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A systemic review on basic knowledge of COVID-19 and evaluation of drug-drug interaction impact of COVID-19 on diabetic patients

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Abstract
Background: Covid-19 has spread its wings over the globe, claiming numerous lives. The virus that causes this is by severe acute respiratory syndrome coronavirus-2. Data from numerous nations suggest that people with comorbid diseases have a higher morbidity and death rate (diabetes, hypertension, cardiovascular illness)
Aim: We wanted to offer a better knowledge of the coronavirus disease in persons with diabetes and its management by providing a quick assessment of the general features of the novel coronavirus. In this review explore the possible danger of medication interactions between drugs used to treat covid-19 infection and drugs used to manage diabetes.
Method: We looked for publications with the following keywords in PubMed and Google Scholar databases till 20 May 2022: SARS-CoV-2, COVID-19, infection, pathophysiology, incubation period, transmission. SARS Cov-2 variations, clinical characteristics, diagnosis, COVID-19 prevention, therapy, and review papers about diabetes patients with covid-19.
Result: COVID-19 has a broad clinical range, ranging from mild flu-like symptoms to acute respiratory distress syndrome, multiple organ failure, and death. Based on the evidence, many antiviral anti-inflammatory drugs have been approved by the Food and Drug Administration to treat covid-19 patients even though not knowing the possible drug-drug interaction and the fact that the potential drug-drug interaction of covid-19 drugs in diabetic patients result in worsening glycaemic control. Older age, diabetes, and other comorbidities have all been identified as important predictors of morbidity and death.
Conclusion: The findings of this study show that covid-19 patients with diabetes had a higher risk of severity, due to drug-drug interaction, and that this primary evidence may consideration the severity, morbidity and mortality of covid-19 patients, based on the mechanism of the relationship between anti-diabetic and covid-19 drugs, which are worsening of glycaemic control.

Keywords: COVID-19, SARS-CoV-2, diabetes, SARS-CoV-2 pathogenesis, treatment, antiviral drug, anti-diabetic drug interaction

Introduction

According to WHO data, an epidemic of acute respiratory disease (ARD) in people has been spreading in Wuhan, Hubei Province, China, since late December 2019. The cause is unknown. Additional deep sequencing analysis of patient samples revealed a novel coronavirus (CoV), which the International Committee on Taxonomy of Viruses named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the ARD caused by this CoV was named coronavirus disease 2019 (COVID19) by the World Health Organization (WHO) [1].

CoVs have a huge genome (the largest genome of all RNA viruses) of 27 to 32 kb as well as a variable number of ORFs (open reading frames) that encode non-structural proteins (the first ORF accounts for 67 percent of the overall genome) as well as accessory and structural proteins (the remaining ORFs) [2].

Coronaviruses are the cause of large upper respiratory tract infection epidemics in both children and adults. COVID-19 can induce pneumonia that is both acute and very virulent. It expanded rapidly from China to neighbouring countries. The most prevalent modes of transmission are respiratory droplets and person-to-person contact. COVID-19 takes around 2 weeks to incubate. The polymerase chain reaction approach confirms the clinical diagnosis of COVID19 [3].

Fever, dry cough, shortness of breath, and exhaustion are the most prevalent COVID-19 symptoms. Several individuals have also experienced gastrointestinal issues such as diarrhoea and nausea. The total mortality rate was given, as well as the number of individuals who had underlying diseases (i.e., cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer). COVID-19 mortality and morbidity can be reduced with proper medication. For the treatment of COVID-19, studies have indicated various combinations of chloroquine, lopinavir/ritonavir (Kaletra), ribavirin (RBV), and tocilizumab (TCZ).

The FDA has approved the use of remdesivir (RDV) for COVID-19 as an emergency treatment on May 2, 2020.

Drug-drug interaction (DDI) is one of the most serious issues in pharmacotherapy, since it can considerably exacerbate the drug's harmful effects. The purpose of this paper is to examine the DDIs of covid-19 medications [3]. DDI may cause either a loss of pharmacological effect or an increase in toxicity [4].
Because of the rising number of diabetic patients and the prevalence of COVID-19, it is clear that diabetic patient care must be improved in order to prevent more problems and mortality [5].
It's tough to say how exactly that care should look because there isn't enough research on the association between COVID19 and diabetes. We did a scoping study to offer a quick overview of COVID-19's basic features, as well as a more extensive description and critical assessment of the novel infectious diseases link to diabetes. We anticipate that this study will give useful information for future research and, as a result, better clinical management preventative and treatment suggestions of COVID-19 and diabetic patients.

A Brief Overview of SARS–CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2).
COVID-19, caused by SARS-CoV-2 and first detected in the Chinese city of Wuhan in December 2019, is currently creating worldwide worry. COVID-19 was designated a pandemic by the World Health Organization (WHO) on March 11, 2020. As of March 20, 2022, over 470,094,652 instances have been registered worldwide. As a result, over 6,098,227 people have died in over 225 countries [6].

1 COVID-19 General Characteristics
1.1 Coronavirus structure in severe acute respiratory illness (SARS-CoV-2)
The SARS-CoV-2 structure contained four important viral structural proteins (Figure 1)
The Nucleocapsid protein (N), a helical capsid that contains the viral genome; Matrix/Membrane protein (M) and tiny Envelope protein (E), both of which are involved in virus assembly; and spike Surface glycoprotein (S), which prevents virus entry into host cells [7, 8]. The S, M, and E proteins are all present in the viral envelope, but the N protein is found in the nucleocapsid, which is located in the viral particle's Centre. The M proteins, which control viral shape, are among the most important and abundant proteins in the virion structure. Their presence is critical because, together with the E proteins, they serve a critical role in coordinating virus assembly and the creation of mature viral envelopes. The E proteins are found in trace levels within viral particles and aid in viral escape from host cells. Although the N protein is required for RNA packing into the viral particle during viral assembly, some researchers believe it is also critical for dampening the host immune response and defence mechanisms against infections [10].

