

Association of hypertension and diabetes with COVID-19 severity in comparison to healthy patients

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ABSTRACT

Introduction: The coronavirus is a novel pandemic disease that began in Wuhan, China, and further spread globally. Therefore, the aim of this retrospective work was to look at the clinical characteristics and outcomes of diabetic and blood pressure patients compared with a healthy patient who was infected with coronavirus disease (COVID-19).

Methods: Data and outcomes were gathered from medical records and analyzed in 150 patients. The disease is frequently diagnosed via nucleic acid-based viral identification from swabs, sputum, or bronchial alveolar lavage fluid (BALF) using diagnostic reagents such as quantitative reverse transcription-polymerase chain reaction (RT-qPCR). COVID-19 chest radiographs were obtained, and clinical characteristics and outcomes were evaluated. In this study, we analyzed and compared the severity of the disease, its outcome, any associated complications, and clinical laboratory findings in COVID-19 patients between diabetic, hypertensive, and healthy individuals.

Results and Conclusion: According to the findings, COVID-19 can cause a wide range of symptoms, which range from asymptomatic to severe respiratory problems and death. Diabetes appears to be one of the most significant comorbidities associated with a worse COVID-19 result. COVID-19 patients with diabetes (50 (33%) and hypertension (50 (33%)) had more ICU admissions compared with the non-diabetic and non-blood pressure patients (50 (33%)). During the treatment follow-up, 10 (6.6%) of the 150 patients passed away, 140 (93%) were released, 110 (73%) were discharged, and 30 (20%) kept in the hospital. Compared to non-diabetic and healthy COVID-19 patients, diabetic COVID-19 patients had a greater mortality rate.

Keywords: Blood pressure, Clinical characteristics, COVID-19, Diabetes mellitus, RT-qPCR

Introduction

By December 2019, an unsolved outbreak of extreme acute respiratory disease in Wuhan, Hubei Province, China, had been reported. The overwhelming majority of these instances were associated with a wholesale market specializing in human seafood (1). "The Severe Acute Respiratory Syndrome – Corona Virus 2 (SARS-CoV-2)" is constantly changing but still remains poorly understood (2). Quickly, this coronavirus (COVID-19) spread throughout the world and caused severe lung inflammation, acute respiratory distress syndrome (ARDS), cardiac and renal injury (3,4). These

viruses consist of genetic material encased in a protein shell and are microscopic pathogens responsible for common infectious diseases such as the common cold, influenza, and warts, as well as more severe illnesses like Ebola, the Spanish influenza, and COVID-19 (5).

Diabetes mellitus patients are more susceptible to viral and bacterial infections, including those of the respiratory tract (6). The lazy leukocyte syndrome, which represents impaired leukocyte phagocytosis function, is one of the mechanisms responsible for this predisposition (impaired immunity) (7). This emphasizes the possibility of a higher risk of COVID-19 infection in diabetic cohorts. Diabetes mellitus causes microangiopathy, which impairs lung compliance and thus affects gaseous exchange, especially in patients over the age of 65 and with comorbidities such as diabetes mellitus, hypertension, and heart failure (8,9). According to the epidemiological studies, people with diabetes and hypertension are more susceptible to catching some kinds of unusual diseases and are more sensitive to specific consequences when infected with pathogens (10,11).

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Furthermore, many diabetes medications, such as GLP-1 agonists, as well as anti-hypertension medications like Angiotensin-Converting Enzyme (ACE) inhibitors and statins, increase ACE2 expression (12). Therefore, the severity of COVID-19 may be increased in diabetes as a result of increased ACE2 receptor expression in a variety of tissues. Moreover, ACE2 has been reported in both the exocrine and endocrine pancreas (13).

The inflammatory process linked with diabetes, as well as chronically high blood glucose levels, might result in a poor immune response, which can exacerbate infections in diabetic individuals (14,15). In addition, people with high blood pressure are at a higher risk of COVID-19 infections and complications, according to growing evidence (16). Preliminary data from both China and the United States show that high blood pressure is the most frequent shared pre-existing condition among those hospitalized, affecting between 30% and 50% of patients (17).

