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*Original Article*

# The Impact of Obesity and Diabetes on COVID-19 Severity

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**ABSTRACT**

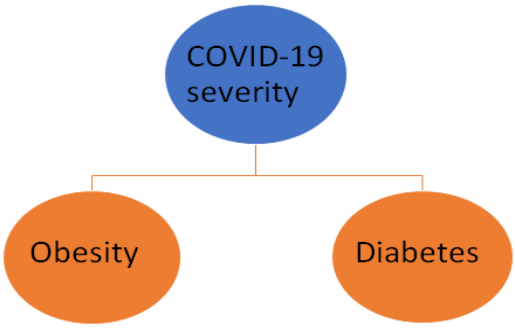
The seven human coronavirus, sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had started a worldwide health pandemic that raised concern regarding its severe outcomes in the healthcare system and specifically for patients who are diagnosed with chronic diseases such as obesity and diabetes. The purpose of the study was to assess the severity of COVID-19 in obese and diabetic hospitalized patients in National Guard Health Affairs (NGHA).

**Methods:** A descriptive cross-sectional study was done at King Abdulaziz Medical City, NGHA in Riyadh, Saudi Arabia. Data was collected from The BestCare system using a non-probability purposive which was done by including all patients applicable to our inclusion criteria. SPSS version 24 was used for data analysis.

**Results:** The study included 5,257 patients that were with positive test results for COVID-19. Of all the patients, 2,499 (47.5%) males and 2,758 (52.5%) females were diagnosed. The majority (97.9%) of the patients were diabetic and more than half of the subjects (53.1%) in the sample were hypertensive. There was a strong association between ICU admission and chronic diseases and between death due to COVID-19 complications and: heart failure, renal disease, and obesity.

**Conclusion:** There was a strong association between ICU admission and diabetes, heart failure, renal disease, and obesity. Moreover, there were a strong association between death due to COVID-19 complications and heart failure, renal disease, and obesity.

**GRAPHICAL ABSTRACT**

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## Introduction

The seventh human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, Hubei Province, China, during a recent pneumonia outbreak in January 2020. Since then, the virus has spread around the world, infecting 4,806,299 individuals, and killing 318,599 people as of May 20, 2020 [1]. The SARS-CoV-2 virus spread quickly throughout China, reaching more than 90 nations. As of February 26, 2020, 78,064 individuals have been cumulatively diagnosed, with 12,224 instances being classified as serious status [2]. Extensive articles have been published about improvement and emergency medical care of COVID 19 [3].

SARS-CoV-2 is the causative pathogen of the pandemic of December 2019, which is now termed COVID-19 (Coronavirus Disease 2019). When affected people cough or sneeze, the spreading of SARS-CoV-2 is established as rapid human-to-human transmission via respiratory droplets [4]. When the virus carried in these droplets enters the cells of the new host via endocytosis, a way of which it merges its own envelope into the membrane of the hosts' cells, its structural protein spike enables its attachment to the angiotensin-converting enzyme-2 (ACE-2) receptor [5], an abundant receptor on several tissues such as pulmonary epithelial cells and white adipose tissue [6]. Upon attachment, SARS-CoV-2 converts the pulmonary alveolar epithelial cells into its replication factory by releasing its RNA contents into the cytoplasm. Once released, the pathogen replicase proteins re-establish the cell's original endoplasmic reticulum into double-membrane vesicles, which promote pathogen replication [4]. A joint immunopathological event following SARS-CoV-2 production is likely observed where lymphocytopenia and cytokine storms occur. This immunological hyperexcitability results in significantly high production of inflammatory cytokines, chemokines, and local free radicals, consequently causing rapid damage to the lungs, liver, and kidney [7].

Although COVID-19 manifestations involve a multi-systemic inflammatory response, the respiratory system is the most distinct among all. Initially, COVID-19 is similar to the common flu symptoms. However, it may progress into more severe manifestations such as acute respiratory distress and pneumonia. According to a recent study, fever, cough, and dyspnea resemble 83%, 82%, and 31% of patients with SARS-CoV-2, respectively [8].

