ISSN 2220-3249 (online)

# World Journal of *Virology*

*World J Virol* 2022 May 25; 11(3): 113-169

Published by Baishideng Publishing Group Inc

World Journal of Virology

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Editorial Board Member of *World Journal of Virology*, Basavraj Nagoba, PhD, Professor, Research Dean, Department of Microbiology, MIMSR Medical College, Latur 413512, Maharashtra, India. dr_bsnagoba@yahoo.com

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**NAME OF JOURNAL**
*World Journal of Virology*

**ISSN**
ISSN 2220-3249 (online)

**LAUNCH DATE**
February 12, 2012

**FREQUENCY**
Bimonthly

**EDITORS-IN-CHIEF**
Mahmoud El-Bendary, En-Qiang Chen

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2220-3249/editorialboard.htm

**PUBLICATION DATE**
May 25, 2022



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*World J Virol* 2022 May 25; 11(3): 113-128

DOI: 10.5501/wjv.v11.i3.113

ISSN 2220-3249 (online)

*REVIEW*

# Severe acute respiratory syndrome coronavirus 2 infection: Role of interleukin-6 and the inflammatory cascade

Mohaddeseh Bahmani, Rojin Chegini, Elham Ghanbari, Elham Sheykhsaran, Parisa Shiri Aghbash, Hamed Ebrahimzadeh Leylabadlo, Ehsan Moradian, Amir Masoud Kazemzadeh Houjaghan, Hossein Bannazadeh Baghi

**Specialty type:** Virology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Singh AK, India; Wang H

**Received:** December 14, 2021
**Peer-review started:** December 14, 2021
**First decision:** February 15, 2022
**Revised:** March 3, 2022
**Accepted:** April 28, 2022
**Article in press:** April 28, 2022
**Published online:** May 25, 2022

**Mohaddeseh Bahmani,** Department of Virology, Student Research Committee, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Rojin Chegini,** Department of Medical Science, Metabolic Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan 81745-33871, Iran

**Elham Ghanbari,** Department of Medical Science, Fertility and Infertility Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah 67159-59167, Iran

**Elham Sheykhsaran,** Department of Microbiology, Student Research Committee, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Elham Sheykhsaran, Parisa Shiri Aghbash,** Immunology Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Parisa Shiri Aghbash,** Department of Virology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Hamed Ebrahimzadeh Leylabadlo,** Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Ehsan Moradian,** Department of Medical Science, Medical Faculty, Tabriz University of Medical Sciences, Tabriz 5165665931, Iran

**Amir Masoud Kazemzadeh Houjaghan,** Department of Internal Medicine, Medical Faculty, Tehran University of Medical Sciences, Tehran 14155-6559, Iran

**Hossein Bannazadeh Baghi,** Department of Virology, Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran

**Corresponding author:** Hossein Bannazadeh Baghi, PhD, Associate Professor, Department of Virology, Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz 15731, Iran. hbannazadeh@tbzmed.ac.ir

## Abstract

Since December 2019, a novel coronavirus that represents a serious threat to human lives has emerged. There is still no definite treatment for severe cases of

the disease caused by this virus, named coronavirus disease 2019 (COVID-19). One of the most considered treatment strategies targets the exaggerated immune regulator, and interleukin (IL)-6 is a crucial pro-inflammatory mediator. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases show an elevated level of IL-6 related to disease severity. IL-6 activity can be inhibited by the following: IL-6 itself, IL-6 signaling pathways such as Janus kinase and signal transducer and activator of transcription (JAK-STAT), gp130, IL-6R, and downstream activated ILs, such as IL-17 and IL-6 cytokine. Currently, according to these studies and their results, IL-6 blockade with anti-IL-6 or its receptor antibodies such as tocilizumab in COVID-19 is beneficial in severe cases and may reduce the mortality rate. JAK-STAT inhibitors block the cytokine storm by inhibiting several crucial pro-inflammatory mediators such as TNF-α and IL-6 and have shown various results in clinical trials. IL-6 induces IL-17 secretion, and IL-17 is involved in the pathogenesis of inflammatory processes. Clinical trials of anti-IL-17 drugs are currently recruiting, and anti-gp130 antibody is preclinical. However, this agent has shown positive effects in inflammatory bowel disease clinical trials and could be tested for SARS-CoV-2. This study aimed to review the role of IL-6 in the cytokine storm and studies regarding IL-6 and blockade of its inflammatory pathways in COVID-19 to determine if any of these agents are beneficial for COVID-19 patients.

**Key Words:** Anti-interleukin-6; COVID-19; Inflammation; Interleukin-6; Interleukin-6 receptor; SARS-CoV-2



**Core Tip:** One of the most considered treatment strategies for severe acute respiratory syndrome coronavirus 2 is targeting the immune response and pro-inflammatory cytokines such as interleukin (IL)-6. Patients with severe acute respiratory syndrome coronavirus 2 show elevated levels of IL-6, which is related to disease severity. Current studies have shown that IL-6 blockade by anti-IL-6 or its receptor antibodies such as tocilizumab is beneficial in severe cases and may reduce the mortality rate. Moreover, the combination of anti-inflammatory agents is more effective than single therapy.

**Citation:** Bahmani M, Chegini R, Ghanbari E, Sheykhsaran E, Shiri Aghbash P, Leylabadlo HE, Moradian E, Kazemzadeh Houjaghan AM, Bannazadeh Baghi H. Severe acute respiratory syndrome coronavirus 2 infection: Role of interleukin-6 and the inflammatory cascade. *World J Virol* 2022; 11(3): 113-128
**URL:** https://www.wjgnet.com/2220-3249/full/v11/i3/113.htm
**DOI:** https://dx.doi.org/10.5501/wjv.v11.i3.113

## INTRODUCTION

In December 2019, an epidemic of secretive pneumonia which started in Wuhan city, Hubei province, China, quickly spread to many other countries and finally resulted in a pandemic[1]. The causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded enveloped RNA virus belonging to Nidovirales and the family Coronaviridae. The analysis of SARS-CoV-2 genome structure has shown that this virus is related to the beta-coronavirus genus, containing bat SARS-identical coronavirus and two previous invasive coronaviruses Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV[2]. Universally, as of September 2021, there have been 226,844,344 recognized cases of SARS-CoV-2, including 4,666,334 victims[3]. The disease caused by the novel coronavirus, coronavirus disease 2019 (COVID-19), is similar to these previous viruses, which is mainly pulmonary disease[4], and all of them have a zoonotic origin. In addition to pulmonary involvement, various organs such as the kidney, gastrointestinal system, nervous system, liver, and coagulation system, may be targets of the virus, leading to serious complications such as acute kidney injury (AKI), acute pulmonary failure, and disseminated intravascular coagulation (DIC) that may lead to death[5]. Currently, this virus is a serious global concern with enormous social and economic damage to societies worldwide[6].

Moreover, the fatality rate is high in severe cases[7]. At present, we do not have any definite treatment for severe cases of this disease, and the management of severe SARS-CoV-2 patients is still challenging. Therefore, various treatment options have been assumed according to the different levels of viral pathogenesis, including viral entry, replication, and effects of the virus on target cells. The antiviral agent remdesivir is the only treatment with Food and Drug Administration (FDA) approval for this disease, and dexamethasone is the only drug to reduce mortality in hospitalized patients with

decreased oxygen saturation but not in others[8]. However, the World Health Organization (WHO) has suggested mortality trials for some repurposed anti-viral drugs, including lopinavir, interferon beta 1a (INF-β1a), and hydroxychloroquine in hospitalized patients with SARS-CoV-2[9].

In this regard, IL-6 is known as a crucial inflammatory mediator with essential roles in the pathogenesis of inflammatory diseases in addition to several chronic disorders such as diabetes mellitus [10]. This cytokine is widely expressed by different immune cells and affects immune function[11]. Thus, the disease has a wide range of symptoms. Clinical deterioration in COVID-19 is mainly due to the effects of inflammatory cytokines such as IL-1, IL-6, IFN-α, and tumor necrosis factor (TNF) that are increased in the cytokine storm phase, and the role of immune cells including neutrophils[12-15]. In this process, when a neutrophil encounters a pathogen, the extensive release of cytokines such as IL-1 and IL-6 may become harmful to the body and lead to multi-organ damage[13]. In this rationale, targeting the cytokine release syndrome (CRS) symbolizes a possible therapeutic goal in managing SARS-CoV-2 related cytokine storms and IL-6[16].

In this study, we aim to review the role of IL-6, the rationale of IL-6 blockade in COVID-19, and the results of recent studies on this topic to determine whether any available anti-IL-6 agents or any other drugs with the ability to inhibit inflammatory pathways induced by this cytokine have shown efficacy in improving patient prognosis in SARS-CoV-2 infection.

## STUDY METHOD

PubMed, Google Scholar, Scopus, and the Web of Science were searched with the following keywords or their combinations, without any time limits: COVID-19, IL-6, IL-6 receptor, SARS-CoV-2, anti-IL-6, Inflammation. Related articles of any type were selected and reviewed. Extracted information included: SARS-CoV-2 pathophysiology and characteristics, IL-6 activities in the immune system and associated pathways, studies focused on the concept of anti-IL-6 antibodies in the treatment of COVID-19, and other methods of IL-6 inhibition [Janus kinase and signal transducer and activator of transcription (JAK-STAT) inhibition and anti-IL-17 therapies] and are discussed further.

## SARS-COV-2 PATHOPHYSIOLOGY AND CHARACTERISTICS

In the last two decades, the third most common coronavirus to cause a pandemic of acute respiratory disease in humans is SARS-CoV-2. These viruses enter the body through respiratory aerosols and are attached to the nasal or paranasal epithelial cells[17]. Angiotensin-converting enzyme 2 (ACE-2) is the major receptor for these viruses to enter host cells, which is expressed in nasal epithelial cells[18,19].

The virus, along with the infection of ciliated cells in the airways, undergoes local replication and dissemination. This stage lasts a few days, and a slight immune response is produced during this process. Despite having a low viral load at this time, infected individuals are highly contagious, and the virus can be identified following a nasal swab[20].

### *Virus entry into the host cell*

Through its spike (S) protein, the virus enters the host cell by binding to ACE-2 on the cellular surface. Transmembrane serine protease 2 (TMPRSS2), then mediates S protein cleavage, and the virus enters the cell[21]. A high virus infectivity rate is associated with mutations in the binding domain of the receptor and the acquisition of a furin cleavage site in the S protein. The association of the virus with ACE-2 can decrease anti-inflammatory function and increase angiogenic activity[22]. The virus migrates from the nasal epithelium to the upper respiratory tract within the conducting airways[23]. The disease presents various signs and symptoms such as fever and dry cough due to involvement of the upper respiratory tract[24].

At this stage, a higher immune response occurs due to the virus-infected cells and results in the secretion of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and -λ). As a result of the sufficient immune response to control the spread of infection, the majority of patients do not advance beyond this point[25]. About one-fifth of infected individuals advance to this point and may experience severe symptoms. The virus, *via* the host receptor ACE-2, targets alveolar epithelial cells type 2 and continues to undergo replication to create more and more viral nucleocapsids[26].