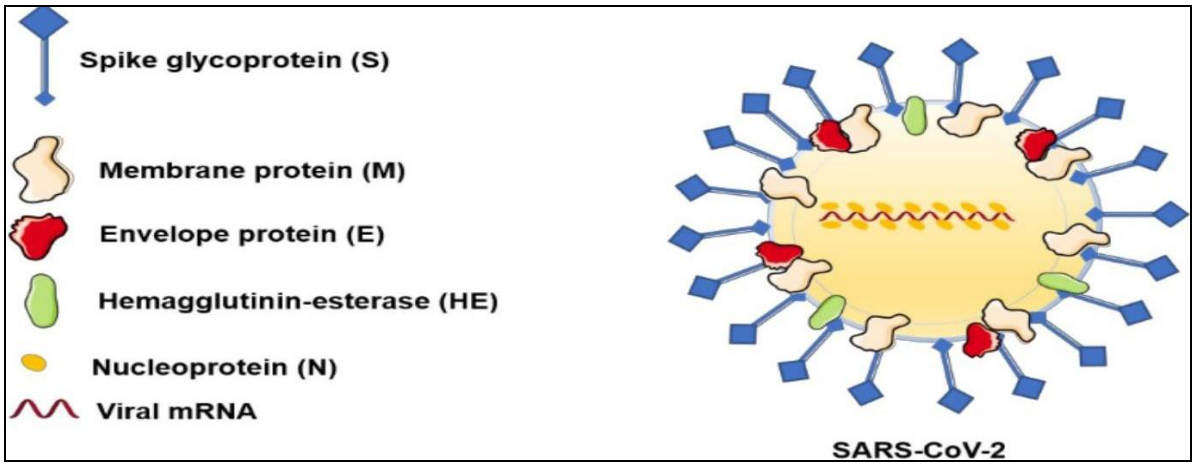

Fig 1: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structure

1.2 Life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
The lifecycle of SARS-related corona viruses (SARS-CoV and SARS-CoV-2) starts with the envelope Spike protein attaching to its cognate receptor, angiotensin-converting enzyme 2 (ACE2). The following factors are required for efficient host cell entry

1. Surface transmembrane protease serine 2 (TMPRSS2) cleavage of the S1/S2 site; and/or
2. Endolysosomal cathepsin L, which is involved in virus–cell membrane fusion at both the cell surface and endosomal compartments. The RNA genome is released into the cytosol via either entry mechanism, where it is translated into replicase proteins (open reading frame 1a/b: ORF1a/b). A virus-encoded protease cleaves the polyproteins (pp1a and pp1b) into individual replicase complex non-structural proteins (NSPS) (including the RNA-dependent RNA polymerase: Rdrp). Virus-induced double membrane vesicles (DMVs) produced from the endoplasmic reticulum (ER) start the replication process, which eventually integrate to create intricate webs of convoluted membranes. The incoming positive-strand genome is used to create full-length negative-strand RNA and sub genomic (sg) RNA. Both structural and auxiliary proteins (simplified as N, S, M, and E) are produced by sgRNA translation and introduced into the ER–Golgi intermediate compartment (ERGIC) for virion assembly. Finally, freshly produced virions released from the plasma membrane are integrated with succeeding positive-sense RNA genomes [11, 12, 13, 14].

