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## ABOUT COVER



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*REVIEW*

# Hypotheses and facts for genetic factors related to severe COVID-19

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## Abstract

Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe coronavirus disease 2019 (COVID-19). Hence, it seems that genetics matters here, as well. Nevertheless, the virus's nature, including its RNA structure, determines the rate of mutations leading to new viral strains with all epidemiological and clinical consequences. Given these observations, we herein comment on the current hypotheses about the possible role of the genes in association with COVID-19 severity. We discuss some of the major candidate genes that have been identified as potential genetic factors associated with the COVID-19 severity and infection susceptibility: *HLA, ABO, ACE2, TLR7, ApoE, TYK2, OAS, DPP9, IFNAR2, CCR2*, *etc.* Further study of genes and genetic variants will be of great benefit for the prevention and assessment of the individual risk and disease severity in different populations. These scientific data will serve as a basis for the development of clinically applicable diagnostic and prognostic tests for patients at high risk of COVID-19.

**Key Words:** Genome-wide association studies; Severe COVID-19; SARS-CoV-2; *ACE2*; *TLR7*; *ApoE*; *TYK2*; *OAS*; *DPP9*; *IFNAR2*; *CCR2*

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**Core Tip:** Understanding what contributes to the development of severe coronavirus disease 2019 (COVID-19) can be of considerable clinical and therapeutic advantage. Severe acute respiratory syndrome coronavirus 2 infection may present with different COVID-19 manifestations, where various host genetic factors influence the viral susceptibility, immune response, disease progression, and outcomes. Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe COVID-19. Hence, it seems that genetics matters here, as well.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19) that emerged in Wuhan, China, in December 2019 and its rapid spread all over the world. COVID-19 was declared a pandemic by the World Health Organization in March 2020. Since then, it has become the leading burden for healthcare[1]. Although healthcare workers have been facing the disease for almost a year, the management of COVID-19 is still a challenge because of the clinical course it may take. On the one hand, about 40% of SARS-CoV-2 infected people present with mild or no symptoms. At the same time, moderate illness is observed in another 40% of them. On the other hand, about 15% manifest with symptoms of pneumonia that requires hospital admission and oxygen support, and 5% develop a critical illness, complicated with respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury[2]. Regarding the World Health Organization data, since the pandemic was declared, more than 2.4 million deaths have been reported to date[3]. Some of the risk factors considered predisposing to a severe course of COVID-19 and higher mortality rates include: Advanced age and smoking, underlying chronic conditions affecting the cardiovascular system, the lungs, and the kidneys, as well as immunosuppression and cancer [4]. However, there is still a lack of predictive features and signatures for severe COVID-19.

Additionally, the clinical course of COVID-19 is closely related to the severity of the inflammatory response conducted by the immune system activation. A complex interaction involving immune cells, cytokines, and mediators leads to systemic immune reactions, which might result in immune hyperactivation or dysregulation. Hence, the cytokine storm is caused by the uncontrolled inflammatory response, and it is crucial for illness's severity and the development of ARDS, multiorgan failure, and fatal outcome[5,6]. Clinical laboratory results might serve useful functions as biomarkers in the management of COVID-19 and prediction of the probable outcome [7]. Laboratory findings in the severe course of COVID-19 usually include low lymphocytic count and hypoalbuminemia, significant elevation of liver transferase enzymes, C-reactive protein, lactate dehydrogenase, ferritin, and D-dimer, along with high levels of some cytokines[8]. However, the influence of various host genetic factors on viral susceptibility, immune response, disease progression, and outcomes has been discussed recently[9,10]. Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe COVID-19. Hence, it seems that genetics matters here, as well. Nevertheless, the virus's nature, including its RNA-genome, determines the enhanced rate of mutations leading to a new viral genome with significant epidemiological and clinical consequences. Given these observations, we herein comment on the current hypotheses about the possible role of the genes for COVID-19 severity. We discuss some of the major human candidate genes that have been identified as potential genetic factors associated with the

different COVID-19 severity and infection susceptibility.

## MAIN CONVENTIONAL RISK FACTORS FOR SEVERE COVID-19

The factors that predispose to a severe course of COVID-19 are of great importance for infection confinement among people from risk groups. Age, gender, and comorbidities, particularly cardiovascular diseases, should be taken as risk factors that depend on one another[11].

In numerous recent research studies, based on the clinical course of COVID-19, age is discussed as a leading risk factor. On the one hand, most of the viral infections affect children, whereas SARS-CoV-2 infection typically occurs in people of advanced age, which might be due to the increased comorbidities as well as to the age-dependent gene expression. In a published study, the death rate among people older than 80 was 14.8%. In contrast, the percentage among those between 70-79.9 years was 8% and 3.6% among those between 60-69.6 years. Owing to the latter, provided the same comorbidities, the younger the age, the lower the death rate is[12].

Gender and its significance as a risk factor are difficult to be evaluated due to the differences in the socio-economical status, lifestyle, and quality of life between men and women. Furthermore, cardiovascular and chronic pulmonary diseases are more frequently observed in men. Moreover, tobacco and alcohol abuse are usual for the male gender and might as well cause respiratory, liver, gastrointestinal illnesses, *etc.* Alternatively, women are commonly involved in caring for sick family members at home and patients at hospital centers, as most nurses are women[13]. Therefore, females are exposed to an increased risk of COVID-19 contraction. Additional factors such as socioeconomic status, menopausal transition, pregnancy and complications during pregnancy, fertility treatment, hormone contraceptive usage, postmenopausal hormone replacement therapy, breast cancer as well as prostate cancer anamnesis are recognized to have an impact on the differences in the COVID-19 course in men and women. Recently, more pieces of evidence have been accumulated about different gender-dependent expression of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin (IL)-12, which play a significant role in the systemic inflammation and cytokine storm[14-16]. According to published data, the death rate is assessed to be 2.5% in the male gender, while in females it is 1.7%. Nevertheless, these values do not provide proof of more severe COVID-19 for men[13].

Additionally, investigations of the laboratory changes in patients with COVID-19 have shown considerably elevated levels of lactate dehydrogenase, alanine transaminase, gamma-glutamyl transaminase, C-reactive protein, IL-6, erythrocyte sedimentation rate, ferritin, coagulation factors (including D-dimer and fibrinogen), along with significant anemia and lymphopenia in patients with accompanying disease in comparison to those without. These findings suggest that underlying comorbidities increase the risk for an uncontrollable inflammatory reaction, hypercoagulation, and excessive release of tissue-damaging enzyme, hence more severe COVID-19[17].

Another critical observation has shown the majority of those diagnosed with COVID-19 had type 2 diabetes. This metabolic illness affects the whole organism and the immune system and, by misbalancing its function, predisposes to infections. Moreover, SARS-CoV-2 disturbs glucose metabolism and increases the insulin requirements of the organism. Thus, diabetes and obesity should be considered risk factors for a severe course of the coronaviral infection as well[17].

Interestingly, during the first wave of COVID-19 in the United Kingdom, younger and less burdened by comorbid illnesses patients were also admitted to intensive care units[18]. These data have only shown us that there might be other factors, including genetic background, related to the severity of COVID-19.

## CHARACTERISTICS OF CRITICALLY ILL COVID-19 PATIENTS

COVID-19 manifests with various or no symptoms. Despite having no symptoms, an asymptomatic person can also be a source of the infection. In symptomatic COVID-19 cases, the symptom onset is after an average incubation period of 5-6 d (up to 14 d). However, there are no specific and pathognomonic symptoms of the illness[5,8]. COVID-19 patients usually present with fever, dry cough, appetite loss, as well as sore throat, nasal congestion, malaise, headache, diarrhea, nausea, and vomiting. Some of the patients experience anosmia and ageusia. People of advanced age may present

with qualitative and quantitative consciousness disorders and lost mobility. Dyspnea and shortness of breath are typically observed in severe cases[19].

Disease physiology includes damage of type 2 pneumocytes, viral pneumonia, cytokine storm, macrophage-activation syndrome, ARDS, disseminated intravascular coagulation, sepsis, and general immune dysregulation, all of which can be combined or present simultaneously[20].

Most of the SARS-CoV-2 infected experience mild to moderate symptoms. Fifteen percent of the patients present with pneumonia that requires hospital admission. According to published data, patients in hospitals develop dyspnea about 5 d after symptom onset. On the contrary, in severely ill patients, the disease may rapidly progress to multiorgan failure[21-23].

A typical complication of SARS-CoV-2 infection is the development of ARDS. The latter is presumed the leading cause of death in patients with COVID-19, particularly among those with underlying diseases and conditions, assessed as risk factors, smokers, and older ones. The immunological events during COVID-19 cause not only severe harm and ventilation collapse of the lung parenchyma, but perhaps, it would eventually lead to complications later in life[5]. Additionally, inflammation destroys the endothelium and contributes to the release of the plasminogen tissue activator that can contribute to COVID-19 associated thromboembolic complications consistent with a hypercoagulable disease. Although the primary cause of death in COVID-19 is thought to be ARDS, the problem associated with bradykinin B1 receptor activation in the lung endothelial cells is another serious cause for severe COVID-19, as well as sepsis-associated disseminated intravascular coagulation[24]. Thromboembolic events are among the most commonly observed complications in COVID-19. Its incidence is higher in critical illness, despite the anticoagulant administration. Thromboembolism may manifest as deep vein thrombosis, pulmonary thromboembolism or may lead to myocardial infarction or cerebral ischemia[21]. We hypothesize that complement overactivation and C1-esterase hyperproduction could be another cause of thromboembolic complication in severe COVID-19.

COVID-19 manifests as a severe illness in patients with underlying chronic conditions, including cardiovascular diseases, hypertension, diabetes, and renal disease. Moreover, the mortality rate is higher among these patients, whereas infants and children experience milder disease, and the mortality rate among them is comparatively lower[21,25,26]. Furthermore, between 3%–29% of the patients develop complications that require intensive care, and the approximate mortality rate is 38%[21,23]. Within a week after the symptoms worsen, pneumonia progresses to ARDS. Along with ARDS, critically ill patients may also develop extrapulmonary manifestations, some of which are cardiovascular, neurological, and gastrointestinal disorders, renal impairment, thromboembolism, sepsis, and septic shock[1,21].

Amongst them, the disorders of the cardiovascular system include myocardial ischemia, myocarditis, myocardial injury, arrhythmias, and cardiogenic shock. Neurological manifestations are observed in about 36% of the patients with severe COVID-19, presented as dizziness, headache, ageusia and anosmia, myalgia, or with more severe manifestations such as acute stroke, consciousness disorders, Guillain-Barré syndrome, meningoencephalitis, and necrotizing encephalopathy, which affects the brain stem and basal ganglia. Acute liver and kidney injuries (31%) are also observed, whereas gastrointestinal bleeding rarely occurs. Elevation of the liver enzymes and the bilirubin level might correlate with the severity of the disease[21].

Critically ill COVID-19 patients may develop sepsis as a result of host response dysregulation to infection, leading to organ dysfunction. It clinically presents with respiratory failure, impaired tissue oxygen supply, tachycardia, hypotension, oliguria, coagulopathy, *etc*. Septic shock occurs in extreme hypotension that is ineffectively treated with infusions and requires vasopressor application[27]. Collectively these observations have shown that a certain genetic background is required.

Besides, the recently published Genome wide association study suggests that individuals with blood group A be predisposed to a severe COVID-19, whereas those with blood group 0 might be at lower risk for developing critical illness[28].

## GENETIC ASSOCIATION STUDIES AND COVID-19 HOST GENETICS INITIATIVE

In recent years, genome-wide association studies (GWAS) have offered the possibility of detecting the most common genetic variants associated with various diseases. To date, a large number of single nucleotide substitutions have been found in different

genes or regulatory regions (polymorphic variants) in the genome that can explain the severity and pathology of these diseases.

In a GWAS that involved patients with severe COVID-19 at seven hospitals in Italy and Spain and a meta-analysis of the two case-control panels, 8582968 single-nucleotide polymorphisms (SNPs) were analyzed. It was identified that the first gene cluster of chromosome 3 covers six genes (*3p21.31-SLC6A20, LZFTL1, CCR9, CXCR6, XCR1,* and *FYCO1*) that aggravate the COVID-19 disease[28]. This study showed the potential involvement of the ABO blood-group system. Other GWAS papers reported results about risk loci in chromosome 19p13.3, 12q24.13, and 21q22.1 associated with severe COVID-19[29]. Some genes belong to the type I interferon pathway and predispose to life-threatening COVID-19 pneumonia. Five common variants were identified (rs3787946, rs9983330, rs12329760, rs2298661 and rs9985159) at locus 21q22.3 within transmembrane serine protease (TMPRSS)2 that showed associations with severe COVID-19[30].

### *Chromosome 3p21.31*

At locus 3p21.31, the association with severe COVID-19 signal spanned the genes *SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6*, and *XCR1*. A candidate in this region is SLC6A20, which encodes the SIT1 (sodium–amino acid transporter 1). It functionally interacts with angiotensin-converting enzyme 2 (ACE2), which SARS-CoV-2 uses for entering the cells[31,32]. The locus also contains genes encoding CCR9 and CXCR6 (chemokine receptors of the C-C and CXC families). They control the cell migration associated with the immune system by trafficking effector cells to the sites of inflammation, especially in the immune response to airway pathogens, including influenza viruses[28,33,34].

A meta-analysis has found a significant association between the severe COVID-19 disease and rs11385942 at locus 3p21.31and rs657152 at locus 9q34.2. Leucine zipper transcription factor-like 1 (LZTFL1) might be the most important, with the rs11385942 variant. LZTFL1 is expressed mainly in human lung cells. It encodes a protein involved in the immunologic synapse with antigen-presenting cells such as dendritic cells[35,36]. Reduced expression of CXCR6 and enhanced expression of SLC6A20 were related to the risk genotype GA of rs11385942. The frequency of the risk allele at 3p21.31 (rs11385942) was increased among patients on mechanical ventilation than those who received only oxygen supplementation. Available database variants suggest that the frequency of this risk allele varies among populations worldwide[28].

### *ABO locus*

A genome wide association analysis has identified the locus 9q34.2 where the rs657152 is located and also includes the ABO blood group locus. A blood-group analysis demonstrated a higher risk for people with blood group A and a protective effect in people with blood group O as compared with other blood groups[28,37]. Variation in the *ABO* gene is the basis of the ABO blood group. Since the 'O' blood group is caused by a deletion of guanine-258 near the N-terminus of the protein, this results in a frameshift mutation and translation of an almost entirely different protein. This 9q34.2 locus has also been identified as a susceptibility locus for severe COVID- 19. Using the combinations of genotypes of three different SNPs, a higher risk among individuals with blood group A and a protective effect of blood group O in the Spanish and Italian analyses was reported[28]. A similar study in China in March 2020 showed that blood group A was associated with a significantly higher risk of COVID-19 compared with the other blood groups[37,38].

### *Human leukocyte antigen (HLA) analysis*

HLA region (6p21.33) was analyzed with GWAS. The spike protein and the nucleocapsid proteins of the SARS-CoV-2 are reported to contain multiple class I epitopes with predicted HLA restrictions. Individual HLA genetic variations can explain different immune responses to different viruses across the population. Nguyen *et al* [39] reported the potential associations between the genetic variants in major histocompatibility complex class I genes (HLA A, B, and C) and the severity of COVID-19. The fewest binding peptides for SARS-CoV-2 were found for HLA-B*46:01, suggesting that individuals with this allele should be more vulnerable to COVID-19 [40]. Conversely, the highly conserved SARS-CoV-2 peptides that are shared among common human coronaviruses were detected for HLA-B:15:03, suggesting that individuals could be protected with T cell immunity[29,39]. Another published report from Italy defined other three HLA alleles-HLA-DRB1*15:01, -DQB1*06:02, and -B* 27:07, which may predispose to a less favorable outcome and severe COVID-19[41].

Preliminary results from China also indicated that the HLA-A*11:01, -B*51:01, and -C*14:02 alleles predispose patients to the worst clinical outcome[42]. Much more studies are needed to understand fully the role of single HLA alleles in COVID-19 severity.

Recently, the HLA system has been under thorough investigation for its crucial role in autoimmunity and infectious disease susceptibility[10,40]. A strong association has been established between the HLA region and autoimmune diseases such as type 1 diabetes (T1D – DR3; DR4; DQB1), multiple sclerosis (MS–DR3), rheumatoid arthritis (RA–DRB1; DR4), Graves' disease (GD–DR3; DRB1*08; B*08; C*07), ankylosing spondylitis (AS–B27;), systemic lupus erythematosus (SLE–DR3; DR8; DR15), Hashimoto's thyroiditis (HT–DR3; DR4), narcolepsy (DQ6), Addison's disease (DR3), and multiple sclerosis (MS-DR15)[43-45]. Nevertheless, a comprehensive explanation of the link between autoimmune diseases and infection susceptibility is yet to be given.

### *TMEM189-UBE2V1*

GWAS in China analyzed 22.2 million genetic variants in 332 COVID-19 patients from the Shenzhen Third People's Hospital. During hospitalization, 64 laboratory analyses were performed for each of the patients to classify their severity condition based on the demographic features age and gender as well as medical comorbidities and treatments[42]. The features of greatest importance that contribute to more severe disease outcomes included decreased lymphocyte and platelet counts, increased C-reactive protein, D-dimer, IL-6, age, and concomitant diseases[29,46]. Obviously, the genes that encode proteins of the immune system are responsible for the disease severity.

The most significant SNP, rs6020298, is located in the intron of the transcript TMEM189–UBE2V1 in the 20q13.13 region. This SNP also affects the genes *UBE2V1* and *TMEM189*. TMEM189–UBE2V1 has been involved in the IL-1 signaling pathway [47]. In COVID-19 patients, IL-1 is elevated, especially in the critically-ill ones who suffer from the cytokine storm[48]. TMEM189-UBE2V1 has a lot of functional associations with the biological processes in different cell types and tissue, but the main function of its protein product has not yet been determined.

### *ACE2 and TMPRSS2*

Depending on virus strains and cell types, coronavirus spike proteins may be cleaved by one or several host proteases-neutrophil elastase (ELANE), furin, cathepsins, TMPRSS-2, and TMPRSS11A[49-53].

The availability of these proteases on the target cells determines whether the virus particles enter the cells through the plasma membrane or endocytosis. SARS-CoV-2 infection of the host depends on two factors: The ACE2 receptor for the viral entry and the TMPRSS2 for the viral spike protein priming[54]. A recently published comparative genetic analysis in different populations has shown possible associations between the coding region variants of ACE2 and TMPRSS2 with COVID-19 severity and outcomes[30].

The *ACE2* gene, located on chromosome Xp22.2, exhibits a high level of polymorphism. The ACE2 receptor is highly expressed in the alveolar type-2 cells in the lung but also in the proximal kidney tubules, liver cholangiocytes, esophagus keratinocytes, myocardial cells, bladder cells, and gastrointestinal epithelial cells[55, 56].

SARS-CoV-2 enters the cell by binding to the ACE2-an integral membrane protein that catalyzes the production of angiotensin 1–7 from angiotensin II[57]. ACE2 is expressed on the vascular epithelium, renal tubular epithelium, and Leydig cells in the testes. In the respiratory system, ACE2 is mainly expressed on type II pneumocytes [54]. After the viral spike protein binds to the ACE2, the S-protein undergoes structural changes through proteolysis by the receptor TMPRSS2[58]. These changes are essential for the fusion between the cellular and viral membrane and the following viral RNA release. In the host cell, the viral genome uses the cellular machinery for new virions formation[6,59]. In the respiratory system, the pneumocytes type II are the target cells that SARS-CoV-2 attacks. Persistent target cell infection leads to ACE2 downregulation and subsequent ACE2 deficiency[59]. The latter prevents angiotensin II conversion to angiotensin I. Angiotensin II excess activates the angiotensin II type 1 receptor and results in vasoconstriction and various physiological effects that include inflammation, fibrosis, thrombosis, and reactive oxygen species (ROS) production. On the other hand, angiotensin has opposite functions by binding to specific receptors, it causes vasodilation, anti-inflammation, anti-fibrosis, anti-thrombosis, and ROS neutralization. That is why ACE2 is considered to provide protection from ROS production in the inflammatory process. Moreover, ACE2 controls the macrophages'

overexpression of tumor necrosis factor-α and IL-6, both playing an essential role in the inflammation[60,61]. Thus, the ACE2 deficiency leads to an imbalance of the renin-angiotensin system, which appears to be a crucial mechanism in COVID-19 pathogenesis[62].

Owing to the fact that the *ACE2* gene is located on the X chromosome, it has been suggested that the higher mortality rate among males should possibly be related to its lower expression. Furthermore, estrogen increases the ACE2 expression and activity in women[63,64]. Renin-angiotensin system balance is maintained by the ACE and ACE2 function; thus, *ACE2* gene variants or their overexpression lead to renin-angiotensin system imbalance resulting in vasoconstriction, hypercoagulation, fibrosis, alveolar cell apoptosis, increased ROS production, and lung damage overall. Common gene polymorphism might alter both *ACE* and *ACE2* gene expression and have a similar effect. It is possible for ACE/ACE2 balance to be influenced by other gene products, for instance, ABO locus, angiotensinogen (AGT), sex-determining region Y gene, SOX3, A disintegrin and metalloprotease 17, angiotensin II receptor type 1, and angiotensin II receptor type 2[10,62,65,66]. Allele frequency variations of the *ACE2* gene in different populations might be due to SNPs. Compared to a global average, the protective variants were found to be of higher frequency in the Asian population, whereas the risk variants were more frequent among the population of European descent[10,63].

Polymorphisms in ACE2 were found to associate with pulmonary and cardiovascular conditions by altering the AGT-ACE2 interactions, such as p.Arg514-Gly in the African and African-American populations[30].

*TMPRSS2* is localized in 21q22.3 and is a key gene in prostate cancer. The product of the gene is plasma membrane-anchored serine protease that participates in proteolytic cascades for the normal physiologic function of the prostate[67,68].

Matsuyama *et al*[69] demonstrated that TMPRSS2-expressing cell lines are highly susceptible to SARS-CoV, Middle East respiratory syndrome coronavirus, and SARS-CoV-2. The susceptibility to COVID-19 could be explained with prevalent polymorphism Val160Met (rs12329760) in TMPRSS2. The harmful effect of the rs12329760 polymorphism in the coding region of the *TMPRSS2* gene has been confirmed by a recent study that used data of the 1000 genome project[70]. The p.Val197Met missense variant that impacts the TMPRSS2 protein stability demonstrated a decreasing allele frequency among the severe patients compared to the higher frequency in the asymptomatic and mild groups. This variant is associated with valine to methionine alteration at the 197$^{th}$ amino acid (p.Val197Met). This results in a decrease in the TMPRSS2 protein stability and ACE2 binding[70]. Moreover, p.Val197Met was previously found to exhibit greater allele frequency in East Asians (0.31–0.41) and Finnish (0.36) but not in South Asians (0.14–0.29) and Europeans (0.17–0.23)[71]. The study of Chinese patients has shown a reduced allele frequency of the p.Val197Met missense variant. That variant affects the stability of the TMPRSS2 protein in the severely infected compared to the mildly infected patients and the general population [42]. The localization of the *TMPRSS2* gene on 21q22.3 suggests that people with Down syndrome are more prone to COVID-19 infection[30].