Many distinct cytokines and inflammatory markers are now produced by virus-laden pneumocytes such as ILs (IL-1, IL-6, IL-8, and IL-12), tumor necrosis factor-alpha (TNF-α), IFN-λ and IFN-β, monocyte chemoattractant protein-1 (MCP-1), CXCL-10, and macrophage inflammatory protein-1 alpha (MIP-1α). This 'cytokine storm' serves as a chemoattractant to neutrophils, CD4 helper, and CD8 cytotoxic T cells, and these cells then become sequestered in the pulmonary tissue[27,28]. In addition to being crucial in fighting the virus, these cells cause inflammation and damage to the lungs and other organs. The host cell undergoes apoptosis and releases new viruses, which will then infect the neighboring type 2 alveolar epithelial cells in the same way. Diffuse trauma to the alveoli eventually results in an acute

respiratory syndrome and finally respiratory distress, owing to the recurrent injuries triggered by the sequestered immune cells and viral replication, contributing to the annihilation of both type 1 and type 2 pneumocytes[29,30].

COVID-19 spreads mainly by the transmission of respiratory droplets from person to person and occurs when someone is in close contact with an infected individual who is coughing or sneezing violently. This occurs as the host's mucosal surfaces, *i.e.*, the eyes, nose, and mouth, are exposed to the infected respiratory droplets[31]. Virus transmission may also occur by fomites, such as bedsheets, towels, kitchen utensils, thermometers, and stethoscopes, used by or used on the infected person. Airborne transmission of COVID-19 can occur especially in situations where aerosol-generating procedures are conducted, *i.e.*, endotracheal intubation, bronchoscopy, open suction, oxygen nebulization, bronchodilators, or steroids, ventilation using a bag and mask, tracheostomy, and cardiopulmonary resuscitation[32]. In this way, the incubation time for SARS-CoV-2 (between the onset of symptoms and exposure to the virus) is about 5 to 6 d. However, it can be up to 14 d. During this time, also known as the 'pre-symptomatic' phase, the affected individual can be contagious and transmit the virus to the healthy population[33,34]. The most frequent symptoms include fever, muscle aches, shortness of breath, malaise, and a dry cough.

While patients can remain asymptomatic or develop a mild, moderate, or severe illness, gastrointestinal manifestations such as stomach pain, vomiting, and loose stools can also occur. Many of the complications seen in SARS-CoV-2 infected individuals are attributed to the CRS[35,36].

### *Cytokine storm*

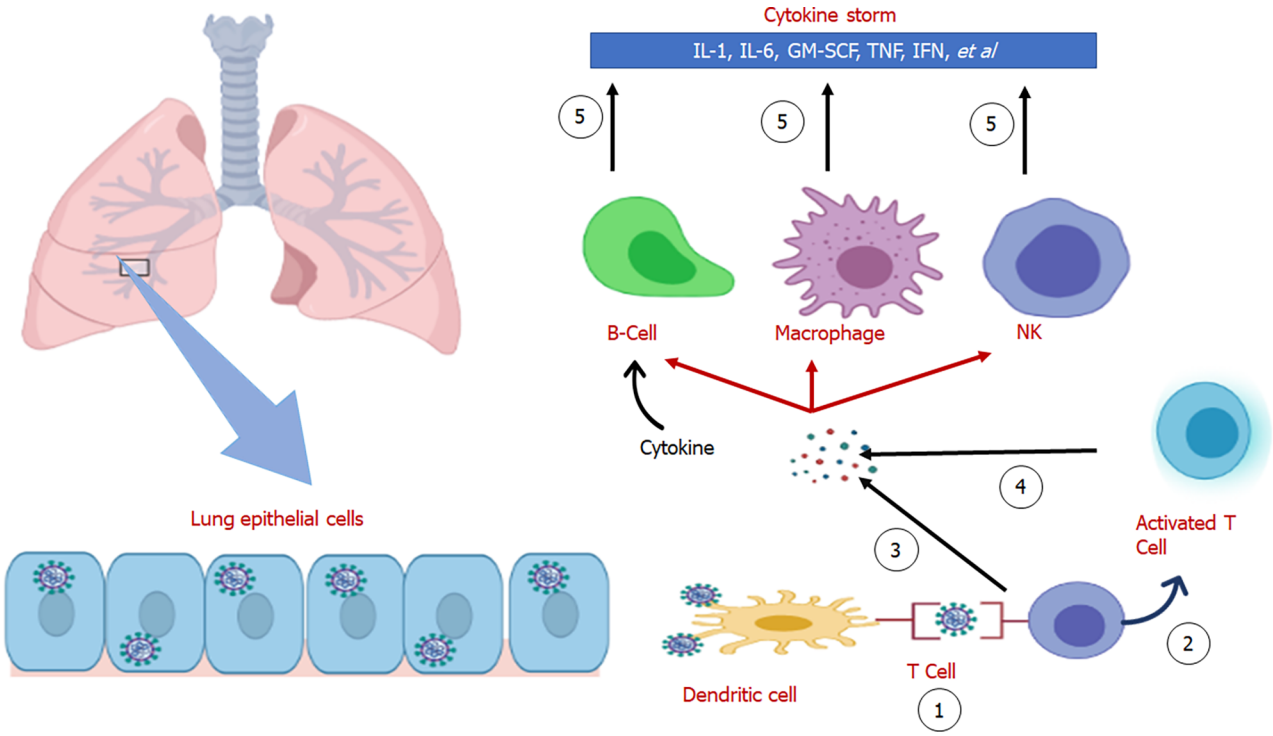
The cytokine storm was historically referred to as an influenza-like syndrome that occurred during systemic diseases such as sepsis and after immunotherapies such as Coley's toxins. *Yersinia pestis* (causative agent of plague or black death) infection has led to extreme pandemics; it induces alveolar macrophages to produce disproportionate quantities of cytokines, resulting in the cytokine storm and has subsequently caused massive pandemics[37]. An intensive inflammatory response and fast release of various cytokines (such as TNF-α-1, 2, IL-6, and IFN-γ) to the circulation are activated by pathogen infection (Figure 1). Patients with viral infections are especially vulnerable to acute respiratory failure due to the cytokine storm[38]. For instance, in other coronaviruses (SARS and MERS), cytokine cascades and low lymphocytes are positively linked to the course and severity of the disease. Recent experiments have supported this conclusion in most cases of SARS-CoV-2, indicating low lymphocyte counts and heightened levels of inflammatory mediators[12,39]. Furthermore, it has been shown that pro-inflammatory cytokines such as IL-6 play an essential role in the progression of COVID-19.

## IMMUNE SYSTEM AND ROLES OF IL-6

IL-6 is a soluble mediator with various functions in the immune system[40]. For example, controlling the differentiation and migration of immune cells, apoptosis of target cells[41], and assembly of acute-phase proteins such as C-reactive protein (CRP), haptoglobin, and fibrinogen. In contrast, IL-6 reduces the production of other proteins such as albumin. Human IL-6 comprises 212 amino acids (28-amino-acid signal peptide), and its controlling gene is located on chromosome 7p21[40]. This interleukin contributes to hypothalamic-pituitary-adrenal axis regulation and glucose homeostasis. It induces the differentiation of T-helper cells, which secrete IL-17. These cells are related to the pathogenesis of chronic inflammatory diseases[42]. IL-6 is produced in the immune system by various cells including endothelial cells and contributes to the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis, atherosclerosis, and systemic lupus erythematosus[41]. This cytokine acts by binding to its receptor on the target cells that consist of CD126 (IL-6 Receptor-α) and glycoprotein 130 (gp130). Therefore, it activates signaling pathways such as JAK-STAT[43] and mitogen-activated protein kinase[11]. Conformational alterations in the gp130 cytoplasmic domain when IL-6 binds to the IL-6 receptor induces activation of JAK-STAT[43], and JAK-STAT signaling pathway activation leads to cytokine release[44]. However, these signaling pathways downregulate IL-6 expression[11].

While the membrane-bound receptor (IL-6Rα) is expressed only on the surface of a small number of cells such as leukocytes and hepatocytes (known as IL-6 classic signaling), IL-6 can affect many other cells through its soluble receptor (sIL-6Rα). It was recently discovered that endothelial cells also express IL-6R. This receptor forms a complex with IL-6 that binds to gp130. This complex then mediates a signal known as IL-6 trans-signaling through which pro-inflammatory responses are mainly mediated. In contrast, the classic signaling pathway is related to anti-inflammatory pathways[41]. Furthermore, IL-6 is produced by the innate immune cells after encountering a pathogen and is critical in the body's defense against the respiratory syncytial virus and influenza virus in the early infection phases[45]. However, in CRS, IL-6 and IL-5 can induce coagulation cascade and complement system overactivation, capillary leakage, hypotension, and myocardial dysfunction[46].

In severe SARS-CoV-2 infection, high levels of pro-inflammatory mediators are present, such as IL-6. Although one study showed that monocytes were a source of IL-1β and IL-8, the exact source of IL-6 remains unclear[47]. In the presence of immune dysregulation, in addition to a non-sufficient anti-viral




**DOI**: 10.5501/wjv.v11.i3.113 

**Figure 1 The mechanism of the inflammatory storm.** ① Antigen presenting; Dendritic cells activate T-cells by processing the antigen and delivering it to these cells; ② Start reproducing; Native T cells become activated by receiving antigens from dendritic cells; ③ A significant quantity of cytokines is secreted during the activation of T cells. These cytokines can activate B cells, macrophages, and NK cells; ④ Activated T cells also release cytokines and further activate macrophages, B cells and NK cells; ⑤ Cytokines secreted; These activated cells, in turn, lead to the secretion of inflammatory and pro-inflammatory cytokines; the resulting cytokine storm leads to the development of clinical signs of infection.

response, there is also a continuous secretion of pro-inflammatory mediators such as IL-6 that resembles the macrophage activation syndrome and lead to multi-organ damage[45]. Also, in COVID-19, multifocal interstitial pneumonia is the chief reason for pulmonary failure and death. In this process, there are inflammatory infiltrates in the interstitial tissue of the lungs, which lead to alveolar damage [48]. These infiltrates consist of mononuclear cells that will be induced after the pro-inflammatory pathways are activated by trans-signal transduction of IL-6[45]. In this way, one study showed that patients with high levels of ACE-2 expression experience more severe tissue damage by IL-6 and the cytokine storm after infection with SARS-CoV-2. These individuals also have a suppressed immune system to fight against the virus[7]. In summary, IL-6 is crucial in both pro-inflammatory and anti-pathogen responses, and trans-signaling is the critical pathway of inflammatory processes conducted by IL-6. A diagram of the significant roles of IL-6 and its location in the immune cascade is summarized in Figure 2.

## DRUGS AVAILABLE TO INHIBIT IL-6 ACTIVITY

According to the signaling pathways induced by IL-6 and its components, IL-6 activity can be inhibited by the following: IL-6 itself, IL-6 signaling pathways such as JAK-STAT, gp130, IL-6R, or the IL-6/sIL-6R complex[49]. Two main drugs in the class of IL-6 receptor blockers are tocilizumab (TCZ) and slumab, which are FDA approved monoclonal antibodies for rheumatoid arthritis, and TCZ is also approved for juvenile idiopathic arthritis (JIA) and giant cell arteritis[50].

TCZ blocks both soluble and membrane-bound receptors and accordingly blocks signal transduction *via* JAK-STAT[51]. JIA, a chimeric antigen receptor (CAR)-T cell-induced CRS, giant cell arteritis, rheumatoid arthritis, and Still's disease are examples of the conditions in which TCZ has been used to control the disease[52]. Siltuximab is an anti-IL-6 agent that has shown more effectiveness than TCZ in some aspects, and although it is not FDA approved, it is used in refractory CRS cases. Data regarding Siltuximab in COVID-19 are currently restricted[46].