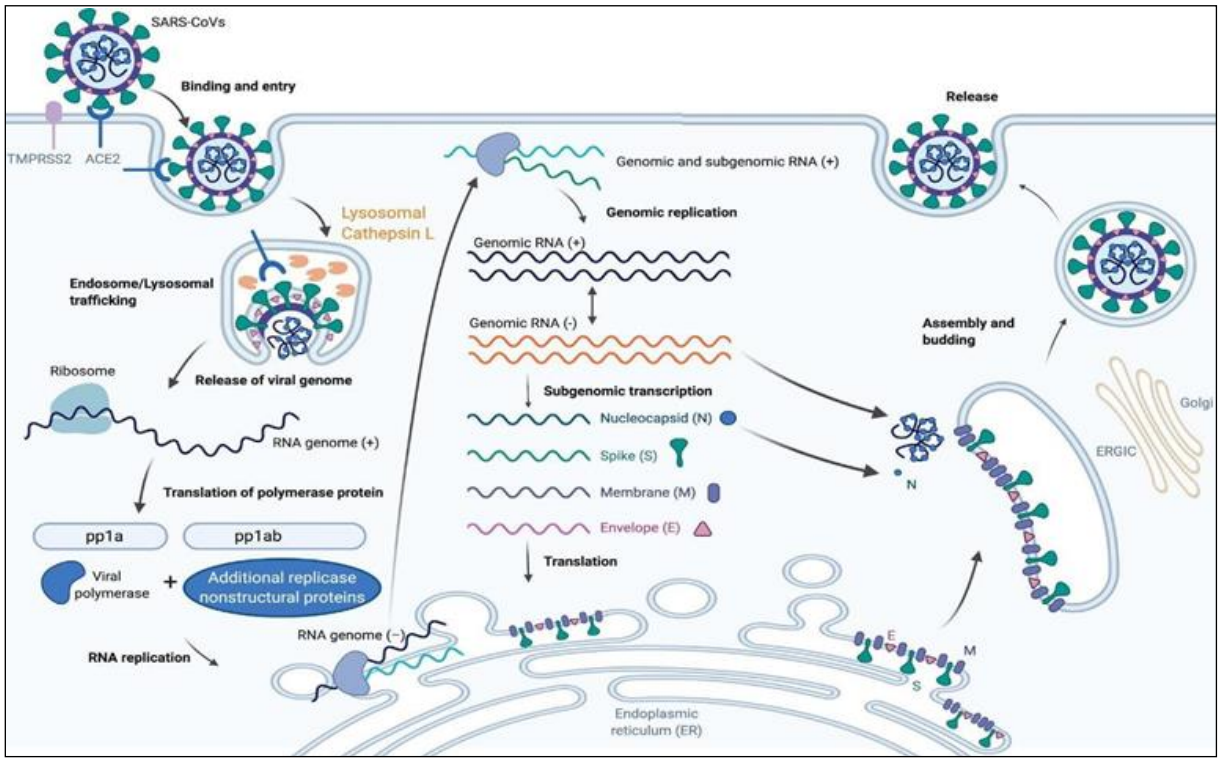

Fig 2: Life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

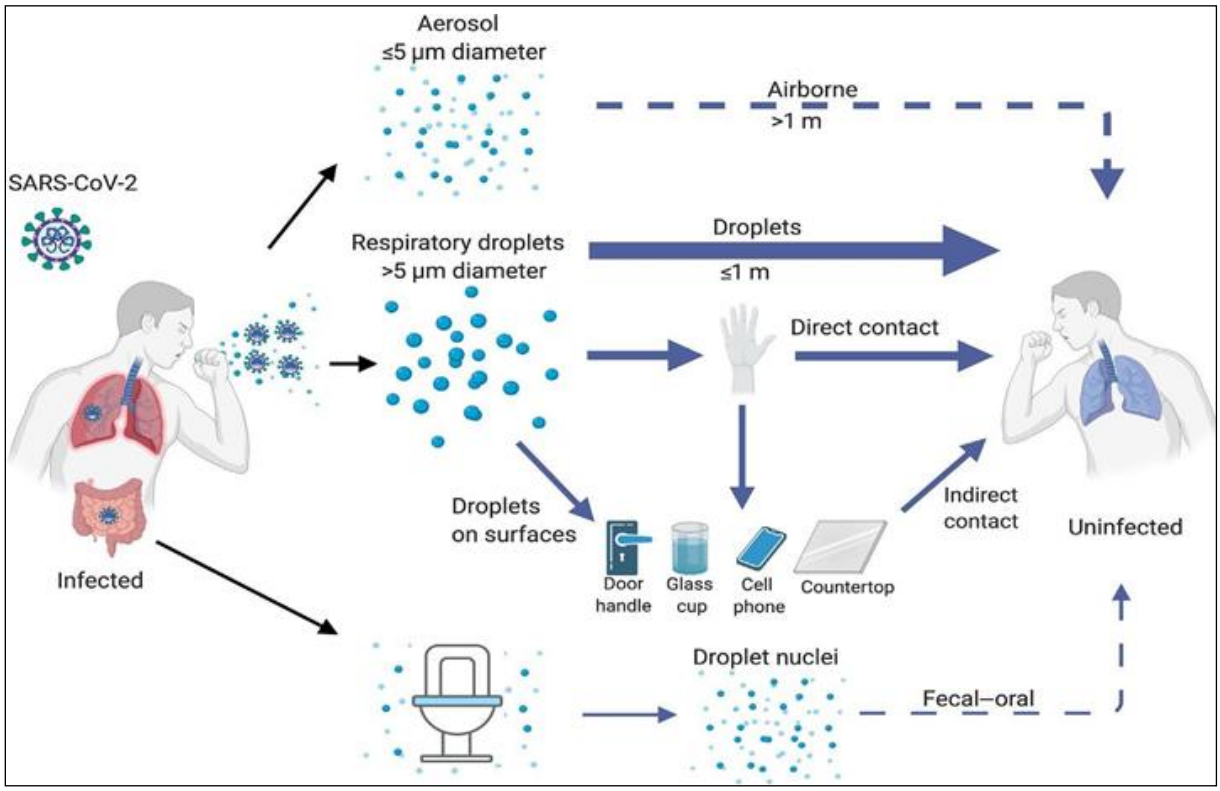

Fig 3: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Transmission- Routes.

2. Modes of Transmission

The majority of COVID-19 patients had direct contact with a local Chinese seafood and wildlife market, suggesting that the predominant method of infection was a common-source zoonotic exposure [15]. SARS-CoV-2 and bat coronavirus (bat CoV) may have shared a same ancestor, according to findings from virus genome sequencing studies [16], despite the fact that bats are not for sale in this seafood market. Later cases were discovered among health care professionals and others who had no previous exposure to animals or who had visited Wuhan, indicating that the disease was spread from person to person [15].

The virus is currently thought to be spread mostly by droplets, direct contact, and aerosols. Figure-3 Droplets transmission can happen when respiratory droplets, such as those formed when an infected person coughs or

sneezes, are swallowed or breathed by people in the vicinity (within about 6 feet). A person can potentially become infected by contacting a virus-infected surface or object and then touching his or her lips, nose, or eyes [17]. Furthermore, it has been demonstrated experimentally that the virus can survive for at least 3 hours in aerosols [18], and that it may be transferred in confined conditions if breathed into the lungs [17]. As a result, during aerosol-generating operations such as endotracheal intubation, bronchoscopy, non- invasive positive-pressure ventilation, tracheostomy, cardiopulmonary resuscitation, and so on, airborne transmission is a potential [19]. The faecal-oral pathway does not appear to be a driver of COVID-19 transmission, may identify the presence of live virus in faeces samples [16].

3. Incubation period

The interval between infection and start of sickness is referred to as the incubation period. The median incubation duration was four days (interquartile range, 2–7) in a study of 1099 Chinese patients with laboratory-confirmed symptomatic COVID-19 [20]. Another research with 181 confirmed cases found that the median incubation time was about 5 days, and that symptoms appeared in 97.5 percent of infected people within 12 days [21]. The US CDC has projected those symptoms of COVID-19 will normally appear 2–14 days after exposure, based on the incubation periods of SARSCoV and MERS-CoV, as well as observational data. As a result, the worldwide standard for monitoring and restricting the mobility of healthy people (quarantine period) is fourteen days [22].