A recently published study from Italy has identified a number of ACE2 variants with a potential effect on the spike protein stability[72]. Three missense changes may interfere with the protein structure and stabilization, p.(Asn720Asp), p.(Lys26Arg), and p.(Gly211Arg). Two rare variants, p.(Leu351Val) and p.(Pro389His), affect the binding and entry of the spike of SARS-CoV-2[40]. Exome sequencing of COVID-19 patients from Italy for genetic variants of *TMPRSS2, PCSK3, DPP4,* and *BSG* genes identified 17 variants[73].

### *The X-chromosomal toll-like receptor (TLR7)*

TLRs are highly conserved from Drosophila to humans. They mediate the production of cytokines that are necessary for the development of effective immunity. The various TLRs exhibit different patterns of expression, TLR7/8 can identify the single-stranded RNA ssRNA of the virus. The immunoinformatic approach revealed that the SARS-CoV-2 genome has more single-stranded RNA fragments that could be recognized by TLR7/8. These findings suggest the innate immune hyperactivation by SARS-CoV-2 and the possibility to provoke a strong proinflammatory response *via* TLR7/8 recognition and to cause severe lung injury, as well[74].

By whole-exome sequencing of the patients and family members in the Netherlands, there have been identified loss-of-function variants of the *TLR7* gene in X–chromosome (Xp22.2) associated with impaired interferon type I and II responses. The first family possessed a 4-nucleotide deletion [c.2129_2132del; p.(Gln710Argfs*18)], which was maternally inherited; and in the affected members of the second family, a

missense variant [c.2383G>T; p.(Val795Phe)] in TLR7 was observed. Thus, TLR7 seems to be an essential component of the innate immune response against SARS-CoV-2[29,75-77]. The study has also provided an explanation for the higher fatalities from COVID-19 in men than in women. Several immune-related genes have been found in the X chromosome. The males are hemizygotes on the X chromosome that they inherit from their mothers. Therefore, any abnormality in the X chromosome genes is more likely to be expressed phenotypically and have more pronounced immunological consequences. Females carry both a maternal and a paternal X chromosome, and due to X chromosome inactivation, they are functional mosaics for X-linked genes[77-79]. Loss-of-function mutation in the *TLR7* gene gives evidence that genetic errors in interferon (IFN)-I and II pathways contribute to severe COVID-19.

### *Apolipoprotein E (ApoE)*

ApoE is synthesized in brain astrocytes, adipocytes, hepatocytes, and arterial wall macrophages. For their role in lipid transport, ApoE is critical for brain, immune, and vascular functions[80-83].

Dementia, cardiovascular disease, and type 2 diabetes were identified as major risk factors for severe COVID-19 in older individuals in the United Kingdom[84-86].

The *APOE* gene, with its three major isoforms APOE2, APOE3, and APOE4, is encoded by ε2, ε3, and ε4 alleles. The ApoE ε4 genotype is associated with dementia and delirium[85], and the ε4ε4 homozygous genotype are at a 14-fold increased risk of Alzheimer's disease[86].

Using the United Kingdom Biobank data, associations between ApoE ε4 alleles and COVID-19 severity have been found. ApoE homozygotes have a 2.2-fold higher risk for severe COVID-19, independently of major risk factors, and 4.3-fold higher case-fatality after COVID-19 than ApoE ε3 homozygotes[84,85]. The heterozygotes (ε3/ε4) are at lower risk.

If the ApoE ε4 allele has an influence on COVID-19 severity, this may explain the prevalence of severe disease amongst certain ethnicities. According to a study, the allele frequency was 29.5% for homozygous individuals *vs* 12.1% for the Caucasian group[87]. Furthermore, till April 2020, 34% of the COVID-19 deaths in the United States occurred amongst homozygotes, despite the population representing only 13% of all Americans[88]. ApoE ε4 may have multiple effects in COVID-19, which may also be reflected in ethnicity.

### *Interferon-induced transmembrane protein 3 (IFITM3)*

Five IFITM genes (interferon-induced transmembrane proteins) have been identified in humans, *IFITM1*, *IFITM2*, and *IFITM3*, as well as *IFITM5* and *IFITM10* with unknown immunity role[89]. Interferon-induced transmembrane proteins are a family of small proteins that are localized in the plasma and endolysosomal membranes. They inhibit viral entry into the host cells and reduce the production of infectious virions. Many SNPs have been identified in these genes, some of which have been associated with the severity of the viral infection.

*IFITM3* gene variants have been related to distinctive clinical responses to viruses like influenza A (H1N1) virus, Marburg virus, Ebola virus, West Nile virus, human immunodeficiency virus type 1, vesicular stomatitis virus, and dengue virus[42-48]. A human IFITM3 SNP rs12252 C/T was associated with the severity of avian influenza and severe illness with influenza H1N1/09. The IFITM3 rs12252 has also been associated with the progression of human immunodeficiency virus type 1 infection [90]. Two polymorphisms have been found to have an association with a severe COVID-19, rs12252-C and rs34481144-A. The SNP rs12252-C/C in the gene *IFITM3* was detected for the first time in a mild-to-moderate COVID-19 patient from Wuhan, China that required hospitalization but eventually recovered[91]. However, this SNP's prevalence was found to be 26.5% in the Chinese population[92]. The results have shown an association between IFTM3 rs12252 polymorphism and the risk of COVID-19 and patient hospitalization[93,94].

Recently, the *IFITM3* gene rs12252 has been associated with the severity of COVID-19 in a cohort of 80 patients admitted to Beijing Youan Hospital[55,56]. Patients were classified as mild and severe, and CC-homozygotes were among the severe cases. The rs12252 C frequency was significantly higher among Chinese compared to individuals of European ancestry. Another study was conducted to determine the link between IFITM3 rs12252 and the risk of developing severe COVID-19 in a Spanish cohort[93].

The significance of the IFITM3 rs12252-C polymorphism for severe COVID-19 seems to be population-dependent. The second IFITM3 SNP, rs34481144-A, was not reported to influence the severity of COVID-19 in humans.

### *Cathepsin B/Cathepsin L*

SARS-CoV-2 uses ACE2 as an entry receptor[95], and TMPRSS2 for the spike protein priming[54]. ARS-CoV-2 could also use cathepsin B (CTSB) or cathepsin L (CTSL) entering TMPRSS2-negative cells[96].

Three variants in the active sites for CTSB (two missense variants and one synonymous variant) and one missense variant for CTSL were found. Although all missense variants on active sites of CTSB/L are associated with severe disease, their allele frequency (AF) was very low (AF < 0.01%). CTSB has 429 nonsynonymous variants including 51 loss-of-function variants (all with AF < 0.01%). CTSL has 211 nonsynonymous variants including 17 loss-of-function variants[97].

Cardiac damage related to SARS-CoV-2 has been attracting more and more attention. The mechanism of cardiovascular injury caused by COVID-19 has not been fully elucidated yet[98].

The increase in the ACE2 and CTSL expression levels creates a favorable condition for the SARS-CoV-2 to invade the heart, and these patients may experience severe cardiac injury. In addition, cytokine storm in severe COVID-19 can aggravate the myocardial damage[99,100].

### *Piezo-type mechanosensitive ion channel component 1 (PIEZO1)*

There is evidence that membrane proteins such as ACE2 and TMPRSS2 are important in SARS-CoV-2 entry[54,101]. It is indisputable that viral entry is affected by other membrane proteins and lipids[102,103].

Membrane proteins are ion channels[104,105] embedded in the membrane. They allow transmembrane flux of ions such as $Ca^{2+}$, an ion that fulfills regulatory functions in coronaviral mechanisms[106,107].

*PIEZO1* gene encodes a non-selective cation channel that mediates endothelial responses to blood flow. It forms $Ca^{2+}$-permeable non-selective cation channels with the capability to respond to membrane tension caused by fluid flow along the endothelial membrane surface[108]. PIEZO1 indents the membrane in an inverted dome-like fashion and therefore modifies the overall structure of the membrane[109]. There is increasing evidence of its roles in many aspects of endothelial function, such as angiogenesis[100] and pulmonary vascular permeability. It also regulates IL-6, which is a key inflammatory mediator of COVID-19[110].

The genome associate analysis suggests three missense PIEZO1 SNPs (rs7184427, rs6500495, and rs7404939) associated with COVID-19 fatality independently of the risk factors. All of them affect amino acids in the proximal N-terminus of PIEZO1. Human PIEZO1 comprises 2521 amino acids in total, and rs6500495 affects position 83, rs7404939 position 152, and rs7184427 position 250. rs6500495 encodes a switch at position 83 from the reference isoleucine to threonine; rs7404939 encodes the reference proline rather than leucine at position 152, and rs7184427 encodes alanine rather than the reference valine at position 250.

A genome sequence analysis showed that these SNPs vary in prevalence with ethnicity and that the most significant SNP (rs7184427) varies between 65% to 90%. The analysis also suggests that rs7184427 affects a residue that is highly evolutionarily conserved and therefore has functional importance for COVID-19 severity and fatality [101].

### *Interferon-α/β receptor (IFNAR), tyrosine kinase 2 (TYK2), Oligoadenylate synthetase 1 (OAS1), dipeptidyl peptidase 9 (DPP9), and CC chemokine receptor 2 (CCR2)*

Recently, the Genetics of Mortality in Critical Care (GenOMICC, https://genomicc.org/) GWAS, which involved 2244 COVID-19 critically ill patients in the United Kingdom intensive care units, has reported robust genetic predisposition related to essential antiviral host defense and inflammatory mediators, associated with severe COVID-19 inflammatory organ damage[24]. It has shown that the low expression of IFNAR2 or the high expression of TYK2 was related to life-threatening illness. In addition, the high expression of the monocyte-macrophage chemotactic receptor CCR2 correlates with extreme COVID-19 viral spread in the lung tissue.

The GenOMICC study has also revealed that hospitalized COVID-19 patients were affected by alterations in two biological mechanisms: Innate antiviral defenses and host-driven inflammatory lung injury. In the early disease, IFNAR2 and interferon-inducible OAS gene cluster (*OAS1, OAS2, OAS3*) have been considered critical, whereas in the late and life-treating disease, the most important are DPP9, TYK2, and CCR2[24,111].

It is well-established that interferons are essential during viral infection; thus, the increased IFNAR2 interferon expression decreases the chances of serious COVID-19

[111]. Since the *IFNAR2* gene has a protective role for severe COVID-19, it was shown that rare loss-of-function mutations in IFNAR2 were related to severe disease and many other viral diseases[112]. One can speculate that interferon administration may reduce the probability of critical COVID-19. However, this was not confirmed by the studies[113]. Furthermore, IFN deficiency, in particular IFN-I, was documented during SARS-CoV-2 infection. These deficiencies can occur by inherited mutations in the genes encoding key antiviral molecules or by producing antibodies that bind and 'neutralize' IFN-I[114]. The latter is mostly seen in severe COVID-19 patients[115]. Zhang *et al*[116] reported that life-threatening COVID-19 pneumonia was observed in people with mutations in genes previously associated with severe influenza. Mice with defective IFN-I pathway are more likely to die of influenza due to disproportionate inflammasome activation, not just because of high levels of viral replication. Probably, this may explain severe COVID-19 cases if IFN deficiency is presented. These genes that belong to the TLR3 and IFN-I signaling pathways were altered in 3.5% of the tested individuals, resulting in the incapability of producing or responding to IFN-I. Another study by Bastard *et al*[117] showed that a form of autoimmunity may contribute to viral infection susceptibility, such as autoantibodies to IFNs. People with autoimmune polyglandular syndrome type 1 were reported to developed severe COVID-19 pneumonia.

Anti-IFN-I autoantibodies have been found in various diseases. However, the underlying mechanisms for severe COVID-19 include uncontrolled viral replication and spread but also disruption of immune system function as suppression of inflammasome or enhanced cytokines production[118-120]. Regarding the gene cluster encoding antiviral restriction enzyme activators (OAS), they encode enzymes, producing a host antiviral mediator [2′,5′-oligoadenylate (2-5A)]. The latter activates an effector enzyme RNase L which degrades double-stranded RNA[121]. Vietnamese and Chinese studies documented the OAS1 variants role in SARS-CoV susceptibility[122, 123]. Variants in chromosome 19p13.3 (rs2109069) that encodes DPP9 were clinically related to pulmonary fibrosis. DPP9 encodes a serine protease with important immune functions such as antigen presentation and inflammasome activation as well as cleavage of CXCL (a key antiviral signaling mediator)[124].

The association between TYK2, CXCR6, CCR2, and CCR3 expression and severe COVID-19 was also demonstrated[24].

CCR2 for monocyte chemoattractant protein-1 is expressed strongly in the lung tissues, promoting chemotaxis of monocytes and macrophages towards sites of inflammation. In critical COVID-19 patients on mechanical ventilation, CCR2 is overexpressed and detectable in bronchoalveolar lavage fluid samples[125]. Moreover, circulating monocyte chemoattractant protein-1 amounts are related to a more serious disease[126].

Data on the candidate genes associated with severe COVID-19 are summarized in Table 1.

## TRENDS IN THERAPEUTIC STRATEGIES AND THE GENETIC FACTORS SIGNIFICANCE

In serious COVID-19, it is the lung inflammation that mainly leads to fatal outcomes. This is why many efforts were given to identify the possible host genetic variants associated with critical illness[127]. Evidence has shown that hospitalized patients differed significantly from those with mild or moderate diseases. Many distinct disorder phenotypes occur with different symptom patterns. Furthermore, they exhibit different responses to immunosuppressive treatment[114].

Some experts suggest that corticosteroid therapy is detrimental in patients with non-respiratory failure, although there are major benefits in patients with critical respiratory failure[113]. Hence, it is considered that different pathophysiologic mechanisms contribute to critical COVID-19 cases with respiratory failure.

Based on the possible genetic alterations harbored by the critically ill COVID-19 patients, some trends were observed regarding the treatment options. For example, individuals with IFN-I genetic mutations would benefit from interferon treatment, but such therapy would not be of any advantage to people who have IFNAR encoding gene mutations. Moreover, whether patients have IFN neutralizing antibodies, therapies such as IFN-β or IFN-α in early infection may also be beneficial[115].

The *OAS* genes are also a potential therapeutic target. Inhibitors of endogenous phosphodiesterase 12 were shown to augment OAS-mediated antiviral activity[128]. In line with this, TYK2 is one of the targets for janus kinase inhibitors (*i.e.*, baricitinib),

**Table 1 Summary of reported genome wide association studies between human genes and severe coronavirus disease 2019**

| Gene(s) | Polymorphism(s) and genotypes | Chromosome location | Reported COVID-19 associations | Ref. |
|---|---|---|---|---|
| *SLC6A20, LZFTL1, CCR9, CXCR6, XCR1, and FYCO1* | Rs11385942-GA | 3p21.31 | Severe disease (respiratory problems) | [28] |
| *ABO* | rs657152 | 9q34.2 | Higher risk of infection in blood group A and a protective effect in blood group O as compared with other blood groups | [37, 38] |
| *HLA* | a/HLA-B*15:03 and HLA-B*46:01; b/HLA-DBR*15:01 HLA-DQB*06:02 and HLA-B*27:07; c/ HLA-A*11:01, HLA-B*51:01 and HLA-C*14:02 | 6p21.33 | Vulnerable to COVID-19 for HLA-B*46:01 and protective T-cell immunity for HLA-B*15:03 may predispose to a less favorable outcome and severe COVID-19; Preliminary results in the worst clinical outcome in China patients | [41] |
| *TMEM189-UBE2V1* | rs6020289-A | 20q13.13 | Severe disease | [42] |
| *ACE2* | p.Arg514-Gly | Xp22.2 | | [30] |
| *TMPRSS2* | p.Val160Met (rs12329760) | 21q22.3 | Severe disease, vulnerable to COVID-19 with risk factors | [29, 30] |
| *TLR7* | g.12905756_12905759del and g.12906010G>T | Xp22.2 | Severe disease | [29] |
| *ApoE* | rs429358-C-C (e4e4) | 19q13.32 | Severe disease especially with dementia, cardiovascular disease and type 2 diabetes | [84, 85] |
| *IFITM3* | rs12252-C/C | 11p15.5 | Mild to moderate disease (with hospitalization) | [91, 94] |
| *CTSB, CTSL* | | 8p23.1, 9q21.33 | Low frequencies; severe disease with cardiovascular conditions | [97, 100] |
| *PIEZO* | rs7184427, rs6500495 and rs7404939 | 16q24.3 | Severe COVID-19 and fatality, independently of the risk factors | [101] |
| *OAS1, OAS2* and *OAS3* | rs10735079 | 12q24.13 | Severe COVID-19 and critical illness | [24] |
| *TYK2* | rs2109069 | 19p13.2 | Critical illness | [24] |
| *DPP9* | rs2109069 | 19p13.3 | Severe COVID-19; Idiopathic pulmonary fibrosis | [24] |
| *IFNAR2* | rs2236757 | 21q22.1 | Severe COVID-19 and other viral diseases | [24] |

COVID-19: Coronavirus disease 2019.

and anti-CCR2 has also shown safety for other diseases, such as rheumatoid disease. However, all these therapies could be called only experimental[129].

Immunosuppressive agents prescribed to patients with autoimmune diseases might have a beneficial effect on the COVID-19 course in these patients by reducing the risk of cytokine storm. Although we have made detailed literature research, sufficient evidence was not found.

Notwithstanding, the continuous search for appropriate therapy insists on further studies on the genetic factors, their contribution to severe COVID-19, as well as their potential role in the invention of effective treatment.

## CONCLUSION

GWAS contributes to understanding the genetic basis of COVID-19 and potential associations between the virus infection severity and specific gene loci. The global aim is to elucidate the molecular mechanisms and the optimizing of prevention and treatment of SARS-CoV-2 infection. In the last year, research on polymorphic variants or in proximity to the candidate genes has shown a strong, statistically significant association with the severity of the disease. Further study of genes and genetic variants will be of great benefit for the prevention and individual risk assessment and disease severity in different populations. These scientific data will serve as a basis for the development of clinically applicable diagnostic and prognostic tests for patients at

high risk of COVID-19.

However, GWAS has some limitations. The present data may not be fully comprehensive, as well as genotype-phenotype elaboration and corrections cannot be made for all conceivable causes of bias (*e.g.*, cardiovascular and metabolic underlying factors contributing to COVID-19). Further studies regarding the genetic data are warranted, both in terms of their utility for the therapeutic risk profiling of COVID-19 patients and in terms of avoiding the mechanical knowledge of infection pathophysiology.

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*MINIREVIEWS*

# Exploiting epidemiological data to understand the epidemiology and factors that influence COVID-19 pandemic in Libya

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## Abstract

There were only 75 confirmed cases of coronavirus disease 2019 (COVID-19) reported in Libya by the National Center for Disease Control during the first two months following the first confirmed case on 24 March 2020. However, there was dramatic increase in positive cases from June to now; as of 19 November 2020, approximately 357940 samples have been tested by reverse transcription polymerase chain reaction, and the results have revealed a total number of 76808 confirmed cases, 47587 recovered cases and 1068 deaths. The case fatality ratio was estimated to be 1.40%, and the mortality rate was estimated to be 15.90 in 100000 people. The epidemiological situation markedly changed from mid-July to the beginning of August, and the country proceeded to the cluster phase. COVID-19 has spread in almost all Libyan cities, and this reflects the high transmission rate of the virus at the regional level with the highest positivity rates, at an average of 14.54%. Apparently, there is an underestimation of the actual number of COVID-19 cases due to the low testing capacity. Consequently, the Libyan health authority needs to initiate a large-scale case-screening process and enforce testing capacities and contact testing within the time frame, which is not an easy task. Advisably, the Libyan health authority should improve the public health capacities and conduct strict hygienic measures among the societies and vaccinate as many people against COVID-19 to minimize both the case fatality ratio and

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socio-economic impacts of the pandemic in Libya.

**Key Words:** COVID-19; Pandemic; Epidemiological patterns; Potential factors; Prevalence; Libya



**Core Tip:** This review is aimed to explain and show potential reasons for having only 75 confirmed cases of coronavirus disease 2019 (COVID-19) reported in Libya during the first two months following the first confirmed case till hundreds of positive cases everyday in the following months. The epidemiological situation markedly changed from mid-July to the beginning of August as the country proceeded to the cluster phase and COVID-19 has spread in almost all Libyan cities. The Libyan health authority needs to improve its service in order to do better job to control the pandemic and reduce the virus spread within the country.

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## INTRODUCTION

In late December 2019, the etiologic agent responsible for the epidemic outbreak emerged in Wuhan, China, where about 27 cases of acute respiratory pneumonia was reported by the Wuhan Municipal Health Commission[1,2]. The first spread was reported in the Huanan Seafood Wholesale Market, an area that is well known for selling live animals[3]. On 9 January 2020, Chinese investigators were able to isolate and obtain the genetic sequence of the virus in a short period of time, which led to the preliminary identification of this novel virus[3,4]. Later, the disease was diagnosed as coronavirus and named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2). According to serological and phylogenetic analyses, coronaviruses are divided into four genera, named Alpha-, Beta-, Gamma- and Delta-coronavirus[5]. SARS-CoV-2 is a β coronavirus of group 2B with at least 70% similarity in its genetic sequence to SARS-CoV[6-8]. SARS-CoV-2 is the seventh member of the family of coronaviruses that infect humans[7]. Despite the coronavirus having been reported in China in late December 2019 and the first sporadic case reported outside China on 13 January 2020, it was not until 30 January 2020 that the World Health Organization (WHO) declared the outbreak as a public health emergency of international concern. In fact, it took a long time for WHO to then announce the coronavirus outbreak as a pandemic on 11 March 2020[9]. Since then, the coronavirus disease 2019 (COVID-19) has spread and struck many countries with a high case fatality rate while others with a moderate to low case fatality rate. Significantly, variations were highly considered and needed to be explained further and clarified. The epidemiological patterns of COVID-19 are unique all over the world, characterized by a highly pathogenic index and strong socio-economic impacts. However, there is a clear variation with respect to the temporal and spatial distribution of COVID-19 among different countries at the same regional level. These variations may be due to factors that influence the distribution of the disease in the populations, many of which remain unknown[10].

Still, there is a little knowledge about the epidemiology and course of COVID-19 in Libya. Therefore, in this review, we have explored the relevant data to understand the epidemiological patterns of COVID-19 in Libya.

## EPIDEMIOLOGICAL PATTERNS IN LIBYA

The first confirmed case of COVID-19 in Libya was reported on 24 March 2020; the affected was a man in Tripoli who had a history of travelling to Saudi Arabia[11]. Since

then, many infected cases were reported with mild clinical signs. It is well known that COVID-19 seems to affect some people more critically than others — some people experience only mild symptoms while others end up hospitalized, requiring intensive care and ventilation[12-14]. During the first two months following the first confirmed case, the epidemic curve was flattened with only 75 confirmed cases[15]. In fact, the low number of reported cases during the months of March, April and May could be attributed to the various reasons provided in the study of Rayes *et al*[15].

