BMI < 30), and obesity (BMI ≥ 30)], according to the recommended classification by the World Health Organization (34, 35). Then, we compared continuous variables across categories of BMI using one-way ANOVA if the distribution of those variables was normal. For the non-normally distributed continuous variables, we used the Kruskal–Wallis test for comparison. To assess the distribution of categorical variables across categories of BMI, we used the Chi-square test. In order to analyze the associations of BMI categories with mortality, delirium, and IMV therapy during treatment, we used univariable and multivariable Cox proportional hazards models. In the time-to-event analysis, follow-up time was considered as the day that outcome occurred or the day that the patient was followed up. To assess the associations of BMI categories with prolonged stay in ICU (≥7 days) or hospital (≥14 days) and odds of re-hospitalization after discharge, we used univariable and multivariable binary logistic regression. In the adjusted models, we controlled for age, gender, taking benzodiazepine during ICU admission, and vitamin D and IL-6 levels. To identify potential confounders, we calculated the magnitude of confounding for each variable as the percent difference between the crude and adjusted measures of association (Supplementary Tables S1, S2). The following formula was used for the relative risk estimates:

$$\text{Magnitude of confounding (\%)} = \frac{RR_{crude} - RR_{adjusted}}{RR_{adjusted}} \times 100.$$

If the value was ≥10% for a variable, that variable was considered a confounding variable. By this approach, we found that age, benzodiazepine intake, and IL-6 levels (only adjusted for death during ICU admission) were confounders for the associations of BMI with delirium, IMV therapy, and COVID-19 mortality. Also, for the associations of BMI with re-hospitalization and prolonged hospital/ICU stays, we considered age, gender, benzodiazepine intake, and vitamin D levels as confounders. In all analyses, normal-weight patients with COVID-19 were considered as a reference group. All statistical analyses were done using the SPSS software version 18 (SPSS, Inc. Chicago, IL, USA). $p < 0.05$ was considered significant.

Results

Of the 392 critically ill elderly patients with Covid-19 admitted to the intensive care unit, 48 patients did not meet the inclusion criteria as shown in Figure 1. Out of 344 patients who met the inclusion criteria, 19 patients died within the first 48 hours of admission to the ICU and 7 patients were discharged from the intensive care unit within the first 48 hours of admission. During the follow-up period of the patients in the ICU, 8 patients were discharged from the ICU with personal consent to continue the treatment process at home. Therefore, the data of 310 patients were included in the final analysis. All patients had received antiviral and antibiotic drugs. Antiviral drugs included remdesivir, favipiravir, tocilizumab, and lopinavir/ritonavir, which were available in Iranian hospitals. During the 45-day follow-up, 190 (61.3%) COVID-19 deaths were recorded among the baseline 310 patients. In addition, during the ICU admission, 217 (70.0%) cases of delirium and 53 (17.1%) patients who required IMV therapy from the beginning of treatment were found in the ICU. Also, during the 45-day follow-up, 65 (21.0%) patients were hospitalized for the second time.

The baseline characteristics of patients across categories of BMI are shown in Tables 1, 2. Patients with obesity had lower ages and were more likely to consume vasopressors compared to those with normal weight. In terms of other variables including government health insurance, laboratory parameters, comorbidities, drug use, duration of hospital and ICU stays, and types of ventilation, we found no significant difference.

Multivariable-adjusted HRs and 95% confidence intervals (CIs) of delirium, COVID-19 mortality, and IMV therapy during treatment across categories of baseline BMI among critically ill elderly patients with COVID-19 are indicated in Table 3. We found no significant association between overweight/obesity and delirium among elderly patients with COVID-19 (overweight; HR: 1.06, 95% CI: 0.77–1.46, obesity; HR: 1.27, 95% CI: 0.81–1.99). However, after controlling for potential confounders including age and benzodiazepine intake, a significant association was seen for obesity; such that obese patients with COVID-19 had a 62% higher risk of delirium compared with normal-weight patients (HR: 1.62, 95% CI: 1.02–2.57). Such an association was not seen for overweight. Before and after taking potential confounders into account, no significant association was found between BMI categories (overweight and obesity) and risk of IMV requirement during treatment. Regarding the risk of mortality during ICU admission and 45 days after the baseline, we found no significant association with overweight or obesity either before or after controlling for potential confounders.