Nomenclature and classification of increasing number of SARS-CoV-2 variants

The WHO has struggled with the naming and categorization of the growing number of SARS-CoV-2 mutations. However, the WHO recommended that emerging SARS- CoV-2 strains be classified as Variants of Interest (VOIs) and Variants of Concern (VOCs) in late 2020. VOIs are variations with mutations that cause alterations in receptor binding, lower therapeutic effectiveness, decreased antibody neutralisation, and a possible increase in disease severity and/or transmissibility. VOCs are also described as variations against which there is substantial evidence of increased trans missibility, increased disease severity, a significant reduction in neutralisation by antibodies produced, and hence a lower responsiveness to therapies and vaccinations [11]. (See Table 1) Additionally, the WHO has advocated the adoption of the Greek Alphabet to uniquely identify each novel SARS-CoV-2 variation in order to establish a common nomenclature that facilitates simplified tracking of each of the developing SARS-CoV-2 variants [23].

Table 1: SARS Cov-2 variants and its impact on transmissibility and treatments

Variant name	Variant classification	WHO label	Country of Origin /Detection date	Attributes
B.1.1.7	VOC	Alpha	United Kingdom/ December 2020	↑Transmissibility (50%) ↑Severity ↑Case fatality No impact on susceptibility to EUA monoclonal antibody treatments Minimal impact on neutralization by convalescent and postvaccination sera
B.1.351 B.1.351.2 B.1.351.3	VOC	Beta	South Africa/ December 2020	↑Transmissibility (50%) ↓Susceptibility to EUA monoclonal antibody treatments ↓Neutralization to convalescent & post-vaccination sera
P.1 P.1.1 P.1.2	VOC	Gamma	Brazil/ January 2021	↓Susceptibility to bamlanivimab/ etesevimab monoclonal antibody treatments ↓Neutralization to convalescent& post-vaccination sera
B.1.617.2 AY.1 AY.2	VOI VOC VOC	Delta	India/ May 2021	↓Transmissibility ↓Susceptibility to EUA monoclonal antibody treatments ↓Neutralisation to post vaccinations
B.1.427 B.1.429 VOC Epsilon California/ July 2020	VOC	Epsilon	California/ July 2020	↑Transmissibility (20%) ↓susceptibility to EUA monoclonal antibody treatments ↓neutralisation to convalescent & post-vaccination sera
B.1.1.529	VOC	Omicron	South Africa/ November, 2021	↑Transmissibility ↑Risk of re-infection

				Deletion in the S gene, leading to S gene target failure (SGTF) in some PCR assays. SGTF can be used as a proxy marker to screen for Omicron.
B.1.525	VOI	Eta	United Kingdom/Nige ria December 2020	↓Susceptibility to EUA monoclonal antibody treatments ↓Neutralization to convalescent & post-vaccination sera
B.1.526	VOI	Iota	United States/ November 2020	↓Susceptibility to bamlanivimab/ etesevimab monoclonal antibody treatments # ↓Neutralisation to convalescent & post-vaccination ser
B.1.617.1	VOI	Kappa	India/ December 2020	↓Susceptibility to EUA monoclonal antibody treatments ↓Neutralization to postvaccination se
C.37	VOI	Lambda	Peru/ August 2020	Unclear data on transmissibility
B.1.621	VOI	Mu	Colombia/ January 2021	↑Transmissibility ↑ Susceptibility to infection
P.3 VOI	VOI	Theta	Philippines/ January 2021	↑Transmissibility ↑ Susceptibility to infection

VOC: Variants of Concerns (VOCs) VOI: Variants of Interests (VOIs)

SARS-CoV-2 Pathogenesis

1. Demography and Clinical Presentation

Despite the fact that COVID-19 has impacted all age groups, the median age appears to be around 47–59 years, with severe cases and non-survivors being older. Although no clear gender bias appears to exist for viral infection, males appear to have a larger tendency for instances [24, 25, 26]. Children and new-borns have been shown to have less instances. Only 2% of those affected were younger than 20 years old, according to a major Chinese study that included 72,314 individuals [27]. In general, common cold CoVs generate moderate URT symptoms and gastrointestinal involvement on occasion (Figure 4). COVID-19 has a wide range of clinical manifestations. Most adults and children have mild flu-like symptoms, but others can quickly develop ARDS, respiratory failure, arrhythmias, abrupt cardiac damage, shock, multiple organ failure, and death [28, 25]. Fever, cough, and dyspnea are the most prevalent symptoms, accounting for 83 percent, 82 percent, and 31 percent of COVID-19 (N = 99) patients, respectively, in one epidemiological investigation [29]. SARS-CoV infections has a long incubation period of 2-11 days in SARS-CoV infections [30]. It can also cause long-term complications including cardiac inflammation [31].