Obesity can be defined as abnormal or excessive fat accumulation that presents a risk to health. According to studies, obesity was found to have a substantial link to severe illness and the severity of COVID-19 symptoms. It has also a significant impact on pulmonary function by lowering expiratory reserve volume and functional residual capacity which worsens the effect of SARS-CoV-2 [9]. The obesity presence particularly has high risk of developing severe disease and longer hospitalization [10].

Diabetes mellitus (DM) can be defined as a set of metabolic diseases associated with excessively high blood glucose levels, also referred to as hyperglycemia. It is divided into two main types depending on its mechanism. In insulin dependent type 1 diabetes, beta cells are destroyed over a long period of time before clinical diabetes is established leading to an inadequate production of insulin. On the other hand, non-insulin dependent type 2 diabetes is characterized by the resistance of the peripheral tissues to the insulin effects [11]. Research showed a 2:1 ratio of hospitalized COVID-19 patients with diabetes mellitus outnumbering COVID-19 patients without diabetes [12]. It is important to understand the pathophysiology of both diseases to understand the relationship between the two. Hospitalized COVID-19 patients with diabetes are at a greater risk of worse prognosis and mortality [13]. In addition to decreased viral clearance, there is a higher-affinity cellular binding and efficient viral entry in diabetic individuals increasing their risk. Furthermore, viral proliferation is supported by hyperglycemia since they are directly proportional. An increase in glucose levels contributes to elevated SARS-CoV-2 replication and sustainability [14].

Diabetes and COVID-19 have a directional relationship, which means diabetic patients are

more likely to have infection for long time and have higher risk for many complications and death from the disease [15]. It is important for health care professionals caring for COVID-19 patients to be aware of the increased prevalence of the disease severity in obese and diabetic patients, which raises scientific questions related to this association [16].

Recognizing the risk factors could be helpful to underline the prevention strategies and high-risk population. In Saudi Arabia, the first official case diagnosed with COVID-19 was announced by the Ministry of Health on March 2, 2020, and as of October 18, 2021, there have been a total of 547,941 confirmed cases along with 8,763 deaths [17].

Given the significant prevalence of diabetes and obesity in Saudi Arabia, as well as their link to COVID-19 comorbidity [18, 19], there must be an awareness of the increased risk of disease severity in obese and diabetic patients. However, the association between diabetes and obesity with the severity of outcomes in patients with COVID-19 is limited to small studies. To address this, in this study we investigated the association of obesity and diabetes with the severity of outcomes in hospitalized SARS-CoV-2 patients in National Guard Health Affairs.

## Materials and Methods

This study has been designed as an observational descriptive cross-sectional study. It was conducted at King Abdulaziz Medical City, National Guard Health Affairs in Riyadh. The facility was inaugurated in May 1983 by a royal decree with an approximate bed capacity of 1,500 beds, providing primary, secondary, tertiary, and quaternary health care services to Saudi Arabian National Guard personnel, civilian employees, and their families. The population estimated according to our literature review was 1158, with a 95% confidence level, and a 5% margin of error. The sample size using the Raosoft calculator size was determined to be 375. A non-probability purposive method was used as a sampling technique. The targeted population included all hospitalized COVID-19 patients who are diabetic, non-diabetic, obese, and non-obese between 2020 to 2022. All patients had positive COVID-19 diagnostic test results (either COVID-19 PCR or COVID-19 Virus (Qualitative) test). The inclusion criteria included: male and female, BMI, fasting plasma glucose, hypertension, ICU, and death. The set exclusion criterion was pregnant women. A data collection sheet was requested from King Abdullah International Medical Research Center (KAIMRC), and it included patient's demographics, disease data, co-morbidities, laboratory tests, and outcomes.