Multivariable-adjusted odds ratios (ORs) and 95% CIs for re-hospitalization and prolonged stay in ICU and hospital across categories of BMI are presented in Table 4. Overweight and obesity were not significantly associated with re-hospitalization and prolonged stay in ICU and hospital. These associations remained non-significant after taking potential confounders into account [re-hospitalization (overweight; OR: 0.98, 95% CI: 0.48–1.99, obesity; OR: 1.12, 95% CI: 0.41–3.06), prolonged stay in ICU (overweight; OR: 1.01, 95% CI: 0.56–1.81, obesity; OR: 1.12, 95% CI: 0.49–2.56), and prolonged stay in ICU and hospital (overweight; OR: 0.99, 95% CI: 0.55–1.78, obesity; OR: 1.57, 95% CI: 0.67–3.64)].

Discussion

Since obesity and overweight are similar in nature, we discussed both in the same manner, particularly when the findings of both conditions were similar. In the current study, we found that elderly patients with COVID-19 with obesity had an increased risk of delirium than those with normal weight. This association was not seen for overweight. In terms of other outcomes including ICU and 45-day mortality, IMV therapy during treatment, prolonged stay in ICU and hospital, and odds of re-hospitalization, we observed no significant association with overweight and obesity.

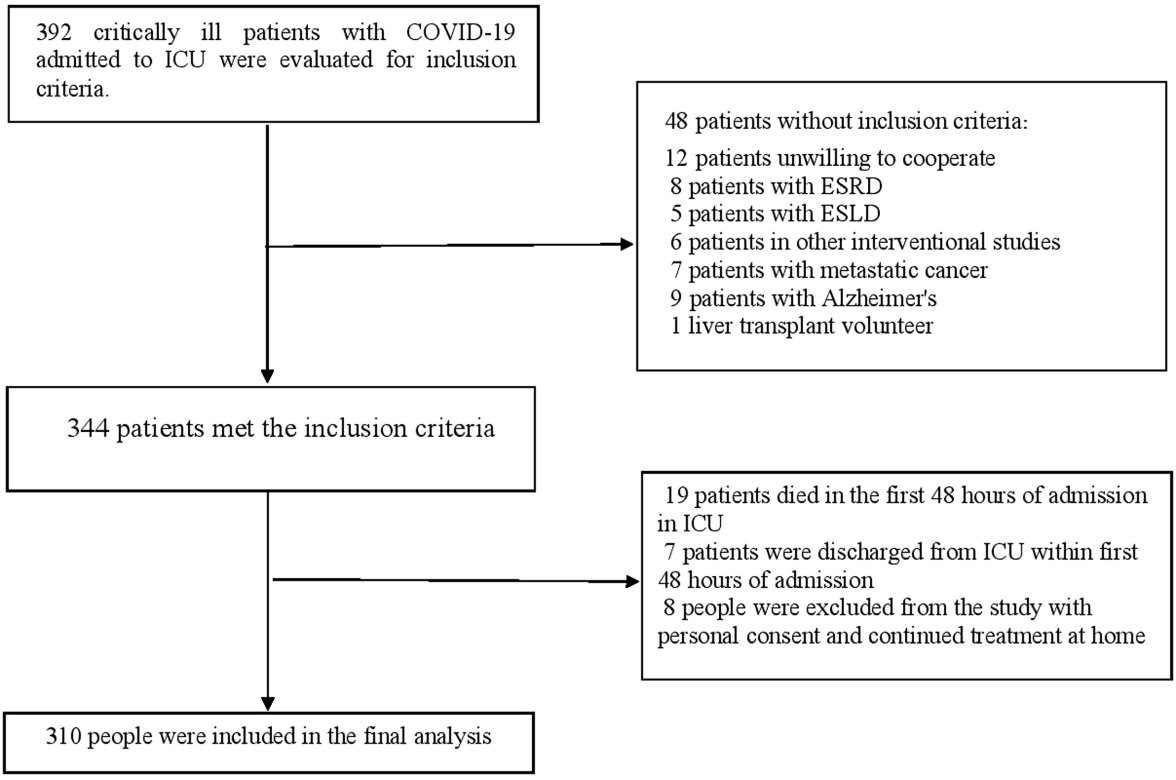

FIGURE 1
Study flow diagram.

Our study represented the overall mortality rate of 42.3% among elderly patients with COVID-19 admitted to the ICU. Compared with the rate obtained from previous studies (36, 37), it seems to be high. In a meta-analysis, Qian et al. (38) indicated a prevalence of 32% for COVID-19 mortality among critically ill patients. The higher prevalence of mortality in the current study might be due to the age range of participants who were 65 years and older. It has been shown that older age is the main risk factor for COVID-19 mortality (39–41). It should be noted that the prevalence of 32% in the study of Qian et al. was obtained by assessing different age groups.

Delirium is an acute disturbance of consciousness that is associated with mental disorders such as sleep disorders, changes in cognitive functions, anxiety, fear, and irritability (42, 43). Delirious patients in ICU have an increased risk of mortality, longer ICU hospitalizations, extended periods of mechanical ventilation, and long-term cognitive and functional deficits. Known risk factors for developing delirium include aging, baseline cognitive impairment, comorbidities (particularly respiratory disease), frailty, sepsis, prolonged mechanical ventilation, and major surgery (44–46). However, few studies investigated the