The specific gp130FC named Olamkicept specifically blocks the trans-signaling pathway. In animals, it showed more effectiveness in controlling the hyper-inflammatory status due to sepsis than anti-IL-6 antibodies. Significantly, it did not impair the anti-inflammatory responses of IL-6 *via* classic signal-transduction[45]. JAK-STAT inhibition is another option. Some of these agents are currently on COVID-19 clinical trials, such as ruxolitinib. A list of these drugs is shown in Table 1.

**Table 1 Drugs with anti-interleukin-6 activity and their side effects with examples of clinical trials in coronavirus disease 2019**

| Ref. | SARS-CoV-2 clinical trials on Clinicaltrial.gov | Side effects | Examples | Category |
|---|---|---|---|---|
| [93] | NCT04661527, NCT04315298, NCT04357808, NCT04386239, NCT04341870, NCT04359901, NCT04380519 | Cytopenia, intestinal perforation, Hypersensitivity, immunosuppression, and the possibility of infections, impairment of liver enzymes | Sarilumab | The anti-receptor of IL-6 |
| [94, 95] | NCT04445272, NCT04331795, NCT04346355, NCT04320615, NCT04356937, NCT04403685, NCT04339712 | Intestinal perforation, Hypersensitivity, immunosuppression, and the possibility of infections, acute liver dysfunction, demyelination, cardiac injury, and hepatitis | Tocilizumab | |
| [96] | NCT04322188, NCT04329650, NCT04330638 | Hypersensitivity disorders, intestinal perforation, risk of infections | Siltuximab | Anti-IL-6 |
| [97] | - | Preclinical; in a phase 2 trial of IBD, it showed effectiveness. Patients in this study who were treated with the drug had hypersensitivity skin reactions and respiratory infections. In animal studies, it did not show serious immunosuppression | Olamkicept | Specific gp130fc |
| [98] | NCT04358614, NCT04401579, NCT04640168, NCT04381936 (RECOVERY Trial), NCT04320277 | Increased risk of infections including reactivation of latent infections, lymphoproliferative disorder, cytopenia, liver enzymes disturbances, clot formation, intestinal perforations | Baricitinib | JAK inhibitors |
| [99] | NCT04348071, NCT04377620, NCT04362137, NCT04366232 | Skin malignancy, exacerbation with drug discontinuation, cytopenia, and immunosuppression, increased risk of infection | Ruxolitinib | |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IL: Interleukin; IBD: Inflammatory bowel disease; JAK: Janus kinase.

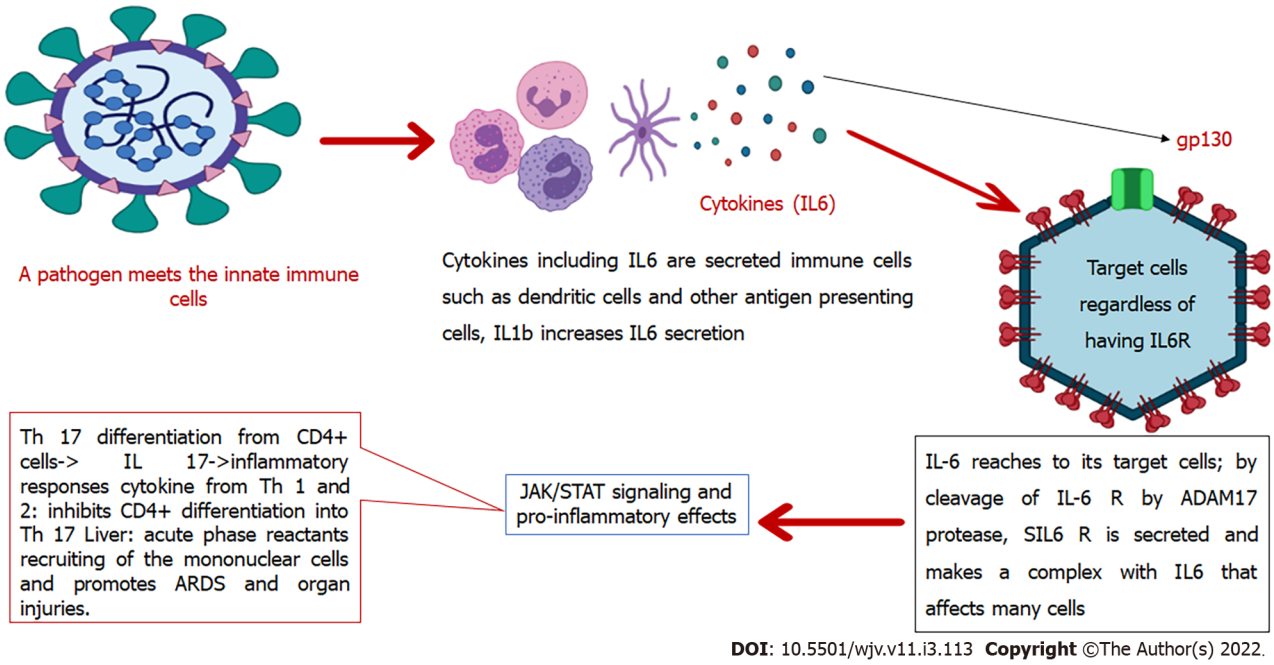



**Figure 2 Interleukin-6 in the immune system.** IL: Interleukin; JAK-STAT: Janus kinase and signal transducer and activator of transcription.

## EXPERIENCE OF IL-6 BLOCKADE IN COVID-19

The cytokine storm is associated with disease intensity in SARS-CoV-2, as also shown in SARS-CoV-1 and MERS-CoV. Although the reports from different studies focused on IL-6 blockade in COVID-19 are inconsistent, it was first shown to reduce the mortality rate in critically ill patients[53].

Considering the presence of lymphopenia in SARS-CoV-2 patients, administration of immunosuppressive agents might increase the risk of secondary fungal or bacterial infections[54]. In a previous study, TCZ induced necrotizing fasciitis and candidemia[55]. Accordingly, the exact place for immunosuppression and anti-IL-6 agents in COVID-19 is crucial. The possible effects of TCZ on management of the COVID-19 related cytokine storm first originated from observational studies that showed it to be effective in the clinical improvement of COVID-19 patients[56]. In a recent clinical trial,

the effect of a single dose of 8 mg/kg TCZ administration *via* the intravenous route in addition to the standard of care in the management of COVID-19 was investigated. In this study, 46 adult patients who were positive for SARS-CoV-2 and had multifocal interstitial pneumonia on imaging studies were enrolled soon after showing clinical worsening. The drug was influential in the clinical improvement of severely ill patients and patients in the early clinical worsening state. However, it did not show significant efficacy in reducing the mortality rate and was accompanied by adverse effects[48].

According to a recent observational study, having an IL-6 level of more than 30 pg/mL is related to the disease severity and need for respiratory support in COVID-19 patients. This study showed the positive effects of TCZ in patients with higher IL-6 levels at baseline, but no positive trends were seen in the group with low IL-6 levels[51].

A recent case series showed the efficacy of subcutaneous TCZ in three severely ill COVID-19 patients in reducing inflammatory-related indices and improving the clinical condition[57]. The results of a prospective phase two cohort study (TOCIVID-19) showed that TCZ effectively reduced the mortality rate at 30 d, especially in severe patients who did not require mechanical ventilation. This effect was independent of corticosteroids and was not accompanied by significant adverse events[58].

One of the concerns regarding the use of anti-immune drugs in SARS-CoV-2 is that they may interfere with the proper immune response to the virus. Cytokines, especially IL-6, play a significant role in the host's fight against viruses through the humoral and cellular responses by affecting helper and cytotoxic T cells. Accordingly, a cohort study conducted in Spain found that these drugs do not pose a problem in the body's fight against the virus. Although the study found that patients treated with anti-cytokines had a longer viral clearance time, they initially had higher virus levels, and their disease was more severe[59]. A preprint study that showed an unexpected increase in inflammatory mediators after TCZ administration supports the fact that IL-6 blockade alone may not be effective in the management of COVID-19[60]. Recently, two studies showed a transient elevation in the D-dimer level in SARS-CoV-2 patients receiving TCZ[61,62]. A recent meta-analysis also demonstrated that IL-6 blockade alone does not lower the mortality rate, although it may effectively reduce the risk of respiratory failure in hospitalized patients[63]. According to another study, administration time is another crucial factor, and treatment with TCZ ten days after disease onset is more beneficial[64]. In contrast, other studies, including the RECOVERY trial, have shown that early administration of TCZ in severe cases before intensive care unit (ICU) admission and the need for mechanical ventilation is effective in reducing the mortality rate,[65,66] and when the patient requires mechanical ventilation, it will not have much effect[66,67]. In general, different methods and inclusion criteria in studies do not result in the same conclusions. A list of recent studies in this regard is summarized in Table 2. According to some clinical trials, TCZ, when added to a corticosteroid, markedly reduces the mortality rate compared with corticosteroids (CSs) alone. Treatments that include agents to target more ILs in addition to IL-6 have more efficacy than only IL-6 blockade[63,68]. IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF, IL-1, and IL-8 are the primary inflammatory mediators that could be targeted in CRS. IL-1 is proximal to IL-6 in the inflammatory cascade, and its blockade has recently been considered. A recent study compared the effectiveness of IL-1 and IL-6 blockade with the standard of care, and it was observed that IL-1 inhibition is more effective in reducing the mortality rate, while positive effects of IL-6 antibodies were restricted to a group of severely ill patients with high CRP levels[50]. Another clinical trial of TCZ in COVID-19 patients with a hyperinflammatory state also stopped recruiting as it failed to reach its primary endpoints (improving the patient's clinical status or reducing the mortality rate)[69]. In general, despite the effect that IL-6 blockade has on the suppression of inflammation, it cannot completely control inflammation as it does not affect the distal inflammatory pathways[70]. However, in severe and critical SARS-CoV-2 patients with a hyperinflammatory state, IL-6 blockade with monoclonal antibodies seems to be effective in reducing the mortality rate, reducing the risk of mechanical ventilation, and improving the clinical condition[67,71-74]. Although all of these studies have been performed in adult patients, the effect of TCZ in the treatment of COVID-19 in children is also being investigated in the RECOVERY trial[67].

To date, several clinical trials have failed to show the efficiency of TCZ in COVID-19 treatment. However, the RECOVERY trial and some other clinical trials showed positive results[67,75,76]. Although meta-analysis had previously demonstrated an 11% reduction in 28-d mortality following TCZ administration in patients with severe SARS-CoV-2 infection, this reduction was significant when the results of the RECOVERY trial were added[67]. In conclusion, this drug can effectively improve the prognosis in extreme cases.

