Morbidity and Mortality of COVID in Relation to Age, Sex and BMI

Mysore S. Bhagavan[1], Srikrishna C. Karnatapu[2*], Saloni Doke[3], Theourrn Amalathasan[4], Thebuoshon Amalathasan[5], Chiraag Ashokkumar[6]

[1]Internal Medicine Doctor, Internal Medicine, Loretto Hospital, 645 South Central Ave, Chicago IL, 60644, **USA**
[2,4,5]All Saints University School of Medicine, Hillsborough St, Roseau, **DOMINICA**
[3,6]Spartan Health Sciences University, Spartan Drive, St. Jude's Highway, **ST. LUCIA**

[*]Corresponding Contact:
Email: srikrishna.karnatapu@allsaintsuniversity.org

Manuscript Received: 26 March 2021 Accepted: 17 May 2022

ABSTRACT

The United States (US) has been the epicenter of the Coronavirus disease pandemic (COVID-19). The underrepresented minorities, which tend to have a higher prevalence of obesity, are affected disproportionately. This study aimed to assess the early outcomes and characteristics of COVID-19 patients in the US and investigate whether age, gender, and obesity are associated with worse outcomes. To determine the effect of body mass index, sex, and age on risk for morbidity and mortality of COVID-19. Compressive systematic research was conducted to pool every relevant article that evaluated COVID's effect on patients with regard to BMI, age, sex, and mortality. Search for articles was conducted in the most widely-used databases such as PubMed, Scopus, EMBASE, and Web of Science. Search terms used for article retrieval included: "BMI," OR "Obesity," OR "BMI," OR "Sex," OR "Age." AND "COVID-19 related mortality." Severe obesity, male sex, and increasing age are associated with a high rate of in-hospital mortality and generally worse in-hospital prognosis.

Keywords: COVID-19, Obesity, SARS-CoV-2, Mortality, Coronavirus, Pandemic, Sex

INTRODUCTION

The COVID-19 outbreak is caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). This disease has spread across the globe and created a great deal of concern (Chen et al., 2020). Healthcare providers and organizations have been working round the clock to find solutions to minimize the spread of the disease and also reduce the fatality rates. The astronomical increase in the number of cases has overburdened the healthcare system, mostly in developing nations with fragile healthcare systems (Ornell et al., 2020; McKibbin & Fernando, 2020). Early diagnosis of severe cases helps reduce mortality and improve patient conditions. Early classification of severe and mild cases was effective in facilitating the efficient utilization of limited resources (Siddiqi & Mehra, 2020). Several studies have reported changes in some laboratory parameters (e.g., lymphocyte count, C-reactive protein (CRP), erythrocyte sedimentation rates (ESR), and interleukin-6 (IL-6) in patients with COVID-19). However, there is not sufficient data to show the correlation between the severity and mortality (Wang et al., 2020; Yang et al., 2020). As such, finding an appropriate risk factor is necessary for the classification of mild and severe patients at an early stage.

COVID-19, caused by severe acute respiratory syndrome coronavirus two, has developed into a global pandemic with no less than two million confirmed cases and at least 200 thousand deaths (WHO, 2020). The first case in the United States was reported on 19th January 2020 in Washington (Bhatraju et al., 2020). Since then, over a million cases and sixty thousand mortalities have been reported (COVID Data Tracker, 2020). In the US, New York City (NYC) serves as the epicenter of the pandemic, with no less than 2.26 million cases and 39,324 deaths to date (NYC Health, 2022). Early reports from Europe and Asia have identified male sex, older age, and chronic medical conditions, like hypertension, diabetes, coronary artery disease, heart failure, and obesity as risk factors associated with poor prognosis (Zhou et al., 2020; Grasselli et al., 2020; Yancy, 2020). However, not much is known about the disease characteristics and risk factors in the United States population, especially in under-represented minorities, who seem to be disproportionally affected by the disease (Yancy, 2020). It is important to note that the age-adjusted rate per 100,000 in New York City exceeds that for African Americans compared to Whites (127.1 vs. 63.5) (NYC Health, 2020). The exceedingly high prevalence of medical conditions seen as risk factors for COVID-19 among African Americans and the high risk for exposure to SARS-CoV-2 due to working and living conditions are plausible explanations for the disproportionate differences in outcomes (Yancy, 2020). For instance, the Bronx, which happens to be the most diverse area in the US as per the 2010 census, ranks last among the 62 counties of New York with regards to the quality of life, health outcomes, and major health and socioeconomic factors according to the County Health Rankings and Roadmaps (County Health Rankings and Roadmaps, 2019). Also, the Bronx is known to have the highest rates of obesity among all boroughs of NYC, which is astonishingly higher than the national average (Montefiore's Office of Community & Population Health, 2018; Centers for Disease Control and Prevention, 2021).

COVID-19 is primarily transmitted via large respiratory droplets, and the severity of the disease ranges from a mild self-limiting flu-like illness to respiratory failure, fulminant pneumonia, and death. The mortality rate, though estimated, varies considerably over geography and time, mainly due to evolving strategies for testing and other factors (Baud et al., 2020). Although the research cites several risk factors for the disease, such as male sex, increasing age, etc., there are other predominating characteristics like geographic region, which may explain the differences in morbidity and mortality of COVID-19. For instance, Italy has the second most geriatric population globally, and the older population has featured immensely in Italy's COVID-19 burden as per the morbidity and mortality (Boccia et al., 2020). In China, old age and comorbidities, such as hypertension, diabetes, and chronic respiratory and cardiovascular diseases, have featured as the most prominent high-risk characteristics (Zhou et al., 2020; Li et al., 2020; Wu & McGoogan, 2020). Obesity is an emerging risk factor in the United States (Petrilli et al., 2020; Stefan et al., 2020; Kass et al., 2020).