link between obesity and delirium in critically ill patients. In the current study, we found that elderly obese patients with COVID-19 had a higher risk of delirium compared with normal-weight patients. Such an association was not seen for overweight. In a study on 9,189 adults, Anand et al. (47) reported that obesity was associated with a reduced cognitive score indicating lower cognitive function. In contrast, Lachmann et al. (48) reported that diabetes, but not obesity or hypertension, was associated with an increased risk of postoperative cognitive dysfunction in older people. In a retrospective cohort study, a high BMI was independently associated with a lower frequency of acute delirium in ICU patients with septic shock (49). Discrepant findings might be explained by the different ages and the different medications of study participants in previous studies. For instance, the administration of analgesic medications, some anticholinergic drugs, and benzodiazepine infusions for mechanical ventilation is associated with a higher risk of delirium. It should be noted that medications among the patients who participated in the current study were not different across categories of BMI. In addition, different cognitive and physical reserves of participants are other reasons for the observed discrepancy among previous studies on the link between obesity and cognitive dysfunction.

The mechanism involved in the association between obesity and delirium in ICU patients with COVID-19 infection is unclear. Recent studies have shown that obese patients with COVID-19 have severe symptoms and more need for IMV compared with normal-weight patients (12, 50). In addition, obesity causes mechanical disturbances because abdominal thrusts increase inter-abdominal pressure, which makes it difficult for the lungs to breathe (51). In addition, hospitalized patients should be lying down, particularly in a supine position. This position in patients with obesity makes breathing more difficult (51). Therefore, patients with obesity commonly develop hypoventilation and sleep apnea syndromes with hypoxic and hypercapnic ventilatory responsiveness (52). This condition disrupts the levels of oxygen and CO2 in the blood, induces cerebral oxygen desaturation, and can cause delirium in patients with obesity (53). It should be noted that in the current study, patients with obesity (7.5%) used IMV less frequently than normal-weight patients (25.3%) and this may increase the rate of

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TABLE 1 Baseline characteristics of critically ill elderly patients with COVID-19 across categories of BMI.