TCZ inhibits both classic and trans-signal transduction through IL-6, thus interfering with this cytokine's anti- and pro-inflammatory functions. As mentioned previously, IL-6 signaling pathways involve the JAK-STAT that could be targeted with drugs such as ruxolitinib, a JAK 1 and 2 inhibitor. This drug lowers the levels of IL-6 and is currently being evaluated for SARS-CoV-2 and had positive effects in one study[77]. However, RUXCOVID, a phase 3 clinical trial of ruxolitinib, revealed no significant efficacy in reducing the death rate and serious complications[78]. Another JAK inhibitor is baricitinib. A recent clinical trial (ACTT2) that evaluated baricitinib in hospitalized patients with SARS-CoV-2 infection indicated that it reduced the recovery time when added to remdesivir, compared with remdesivir alone[79,80]. Another study also investigated the potency of the anti-myeloproliferative agent ruxolitinib and included the patients requiring supplementary oxygen but not with respiratory

**Table 2 List of recent clinical trials and observational studies regarding interleukin-6 blocker monoclonal antibodies in severe acute respiratory syndrome coronavirus 2**

| Study design | Inclusion criteria | Interventions | Number of patients | Results | Ref. |
|---|---|---|---|---|---|
| Observational retrospective | Severe SARS-CoV-2 positive ICU admitted patients, with or without respiratory failure | Single 400 mg TCZ dose, without antimicrobialpro-phylaxis | 55 severe patients were treated,Compared with 41 untreated (non-severe) patients | Lower mortality rate among treated patients against more disease severity, with no serious side effects and no significantly different increased infection rates | [53] |
| Quasi-experi-mental | SARS-CoV-2 positive patients with respiratory failure or a need for supplemental oxygen, with clinical or laboratory signs of acute inflammation | Comparing CSs, and TCZ (8 mg/kg up to 800 mg/dose up to 3 doses) | 33 patients in the TCZ group and 60 in the CS group. | These drugs both reduced the need for supplemental oxygen and ICU stay to the same level, but in the CS group the survival rate was higher, use of TCZ was safe | [100] |
| Cohort | COVID-19 patients with respiratory failure and acute inflammatory laboratory findings, such as an elevated CRP level | Anakinra: 5 mg/kg BD until clinical improvement; TCZ: 400 mg single dose, repeated according to the clinical condition; Sarilumab: 400 mg single dose | 62 patients received IL-1 blocker and 55 IL-6 blocker (26 sarilumab and 29 TCZ) (severe patients); 275 without IL blockade (standard of care only) | IL-6 blockade had only limited effectiveness in individuals with high concentrations of CRP, but IL-1 blockade reduced the mortality rate in all patients | [50] |
| Retrospective observational | Severe patients | Tocilizumab use was compared with standard of care in ICU patients | 78 severe patients received tocilizumab and were compared with 112 severe patients who received standard of care | Patients on tocilizumab had a longer hospital and ICU stay and more costs with no reduction in the mortality rate | [101] |
| Retrospective observational | Severe SARS-CoV-2 patients with respiratory failure | TCZ 8 mg/kg | 30 severe patients with respiratory failure who received TCZ were evaluated for inflam-matory markers and clinical condition after treatment | Patients had better oxygenation and inflam-matory markers decreased after treatment with TCZ | [102] |
| Randomized, double-blindclinical trial | Hospitalized patients without respiratory failure and mechanical ventilation, but with decreased SpO2 in room air | 8 mg/kg up to 800 mg, TCZ; One-two doses | 249 TCZ; 128 SOC | Likelihood ratio of; serious adverse outcomes were significantly lower in the treatment group; But no reduction in all-cause mortality rate | [8] |
| Clinical trial | Moderate and severe patients according to the clinical status, with higher IL-6 levels, neither ICU admitted nor on mechanical ventilation | TCZ 400 mg; Single-dose | 29 patients were treated with TCZ and 32 received standard of care only | TCZ was safe but did not show any significant difference in clinical improvement | [103] |
| Cross-sectional, observational | Severe patients with high levels of inflammatory markers | TCZ 4 mg/kg | 54 patients were treated with TCZ | Significant reduction in neutrophil count and CRP | [104] |
| Clinical trial | Patients with hyper-inflam-matory state and acute respiratory failure | TCZ 8 mg/kg (up to 800 mg); After 12 h: second dosage | 66 severe patients received TCZ and were compared with 60 patients who received standard of care | Not effective in decreasing the risk of disease deteri-oration | [105] |
| Open-label clinical trial | Proven SARS-CoV-2 infection, with the need for respiratory support and recent worsening in the clinical condition | TCZ 8 mg/kg | 46 moderate and severe patients were treated with TCZ | Treatment improved respiratory function | [48] |
| Clinical trial | High levels of IL-6Moderate and severe disease severity | TCZ 400 mg (second dosage after 24h) | 34 patients were treated and 31 were not | Treatment with TCZ improved respiratory condition without reducing the mortality rate | [106] |
| Clinical trial | Severe and critical patients | Sarilumab 400 mg | Total = 416 (Sarilumab 400 mg, $n$ = 173; Placebo, $n$ = 84; Sarilumab 200 mg, $n$ = 159); Primary analysis between 194 severely ill | Did not meet the primary and secondary endpoints in improving disease progression and the study stopped further | NCT04315298 [107,108] |

| | | | | | |
|---|---|---|---|---|---|
| | | | patients who needed respiratory support | recruitment | |
| Randomized, double-blindclinical trial | Severe patients with decreased SpO2 without supplemental oxygen | TCZ 8 mg/kg up to 800 mg | 2:1 Placebo+ Standard of care (151); TCZ+ SOC (301) | No significant benefits on mortality rate or clinical improvement, but a positive effect on hospitalization duration was observed with no significant side effects compared with the control group | NCT04320615 [109] |
| Retrospective cohort | SARS-CoV-2 positive patients with severe pneumonia | TCZ one to two doses, 400–800 mg every 12 h | $n$ = 62 treated, $n$ = 86 untreated | Treated patients showed significantly lower leukocytosis compared to the control group after 14 d. D-dimer and ferritin initially increased and then decreased in the treated group. The mortality rate at 28 d was statistically lower in the TCZ group. A longer hospital stay was shown in these patients although this was not statistically significant. Ten patients developed an infection during hospitalization | [62] |
| Retrospective cohort | Moderate to severe SARS-CoV-2 patients | One to two doses of TCZ 8 mg/kg | 170 treated; 655 untreated | Clinical improvement was significantly better in the treatment group compared with the control group. A significant reduction in the mortality rate at 21 and 28 d was found in patients with respiratory failure and patients with IL-6 levels above 100 pg/mL | [110] |
| Randomized clinical trial | Critical patients with respiratory failure who were admitted to the ICU | TCZ one to two doses (8 mg/kg); Sarilumab (a single dose of 400 mg); Other interventions: Anakinra and interferon beta-1a | 350 on TCZ; 45 on sarilumab; 1136 on another immunomodulator; 397 on no immunomodulation | IL-6 blocking agents were effective in reducing the mortality rate. When added to corticosteroids, this effect was stronger compared with IL-6 blockade alone | NCT02735707 [74] |
| Randomized, controlled, open-label clinical trial | COVID-19 patients with worsening clinical status or with high CRP levels after 21 d of the first randomization to dexamethasone, lopinavir–ritonavir, hydroxychloroquine, azithromycin, or colchicine or convalescent plasma or a combination of two anti-SARS-CoV-2 spike protein antibodies (REGN-COV2) or aspirin | A single dose of TCZ according to the patient's weight | 2022 received TCZ; 2094 received standard of care | TCZ group had a significantly lower mortality rate, need for mechanical ventilation, and higher chance of hospital discharge at day 28. This effect was similar in patients randomized less than or more than two days from hospitalization. In patients who were on mechanical ventilation at the time of drug administration, this drug had no significant effect on improving prognosis | [67] |
| Randomized, double-blindclinical trial | Severe COVID-19 patients | Sarilumab 200 or 400 mg, single dose | $n$ = 153 sarilumab 400 mg, $n$ = 141 sarilumab 200 mg, $n$ = 75 placebo | No significant effectiveness was found in the treatment groups compared with the control group | [111] |
| Randomized, double-Blind, placebo-controlled trial | Patients with COVID-19 in a hyper-inflammatory state | TCZ 8 mg/kg up to 800 mg | TCZ ($n$ = 161); Placebo ($n$ = 81) + standard of care | No significant benefits from early TCZ administration in COVID-19 were observed | [112] |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ICU: Intensive care unit; TCZ: Tocilizumab; CSs: Corticosteroids; COVID-19: Coronavirus disease 2019.

failure. This study found that inflammatory mediators significantly reduced after ruxolitinib administration which also improved clinical conditions. These successes were not accompanied by any severe effects[81]. Another effect of JAK inhibitors in hampering the cytokine storm is related to TNF, the other crucial inflammatory mediator in the cytokine storm that uses JAK signaling and can be inhibited by JAK inhibitors. A recent study evaluated the concurrent administration of an IL-1 blocker antibody and ruxolitinib in critical patients with SARS-CoV-2. The preliminary report of this study demonstrated that this combination was beneficial in clinical improvement, and the lymphocyte count increased after this treatment[82]. In addition, no treatment-related severe complications were observed. Tofacitinib is another JAK inhibitor that was shown to reduce adverse outcomes and mortality in COVID-19 patients in a previous retrospective cohort study[83]. Another exciting intervention for IL blockade with positive effects in patients on ECMO in previous research was extracorporeal cytokine adsorption which showed a significant decrease in IL-6 in treated patients[84,85]. Other agents with anti-IL-6 properties have not yet been entered in clinical trials of COVID-19. However, targeting the trans-signaling pathway seems more efficient than non-specific IL-6 blockade with monoclonal antibodies.

## IL-6 INDUCES TH17 LINEAGE DIFFERENTIATION

Th17 is related to inflammatory processes. As mentioned in Figure 2, when the IL-6-sIL-6R complex reaches CD4+ T cells, it causes them to differentiate into Th17 cell lineage. This action is mediated through the JAK-STAT signaling pathway (IL-6 recruits JAK 1 and 2). These cells can secrete IL-17, 21, and 22 and GM-CSF, and therefore contribute to the pathogenesis of inflammatory processes and chronic diseases. Viral diseases also promote Th17 related responses, and severe cases show higher Th17-related cytokines. Accordingly, Th17 blockade seems to be another way to fight against COVID-19, especially in extreme cases. One study showed that fedratinib reduced Th17 related cytokines in mouse models. Fedratinib is a JAK 2 inhibitor[86].

It was shown that the Th17 subgroup of T cells is increased relative to the other subgroups in severe COVID-19 cases. The role of these cells in SARS-CoV-2 patients with lung injuries has been revealed. Drugs with anti-IL-17 activities include ixekizumab, secukinumab, and brodalumab, and they are used in moderate to severe cases of psoriasis[87,88]. Ixekizumab is an anti-IL-17 antibody and is currently being evaluated in a COVID-19 clinical trial. Inclusion criteria in this study are those with high serum levels of IL-6 and not admitted to the ICU[89]. When IL-17 is secreted from Th17 cells, it causes target cells to produce inflammatory mediators, including IL-6, TNF-α, chemokine C-C motif 2 (CCL2), and IL-1β. These procedures lead to CRS and clinical worsening in SARS-CoV-2[87]. IL-17 is also related to the cutaneous manifestations of COVID-19[90]. However, recent evidence has shown undetectable quantities of IL-17A expression in COVID-19 patients[91]. In a previous study, secukinumab, an anti-IL-17A selective antibody, resulted in clinical improvement in severe SARS-CoV-2 patients[92].

## CONCLUSION

According to the above-mentioned data, IL-6 blockade alone with anti-IL-6R monoclonal antibodies has no significant benefits in improving the prognosis of patients, except for those in a critical condition and in the hyper-inflammatory state before mechanical ventilation. Many factors are related to a patient's response to IL-6 blockade, such as baseline IL-6 level and disease severity. It may also be associated with some worrying side effects. According to recent data, a combination of anti-inflammatory agents is more effective than any one agent alone. Other ways to inhibit IL-6, such as a selective trans-signaling pathway and JAK-STAT inhibition, should be investigated further.