It is important to note that at least 42.4% of the United States' adult population is obese. 9.2% are classified as *severely obese* (Hales et al., 2020). According to the Centres for Disease Control and Prevention, severe obesity occurring at any age (BMI ≥ 40kg/m2) is listed as a high-risk condition for COVID-19 (Kompaniyets et al., 2021). Given that obesity has a very high prevalence in the United States, it would not be wrong to say that COVID-19 has a tremendous effect on the population of the United States.

Social determinants of health, including income level, race and ethnicity, and education, are listed as risk factors for both COVID-19 and obesity (Yancy, 2020; Webb Hooper et al., 2020). The link between obesity and other chronic conditions, such as hypertension, diabetes, cardiac conditions, and cerebrovascular disease, is well documented. However, we do not have a full understanding of its relationship with critical health conditions. High risk for prothrombotic and pro-inflammatory states as well as poor ventilatory lung mechanics linked with obesity are poor prognostic factors in severe conditions, including H1N1 influenza, and likely contribute to the outcomes of COVID-19 (Jain & Chaves, 2011; Hanslik et al., 2010; Louie et al., 2011; Morgan et al., 2010; Díaz et al., 2011). On the other hand, some studies have demonstrated an inverse relationship between mortality and obesity among patients who are critically ill, including those suffering from acute respiratory distress syndrome (O'Brien et al., 2004; Zhi et al., 2016; Ni et al., 2017).

METHODS

Goal of study

The objectives of this rigorous and comprehensive literature review were to investigate relevant epidemiological studies for analyzing the association between sex, BMI, and age with morbidity and mortality of COVID-19 patients. The results and findings from this study could assist healthcare providers in adopting and employ preventive measures and also use early treatment strategies for these groups (considered as high risk).

Research aims

- To determine whether obesity and BMI are associated with a high rate of mortality among COVID-19 patients.
- To elucidate the association between age, sex, and BMI with mortality of COVID-19.

Search strategy

We performed compressive systematic research to pool every relevant article that evaluated COVID's effect on patients with regards to BMI, age, sex, and mortality. We considered including articles published in English; a search strategy was created to retrieve articles published mostly in 2020. Search for articles was conducted in the most widely-used databases such as PubMed, Scopus, EMBASE, and Web of Science. Search terms used for article retrieval included: "BMI," OR "Obesity," OR "BMI," OR "Sex," OR "Age." AND "COVID-19 related mortality." All duplicate articles were removed, and a final search for relevant articles was done on the reference list of articles reviewed.

Data extracted included baseline demographic information (gender, age, residence status, race/ethnicity), clinical characteristics (BMI), history of smoking and alcohol use, hypertension, intravenous drug use, coronary artery disease, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (COPD), active malignancy, asthma, chronic kidney disease, liver cirrhosis, end-stage renal disease, and human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), symptomatology, pertinent home medications, level of oxygen required in the ER, laboratory data obtained on the first hospital day (white blood cell count, hemoglobin, lymphocyte count, creatinine, platelet count, aspartate, alanine transaminase, transaminase, creatinine kinase, ferritin, lactate dehydrogenase, c-reactive protein, hemoglobin A1c for diabetics, procalcitonin, intubation, acute respiratory distress syndrome, oxygen requirements during stay at the hospital, acute kidney injury, ICU admission, length of stay, need for renal replacement therapy, death, hospital discharge.

Discussion

BMI in association with COVID-19

For individuals with COVID-19 caused by SARS-CoV-2, there appears to be a solid relationship between being an obese or overweight individual and the risks of hospitalization and requiring treatment in intensive care units. Data from emerging literature suggests that adults under 60 years of age have a higher chance of being hospitalized (Lighter et al., 2020). The pandemic has occurred at such a time when there is an astronomical increase in the prevalence of individuals with obesity and overweight in virtually the whole world. It is important to note that almost every country in the world has a prevalence of obese and overweight individuals exceeding 20% (NCD Risk Factor Collaboration (NCD-RisC), 2019; NCD Risk Factor Collaboration (NCD-RisC), 2016; Popkin et al., 2020). To date, no country in the world has experienced any reduction in the prevalence of obese and overweight individuals.

It is also important to note that a great deal of economic hardship is created by policy responses designed to mitigate COVID-19. The pandemic has brought all the nations of the world the need to restrict movement, impede economic activities, and implement social distancing across a spectrum of nonessential occupations. These adjustments have triggered problems with the food system, such as changes in consumption of food and patterns of physical activity, and remote work environments that may exacerbate trends in the prevalence of obese individuals, while another effect may be to boost the proportion of food insecure as well as the malnourished and stunted. These changes have prolonged implications beyond mitigating the current spread of SARS-CoV-2 and may be injurious to the health.