The first confirmed case in Libya was on 24 March 2020. The next day, there were huge differences between the total number of confirmed COVID-19 cases reported in Libya and those of the neighbouring Arab countries (Figure 1).

The epidemic curve of COVID-19 in Libya could have been influenced by the travellers returning from different countries (Figure 2).

The distribution of the number of daily cases, total cases and deaths of SARS-CoV-2 reported between 24 March and 22 April 2020, *i.e.*, over a 30-d period, with about 1181 samples screened by reverse transcription polymerase chain reaction, revealed 59, 1 and 15 confirmed cases, deaths, and recovered cases respectively (Figure 3). However, the epidemiological situations of the neighbouring countries were highly variable and significant in comparison to the confirmed cases reported in Libya (Figure 1).

The first confirmed case of COVID-19 in Egypt was on 14 February 2020, in Algeria on 25 February 2020, in Morocco on 2 March 2020, in Tunisia on 4 March 2020 and in Libya on 24 March 2020; however, the disease pattern was different for each country [16].

In Libya, there were 9 and 13 confirmed cases of COVID-19 reported on 14 and 15 April respectively, clearly indicating the presence of asymptomatically underestimated active cases before this time[17,18]. Consequently, on 16 April 2020, following the recommendation of the Scientific Advisory Committee (SAC), the Libyan authorities imposed a complete lockdown for one week, starting from 17 April 2020. Indeed, the early lockdown and various precautionary measures that were taken by Libyan authorities were highly significant in preventing the transmission of the virus among the populations.

Several precautionary measures have been implemented by Libyan authorities following the recommendation of SAC, including the closing of schools, cancelling of all festivals, closing of airports, and lockdown of most commercial private industrial units. These precautionary measures were taken for COVID-19 control and prevention, as recommended by WHO, to reduce the exposure and transmission of virus infection among the population.

Thus, the country attempted to prevent the spread of the infection and minimize the risk of virus transmission. Further, the political instability of the country and civilian war indirectly impacted the prevention of virus transmission at the beginning of COVID-19 in Libya.

Despite the precautionary measures taken to minimize the possibility of transmission of the virus from travellers coming from infected countries, there were many confirmed cases of SARS-CoV-2 among those who returned to Libya. These travellers belong to different regions of the country, which resulted in a change in the epidemiological situation of the disease and led to an increase in the number of cases recorded in different cities.

The first batch of returning flights to Libya was on 5 May 2020, during which time the epidemiological situation of COVID-19 in Libya was stable, and the number of confirmed cases started to increase by the end of May (Figure 4).

## COVID-19 IN THE SOUTH OF LIBYA

On 26 May 2020, two cases (36-year-old male and 55-year-old female) of COVID-19 were reported for the first time in the southern region of the country (Sabha province). These cases might be linked with the history of the travellers returning from countries highly affected by COVID-19. However, according to the National Center for Disease Control (NCDC), the COVID-19 cases that were reported in Sabha were found to have resulted from contact with a woman who had been suffering from respiratory symptoms and died on 26 May 2020. In fact, there are two potential pathways for the entrance of disease to the south of Libya: first, the return of travellers from infected countries; and second, from asymptomatically infected immigrants crossing the southern Libyan border from the neighbouring countries. It took only one week, *i.e.*, from the end of May to the beginning of June, for southern Libya to report 80 new confirmed cases of COVID-19. Therefore, the epidemiological patterns of COVID-19 in

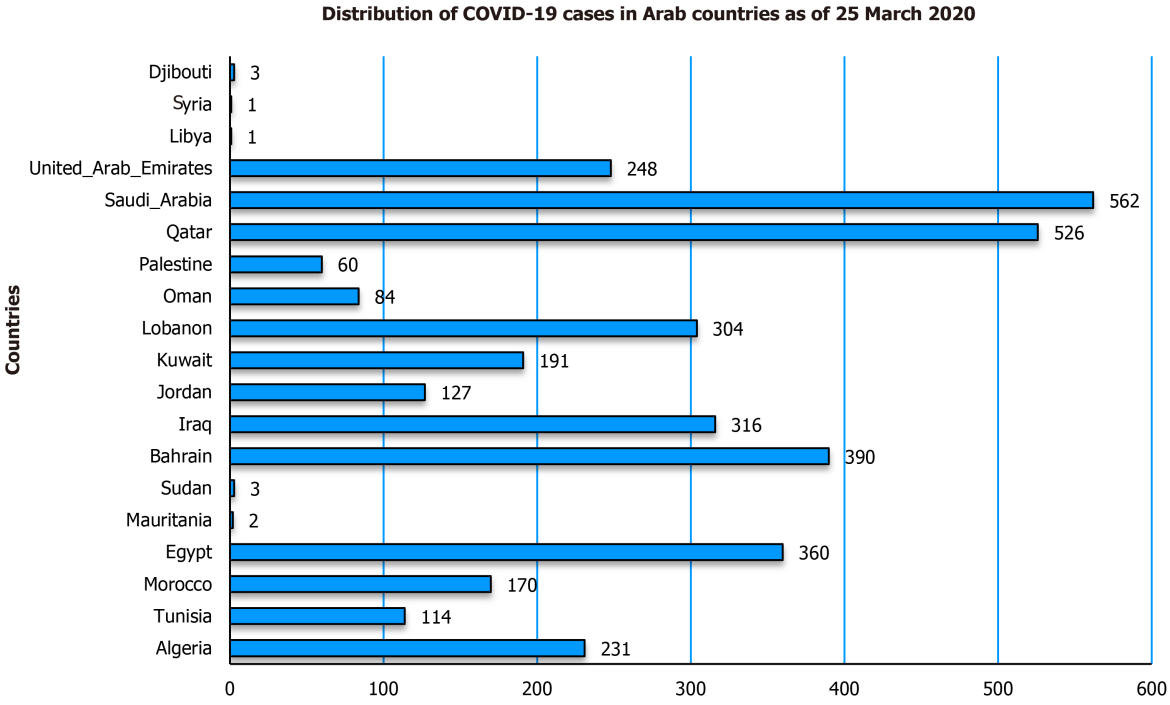


**Figure 1 Distribution of coronavirus disease 2019 cases in Arab Countries as of 25 March 2020.** COVID-19: Coronavirus disease 2019.

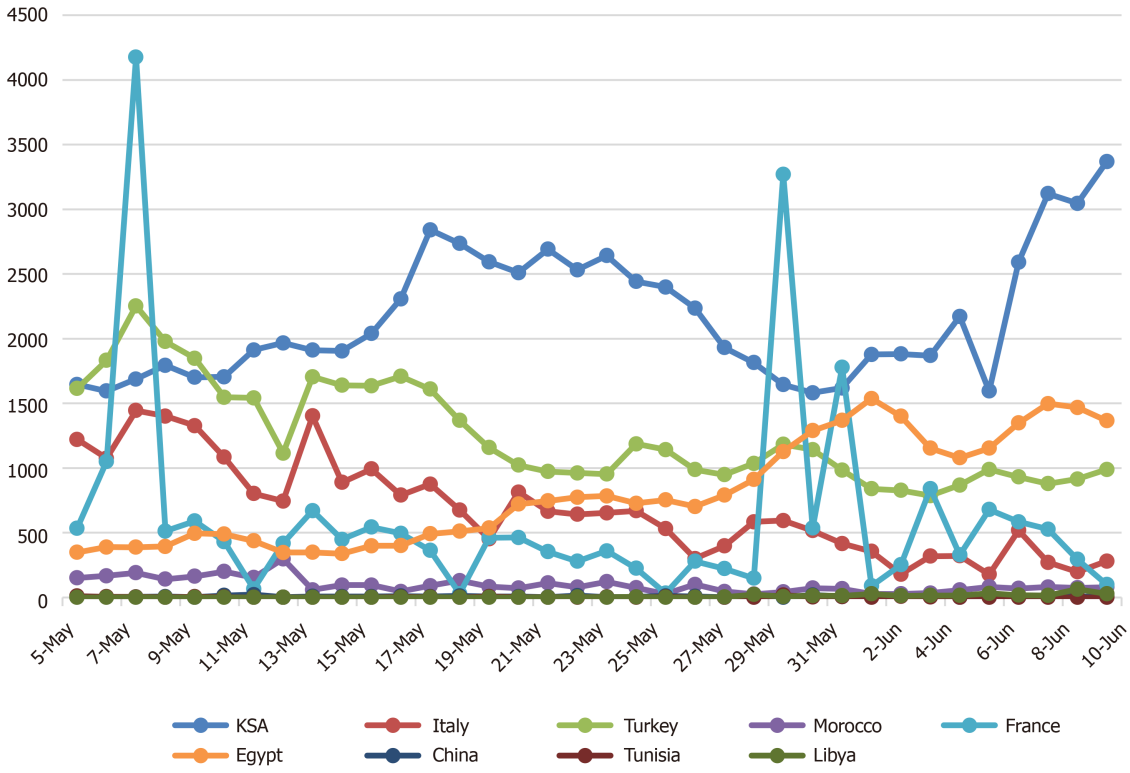


**Figure 2 Distribution of coronavirus disease 2019 cases as of 5 May 2020 (in some countries with a history of being linked with Libyan travellers).**

southern Libya, especially in the Sabha province, were totally different from the Tripoli area and the rest of the Libyan region. For the given period, the WHO published an estimation of R0 to be 1.4-2.5 in the southern region (Sabha), which was higher than that of Tripoli. Expectedly, a high number of COVID-19 confirmed cases reported in the southern region were attributed to multifactorial determinant causes correlated to the social lifestyle of the people in the area, which included unrestricted

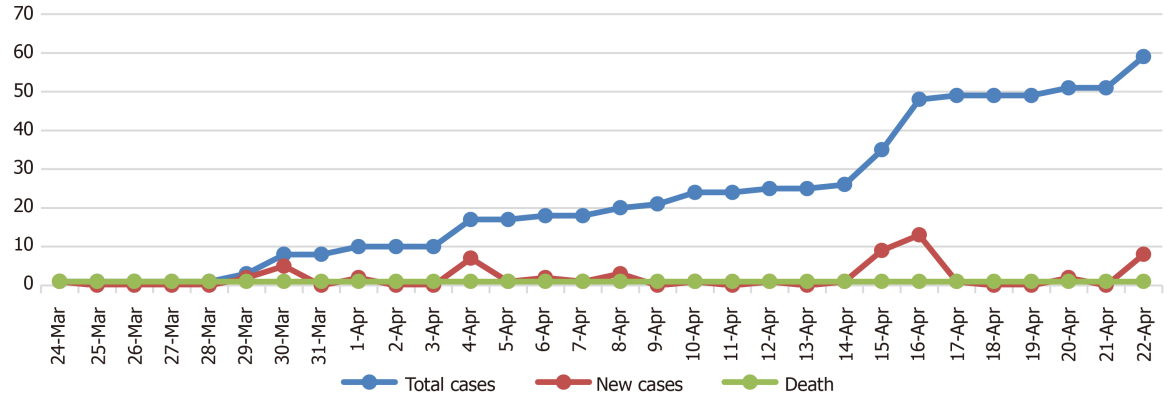


**Figure 3 Distribution of coronavirus disease 2019 total cases, new cases and deaths from 24 March to April 2020.**

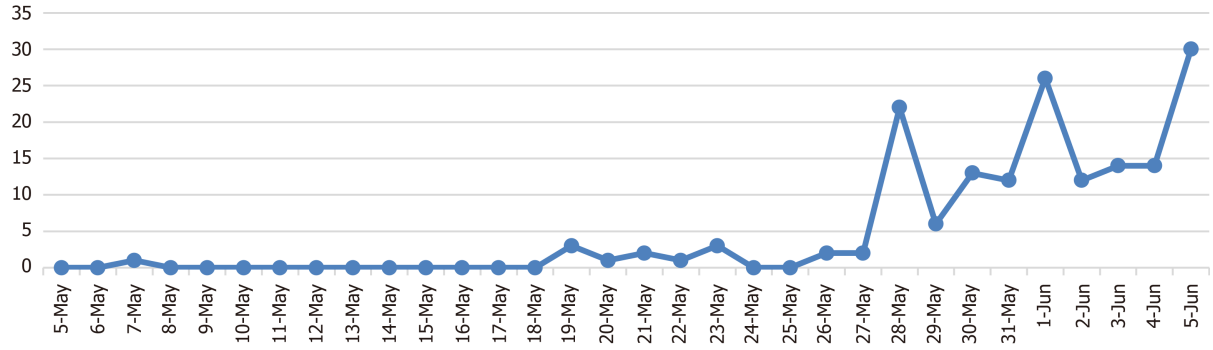


**Figure 4 Daily reported positive cases of coronavirus disease 2019 in Libya as of 05 May 2020.**

transitional movements between small villages and cities of the south. Additionally, weak quarantine measures that led to the easy movement of people from known infected areas to others without control from the authorities was another contributing factor. Consequently, on 28 May 2020, the Libyan authorities decided to block all the administrative borders of Sabha city and impose a lockdown and curfew within the city for seven days.

The return of Libyan travellers from high-risk areas was considered the principal factor for the entrance of COVID-19 into the southern region, despite the measures taken by the Libyan authorities to minimize the likelihood of the virus' entrance into the country. Over the previous years, various transboundary viral diseases of public health and socio-economic importance, including the rift valley fever, were reported in the southern region of the country[19,20]. Further, despite the period of pre-quarantine measures and the quarantine throughout the pandemic, there was uncontrolled transportation between the cities and within the cities of the country, which potentially influenced the positive test rate of COVID-19. According to the CDC, Libya, the individuals who were COVID-19 positive, as reported in different Libyan cities, had a history of traveling to the southern region. At the beginning of June 2020, 30 of the 62 confirmed cases of COVID-19 were linked to people with a history of traveling to infected countries.

## CLUSTER PHASE

Predictably, the epidemiological situation markedly changed from mid-July to the beginning of August, and the country proceeded to the cluster phase. There was an increase in the testing capacities by mid-July; consequently, the positive test rate increased as well. The average daily positivity rate from mid-July to August was estimated to be 14.54% (Figure 5A and B), while throughout September this rate was

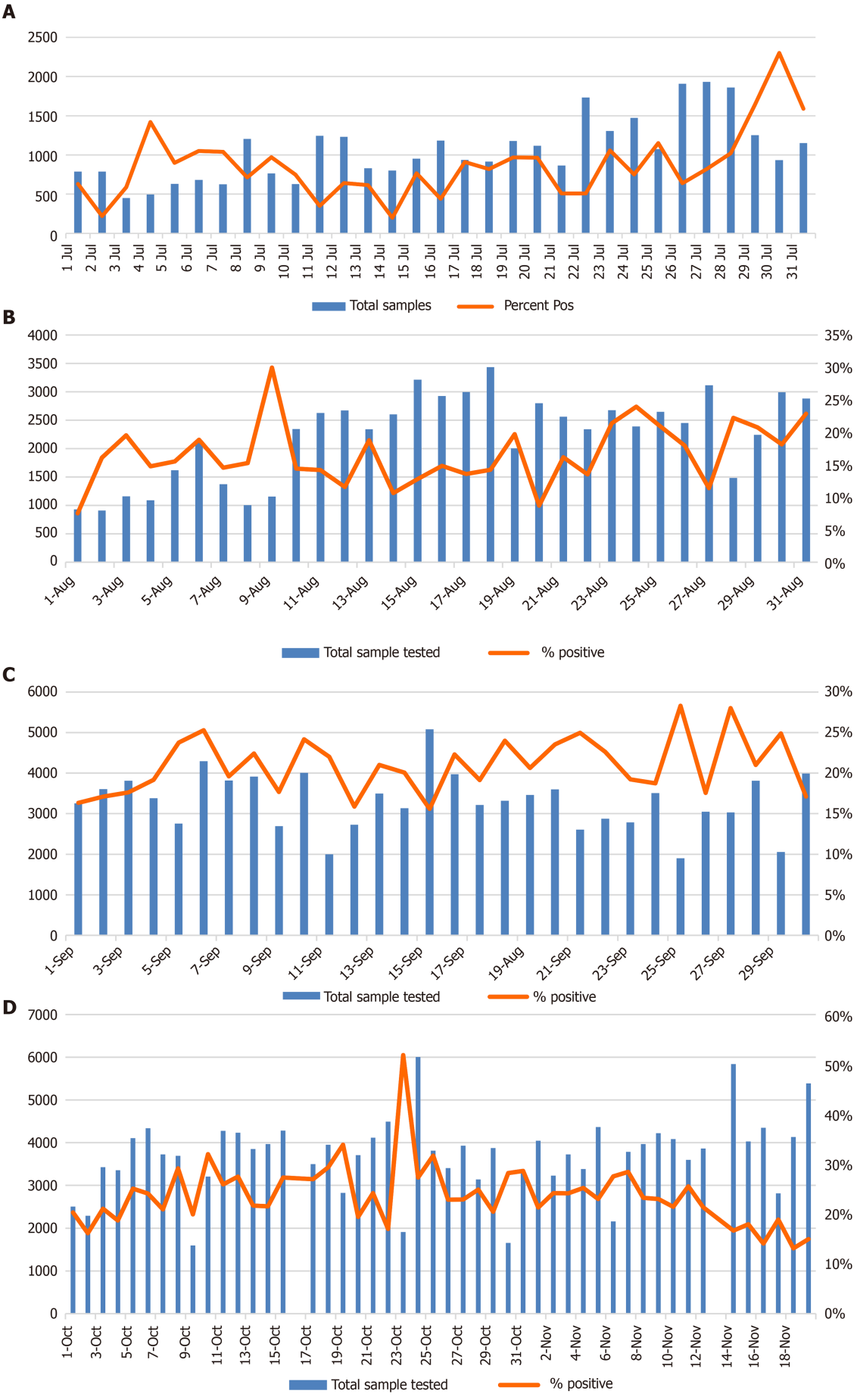


**Figure 5 Percent of positive coronavirus disease 2019 cases correlated to the total of samples tested in Libya.** A: During July 2020; B: During

August 2020; C: During September 2020; D: During October and until 19 November 2020.

estimated to be 21% (Figure 5C). The average positivity rate from October to 19 November 2020 was estimated to be 23.84% (Figure 5D).

## COVID-19 SITUATION IN CITIES

COVID-19 prevalence has been reported in many cities of the country, and this reflects the high transmission rate of the virus at the regional level (Figure 6). However, a significant difference in the prevalence rate of COVID-19 has been found between the cities. This variation might be attributable to the following factors: (1) The number of samples tested per day; (2) Population density in each city; (3) Different activities for different cities; and (4) Different cultural and social lifestyles in each city. The highest positivity rates were estimated to be 44.09%, 36.56%, 23.05%, 22.23%, 18.50% and 16.14% in the cities of Surman, Alzintan, Sabratha, Zliten, Sabha and Misrata respectively, while the lowest positivity rates were estimated to be 11.05%, 11.39%, 7.90% and 4.90% in Zawiya, Nalut, Tripoli and Benghazi respectively. The aforementioned rates in Libyan cities have not been constant and have changed every month. Indeed, the high average positivity rates in Libya from September to mid-November (21%; 23.84%) constitute another indicator of the high transmission rate among the population (Figure 5C and D). According to the WHO's recommendation, the capacity for testing should be increased, and the positivity rate should remain below 10%. A positivity rate of less than 5% is recommended before the reopening of schools and businesses. According to the CDC, Libya, 76808 confirmed cases, 28153 active cases, 47587 recovered cases and 1068 deaths have been announced as of 19 November 2020, while the case fatality ratio (CFR) was estimated to be 1.40%; and as of 19 November 2020, Libya has a COVID-19 mortality rate of 15.90 deaths/100000 people.

## THE POTENTIAL FACTORS THAT INFLUENCE THE COVID-19 COURSE IN LIBYA

The epidemiological situation of COVID-19 in Libya may be influenced by the following potential risk factors: the government's level of transparency, prevention and control measures, population density, susceptibility of the population, age structure, *etc.* These factors contribute to and potentially influence the course of the disease in the country, and they might be variable in different environments.

In general, if any government has low or a complete lack of transparency, it will have a negative impact on the success of any strategy to combat or confront the pandemic. However, if the government prioritizes transparency, it would prompt trust and sentiments of solidarity and belief among the citizens. It is difficult to build up trust between the government and citizens. Therefore, all the governmental authorities must work hard in collaboration to improve their communications and make all the relevant information available. It is clear that transparency and the sharing of information among the authorities are of great importance to the success of the prevention and control strategies of COVID-19. Indeed, misleading and false information as well as a shortage of data about the epidemiological situation in the country could lead to the wrong decision by the government with regard to the implementation of strategies for the prevention and control of COVID-19.

## THE NATIONAL STRATEGY FOR THE PREVENTION AND CONTROL OF THE COVID-19 EPIDEMIC

The strategy for the prevention and control of the epidemic must be well designed and established according to the situation of the country and epidemiological patterns of the disease in the country so that it can be linked to and complemented by the data collected; therefore, this strategy reflects the real situation of the epidemic. The Libyan strategy for prevention and control of COVID-19 was performed and implemented according to the WHO recommendation criteria[21]. The Libyan Ministry of Health

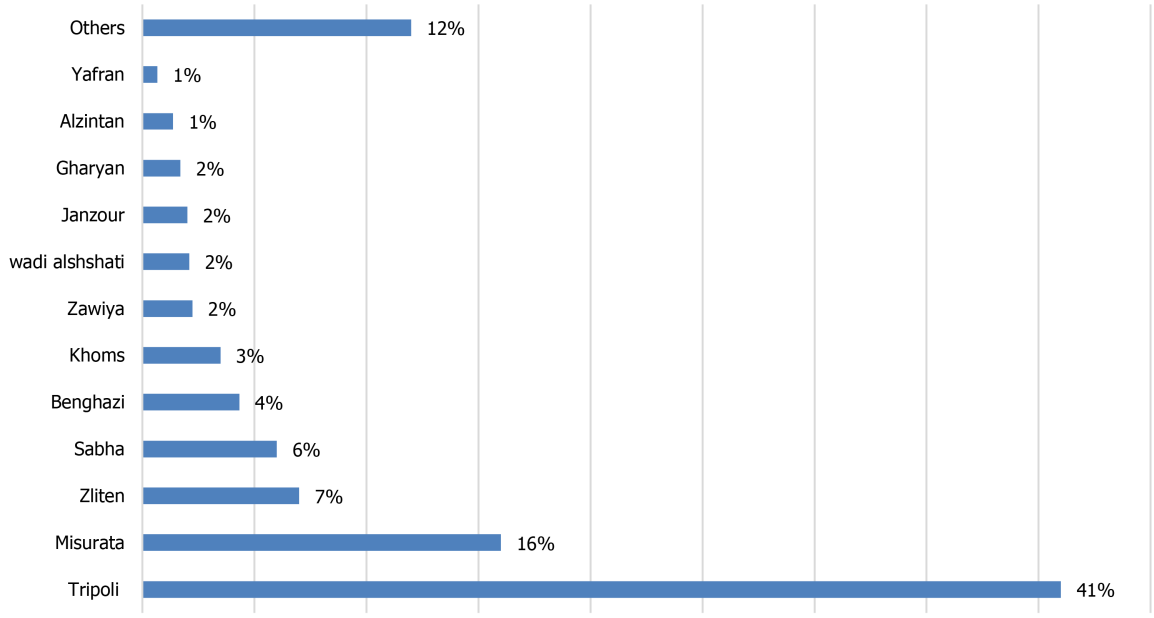


**Figure 6 The percent of severe acute respiratory syndrome coronavirus 2 infection in different Libyan Municipalities as of 30 August 2020.**

and CDC of Libya formulated response plans and alertness measures and issued early announcements, recommending the government authorities to prepare for combating the novel pandemic. As a result, the Libyan government designated members for the SAC of COVID-19. The Libyan SAC of COVID-19 has issued many sanctions, which include recommendations related to the strategy for combating the disease all over the country. Since the first case of COVID-19 was reported in Libya, the government authorities have followed these recommendations and have taken early action responses, as mentioned previously.