	Total	Normal	Overweight	Obesity	*p*-value*
n	310	79	191	40	
Demographic characteristics					
Age, y	73.29 ± 6.91	76.90 ± 6.87	72.19 ± 6.36	71.37 ± 7.11	<0.001
Weight, kg	72.77 ± 10.50	61.80 ± 6.43	74.39 ± 7.01	87.00 ± 9.24	<0.001
BMI, kg/m^2	26.88 ± 3.28	23.17 ± 1.29	27.19 ± 1.38	32.79 ± 2.92	<0.001
Female, %	128 (41.3)	32 (40.5)	73 (38.2)	23 (57.5)	0.08
Smokers, %	82 (26.5)	21 (26.6)	49 (25.7)	12 (30)	0.85
Government health insurance,%	252 (81.3)	63 (79.7)	155 (81.2)	34 (85)	0.78
Alcohol intake, %	24 (7.7)	6 (7.6)	16 (8.4)	2 (5)	0.76
Comorbidities					
Pulmonary disease, %	77 (24.8)	23 (29.1)	46 (24.1)	8 (20)	0.51
Hyperlipidemia, %	124 (40.0)	38 (48.1)	69 (36.1)	17 (42.5)	0.17
Diabetes, %	141 (45.5)	37 (46.8)	90 (47.1)	14 (35)	0.36
Hypertension, %	155 (50.0)	50 (63.3)	100 (52.4)	20 (50)	0.20
CVD, %	139 (44.8)	43 (54.4)	79 (41.4)	17 (42.5)	0.13
Chronic renal disease, %	111 (35.8)	31 (39.2)	68 (35.6)	12 (30.0)	0.60
Liver disease, %	28 (9.0)	9 (11.4)	15 (7.9)	4 (10.0)	0.63
Stroke, %	17 (5.5)	7 (8.9)	9 (4.8)	1 (2.6)	0.28
Organ failure, %[a]	149 (48.1)	36 (45.6)	92 (48.2)	21 (52.5)	0.77
Ear problems, %	27 (8.7)	9 (11.4)	17 (8.9)	1 (2.5)	0.26
Eye problems, %	17 (5.5)	6 (7.6)	10 (5.2)	1 (2.5)	0.49
Medication					
Propofol, %	20 (6.5)	3 (3.8)	16 (8.4)	1 (2.5)	0.20
Opioid drugs, %	182 (58.7)	51 (64.6)	109 (57.1)	22 (55.0)	0.46
Glucocorticoids, %	203 (65.5)	55 (69.6)	120 (62.8)	28 (70.0)	0.45
Benzodiazepine, %	219 (70.6)	59 (74.7)	137 (71.7)	23 (57.5)	0.13
Vasopressor, %	145 (46.8)	34 (43.0)	83 (43.5)	28 (70)	0.007
Oxygen therapy at baseline					0 ()
IMV, %	20 (6.5)	3 (3.8)	16 (8.4)	1 (2.5)	0.20
NIV, %	185 (59.7)	48 (60.8)	113 (59.2)	24 (60.0)	0.97
High flow nasal cannula, %	7 (2.3)	5 (6.3)	1 (0.5)	1 (2.5)	0.01
Face mask, %	183 (59.0)	41 (51.9)	115 (60.2)	27 (67.5)	0.22

Data are presented as mean ± SD for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and percent for categorical variables. BMI: body mass index, CVD: cardiovascular disease, IMV: invasive mechanical ventilation, NIV: non-invasive ventilation, SD: standard deviation.[a]Considered as the incidence of failure of ≥ 2 organs. *Obtained from the one-way ANOVA (normally distributed continuous variables), the Kruskal–Wallis test (non-normally distributed continuous variables), or the chi-square test (categorical variables).

cerebral oxygen desaturation and might be a reason for the increased odds of delirium among patients with obesity. Another proposed mechanism is the effect of obesity on cognitive function. In a review article, Miller et al. (54) concluded that obesity-induced inflammation (particularly elevated circulating IL-12 and IL-6) was associated with disruption to cognitive function mediated by brain regions such as the hippocampus, amygdala, and reward-processing centers.