## ACKNOWLEDGEMENTS

The authors would like to thank the Clinical Research Development Unit and Tabriz University of Medical Sciences Faculty of Medicine for providing the expertise that greatly assisted in this work.

## FOOTNOTES

**Author contributions:** Bahmani M, Bannazadeh Baghi H, and Chegini R contributed to the conceptualization; Bahmani M, Chegini R, and Ghanbari E contributed to writing - original draft; Shiri Aghbash P, and Bannazadeh Baghi H contributed to writing - review and editing; Shiri Aghbash P, Bannazadeh Baghi H, Chegini R, and Sheykhsaran E contributed to the visualization; Leylabadlo HE, Bannazadeh Baghi H, Shiri Aghbash P, Ghanbari E, and Sheykhsaran E contributed to the supervision; Bannazadeh Baghi H and Shiri Aghbash P contributed to the project administration; Moradian E, and Kazemzadeh Houjaghan AM contributed to the language editing.

**Conflict-of-interest statement:** The authors declare that there are no conflicts of interest.



**Country/Territory of origin:** Iran

**ORCID number:** Mohaddeseh Bahmani 0000-0002-7438-7653; Rojin Chegini 0000-0001-8505-1728; Elham Ghanbari 0000-0001-6040-1912; Elham Sheykhsaran 0000-0002-9273-433X; Parisa Shiri Aghbash 0000-0001-6733-4556; Hamed Ebrahimzadeh Leylabadlo 0000-0002-3790-9176; Ehsan Moradian 0000-0003-1218-1059; Amir Masoud Kazemzadeh Houjaghan 0000-0001-5456-3835; Hossein Bannazadeh Baghi 0000-0002-2513-5361.

**S-Editor:** Ma YJ
**L-Editor:** Webster JR
**P-Editor:** Ma YJ

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World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

*World J Virol* 2022 May 25; 11(3): 129-136

DOI: 10.5501/wjv.v11.i3.129

ISSN 2220-3249 (online)

*MINIREVIEWS*

# Impact of COVID-19 on mental health and emotional well-being of older adults

Letha Mullamkuzhy Joseph

**Specialty type:** Virology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Tran NMH, Viet Nam

**Received:** February 26, 2021
**Peer-review started:** February 26, 2021
**First decision:** July 15, 2021
**Revised:** July 28, 2021
**Accepted:** April 1, 2022
**Article in press:** April 1, 2022
**Published online:** May 25, 2022

**Letha Mullamkuzhy Joseph,** Nurse Practitioner, Geriatric Research Education and Clinical Center, Durham VA Healthcare System, Durham, NC 27705, United States

**Letha Mullamkuzhy Joseph,** Consulting Associate, Duke University School of Nursing, Durham, NC 27710, United States

**Corresponding author:** Letha Mullamkuzhy Joseph, RN, Instructor, Nurse, Nurse Practitioner, Geriatric Research Education and Clinical Center, Durham VA Healthcare System, 508 Fulton Street, Durham, NC 27705, United States. letha.joseph@va.gov

## Abstract

Older adults faced unique challenges in the pandemic due to their increased vulnerability to coronavirus disease 2019 (COVID-19) and its complications. Pandemic-related restrictions such as physical distancing, stay-at-home orders, lock-down, and mandatory face cover affected older adults in unique ways. Additionally, older adults experienced psychosocial concerns related to discrimination based on ageism and emotional distress from exposure to conflicting messages in the media. They experienced several forms of loss and associated grief and survivor guilt. Pandemic added to their loneliness and social isolation. Furthermore, older adults experienced the fear and anxiety related to COVID and the fear of contracting the disease and dying from it. Pandemic experience included events potential to generate the desire and capability for suicide. Several studies report varying symptoms such as loneliness, anxiety, and depression among older adults during the pandemic. However, during the initial months of the pandemic, there were reports on coping and resilience among this population. The impact of COVID-19 on older adults' mental health may have long-term implications. This narrative review examines the impact of COVID-19 on older adults' mental health and psychosocial wellbeing. Additionally, the review highlights various factors that affected their psychosocial wellbeing during the COVID-19 pandemic.

**Key Words:** COVID-19; Pandemic; Older adults; Geriatrics; Mental health; Psychosocial wellbeing

**Core Tip:** Coronavirus disease 2019 (COVID-19) disproportionately affected older adults. Several studies report varying symptoms such as loneliness, anxiety, and depression among older adults during the pandemic. However, during the initial months of the pandemic, there were reports on coping and resilience among this population. Implications of COVID-19 on older adults' mental health can have long-lasting consequences. This review focuses on several factors that impacted older adults' psychosocial wellbeing during the pandemic.

**Citation:** Joseph LM. Impact of COVID-19 on mental health and emotional well-being of older adults. *World J Virol* 2022; 11(3): 129-136
**URL:** https://www.wjgnet.com/2220-3249/full/v11/i3/129.htm
**DOI:** https://dx.doi.org/10.5501/wjv.v11.i3.129

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has a disparate effect on older adults due to their increased risk for developing severe disease and poor disease outcomes[1]. Stay–at–home orders, lock-down, and mandatory face-covering created unique challenges for older adults. The impact of COVID and COVID-related restrictions can have long-lasting effects on older adults' mental health and wellbeing. During the pandemic's initial months, healthcare professionals from several countries expressed their concern over the pandemic's potential mental health effects and alerted the global community[2-5]. Over a year into the pandemic, it may be beneficial to review the pandemic's psychosocial impact on the older adult population. This narrative review focuses on the pandemic's impact on older adults' psychosocial wellbeing and highlights various elements that influenced the pandemic's impact on older adults' mental health.

## PANDEMIC AND MENTAL HEALTH

Several studies globally explored the pandemic's effect on older adults' mental health (Table 1). During the initial weeks of the pandemic, Klaiber *et al*[6] examined emotional wellbeing and reactivity to COVID-19 stressors among adults living in the United States and Canada and noted that older adults reported better emotional wellbeing and less reactivity to stressors with similar exposure to COVID-19 stressors as young adults. Similarly, van Tilburg *et al*[7] reported stable mental health and wellbeing despite increased loneliness among the older adults in Netherland. A large study among Spanish adults also reported that older adults had lower depression, anxiety, and post-traumatic stress in the early weeks of the pandemic than young adults[8]. However, this Spanish study[8] had a low representation of older adults.

In June 2020, the Centers for Disease Control and Prevention[9] reported the findings of a survey conducted among adults in the United States where the prevalence of depressive symptoms, anxiety and trauma-related stress, suicidal ideations, and substance abuse to cope up with the pandemic related stress was low among older adults as compared to other age groups. This survey's follow-up in September 2020 also supported the lower prevalence of mental health concerns among older adults than young adults[10]. However, in a longitudinal study, Krendl and Perry[11] reported an increase in depressive symptoms and loneliness among older adults living in the United States. Studies from some other countries also reported similar results, as noted below.

In a longitudinal study among community-dwelling older adults in Japan, Fujita *et al*[12] compared the participant's mental health before and during the pandemic. They reported worsening depressive symptoms and apathy among the participants. Additionally, participants 65 years to 75 years of age reported worse symptoms[12]. In Hong Kong, Wong *et al*[13] explored the level of loneliness, anxiety, depression, and insomnia among an established cohort of older adults with multiple chronic medical conditions. Compared to pre-COVID data, these participants reported increased loneliness, anxiety, depression, and insomnia[13]. In Greece, a cross-sectional survey[14] among older adults conducted in the early period of the pandemic noted moderate to severe depressive and anxiety symptoms in 80% of the participants. A similar study from Turkey[15] also reported depressive symptoms (37.5%) and anxiety (29.8%) among the participants.

COVID-related stress and the resulting emotional distress can be explained based on Neuman's systems model, where each client is considered a unique system[16]. Several lines of intrapersonal, interpersonal, and extrapersonal stressors act on the environment of the client system and affect its stability. Each individual has an imaginary 'central core' to survive the effect of such stressors[17]. Several imaginary 'lines of defense' protect the 'central core.' The individual's wellness and adaptation serve as the 'inner line of defense,' whereas the flexible 'outer line of defense' responds to each stressor.

**Table 1 Studies exploring the impact of pandemic on mental health**

| Ref. | Title of the study | Type of study | Sample size and country | Outcomes |
|---|---|---|---|---|
| Klaiber *et al* [6], 2021 | The Ups and Downs of Daily Life During COVID-19: Age Differences in Affect, Stress, and Positive Events | Short term longitudinal study | *n* = 776, Canada and the United States | Older adults showed better emotional well-being and less reactivity to COVID-related stressors |
| van Tilburg *et al*[7], 2020 | Loneliness and mental health during the COVID-19 pandemic: A study among Dutch older adults | Longitudinal study | *n* = 1679, The Netherlands | Increased loneliness in older adults. However, mental health remained roughly stable |
| González-Sanguino *et al* [8], 2020 | Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain | Cross-sectional study | *n* = 3480, Spain | Older age group was negatively related to depression, anxiety and post traumatic stress disorder |
| Czeisler *et al* [9], 2020 | Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic - United States June 24-30, 2020 | Representative panel surveys | *n* = 5470, United States | Prevalence of mental health symptoms 15.1% in older adults and 74.9% in young adults |
| Czeisler *et al* [10], 2021 | Follow-up Survey of US Adult Reports of Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic, September 2020 | Representative panel surveys | *n* = 5285, United States | Mental health symptoms were less prevalent among older adults than in younger adults |
| Krendl and Perry[11], 2021 | The Impact of Sheltering in Place During the COVID-19 Pandemic on Older Adults' Social and Mental Well-Being | Longitudinal study | *n* = 93, United States | Older adults reported increased depressive symptoms over sheltering in-place period |
| Fujita *et al*[12], 2021 | Mental Health Status of the Older Adults in Japan During the COVID-19 Pandemic | Longitudinal study | *n* = 519, Japan | Community-dwelling older adults had worsening of mood. Worse symptoms in adults 65-75 yr of age |
| Wong *et al* [13], 2020 | Impact of COVID-19 on loneliness, mental health, and health service utilization: a prospective cohort study of older adults with multimorbidity in primary care | Longitudinal study | *n* = 583, Hong Kong | A pre-existing cohort of older adults reported significant worsening of loneliness, anxiety, and insomnia, after the onset of the pandemic |
| Parlapani *et al* [14], 2020 | Intolerance of Uncertainty and Loneliness in Older Adults During the COVID-19 Pandemic | Cross-sectional study | *n* = 103, Greece | Moderate to severe depressive symptoms (81.6%) anxiety (84.5%), disrupted sleep (37.9%) |
| Cigiloglu *et al* [15], 2021 | How have older adults reacted to coronavirus disease 2019? | Cross-sectional study | *n* = 104, Turkey | 37.5% reported depressive symptoms and 29.8% reported anxiety; Worse symptoms in those with age ≥ 85 yr |

COVID-19: Coronavirus disease 2019.

The 'line of resistance' determines the individual's response to the stressors. In Neuman's system model, the environment constitutes internal and external factors that influence the client or are influenced by the client. If the lines of defense and the line of resistance are strong enough to keep the stressors away from the core, the stressors will not impact the individual. Additionally, the individual's perception of the stressors as beneficial strengthens the core stability, whereas the opposite perception weakens the core stability[16]. The individual's immediate life circumstances impact the flexible outer line of defense. During the pandemic, older adults faced several life circumstances, potential stressors that affected the core's stability.