Consequently, at the beginning of the pandemic, Libyan citizens were strictly following all those recommendations related to the basic principles and precaution measures for preparedness and prevention from the infection and transmission of the virus. During the first two months following the first reported case, the number of confirmed cases were low as compared to other countries.

Currently, the epidemiological situation of COVID-19 has changed and worsened; there are many reasons for this, such as people losing their trust in the government and several people not following the health instructions. As a consequence, it was considerably difficult to implement the Libyan national strategy for the prevention and control of COVID-19.

## THE LIBYAN PUBLIC HEALTH CAPACITIES

The countries with the weakest and lowest strength of the public health system face the most challenges in the control and prevention of COVID-19. The public health system capacities play a crucial role in the control of the infection, and any weakness affects the strategy for the control and prevention of COVID-19. The Libyan authorities did not sufficiently prepare to improve their health capacities to face the pandemic. The diagnostic capacity and the tracing of contacts or suspected cases are crucial factors in combatting and minimizing the virus infection among the populations. Notwithstanding the high financial support extended by the Libyan authorities, the medical capacities are still lacking to address the minimum healthcare priorities. Most of the healthcare workers (HCWs) at the beginning of the pandemic were afraid because they did not have proper preventive measures in place; moreover, there was a deficiency in the availability of personal protective equipment (PPE). In the healthcare units, there is a shortage in the medical supplements and most of the hospitals do not provide triages or filter rooms. In fact, the challenge is that when a country faces a rise in the COVID-19 cases above their public health capacity, they will not be able to

mitigate deaths from the viral spread within the community or among their HCWs. The efficiency of health services in isolation centres and hospitals is a significant factor that contributes to reducing the impact of the viral spread and improving the recovery of infected patients. The health sector, including HCWs, laboratory technicians and groups of high-risk professionals, are considered the first line of defence during the COVID-19 pandemic in all medical care units; therefore, those in the frontline during an infectious disease's outbreak must especially be well trained. Healthcare units must meet the standard level and follow the criteria as required by the WHO and Libyan CDC to prevent the medical staff from exposure to the viral infection. Many HCWs have been infected by SARS-CoV-2 and sacrificed their lives to save their patients during the COVID-19 pandemic; according to data published on 23 July 2020 by the WHO, approximately over 10000 HCWs in Africa were infected with COVID-19. Many countries had low levels of medical service and a lack of PPE at the beginning of the pandemic. In contrast, the scenario in China has indicated that the Chinese health authorities were well prepared to combat the outbreak of any epidemic disease, having learnt from previous outbreaks such SARS 2003, HIV and human avian flu; accordingly, China was able to implement a consolidated and comprehensive blended strategy for the prevention and control of COVID-19 and also strengthen the public health capacity, which is one of the key factors for the effective combating of COVID-19. The strict quarantine measures constituted another key factor for success of the Chinese strategy. The Chinese health authorities were further able to isolate the virus and perform the genetic sequence of SARS-CoV-2 in a short time[22].

## POPULATION DENSITY

Libya is situated on the coast of North Africa, and it belongs to the Maghreb region in North Africa, bordered by the Mediterranean Sea to the north, Egypt to the east, Sudan to the southeast, Chad to the south, Niger to the southwest, Algeria to the west and Tunisia to the northwest. It is a large country with a relatively small population density of about 50 persons per km² (130/sq. mi.). 90% of the people live in less than 10% of the area, primarily along the coast. About 88% of the population is urban, mostly concentrated in the largest cities such as Tripoli (1150989), Benghazi (650629), Misrata (386120), Tarhuna (210697) and Al Khums (201943). Libya has a population of about 6.7 million, and about four people per km² (10 people/ sq. mi), calculated on a total land area of 1759540 km² (679362 sq. miles)[23,24]. The population density is one of the potential factors that increases community spread and individual risk of COVID-19. Consequently, the epidemiological patterns of COVID-19 in Libya could also be greatly influenced by the crowded situation due to the high population density; however, in contrast, most of the Libyan population live in independent department with low crowded. Therefore, the risk of exposure to SARS-CoV-2 infection among the Libyan community is limited as compared to other international societies characterized by crowded situations and of high public traffic within cities. According to the population data, it was suggested that the population density might be linked with the COVID-19 pandemic, especially in the urban areas and big cities around the world that are characterized by intense crowds, which could lead to the virus spreading within and outside those cities[25,26]. In contrast to study led by Johns Hopkins University, the study revealed that urban density is not linked to higher COVID-19 infection and death[27].

## DISPLACED POPULATIONS

Libya is a country with a moderate level of population displacement. According to the data published by the UNHCR and the International Organization for Migration (IOM), the country had the worst displacement scenario for a period of time since 2014, with approximately 217002 people being displaced inside the country and 348372 internally displaced persons[28]. The instability of the country and the fragility of the quarantine measures in Libyan borders made it easy for refugees to travel alongside migrants through dangerous routes towards Europe. In Libya, about 43113 refugees and asylum-seekers are registered with UNHCR. However, since 2016, the IOM and Displacement Tracking Matrix identified and located 276957 migrants out of around 700000 to 1 million migrants expected to be within the country[28].

## COVID-19 VACCINATION IN LIBYA

Libya is one of the self-financing participants under the COVAX facility. Total of 9.7 million US dollars has been transferred to the COVAX Facility to secure 2.8 million doses of COVID-19 vaccines. This amount of vaccine doses will be enough to vaccinate around 1.25 million people as two doses per person in addition to 10% as vaccine wastage. However, the country is hosting over 574 000 migrants and refugees who have not been included in Libya's national vaccination plan for COVID-19. The government is revising the plan to add a component addressing those vulnerable group. Once the revised plan is endorsed, WHO will ask the Global Vaccine Alliance to consider making vaccines available for around 16200 high-risk migrants and refugees under its Humanitarian Buffer fund.

The Libyan Ministry of Health has secured enough vaccines from the COVAX Facility to immunize approximately 20% of the Libyan population. Priority will be given to frontline health care workers, adults over 60 years of age, and patients with chronic underlying health conditions in all areas of the country[29]. Online registration for COVID-19 vaccination has already started in Libya on the first of March 2021 using the following link: https://www.eservices.ly.

The Libyan NCDC is responsible for coordinating vaccination throughout the country.

The Libyan Government of National Unity has received the first shipment of 101250 doses of Sputnik V vaccines on the April 4, 2021, and the second shipment with 100000 doses of Sputnik V vaccines was received on the 9$^{th}$ of April.

The only vaccine that was sent to Libya through COVAX Facility was AstraZeneca vaccine on the 8$^{th}$ of April with a total of 57600 doses.

A shipment of a total of 150000 doses of Sinovac vaccine was received as a gift to Libya from the Turkish government on the 14$^{th}$ of April. The vaccination campaign has started on the 10$^{th}$ of April and up to the 10$^{th}$ of May a total of about 100000 people have been vaccinated with a single dose.

## CONCLUSION

The information and data across the country regarding COVID-19 still remain unclear; consequently, the Libyan authorities need to initiate large-scale case screening, improve testing capacities and enforce contact tracing within the time frame, which are not easy tasks to perform in a country facing troubles, conflicts and instability. Currently, neither an increase in the testing capacities nor quarantine or lockdown of the cities would be a unique solution or strategy for the control and prevention of COVID-19. Advisably, the Libyan health authority should improve the public health capacities and enforce strict hygiene measures within the societies to minimize both the CFR and socio-economic impacts of the SARS-CoV-2. Most important that Ministry of health and NCDC should focus and do all possible efforts in order to get as many people vaccinated within a short period of time.

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ORIGINAL ARTICLE

Retrospective Study

# Bacterial co-infection in patients with SARS-CoV-2 in the Kingdom of Bahrain

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**Institutional review board statement:** The study was approved by the National COVID-19 Research Team and Secondary Care Research Committee of Salmaniya Medical Complex, Ministry of Health, the Kingdom of Bahrain.

**Informed consent statement:** The study had no ethical consideration as it was a retrospective non-interventional study with no exposure to any patient data.

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## Abstract

*BACKGROUND*

The coronavirus disease 2019 (COVID-19) pandemic presents a significant challenge to the medical profession, increasing in the presence of microbial co-infection. Bacterial and Fungal co-infections increase the risk of morbidity and mortality in patients with COVID-19.

*AIM*

To study the bacterial profile in patients with COVID-19 who needed admission to receive treatment in the main centres concerned with managing COVID-19 disease in the Kingdom of Bahrain.

*METHODS*

**Data sharing statement:** The data that support the findings of this study are available from the corresponding author, [Al-Biltagi M], upon reasonable request.



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The study was a retrospective observational analysis of the bacterial profile and the bacterial resistance in patients with confirmed COVID-19 disease who needed admission to receive treatment in the main centres assigned to manage patients with COVID-19 disease in the Kingdom of Bahrain from February to October 2020. We used the electronic patients' records and the microbiology laboratory data to identify patients' demographics, clinical data, microbial profile, hospital or community-acquired, and the outcomes.

*RESULTS*
The study included 1380 patients admitted with confirmed COVID-19 disease during the study period. 51% were admitted from February to June, and 49% were admitted from July to October 2020, with a recurrence rate was 0.36%. There was a significant increase in bacterial and fungal co-infection in the second period compared to the first period. The most common isolated organisms were the gram-negative bacteria (mainly *Klebsiella pneumoniae, Pseudomonas aeruginosa,* multi-drug resistant *Acinetobacter baumannii*, and *Escherichia coli*), the gram-positive bacteria (mainly coagulase negative *Staphylococci, Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus)* and fungaemia (*Candida galabrata, Candida tropicalis, Candida albicans, Aspergillus fumigatus, Candida parapsilosis, Aspergillus niger*). The hospital-acquired infection formed 73.8%, 61.6%, 100% gram-negative, gram-positive and fungaemia. Most of the hospital-acquired infection occurred in the second period with a higher death rate than community-acquired infections.

*CONCLUSION*
Bacterial and fungal co-infections in patients admitted with confirmed COVID-19 disease pose higher morbidity and mortality risks than those without co-infections. We should perform every effort to minimize these risks.

**Key Words:** COVID-19; Bacterial co-infection; Fungi; Hospital-acquired infection; Kingdom of Bahrain



**Core Tip:** Coronavirus pandemic presents a significant challenge to the medical profession. Bacterial and fungal co-infections are common complications of viral infections with increasing morbidity and mortality. We observed a significant increase in the number of bacterial and fungal co-infection over the study period. In addition, gram-negative infections carry a higher risk of morbidity and mortality.

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, which began with the first reported case in December 2019 in China, led to a Public Health Emergency worldwide, including in Bahrain. This pandemic presents a significant challenge to the medical profession, especially with the contradicting data about the origin of the virus [1-3].

Bacterial co-infection is a common complication of viral infections with increasing morbidity and mortality in conjunction with more burden on healthcare resources. Serious bacterial infections may be missed when all attention focuses on COVID-19. Therefore, recognition of co-infection in patients with COVID-19 is of utmost importance. It enables us to implement the appropriate management and proper control of antibiotic use, with effective delivery of antimicrobial stewardship[4]. There

are different reports about the prevalence of bacterial co-infection with COVID-19 assuming less bacterial co-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than influenza and other viral diseases[5]. On the other hand, some opinions based on the previous experience with the severe acute respiratory syndrome (SARS) outbreak in 2003 and the Middle East Respiratory Syndrome outbreak in 2012 suggest underestimation of bacterial co-infections in COVID-19 because of non-discriminatory use of antibiotics or the limitation of the overwhelmed clinical examinations in healthcare systems during the pandemic[6]. Bacteria can promote viral capability by augmenting virion stability, promoting viral infection of eukaryotic cells, and increasing co-infection rates. At the same time, virus binding of bacteria can also impact bacterial biology, including bacterial adherence to eukaryotic cells[7].

Bacterial co-infections in patients with COVID-19 are especially important when they require intensive care, including invasive mechanical ventilation support. For example, bacterial co-infections occurred in more than a third of children requiring invasive ventilation for bronchiolitis and were associated with more extended pediatric intensive care unit stay and mechanical ventilation[8]. Furthermore, patients admitted to intensive care unit (ICU) with prolonged illness/intubation have more frequent detection of multidrug-resistant gram-negative pathogens, likely reflecting hospital-acquired infection[9]. Therefore, it is vital to consider (investigate and empirically treat) bacterial co-infection when assessing these patients. Unfortunately, there is no consensus about treating patients with COVID-19 disease, which differs from one setting to another and from one country to another. Therefore, experts suggest not to use prophylactic antibiotics as a routine in patients with COVID-19, especially at the early stage or for non-intubated patients and recommend close monitoring of the signs of secondary infection, especially in critically ill patients who have been admitted to ICU for more than 48 h[10]. Furthermore, considering the long-term impact of the antimicrobial resistance development due to the unnecessary usage of antimicrobial agents, we should know the common bacterial and fungal infections that could complicate COVID-19, and know their expected antibiogram, and strictly monitor the rate of development of resistant bacterial strains[11]. Unfortunately, there are not enough data about the bacterial co-infections in patients admitted with COVID-19 disease. Therefore, we aimed to study the microbiological profile and the bacterial antibiogram in patients with COVID-19 who needed admission to receive treatment in the main centres concerned with managing COVID-19 disease in the Kingdom of Bahrain.

## MATERIALS AND METHODS

### *Study design and setting*

The study was a retrospective observational analysis of the microbiological profile of the patients admitted with confirmed COVID-19 disease to the different Ministry of Health (MOH) COVID isolation and treatment centres in the Kingdom of Bahrain for nine months period from February 2020 to October 2020. Inpatients with confirmed SARS-CoV-2 infection who had clinical suspicion of sepsis and/or bacterial co-infection were included in the study. Data were extracted and reviewed from the inpatients' electronic health medical records from all MOH inpatients. The demographics, clinical data, microbiological profile, and outcomes of included patients were extracted, and the data were tabulated using the Microsoft Excel database.

### *Definitions*

According to the national guidelines, the patients were stratified and allocated to specific COVID-19 Care centres into mild, moderate, and severe. The severe cases were assigned to the tertiary care centres with advanced care facilities. The medications differed according to the severity of the case and the presence of criteria of suspected sepsis.

**Inpatients with the clinical suspension of sepsis/bacterial co-infection:** COVID inpatients suspected clinically to have bacterial co-infection as decided by their treating physician during their clinical care, and septic workup were collected and sent to the microbiology laboratory.

**Community-acquired infection:** When clinical suspicion of sepsis/bacterial co-infection and the clinical samples for microbiology testing were collected from patients

at the time of admission or within the initial 48 h from admission to COVID-19 facility.

**Hospital-acquired infection:** When clinical suspicion of sepsis/bacterial co-infection and the clinical samples for microbiology testing were collected after 48 h from the time of admission to COVID-19 facility.

**Clinical isolates:** The first bacterial pathogen growth for each patient from any clinical specimen was counted as a clinical isolate. Isolates were considered duplicate and not considered if identified from the same patient with the same organism and antimicrobial profile.

### *Laboratory technique*

All the patients confirmed to have COVID-19 disease by positive testing using real-time reverse transcriptase-polymerase chain reaction for nasopharyngeal, sputum, endotracheal aspiration, or bronchoalveolar lavage samples. Clinical samples such as blood culture, sputum culture, stool culture, endotracheal aspirate or bronchoalveolar lavage culture were ordered according to the clinical indications when bacterial co-infection was suspected. These samples were cultured with the relevant media (nutritive, differential and/or selective), atmospheres and duration. The phenotypic detection was done using MALDI-TOF MS (Bruker Daltonics, Germany). Antimicrobial Susceptibility Testing was performed using BD Phoenix (BD Diagnostics, Baltimore, MD, United States) and interpreted according to the Clinical Laboratory Standards Institute[12]. We followed the trend of antibacterial sensitivity to evaluate the antimicrobial resistance.

### *Data analysis*

All data were anonymized and collated on Excel 2017 (Microsoft, Redmond, WA, United States). We used TexaSoft, WINKS SDA Software 2011 (Sixth Edition, Cedar Hill, TX, United States) to perform the statistical analysis. We computed the percentages and frequencies for different categorical variables, and a cross-tabulation was computed between every two categorical variables. Finally, the Chi-Squared test determined whether there were significant relationships between every two categorical variables. We considered a $P$ value of less than 0.05 as statistically significant. A biomedical statistician performed the statistical review of the study.

### *Ethical approval*

The study was approved by the National COVID-19 Research Team and Secondary Care Research Committee of Salmaniya Medical Complex, Ministry of Health, the Kingdom of Bahrain. However, the study had no ethical consideration as it was a retrospective non-interventional study with no exposure to any patient data.

## RESULTS

Table 1 showed the demographics of the included inpatients. The study included 1380 patients admitted with confirmed COVID-19 disease and had clinical suspicion of sepsis during the study period from February to October 2020, with a Male: Female ratio of 0.9, mean age of 50.2 ± 18.1 years, and 73% of them were Bahraini. The death rate was 11.5% for all the admitted patients during the study period. 51% of inpatients with clinical suspicion of sepsis were admitted from February to June, and 49% were admitted from July to October 2020. Five patients had confirmed recurrences (0.36%), all five patients recovered. From those admitted patients with confirmed COVID-19 diseases and clinical suspicion of sepsis, 261 patients (19%) had confirmed bacterial and fungal co-infections, 75% of them were Bahraini with a mean age of 58.5 ± 18.7 years, Male: Female ratio of 0.8, and a death rate of 42.5%. Two of these patients had a recurrence, and both survived. The remaining 1119 admitted patients (81%) had negative bacterial and fungal culture. Their mean age was 48.4 ± 17.6 years, with a male: female ratio of 0.9; 73% of them were Bahraini with a death rate of 4.3%. The group with confirmed bacterial and fungal co-infections had a significantly higher age ($P < 0.0001$) and rate of death ($P < 0.0001$) than the group without confirmed bacterial or fungal co-infection.

Table 2 showed the demographics of the patients with gram-positive, gram-negative bacteria, fungal and mixed infections. There were no significant differences between the number, age, gender, and nationality between the gram-positive and gram-negative bacteria. However, gram-negative infection occurred in older age and has a

**Table 1 Comparison patients' demographic for total admitted patients with/without Bacterial or fungal coinfections**

| | Total admitted patients (COVID with clinical suspicion of sepsis) | Patients without coinfection (negative bacterial culture) | Patients with coinfection (positive bacterial culture) | *P* value |
|---|---|---|---|---|
| *n* (%) | 1380 | 1119 (81.1) | 261 (18.9) | < 0.0001 |
| Male/female | 0.92 | 0.87 | 1.13 | > 0.05 |
| Bahraini/non-Bahraini | 2.80 | 2.70 | 3.10 | > 0.05 |
| Mean age (yr) ± SD | 50.2 ± 18.1 | 48.4 ± 17.6 | 58.5 ± 18.7 | < 0.0001 |
| Death | 159 (11.5%) | 48 (4.30%) | 111 (42.5%) | < 0.0001 |
| Recurrences | 5 (0.36%) | 3 (0.27%) | 2 (0.77%) | > 0.05 |

COVID: Corona virus disease; SD: Standard deviation.

**Table 2 Comparison patients' demographics and microbial profile for patients with gram-positive and gram-negative Bacteria and mixed infections**

| | Gram + ve coinfection | Gram-ve coinfection | Mixed coinfection | Candida | *P* value[1] | *P* value[2] | *P* value[3] |
|---|---|---|---|---|---|---|---|
| *n* (%) | 136 (54) | 115 (46) | 82 (23.8) | 115 (46) | > 0.05 | < 0.0001 | < 0.0001 |
| Male/female | 0.82 | 0.67 | 0.74 | 0.88 | > 0.05 | > 0.05 | > 0.05 |
| Bahraini/non-Bahraini | 2.50 | 3.10 | 1.90 | 2.10 | > 0.05 | > 0.05 | > 0.05 |
| Mean age (yr) ± SD | 57.7 ± 18.2 | 60 ± 18.2 | 64.3 ± 14.3 | 63.4 ± 16.4 | > 0.05 | < 0.01[a] | < 0.05 |
| Death | 39 (28.7%) | 61 (53%) | 62 (75.6%) | 81 (70.4%) | < 0.0001 | < 0.0001 | < 0.01 |
| HA infection | 78 (57.3%) | 86 (75%) | 79 (96%) | 97 (84.3%) | < 0.001 | < 0.0001 | < 0.0001 |

[1]Comparison between gram + ve and gram-ve coinfection.
[2]Comparison between gram + ve and mixed coinfections.
[3]Comparison between gram-ve and mixed coinfections. HA: Hospital acquired; SD: Standard deviation.

significantly higher death rate and more hospital-acquired infection rates than gram-positive bacteria. All the gram-negative isolates were detected from the centres allocated for the severe cases. Moreover, mixed infections occurred in less than a quarter of cases, with significantly higher age and death rate than other types of co-infections. All cases of mixed infections were hospital-acquired. We also observed that the number of patients with bacterial or fungal infection was significantly higher in the July-to-October period ($P < 0.0001$) with higher mean age ($P < 0.01$) compared to the first period of the study between February to June. In addition, the number of co-infections with gram-negative bacteria was significantly higher ($P < 0.0001$) in the July to October period than that of the February-to- June. The same also was observed in fungal co-infections. The number of mixed co-infections was also significantly higher in the July-to-October period ($P < 0.01$).