In the current study, we found no significant association between BMI categories and IMV requirement among elderly patients with COVID-19 hospitalized in ICU. In line with our findings, Rovirosa et al. (55) showed that patients with obesity and overweight, according to the WHO classification, had no significant association with requiring intubation and IMV in patients with COVID-19. In a study in the US, Kompaniyets et al. (50) reported that overweight and obesity were risk factors for IMV in patients with COVID-19. The study by Kim et al. (56) showed that overweight and all classes of obesity were associated with increased odds of IMV. That study showed that the use of IMV in patients who are overweight and with obesity may be affected by clinical bias toward early intervention based on proven pulmonary complications in patients with obesity. This finding is limited in generalizability due to the differences between the patient populations. Limitations on clinical information

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TABLE 2 Clinical characteristics of critically ill elderly patients with COVID-19 across categories of BMI.

	Total	Normal	Overweight	Obesity	*p*-value*
n	310	79	191	40	
Hematology					
WBC, 10^3/μL	9.37 ± 4.51	9.14 ± 4.94	9.39 ± 4.26	9.75 ± 4.84	0.78
Neutrophil, 10^3/μL	83.43 ± 8.80	82.59 ± 9.34	83.99 ± 8.30	82.42 ± 10.01	0.38
Lymphocyte, 10^3/μL	12.20 ± 12.17	13.15 ± 12.76	12.15 ± 12.64	10.72 ± 8.29	0.59
Neutrophil/lymphocyte ratio	12.04 ± 10.24	12.80 ± 14.58	11.59 ± 7.99	12.65 ± 9.56	0.48
Albumin, g/dL	3.05 ± 0.65	2.92 ± 0.67	3.08 ± 0.66	3.14 ± 0.57	0.11
Biochemical assessment					
CRP, mg/L	87.41 ± 47.31	85.64 ± 44.29	88.66 ± 48.13	84.95 ± 50.02	0.83
IL6, pg./mL	159.47 ± 216.41	142.91 ± 137.59	164.80 ± 241.15	166.69 ± 221.72	0.73
Creatinine, mg/dL	1.40 ± 0.62	1.40 ± 0.63	1.36 ± 0.50	1.56 ± 1.02	0.20
FBS, mg/dL	168.89 ± 53.83	170.87 ± 55.78	171.17 ± 53.02	154.20 ± 52.85	0.18
Vitamin D, ng/mL	30.03 ± 8.76	29.55 ± 8.19	30.32 ± 9.06	29.58 ± 8.56	0.75
Bilirubin, mg/dL	0.83 ± 1.14	0.80 ± 0.91	0.89 ± 1.32	0.63 ± 0.32	0.38
Urea, mg/dL	27.69 ± 16.15	27.14 ± 16.33	27.08 ± 13.71	31.63 ± 24.46	0.25
Magnesium, mEq/L	1.98 ± 0.39	1.97 ± 0.37	1.98 ± 0.40	2.01 ± 0.36	0.90
Calcium, mg/dL	8.11 ± 0.57	8.13 ± 0.49	8.13 ± 0.61	8.01 ± 0.55	0.50
Sodium, mEq/L	136.43 ± 8.85	135.46 ± 16.06	136.59 ± 4.21	137.55 ± 3.80	0.44
Potassium, mmol/L	4.00 ± 0.69	4.08 ± 0.84	3.95 ± 0.65	4.07 ± 0.58	0.36
Blood pressure					
SBP, mmHg	139.09 ± 22.20	139.44 ± 23.49	139.99 ± 22.00	134.10 ± 20.29	0.30
DBP, mmHg	81.28 ± 15.30	80.50 ± 15.01	82.17 ± 15.18	78.59 ± 16.41	0.35
Mean arterial pressure, mmHg	100.55 ± 16.69	100.14 ± 16.92	101.44 ± 16.53	97.09 ± 16.94	0.31
Outcomes during follow-up					
IMV therapy,%	53 (17.1)	20 (25.3)	30 (15.7)	3 (7.5)	0.03
Delirium,%	217 (70.0)	54 (68.4)	133 (69.6)	30 (75.0)	0.74
Death during ICU admission,%	132 (42.6)	42 (53.2)	76 (39.8)	14 (35)	0.07
Death during 45 days,%	190 (61.3)	52 (65.8)	117 (61.3)	21 (52.5)	0.23
Re-hospitalization,%	65 (21.0)	19 (24.1)	38 (19.9)	8 (20)	0.73
Acute renal failure, %	82 (26.5)	17 (21.5)	53 (27.7)	12 (30)	0.49
Hospitalization					
Length of hospital stay (day)	14 (10–19)	13 (10–18)	14 (10–19)	16 (12–21)	0.13
Length of ICU stay (day)	8 (6–10)	8 (6–10)	8 (6–10)	8 (5–10)	0.96
APACHE II score	17 (11–21)	17 (11–21)	17 (12–21)	16 (11–19)	0.54