All data were collected from King Abdulaziz Medical City in Riyadh through the BestCare system (electronic patients' files). The data received from KAIMARC of all COVID-19 diagnosed patients from 2020-2022 was 15,692 patients. All the obtained data were further refined by removing any repetitive information and classifying data into subcategories relevant to the previously set criteria and only 5,257 who matched our criteria were included. All the data were then coded for further analysis processing. Since this is a retrospective cross-sectional study, no validation was required. As all data has been collected and obtained from the BestCare system, no consent form was required. All data received was in a single device and reviewed by only the research team. Therefore, patient confidentiality and privacy were ensured. During the process of data collection, other co-morbidities (arthritis, asthma, cancer, heart failure, and renal disease) appeared to show significant association and hence were included in the results.

### *Data analysis*

Data was coded for entry and analysis using SPSS statistical software package version 24. Data was presented using descriptive statistics in the form of frequencies and percentages. Nominal and ordinal variables were presented in the form of numbers and percentages. Chi- square test was used to test the correlation between categorical variables such as ICU admission and presence of chronic conditions. The significance level was chosen as $P < 0.05$. Regarding ethical considerations, permission from KAIMRC was received to collect the data (IRB approval number: IRB\0421\22.

## Results and Discussion

A descriptive cross-sectional design was used to assess the influence of common chronic diseases such as diabetes and obesity on the prognosis of patients diagnosed with COVID-19 at King Abdulaziz Medical City in Riyadh, Saudi Arabia. All patients with positive COVID-19 test were included in the study. The sample included 5,257 patients.

The sample included 2,499 (47.5%) males and 2,758 (52.5%) females. COVID-19 PCR test was positive for 2,510 subjects (47.7%) while COVID-19 virus (Qualitative) test was positive for 2,746 (52.2%). The majority (4,756 patients, 90.5%) of the patients diagnosed with COVID-19 were not admitted to ICU. Only small percent (276 patients, 5.3%) of the sample died (Table 1).

The majority (5,148 patients, 97.9%) of COVID-19 patients were diabetic. More than half of the subjects (2,790 patients, 53.1%) in the sample were hypertensive. Fifteen percent of the subjects in the sample (789 patients) had arthritis, 571 (10.9%) had renal disease, 384 (7.3%) had asthma, and 320 (6.1%) had heart failure. Only 273 patients (5.2%) of the subjects were obese (Table 2).

There was a strong association between ICU admission and diabetes, heart failure, renal disease, and obesity (P = 0.000 for each of them). There was an association between ICU admission and both arthritis and asthma (P = 0.002 and P = 0.004, respectively). However, there was no association between ICU admission and cancer (P = 0.307) (Table 3).

There were a strong association between death due to COVID-19 complications and heart failure, renal disease, and obesity (P = 0.000). There was an association between death due to COVID-19 complications and diabetes (P = 0.019).

**Table 1:** General characteristics of the samples (N = 5,257)

| Characteristics | Number | Percent |
|---|---|---|
| Gender<br>Male<br>Female | <br>2,499<br>2,758 | <br>47.5<br>52.5 |
| Diagnostic Exam<br>COVID-19 PCR<br>COVID-19 Virus (Qualitative) | <br>2,510<br>2,746 | <br>47.7<br>52.2 |
| ICU admission<br>No<br>Yes | <br>4,756<br>501 | <br>90.5<br>9.5 |
| Prognosis<br>Death<br>Recovered | <br>276<br>4,981 | <br>5.3<br>94.7 |

**Table 2:** Prevalence of chronic diseases among the samples (N = 5,257)

| Chronic condition | Number | Percent |
|---|---|---|
| Arthritis | 789 | 15.0 |
| Asthma | 384 | 7.3 |
| Cancer | 308 | 5.9 |
| Diabetes | 5,148 | 97.9 |
| Heart Failure | 320 | 6.1 |
| Hypertension | 2,790 | 53.1 |
| NAFLD | 75 | 1.4 |
| Renal Disease | 571 | 10.9 |
| Stroke | 223 | 4.2 |
| Obesity | 273 | 5.2 |

**NAFLD: Non-alcoholic fatty liver disease.*

However, there was no association between death due to COVID-19 complications and arthritis, cancer, and asthma (P = 0.058, P = 0.084, and P = 0.132, respectively) (Table 4).