Table 3 showed the microbiological profile in patients with confirmed COVID-19 disease in the whole study period with a total of 472 isolates from 261 admitted patients. The gram-negative bacteria were isolated from 34.7% [59% showed Multidrug-resistant (MDR) strains], and gram-positive isolates were isolated from 34.7% of the patients (53% showed MDR strains). In comparison, fungal infections were isolated from 32% of the patient, 25% were isolated from the blood (Fungaemia). There was no significant difference in the isolates number in the two study periods, from February to June and July to October. However, the percentage of gram-negative isolates increased from 26.8% in the first period to 73% in the second period ($P < 0.0001$) and the percentage of MDR among gram-negative strains increased from 41% in the first period to 65.8% in the second period ($P < 0.01$). Thus, the MDR gram-negative strains isolated in the second period formed 81.4% of the total MDR strains isolated throughout the study ($P < 0.0001$). The most common gram-negative strains

**Table 3 Microbiological profile in the admitted patients with confirmed coronavirus disease 2019 during the study period (472 isolates)**

| Type of the organism | | | | Number | % of MDR |
|---|---|---|---|---|---|
| Gram Negative Isolates (164) | *Klebsiella pneumoniae* | | Total | 39 | 97.4 |
| | | | ESBL | 11 | |
| | | | CRE | 27 | |
| | *Pseudomonas aeruginosa* | | Total | 38 | 26.3 |
| | | | CRP | 8 | |
| | | | MDR | 2 | |
| | *Acinetobacter baumannii* (MDR) | | | 36 | 100 |
| | *Escherichia coli* | | Total | 28 | 68 |
| | | | ESBL | 11 | |
| | | | CRE | 8 | |
| | *Stenotrophomonas maltophilia* | | | 12 | 0 |
| | *Enterobacter cloacae* | | Total | 2 | 100 |
| | | | CRE | 2 | |
| | *Other* | | | 9 | 0 |
| | Total G-ve isolates | | | 164 | 59 |
| | Total G-ve MDR strains | | | 97 | |
| Gram positive isolates (164) | Coagulase negative *Staphylococci* (CoNS) | *Staphylococcus hominis* | Total | 31 | 58 |
| | | | MRCoNS | 18 | |
| | | *Staphylococcus epidermidis* | Total | 25 | 78.6 |
| | | | MRCoNS | 22 | |
| | | *Staphylococcus heemolyticus* | MRCoNS | 18 | 100 |
| | | *Staphylococcus capitis* | Total | 10 | 50 |
| | | | MRCoNS | 5 | |
| | | *Staphylococcus pettenkoferi* | MRCoNS | 1 | 100 |
| | | Total CoNS | Total | 85 | 75.3 |
| | | | MRCoNS | 64 | |
| | *Enterococcus faecium* | | Total | 24 | 16.6 |
| | | | VRE | 3 | |
| | | | HLGR | 1 | |
| | *Enterococcus faecalis* | | Total | 20 | 5.0 |
| | | | HLGR | 1 | |
| | *Staphylococcus aureus* | | Total | 15 | 53.3 |
| | | | MRSA | 8 | |
| | Others | | | 20 | |
| | Total G + ve isolates | | | 164 | 47 |
| | Total G + ve MDR Strains | | | 77 | |
| Fungal isolates(144) | Fungaemia | | *Candida galabrata* | 11 | |
| | | | *Candida tropicalis* | 9 | |
| | | | *Candida albicans* | 7 | |
| | | | *Aspergillus fumigatus* | 3 | |
| | | | *Candida parapsilosis* | 3 | |

| | | | |
|---|---|---|---|
| | *Aspergillus niger* | 3 | |
| | Total | 36 | |
| *Candida species* | | 108 | |
| Total fungal isolates | | 144 | |
| Total number of the microbial isolates | | 472 | 36.9 |
| Total number of mdr bacterial strains | | 174 | |

CRE: Carbapenem-resistant Enterobacteriaceae; ESBL: Extended spectrum beta-lactamase; HLGR: High level aminoglycoside resistance; MDR: Multidrug-resistant; MRCoNS: Methicillin-resistant coagulase-negative *Staphylococci*; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: *Vancomycin-resistant enterococci*; Other gram-negative bacteria: *Citrobacter freundii, Salmonella* species, *Pantoea* species, *Proteus mirabilis*, *Serratia marcescens*, *Elizabethkingia* meningoseptica; Other gram-positive bacteria: *Streptococcus agalactiae* (Strep. Group B), *Corynebacterium afermentans, Bacillus licheniformis, Leuconostoc mesenteroides, Staphylococcus caprae, Staphylococcus lugdunensis, Staphylococcus warneri, Streptococcus parasanguinis, Gemella sanguinis, Micrococcus luteus, Propionibacterium acnes, Rhodococcus erythropolis, Aerococcus viridans, Staphylococcus gallinarum.*

isolated through the study were *Klebsiella pneumoniae* (*K. pneumoniae*) followed by *Pseudomonas aeruginosa* (*P. aeruginosa*), then MDR *Acinetobacter baumannii* (*A. baumannii*), *Escherichia coli* (*E. coli*), *Stenotrophomonas maltophilia* (*S. maltophilia*), and *Enterobacter cloacae* (*E. cloacae*).

On the other hand, the gram-positive bacteria showed a significant increase in the total number of isolates in the second period but no significant difference in the number of total MDR strains or the number of coagulase-negative *Staphylococci* in the two study periods. Moreover, there was a significant increase in the number of methicillin-resistant coagulase-negative *Staphylococci* (MRCoNS) in the second period compared with the first periods. The most common gram-positive strains isolated throughout the study were *Staphylococcus hominis* (*S. hominis*) (MRCoNS), followed by *Staphylococcus epidermidis* (*S. epidermidis*) (CoNS), *Enterococcus faecium* (*E. faecium*), *Enterococcus faecalis* (*E. faecalis*), and *Staphylococcus aureus* (*S. aureus*). In addition, the rate of fungaemia was significantly higher in the second period (6-fold increase) compared to the first period ($P < 0.0001$).

Table 4 and Figure 1 showed a comparison between the community and hospital-acquired infections (HAI) and their microbiologic profile in patients with confirmed COVID-19 disease with a total of 472 isolates during the whole study periods. Hospital-acquired infections formed 70% of the total infections. Those patients with HAI had a significantly higher mean of age ($P < 0.01$) than those of CAI. In addition, the percentage of the gram-negative isolates, including the MDR strains, were significantly higher in the HAI than CAI. The most common gram-negative strains were *K. pneumoniae,* followed by MDR *A. baumannii*, *P. aeruginosa, E. coli,* and *S. maltophilia.* At the same time, the total number of gram-positive isolates, including the MDR strains, were significantly higher in patients with HAI compared to patients with CAI ($P < 0.0001$). The most common gram-positive strains were *S. epidermidis* (CoNS), followed by *E. faecium*, *E. faecalis*, *Staphylococcus haemolyticus* (CoNS), *S. hominis* (CoNS), and *S. aureus,* as shown in the table. All isolates with fungaemia were obtained from patients with HAI. No cases with fungaemia were recorded from CAI.

## DISCUSSION

Microbial co-infections are commonly identified in viral respiratory infections. They are key reasons for difficult diagnosis, poor prognosis, increased morbidity and mortality, and greater use of healthcare resources. The prevalence and characteristic of bacterial co-infection in patients with confirmed COVID-19 disease are not well studied, especially in the Kingdom of Bahrain, with a broad knowledge gap. Bacterial co-infection could occur before admission of the patient to the hospital (Community-acquired) or could complicate the course of the illness as a secondary infection (Hospital-acquired). Our observational study identified a rate of 19% of bacterial co-infection through the study with increased rates of laboratory-confirmed bacterial and fungal co-infections in patients admitted with confirmed COVID-19 disease during the second period compared to the first period of the study despite that the total number of the admitted patients remained nearly the same. A study by Garcia-Vidal *et al*[13] had similar results to our results in the first period. They found an incidence of 7.2% of bacterial co-infection in their study, which conducted between February and April

**Table 4 Comparison between the community and hospital acquired infections and their microbiologic profile from coronavirus disease 2019 confirmed patients (total isolates 472)**

| Character | | | | HA infection | CA infection | *P* value |
|---|---|---|---|---|---|---|
| Patient number (total 261) 22 patients has both HA and CA | | | | 185 (70.8%) | 98 (37.5%) | < 0.0001 |
| Age | | | | 60.8 ± 16.8 | 54. ± 20.6 | < 0.01 |
| Male: Female | | | | 0.85 | 0.80 | > 0.05 |
| Bharani | | | | 137 (74%) | 71 (72.4%) | > 0.05 |
| Death | | | | 102 (55%) | 23 (23.5%) | < 0.0001 |
| Gram negative isolates (164) | *Klebsiella pneumoniae* | | Total | 30 | 9 | |
| | | | ESBL | 11 | 0 | |
| | | | CRE | 15 | 2 | |
| | *Acinetobacter baumannii* (MDR) | | | 29 | 7 | |
| | *Pseudomonas aeruginosa* | | Total | 28 | 10 | |
| | | | CRP | 6 | 2 | |
| | | | MDR | 2 | 2 | |
| | *Escherichia coli* | | Total | 13 | 15 | |
| | | | ESBL | 6 | 6 | |
| | | | CRE | 5 | 2 | |
| | *Stenotrophomonas maltophilia* | | | 11 | 1 | |
| | *Enterobacter cloacae* | | Total | 2 | 0 | |
| | | | CRE | 1 | 0 | |
| | Others | | | 8 | 1 | |
| | Total number of the G-ve isolates (164) | | | 121 (73.8%) | 43 (26.2%) | < 0.0001 |
| | Number of G-ve resistant Strains | | | 75 (62%) | 21(48.8%) | > 0.05 |
| | % from total Resistant strains (96) | | | 78.1% | 21.9% | < 0.0001 |
| Gram positive isolates (164) | Coagulase negative *Staphylococci (CoNS)* | *Staphylococcus epidermidis* | Total | 19 | 6 | |
| | | | MRCoNS | 18 | 4 | |
| | | *Staphylococcus haemolyticus* | MRCoNS | 14 | 4 | |
| | | *Staphylococcus hominis* | Total | 12 | 19 | |
| | | | MRCoNS | 6 | 13 | |
| | | *Staphylococcus capitis* | Total | 5 | 5 | |
| | | | MRCoNS | 5 | 0 | |
| | | *Staphylococcus pettenkoferi* | MRCoNS | 1 | 0 | |
| | | Total CoNS | Total | 41 (40.6%) | 31 (49.2%) | > 0.05 |
| | | | MRCoNS | 37 (90%) | 21 (67.7%) | < 0.05 |
| | *Enterococcus faecium* | | Total | 17 | 7 | |
| | | | VRE | 2 | 1 | |
| | | | HLGR | 1 | 0 | |
| | *Enterococcus faecalis* | | Total | 16 | 4 | |
| | | | HLGR | 1 | 0 | |
| | *Staphylococcus aureus* | | Total | 8 | 8 | |
| | | | MRSA | 3 | 5 | |
| | Others | | | 9 | 10 | |

| | | | | | |
|---|---|---|---|---|---|
| | Total number of the G + ve isolates (164) | | 101 (61.6%) | 63 (38.4%) | < 0.0001 |
| | Number of G + ve resistant strains | | 51 (50.5%) | 27 (42.9%) | > 0.05 |
| | % from total Resistant strains (78) | | 65.4% | 34.6% | < 0.0001 |
| Fungal isolates (144) | | *Candida galabrata* | 11 | 0 | |
| | | *Candida albicans* | 7 | 0 | |
| | | *Candida tropicalis* | 9 | 0 | |
| | | *Candida parapsilosis* | 3 | 0 | |
| | | *Aspergillus fumigatus* | 3 | 0 | |
| | | *Aspergillus niger* | 3 | 0 | |
| | | Total | 36 | 0 | |
| | *Candida* species | | 95 | 13 | |
| | Total fungal isolates (144) | | 131 (91%) | 13 (9%) | < 0.0001 |
| Total microbial isolates (472) | | | 353 (74.8%) | 119 (25.2%) | < 0.0001 |
| Total number of resistant bacterial strains | | | 126 (35.7%) | 48 (40.3%) | > 0.05 |
| Percentage from total resistant bacterial strains (174) | | | 72.4% | 27.6% | < 0.0001 |

CA: Community Acquired; CRE: Carbapenem-resistant Enterobacteriaceae; ESBL: Extended spectrum beta-lactamase; HA: Hospital acquired; HLGR: High level aminoglycoside resistance; MDR: Multidrug-resistant; MRCoNS: Methicillin-resistant coagulase-negative *Staphylococci*; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: *Vancomycin-resistant enterococci*; Other gram-negative bacteria: *Citrobacter freundii, Salmonella species, Pantoea* species, *Proteus mirabilis*, *Serratia marcescens*, *Elizabethkingia* meningoseptica; Other gram-positive bacteria: *Streptococcus agalactiae* (Strep. Group B), *Corynebacterium afermentans, Bacillus licheniformis, Leuconostoc mesenteroides, Staphylococcus caprae, Staphylococcus lugdunensis, Staphylococcus warneri, Streptococcus parasanguinis, Gemella sanguinis, Micrococcus luteus, Propionibacterium acnes, Rhodococcus erythropolis, Aerococcus viridans, Staphylococcus gallinarum.*

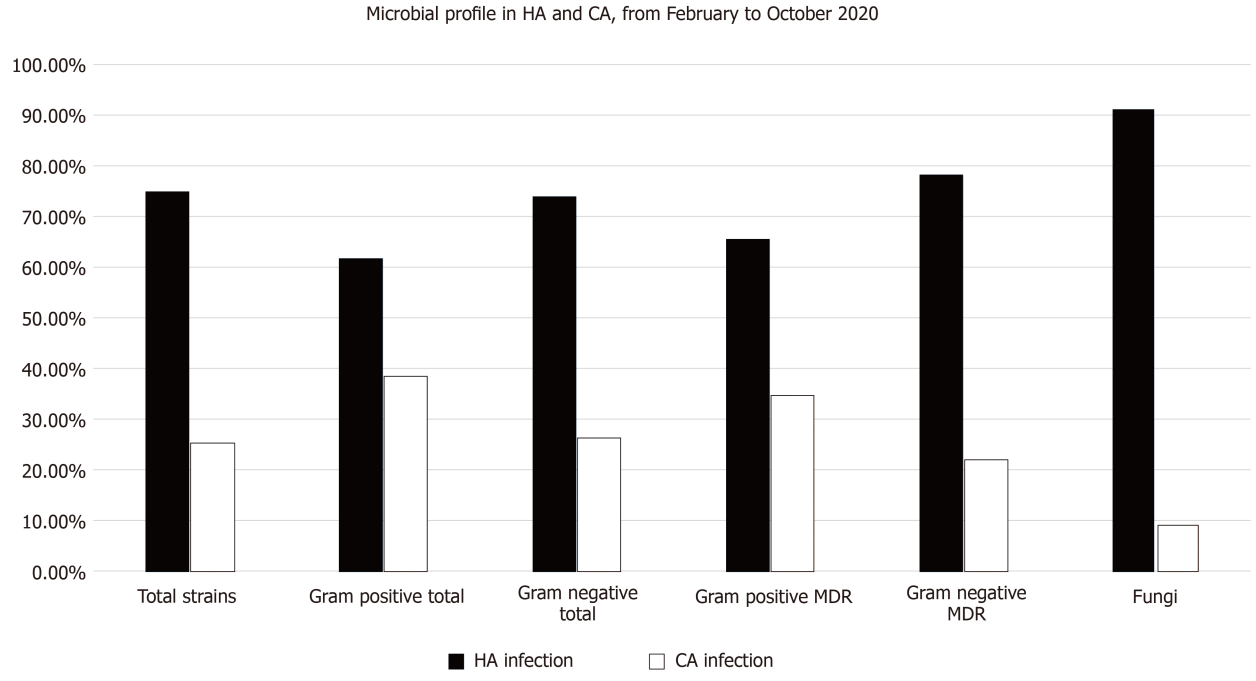


**Figure 1 Microbial profile in hospital-acquired infections and community-acquired infections from February to October 2020.** MDR: Multidrug-resistant; HA: Hospital-acquired; CA: Community-acquired.

2020[13]. Zhang *et al*[14] showed that the severely affected patients with COVID-19 disease had a significantly higher rate of bacterial (25.5%) and fungal (10.9%) co-infections. At the same time, a meta-analysis by Lansbury *et al*[5] indicated that about 7% of hospitalized patients with COVID-19 disease had bacterial co-infections, which increased to 14% in studies that only included ICU patients.

Nevertheless, this meta-analysis had a lower rate than that observed in our study, as it analyzed data from the earliest cases of the SARS-CoV-2 pandemic, which could differ from the current situation. Another metanalysis by Langford *et al*[15] showed that the overall proportion of COVID-19 patients with bacterial infection was 6.9% and increased to 8.1% of critically ill patients. The increased rate of bacterial co-infection in the second period in our study is related to the change in the admission criteria in the second period of the study to be more selective for the sick patients with medical comorbidities that need hospital management and allowing asymptomatic and mildly symptomatic patients to be managed at home. The death rate reached 42.5% in patients with bacterial co-infection than the patients without (4.3%). This high rate of death in the presence of microbial co-infection was also reported in a previous study in China which showed that 96% of patients with confirmed COVID-19 disease and secondary bacterial infections died. About half of the non-survivors experienced a secondary infection[16].

In the current study, there was a high incidence of gram-negative bacteria in patients who need hospitalization with increased mortality rates. Most of the gram-negative bacterial co-infections were hospital-acquired (75%). Consequently, every effort should be made to minimize this risk. Multi-drug resistant strains were present in more than half of the gram-negative bacterial isolates. This point should be considered during the management till the results of the antibiotic sensitivity are achieved. Being male and older than 60 years carries a higher risk for gram-negative as well as mixed co-infections. There was also a marked increase in the rate of gram-negative bacteria in the second period of the study, notably *K. pneumoniae,* followed by *P. aeruginosa*, MDR *A. baumannii, E. coli, S. maltophilia*, and *E. cloacae, K. pneumoniae* and *P. aeruginosa* were attributed to respiratory, then blood and urine-sourced infections. The MDR rate among the gram-negative bacteria was 65.8% in the second period and 41% in the first period of the study. This agreed with the work of Kokkoris *et al*[17], who reported an increase in the gram-negative blood-stream infections identified in ICU-admitted patients with confirmed COVID-19 disease, primarily due to MDR pathogens. A similar study in Egypt showed that MDR *K. pneumoniae* and *A. baumannii* were the predominant gram-negative bacteria that carried different resistance-associated genes[18]. The improper use of antibiotics could be implicated in increasing the resistance frequency. Many studies showed that antimicrobials were being administered at a high rate in patients with COVID-19 disease even in the presence of a low number of confirmed bacterial infection[19].

In the present study, the rate of co-infection with gram-positive bacteria in admitted patients was 11.8%. The most common isolated organisms were coagulase-negative *Staphylococci* (*S. hominis, S. epidermidis, Staphylococcus heemolyticus,* and others), forming 52.5% of total gram-positive isolates, followed by *E. faecium, E. faecalis,* and *S. aureus* with 47% of them were MDR strains. There was a significant increase in gram-positive bacteria in the second period than the first period of the study ($P < 0.05$). However, the resistance rate non-significantly decreased in the second period compared with the first period ($P > 0.05$). This observation agreed with the work of Sepulveda *et al*[20], who found that coagulase-negative *staphylococcus* species accounted for 59.7% of all positive cultures among patients with COVID-19 disease in New York City. Hughes *et al*[21] also found that coagulase-negative *Staphylococcus* species were the most common organisms isolated from the blood culture, followed by *Acinetobacter species*. Thus, infection with SARS-CoV-2 may reduce the patient's immunity and increase the risk of bacterial infections. In a retrospective study in Wuhan, China, 19 patients in the ICU with confirmed COVID-19 disease had markedly reduced CD4 and CD8 T-cells[22]. This immune compromise increases the risk of co-infection with both viruses and bacteria, increases the risk of bacterial resistance, and the requirements of the patients to extended courses of IV antibiotic therapy[23].

In the current study, we observed the presence of fungaemia in about 10% of microbial co-infection. The most common fungi isolated were *Candida galabrata, Candida tropicalis, Candida albicans,* and *Aspergillus fumigatus*. The death rate in our patients who had fungal co-infection was very high (70.4%). This finding agreed with the study done in Upper Egypt by Ramadan *et al*[18], who found that *Candida albicans* and *Candida glabrata* were the most common fungal isolates. Patients hospitalised for COVID-19 are at risk for HAIs, with fungaemia; bloodstream infections caused by *Candida* or *aspergillus*. Invasive fungal infections add more prudent to the already immune-compromised patients with COVID-19 disease, especially diagnostic tools' limitations and the critical clinical settings that put these patients at additional risk. Fungal infections resistant to antifungal treatment have also been described in patients with severe COVID-19. Early diagnosis and monitoring for *Candida* infections and antifungal resistant infections are essential to reduce death from COVID-19 in patients

with severe COVID-19[24,25]. Mixed infections in the current study had a very high death rate, representing a significant threat to the patients with COVID-19 and necessitate aggressive treatment. To avoid missing these types of severe infection, patients should be recruited on admission to intensive care units and sampled longitudinally throughout the disease course using culture-independent techniques capable of identifying complex mixed infections[26].

In the current study, the HAI was about 71% of the total bacterial, and fungal infections in patients admitted with COVID-19 disease. The death rate in HAI was 55% compared to 23.5% in community-acquired infection. The age in HAI was also higher than in CAI. Older age is a significant risk factor to have HAI in patients with COVID-19[27]. Intrahospital and interhospital clonal transmission of bacteria could be a factor for HAI. Rational utilization of antibiotics and steroids to treat patients with COVID-19 is essential in preventing nosocomial infection. We should give particular attention to diabetic patients and patients with invasive devices[28]. HAI is a risk factor to have resistant strains. The percentage of resistant strains in HAI reached 62% in gram-negative and 50.5% in gram-positive isolates in the current study.

Antimicrobial resistance is a global problem, especially among gram-negative pathogens. The current study showed a high resistance pattern in bacterial co-infection in patients with COVID-19. In the gram-negative bacteria, about 28% of *K. pneumoniae* were extended spectrum beta-lactamase (ESBL), and 69% were CRE. All *A. baumannii* strains were MDR. About 39% of *E. coli* were ESBL, and 22% were CRE. In *P. aeruginosa,* 21% were CRP, while 8% were MDR. In gram-positive isolates, 75% of coagulase-negative *Staphylococci* and 53% of *S. aureus* were Methicillin-resistant. Antibiotic resistance is a critical reason for the failure of antibiotic therapy. At the same time, COVID-19 disease can exacerbate antibiotic resistance[29]. This increased resistance results from the interplay of different factors, including the micro-organisms, patients, and hospital environment, including the antibiotic use and the infection control practices. Increasing antibiotic resistance is also caused by improper antibiotic prescription and transmission of resistant bacterial strains within the hospitals by cross colonisation of patients *via* the hands of healthcare staff and subsequent spread between hospitals by transfer of the colonised patients[30]. Strategies to control antibiotic resistance in hospitals include multidisciplinary cooperation in implementing local policies on the use of antibiotics and infection control measures, timely detection with adequate microbiology laboratory standards and reporting of the antibiotic-resistant strains, improved surveillance, and aggressive control of transmission of epidemic resistant bacteria. We should integrate the antimicrobial stewardship activities into the pandemic response across the broader health system[31].

### *Limitation of the study*

Despite being a multicentre study, it had some limitations. Being a retrospective study reduces control over multiple confounders and data collection. We did not study the mechanism of bacterial resistance due to lack of time and the workload during the pandemic. We also included only the infections that were documented by culture and, therefore, some episodes may be missing, and viral co-infection was not included. Finally, this study was done in the Kingdom of Bahrain, with its own unique local epidemiologic effects on antimicrobial resistance, limiting the generalisability of the findings.