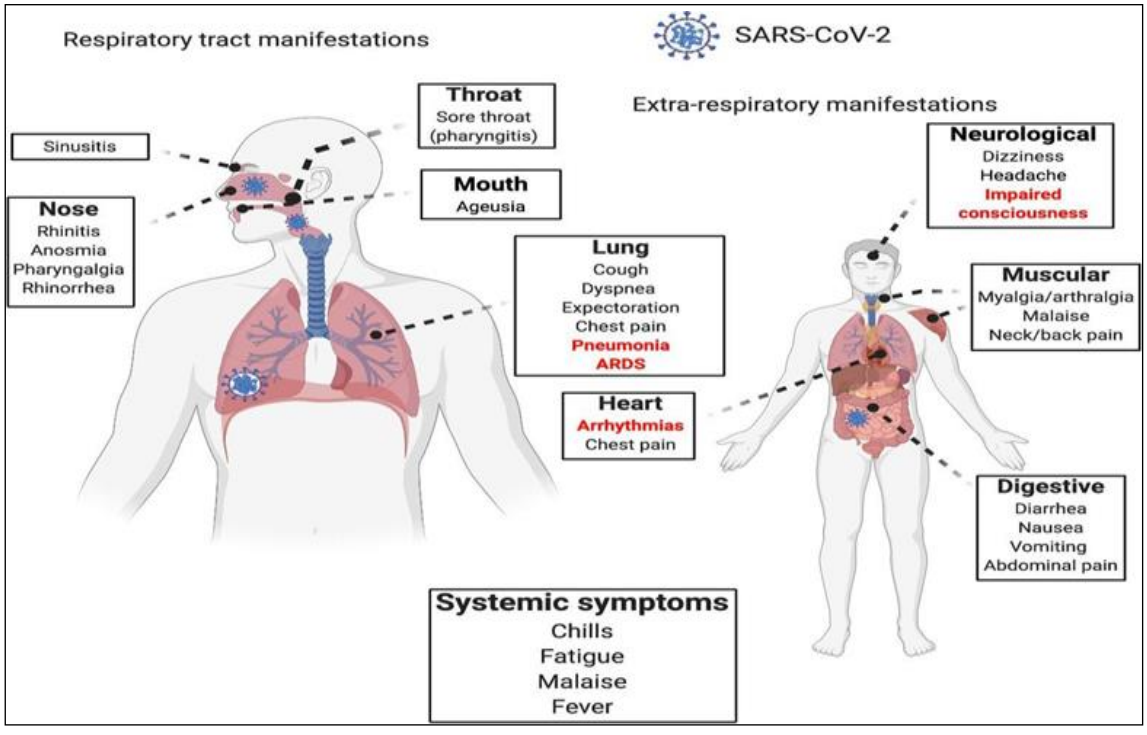

Fig 4: Clinical Symptoms of Coronavirus Infectious Disease 2019 (COVID-19)

Multiple bodily systems have been implicated with COVID-19 symptoms in humans, with varied degrees of onset and severity. If a patient is not asymptomatic, upper respiratory and lower respiratory tract manifestations are generally the most obvious. The signs/symptoms shown in red are over-represented in severe individuals, however typical symptoms can also be found in more advanced patients.

Diagnosis

COVID-19 cannot be diagnosed without a microbiologic examination. Patients who fit the criteria outlined below should be tested for SARS-CoV-2 as well as other respiratory viruses (e.g., influenza, respiratory syncytial virus, and so on). Because capacity for testing for COVID-19 in suspected cases is limited, local health authorities may establish particular criteria for priority cases [32]. Although numerous laboratory tests have been developed, the current standard diagnostic approach for COVID-19 identification is real-time fluorescence (RT-PCR), which detects the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples [32,33].

SARS-CoV-2 detection procedures, according to another research, primarily target particular viral nucleic acids (molecular testing), proteins (antigen testing), or anti-SARS-CoV-2 antibodies (serological testing). Because the detection of viral nucleic acid/antigen/antibody changes at different times during infection, choosing the correct test, right sample, and right timing is critical [34].

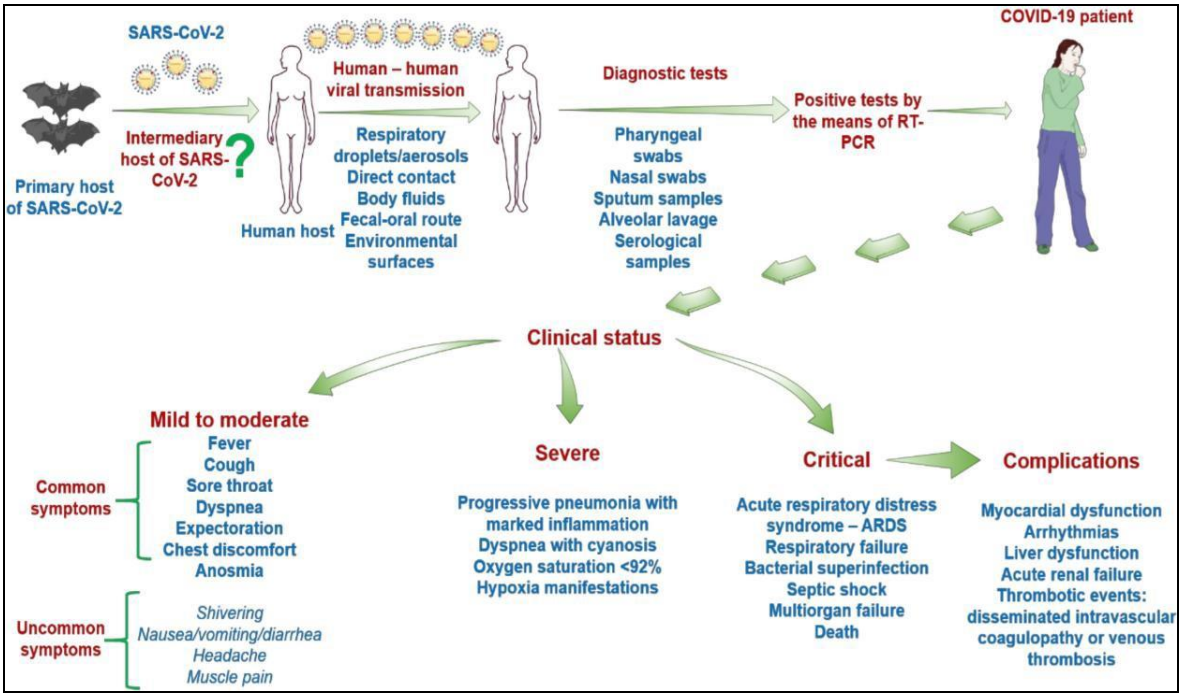

Fig 5: Schematic overview of the steps involved in SARS-CoV-2 infection

From the first contact with the virus until the final phase—death or recovery. This image contains Servier Medical Art elements, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

Drugs Recommended in COVID-19 Therapeutic Guidelines

Initial stage, no specific drug is suggested to prevent or treat the new coronavirus,' according to the WHO [35]. Because there are no recognised treatments or vaccinations for treating COVID-19, many people are resorting to natural therapies from India or China. Many herbs used in Indian Ayurveda have been shown to be effective in the prevention and treatment of corona virus infection.