Several COVID-19 patients possess pre-existing hypertension, and numerous medications can raise the risk of hypertension. Stroke and other heart problems are caused by high blood pressure, which can damage your arteries and reduce blood flow to your heart in patients infected with the virus, which can lead to death in aged patients (18,19). A compromised immune system is one reason why people with high blood pressure, diabetes, and other health conditions are more susceptible to coronavirus. The immune system is weakened by long-term health problems and aging, making it less effective in fighting the infection (20,21).

High blood pressure affects nearly two-thirds of people over the age of 60, resulting in greater mortality rates among patients with diabetes and high blood pressure (22). Both diseases are highly contagious, with incubation periods ranging from a few days to two weeks. Fever, tiredness, and a dry cough are common early symptoms of the disease. Some patients experience a “cytokine storm” during the advanced, more acute phase, which leads to severe consequences such as acute respiratory distress syndrome (ARDS), shock, multiorgan failure, and possibly death, which is caused by both the viral infection and the host response (23,24). Laboratory testing may reveal a low white blood cell count, lymphopenia, hypoxemia, and abnormal liver and renal function (25,26).

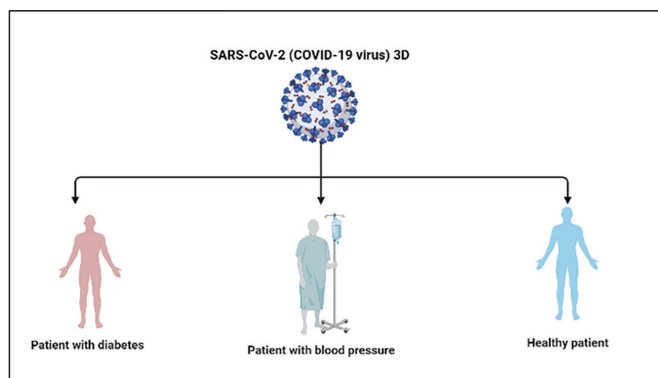


FIGURE 1 - Three separate groups were chosen to be tested in the presence of COVID-19 infection. The diagram was generated using BioRender.com.

The purpose of this study was to assess the prognosis of COVID-19 diabetic patients and high blood pressure compared with the healthy COVID-19 patients, as well as the impact of previous glycemic control. Furthermore, the effect of the generally utilized antidiabetic and antihypertensive medicines on the prognosis of diabetic patients and high blood pressure patients with COVID-19 infection. In this work, we looked at COVID-19 infection in three different groups, including diabetes patients, blood pressure patients, and healthy people, as clarified above in Figure 1.

Methodology

Study Design and Participants

This comparative effectiveness study was carried out at Al Karama Teaching Hospital, Baghdad, Iraq. One hundred and fifty COVID-19 patients with diabetes and elevated blood pressure were admitted to the hospitals. All patients enrolled were confirmed positive for SARS-CoV-2 by physicians who performed quantitative reverse transcription polymerase chain reaction on nasopharynx swab samples, and outcome data were collected prospectively. All of the patients self-reported their hypertension history, blood pressure medications, and diabetes. Cases of COVID-19 that had an epidemiological history, two clinical symptoms, and microbiological evidence were considered established.

Category for determination between severe vs. mild COVID-19 disease

Patients admitted to the intensive care unit (ICU) and given medication for more than 3 days were categorized as extreme cases, whereas other known cases were classified as moderate. Patients with COVID-19 were divided according to their medical history into three groups: patients with diabetes, patients with high blood pressure, and healthy patients. Based on age, gender, and comorbidities, patients without diabetes were compared to those with diabetes and high blood pressure (hypertension, hyperlipemia, and chronic renal diseases).