## CONCLUSION

Bacterial and fungal co-infections are common and place a significant threat to the patient with COVID-19 disease. At the same time, COVID-19 disease increases the risk of bacterial and fungal co-infections. We observed a high death rate in patients with hospital-acquired gram-negative co-infections. At the same time, older age was noted, especially in HAI. In addition, bacterial resistance was a significant problem in bacterial co-infection. Therefore, we should perform every effort to prevent microbial co-infections to minimize both morbidity and mortality.

## ARTICLE HIGHLIGHTS

### *Research background*

The coronavirus (COVID-19) pandemic presents a significant challenge to health worldwide. Bacterial and Fungal co-infections increase the risk of morbidity and mortality in patients with COVID-19, in conjunction with more burden on healthcare resources.

### *Research motivation*

With the increasing risk of mortality among patients with COVID-19, there is a solid need to study the different factors that could increase or decrease this risk. Therefore, recognition of co-infection in patients with COVID-19 is of utmost importance. It enables us to implement the appropriate management and proper control of antibiotic use, with effective delivery of antimicrobial stewardship. Therefore, the centres that provide care for patients with COVID-19 in the kingdom of Bahrain participated in the current research.

### *Research objectives*

We aimed to study the microbiological profile and the bacterial antibiogram in patients with COVID-19 who needed admission to receive treatment in the main centres concerned with managing COVID-19 disease in the Kingdom of Bahrain.

### *Research methods*

The study was a retrospective observational analysis of the microbiological profile of the patients admitted with confirmed COVID-19 disease to the different Ministry of Health COVID isolation and treatment centres in the Kingdom of Bahrain for nine months period from February 2020 to October 2020.

### *Research results*

There was a significant increase in the number of bacterial and fungal co-infection over the study period. The most common isolated organisms were the gram-negative bacteria (mainly *Klebsiella pneumoniae, Pseudomonas aeruginosa,* multi-drug resistant *Acinetobacter baumannii*, and *Escherichia coli*), the gram-positive bacteria (mainly coagulase negative *Staphylococci, Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus)* and fungaemia (*Candida galabrata, Candida tropicalis, Candida albicans, Aspergillus fumigatus, Candida parapsilosis, Aspergillus niger*). The hospital-acquired infection formed 73.8%, 61.6%, 100% gram-negative, gram-positive, and fungaemia. Most of the hospital-acquired infection occurred in the second period with a higher death rate than community-acquired infections.

### *Research conclusions*

Bacterial and fungal co-infections in patients admitted with confirmed COVID-19 disease pose higher morbidity and mortality risks than those without co-infections. Therefore, we should perform every effort to minimize these risks.

### *Research perspectives*

We need to study bacterial resistance mechanisms among the patients infected with COVID-19 and have co-infection with resistant bacterial strains. We also need to study viral co-infection and its effects on morbidity and mortality. Finally, we should compare our data with the data from other countries to generalize the obtained results.

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SYSTEMATIC REVIEWS

# Current systematic reviews and meta-analyses of COVID-19

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## Abstract

***BACKGROUND***

Coronavirus disease 2019 (COVID-19) has left a significant impact on the world's health, economic and political systems; as of November 20, 2020, more than 57

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**Conflict-of-interest statement:** All authors confirm the absence of personal and financial interests impacting the outcomes of this research study.

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million people have been infected worldwide, with over 1.3 million deaths. While the global spotlight is currently focused on combating this pandemic through means ranging from finding a treatment among existing therapeutic agents to inventing a vaccine that can aid in halting the further loss of life.

***AIM***

To collect all systematic reviews and meta-analyses published related to COVID-19 to better identify available evidence, highlight gaps in knowledge, and elucidate further meta-analyses and umbrella reviews that are yet to be performed.

***METHODS***

We explored studies based on systematic reviews and meta-analyses with the key-terms, including severe acute respiratory syndrome (SARS), SARS virus, coronavirus disease, COVID-19, and SARS coronavirus-2. The included studies were extracted from Embase, Medline, and Cochrane databases. The publication timeframe of included studies ranged between January 01, 2020, to October 30, 2020. Studies that were published in languages other than English were not considered for this systematic review. The finalized full-text articles are freely accessible in the public domain.

***RESULTS***

Searching Embase, Medline, and Cochrane databases resulted in 1906, 669, and 19 results, respectively, that comprised 2594 studies. 515 duplicates were subsequently removed, leaving 2079 studies. The inclusion criteria were systematic reviews or meta-analyses. 860 results were excluded for being a review article, scope review, rapid review, panel review, or guideline that produced a total of 1219 studies. After screening articles were categorized, the included articles were put into main groups of clinical presentation, epi-demiology, screening and diagnosis, severity assessment, special populations, and treatment. Subsequently, there was a second subclassification into the following groups: gastrointestinal, cardiovascular, neurological, stroke, thrombosis, anosmia and dysgeusia, ocular manifestations, nephrology, cutaneous manifestations, D-dimer, lymphocyte, anticoagulation, antivirals, convalescent plasma, immunosuppressants, corticosteroids, hydroxychloroquine, renin-angiotensin-aldosterone system, technology, diabetes mellitus, obesity, pregnancy, children, mental health, smoking, cancer, and transplant.

***CONCLUSION***

Among the included articles, it is clear that further research is needed regarding treatment options and vaccines. With more studies, data will be less heterogeneous, and statistical analysis can be better applied to provide more robust clinical evidence. This study was not designed to give recommendations regarding the management of COVID-19.

**Key Words:** Systematic review; Meta-analyses; COVID-19; Review; Coronavirinae



**Core Tip:** Coronavirus disease 2019 (COVID-19) has left a significant impact on the world's health, economic and political systems. This study was not designed to give recommendations regarding the management of COVID-19. There is a need for future research to understand the scope of possible vaccines and prevention/treatment options in the setting of COVID-19.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has left a significant impact on the world's health, economic and political systems; as of November 20, 2020, more than 57 million people have been infected worldwide, with over 1.3 million deaths[1]. While the global spotlight is currently focused on combating this pandemic through means ranging from finding a treatment among existing therapeutic agents to inventing a vaccine that can aid in halting the further loss of life.

The scientific community has been extremely busy with COVID-19. Thousands of research articles have been published to date, with centers worldwide trying to take the lead and find a solution to this problem.

Systematic reviews and meta-analyses represent the highest level of evidence given to a structured search method, with critical appraisals limiting bias and reaching a summative conclusion. Systematic reviews and meta-analyses are now an integral part of clinicians' daily practice. They help busy clinicians stay up-to-date by supplying aggregate data from multiple studies and facilitates evidence-based medicine. These studies are also often used in the synthesis of clinical guidelines[2].

Herein, we aimed to collect all systematic reviews and meta-analyses published related to COVID-19 to better identify available evidence, highlight gaps in knowledge, and elucidate further meta-analyses and umbrella reviews need that to be performed.

## MATERIALS AND METHODS

### *Searching strategy*

We extracted systematic reviews and meta-analyses covering a range of aspects related to COVID-19 (coronavirus disease) assessment, prevention, management, testing, analysis, and epidemiological findings. We accessed full-text articles in the English language on COVID-19 across databases including Embase, Medline, and Cochrane. We focused on extracting coronavirus disease data and findings published between January 01, 2020, and October 30, 2020. We formulated various combinations of keywords, including severe acute respiratory syndrome (SARS), SARS virus, coronavirus disease, COVID-19, and SARS coronavirus-2 (SARS-CoV-2), to fetch the articles of interest.

### *Inclusion/exclusion parameters*

We did not consider the retrieval of rapid reviews, scope reviews, opinion papers, guidelines documents, panel reviews, and other review articles for our narrative review—the included articles are based on full-text and freely accessible studies available in the public domain. Our articles specifically included systematic reviews and meta-analyses on coronavirus disease. We excluded systematic reviews/meta-analysis with COVID-19 as the secondary focus or data/analyses of morbidities/comorbidities other than coronavirus disease.

### *Selected studies*

The full-text publicly accessible studies were copied into our centralized database for their data assessment and thematic analyses.

## RESULTS

Searching Embase, Medline, and Cochrane databases resulted in 1906, 669, and 19 results, respectively, that comprised 2594 studies. 515 duplicates were subsequently removed, leaving 2079 studies.

The inclusion criteria were systematic reviews or meta-analyses. Of 860 results were excluded for being a review article, scope review, rapid review, panel review, or guideline that produced a total of 1219 studies (Figure 1).

After screening, articles were then categorized into clinical presentations, epidemiology, screening and diagnosis, severity assessment, special populations, and treatment. Subsequently, the articles were then divided into another subclassification of the following groups: gastrointestinal, cardiovascular, neurological, stroke, thrombosis, anosmia, and dysgeusia, ocular manifestations, nephrology, cutaneous manifestations, D-dimer, lymphocyte, anticoagulation, antivirals, convalescent plasma, immunosuppressants, corticosteroids, hydroxychloroquine (HCQ), renin-angiotensin-aldosterone system (RAAS), technology, diabetes mellitus (DM), obesity, pregnancy, children, mental health, smoking, cancer, and transplant, as seen in Table 1.

## DISCUSSION

### *Epidemiology*

We have reviewed 171 systematic reviews regarding the epidemiology of COVID-19 infection. The incubation period of COVID-19 showed a median of 5.1 d with the 95$^{th}$ percentile of 11.7 d. The incubation period of COVID-19 that induced severe acute respiratory distress syndrome had an average of 6.0 d[3].

Several systematic reviews showed mortality with hospitalization was invasive mechanical ventilation was 13%[4]. Higher mortality was seen in patients with the following factors: Living in the European region, male sex, older age, active smoking, alcohol use, intensive care unit admission, comorbid conditions such as DM, obesity, hypertension, chronic lung disease, cerebrovascular disease, coronary heart disease, chronic renal disease, chronic liver disease and presence of malignancies[5,6]. The fatality rate was approximately 0.68%, with very high heterogeneity[5]. Some reviews described specific gene susceptibilities and recommended further genetic research[6]. O blood group is thought to be protective against COVID-19 with regard to mortality and susceptibility[7].

Several systematic reviews showed the most common laboratory or radiological finding of COVID-19 was lymphopenia, bilateral ground opacities in lungs, elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or creatinine. Fever, cough, and fatigue were the most common presenting clinical symptoms[8]. Dyspnea, anosmia, diarrhea, and myalgia were also frequently found in patients[9]. Healthcare workers (HCWs) who were positive with real-time reverse transcription polymerase chain reaction (RT-PCR) showed no symptoms in 40% of cases, 5% showed severe clinical complications, and 0.5% unfortunately died[9].

Regarding personal protective equipment (PPE), face mask users had decreased transmission, especially with N95 or similar equipment level[10]. Maintaining a physical distance of 1 meter or more and eye protection also revealed lower transmission rates[11]. Reusing masks did not yield a statistically significant result. Duration of PPE usage was recommended for no more than six hours of continuous use, with a break needed every two to three hours. PPE use is advised with appropriate hydration and skincare. The use of a powered air-purifying respirator (PAPR) is associated with greater heat tolerance but lower scores for mobility and communication ability. However, the reviews do not indicate a difference in HCW infection utilizing PAPR devices *vs* other compliant respiratory equipment. PPE can also be reused if they receive the appropriate dose of ultraviolet germicidal irradiation (UVGI) treatment[12].

Systematic reviews regarding disinfectants recommended using UVGI with vaporized hydrogen peroxide, non-thermal plasma, and air filters with photocatalytic disinfection[13]. Irritability of skin with propanol and isopropanol use was noticed but was less than frequent hand washing with detergent[14].

Systematic reviews regarding transmission showed inconclusive evidence about the viability and infectivity of SARS-CoV-2 in aerosol-generating procedures, but some studies showed an increased risk of infection with endotracheal intubation[15]. Clusters of infection played an important role. Frequently touching the T-zone (eyes, nose, mouth, chin) increases the chance of COVID-19 infection[16]. Transmission from an asymptomatic/pre-symptomatic patient is possible and more significant with pre-symptomatic patients. Quarantine is an essential factor in reducing the incidence of transmission[17]. No sexual or vertical transmission was observed and was not related to the route of delivery or breastfeeding[18]. A warm and humid climate reduced the

**Table 1 Classification of the systematic reviews**

| No. | | Clinical presentation | Epidemiology | General | Screening and diagnosis | Severity assessment | Special populations | Treatment | Grand total |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Mental | 15 | 6 | | 2 | 2 | 34 | 4 | 63 |
| 2 | Gastrointestinal | 33 | 3 | | 6 | 6 | 9 | | 57 |
| 3 | Cardiovascular | 15 | 3 | | 3 | 7 | 9 | 2 | 39 |
| 4 | Children | 4 | | 1 | 1 | | 33 | | 39 |
| 5 | Neurology | 33 | | | | 1 | 2 | | 36 |
| 6 | Diabetes | 5 | 2 | | 1 | 8 | 11 | 2 | 29 |
| 7 | Hydroxychloroquine | | | | | | | 28 | 28 |
| 8 | Technology | | 1 | | 5 | | 14 | 4 | 24 |
| 9 | RAAS | | | | | 5 | 1 | 15 | 21 |
| 10 | Antiviral | | | | | | | 20 | 20 |
| 11 | Cancer | | | | | | 20 | | 20 |
| 12 | Pregnancy | 1 | 1 | 1 | 1 | | 16 | | 20 |
| 13 | Transmission | | 18 | | | | | | 18 |
| 14 | General | 16 | | 1 | | | | | 17 |
| 15 | Smoking | 1 | 3 | | | 3 | 8 | 1 | 16 |
| 16 | Thrombosis | 13 | | | 2 | 1 | | | 16 |
| 17 | Obesity | | 1 | | | 7 | 6 | | 14 |
| 18 | Smell | 14 | | | | | | | 14 |
| 19 | Corticosteroids | | | | | | | 13 | 13 |
| 20 | Stroke | 7 | 1 | | | 2 | 3 | | 13 |
| 21 | D-dimer | | | | 9 | 3 | | | 12 |
| 22 | Renal | 9 | | | | 1 | 1 | | 11 |
| 23 | Lymph | | | | 6 | 3 | | | 9 |
| 24 | Cutaneous | 8 | | | | | | | 8 |
| 25 | Ocular | 8 | | | | | | | 8 |
| 26 | Anticoagulation | | | | | | | 7 | 7 |
| 27 | Convalescent plasma | | | | | | | 6 | 6 |
| 28 | Immunosuppressive | | | | | | | 6 | 6 |
| 29 | Transplant | | | | | | 5 | | 5 |
| 30 | Hospital | 1 | | | | 1 | 2 | | 4 |
| 31 | Incubation | 1 | 3 | | | | | | 4 |
| 32 | PPE | | 4 | | | | | | 4 |
| 33 | Traditional Chinese | | | | | | | 4 | 4 |
| 34 | Chinese | | | | | | | 3 | 3 |
| 35 | Older adult | 2 | | | | | 1 | | 3 |
| 36 | Rehab | | | | | | 2 | 1 | 3 |
| 37 | Sex | | 2 | | | 1 | | | 3 |
| 38 | Asthma | 2 | | | | | | | 2 |
| 39 | Asymptomatic | 2 | | | | | | | 2 |
| 40 | Cytokine | | | | | 2 | | | 2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 41 | Disinfection | | 2 | | | | | | 2 |
| 42 | Fatality | | 1 | | | | 1 | | 2 |
| 43 | Fibrin | | | | 2 | | | | 2 |
| 44 | Guillain-Barre | 2 | | | | | | | 2 |
| 45 | Oral | 1 | | | | | 1 | | 2 |
| 46 | Thrombocytopenia | 2 | | | | | | | 2 |
| 47 | Kawasaki | 1 | | | | | | | 1 |
| 48 | Multisystem inflammatory | 1 | | | | | | | 1 |
| 49 | Obstructive sleep apnea | | | | | | 1 | | 1 |
| 50 | Unclassified | 27 | 120 | 14 | 139 | 62 | 82 | 155 | 579 |
| | Grand Total | 223 | 171 | 17 | 177 | 115 | 263 | 271 | 1219 |

RAAS: Renin-angiotensin-aldosterone system; PPE: Personal protective equipment.

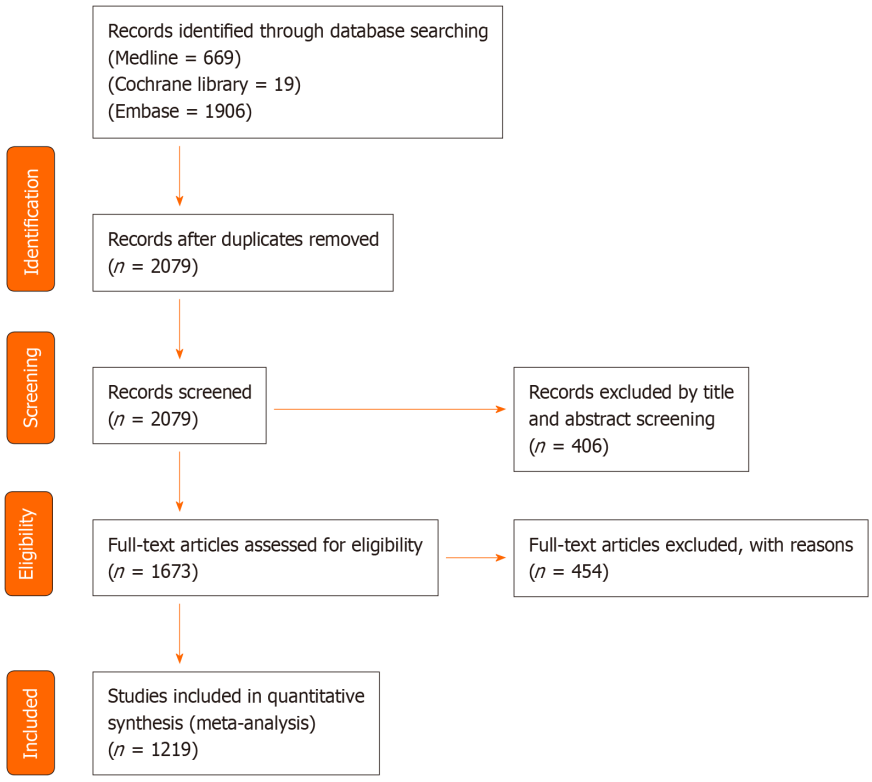


**Figure 1 Shows a PRISMA flow diagram of our literature search.**

spread of COVID-19. Viral carriage on the outer surface of surgical masks worn by HCW who treat patients with clinical respiratory illness is low[19].

### *Transmission*

In a review of the 18 systematic reviews regarding the transmission of SARS-CoV-2, the consensus remains that respiratory infection *via* droplet and aerosolization in the human-to-human setting remains the most likely form of infection and that other forms such as contact with fomites and vertical transmission played a small role in contamination with the disease[20,21].

In one review article, the aerosolized transmission of SARS-CoV-2 showed that the virus was still viable. However, no correlation was shown regarding aerosolized transmission and disease[20]. If infection were to occur, contact would have to be in an

enclosed environment. For aerosol transmission, the highest risk was related to health care workers involved in aerosol-generating procedures with the high-risk involving direct airway manipulation such as manual ventilation with intubation[15].

With the onset of the SARS-CoV-2 pandemic, data regarding all transmission forms has been researched, leading to one systematic review that found no direct virologic evidence of vertical transmission. Another review concluded that neonatal infection with SARS-CoV-2 was uncommon and that the rate of infection was no more significant than when the baby was born vaginally, *via* cesarean section, or if the baby breastfed and remained with the mother[22].

As human-to-human contact is responsible for SARS-CoV-2 infection, one systematic review analyzed 108 cluster infections from 13 countries[23]. This concludes that because the most common places associated with infection were family contact, community transmission, transportation, and healthcare-related facilities[23], minimizing unnecessary contact and social distancing should be strictly implemented to contain infection clusters.

### *Screening and diagnosis*

One hundred seventy-seven articles were reviewed regarding the screening and diagnosis of COVID-19. The most common presenting symptoms to screen for were fever and cough. Studies also showed associated anosmia and loss of taste[24]. The most susceptible patients seem to be those with hypertension, diabetes, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Males older than 50 with comorbidities were more likely than females to have severe pneumonia and dyspnea[25]. The pediatric population presented more commonly with diarrhea, and the infection was notably less severe. Innovations in technology such as contact tracing applications and telemedicine have been able to help promote surveillance of the disease and have been integrated into traditional medicine. Contact tracing tools have been shown to reduce transmission but can be challenging to implement in large populations[26]. There are privacy concerns, and further studies would be needed to show their effectiveness. Furthermore, infrared thermal screening was studied against the traditional thermometer, and it showed a low positive predictive value during the initial outbreak but continued to have a high negative predictive value throughout the pandemic's early and later stages[23].

Many labs were significantly appropriate for screening purposes. Elevated inflammatory markers, biochemical biomarkers, and hematological markers such as CRP, erythrocyte sedimentation rate (ESR), troponin, decreased lymphocyte count, fibrinogen, fibrinogen degradation products level, LDH, ferritin, and D-dimer on admission were associated with a poor outcome and were predictive of the severity and mortality of COVID-19 pneumonia[27]. An elevated D-dimer was linked to an overdiagnosis of disseminated intravascular coagulation (DIC) and led to inappropriate treatment with anticoagulation therapy[28]. Platelet count did not correlate with the severity of the disease. High levels of ferritin and interleukin-6 (IL-6) were elevated due to the cytokine storm from COVID-19, which correlated with increased intensive care unit (ICU) stays and mechanical ventilation requirements. The most common abnormality for the liver function test was hypoalbuminemia. However, some studies have shown elevated ALT, AST, and total bilirubin. An elevated Red Cell Distribution Width also correlated with the disease's severity[29].

There were numerous tools used for diagnosis. Stool studies exhibited more viral shedding than respiratory tract samples, which were easier to collect from the pediatric population. Studies showed that the RNA strains could be found in the saliva within seven to ten days of onset. Nasopharyngeal swabs showed more sensitivity than oropharyngeal swabs. Salivary samples are questionable, with inadequate sample power to comfortably substitute for the PCR based nasopharyngeal swab. The Reverse Transcriptase PCR has a sensitivity of 64% and specificity of nearly 100% but should not be used alone as the gold standard due to bias in measurements[30]. No evidence has shown a practical point of care serologic test at the time of this analysis. The virus uses Angiotensin-converting enzyme-2 (ACE2) receptors to enter the body. ACE2 receptors are found in the respiratory epithelium, gastrointestinal mucosa, and liver cholangiocytes. A portion of the adult patients presented with gastrointestinal symptoms, where computed tomography (CT) scans of the abdomen showed findings including small and large bowel wall thickening and pneumatosis intestinalis. The indications that the Infectious Disease Society of America recommends for serologic testing for antibodies are patients with clinical symptoms who have a negative diagnostic test and children with multisystem inflammatory syndrome to estimate antibody levels against the disease. The virus is positive in blood, urine, and stool, with higher viral shedding in blood and stool. Urine has been shown to have increased

viral shedding in more severe patients with systemic disease and those requiring ICU admissions[31].