The link between individuals with a high percentage of body fat, especially visceral adipose tissue, obese individuals, major cardiometabolic conditions, ranging from hypertension to cardiovascular conditions, Type 2 diabetes mellitus, and several cancers is strong (WCRF, 2018a; WCRF, 2018b; Afshin et al., 2017; Kantar, 2020). The underlying inflammatory and metabolic factors of obese individuals also play a major role in the onset of severe lung diseases. It is important to note that obese individuals are more susceptible to acute respiratory distress syndrome (ARDS), and ARDS is known to be the primary cause of COVID-19 (Gong et al., 2010). Also, being an obese individual increase the risk of influenza mortality and morbidity (Louie et al., 2011), most likely via impairments in adaptive and innate immune responses (Karlsson et al., 2019). The endpoint is that vaccines developed for the treatment of COVID-19 will have a weak effect on obese individuals due to a compromised immune response.

We found ten studies that assessed the link between obese individuals and COVID-19. All studies showed that obese individuals had a significantly higher risk of COVID-19 (Leung et al., 2020; Cho et al., 2020; Bello-Chavolla et al., 2020; Berumen et al., 2020; Darling et al., 2020; de Lusignan et al., 2020; ICNARC, 2020; Ho et al., 2020; Khawaja et al., 2020; Gao et al., 2020).

A Denmark study showed that the prevalence of overweight and obese individuals was lower in cases that tested positive for SARS-CoV-2 compared to individuals that tested negative for SARS-CoV-2 (Reilev et al., 2020). It is important to note that these may be biased results because body weight was determined during discharge from the hospital. One study used data from U.K. Biobank (n = 285 817) to show that overweight caused an over 44% increase in the risk of COVID-19 (relative risk RR = 1.44; 95% CI, 1.0 – 1.92; p = 0.0100). The risk was almost doubled by individuals with obesity (RR = 1.9; CI 95%; 1.46 – 2.65; $p < 0.0001$). This figure was adjusted for ethnicity, sex, age, and socioeconomic deprivation as determined by assets, household density, and unemployment (Ho et al., 2020). The researchers tested only a minute portion of individuals for COVID-19 (0.5%). This may be considered a major limitation of the study.

Being an obese individual is a major risk factor for severe infectious conditions, such as hepatitis, nosocomial infections, and influenza (Huttunen & Syrjänen, 2010; Huttunen & Syrjänen, 2013). Other infections, such as sepsis, community-acquired pneumonia, and tuberculosis, have a better prognosis in obese adults compared with lean adults (Roth et al., 2017). This supports the hypothesis of 'obesity paradox' where underlying characteristics of individuals with high BMI affect the physiological response to infection. Just like influenza infections, obesity or a high BMI increases the severity of COVID-19. It is important to note that obesity is a metabolic disease featuring alterations in systematic metabolisms, such as increased serum glucose, insulin resistance, altered adipokines (such as decreased adiponectin and increased leptin), and low-grade inflammation (Rasouli & Kern, 2008; Singla et al., 2010). There is evidence that nutrient and hormone dysregulation in obese individuals can alter their response to infection.

Hyperglycaemia, a hallmark of Type 2 diabetes, is associated with obesity. It is also worth mentioning that unregulated serum glucose significantly increases COVID-19 related mortality (Zhu et al., 2020). When a person is infected, unregulated serum glucose can impair the function of immune cells either directly or indirectly through the generation of glycation products and antioxidants (Sheetz & King, 2002). Also, both leptin and insulin signaling play critical roles in the T-cell inflammatory effector response via the upregulation of cellular glycolysis, enhancing the production of effector cytokines like IFN-γ and TNF-α. The combination of these metabolic factors influences immune cell metabolism, which dictates physiological response to invasion by pathogens, such as SARS-CoV-2.

Fatty acid consumption also has an influence on inflammatory responses. Prostaglandins, derivatives of long-chain fatty acids, are basically acute phase pyrogens that trigger inflammatory responses during an infection. Anti-inflammatory responses may be induced by omega-3 polyunsaturated fatty acids through cyclooxygenase activity, while omega-6 fatty acids may mediate pro-inflammatory cyclooxygenase production of prostaglandins. Modern-day dietary intake favors omega-6 fatty acids compared to omega-3s. In the US, consumption is currently in a 10:1 ratio owing to the excessive and widespread consumption of vegetable oils (Kris-Etherton et al., 2000). Derivatives of fatty acids have a direct influence on COVID-19 in obese or high-BMI individuals. Analysis of preclinical data suggests that fatty acid-derived pro-resolving lipid mediators may play a role, as they may be highly deficient in obese individuals and, as such, cannot resolve inflammatory responses well enough during infection (Crouch et al., 2021).

Cholesterol and other fatty acids are vital in the spread of RNA viruses, such as influenza and respiratory syncytial viruses. SARS-CoV, the closest relative to SARS-CoV-2, facilitates viral budding using cholesterol. The viral budding follows the S protein binding of cellular ACE2 receptors, enhancing the spread to close cells. Depletion of cholesterol in cells that express ACE2 results in significantly reduced viral S protein binding (Glende et al., 2008). A higher-than-normal BMI (obesity) increases the risk of a severe COVID-19 among patients with fatty liver disease, whereas obese adults have an extremely high risk for COVID-19 irrespective of sex, age, or comorbidities, like diabetes, hypertension, and dyslipidemia.

Physical features of obese individuals may also increase the risk and severity of COVID-19. Obstructive sleep apnoea and other conditions affecting the respiratory system in obese individuals often raise the risk of pneumonia associated with hypoventilation, cardiac stress, and pulmonary hypertension (Stefan et al., 2020). Large waist circumference and higher body mass make it more difficult to provide care in hospital settings for supportive therapies, like mask ventilation, intubation, and prone positioning to minimize abdominal tension and increase the capacity of the diaphragm (Sattar et al., 2020). As such, prognoses of obese individuals with COVID-19 may be complicated by the high burden of clinical care among this vulnerable group.