Data are presented as mean ± SD for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and percent for categorical variables. BMI: body mass index, WBC: white blood cell, IL-6: interleukin-6, CRP: C-reactive protein, FBS: fasting blood sugar, SBP: systolic blood pressure, DBP: diastolic blood pressure, CVD: cardiovascular disease, IMV: invasive mechanical ventilation, SD: standard deviation, APACHE II: acute physiology and chronic health examination II.*Obtained from the one-way ANOVA (normal-distributed continuous variables), the Kruskal–Wallis test (non-normally distributed continuous variables), or the chi-square test (categorical variables).

include the severity of dyspnea, resuscitation and/or intubation status, or the reason for clinical decision-making to explain which patients were intubated. The results of the CORONADO study, with a large population and good phenotypes of COVID-19 individuals with diabetes admitted to the hospital ward and ICU, showed that the relationship between IMV and BMI appeared with overweight (57). In a case–control study, Ferreira et al. (58) reported that the need for IMV was higher among patients with COVID-19 if they were obese. Different medications, different cutoff points used for the definition of obesity, and different quality of previous studies are probable

TABLE 3 Hazard ratios for some outcomes of critically ill elderly patients with COVID-19 across categories of BMI.

	Normal	Overweight	Obesity
Delirium			
Cases	54	133	30
Unadjusted	1.00	1.06 (0.77–1.46)	1.27 (0.81–1.99)
Adjusted model[b]	1.00	1.20 (0.86–1.67)	1.62 (1.02–2.57)
IMV therapy during treatment[a]			
Cases	20	30	3
Unadjusted	1.00	0.66 (0.37–1.17)	0.30 (0.90–1.02)
Adjusted model[b]	1.00	0.95 (0.52–1.74)	0.56 (0.16–1.92)
Death during 45 days			
Cases	52	117	21
Unadjusted	1.00	0.90 (0.65–1.25)	0.73 (0.44–1.21)
Adjusted model[b]	1.00	1.16 (0.82–1.64)	1.10 (0.65–1.86)
Death during ICU admission			
Cases	42	76	14
Unadjusted	1.00	0.79 (0.54–1.16)	0.67 (0.37–1.23)
Adjusted model[b]	1.00	0.97 (0.65–1.45)	0.96 (0.52–1.79)

Data are presented as HR (95% CI).
BMI: body mass index, IMV: invasive mechanical ventilation, HR: hazard ratio, ICU: intensive care unit.[a]With considering IMV therapy at baseline.
[b]Adjusted for age, benzodiazepine intake, and IL6 levels (only adjusted for death during ICU admission).
HRs were obtained from the Cox regression analysis.