COVID-19 has predominantly been diagnosed using a real-time PCR test and/or chest CT with no consensus on which method is superior[32,33]. CT scans are sensitive but not specific, as imaging cannot differentiate coronavirus from other respiratory diseases. A chest CT with no pathologic findings cannot exclude COVID-19 alone, even if the patient has no symptoms. Also, positive CT findings with no symptoms may still warrant further testing because 90% of those patients later developed symptoms. The most common findings are ground-glass opacities with a distribution in the peripheral regions[34,35]. Other common findings are interlobular septal thickening and air bronchograms. COVID-19 lung pathology has consistently shown histology consistent with acute respiratory distress syndrome (ARDS) with frequent microthrombi[36]. Patients do not usually present with lymphadenopathy or pleural effusions. Lung ultrasounds of COVID-19 patients most commonly show the B-line interstitial pathology pattern[37]. CT scans of the chest still seem to be the most helpful imaging modality in pediatric patients and can detect pneumonia even before presenting symptoms.

### *Clinical presentation*

We included 204 systematic review articles looking at clinical presentations of COVID-19. This disease can present in many ways. Nearly all organ systems can be affected, including the respiratory, cardiovascular, renal, gastrointestinal, endocrine, reproductive, central nervous system, bone marrow, and skin. Although most COVID-19 patients typically present with respiratory symptoms, ranging from upper airway disease to severe ARDS with multiorgan failure, many systematic reviews examined other organ systems implicated in the body. Several review studies concluded that cardiac and renal complications following respiratory complications are the most common clinical complications of COVID-19[38,39]. The most prevalent comorbid condition in patients with COVID-19 is diabetes, with it being both a significant risk factor and an indicator of poor prognosis[40]. Also, studies have shown that the elderly population has been affected by COVID-19 with high severity[41].

High rates of cardiovascular disease have been reported, and several studies showed a significant association with increased mortality and ICU admissions. Arrhythmias are prevalent and are reportedly the second most common cardiovascular complication[42,43].

Many reports are available that look at COVID-19 infection and the prothrombotic state, explained by coagulation activation, endothelial dysfunction, and formation of in situ thrombi rather than embolization of peripheral thrombi. This cascade of events causes deep venous thrombosis, pulmonary microthrombi, pulmonary embolism, cerebral venous thrombosis, and acute ischemic strokes that in some cases lead to a critical condition with poor long-term outcomes, residual disability, and prolonged rehabilitation[44]. Some studies showed ischemic strokes to be the most important prognostic marker and indicator of severity and poor clinical outcome. Prompt evaluation and early treatment with anticoagulation were associated with reduced mortality and better clinical outcome[45].

It has been found that many patients experience digestive symptoms as the primary complaint. Some studies have reported that patients with digestive symptoms had a trend to develop severe critical illnesses. Several available meta-analyses suggest that acute liver injury and elevated liver enzymes were significantly associated with COVID-19 severity and predicted worse outcomes.

Acute kidney injury (AKI) is a common complication of COVID-19. AKI's incidence is between 8%-20% depending on the study. In some studies, the presence of AKI is associated with a 13-fold increased risk of mortality[46]. Age, DM, hypertension, and baseline serum creatinine (SCr) levels are associated with increased AKI incidence. Concerns have emerged about the potential impact of COVID-19 on male reproductive organs and male fertility.

There is strong evidence of neurological involvement ranging from Guillain–Barré syndrome, delirium, and encephalitis, to cerebral venous thrombosis and ischemic strokes, with acute ischemic strokes being the most frequently reported complication with the highest mortality rate. Neurologic manifestations are shown to develop approximately one to two weeks following the onset of respiratory symptoms[47]. Olfactory and gustatory dysfunction have been described and used to aid in clinical diagnosis as they present reasonably early after the disease's contraction. Cutaneous involvement has been described in several review articles and was shown to manifest occasionally in asymptomatic carriers. Several ongoing studies investigate the role of early identification of cutaneous involvement, which may be vital to early diagnosis

and lead to a possible better prognosis[39].

Finally, several systematic reviews have looked at the implication of COVID-19 on mental health and reported increased suicide risk, depression, and anxiety levels in the general population irrespective of COVID-19 status.

### Gastrointestinal

We included 57 systematic review articles regarding the association of COVID-19 with the gastrointestinal system. These studies found that those with high rates of digestive symptoms, acute liver injury, and elevated liver enzymes are more likely to develop severe/critical illnesses. Common presenting gastrointestinal symptoms included abdominal pain, nausea, vomiting, and diarrhea. Frequent abnormalities in liver function tests included hypoalbuminemia, derangements in gamma-glutamyl-transferase, increased bilirubin values, prolonged prothrombin time, and deranged aminotransferases[48]. Patients with preexisting liver abnormalities such as hepato-cellular carcinoma, metabolic associated fatty liver disease, and chronic liver disease had an increased risk of COVID-19 disease progression, more severe COVID-19 infection, and increased mortality rates[49]. Two systematic reviews found that in patients with inflammatory bowel disease and COVID-19, diarrhea occurred more frequently; however, these patients did not appear to be at a higher risk of developing COVID-19 than those in the general population[50,51]. One systematic review investigated the relationship between COVID-19 and fecal nucleic acid testing in the pediatric population and found that the positive rate for fecal nucleic acid testing in COVID-19 children was relatively high, suggesting that fecal nucleic acids can be used as a method of detecting COVID-19 in this population[52]. Additionally, several studies observed that the gastrointestinal manifestation of COVID-19 raises the question of possible transmission through the fecal-oral route in both the adult and pediatric populations, indicating that healthcare workers should exercise caution when collecting stool samples.

### Cardiovascular

We included 39 systematic reviews about patients' cardiovascular manifestations with COVID-19 infection and the clinical significance of biomarkers, preexisting cardiovascular disease, and thromboembolic disease risk.

The most common comorbidities associated with increased mortality among patients with COVID-19 infection were hypertension, coronary artery disease, and heart failure. These factors were positively correlated with an augmented risk of hospitalization, poor outcomes, and death. Although preexisting conditions consistently demonstrated increased complications and mortality, COVID-19 also increased cardiovascular disease by inducing cytokine storms[53]. There was an association between COVID-19 infection and direct cardiovascular complications, including myocardial injury, heart failure, myocardial infarction, myocarditis, arrhythmias, and blood clots, leading to increased mortality and adverse outcomes. There was poor documentation about the incidence and nature of arrhythmias in the setting of COVID-19. A systematic review reported Takotsubo syndrome could be associated with COVID-19 infection and demonstrated a higher prevalence in older women with higher rates of complications[54].

The biomarkers associated with increased mortality were LDH, creatinine kinase, brain natriuretic peptide, and troponin I. Lastly, the coagulopathies observed in patients with COVID-19 infection ranged from mild laboratory alterations to DIC. It is proposed that the endotheliopathy could be from direct endothelial infection with SARS-CoV-2 and indirect damage caused by the inflammation.

Cardiovascular complications added to the elevated morbidity and mortality in patients with preexisting cardiovascular risk factors. Further studies could help better to identify the role of SARS-CoV-2 in this population.

### Neurology

The most common neurological symptoms in our analyses of COVID-19 patients included chemosensory dysfunction, vascular events, neurologic syndromes, encephalopathies, and inflammation[55,56]. Strokes were associated with the highest mortality rate. Neurological manifestations developed one to two weeks after the onset of respiratory disease, but they were also seen in patients who did not have any respiratory disease. One systematic review article regarding the severity assessment of COVID-19 patients with neurological symptoms described that the predominant central nervous system symptoms were headaches and dizziness, while the most common peripheral nervous system symptoms were dysfunction in taste and smell.

Neurologic similarities were seen in the symptomatology of COVID-19, SARS, and Middle East respiratory syndrome[53,57]. All three viral syndromes were associated with similar neurologic complications, such as fatigue, headache, and smell and taste disorders. The myriad of neurological manifestations in COVID-19 syndrome should be further explored to elucidate the pathogenesis of COVID-19 related neurologic disease.

### Stroke

According to 13 articles, including multiple meta-analyses and systematic reviews, COVID-19 infection has been associated with significant neurological manifestations within the central nervous system, including stroke, intracranial hemorrhage, encephalomyelitis, and acute myelitis. We included one systematic review and meta-analysis that suggests an increased risk of stroke in hospitalized patients with preexisting cerebral vascular disease. This increased risk of stroke was associated with an increase in adverse outcomes, most notably mortality. One multicenter study and meta-analysis suggest that more severe COVID-19 infections are associated with a higher risk of stroke, with an overall pooled risk estimated at 2.9%[58].

One systematic review and analysis showed COVID-19 patients who suffered from stroke symptoms developed neurologic symptoms after an average of nine days from the onset of their respiratory illness[59]. Multiple studies suggest that pro-inflammatory markers associated with COVID-19 infection, including D-dimer, IL-6, ferritin, and fibrinogen, may contribute to an inflammatory process mediating cerebrovascular accidents. One study found correlations with large vessel thrombosis and anterior circulation strokes[60], but more data and institutional collaboration of information are needed to understand the significance of the anatomic locality of strokes associated with COVID-19 infection. This multi-centered approach may elucidate future guidelines for certain patients, risk factors, or clinical findings unique to COVID-19 patients with neurologic symptoms.

### Thrombosis

We included 16 systematic review articles regarding arterial and venous thromboembolism in patients with COVID-19 infection. Thromboembolic events in the deep veins of the lower extremities, pulmonary arteries, and cerebral veins suggested that the high rate of pulmonary artery occlusion was secondary to both embolic events from deep veins of legs and in situ thrombosis in pulmonary arteries. The proposed mechanism for these thrombotic events includes a combination of endothelial injury, platelet activation, hyperviscosity, blood flow abnormalities, and immune reactions. Segmental and subsegmental arteries were more commonly involved than the main pulmonary arteries[61]. The severity of COVID-19 infection correlates directly with thrombotic events, with a higher incidence of pulmonary embolism reported in ICU patients than general medical floor patients.

Additionally, it was discovered that ICU level patients also experienced a higher incidence of failed or inappropriate dosing of anticoagulation, whether preventive or therapeutic. Overall, higher mortality was seen in COVID-19 patients with thromboembolic events. However, data is limited in addressing whether or not there are mortality benefits seen with anticoagulation.

### Anosmia and dysgeusia

There are 14 systematic review articles about chemosensory dysfunction. Ten articles discussed anosmia and dysgeusia, three articles for anosmia only, and one article for dysgeusia. Anosmia and dysgeusia are common early symptoms of COVID-19. There is a discrepancy in the prevalence of anosmia and dysgeusia according to sensitivity [62]. The prevalence of anosmia in an average individual was shown to vary according to age, sex, and testing technique[63]. The prevalence of anosmia, dysgeusia, or both as a symptom for COVID-19 was less often seen in male and geriatric patients. Anosmia was shown to be highly specific for COVID-19 and should be included in the evaluation process of suspected patients. As these dysfunctions were often seen early in the disease course, their presence may indicate early disease onset and indicate the clinician recommended isolation to prevent transmission. The mechanism of viral pathogenesis and causality remains a topic of study.

### Ocular manifestations

The most common ocular presentations of COVID-19 are conjunctivitis, hyperemia, photophobia, dry eyes, chemosis, epiphora, blurry vision, foreign body sensation, ocular pain, floaters, and eyelid dermatitis. Patients may present with mild eyelid

edema and/or tender, palpable preauricular and submaxillary lymph nodes. Rare presentations include herpes-like pseudo-dendritic infiltration of the cornea and bilateral pseudomembranous conjunctivitis.

COVID-19 virus entry is mediated by the binding of viral surface spike (S) glycoprotein to the ACE2 receptor[64]. Two primary mediators (the ACE-2 receptor and cell surface protease enzyme, TMPRSS2) are involved in this mechanism. Immunohistochemistry has shown the presence of ACE-2 receptors on the conjunctiva, limbus, and cornea. The ocular manifestations' treatment options include topical and systemic preparations, with antibiotic eye drops and artificial tears with or without corticosteroid eye drops.

COVID-19 patients treated with proning have had additional side effects, including exposure keratopathy, microbial keratitis, increased intraocular pressures, occlusion of the central retinal artery, and in some severe cases, orbital compartment syndrome. The prevention of acute orbital compartment syndrome was achieved with surgical interventions such as lateral canthotomy and cantholysis. Keratopathy can be prevented by lubricant ointments, moisture chambers, and polyethylene films. Topical viscous lubricants and mechanical closure of the eyes with hypoallergenic tapes or topical dressings may also be used.

This meta-analysis emphasizes the need for PPE for all healthcare workers involved in the care of COVID-19 patients to prevent exposure and infection. Along with a gown and gloves, wearing eye protection is also essential to prevent the spread of COVID-19 infection as eye mucous membranes can play a crucial part in transmitting COVID-19 viral particles.

### Nephrology

A review of 10 literature publications showed that kidney injury incidence varies widely across studies, depending primarily on the severity of the disease. In one pooled analysis, AKI was detected in 8.3% of patients with COVID-19 *vs* 19.9% in critically ill patients[65]. Moreover, the association between renal impairment and poor outcomes is well established, with significantly increased mortality and need for ICU level of care. These findings were irrespective of age, sex, or other comorbidities such as hypertension, diabetes, and respiratory diseases. The association of mortality between preexisting chronic kidney disease (CKD) and the severity of COVID-19 infection has been studied[66]. The need for renal replacement therapy (RRT) correlated with poor outcomes. Mortality was also significantly increased in renal transplant recipients. Several studies found a statistically significant rise in SCr and blood urea nitrogen in patients with COVID-19, as well as the severity of proteinuria, hematuria, and decline in estimated glomerular filtration rate. Viral RNA positivity was detected in the urine of 5.7% of patients in some studies[67], but it is unclear if this correlated with disease severity. While both the occurrence of and mortality due to kidney injury seem to be declining (≥ 75% in critically ill patients with mortality of 67% in studies published before the end of May 2020), it still constitutes a significant morbidity and mortality factor in COVID-19 patients. For this reason, health experts call for the early detection of renal dysfunction in patients with COVID-19 to prevent further kidney damage and provide appropriate renal support.

### Cutaneous manifestations

While respiratory and gastrointestinal manifestations are the predominant presenting features of COVID-19 patients, reports on cutaneous manifestations are increasingly noted. In some studies, the estimated prevalence of cutaneous manifestations in COVID-19 ranges between 0.2%-20%. The cutaneous manifestations recorded are urticaria, chilblain-like lesions, livedo reticularis, petechial rash, and finger/toe gangrene, with the majority of lesions localized on the trunk, followed by extremities [68]. Cutaneous involvement usually follows the respiratory symptoms; nonetheless, in the minority, it preceded systemic features.

Histopathological analyses suggested a predominance of spongiosis, perivascular infiltrate of lymphocytes, and thrombogenic vasculopathy, but the potential mechanisms remain to be investigated. One small systematic review of 507 European patients suggested that the presence of the ACE-2 receptor on skin keratinocytes proposes that skin might be a potential target for the virus[69].

A systematic review from Switzerland mentions vesicular rashes during an initial diagnosis of COVID-19, suggesting cutaneous involvement as a valuable prognostic factor for disease progression and correlation to disease severity[70].

Overall, developing a comprehensive understanding of all clinical manifestations of COVID-19 infection will require knowledge of all possible disease presentations. It is suggested that accurate and rapid identification of cutaneous manifestations may be

vital to early diagnosis and can portend a better prognosis in COVID-19 patients. Notably, the majority of these studies failed to report any correlation between COVID-19 severity and skin lesions.

### Severity assessment

Although the reported mortality rates through the pandemic's progression have decreased, ICU mortality rates remain higher than those seen in ICU admissions for non-COVID viral pneumonia. Over 110 systematic review articles investigating the aspects of severe COVID-19 infection were analyzed with the goal of risk stratification and the mitigation of poor outcomes.

Predisposing factors which increase the patient's risk of severe disease should be assessed at the onset of admission. Multiple studies found that individuals with obesity, cardiovascular disease, hypertension, diabetes, chronic lung disease/smoking history, CKD, chronic liver disease, history of cerebrovascular events, male sex, or older age were found to have a more severe illness (with hypertension, cardiovascular disease, and diabetes conferring the most significant risk). Specific clinical assessments were found to have a greater likelihood of severe disease burden, including dyspnea at presentation, elevated pro-inflammatory markers, evidence of coagulopathy, signs of cardiac damage, acute kidney injury, lymphopenia, or neutrophilia[71].

Next, physical and lab assessments that have been found to indicate a greater likelihood of more severe disease are patients presenting with dyspnea, elevated inflammatory markers (CRP, ESR, somatostatin analogue, IL-6, IL-8, PCT, D-dimers, ferritin, interferon-α, tumor necrosis factor-α), evidence of coagulopathies (elevated D-dimers, thrombocytopenia, DIC, thromboembolic events), signs of cardiac damage (elevated LDH, IL-6, creatine kinase MB, elevated Pro-B-type natriuretic peptide, right ventricular dilation/evidence of right heart strain, emerging arrhythmias), acute kidney injury, and white blood cell findings consistent with either lymphopenia or neutrophilia (the high neutrophil-to-lymphocyte ratio is positively associated with disease severity)[72,73].

Critical care management of diffuse alveolar damage and pulmonary vasculature microthrombi can be achieved through mechanical ventilation or extracorporeal membrane oxygenation (ECMO). However, there have been increasing incidents of complications seen in patients requiring ECMO with concurrent COVID-19 infection, likely due in part to the hematological dynamic changes inherently involved in ECMO, coupled with the pro-inflammatory and pro-coagulopathic nature of the COVID-19 disease itself. Due to the reliable association with IL-6 and COVID-19 disease severity, tocilizumab and monoclonal antibody therapy early in the disease course have shown promising results. Additionally, RAAS inhibitors in hypertensive patients showed an improved prognosis in many cases[74].

The severity of COVID-19 infection in adults with the comorbidities mentioned above differs from pediatric and immunosuppressed patients. While the severity of the organic disease is severe, the psychological burden develops as the global pandemic continues. Studies show that isolation and social distancing measures necessary in epidemic states to minimize the spread of communicable diseases have significant psychological impacts on parents, children, and adolescents. Although long-term and persistent effects of the pandemic are currently unknown in instances of anxiety, depression, stress, and other mental strains yet to be discovered, what has been observed is that the duration of the isolation is having a more significant impact on the mental well-being of children and adolescents than the intensity of isolation. Solutions to mediate psycho-social burdens associated with the pandemic are evolving, but the child and adolescent developmental impact remain to be seen.

### D-dimer

D-dimer elevations as a sign of pro-inflammation are significantly related to COVID-19 infections. The activation of the coagulation cascade is a common feature of DIC and adverse clinical outcomes in COVID-19. D-dimer is an important prognostic tool that is often found to be elevated in patients with severe infection. Regardless of the D-dimer reference value, the studies show that D-dimer concentrations were significantly higher in patients with more severe infection than non-severe forms and were associated with an increased risk of mortality[75]. Early integration of D-dimer testing can be practical for better risk stratification and guidance in clinical decision-making. Further investigation is warranted to evaluate the appropriateness of D-dimer monitoring as a management tool for this disease.

### Lymphocytes

Meta-analyses evaluating the feasibility of specific markers in assessing the severity and prognosis of COVID-19 patients demonstrated a significant inverse association of peripheral lymphocyte levels with progression and mortality. Those patients with a low lymphocyte count at baseline were found to have a higher risk of disease severity. A meta-analysis reported that lymphopenia and neutrophilia on admission were significantly associated with increased risk of progression to severe disease and death, suggesting that these variables may help risk stratification models[76].

However, the results of studies regarding the prognostic value of lymphocyte subsets are inconsistent. A meta-analysis concluded that increased neutrophil/lymphocyte levels and a low lymphocyte-to-CRP ratio might indicate a poor prognosis in COVID-19 patients[77]. COVID-19 predictive equations were generated in another meta-analysis based on CRP and D-dimer levels and lymphocyte or the neutrophil count. These equations exhibited high specificity, sensitivity, positive and negative predictive values and suggested that the equations could predict the severity of outcomes of COVID-19 patients[78].

### Treatment

Treatment articles reviewed included those studying antiviral drugs such as Lopinavir/Ritonavir, Favipiravir, and Remdesivir. Lopinavir/Ritonavir did not show any significant difference in mortality or progression to a more severe course or cure. However, some benefits were seen in the duration of hospital stay. Favipiravir may have some role in improving clinical and radiological imaging but has no benefit on oxygen requirements or viral clearance. Remdesivir is the only antiviral drug that has been shown to improve recovery and reduce serious adverse events[79-81]. Additionally, it may reduce mortality, though some studies did not show mortality benefits. It was also seen that five-day treatment with Remdesivir might provide similar benefits with fewer harmful effects than a 10-d course[82].

The prevalence of venous thromboembolism in COVID-19 patients has been reported to be about 10%-35%, with autopsy results rising to 60%. Biomarkers related to platelet activation like D-dimer have been shown to have prognostic value in COVID-19 patients. There was a slight tendency to reduce the mortality rate using therapeutic anticoagulation in patients with COVID-19 on mechanical ventilation.

Current evidence shows no benefit in using HCQ in patients with mild to moderate COVID-19 infection. Additionally, HCQ has been associated with higher adverse events, including skin pigmentation, ocular toxicity, QT prolongation, and worsening psoriasis lesions[83].

The effect of convalescent plasma products is based on randomized controlled trials (RCT). In these trials, convalescent plasma did not decrease all-cause mortality, but early initiation may decrease mortality rate compared to late initiation. Convalescent plasma and immunoglobulin were both effective in relieving symptoms of COVID-19 [84,85].

Corticosteroids may reduce mortality in patients with COVID-19 and ARDS, but the evidence is inconsistent for patients with COVID-19 without ARDS. Excessive inflammatory response and lymphopenia were both associated with severity, leading to the recommendation that, if not contraindicated, steroids should be considered in the absence of adverse effects.

Tocilizumab is an interleukin-6 receptor antagonist that has been used in the treatment of severe COVID-19 infections[86]. There are indications that tocilizumab can reduce mortality and prevent mechanical ventilation in severe COVID-19 infections, but results need to be confirmed with high-quality clinical trials before the drug is implemented as a standard of care.

### Anticoagulation

Anticoagulation methods studied in the treatment of COVID-19 included unfractionated and low molecular heparin, apixaban, clopidogrel, dipyridamole, and tissue plasminogen activator. The association between mortality rate and incidence of thromboembolic events in patients with COVID-19 infection receiving venous thromboembolism prophylaxis was evaluated as combination therapy or single-drug therapy, with studies showing no superiority of any anticoagulant.

According to one article that looked at three separate studies[87], thromboembolism in COVID-19 infected patients does not warrant a change in guidance on thromboprophylaxis among hospitalized patients, but the studies have overall poor quality due to methodological limitations. The rest of the articles emphasize the importance of anticoagulation. Overall, the findings indicate that therapeutic doses might be associated

with better survival compared to prophylactic doses. Data suggests that prophylactic and therapeutic anticoagulation may reduce mortality in COVID-19 patients[88].

### Antiviral

Favipiravir, Lopinavir/Ritonavir, and Remdesivir were evaluated in our analysis, being studies in combination or as single-agent therapy. These articles compared antiviral drugs with other medications used for COVID-19 or standard of care. Favipiravir has a more favorable safety profile than other antivirals with mild and manageable side effects. The available data about combination therapy of Favipiravir with Lopinavir/Ritonavir is not enough to favor this combination over other treatments[89]. Remdesivir showed a positive impact on the hospitalized patients compared to the standard of care. The safety profile of Remdesivir in COVID-19 patients requires further studies with adequate design and power.