Sex (gender) in association with COVID-19

Genetics

The expression of receptors and their distribution affects the route of viral infection, which affects our understanding of the pathogenesis and also dictates the therapeutic strategies (Zhao et al., 2020). Angiotensin-converting enzyme-2 (ACE 2) with ACE 2 gene encoding is the receptor for SARS-COV and the human respiratory coronavirus NL63 (Cao et al., 2020). Current evidence as per SARS-CoV-2 receptors suggests that ACE 2 are the primary receptors for SARS-CoV-2. Lu et al. (2020), in their study, reported that SARS-CoV-2 and SARS-CoV shared striking similarities in receptor-binding properties. An *in vitro* study showed that expression of ACE2 correlated positively with SARS-CoV infection (Li et al., 2007). The implication is that an organism with a high expression of ACE 2 protein has an environment that will support the pathogenesis of coronavirus. With this positive correlation between coronavirus and ACE 2, various studies quantified ACE 2 expression in human cells based on gender and ethnicity, for instance, in analyzing the level of expression and pattern of ACE 2 in humans using a single-cell RNA sequencing (RNA-seq), the analysis showed that Asian males had a high expression of ACE 2 compared to the females (Zhao et al., 2021). It is also important to note that there was evidence of variation in ACE 2 expression between different ethnicity (Cao et al., 2020). Conversely, in establishing ACE 2 expression in the primary affected organ, a Chinese-based study found that ACE 2 expression in human lungs was more expressed in Asian males than in females (Zhao et al., 2021).

Immunology

To generate a rightly controlled response during infections, immune checkpoints, like the CD200 receptor (CD 200R), plays a great role in balancing immunity during microbial infection via stimulation and control of hyperimmune mediated response (Wright et al., 2003). CD200R occurs in the myeloid receptor (Mihrshahi et al., 2009) and is expressed on granulocytes, macrophages, and dendritic cells. It is also expressed on immune cell components like B and T cells, as well as natural killer cells (Karnam et al., 2012). Karnan *et al.* observed that sex and CD200 – CD200R are the primary factors that determine the outcome of a viral infection. In a rodent study, CD200R deficiency signaled strong expression of type 1 interferon (IFN) production and viral clearance and improved the outcome of hepatitis coronavirus infection in mice, especially in female mice. This implies that organisms having high CD200R signaling have better clearance of viral infection. A review that analyzed the association between gender differences in immune response concluded that gender-based immunological differences play important roles in variations in susceptibility to infectious diseases as well as responses to vaccines in both genders. For instance, gender-based differences in human leucocytes antigen (HLA) genes and alleles that encode for interleukin 4, 10, and 12 receptors (IL-4, IL-6, IL-10) have been associated with differential antibody responses to vaccines against mumps, measles, tetanus, hepatitis A, and diphtheria in adults and children where the effects are believed to be caused by hormonal mechanisms (Klein & Flanagan, 2016). In another review, it was documented that women, most especially in their reproductive years, are at a high risk of developing autoimmune diseases but have a higher level of resistance to infections compared to men. Several factors may contribute to this, including sex hormones (Ghazeeri et al., 2011). The concept of immunological differences based on sex and driven by an X and a sex chromosome has been documented by Elgendy & Pepine, (2020), where blockage of estrogen receptors increased mortality due to infection by SARS-COV-2 among female mice. This suggests that estrogen receptors may play a role in blocking certain viral infections.

Aging in COVID-19

It is important to note that most cases of COVID-19 are mild. Some infected people may not experience any clinical symptoms after infection with SARS-CoV-2 (Gao et al., 2021; Wiersinga et al., 2020). Such asymptomatic individuals can also be a source of viral spread (Gao et al., 2021; Rothe et al., 2020). A March 2021 New York State report showed that 47,326 persons out of 141,495 tested positive for COVID-19. This accounts for over 33%, and most positives were asymptomatic (Rosenberg et al., 2020).

However, there is a need for more surveillance data to evaluate the extent of symptomatic infection. Machine learning and artificial intelligence may help address this as new research and evidence suggests the use of such technologies in SARS-COV-2 screening and diagnosis as well as clinical care and other public health measures, e.g., contact tracing (Halamka et al., 2020; Lalmuanawma et al., 2020; Minaee et al., 2020). In heterogeneous infectious diseases such as COVID-19, host factors play key roles in determining the severity and progression of diseases (Wiersinga et al., 2020). For a severe state of COVID-19, major risk factors include male sex, age, obesity, smoking, and comorbid chronic diseases like type 2 diabetes mellitus, hypertension, and others (Zhou et al., 2020; Wu et al., 2020; Garibaldi et al., 2021). Solid evidence globally suggests that age is a significant factor that increases the risk for severe COVID-19 disease and its attendant complications.