## CONTRIBUTORS OF EMOTIONAL DISTRESS

Several elements such as culture, socio-economic status, prior mental illness, and poor access to care may determine the pandemic's impact on older adults' mental health and resilience. Physical distancing, stay-at-home mandates, anxiety about contracting Corona viral disease, and fear of death from complications of the disease may have created unique challenges for older adults. Whitehead and Torossian[18] explored the older adults' pandemic experience and assessed their 'stresses and joys.' An online survey of 825 United States adults aged 60 and above[18] reported confinement and restrictions from the lock-down, isolation, and loneliness from physical distancing and concern for others as the participants' everyday stressors during the pandemic.

### *Physical distancing and lock-down*

In an attempt to contain the virus, government authorities and public health professionals advocated for non-essential service shutdowns, travel bans, and mandatory stay-at-home orders. Physical distancing mandates urged people to avoid or limit face-to-face interactions, group events, travel, and visiting

places of worship, shopping places, and healthcare facilities. Most of the services were closed for in-person activities. Such restrictions affected older adults, especially those with limited technology access or technology skills.

### Activity restrictions

During the pandemic, concerns related to the difficulty in performing everyday activities, wearing face cover, inability to leave home for the job or voluntary activities, inability to attend religious and social activities such as entertainment and sports events, canceled healthcare visits, and the inability to go to stores and select merchandise were contributing to stress[19]. Older adults with solid religious affiliations reported unmet spiritual needs leading to social isolation and sadness[2]. Moreover, physical distancing led to stress factors such as helplessness, concerns related to dependency and timely help, and worry about the pandemic and future[19].

### Bereavement and grief

During the pandemic, the global community suffered COVID-related death and loss of life from other causes. Unlike regular times, many of these people died alone. Several of them did not receive the usual religious rights and social rituals. Many people could not see their loved ones and say final goodbyes. Survivor guilt can contribute to intense grief. In the normal process, people adapt to grief gradually without additional effort. However, in situations with unresolved grief, which happens when something about the loss is troubling for the bereaved person, the stalled grief can give rise to prolonged grief disorder[20]. Death during the pandemic has characteristics such as the sudden and unexpected event in the absence of familiar people, which can precipitate grief that is difficult to resolve.

### Ageism and stereotyping

As the pandemic emerged, discussion on older adults increased risk for contracting the disease, developing severe illness and complications, and poor disease outcomes dominated in healthcare, media, and public discussions. The concept of high vulnerability might have created anxiety and fear among older adults. As Previtali *et al*[21] argued, generalizing older adults' increased risk based on their chronological age was probably an expression of ageism, which was unfair. During the pandemic's initial months, the media highlighted fatality among older adults while giving a relatively minor focus on fatality in other age groups. Older adults' heightened COVID fears might have contributed to higher social isolation and basic needs dependency. Stereotyping older adults based on their age is unfair as several factors determine their overall health status. During the initial months of the pandemic, there was a shortage of resources and associated fear about 'triaging' and rationing the care, which might have created anxiety and worsened older adults' emotional discomfort. Emotional trauma from COVID positive status and isolation and fear of dying alone might have aggravated emotional discomfort among older adults who tested positive for COVID.

### Effect of social media

There was an 'infodemic' related to the pandemic. Social media and communication outlets contributed to the fear and anxiety by spreading conflicting information. Social media expressions such as "Boomer Remover," a trending hashtag on Twitter in March 2020 was potentially hurtful to older adults. During the pandemic, Jimenez-Sotomayor *et al*[22] analyzed the tweets related to COVID-19 and older adults and found that 21.1% of the tweets communicated the notion that older adults' lives were less valuable. Gao *et al*[23] identified a positive association between social media exposure and mental health concerns in Chinese citizens. Though this study included adults in general, not just older adults, the results may have implications on older adults who access social media.

Data related to older adults' mental health implications mainly included the experience of community-dwelling participants who had web or telephone access and physical and cognitive ability to respond to the surveys. Long-term care facilities, assisted living facilities, and group care homes house older adults who require care for their chronic illnesses, disability related to physical or mental illness, or cognitive dysfunction. Residents in care homes encountered additional challenges during the pandemic.

## CHALLENGES IN CARE FACILITIES

Van der Roest *et al*[24] examined the impact of COVID-19 measures on long-term care residents' mental health in the Netherlands. In this cross-sectional analysis, 77% of the participants reported loneliness, and 51% reported poor mental health. Furthermore, most of the staff noted increased agitation, depression, irritability, and anxiety among the residents[24]. Care facilities are high-risk settings for transmitting infectious diseases and were inadequately prepared to manage the pandemic[25]. To combat the pandemic, these facilities employed several interventions that inadvertently affected resident's psychosocial wellbeing. For instance, facilities employed strict visitation policies and physical

distancing policies. As a result, facilities canceled or modified activities such as community dining, group recreational activities and worship services, group exercises, celebrations, and out-of-facility pleasure trips. Physical distancing policies required the residents to stay in their rooms and keep the doors closed. Stopping visitations from family, volunteers, and pets limited older adults' opportunities for socialization. Several care facilities had to employ temporary staff leading to inconsistent caregiving. Receiving care from unfamiliar staff could be anxiety-provoking even for older adults without prior mental health concerns or dementia. Care from healthcare professionals wearing personal protective equipment potentially decreased the 'human touch' in the care. Healthcare professionals limited their face-to-face time with the residents due to the physical distancing policy that worsened the residents' loneliness. Fear about contracting the illness from the asymptomatic carriers and regular surveillance screening and waiting for the results can make the residents anxious. These are some of the examples of challenges that exposed care home residents' vulnerability to emotional distress.

## PANDEMIC AND EMOTIONAL DISTRESS

During the pandemic, the initial three levels of Maslow's hierarchy of needs- physiological need, need for safety and security, and the need for love and belongingness dominated people's needs irrespective of their pre-pandemic position in the hierarchy of needs[26]. Therefore, a rapid change in needs and the reassignment to a lower level of need in the hierarchy could create negative emotions in people. These negative emotions manifest in several forms.

### *Suicide risk*

Before COVID, evidence supported older adults' increased risk for suicide[27-29]. Direct impact of COVID-19 on the suicidal risk of older adults is yet to be known. However, the pandemic's mental health consequences can precipitate the risk factors of suicidal behavior. According to the interpersonal theory of suicide, the simultaneous presence of 'thwarted belongingness' and 'perceived burdensomeness' produced the desire for suicide. Furthermore, the repeated exposure to painful and fear-inducing experiences contributes to the capability of suicide behavior[30]. Pandemic's effect on mental health, such as social isolation, perceived ageism, and fear of delayed or denied healthcare, may contribute to the interpersonal constructs of thwarted belongingness and feelings of burdensomeness. Additionally, emotional distress may contribute to the feeling of hopelessness and increase older adults' risk for suicide[31]. Emotional experiences become distressing under several circumstances.

### *Social isolation*

Heid *et al*[19] explored older adults' adherence to physical distancing mandates and their pandemic stressors. Participants were community-dwelling older adults from New Jersey, the state once considered the pandemic's epicenter in the United States. The majority of the participants reported avoidance of usual activities that required in-person presence. Participants identified that continuing their social relationships and following activity restrictions were their significant challenges related to physical distancing[19]. Participants also reported stress related to missed social interactions with family and friends, especially grandchildren, and canceled social events[19]. Kim and Jung[32] analyzed the link between social isolation and mental wellbeing in older adults from 62 countries who responded to an online survey, 'Global Behaviors and Perceptions in the COVID-19'. The survey[32] response supported social isolation related to physical distancing and its association with psychological distress. Since social connectedness positively impacts health and longevity[33-35], appropriate interventions to improve social connectedness while maintaining physical distancing were essential. A feeling of inadequate social connectedness gives rise to loneliness.

### *Loneliness*

Loneliness, the subjective feeling of being alone, has physical and mental health effects in older adults. Kotwal *et al*[36] examined the experience of loneliness and social isolation among community-dwelling older adults in San-Francisco, California, during the shelter-in-place period. Fifty-four percent of the participants reported worsening loneliness due to the pandemic leading to worsening depression and anxiety[36]. Krendl and Perry[11] also reported increased depressive symptoms and loneliness during the shelter-in-place period. In a similar study in Austria, Stolz *et al*[37] reported increased loneliness in 2020 than in previous years, resulting from the pandemic-related social isolation. Furthermore, loneliness was more significant during the lock-down period than the reopening phase[37]. Researchers reported sleep deprivation and depressive symptoms in older adults with subjective or objective social isolation and loneliness even before the pandemic[38]. Moreover, pre-pandemic studies supported the positive impact of resilience on sleep in other populations[39,40]. Grossman *et al*[41] reported increased sleep concerns and insomnia in older adults who reported loneliness during the pandemic and attributed it to their insecurity from loneliness leading to alertness preventing them from getting a restful night's sleep. Further, the sleep deprivation-loneliness connection was stronger in those with more COVID-related worries or low resilience[41].

## RESILIENCE IN OLDER ADULTS DURING THE PANDEMIC

Despite experiencing stressful situations and facing hardships associated with emotional distress, older adults used their coping skills and created resilience during the pandemic. Several studies attest that older adults did reasonably well in their emotional status compared to other age groups[42]. This observation is similar to the strength and vulnerability integration model, which suggests older adults' ability to regulate their emotions constructively and navigate their stressful experiences compared to other age groups[43]. Furthermore, coping skills accumulated over time might have helped the older adults employ better coping mechanisms and stay positive. Older adult's coping strategies during COVID-19 are yet to be explored. However, older adults tend to anticipate hardships and take proactive measures to cope with possibly stressful situations in life[44]. In addition, proactive coping might have led the older adults to employ wishful thinking, support seeking, and empathetic responding, common coping mechanisms reportedly beneficial in past disasters[45].

## CONCLUSION

During the pandemic, older adults experienced unique challenges with detrimental effects on their mental health and wellbeing. Older adults' pandemic-related psychosocial challenges may harbinger their post-pandemic mental health needs. Post pandemic psychosocial implications are overwhelming. Communities and care homes implemented multidimensional interventions to mitigate the psychosocial impact of the pandemic. Evaluating those interventions' success and adopting the successful interventions as a standard of practice will help create resilience and improve older adults' coping.