### Convalescent plasma

Articles focusing on the effectiveness of convalescent blood product (CBP) therapy in COVID-19 infection and severe acute respiratory infections of viral etiology showed that most of the included studies had a critical risk of bias, leading to their exclusion from the analysis. From the remaining studies, a decline of all-cause mortality was observed only in observational studies, where using CBPs earlier compared to using CBPs later was associated with a significant reduction in all-cause mortality. Additionally, CBPs did not increase the risk of adverse events between intervention and control groups. However, in RCTs, the all-cause mortality showed no difference between the interventional and control groups.

Overall, the certainty of the evidence was low to very low. The effectiveness of CBPs in COVID-19 infection has poor validated results, but their use appears to be safe[90]. This observation contrasts with SARS coronavirus infection, which was similarly low to very low-quality studies that have effectively proven CBPs reduce both all-cause mortality and symptom duration.

### Immunosuppressants

The role of immunosuppressants has been proposed as a possible treatment for the hyper-immune response in later stages of the infection, developing acute respiratory distress syndrome, multiorgan failure, and increasing mortality. The most discussed drug in our evaluation was the interleukin-6 receptor inhibitor monoclonal antibody tocilizumab (all six reviews), followed by corticosteroids, calcineurin inhibitors, and other immunosuppressants (one systematic review). The efficacy, mortality reduction, complication prevention, and their use alone or with the standard of care were discussed. The majority of the reviews show that the use of tocilizumab (either alone or in addition to the standard of care) has the potential to treat effectively, reduce mortality, and prevent mechanical ventilation[91]. One of the reviews evaluated provided no conclusive findings based on the low quality of evidence.

### Corticosteroids

The administration of systemic corticosteroids compared with usual care or placebo in critically ill patients with COVID-19 was associated with lower 28-d-all-cause mortality[92]. Most studies show that the late administration of steroids in the course of the disease provides benefit in most patients and more severe, critically ill patients; however, other studies instead demonstrated that there was no survival benefit found with the use of corticosteroids[93] and that mortality risk was increased with the use of corticosteroids, likely secondary to a longer length of stay, a higher rate of bacterial infection, hypokalemia, and several other adverse effects[94]. Therefore, although the use of corticosteroids in some cases improved the clinical features of viral pneumonia, there was no confirmed evidence of corticosteroid therapy reducing the mortality in all COVID-19 patients. Results from the RECOVERY trial highlighted that steroids could potentially be an excellent therapeutic weapon against the coronavirus[95]. There was also a significant reduction in death with dexamethasone, which was seen only in severe cases of patients on ventilators or moderate cases requiring supplemental oxygen therapy[96]. However, there was no benefit observed in mild to moderate patient cases without hypoxia who did not require oxygen. Nonetheless, further studies are required to account for the range of co-variables and confounders, which would detail the dosing regimen and the duration of corticosteroid therapy and the stage at which therapy should be initiated to benefit patients and avoid adverse effects of corticosteroids.

### HCQ

HCQ is an antimalarial drug used to treat rheumatological conditions, such as rheumatoid arthritis and systemic lupus erythematosus. It has been shown to have antiviral properties against COVID-19 "*in vitro*," but the evidence regarding its efficacy "in vivo" lacks the scientific support for its use[97]. Although considered a commonly well-tolerated drug, adverse effects to the gastrointestinal, cardiac, ocular, nervous, and dermatological systems were noted. The use of HCQ to treat SARS-COV-2 infection lacks efficacy in decreasing the risk of hospitalization or short-term mortality. This finding challenges the proposed association with increased mortality (either alone or in combination with azithromycin) and elicits the need for high-quality data from multicentric randomized control trials.

### RAAS

A review of 21 systematic reviews of dozens of studies across the globe has, for the most part, failed to find a significant association between RAAS blockade by either agent–or even by both combined in some studies–with the risk, severity, or mortality of COVID-19 infection.

A massive debate on the role of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in patients with COVID-19 and whether these agents should be continued in infected individuals was a significant question in the medical community at the onset of the pandemic[64,98]. Many global studies have mostly failed to find a significant association between RAAS blockade with risk, severity, or mortality in COVID-19 patients. While the viral spike coat protein of SARS-CoV-2 binds to the human ACE-2 cell surface receptor to cause infection, those hypertensive patients currently managed on ACEi or ARBs had a small, albeit significant, decrease in mortality. Some studies found this mortality benefit to be associated only with ARBs, not ACEi, while others have reduced death rates with both classes of medicines. This fact has encouraged some health experts to suggest that RAAS inhibition may be protective against COVID-19; however, such a recommendation requires more robust evidence. Current guidelines advise that hypertensive patients should continue taking ACEi or ARBs if they become infected with COVID-19; they do not recommend the initiation of ACEi or ARBs to treat COVID-19 infection.

### Technology

We included 24 systematic review articles about the technology used to deliver quality healthcare during the COVID-19 pandemic. As face-to-face encounters have become more restricted over the past several months, the rise of telemedicine has allowed many health care professionals to provide continuity of care for patients. The introduction of various telecommunication modalities, including videoconferencing, telerehabilitation, tele-neuropsychology, teledermatology, telemonitoring, teletherapy, and telementoring, have been a great way to curb the transmission of COVID-19, increase access to healthcare, and triaging patients suffering from various ailments [99]. Analysis of these articles has revealed that the general population has adopted an overall favorable telemedicine response because of its convenience and comfort.

Unfortunately, telemedicine also has several drawbacks. Many patients do not have adequate internet access and/or are not technology savvy. Furthermore, patients may have limited care because telemedicine services do not always guarantee the same medical care team. Additionally, telemedicine is more beneficial for patients with chronic conditions that do not always require a physical examination. Although telemedicine benefits are irrefutable, we will need more RCT to determine the long-term effects and costs of telemedicine on society.

### Special populations

Regarding special populations with COVID-19, we included 263 systematic reviews. Of these, children were the most common, with 33 articles reported. These articles' overall consensus pointed out that most children tend to have mild disease and a better prognosis. Physicians needed to be mindful of this population: Multisystem inflammatory syndrome cases in children (MIS-C), which is fatal if early recognition, supportive management, and early immunomodulators are not implemented. Morbidity and mortality were low overall In the neonatal population[100-102]. The second special population we looked at was pregnant women, with 16 articles evaluated. Most pregnant women were reported to be asymptomatic, although it was observed that preterm birth rates in some women were higher compared to COVID-19 negative pregnant women. Some unique findings included decreased white cell count

and possible impairment in follicular and luteal phases. Vertical transmission of COVID-19 was reported to be low.

Patients with malignancies and COVID-19 were reviewed, included in 19 articles. Cancer patients tend to have higher inflammatory markers at presentation, more severe symptoms clinically, greater risk of complications, and increased ICU admissions. Chemotherapy in these patients has not been associated with an increased risk of severe COVID-19. Delay in cancer treatment in COVID-19 positive cancer patients has been favored by many oncologists, although no evidence of interactions of COVID-19 treatment and chemotherapy has been identified[103].

Regarding diabetic patients with COVID-19 infection, they were reported to have a higher prevalence of progression to ARDS, which led to a higher rate of ICU admissions and subsequent mortality. It was also noted that diabetic ketoacidosis (DKA) in COVID-19 patients tended to lead to mortality that approached 50%. Eight articles regarding smoking and COVID-19 were analyzed. There seems to be a positive correlation between smoking and disease severity. This applies to both current and past smokers, although further studies need to be performed before establishing this connection. The obese population was reviewed in five articles. Findings showed obese individuals had a higher risk of contracting COVID-19, increased risk of ICU hospitalizations, severe disease, as well as diminished prophylactic and therapeutic responses to standard treatment. Lastly, we evaluated transplant patients with COVID-19 infection, covered in five articles. Higher mortality rates were observed in patients with solid organ transplants older than 60 years of age. There was a low incidence of reported COVID-19 infections in renal transplant patients; however, patients were reported to have more severe disease progression in those who were infected. This particular population was at greater risk of acute renal failure, ICU admission, and RRT[104]. As we look at the diverse populations studied, we find that COVID-19 not only impacts our ability to diagnose and treat early but may affect each population differently.

### DM

We included two systematic review articles regarding the epidemiology of COVID-19 patients with DM. The articles found diabetes had a negative effect on the health impact of COVID-19, and the prevalence of DM in patients with severe COVID-19 was significantly higher than moderate patients with COVID-19. Five systematic review articles were evaluated regarding the clinical features of COVID-19 in patients with DM; these articles concluded that those with severe COVID-19 had higher blood glucose levels, especially with the use of corticosteroids. It was observed that DM was associated with increased mortality, severe COVID-19 infection, ARDS, and disease progression[105,106].

We included three articles regarding the treatment of COVID-19 patients with DM. Due to media coverage of dexamethasone benefits in COVID-19, this may increase patients' self-medicating themselves[107]. Studies have shown that corticosteroid use in diabetic patients puts them at a higher risk of hospitalization due to diabetic complications. Therefore, healthcare workers should be avidly aware of the potential risk of using these medications[107].

One systematic review demonstrated COVID-19 patients with combined DKA and hyperosmolar hyperglycemic state (HHS) had higher mortality than DKA alone, with DKA/HHS representing 20% of the total cases of DKA, concluding the importance of differentiating between these two groups[108]. One meta-analysis showed an increased risk of ICU admission for COVID-19 in diabetic patients and increased mortality in these populations[109]. The majority of studies were performed in COVID-19 patients with DM type 2; DM type 1 poses unique challenges, with research showing that in COVID-19 patients with DM type 1, modified management and telemedicine have been practical tools for patient care.

### Obesity

We reviewed a total of 14 systematic review articles on the relationship between obesity and COVID-19. We included one systematic review article regarding the epidemiology of obesity pertaining to COVID-19[110]. Obese patients with hypertension, type 2 DM, active smokers, lung disease, and/or cardiovascular disease are at higher risk for ICU admissions, severe COVID-19, and disease progression. The six articles discussed patients suffering from obesity and COVID-19 show a positive correlation between higher body mass index and severe COVID-19 cases. COVID-19 patients with obesity were significantly affected and had a worse prognosis than those without. In one particular review article, the mechanistic pathways in obese individuals were investigated, evaluating factors linked with COVID-19 risk, severity,

and the potential for diminished therapeutic and prophylactic treatments among these individuals. These studies concluded that individuals with obesity are linked with a significant risk of morbidity and mortality from COVID-19[111].

Regarding the severity assessment of COVID-19 in obesity, there were seven articles discussed. A meta-analysis suggested a linear association between the severity and mortality of COVID-19 and body mass index (BMI)[112]. Also, a BMI ≥ 30 kg/m$^2$ was associated with a higher risk of increased severity in COVID-19 and in-hospital mortality. Furthermore, the study revealed obesity and being overweight were represented as unfavorable factors for COVID-19 infection, where the higher the BMI, the worse the outcome. This occurred by worsening infection, resulting in increased hospitalizations, worse outcomes, and markedly significant mortality, especially when coinciding with other chronic conditions and in the elderly. BMI is an essential routine measurement that should be regularly assessed in the management of COVID-19 patients, and special attention should be given to patients with obesity. Obesity may serve as a clinical predictor for adverse outcomes; therefore, BMI in prognostic scores may play an essential role in predicting the clinical outcomes[113].

### *Pregnancy*

We included one systematic review assessing the clinical presentation of COVID-19 infection in pregnant women[114], which found the most reported clinical symptoms were fever, cough, and dyspnea. Commonly reported laboratory abnormalities included elevated CRP or procalcitonin, lymphopenia, and elevated transaminases. Some complications also included preterm birth and maternal ICU admission. Maternal mortality, however, reported a low prevalence. Another systematic review article evaluated screening and diagnosis of COVID-19 during pregnancy[115], demonstrating the most common symptoms included fever and cough, and for accurate diagnosis, RT-PCR and CT scan can be used together. Further studies showed the clinical characteristics of pregnant women with COVID-19 are similar to those of non-pregnant adults[116], but available data only include pregnant women infected in their third trimesters.

One systematic review article regarding the epidemiology of pregnancy showed insufficient data to suggest if there is transplacental transmission to neonates, with only one neonatal death reported, and 3.4% of neonates suffered from COVID-19[117]. Regarding the special population of pregnancy, we included 16 systematic review articles that showed there is not enough evidence to suggest vertical transmission, most articles stating that it is unlikely although suggesting that it cannot be ruled out. However, the data suggested an increased risk of preterm birth and SARS-CoV-2, leading to an increased need for cesarean delivery. The clinical presentation might not be drastically different as compared to non-pregnant adults[118]. The effect on fertility is not apparent[119].

### *Children*

We looked at 39 systematic review articles regarding the relationship between COVID-19 and the pediatric population. Compared to adults, children presented with milder symptoms. The most common symptoms included fever, cough, vomiting, and diarrhea. Approximately one-third of the pediatric population were asymptomatic, raising concerns for children unknowingly transmitting the virus to at-risk individuals [116]. Overall, the disease course for children was milder, with fewer hospitalizations, ICU admissions, mechanical ventilation, and mortality. There are multiple theories as to why the pediatric population is not severely affected by COVID-19. The theories are as follows: an immature immune system resulting in no cytokine storm, poorly developed ACE2-receptors, fewer comorbidities, and the development of antibodies due to children being infected by other respiratory viruses that can protect against COVID-19[117].

The primary avenue for children contracting the virus was through family members. If a family member tested positive, it is recommended that children be tested as asymptomatic carriers[120].

Children were rarely the cause of significant outbreaks, bringing into question the efficacy of school closures. According to public health experts, school closures could do more harm than good. School closures could increase childhood depression and anxiety rates and cut children from vital resources such as meals, school nurses, and quality education. A small percentage of children did develop severe symptoms of COVID-19 resulting in ICU admissions, mechanical ventilation, and death. Children with comorbidities were at increased risk of a more severe form of infection. The comorbidities most associated with severe COVID-19 infections included cardiac diseases, diabetes, chronic non-asthmatic pulmonary disease, asthma, and obesity.

Several MIS-C were reported, which resulted in shock, multiorgan failure, and death [121,122]. However, a clear correlation between COVID-19 and MIS-C does not exist. It must be determined if COVID-19 increases the risk of MIS-C or if there is simply a temporal relationship between both conditions. The primary form of treatment for severely ill children included intravenous immunoglobulins, corticosteroids, and immunomodulators. However, the efficacy of these treatments is not known. Therefore, the systematic review articles highlight the potential for additional studies to truly understand the effects of COVID-19 in children. The areas that need to be further studied include the possibility of vertical transmission, the extent to which children are transmitters of the virus, the efficacy of school closures in fighting the outbreak, and the ideal treatment course for severely infected children[120].

### Mental health

Sixty-three articles were reviewed regarding the mental health impact of COVID-19. COVID-19 has caused many mixed emotions and has impacted people from a mental health perspective due to the isolation and "social distancing" components. It is estimated that a quarter of the population experienced significant stress due to the pandemic. Given that many stores had limited supplies, it created a panic buying atmosphere[123]. This was mainly due to the survival of the fittest mentality, the fear of the unknown, and coping mechanisms. Bereavement and grief were important aspects many dealt with due to the numerous deaths from the pandemic. Having afterlife ceremonies such as funerals benefited many family members as it was a more sentimental way of saying goodbye[124].

Studies showed that isolation could cause neuroendocrine-immune changes, which further exacerbates COVID-19 and mental health associations. The early stages of the virus caused delirium in a large proportion of the patients. Pulmonary insults of the disease tended to show high amounts of cognitive dysfunction. The elderly were at an increased risk from both a physical and mental perspective from the increased social distancing. It was recommended that this group have more activity and exercise planned before enforcing the lockdowns. The pediatric population's most common disorders were acute stress disorder, post-traumatic stress disorder, adjustment disorder, and grief[125]. The younger population of children also will have higher effects from depression and anxiety. Laws should be more intentional about providing counseling[126].

Though beneficial from a public health standpoint, quarantine has the propensity to impact an individual's psyche negatively and has in some ways passed the brink of being considered clinically relevant. Many of the mental health problems included depression, anxiety, mood disorders, and lack of self-control. Age and sex did not correlate with anxiety disorders. These conditions not only impacted the public and patients but healthcare providers as well[127].

Healthcare workers may be presented with anxiety, depression, and insomnia. Studies showed that HCWs who worked in areas with fewer resources and protective gear tended to be more stressed. Comparing HCWs to non-healthcare workers found their psychological stress level was similar in many factors, except that HCWs had higher amounts of insomnia. Physicians and nurses were the most impacted and resulted in many sleep disturbances. Other studies showed evidence that those with comorbidities had even more stress than health care workers. The virus has shed light on the importance of and need for solutions to improve the well-being of HCWs by providing more education and counseling through policy change[125].

### Smoking

We included 16 systematic review articles that investigated the relationship between smoking and COVID-19 infection. Severity, progression, and adverse outcomes of COVID-19 infection were discussed in relation to smoking status, comparing past and current smokers to non-smokers[128]. Severe cases were defined as critical with the need for ICU, refractory, and non-survivors. Several studies found patients who are both current and former smokers are at an increased risk of severe infection and progression[129]. Meanwhile, a few studies suggested that current smokers have a reduced risk of infection than both former and non-smokers, evidenced by an unexpectedly low prevalence of current smokers among hospitalized patients with COVID-19. However, those hospitalized were at higher odds of adverse outcomes than non-smokers and lower odds than former smokers. Furthermore, due to the low prevalence of hospitalized current smokers, further exploration of nicotine as a therapeutic option is suggested as a potential treatment in COVID-19.

In particular, patients with the chronic obstructive pulmonary disease have a significantly higher odds ratio of severe infection *vs* current smokers[130]. Findings showed that these patients were older and predominantly males compared to non-severe cases. With most studies finding an increased risk between smoking and COVID-19 severity, a continued focus on smoking cessation efforts is recommended [131].

### Cancer

Twenty articles were reviewed regarding the special populations of cancer patients with COVID-19 infection. It was hypothesized that the unique nature of the pathophysiology and the treatment protocols utilized for cancer patients might lend themselves to specific considerations regarding precautions, screening, treatment, and outcomes. Overall, cancer patients were more likely to experience severe COVID-19 disease when compared to those without malignancy. Additionally, cancer patients were found to have lower platelet levels with higher inflammatory markers, leading to increased susceptibility for complications[132].

Certain risk factors were found to be significantly predictive of increased mortality in this population. It was found that the male gender, age greater than 65 years, history of hypertension, and history of chronic obstructive pulmonary disease were associated with an elevated risk of death. Interestingly, many studies found that while symptoms on admission such as dyspnea, cough, and increased sputum were more likely to predict severity, the use of antibiotics, glucocorticoids, interferon, and invasive ventilation were associated with a higher probability of death. This finding likely elucidates the fact that severe infections were treated with complex, invasive medical care. Patients undergoing chemotherapy targeted radiotherapy or immunotherapy had a more aggressive infection course, with significant interactions seen with tocilizumab, ruxolitinib, and colchicine[103]. However, increased mortality was not significantly associated with recent anti-cancer treatments, except when patients were given chemotherapy within 28 d of infection or immunotherapy within 90 d of infection[133]. These findings led to the recommendation that deviations from the standard of care for more extended periods (*i.e.*, beyond four to six weeks) may not be necessary and indeed may lead to a significant impact on overall outcomes.

While many studies have proposed identifying outcomes in all-cause mortality within the general cancer population, some studies have focused on specific cancer types. Multiple myeloma patients were found to have a higher risk of a severe infection due to their immunocompromised status, while treatment protocols for prostate cancer patients with very low, low, or favorable intermediate-risk diseases were avoided or delayed[134].

Overall, it was found that compared to other types of cancer, lung and colorectal cancer patients were more susceptible to COVID-19 infection[135]. Cancer patients are a special population due to their immunocompromised status, cytotoxicity of their treatment regimen, nutritional status, and already increased inflammatory markers.

Cancer patients had worse outcomes from COVID-19 when compared with the general population. Despite all efforts, finding the ideal approach for cancer patients with COVID-19 is not evident. The approach to high-risk patients in this group should include vigorous screening and intensive surveillance. The approach must be dynamic and anti-cancer treatment should be modified based on the cancer type and the patient's prognosis[135].

### Transplant medicine

Five systematic review articles evaluated the presentation of COVID-19 in kidney transplant recipients, who had poorer outcomes on average compared to the general adult population. This subpopulation of patients developed acute kidney injury at higher rates, subsequently requiring RRT. Kidney transplant recipients had increased rates of hospitalizations, ICU admissions, and mechanical ventilation. Compared to the general adult population, the kidney transplant subgroup was elder and had higher mortality rates. Presenting symptoms in this subgroup differed from the general population, presenting with atypical symptoms such as lack of fever and predominance of gastrointestinal symptoms[136]. An area that will need further exploration is the treatment of COVID-19 in kidney transplant recipients. The systematic review articles discussed the risks *vs* benefits of down-titrating immunosuppressive medications while patients are infected with COVID-19.

Additionally, HCQ showed no additional benefit in kidney transplant recipients in the treatment of COVID-19[108,137]. The systematic review articles highlight the need for additional studies to determine the optimal therapeutic approach for the treatment of COVID-19 in this population. A better understanding of treating kidney transplant

recipients could potentially lead to the development of guidelines for any transplant recipient's treatment.

## CONCLUSION

Among the included articles, it is clear that further research is needed regarding treatment options and vaccines. With more studies, data will be less heterogeneous, and statistical analysis will be applied and provide more robust clinical evidence. This study was not designed to give recommendations regarding the management of COVID-19.

## ARTICLE HIGHLIGHTS

### *Research background*

The coronavirus disease 2019 (COVID-19) pandemic continues to impact the sociopolitical, economic, and health care systems across the globe. Robust strategies to control this pandemic's unchecked progression are vital to restore and normalize the health and wellness of human populations. This article summarizes facts and evidence from the current body of literature concerning multiple aspects of COVID-19.

### *Research motivation*

No research studies so far have succeeded in recommending a definite remedy to contain coronavirus infection transmission. The current study's motivation emanated from the requirement of improving the current knowledge base about COVID-19 prevalence, progression, incidence, management, and outcomes.

### *Research objectives*

The research objective included the critical assessment of COVID-19-related meta-analyses and systematic reviews to explore the current knowledge gaps and track the best evidence to inform the scientific community.

### *Research methods*

The research method relied on a robust search strategy based on the combination of various key terms while excluding panel reviews, guideline documents, opinion papers, scoping reviews, and rapid reviews related to COVID-19.

### *Research results*

The research results generated 1219 studies concerning the COVID-19 knowledge base based on fifty predefined attributes.

### *Research conclusions*

The outcomes of our study emphasized the need for future research to understand the scope of possible vaccines and prevention/treatment options in the setting of COVID-19.

### *Research perspectives*

Prospective studies should deploy multicentred approaches to unravel the clinical findings, risk factors, and prevention/treatment guidelines in COVID-19 scenarios.

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