Immunity is a cornerstone of host-pathogen interaction in every infectious disease. It involves three interrelated key aspects: potential immune pathology, immune response and protection, and vulnerability. In many cases, one may gain partial immune protection from prior exposure to the same pathogen or via vaccination with a dominant antigen. The level of vulnerability involves innate immunity that is independent of immune responses specific to antigens and other physiological protective mechanisms. Dysregulation of the immune response to the current infection may cause immune pathology leading to the pathogenesis of the disease. Because SARS-CoV-2 is a novel coronavirus without a prior immune response, the population is highly susceptible without any herd immunity. However, under specific circumstances, older adults may enjoy some form of protection than the young ones against strains that were in vogue when they were young. This is by virtue of cross-reactivity and/or immunological memory. It is important to note that a considerable fraction of healthy persons not infected with SARS-CoV-2 possess T cells that are highly reactive to SARS-CoV-2 antigens due to cross-reactivity with other coronaviruses. It has not been confirmed whether this protects against COVID-19.

Patients with severe COVID-19 typically develop acute respiratory distress syndrome (ARDS), requiring ventilator support and intubation as well as major involvement of other organ systems. For instance, "neuro-COVID" occurs in at least a third of COVID-19 patients (Chiappelli, 2020; Ferrarese et al., 2020). Although SARS-CoV-2 has been characterized regarding its neuroinvasive and neurotrophic properties (Baig et al., 2020; Puelles et al., 2020), inflammatory cytokine release and immunopathology due to the presence of this virus may also contribute to neuro-COVID and other systemic conditions. In fact, clinical observations made in Wuhan indicated that COVID-19 patients manifest an acute increase in serum levels of C-reactive protein (CRP) and IL-6 (Chen et al., 2020). Other inflammatory mediators whose level may be elevated in COVID-19 patients include interferon (IFN)-γ, monocyte chemotactic protein-3, induced protein 10 (CXCL-10 or IP-10), and it is important to note that such elevation contributes to disease severity and progression (Lagunas-Rangel & Chávez-Valencia, 2020).

CONCLUSION

Severe obesity, male sex, and increasing age are associated with a high rate of in-hospital mortality and generally worse in-hospital prognosis.

REFERENCES

Afshin, A., Forouzanfar, M.H., et al. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. *377*(1), 13-27. https://doi.org/10.1056/NEJMoa1614362

Baig, A.M., Khaleeq, A., Ali, U., Syeda, H. (2020). Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*., *11*(7), 995-998. https://doi.org/10.1021/acschemneuro.0c00122

Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis.*, *20*(7), 773. https://doi.org/10.1016/S1473-3099(20)30195-X

Bello-Chavolla, O.Y., Bahena-López, J.P., Antonio-Villa, N.E., et al. (2020). Predicting Mortality Due to SARS-CoV-2: A Mechanistic Score Relating Obesity and Diabetes to COVID-19 Outcomes in Mexico. *J Clin Endocrinol Metab*., *105*(8), dgaa346. https://doi.org/10.1210/clinem/dgaa346

Berumen, J., Schmulson, M., Alegre, J., et al. (2020). Risk of infection and hospitalization by Covid-19 in Mexico: a case-control study. *medRxiv.* https://doi.org/10.1101/2020.05.24.20104414

Bhatraju, P.K., Ghassemieh, B.J., Nichols, M., et al. (2020). Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *New England Journal of Medicine, 382*(21), 2012-2022. https://doi.org/10.1056/NEJMoa2004500

Boccia, S., Ricciardi, W., Ioannidis, J.P.A. (2020). What Other Countries Can Learn From Italy During the COVID-19 Pandemic. *JAMA Intern Med*., *180*(7), 927-928. https://doi.org/10.1001/jamainternmed.2020.1447

Cao, Y., Li, L., Feng, Z., et al. (2020). Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov.*, *6*(11). https://doi.org/10.1038/s41421-020-0147-1

Centers for Disease Control and Prevention. (2021). *Adult obesity prevalence maps. Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion*. https://www.cdc.gov/obesity/data/index.html

Chen, G., Wu, D., Guo, W., et al. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.*, *130*(5), 2620-2629. https://doi.org/10.1172/JCI137244

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet, 395*(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chiappelli, F. (2020). Towards Neuro-CoViD-19. *Bioinformation, 16*(4), 288-292. https://doi.org/10.6026/97320630016288

Cho, E.R., Slutsky, A.S., Jha, P. (2020). Smoking and the risk of COVID-19 infection in the UK Biobank Prospective Study. *medRxiv.* https://doi.org/10.1101/2020.05.05.20092445

County Health Rankings and Roadmaps. (2019). *2019 County Health Rankings Key Findings Report*. https://www.countyhealthrankings.org/reports/2019-county-health-rankings-key-findings-report

COVID Data Tracker. (2020). United States COVID-19 Cases, Deaths, and Laboratory Testing (NAATs) by State, Territory, and Jurisdiction. *Centers for Disease Control and Prevention*. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html

Crouch, M., Al-Shaer, A., Shaikh, S.R. (2021). Hormonal Dysregulation and Unbalanced Specialized Pro-Resolving Mediator Biosynthesis Contribute toward Impaired B Cell Outcomes in Obesity. *Mol Nutr Food Res.*, *65*(1), e1900924. https://doi.org/10.1002/mnfr.201900924

Darling, A.L., Ahmadi, K.R., Ward, K.A., et al. (2020). Vitamin D status, body mass index, ethnicity and COVID-19: initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). *medRxiv.* https://doi.org/10.1101/2020.04.29.20084277

de Lusignan, S., Dorward, J., Correa, A., et al. (2020). Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. *Lancet Infect Dis.*, *20*(9), 1034-1042. https://doi.org/10.1016/S1473-3099(20)30371-6