Laboratory Tests

Clinical and laboratory findings, including signs and symptoms, illness severity of COVID-19 patients were classified as mild, moderate, severe, or critical according to the novel Coronavirus Pneumonia. The Berlin definition of ARDS was used to make the diagnosis. Laboratory data, complete blood count, white blood cell count, lymphocyte count, C-reactive protein (CRP), coagulation profile, D-dimer, urea, and creatinine (Crea), renal and liver function, were retrospectively collected. Clinical symptoms were those present at the time of admission, and laboratory examinations were performed using a blood test. Figure 2 depicts the COVID-19 molecular diagnostic used in this study. The first step in the testing procedure was to collect respiratory specimens such as nasal swabs, sputum, and bronchoalveolar lavage fluid (BALF) from patients who were exhibiting symptoms, after which the specimens were sent for RNA extraction. The quantitative reverse transcription

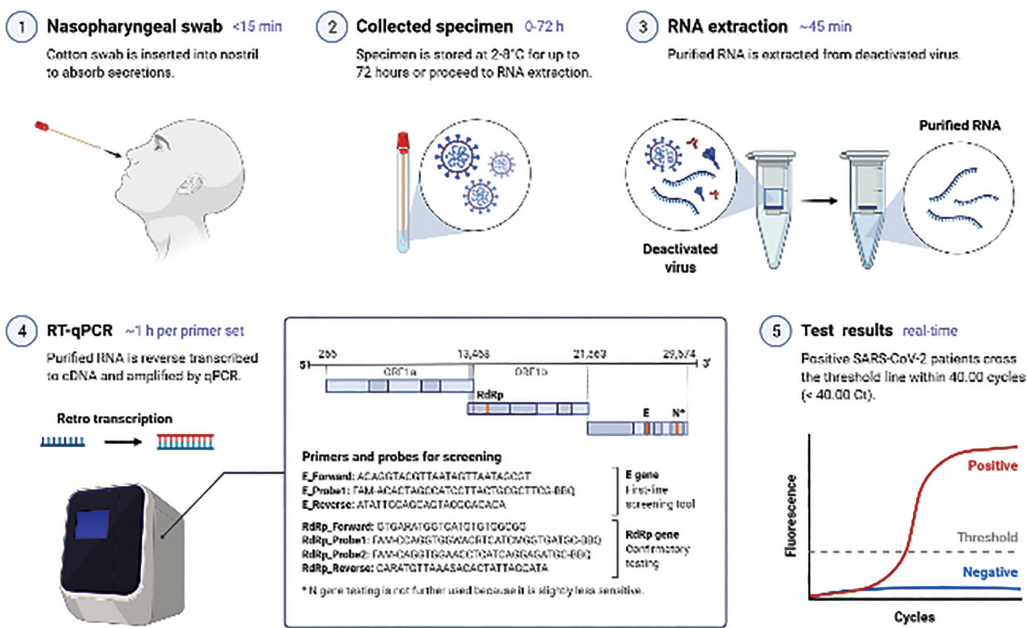


FIGURE 2 - Explaining the molecular diagnosis process for COVID-19. The diagram was created with BioRender.com.

PCR (RT-qPCR) technique was used to analyze SARS-CoV-2, because RT-qPCR can detect the novel coronavirus genetic information (RNA) even if the virus is present in very small amounts.

Results and Discussion

In this work, 150 patients with COVID-19 were included, and the reverse transcription-polymerase chain reaction (RT-PCR) test was used to confirm their infection. They were divided into three groups: 50 of them were found to be diabetics, 50 were non-diabetics, and blood pressure and COVID-19 patients, respectively. Tables 1, 4, and 5 indicate the general information of these patients and the samples collected, as well as the characteristics of the patients with diabetes and high blood pressure. The average length of hospitalization was 2 weeks. The most prevalent symptoms at the start of the infection were fever, dry cough, dyspnea, fatigue, Myalgia/arthritis, and cold. In addition, headache, nausea or vomiting, chest pain, diarrhea, taste loss, sputum production, and smell loss were some of the less prevalent symptoms, and earache and haemoptysis were uncommon.

As shown in Table 1, a total of 50 specimens were taken, which were classified depending on their age, from mild patients to severe diabetic patients. Among them, 5% (2/40) of patients were under the age of 18, 20% (8/40) were between the ages of 19 and 40, 50% (10/40) were between the ages of 41 and 60, and 25% (20/40) were beyond the age of 60. 20% (10/50) of these patients progressed to severe COVID-19. Twenty percent (2/10) of these patients were between the ages of 19 and 40, 30% (3/10) were between the ages of 41 and 60, and 50% (5/10) were over the age of 60. There was a significant difference in the age of severe patients (age 60 years) compared to moderate

patients. The diabetic group experienced more fever, shortness of breath, and fatigue than the non-diabetic group. However, the differences in other symptoms between the two groups were not significant. Diabetes and blood pressure were associated with a higher prevalence of comorbidities such as asthma, cardiovascular disease, and chronic renal disease.