COVID-19 is responsible for a significant number of deaths and health complications worldwide and is associated with several health issues. This cross-sectional analysis aimed to assess the severity of COVID-19 in obese and diabetic hospitalized patients in National Guard Health Affairs. This study revealed a significant relationship between patients diagnosed with COVID-19 and complications of their pre-existing chronic diseases such as diabetes and obesity. It has also demonstrated a strong association between ICU admission and diabetes, obesity, renal disease, and heart failure. Death was significantly related to COVID-19 complications and diabetes.

Obesity has shown to directly affect normal respiratory function by damaging respiratory drive mechanisms [19]. It is associated with decreased respiratory muscle, reduced lung volume, high airway resistance, and gas exchange impairment [20]. It is also associated with pro-inflammatory processes in obstructive sleep apnea disease which gets further worse in COVID-19 patients as the disease progresses, by repeated airway obstruction [21]. Moreover, in obese individuals, changes in the lung affect the immune response to viral pathogens leading to impaired antiviral response with subsequent secondary infections and increased susceptibility to viral spread [22].

There are multiple challenges imposed by ICU admittance of obese COVID-19 patients [23] including rapid desaturation requiring early intubation by anesthesiologists or highly trained intensivists [24]. Patients with diabetes mellitus (DM) have shown to be more prone to infectious diseases through multiple mechanisms that impairs their immunity, including impaired polymorphonuclear function (adherence, chemotaxis, phagocytosis, and intracellular killing) [25] and decreased IFN-α recruitment [26, 27].

**Table 3:** Relationship between ICU admission and specific chronic conditions among the samples (N = 5,257)

| Chronic Condition | ICU Admission | | Chi-square | P-value |
|---|---|---|---|---|
| | No | Yes | | |
| Obesity | | | | |
| No | 4,490 (94.4%) | 494 (98.6%) | 16.207 | 0.000 |
| Yes | 266 (5.6%) | 7 (1.4%) | | |
| Diabetes | | | | |
| No | 108 (2.3%) | 1 (0.2%) | 9.576 | 0.000 |
| Yes | 4,648 (97.7%) | 500 (99.8%) | | |
| Arthritis | | | | |
| No | 4,021 (84.5%) | 447 (89.2%) | 7.768 | 0.002 |
| Yes | 735 (15.5%) | 54 (10.8%) | | |
| Asthma | | | | |
| No | 4,394 (92.4%) | 479 (95.6%) | 6.942 | 0.004 |
| Yes | 362 (7.6%) | 22 (4.4%) | | |
| Cancer | | | | |
| No | 4,480 (94.2%) | 469 (93.6%) | 0.280 | 0.327 |
| Yes | 276 (5.8%) | 32 (6.4%) | | |
| Heart Failure | | | | |
| No | 4,485 (94.3%) | 452 (90.2%) | 13.214 | 0.000 |
| Yes | 271 (5.7%) | 49 (9.8%) | | |
| Renal Disease | | | | |
| No | 4,268 (89.7%) | 418 (83.4%) | 19.617 | 0.000 |
| Yes | 488 (10.3%) | 83 (16.6%) | | |