TABLE 4 Odds ratios for re-hospitalization and prolonged stay in ICU and hospital across categories of BMI in critically ill elderly patients with COVID-19.

	Normal	Overweight	Obesity
Hospital stay ≥ 14 days			
Cases	38	97	26
Unadjusted	1.00	1.11 (0.65–1.88)	2.00 (0.91–4.39)
Adjusted model[a]	1.00	0.99 (0.55–1.78)	1.57 (0.67–3.64)
ICU stay≥7 days			
Cases	50	118	25
Unadjusted	1.00	0.93 (0.54–1.61)	0.96 (0.44–2.12)
Adjusted model[b]	1.00	1.01 (0.56–1.81)	1.12 (0.49–2.56)
Re-hospitalization			
Cases	19	38	8
Unadjusted	1.00	0.78 (0.41–1.46)	0.79 (0.31–2.00)
Adjusted model[c]	1.00	0.98 (0.48–1.99)	1.12 (0.41–3.06)

Data are presented as OR (95% CI).
BMI: body mass index, ICU: intensive care unit, OR: odds ratio[a]Adjusted for age, gender, and benzodiazepine intake.
[b]Adjusted for gender.
[c]Adjusted for vitamin D levels.
ORs were obtained from the binary logistic regression.

reasons for the observed discrepancy. In addition, limited facilities in hospitals might be another reason. On the other hand, a limited number of hospital beds with ventilators and not using them for qualified patients may affect the risk estimates obtained from the current and previous studies. However, it must be kept in mind that the hospital where we recruited patients with COVID-19 for the current study had 98 ICU beds and all of them had ventilators for IMV therapy. Therefore, there was no limitation for IMV therapy for patients admitted to ICU. However, because of the low number of ICU beds in that hospital, IMV therapy may not be done for some qualified patients admitted to other wards of the hospital.

Regarding COVID-19 mortality and prolonged hospital stay, no significant association was seen between overweight and obesity in the current study. In agreement with our findings, Pouwels et al. (59) reported that obesity was not related to 28-day mortality and duration of ICU and hospital stay among critically ill patients with COVID-19 infection. In contrast, Kompaniyets et al. (50) indicated that higher BMI in patients with COVID-19 was associated with an increased risk of mortality, hospitalization, and ICU admission. Another study revealed that obesity was an independent risk and prognostic factor for the disease severity and the requirement for advanced medical care in patients with COVID-19 (60). The discrepant findings on obesity and COVID-19 mortality might be due to the obesity paradox. Al-Salameh et al. (61) study showed that the relative risk of transfer to ICU and occurrence of some outcomes, including intubation for mechanical ventilation, ARDS, and acute renal injury, were high in the overweight group, but without the risk of mortality, which indicates the "survival paradox of obesity". Previous studies on ICU patients have shown a J-shaped association between BMI and mortality, with overweight and moderate obesity being protective compared with a normal BMI or more severe obesity (62). This is in line with our findings, in which a non-significant inverse association was seen between overweight and ICU mortality among patients with COVID-19. Despite this protective effect regarding mortality, it has been shown that obesity among ICU patients increases the risk of infection and respiratory and cardiovascular complications (62). These complications are associated with an increased risk of mortality among ICU patients (63). In addition, using different cutoff points for the definition of overweight and obesity might be involved in the discrepant findings. In terms of different findings on the link between overweight/obesity and prolonged hospitalization, we may justify different treatment protocols and different hospital admission capacities in different countries. Because of a high incidence of COVID-19 infection and limited hospital beds, patients may be discharged prematurely. Therefore, the lack of significant association between overweight/obesity and prolonged hospitalization should be considered with caution. Further studies are needed to substantiate these findings.