TABLE 1 - Clinical characteristics of diabetic patients infected with COVID-19 (n = 50)

Characteristics	Total (n = 50)	Mild (n = 40)	Severe (n = 10)
Age groups: n (%)			
≤ 18	2	2 (5)	0 (0)
19-40	10	8 (20)	2 (20)
41-60	15	10 (50)	3 (30)
61-80	24	20 (25)	5 (50)
Female	22	16 (40)	3 (30)
male	28	24 (60)	7 (70)
Total	50	40 (80%)	10 (20%)

COVID-19 patients may undergo several hemodynamic changes during hospitalization, affecting their BP level. In case of persistently elevated/fluctuating BP values in the clinic, an ambulatory BP monitoring should be performed to evaluate the hypertension state, assess BP control, and detect other risk features of 24-hour BP, for instance, non-dipping pattern, nocturnal hypertension, and morning surge, as well as assess heart rate response. The optimization of antihypertensive treatment and close follow-up at the hypertension clinic is essential to achieve BP control and avoid hypertension-induced target organ damage in these vulnerable patients.



Also, 50 samples were taken from high blood pressure patients infected with COVID-19. Among them 10 samples were from patients with severe blood pressure as presented in Table 2. 2.5% (1/40) of these patients were under the age of 18, 12.5% (5/40) were between the ages of 19 and 40, 30% (12/40) were between the ages of 41 and 60, and 55% (22/40) were above the age of 60. 20% (10/50) progressed to severe COVID-19. Also, 40% (4/10) were aged 41–60, and 60% (6/10) were older than 60.

TABLE 2 - Clinical characteristics of blood pressure patients infected with COVID-19 (n = 50)

Characteristics	Total (n = 50)	Mild (n = 40)	Severe (n = 10)
Age groups: n (%)			
≤ 18	1	1 (2.5)	0
19-40	5	5 (12.5)	0
41-60	20	12 (30)	4 (40)
61-80	24	22 (55)	6 (60)
Female	24	22 (55)	6 (60)
Male	26	18 (45)	4 (40)
Total	50	40 (80%)	10 (20%)

A total of 50 samples were taken from 40 mild patients and 10 severe patients, as well as from healthy people, as can be seen in Table 3. From these patients, 5 % (2/ 40) were younger than 18, 45% (18/40) were aged 19-40, 35% (14/40) were aged 41-60, and 15% (6/ 40) were older than 60. Moreover, 20% (10/50) progressed to severe COVID-19, 30% (3/10) were aged 19-40, 40% (4/10) were aged 41-60, and 30% (3/ 10) were older than 60.

TABLE 3 - Clinical characteristics of healthy patients infected with COVID-19 (n = 50)

Characteristics	Total (n = 50)	Mild (n = 40)	Severe (n = 10)
Age groups: n (%)			
≤ 18	2	2 (5)	0
19 - 40	22	18 (45)	3 (30)
41- 60	18	14 (35)	4 (40)
61- 80	8	6 (15)	3 (30)
Female	28	24 (60)	2 (20)
Male	22	16 (40)	8 (80)
Total	50	40 (80%)	10 (20%)

Age and Gender

As presented in Table 3, the characteristics of COVID-19 patients with diabetes were classified based on disease severity at the time of admission. Patients with severe/critical COVID-19 were older and had diabetes for a longer period of time than patients with moderate disease. Men made up a higher proportion of hospitalized patients, showing that men are more sensitive to COVID-19 infection, which has been associated with a higher prevalence of smoking in men in several studies. However, current smokers made up a small percentage of COVID-19 patients and there was no significant link between smoking and COVID-19 (27,28).