## FOOTNOTES

**Author contributions:** Joseph LM reviewed the current literature on this topic and wrote this manuscript.

**Conflict-of-interest statement:** The author has no conflict of interest to disclose.



**Country/Territory of origin:** United States

**ORCID number:** Letha Mullamkuzhy Joseph 0000-0001-8347-5850.

**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Gao CC

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World Journal of Virology

Submit a Manuscript: https://www.f6publishing.com

*World J Virol* 2022 May 25; 11(3): 137-143

DOI: 10.5501/wjv.v11.i3.137

ISSN 2220-3249 (online)

*MINIREVIEWS*

# SARS-CoV-2 Omicron variant (B.1.1.529): A concern with immune escape

Adekunle Sanyaolu, Aleksandra Marinkovic, Stephanie Prakash, Nafees Haider, Martina Williams, Chuku Okorie, Olanrewaju Badaru, Stella Smith

**Specialty type:** Virology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Diab R, Iran; Islam SMRU, Bangladesh; Vij M, India

**Received:** December 28, 2021
**Peer-review started:** December 28, 2021
**First decision:** February 8, 2022
**Revised:** March 5, 2022
**Accepted:** April 21, 2022
**Article in press:** April 21, 2022
**Published online:** May 25, 2022

**Adekunle Sanyaolu,** Department of Public Health, Federal Ministry of Health, Abuja 0000, Nigeria

**Aleksandra Marinkovic, Stephanie Prakash, Martina Williams,** Department of Basic Sciences, Saint James School of Medicine, The Valley 0000, Anguilla

**Nafees Haider,** Department of Basic Sciences, All Saints University School of Medicine, Roseau 0000, Dominica

**Chuku Okorie,** Department of Allied Sciences, Union County College, Plainfield, NJ 07060, United States

**Olanrewaju Badaru,** Department of Public Health, Nigeria Centre for Disease Control, Abuja 0000, Nigeria

**Stella Smith,** Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Lagos 100001, Nigeria

**Corresponding author:** Adekunle Sanyaolu, PhD, Academic Research, Director, Department of Public Health, Federal Ministry of Health, New Federal Secretariat Complex, Phase III, Ahmadu Bello Way, Central Business District, Abuja 0000, Nigeria. sanyakunle@hotmail.com

## Abstract

Omicron, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant that is now spreading across the world, is the most altered version to emerge so far, with mutations comparable to changes reported in earlier variants of concern linked with increased transmissibility and partial resistance to vaccine-induced immunity. This article provides an overview of the SARS-CoV-2 variant Omicron (B.1.1.529) by reviewing the literature from major scientific databases. Although clear immunological and clinical data are not yet available, we extrapolated from what is known about mutations present in the Omicron variant of SARS-CoV-2 and offer preliminary indications on transmissibility, severity, and immune escape through existing research and databases.

**Key Words:** SARS-CoV-2; COVID-19; Omicron; B.1.1.529; Variant of concern; Emerging variants

**Core Tip:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, Omicron (B.1.1.529), was first reported to World Health Organization from South Africa on November 24, 2021. Omicron has been labeled a variant of concern because of genetic changes that increase transmissibility and decrease the effectiveness of health measures, vaccines, and therapeutics. This variant has 32 mutations in the spike protein, which is problematic because vaccinations designed to prevent SARS-CoV-2 infections target spike proteins. Despite some evidence that vaccination alone may not be enough, non-pharmaceutical practices such as continued use of face masks, proper hygiene precautions, and social distancing, are required to successfully combat this variant.

**Citation:** Sanyaolu A, Marinkovic A, Prakash S, Haider N, Williams M, Okorie C, Badaru O, Smith S. SARS-CoV-2 Omicron variant (B.1.1.529): A concern with immune escape. *World J Virol* 2022; 11(3): 137-143
**URL:** https://www.wjgnet.com/2220-3249/full/v11/i3/137.htm
**DOI:** https://dx.doi.org/10.5501/wjv.v11.i3.137

## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, Omicron (B.1.1.529), was first reported to the World Health Organization (WHO) from South Africa on November 24, 2021[1]. The Omicron infection was first confirmed from a sample collected on November 9, 2021[1,2]. The variant was also detected in Botswana in samples collected on November 11, 2021[1,3]. As of January 10, 2021, B.1.1.529 had spread across 105 countries, with most states and territories in the United States testing positive for the variant[3,4]. The Centers for Disease Control and Prevention (CDC) reported that of the 43 Omicron cases initially detected in the United States, 34 had been fully vaccinated, and 25 cases were adults aged 18 years to 39 years[5,6]. By the week of December 25, 2021, the Omicron variant accounts for approximately 95.4% of circulating SARS-CoV-2 strains, while Delta accounts for 4.6%[3].

Many of the cases included mild symptoms such as coughing, congestion, and fatigue; among the less frequently reported symptoms are nausea and vomiting, diarrhea, shortness of breath, difficulty breathing, and loss of smell or taste[6]. As of November 28, 2021, there is no evidence that the symptoms linked with Omicron are distinct from those associated with other variants, according to the WHO[1]. The severity of the condition, as well as its precise signs and symptoms, are still unknown[3].

Omicron has been labeled a variant of concern (VOC) by the WHO and European Center for Disease Prevention and Control (ECDC) on November 26, 2021, because it contains genetic changes that are predicted to increase transmissibility and decrease the effectiveness of social and public health measures along with available vaccines and therapeutics[7,8]. Its genetic profile consists of 26 unique mutations that make it significantly different from other existing variants and indicate that it is a new lineage of SARS-CoV-2[9]. This variant carries 32 mutations in the spike protein alone[7]. Omicron poses an issue because vaccines that have been created to mitigate SARS-CoV-2 infections target spike proteins. Studies in Germany, South Africa, Sweden, and Pfizer have shown a 25 to 40 times decrease in the ability of antibodies created by the Pfizer BioNTech vaccine to neutralize the variant after two doses[10,11]. However, severe coronavirus disease 2019 (COVID-19) can still be managed with the use of corticosteroids to induce T-cell apoptosis and act as an NF-KB inhibitor, and interleukin 6 (IL-6) receptor blockers, which act by targeting the IL-6/IL-6R/JAK pathway to suppress the overreaction of the immune system in COVID-19 patients and blocking the binding of IL-6 to its receptor[1]. Other studies underway to assess treatment efficacy against the Omicron variant include British drugmaker GSK and its United States partner Vir Biotechnology. According to data from their investigation, all spike mutations are effectively treated by their antibody-based COVID-19 therapy[12]. Although science and knowledge about this variant keep changing as they emerge, this report evaluates the literature from key scientific databases to provide an overview of the SARS-CoV-2 variant Omicron (B.1.1.529).

## GLOBAL EPIDEMIOLOGY OF THE OMICRON VARIANT

Despite efforts to better understand viral neutralization and how antibodies and T-cells respond to the SARS-CoV-2 variant, Omicron remains a mystery[13]. On November 11, 2021, the variation was discovered in samples collected in Botswana and then in South Africa by November 14, 2021[3,8,13]. Depicted in Figure 1, most countries and territories have been affected by the Omicron variant, with the United Kingdom, United States, Denmark, France, and Germany most severely impacted, as this variant is presumed to spread more easily, even among the vaccinated population and those who do not show

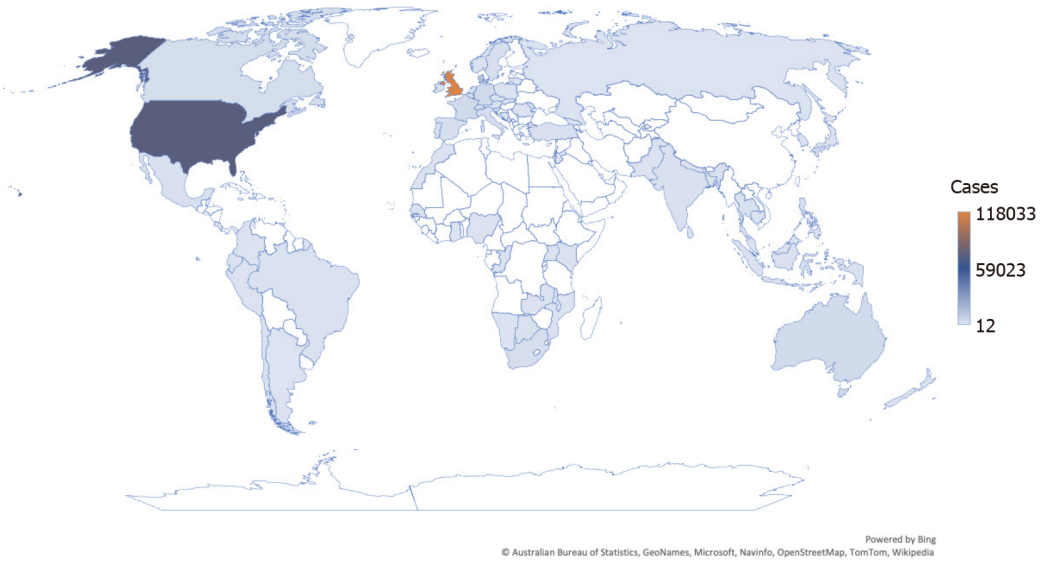


**Figure 1 Confirmed Omicron cases worldwide.** Data recreated and reported by GISAID as of January 10, 2022, with 242159 Omicron genome sequences reported across 105 countries[4].

symptoms; therefore, increasing the overall proportion of COVID-19 cases[3,4].

### *Genomic sequence*

As a result of genomic surveillance, thousands of mutations have been found in the SARS-CoV-2 genome[14-16]. Numerous viral variants with mutations in the spike protein, including Alpha, Beta, and Delta, have been found[17]. These variants exhibited alterations in the receptor-binding domain (RBD), and the 25 amino acids connected to the spike protein showed an increased affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, boosting transmissibility[14,18].

A recent report presented by Dejnirattisai *et al*[14] compared neutralization titers of the SARS-CoV-2 Omicron variant with the titers of the Victoria, Beta, and Delta variants[14,19]. Sera were acquired from individuals who received the AstraZeneca or Pfizer vaccine, both of which were administered in two doses[14,20]. According to the findings, there was a considerable decrease in neutralization titers, with evidence that some individuals were unable to neutralize at all; this can lead to breakthrough vaccine infections in previously infected patients or those who completed double doses of vaccination[21-23].

Although the amino acid sequence of the Omicron spike protein can be altered by nine different mutations (S: N440K, S: G446S, S: S447N, S: T4+78K, S: E484A, S: Q493R, S: G496S, S: Q298R, and S: N501Y), the research found that antibodies can still adhere to the mutated spike protein[24]. The Omicron variant mutations do not show any structural changes that would suggest antibody evasion; nevertheless, alterations in amino acid attachments to various locations of the binding site can cause interference when engaging with antibodies[24].

### *Mutations*

Approximately 30 mutations in the viral spike protein have been discovered, including three small deletions and one small insertion[8]. Roughly half of the mutations affect the RBD, which serves as the virus's principal site of interaction of the virus with human cells and the target protein for several current COVID-19 vaccines[8,13]. Previously, many SARS-CoV-2 variant strains revealed distinct mutations; however, the Omicron variant shows numerous types of mutations, as well as novel mutations[13]. Although the actual origin of Omicron is unknown, numerous possibilities are now being pursued, including evolution in animal reservoirs and human reinfection, or co-infection with seasonal human coronaviruses (HCoVs), such as HCoV-229E[25-27]. Chronically infected individuals are suggested to be the source of origin, as evidenced by viral sequencing[25]. Additional research revealed that when faced with a strong immune response, SARS-CoV-2 may acquire the ability to avoid antibodies through two deletions in the N-terminal domain and a mutation in the spike protein[28]. Finally, it has been proposed that natural selection can arise as a result of mutations that increase viral infectivity, antibody resistance, and vaccine breakthrough[25,29-32]. Evolutionary descent of the Omicron lineages showed that mutations arose under selection pressure due to antibodies elicited by infection, vaccination, or both, in the human population on a large scale. As of February 2022, the Omicron variant has mutated into three lineages: BA.1, BA.2, and BA.3. A sub-lineage of BA.1 with an R346K substitution in the spike protein is classified as BA.1.1. BA.1 emerged first, which was followed by BA.2 and BA.3. Like BA.1, the earlier strains of BA.2, BA.3, and BA1.1 were detected in the Gauteng Province in South Africa. It thus suggests that the diversification of Omicron occurred in South Africa.