Díaz, E., Rodríguez, A., Martin-Loeches, I., et al. (2011). Impact of obesity in patients infected with 2009 influenza A(H1N1). *Chest.*, *139*(2), 382-386. https://doi.org/10.1378/chest.10-1160

Elgendy, I.Y., Pepine, C.J. (2020). Why are women better protected from COVID-19: Clues for men? Sex and COVID-19. *International Journal of Cardiology, 315*, 105-106. https://doi.org/10.1016/j.ijcard.2020.05.026

Ferrarese, C., Silani, V., Priori, A., et al. (2020). An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROCOVID). *Neurol Sci.*, *41*(6), 1355-1359. https://doi.org/10.1007/s10072-020-04450-1

Gao, F., Zheng, K.I., Wang, X.B., et al. (2020). Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care, 43*(7), e72-e74. https://doi.org/10.2337/dc20-0682

Gao, Z., Xu, Y., Sun, C., et al. (2021). A systematic review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect.*, *54*(1), 12-16. https://doi.org/10.1016/j.jmii.2020.05.001

Garibaldi, B.T., Fiksel, J., Muschelli, J., et al. (2021). Patient Trajectories Among Persons Hospitalized for COVID-19: A Cohort Study. *Ann Intern Med.*, *174*(1), 33-41. https://doi.org/10.7326/M20-3905

Ghazeeri, G., Abdullah, L., Abbas, O. (2011). Immunological differences in women compared with men: overview and contributing factors. *Am J Reprod Immunol.*, *66*(3), 163-169. https://doi.org/10.1111/j.1600-0897.2011.01052.x

Glende, J., Schwegmann-Wessels, C., Al-Falah, M., et al. (2008). Importance of cholesterol-rich membrane microdomains in the interaction of the S protein of SARS-coronavirus with the cellular receptor angiotensin-converting enzyme 2. *Virology, 381*(2), 215-221. https://doi.org/10.1016/j.virol.2008.08.026

Gong, M.N., Bajwa, E.K., Thompson, B.T., Christiani, D.C. (2010). Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax*, *65*(1), 44-50. https://doi.org/10.1136/thx.2009.117572

Grasselli, G., Zangrillo, A., Zanella, A., et al. (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA, 323*(16), 1574-1581. https://doi.org/10.1001/jama.2020.5394

Halamka, J., Cerrato, P., Perlman, A. (2020). Redesigning COVID-19 Care With Network Medicine and Machine Learning. *Mayo Clin Proc Innov Qual Outcomes.*, *4*(6), 725-732. https://doi.org/10.1016/j.mayocpiqo.2020.09.008

Hales, C.M., Carroll, M.D., Fryar, C.D., Ogden, C.L. (2020). Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. *NCHS Data Brief*, *2020*(360), 1-8.

Hanslik, T., Boelle, P.Y., Flahault, A. (2010). Preliminary estimation of risk factors for admission to intensive care units and for death in patients infected with A(H1N1)2009 influenza virus, France, 2009-2010. *PLoS Curr.*, *2*(RRN1150). https://doi.org/10.1371/currents.rrn1150

Ho, F.K., Celis-Morales, C.A., Gray, S.R., et al. (2020). Modifiable and non-modifiable risk factors for COVID-19: results from UK Biobank. *medRxiv.* https://doi.org/10.1101/2020.04.28.20083295

Huttunen, R., Syrjänen, J. (2010). Obesity and the outcome of infection. *Lancet Infect Dis.*, *10*(7), 442-443. https://doi.org/10.1016/S1473-3099(10)70103-1

Huttunen, R., Syrjänen, J. (2013). Obesity and the risk and outcome of infection. *Int J Obes (Lond).*, *37*(3), 333-340. https://doi.org/10.1038/ijo.2012.62

ICNARC. (2020). *ICNARC report on COVID-19 in critical care 10 July 2020*. ICNARC, London.

Jain, S., Chaves, S.S. (2011). Obesity and influenza. *Clin Infect Dis.*, *53*(5), 422-424. https://doi.org/10.1093/cid/cir448

Kantar. (2020). Covid-19: wave 2, 27-30 March among connected South African consumers. *Kantar World Panel*. Johannisberg.

Karlsson, E.A., Milner, J.J., Green, W.D., Rebeles, J., Schultz-Cherry, S., Beck, M. (2019). Chapter 10—influence of obesity on the response to influenza infection and vaccination In: Johnston RA, Suratt BT, eds. *Mechanisms and Manifestations of Obesity in Lung Disease*. Cambridge, Massachusetts: Academic Press, 227-259.

Karnam, G., Rygiel, T.P., Raaben, M., et al. (2012). CD200 receptor controls sex-specific TLR7 responses to viral infection. *PLoS Pathog.*, *8*(5), e1002710. https://doi.org/10.1371/journal.ppat.1002710

Kass, D.A., Duggal, P., Cingolani, O. (2020). Obesity could shift severe COVID-19 disease to younger ages. *The Lancet, 395*(10236), 1544-1545. https://doi.org/10.1016/S0140-6736(20)31024-2

Khawaja, A.P., Warwick, A.N., Hysi, P.G., *et al.* (2020). Associations with covid-19 hospitalisation amongst 406,793 adults: the UK Biobank prospective cohort study. *medRxiv.* https://doi.org/10.1101/2020.05.06.20092957

Klein, S.L., Flanagan, K.L. (2016). Sex differences in immune responses. *Nat Rev Immunol.*, *16*(10), 626-638. https://doi.org/10.1038/nri.2016.90