Patients who had recovered had a lower chance of severe COVID-19 infection, which required ICU and hospitalization, as well as a faster recovery rate from SARS-CoV-2 infection. Diabetes prevalence rises with age in both the general population and COVID-19 patients. COVID-19 patients who also had hypertension had a high average SBP and a lot of SBP/DBP variability throughout their hospital stay, which was linked to in-hospital mortality, ICU admission, and heart failure.

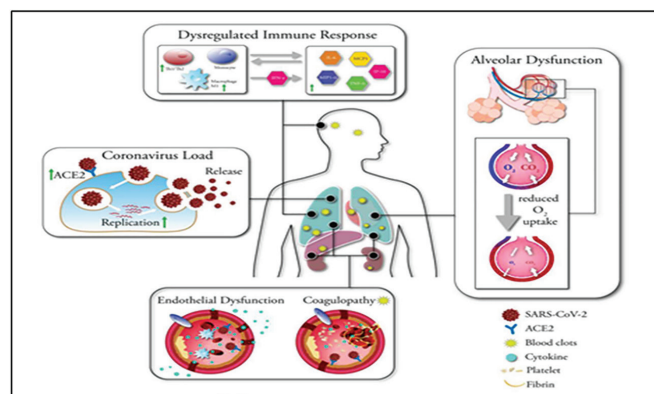


FIGURE 3 - The mechanisms associated with increased COVID-19 severity in individuals with diabetes, the source of the image is (37).

However, the possible pathways by which diabetes increases COVID-19 morbidity and death were described by Muniyappa and Gubbi as follows: improved cellular attachment affinity and viral entry efficiency (29), reduced viral clearance, alveolar dysfunction showed (30), higher sensitivity to cytokine storm and hyper-inflammation (31), and coagulopathy (32). According to a study conducted in Italy during the present COVID-19 pandemic, diabetes mellitus scores high among the comorbidities in COVID-19 patients compared with healthy people (33). Systemic hypertension and ischemic heart disease were also shown to be common, as illustrated in (Fig. 3).

Besides, Angiotensin II receptor blockers (ARBs) medications did not increase the risk of adverse outcomes in hypertensive patients and even provided a benefit in terms of heart failure. This suggests that ARB medications should be continued in COVID-19 patients, and the statistics showed that of the people were hypertensive. Patients on ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) showed reduced mortality rates compared to those taking other antihypertensive medicines. Also, it was found that patients aged 20-40 who had acute respiratory distress syndrome, and some of them died because of no treatment after injury.

Laboratory Findings

Diabetes patients showed greater white blood cell count, neutrophil count, levels of "C-Reactive Protein (CRP)," blood urea nitrogen, lower red blood cell count, hemoglobin level, and lymphocyte count when compared to patients without diabetes, according to laboratory test results. The results indicate that in COVID-19 patients with coexisting hypertension,

maintaining a low and stable blood pressure is ideal for a favorable prognosis. Subsequently, in the absence of other comorbidities, a similar analysis was conducted to assess whether diabetes independently affects disease severity and mortality.

In patients with COVID-19, we discovered a substantial link between D-dimer levels and diabetes. The group with diabetes and blood pressure had significantly higher D-dimer levels (500-2000 ng/mL) than the group of healthy patients, which had levels less than 500 ng/mL.

However, it is found that diabetics had much greater white blood cell counts than non-diabetics. CRP, ESR, and LDH levels were higher than normal in diabetic patients, indicating a more severe inflammatory response. Patients developed bilateral pneumonia and patchy ground-glass opacity, according to chest radiography or CT results (Figure 4). Diabetes patients had a higher white blood cell count than non-diabetics, according to laboratory test results (34).

COVID-19 severity, outcome, and associated complications

Patients were also given plasma therapy and were treated with interferon injections. Acute respiratory distress syndrome (ARDS), shock, and secondary infection were the most prevalent consequences. Among the 150 patients, 10 (6.6%) died during follow-up, 30 (20%) remained hospitalized, and 110 were discharged. Patients with diabetes require more oxygen than individuals without the disease. Furthermore, ARDS was more common in diabetic patients than in non-diabetic and high blood pressure patients. When compared to the non-diabetic group, the diabetic group had a significantly higher prevalence of complications such as sepsis, ARDS, cardiovascular disease, heart failure, and kidney injury.