Three immunity-boosting strategies are recommended by the Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) of the Government of India. The first is to take 10 g of Chyavanprash every day (not suitable for formulation as ODFs due to its high dose), the second is to drink golden milk (milk with turmeric) twice a day, and the third is to drink herbal tea or a drink made by boiling tulsi, cinnamon, black pepper, dry ginger, and raisin, and then adding jiggery (natural sweetener) or lemon juice for taste, if desired – once or twice a day Clinical studies on AYUSH-64, a polyherbal anti-malarial Ayurvedic formulation, have also begun, according to the Ministry of AYUSH [36].

After the discovery of innovative medicines and vaccines at an unprecedented rate, a number of treatment choices are now accessible. Antiviral medications (molnupiravir, paxlovid, remdesivir), anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory pharmaceuticals (e.g., dexamethasone), andimmunomodulators agents (e.g., baricitinib, tocilizumab) are accessible under FDA [37].

Prevention of COVID-19

Aside from enacting public health and infection control measures to prevent or reduce SARS- CoV-2 transmission, the most important step in containing this worldwide pandemic is vaccination to prevent SARS-CoV-2 infection in communities all over the world. The immune system is triggered by vaccination, which results in the creation of neutralising antibodies against SARS-CoV-2. According to the WHO Coronavirus (COVID-19) Dashboard, 11,242,252,352 vaccine doses have been administered, as of 4 April 2022 [38].

The first mass vaccination programme started in early December 2020.As of 12 January 2022, the following vaccines have obtained EUL: [39]

- The Pfizer/BioNTech Comirnaty vaccine, 31 December 2020.
- The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines, 16 February 2021.
- The Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson, 12 March 2021.
- The Moderna COVID-19 vaccine (mRNA 1273), 30 April 2021.
- The Sinopharm COVID-19 vaccine, 7 May 2021.
- The Sinovac-CoronaVac vaccine, 1 June 2021.
- The Bharat Biotech BBV152 COVAXIN vaccine, 3 November 2021.
- The Covovax (NVX-CoV2373) vaccine, 17 December 2021.
- The Nuvaxovid (NVX-CoV2373) vaccine, 20 December 2021

COVID-19 and comorbidities

Although the pathophysiological causes are yet unknown, the majority of severe and fatal COVID-19 cases have been found in the elderly or in patients with underlying comorbidities, such as CVDs, diabetes, chronic lung and renal illness, hypertension, and cancer [40, 41, 42, 43].

A total of 1786 individuals were included in a meta-analysis research on COVID-19 comorbidities, 1044 were male and 742 were female, with a mean age of 41 years old. Hypertension (15.8%), cardiovascular and cerebrovascular disorders (11.7%), and diabetes (9.4%) were the most prevalent comorbidities seen in these individuals. Coexisting HIV and hepatitis B infection (1.5 percent), malignancy (1.5 percent), respiratory diseases (1.4 percent), renal disorders (0.8 percent), and immunodeficiencies were the less prevalent comorbidities (0.01 percent) [44].

Table 2: Clinical data study for the impact of SARS-CoV-2 on comorbidities

Patients (No.)			Age (years)	Comorbidities %				References
All		Male		HT	DM	RD	CVD	
41	30		49.0	15.0	20.0	2.0	15.0	(Yang *et al*., 2020)
137	61		57.0	9.5	10.2	1.5	7.3	(K. Liu *et al*., 2020)
12	8		53.7	25.0	16.7	8.3	33.3	(Y. Liu *et al*., 2020)
138	75		56.0	31.2	10.1	2.9	14.5	(Bai *et al*., 2020)
140	71		57.0	30.0	12.1	1.4	5.0	(J. jin Zhang *et al*., 2020)
9	5		35.2	0	11.1	0	0	(MQ *et al*., 2020)
1099	640		47.0	14.9	7.4	1.4	2.5	(Guan *et al*., 2020)

HT: Hypertension, DM: Diabetic mellitus, RD: Renal disorder, CVD: Cardiovascular and cerebrovascular disorders

Association between COVID-19 and diabetes

Diabetes is one of the most common causes of illness and mortality worldwide. The illness is linked to a number of macrovascular and microvascular problems that have an influence on the patient's overall survival [45]. Clinically, a link between diabetes and infection has long been known [46]. Infections, particularly influenza and pneumonia, are typically prevalent and more dangerous in older people with type 2 diabetes mellitus (T2DM) [47, 48].

1. Impact of COVID-19 on diabetes Mellitus

COVID-19 causes a worsening of glycemic profile in patients with underlying DM, which further weakens the innate immune response and stimulates the production of pro- inflammatory cytokines, resulting in a vicious cycle (Fig. 6).