Kompaniyets, L., Goodman, A.B., Belay, B., et al. (2021). Body Mass Index and Risk for COVID-19–Related Hospitalization, Intensive Care Unit Admission, Invasive Mechanical Ventilation, and Death — United States, March–December 2020. *Morbidity and Mortality Weekly Report (MMWR), 70*(10), 355–361. http://dx.doi.org/10.15585/mmwr.mm7010e4

Kris-Etherton, P.M., Taylor, D.S., Yu-Poth, S., et al. (2000). Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr.*, *71*(1 Suppl), 179S-88S. https://doi.org/10.1093/ajcn/71.1.179S

Lagunas-Rangel, F.A., Chávez-Valencia, V. (2020). High IL-6/IFN-γ ratio could be associated with severe disease in COVID-19 patients. *J Med Virol.*, *92*(10), 1789-1790. https://doi.org/10.1002/jmv.25900

Lalmuanawma, S., Hussain, J., Chhakchhuak, L. (2020). Applications of machine learning and artificial intelligence for Covid-19 (SARS-CoV-2) pandemic: A review. *Chaos Solitons Fractals.*, *139*(110059). https://doi.org/10.1016/j.chaos.2020.110059

Leung, N.Y., Bulterys, M.A., Bulterys, P.L. (2020). Predictors of COVID-19 incidence, mortality, and epidemic growth rate at the country level. *medRxiv.* https://doi.org/10.1101/2020.05.15.20101097

Li, W., Sui, J., Huang, I.C., et al. (2007). The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. *Virology.*, *367*(2), 367-374. https://doi.org/10.1016/j.virol.2007.04.035

Li, X., Xu, S., Yu, M., et al. (2020). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol.*, *146*(1), 110-118. https://doi.org/10.1016/j.jaci.2020.04.006

Lighter, J., Phillips, M., Hochman, S., et al. (2020). Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. *Clin Infect Dis.*, *71*(15), 896-897. https://doi.org/10.1093/cid/ciaa415

Louie, J.K., Acosta, M., Samuel, M.C., et al. (2011). A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). *Clin Infect Dis.*, *52*(3), 301-312. https://doi.org/10.1093/cid/ciq152

Lu, R., Zhao, X., Li, J., et al. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet, 395*(10224), 565-574. https://doi.org/10.1016/S0140-6736(20)30251-8

McKibbin, W.J., Fernando, R. (2020). The global macroeconomic impacts of COVID-19: seven scenarios. *CAMA Working Paper No. 19/2020*. The Australian National University, 1-43. https://doi.org/10.2139/ssrn.3547729

Mihrshahi, R., Barclay, A.N., Brown, M.H. (2009). Essential roles for Dok2 and RasGAP in CD200 receptor-mediated regulation of human myeloid cells. *J Immunol.*, *183*(8), 4879-4886. https://doi.org/10.4049/jimmunol.0901531

Minaee, S., Kafieh, R., Sonka, M., Yazdani, S., Jamalipour Soufi, G. (2020). Deep-COVID: Predicting COVID-19 from chest X-ray images using deep transfer learning. *Med Image Anal.*, *65*(101794). https://doi.org/10.1016/j.media.2020.101794

Montefiore's Office of Community & Population Health. (2018). *Bronx Community Health Dashboard: Nutrition, physical activity and obesity*. https://www.montefiore.org/documents/communityservices/OCPH-Dashboard-Obesity.pdf

Morgan, O.W., Bramley, A., Fowlkes, A., et al. (2010). Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One*, *5*(3), e9694. https://doi.org/10.1371/journal.pone.0009694

NCD Risk Factor Collaboration (NCD-RisC). (2016). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants [published correction appears in Lancet. *Lancet*, *387*(10026), 1377-1396. https://doi.org/10.1016/S0140-6736(16)30054-X

NCD Risk Factor Collaboration (NCD-RisC). (2019). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature*, *569*(7755), 260-264. https://doi.org/10.1038/s41586-019-1171-x

Ni, Y.N., Luo, J., Yu, H., et al. (2017). Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Crit Care.*, *21*(1), https://doi.org/10.1186/s13054-017-1615-3

NYC Health. (2020). Promoting and Protecting the City's Health. *COVID-19: Data*. https://www1.nyc.gov/site/doh/covid/covid-19-data.page

NYC Health. (2022). *COVID-19: Data*. https://www1.nyc.gov/site/doh/covid/covid-19-data.page

O'Brien, J.M. Jr., Welsh, C.H., Fish, R.H., Ancukiewicz, M., Kramer, A.M. (2004). National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Excess body weight is not independently associated with outcome in mechanically ventilated patients with acute lung injury. *Ann Intern Med.*, *140*(5), 338-345. https://doi.org/10.7326/0003-4819-140-5-200403020-00009

Ornell, F., Schuch, J.B., Sordi, A.O., Kessler, F.H.P. (2020). "Pandemic fear" and COVID-19: mental health burden and strategies. *Braz J Psychiatry*, *42*(3), 232–235. https://doi.org/10.1590/1516-4446-2020-0008

Petrilli, C.M., Jones, S.A., Yang, J., et al. (2020). Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*, *369*(m1966). https://doi.org/10.1136/bmj.m1966