This study had some strengths. To the best of our knowledge, this was the first study that examined the link between obesity and the risk of delirium among critically ill elderly patients with COVID-19. The prospective design of our study and controlling for potential confounders were other strengths. Our present study was subjected to some limitations. First, the sample size of this study did not allow us to perform subgroup analyses based on gender and other important variables. In addition, because of the low sample size, we had a lower number of patients in the normal-weight and obese groups compared with the overweight group. Second, the number of patients in the obese group was too small which may reduce the robustness of the analysis result. Third, although we extracted data on height and weight values from medical chart records, some values might have been self-reported, which may lead to measurement bias. Fourth, even though potential confounders had been adjusted in the analysis, our results might be still affected by residual confounders such as lifestyle

information and therapeutic protocols used for controlling COVID-19 infection. In addition, the low number of nurses and physicians in the hospital may affect the quality of health services and consequently the risk estimates obtained in the current study. Fifth, we excluded patients with cancer, end-stage liver disease, and end-stage kidney disease. These patients usually have obesity and severe outcomes of COVID-19. Therefore, this exclusion may attenuate the risk estimates calculated for the association between obesity and clinical outcomes of COVID-19. This may also explain the non-significant association between obesity and COVID-19 mortality in the current study.

In conclusion, we found that elderly patients with COVID-19 with obesity have an increased risk of delirium compared with normal-weight patients. However, overweight was not significantly associated with the risk of delirium. Also, overweight and obesity were not significantly associated with other outcomes of elderly patients with COVID-19 such as IMV requirement, ICU/45-day mortality, and prolonged hospitalization. Further studies with higher sample sizes and considering a wide range of confounders are needed to confirm our findings.

What is already known on this subject?

Previous studies presented inconsistent results on the association between obesity and COVID-19 mortality. Few studies have been done on elderly patients. Also, the influence of obesity on other outcomes of critically ill patients with COVID-19 such as delirium and duration of ICU stay has not been studied.

What this study adds?

We found that obese elderly patients with COVID-19 have an increased risk of delirium compared with normal-weight patients. Regarding other outcomes including IMV requirement, death, prolonged hospitalization, and ICU admission, we found no significant association with overweight or obesity among elderly patients with COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZGh, DY, HEZ, and ZVSh designed the research project. ZGh and ZVSh conducted the research; ZGh analyzed data; ZGh and ZVSh wrote the paper; ZGh and ZVSh had primary responsibility for final content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.993292/full#supplementary-material

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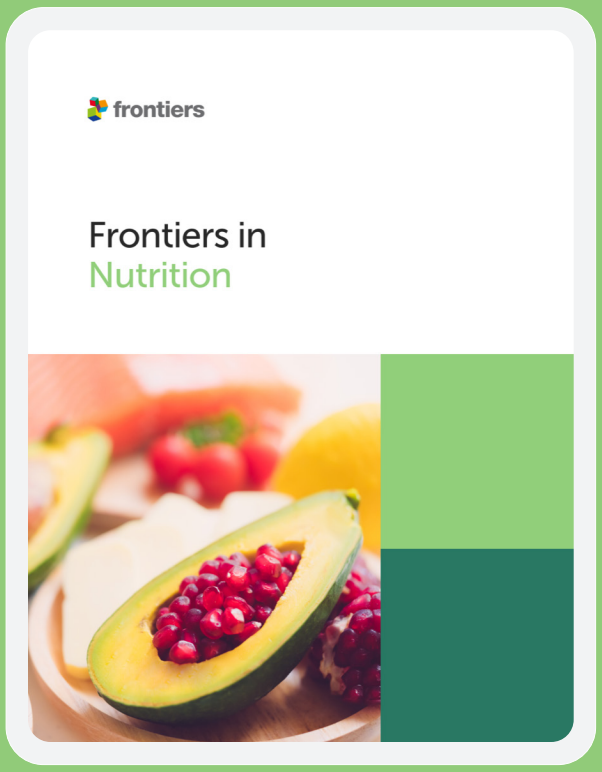

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