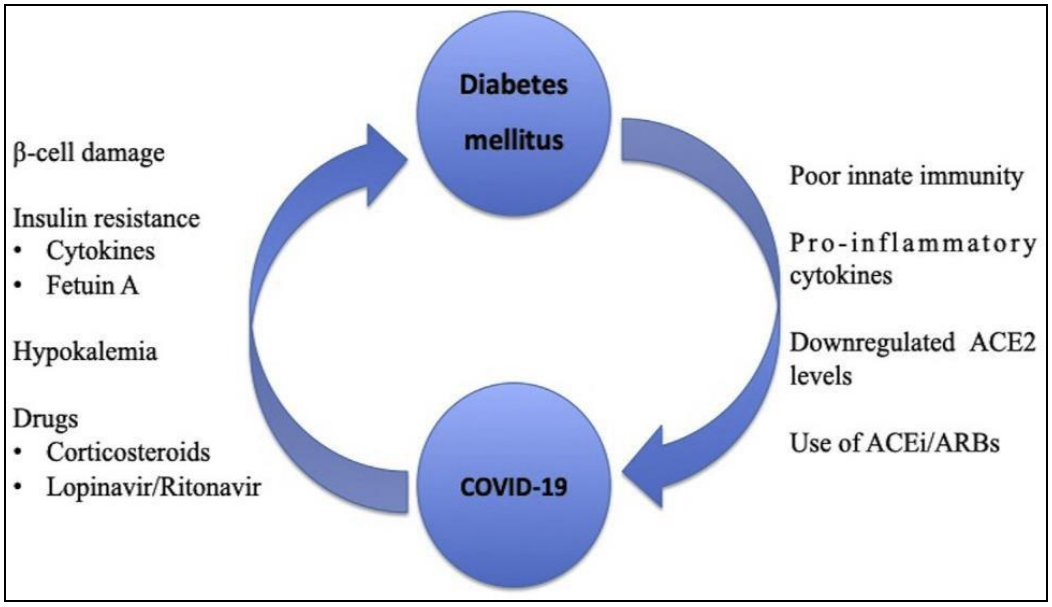

Fig 6

Figure 6: Shows the two-way interaction between the new coronavirus illness (COVID-19) and diabetes mellitus in a schematic form. Diabetes mellitus adds to COVID-19 disease severity by compromising innate immunity, causing an enhanced pro-inflammatory cytokine response, and lowering angiotensin-converting enzyme 2 expression (ACE2). Furthermore, the usage of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARBs) in patients with diabetes has been widely linked to disease severity in COVID-19. COVID-19, on the other hand, worsens glucose control in persons with diabetes mellitus, perhaps due to direct virus-mediated b-cell destruction, increased insulin resistance via cytokines and fetuin A, and hypokalemia. In addition, medicines being utilised in the therapy of COVID-19 as cortico- steroids and lopinavir/ritonavir can potentially lead to dysglycemia.

SARS-CoV-2 necessitates the presence of the ACE-2 receptor, as a point of entry into the host cell's pneumocytes Therefore Overexpression of ACE-2 would make it easier for the coronavirus to replicate. Fill in the blanks and multiply. When viruses employ the enzyme to gain entry to the host, ACE-2 is downregulated in the host tissue, and it can no longer defend itself. Infection in the lungs (Pal, 2020). According to the findings of a recent study, Non- structural proteins from SARS-CoV-2 attack haemoglobin's b1-chain. Iron dissociates from porphyrin, resulting in a decrease in iron concentration. The capacity of haemoglobin to transport oxygen [49].

2. Potential interaction risk between Medications used to treat COVID-19 and drugs used to treat comorbid like diabetic mellitus

Hypoglycemia, lactic acidosis, and poor glycemic control are all possible side effects of antidiabetic medicines and covid therapy drugs interacting. Because drug interactions can cause toxicity or therapeutic failure, which is typical in individuals who take many medications. It is unavoidable to be concerned about medication interactions. Based on the specific patient's pharmacokinetics and pharmacodynamics, these interactions may or may not effect therapy [50].

As a result, health care workers must be aware of the potential side effects related with medication interactions. In this Review, we looked at six databases to see whether there were any probable interactions between COVID-19 therapy medications and commonly given pharmaceuticals for comorbid illnesses like diabetes, which are still substantial mortality risk factors during the COVID-19 pandemic. Biguanides (metformin), sulfonylureas (glimepiride and gliclazide), dipeptidyl peptidase (DPP) 4 inhibitors (linagliptin and sitagliptin), and alpha1 glucosidase inhibitors are all used to treat diabetes (acarbose). As a result, metformin and glipizide were chosen as anti-diabetic medicines to assess for interactions with COVID-19 therapy agents.

Brief details and Mechanism of action of drugs used to treat covid-19 disease

1. Favipiravir

Favipiravir is an antiviral medication that is used to treat influenza. Because there was no standard of care (SOC) available during the 2014 Ebola epidemic in West Africa, it rose to prominence for Ebola treatment. Favipiravir was also shown to be effective in prophylactic and infectious animal models of the fatal Ebola virus [51].

Favipiravir is an experimental medication that fights the SARS CoV-2 virus. It is well-known for its ability to neutralise RNA viruses. It's a pyrazine carboxamide derivative that inhibits influenza virus RNAdependent-RNA-polymerase by converting to ribofuranosyl triphosphate derivate with the help of a host enzyme. It stops viruses from reproducing by inhibiting RNA polymerase, which inhibits the viral genome from being copied [52]. Favipiravir had been approved for a clinical trial in adult COVID-19 patients' therapy on an urgent basis (2020L00005) [53].

Mechanism of action
Favipiravir suppresses viral RNA production by inhibiting RNA polymerase that is reliant on RNA. Because host cell enzymes convert Favipiravir to Favipiravir ribofuranosyl phosphate, it targets influenza virus polymerase without disrupting cellular RNA or DNA synthesis [54].

2. Remdesivir
Is a broad-spectrum antiviral medication that exhibits antiviral activity against SARS-CoV-2 *in vitro* [55]. The US Food and Drug Administration (FDA) approved remdesivir for clinical use in adults and paediatric patients (over the age of 12 years and weighing at least 40 kilogrammes or more) to treat COVID-19-infected hospitalised patients based on findings from three randomised, controlled clinical trials that showed remdesivir was superior to placebo in reducing the time to recovery in adults with mild-to-severe COVID-19 infection. [56, 57, 58].The WHO SOLIDARITY Trial, which involved 11,330 inpatients with COVID-19 who were randomised to receive remdesivir (2750) or no drug (4088) in 405 hospitals across 40 countries, found that remdesivir had little or no effect on overall mortality, initiation of mechanical ventilation, or length of hospital stay [103]. When at-risk non-hospitalized COVID- 19 patients were treated with a 3-day course of remdesivir, they had an 87 percent reduced chance of hospitalisation or mortality than placebo, according to a recently published randomised double blind placebo controlled study [59].