Diabetes has been detected in COVID-19 as a major predictor of disease severity. Diabetes patients may also be at an increased risk of thrombotic events due to the link between diabetes, clotting factors, and fibrinolysis imbalance.

Furthermore, COVID-19 patients with uncontrolled diabetes had a higher risk of death than other patients. Uncontrolled diabetes, with a focus on hyperglycemia, appears to be a consistent predictor of a worse COVID-19 outcome. Therefore, hyperglycemia may play a negative role in the overproduction of interleukin-6 (IL-6), which has been linked to increased lung infiltration and the severity of COVID-19 (35). The data imply that for COVID-19 patients with coexisting hypertension, having a low and stable blood pressure is indeed the best way to achieve a positive prognosis. The diabetes group had a significantly higher percentage of deaths compared with the blood pressure and healthy patients' groups. This could be owing to the fact that diabetes is linked to other risk factors such as age and obesity. This could possibly be owing to the fact that persons with diabetes have a dysregulated innate and adaptive immune response, as well as persistent low-grade inflammation, making them more vulnerable to cytokine storm. People with diabetes could also be at higher risk for thrombotic events because diabetes is linked to a clotting factor and fibrinolysis imbalance.

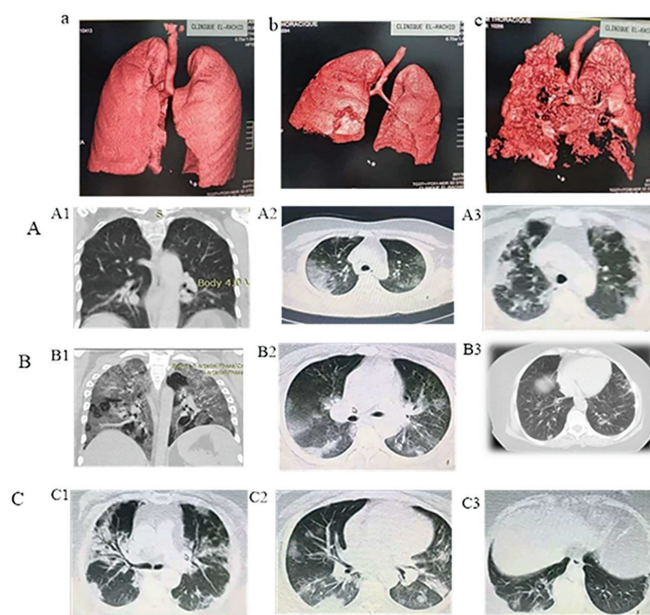


FIGURE 4 - The chest CT images of infected patients with COVID-19 during their hospitalization. **A:** healthy patient. **B:** blood pressure patients. **C:** diabetes patient. **A)** Healthy patients and their ages range from 28 to 50 with mild to severe injury. **B)** Patients with blood pressure with ages range from 35 to 70 with mild to severe injury. **C)** Patients with diabetes, ages ranging from 40 to 75, with severe injury.

Drugs Uses and Vaccines

Patients infected with SARS-CoV-2 are now being treated mostly through the repurposing of available therapeutic medications and a focus on symptomatic symptoms (36). Antibiotics, antiviral medicines, systemic corticosteroids, and anti-inflammatory pharmaceuticals (including anti-arthritis therapy) are widely used to treat ARDS, which is sometimes complicated by secondary infection. In addition to antiviral interferers and antibiotics, COVID-19 has been treated with neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and traditional herbal medicines, as shown in Figure 5. Diabetes patients with COVID-19 should have adequate glycemic control, medical teams should ensure this. This involves a thorough assessment of all possible problems caused by the therapies that will be used for those patients. Insulin therapy is a treatment that is used to treat both forms of diabetes. Although insulin therapy for severe COVID-19 individuals with diabetes has been recommended, it should be determined based on the severity of COVID-19, and those patients should be constantly followed (37).