Popkin, B.M., Corvalan, C., Grummer-Strawn, L.M. (2020). Dynamics of the double burden of malnutrition and the changing nutrition reality. *Lancet*, *395*(10217), 65-74. https://doi.org/10.1016/S0140-6736(19)32497-3

Puelles, V.G., Lütgehetmann, M., Lindenmeyer, M.T., et al. (2020). Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med.*, *383*(6), 590-592. https://doi.org/10.1056/NEJMc2011400

Rasouli, N., Kern, P.A. (2008). Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab*., *93*(11 Suppl 1), S64-S73. https://doi.org/10.1210/jc.2008-1613

Reilev, M., Kristensen, K.B., Pottegård, A., et al. (2020). Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *Int J Epidemiol*., *49*(5), 1468-1481. https://doi.org/10.1093/ije/dyaa140

Rosenberg, E.S., Dufort, E.M., Blog, D.S., et al. (2020). COVID-19 Testing, Epidemic Features, Hospital Outcomes, and Household Prevalence, New York State-March 2020. *Clin Infect Dis*., *71*(8), 1953-1959. https://doi.org/10.1093/cid/ciaa549

Roth, J., Sahota, N., Patel, P., et al. (2017). Obesity paradox, obesity orthodox, and the metabolic syndrome: An approach to unity. *Mol Med*., *22*, 873-885. https://doi.org/10.2119/molmed.2016.00211

Rothe, C., Schunk, M., Sothmann, P., et al. (2020). Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med*., *382*(10), 970-971. https://doi.org/10.1056/NEJMc2001468

Sattar, N., McInnes, I.B., McMurray, J.J.V. (2020). Obesity Is a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. *Circulation*, *142*(1), 4-6. https://doi.org/10.1161/CIRCULATIONAHA.120.047659

Sheetz, M.J., King, G.L. (2002). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA*, *288*(20), 2579-2588. https://doi.org/10.1001/jama.288.20.2579

Siddiqi, H.K., Mehra, M.R. (2020). COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*, *39*(5), 405-407. https://doi.org/10.1016/j.healun.2020.03.012

Singla, P., Bardoloi, A., Parkash, A.A. (2010). Metabolic effects of obesity: A review. *World J Diabetes*., *1*(3), 76-88. https://doi.org/10.4239/wjd.v1.i3.76

Stefan, N., Birkenfeld, A.L., Schulze, M.B., Ludwig, D.S. (2020). Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol*., *16*(7), 341-342. https://doi.org/10.1038/s41574-020-0364-6

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*, *323*(11), 1061-1069. https://doi.org/10.1001/jama.2020.1585

WCRF. (2018a). Diet, nutrition, physical activity and cancer: a global perspective: A summary of the third expert report. *World Cancer Research Fund/American Institute for Cancer Research.* https://www.wcrf.org/wp-content/uploads/2021/02/Summary-of-Third-Expert-Report-2018.pdf

WCRF. (2018b). Diet, nutrition, physical activity and cancer: a global perspective. Continuous Update Project Expert Report. *World Cancer Research Fund/American Institute for Cancer Research*.

Webb Hooper, M., Nápoles, A.M., Pérez-Stable, E.J. (2020). COVID-19 and Racial/Ethnic Disparities. *JAMA*, *323*(24), 2466-2467. https://doi.org/10.1001/jama.2020.8598

WHO. (2020). *World Health Organization Coronavirus disease 2019 (COVID-19) situation report – 87*. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200427-sitrep-98-covid-19.pdf?sfvrsn=90323472_4

Wiersinga, W.J., Rhodes, A., Cheng, A.C., Peacock, S.J., Prescott, H.C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA, 324*(8), 782-793. https://doi.org/10.1001/jama.2020.12839

Wright, G.J., Cherwinski, H., Foster-Cuevas, M., et al. (2003). Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. *J Immunol*., *171*(6), 3034-3046. https://doi.org/10.4049/jimmunol.171.6.3034

Wu, C., Chen, X., Cai, Y., et al. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*., *180*(7), 934-943. https://doi.org/10.1001/jamainternmed.2020.0994

Wu, Z., McGoogan, J.M. (2020). Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *The JAMA, 323*(13), 1239-1242. https://doi.org/10.1001/jama.2020.2648

Yancy, C.W. (2020). COVID-19 and African Americans. *JAMA, 323*(19), 1891-1892. https://doi.org/10.1001/jama.2020.6548

Yang, W., Cao, Q., Qin, L., Wang, X., Cheng, Z., Pan, A., Dai, J., Sun, Q., Zhao, F., Qu, J., Yan, F. (2020). Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *Journal of Infection, 80*(4), 388-393. https://doi.org/10.1016/j.jinf.2020.02.016

Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W. (2020). Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *bioRxiv.* https://doi.org/10.1101/2020.01.26.919985

Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W. (2021). Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med*., *202*(5), 756-759. https://doi.org/10.1164/rccm.202001-0179LE

Zhi, G., Xin, W., Ying, W., Guohong, X., Shuying, L. (2016). "Obesity Paradox" in acute respiratory distress syndrome: A Systematic Review and Meta-Analysis. *PLoS One, 11*(9), e0163677. https://doi.org/10.1371/journal.pone.0163677

Zhou, F., Yu, T., Du, R., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet, 395*(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhou, F., Yu, T., Du, R., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet, 395*(10229), 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhu, L., She, Z.G., Cheng, X., et al. (2020). Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab*., *31*(6), 1068-1077. https://doi.org/10.1016/j.cmet.2020.04.021

--0--