**Table 4:** Relationship between death due to COVID-19 complications and specific chronic conditions among the samples (N = 5257)

| Chronic Condition | Death | | Chi-square | P-value |
|---|---|---|---|---|
| | No | Yes | | |
| Obesity | | | | |
| No | 273 (98.9%) | 4,711 (94.6%) | 9.905 | 0.000 |
| Yes | 3 (1.1%) | 270 (5.4%) | | |
| Diabetes | | | | |
| No | 1 (0.4%) | 108 (2.2%) | 2.400 | 0.019 |
| Yes | 275 (99.6%) | 4,873 (97.8%) | | |
| Arthritis | | | | |
| No | 244 (88.4%) | 4,224 (84.8%) | 2.662 | 0.058 |
| Yes | 32 (11.6%) | 757 (15.2%) | | |
| Asthma | | | | |
| No | 261 (94.6%) | 4,612 (92.6%) | 1.504 | 0.132 |
| Yes | 15 (5.4%) | 369 (7.4%) | | |
| Cancer | | | | |
| No | 254 (92.0%) | 4,695 (94.3%) | 2.356 | 0.084 |
| Yes | 22 (8.0%) | 286 (5.7%) | | |
| Heart Failure | | | | |
| No | 240 (87.0%) | 4,697 (94.3%) | 24.658 | 0.000 |
| Yes | 36 (13.0%) | 284 (5.7%) | | |
| Renal Disease | | | | |
| No | 212 (76.8%) | 4,474 (89.8%) | 45.715 | 0.000 |
| Yes | 64 (23.2%) | 507 (10.2%) | | |

Diabetic patients have changes in their immune systems with enhanced pro-inflammatory cytokine production as well as impaired IFN-1 production in response to viral infections [28].

Due to the complexity and novelty of COVID-19, there is no data on any specialized therapeutic regimens for COVID-19 patients with diabetes. However, it is crucial to monitor blood glucose levels more frequently and maintain adequate glycemic control as it might decrease the likelihood and severity of infection. Hyperglycemia has proved to be a significant prognostic indicator of mortality and morbidity in hospitalized COVID-19 patients [29]. Hyperglycemic patients who received insulin infusion therapy have shown to have a decreased probability of developing severe illnesses [30].

A study was published by Al Sabah in 2020 in Kuwait aiming to determine potential associations between obesity, diabetes, and serious outcomes in patients hospitalized with SARS-CoV-2 infection in a sample of 1,158 patients. It was found that diabetes was an independent predictor of ICU admission [31]. In agreement with our findings, it concluded that diabetes and obesity were linked to severe COVID-19 outcomes.

Heart failure (HF) is another major health problem affecting up to 2% of the worldwide population. Mechanistically, it is a reduction of cardiac output and/or an elevation of intracardiac pressures caused by a structural or functional cardiac abnormality [32]. The entry of SARS-CoV-2 into cells is facilitated by ACE-2 receptor, leading to the postulation that dysregulation of the renin-angiotensin system may contribute to COVID-19 severity. Heart failure, retrospectively, induces dysfunctional activation of the renin-angiotensin system making HF patients further prone to COVID-19 complications [33]. Another study in China by Peng in 2020 aimed to assess the clinical characteristics and laboratory results of cardiovascular disease COVID-19 patients. It

demonstrated that 57.4% of COVID-19 patients with HF were deceased while 29.44% fully recovered. The study concluded that the proportion of HF patients was considerably greater among the deceased patients [34]. Our findings were consistent with these results since heart failure and COVID-19 complications showed to have a strong association with mortality.

Reports have demonstrated that in cancer patients, the immune system undergoes significant alterations due to treatment regimens, inducing an immunocompromised state and enhancing their susceptibility to infections. However, lack of association between cancer and ICU admissions in COVID-19 patients in our study is consistent with a study conducted in France including 17 hospitals [35].

Bronchial Asthma is a chronic inflammatory disease of the respiratory system with several inflammatory cells' involvement such as eosinophils, T-lymphocytes, mast cells, and other inflammatory mediators. The inflammation causes bronchial obstruction and results in respiratory symptoms [36, 37]. Despite that viral infection can exacerbate asthma [38], it is still unclear whether asthma can lead to deterioration of clinical outcomes or increases the susceptibility to COVID-19 [39]. systematic analysis conducted in 2021 reviewing 57 studies with an overall sample size of 587,280 patients contrasted the association we found between ICU admission and asthma in COVID-19 [40]. However, multiple studies performed during the period between 2020 and 2022 supported lack of association between asthma and mortality in COVID-19 patients [41-43].