Vaccines work in a variety of ways to provide protection. However, with every vaccine (Fig. 6), the body is left with a supply of memory T- and B-lymphocytes that will remember how to fight that virus in the future. T-lymphocytes and B-lymphocytes are typically produced a few weeks after vaccination. As a consequence, a person may become infected with the virus that causes COVID-19 just before or shortly after immunization and subsequently become sick as a result of the vaccine failing to provide sufficient protection.

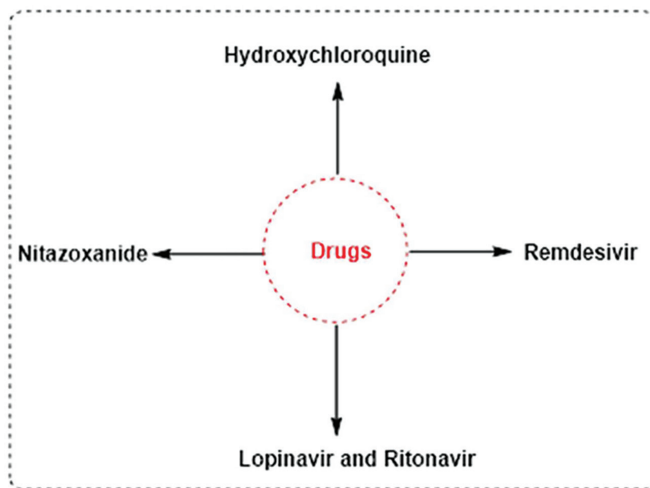


FIGURE 5 - An overview of the drugs used and their mode of action in the treatment of SARS-CoV-2 infection. The diagram was modified from (38).

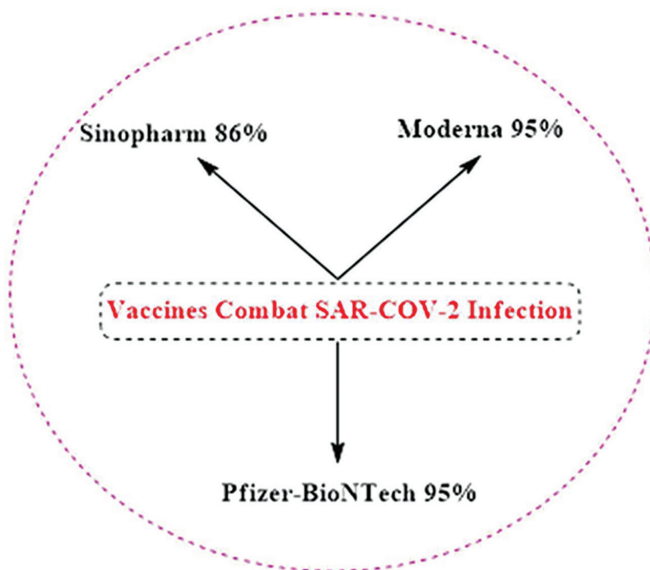


FIGURE 6 - Types of vaccines used to protect humans against SARS-CoV-2 infection. The diagram was adapted from (39).

Symptoms such as fever can occur after vaccination due to the process of building immunity. These symptoms are typical and indicate that the body is strengthening its defenses.

Conclusion

In conclusion, diabetes has been exhibited in studies to be highly prevalent in critically ill patients with severe coronavirus disease, which led to heart attacks in some cases. Diabetes patients who were infected with COVID-19 showed more severe illness and a worse prognosis than non-diabetic patients. After diabetes, COVID-19 patients with hypertension have a considerably higher mortality risk. Furthermore, the study showed that the severely ill patients have higher

maximal viral concentrations and a slower decline of viral concentration compared to mildly affected patients. Diabetes may be a risk factor for disease progression and an increase in COVID-19 patients' in-hospital mortality. The results of this study emphasized the necessity of understanding COVID-19 clinical characteristics in order to put in place effective control strategies.

Disclosures

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Data availability statement: The authors confirm that the data supporting the findings of this study are available within the supplementary materials.

Ethical Statement: Our study did not require ethical board approval because it did not involve human or animal trials.

Author Contributions: All the authors contributed to the conceptualization, writing the original draft, and preparation. The authors have read and agreed to the published version of the manuscript.

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