Mechanism of action
Remdesivir is an RNA-dependent RNA polymerase inhibitor (RdRp). It competes with adenosine triphosphate and assimilates into viral RNA chains. RDV-TP (remdesivir triphosphate) does not trigger chain termination right away. Remdesivir is a remdesivir triphosphate (RDV-TP) prodrug [60]. It prevents viral duplication in the infectious cycle by inhibiting the activity of RNA polymerase [61].

3. Lopinavir/ritonavir
Lopinavir (LPV) is an anti-HIV medication that is used in conjunction with ritonavir to treat HIV infection (RTV). Ritonavir increases the half-life and activity of lopinavir by inhibiting its hepatic drug metabolism. For HCV patients, the Infectious Diseases Society of America (IDSA) recommended a ritonavir-boosted combination as first-line therapy [62]. *In-vitro,* LPV/RTV has demonstrated anti-SARS-CoV-2 efficacy by inhibiting the protease in Vero E6 cells [63]. LPV/RTV and ribavirin both showed a risk in SARS-CoV in a comparative research [64]. In addition, SARS patients demonstrated that lopinavir-ritonavir plays a critical role in explaining clinical outcomes [65]. According to the most recent trial, LPV had little or no effect on hospitalised COVID-19 patients, as evidenced by overall mortality, ventilation initiation, and hospital stay duration [66].

Mechanism of action
Combination of these two drug known as Kaletra - Lopinavir; Ritonavir may decrease coronavirus activity by binding to one of the essential enzymes Mpro, according to clinical research. The plasma level of lopinavir is raised due to ritonavir-induced suppression of lopinavir's CYP3A-mediated metabolism [67].

4. Chloroquine, hydroxy chloroquine
Malaria and rheumatic disorders are treated with the aminoquinolines chloroquine (CQ) and hydroxychloroquine (HCQ). They demonstrated COVID-19 activity in Vero E6 cells [68] and suggested it as a key therapeutic option for COVID-19 [69–70]. CQ and HCQ have mild diprotic properties, and they may raise the pH of the endosome during virus-host cell fusion [134]. Several clinical studies with CQ and HCQ on COVID-19 infected individuals have already been conducted in China. One of them revealed that there were encouraging outcomes in terms of slowing disease development [71]. Despite the positive outcomes of this investigation, further clinical data is needed to validate the effectiveness and safety of HCQ in combination with azithromycin. Similarly, in the United States, a postexposure prophylaxis clinical study (NCT04308668) employing an oral dosage regimen was completed. According to the most recent trial, HCQ had little or no effect on hospitalised COVID-19 patients, as evidenced by overall mortality and ventilation start [66].

Mechanism of action
Through its interaction with DNA, hydroxychloroquine sulphate can block specific enzymes. It can stop virus release, virus particle movement, viral protein glycosylation, and DNA and RNA polymerase from working. Through acidity of cell membrane surfaces, it can prevent viral fusion. It also prevents heme polymerization [72].

Antiviral drug and anti diabetic drug interaction
Here metformine and glipizides are chosen to check drug drug interaction study, Interaction effects with medicines used in COVID-19 therapy might include decreased glycemic control, hypoglycaemia, and an increased risk of lactic acidosis. Table 3 summarises the outcomes of the interaction. The medications lopinavir/ritonavir and chloroquine have a significant interaction. Concurrent use of lopinavir/ritonavir with metformin has been linked to an increased risk of lactic acidosis, hence it is not advised in individuals with renal or hepatic impairment.

Because of the synergistic impact, chloroquine increases the hypoglycaemic effect when used with antidiabetic medications. As a result, the risk of hypoglycaemia has been identified as a prospective consequence,
When taken for a long time, nirmatrelvir/ritonavir can change the action of antidiabetic medicines via inducing enzymes. Although the danger is modest, it is suggested that blood glucose levels be monitored during therapy. As previously stated, these interaction effects may or may not be at a greater risk in all individuals. However, it is critical to keep track of the patient's glycemic level since these combinations might cause toxicity or result in treatment failure [73].

Table 3

SI No	Antiviral drug	MOA	Drug-drug interaction with antidiabetic drugs		Effect on glucose level
			Metformin	glipizide	
1	Favipiravir	suppresses viral RNA production by inhibiting RNA polymerase [54]	Moderate interaction	Moderate interaction	The increment in insulin sensitivity and reduction of blood glucose noticeably increces the disease severity and susceptibility to viral infections among affected patients [51]
2	Remdesivir	Inhibits viral RNA polymerase	No interaction	No interaction [73]	Increased blood glucose seen in 7% of patients in remdesivir vs. 8% in placebo group [45]
3	Lopinavir, ritonavir	inhibit 3- chymotrypsin-like protease in viral RNA Processing with antiviral activity against SARS-CoV-2	Major interaction	Moderate interaction [73]	Lipodystrophy [73]
4	Chloroquine, hydroxy chloroquine	Inhibit SARS-CoV-2 entry and viral replication	Major interaction	Major interaction [73]	Improves glucose profile and HbA1c in people with T2DM [73]

Conclusion

the present study describe basic characters of covid-19 and drug drug interaction with anti-diabetic drugs and antiviral drug, management of comorbid condition, drug- drug interaction is one of the challenging issue during treatment because they may be develop either toxicity or therapeutic failure, so safety concern of patients remains mandatory during treatment therefore this review may concern about preventing potential or unpotential effects resulting from drug- drug interaction and drug-disease interaction to reduce the mortality rate.

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