One of the comorbidities with uncertainty as to whether it has an association with COVID-19 severity is arthritis. As the effect of autoimmune disease on COVID-19 severity and susceptibility remains unclear, numerous studies demonstrated conflicting results. A study in South Korea with a total of 8,070 COVID-19 patients found that rheumatoid arthritis was not associated with COVID-19 severity [44]. However, a 2021 study in the US concluded that patients with rheumatoid arthritis are at higher risk of developing severe COVID-19 which leads to hospitalizations or death [45].

The pathophysiology of COVID-19 in acute renal damage is complex and not entirely understood. Acute kidney damage in COVID-19 patients can be prerenal or renal. COVID-19 can affect the kidneys through dehydration caused by fever (temperature > 38.5 °C), nausea, vomiting, or diarrhea, which frequently accompany COVID-19 (11% of COVID-19 patients experience gastrointestinal symptoms, which are important pathophysiological processes of prerenal acute kidney damage in COVID-19 patients) [46]. Dehydration can also be caused by fluid displacement into the so-called third space (fluid escapes into the pleural cavities or buildup in skeletal muscles during rhabdomyolysis). Furthermore, hypotension caused by dehydration, infection, or heart failure (as a result of myocarditis or cardiomyopathy) contributes to the pathophysiology of prerenal acute kidney damage in COVID-19 patients [47, 48]. Hirsch *et al.* found that urine sodium content was less than 35 mmol/L in 66% of COVID-19 patients with acute kidney damage, indicating a prerenal cause of acute kidney injury [49]. Infiltration of mononuclear cells into the renal interstitium has been identified in some COVID-19 patients with acute kidney damage [50]. Increased expression of signal transducer and activator of transcription 1 (STAT1) and interferon regulatory factor 3 (IRF3) by interferon (INF-γ) and TNF-α, as well as increased secretion of pro-inflammatory cytokines by macrophages, are among the pathophysiological mechanisms involved in the pathogenesis of acute interstitial nephritis [51, 52].

Although the study's large sample size is considered an advantage for better representation of the population and more accurate results, our study had some limitations. The study was conducted in a single center, which limits the ability to share resources across other centers with different geographic locations. Moreover, detailed data about comorbidity classifications, such as cancer and arthritis, should be considered in future studies to better compare the impact of these diseases.

## Conclusion

To sum up, diabetes, heart failure, renal disease, and obesity all had a significant correlation with ICU admission due to COVID-19. Moreover, heart failure, renal disease, and obesity were strongly associated with mortality from COVID-19 complications. The new COVID-19 epidemic has brought about new challenges to global healthcare systems, emphasizing the need to enhance medical resources at the global level. Furthermore, obesity and diabetes have increased at an alarming rate, and medical professionals have become aware of the impact this has had on the medical care system. As a result, patients with COVID-19 who have also diabetes or obesity must be classified as high-risk groups. Our study highlighted the importance of proper management and monitoring of these patients during the epidemic. Special care and attention must be provided to these patients by medical staff to ensure proper protection of this significant group of COVID-19 patients and prevent further complications as well as reduce the mortality rate. Further studies are needed for better understanding of the mechanistic link between these comorbidities and COVID-19 both at the molecular and cellular level. Furthermore, a more precise estimate of the nation's in-hospital mortality rates will require larger epidemiologic research including many institutions. Our knowledge of the management of COVID-19 in diabetic and/or obese patients requires further studying to improve mortality and morbidity rate. With more thorough analysis, our understanding of COVID-19 prevalence and disease progression in diabetic and obese patients will grow.

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## Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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