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

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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

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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 (ACE2) with ACE2 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 ACE2 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 ACE2 protein has an environment that will support the pathogenesis of coronavirus. With this positive correlation between coronavirus and ACE2, various studies quantified ACE2 expression in human cells based on gender and ethnicity, for instance, in analyzing the level of expression and pattern of ACE2 in humans using a single-cell RNA sequencing (RNA-seq), the analysis showed that Asian males had a high expression of ACE2 compared to the females (Zhao et al., 2021). It is also important to note that there was evidence of variation in ACE2 expression between different ethnicity (Cao et al., 2020). Conversely, in establishing ACE2 expression in the primary affected organ, a Chinese-based study found that ACE2 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 (Mihreshahi 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.

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