Although BA.1 is spreading quicker than BA.2, the BA.2 lineage has become more prominent in several nations after January 2022. The genetic sequence in the spike protein of the BA.2 lineage differs from the BA.1 lineage suggesting it may confer greater immune resistance against antibodies[33-35].

### *Containment strategy*

The U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA) diagnostic developer, DTPM, identifies and develops assays capable of diagnosing COVID-19[36]. However, due to a nine-nucleotide deletion in the N gene, exclusive to the Omicron variant, this single target test known as the reverse transcription-polymerase chain reaction (RT-PCR) of DTPM is predicted to fail, resulting in false-negative findings in patients[36]. The specific deletion of nine nucleotides is unique to the Omicron variant and poses a potential diagnostic problem, although previously detected variants should not be affected[36].

Mutations have the potential to change the accuracy of these tests, resulting in unpredictable analytical performance characteristics and false-negative results. Using a widely available commercial assay, a G-to-U transversion (nucleotide 26372) was found in the SARS-CoV-2 E gene in three cases with low viral detection efficiency[37]. Current SARS-CoV-2 PCR tests still detect the Omicron variant[7,36]. According to reports, one of the three target genes is not detected in a commonly used PCR test[7]. This targeted gene is referred to as an S gene dropout or S gene target failure[7]. As a result, pending sequencing confirmation, this test can be utilized as a marker for the Omicron variant[7]. Furthermore, the FDA is continuing to assess the impact of Omicron on SARS-CoV-2 diagnostic tests in partnership with government authorities and test producers[36]. The FDA's current investigation shows that the performance of some EUA-authorized molecular tests (*i.e.*, PCR) may be affected by the mutations in the SARS-CoV-2 Omicron variant[36]. As a response, the FDA has classified the different tests into two categories: those that are predicted to fail to identify the Omicron variant and those that are expected to detect the variant using a unique gene dropout detection pattern[36]. In addition to molecular diagnostics (*i.e.*, PCR), early evidence suggests that antigen tests can detect the SARS-CoV-2 Omicron form, although that sensitivity may be low[36].

There is much to learn about the reinfected population and effective treatment and management procedures with the Omicron variant, which has led many healthcare providers to doubt existing treatment modalities[38]. Mayer *et al*[38] conducted a recent case series investigation after a rise in people with mild respiratory symptoms of SARS-CoV-2 infections in the Western Cape province. After the patients received confirmation of their COVID-19 using molecular assays, they were placed in isolation and required a daily diary to record their symptoms[38]. A total of 7 patients were studied; of which, 6 of the 7 were fully vaccinated with a respective booster shot, and 5 of the 7 presented with the Omicron genome sequence[38]. Although the study reported breakthrough infections experienced by completely vaccinated patients and some who had also received a booster vaccine, all cases had increased levels of antibodies against the spike protein, a common finding in patients vaccinated with a booster dose[38,39]. Despite the inability to get accurate RNA viral loads, it is hypothesized that these individuals will have an increase in viral loads, suggesting that the Omicron variant could evade vaccine-induced immunity[38]. In another study on naive individuals following a booster shot (third dose), a 14-fold reduction in neutralizing activity against Omicron was observed; thus, the findings suggest the need for a third dose vaccination to provide robust neutralizing antibody responses against the Omicron variant[40].

Most COVID-19 vaccines have remained successful in preventing severe COVID-19, hospitalization, and death for all preceding variants, due to T-cell immune responses being more significant than antibodies[2]. In a matched study of more than 9000 Omicron cases in Ontario, the risk of hospitalization or death was lower for Omicron cases when compared with Delta cases[41]. Importantly, the implications of the remaining Omicron mutations are unknown, leaving a great deal of ambiguity about how the complete mix of deletions and mutations may affect viral behavior and vulnerability to natural and vaccine-mediated immunity[2]. Furthermore, a brief clinical course indicated that fully vaccinated patients who had received a booster dose retained sufficient protection against severe COVID-19 infections; thus, this supported the continued use of booster doses to help combat the spread of the Omicron variant[38,42].

COVID-19 has presented different lessons and challenges to various regions and countries of the world, and long-term data will be needed to assess vaccine efficacy in the face of the potential appearance of novel variants like Omicron[43]. Despite some evidence that vaccination alone may not be enough to prevent symptomatic infection, non-pharmaceutical practices such as continued use of face masks in the public despite vaccination and booster status of the vaccine, proper hygiene precautions, and social distancing, as well as genomic surveillance, are required to successfully combat this variant[38,44].

## CONCLUSION

The emergence and global spread of Omicron, which may be antibody-resistant and appears to be

highly transmissible, emphasize the importance of genomic surveillance in conjunction with immune profiling. Reduced antibody titers may impair the ability of vaccines to prevent infection, but protection against severe disease is likely to be maintained. To avoid or minimize further spread and mutations, preventive measures such as adequate patient care management, early detection of suspicious cases, outbreak tracing, isolation protocols for the infected, continued adherence to social distancing, wearing a face mask, and vaccination must be accepted by the public and encouraged by public health professionals, government officials, and community leaders.

## FOOTNOTES

**Author contributions:** Sanyaolu A, Marinkovic A, Prakash S, Haider N, Williams M, Okorie C, Badaru O and Smith S contributed to the design, writing and final approval of the manuscript.

**Conflict-of-interest statement:** The authors have no conflict of interest to this manuscript.



**Country/Territory of origin:** Nigeria

**ORCID number:** Adekunle Sanyaolu 0000-0002-6265-665X; Aleksandra Marinkovic 0000-0002-3672-0777; Stephanie Prakash 0000-0003-2664-9775; Nafees Haider 0000-0003-4449-0905; Martina Williams 0000-0001-5136-4179; Chuku Okorie 0000-0001-5483-0032; Olanrewaju Badaru 0000-0003-3035-2640; Stella Smith 0000-0003-2163-1189.

**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Gao CC

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World Journal of Virology

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*World J Virol* 2022 May 25; 11(3): 144-149

DOI: 10.5501/wjv.v11.i3.144

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Basic Study

# Omicron variant and change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor

Rujittika Mungmunpuntipantip, Viroj Wiwanitkit

**Specialty type:** Infectious diseases

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Casaca W, Brazil; Nazari N, Iran; Ren S, China

**Received:** December 16, 2021
**Peer-review started:** December 16, 2021
**First decision:** February 21, 2022
**Revised:** February 21, 2022
**Accepted:** April 26, 2022
**Article in press:** April 26, 2022
**Published online:** May 25, 2022

**Rujittika Mungmunpuntipantip,** Consultant, Private Consultant, Bangkok 102002022, Thailand

**Viroj Wiwanitkit,** Department of Community Medicine, Dr. DY Patil University, Pune 310330, India

**Corresponding author:** Rujittika Mungmunpuntipantip, PhD, Academic Research, Additional Professor, Consultant, Private Consultant, Bangkok 102002022, Thailand. rujittika@gmail.com

## Abstract

***BACKGROUND***

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants are currently a new hazard. Since the first appearance of classical SARS-CoV-2 in late 2019, pathogen genetic alterations have continued to occur, and some new hazardous forms have already emerged. The underlying pathophysiological process leading to clinical issue is molecular change caused by genetic mutation.

***AIM***

To determine the change in the interaction between receptor binding domain of omicron variant SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2).

***METHODS***

The researchers investigated how alterations in the binding area of the SARS receptor CoV2 interacted electrostatically with the ACE2 receptor. In this report, three important coronavirus disease 2019 variants, beta, delta, and omicron, were investigated.

***RESULTS***

According to this study, there was a change of electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor due to each studied variant. The most change was detected in omicron variant followed by delta variant and beta variant.

***CONCLUSION***

Our results may support the clinical finding that the omicron variant is more transmissible than the wild type and other variants.

**Key Words:** Omicron; COVID-19; SARS-CoV-2; ACE2; Electrostatic



**Core Tip:** Change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor can support the clinical observation that the omicron variant has increased transmissibility compared to the wild type and other variants.

**Citation:** Mungmunpuntipantip R, Wiwanitkit V. Omicron variant and change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 with the angiotensin-converting enzyme 2 receptor. *World J Virol* 2022; 11(3): 144-149
**URL:** https://www.wjgnet.com/2220-3249/full/v11/i3/144.htm
**DOI:** https://dx.doi.org/10.5501/wjv.v11.i3.144

## INTRODUCTION

In late 2019, a novel coronavirus epidemic emerged in Asia and quickly spread throughout the world [1]. A pandemic occurred, resulting in millions of cases of coronavirus disease 2019 (COVID-19) all across the world. The disease has already infected over 200 million individuals worldwide, resulting in millions of deaths. Since the initial appearance of classical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, scientists have been keeping a tight eye on the pathogen's genetic mutations all across the world[2]. Several pathogenic genetic mutations have been identified, and several variants have already proven to be troublesome novel variants[2,3].

The delta variant is one of the dangerous mutations that has spread globally[4,5]. Because transmission of the delta variation is higher than that of COVID-19, it can provide a concern in disease control. A newer form, the delta plus variant, has also been discovered, and it is now being considered in clinical practice[6,7]. The impact of novel variations on disease epidemiology and clinical characteristics is interesting. The newest troublesome variant of concern, the omicron variant, was discovered in Africa in November 2021[8]. There are various structural alterations in this new variant molecule. Omicron is spreading in a rapid manner, and many nations have already reported cases[9].

Clinically, the underlying pathophysiological mechanism that can result in a clinical disease is molecular change caused by genetic mutation. The impact of molecular changes is interesting, but it has received little research. The clinical impact of the omicron mutation is unknown. Pathogenesis may change as a result of molecular changes. A change in the interaction between receptor binding domain of SARS-CoV-2 with the ACE2 is an interesting issue. The authors conducted this study to see how mutations are associated with electrostatic interactions between the receptor binding domain of SARS-CoV-2 and the ACE2 receptor. In this report, three important COVID-19 variants, beta, delta, and omicron, are investigated.

## MATERIALS AND METHODS

The current research is in the field of medical molecular bioinformatics. It is part of a series of experiments aimed at determining the effects of molecular changes in mutants of SARS-CoV-2. The goal of this research is to see how electrostatic interactions between SARS-CoV-2 and ACE2 receptor change according to the emerging variants. For the investigation of change of electrostatic interactions between receptor binding domain of SARS-CoV-2 with the ACE2 receptor, the authors applied a conventional informatics technique, as described in a recent publication[10].

Various protein-protein interactions are known to be dominated by electrostatic interactions[11]. Analysis was performed according to the published protocol[10]. Briefly, we examined the impact of electrostatic interactions on binding energetics. At the molecular level, both molecular mechanics and Monte Carlo simulations were used to assess the interaction between the receptor binding domain of spike viral protein and ACE2. The protein structure was obtained from the protein data bank and used in all computations (PDB ID: 6m17). To begin, the crystal structure was optimized using the python-based open technique[12]. Then, using multiconformation continuum electrostatics[13], rotamers were created, with each rotatable bond rotated by 60 degrees to sample precisely the sidechain conformations. Finally, the Poisson Boltzmann equation was utilized to calculate electrostatic interactions using optimized protein structures with the most occupied conformers[10]. When DELPHI was used to

calculate pairwise electrostatic interactions between conformers, it is referred to as DELPHI[10]. The Boltzmann distribution for all conformers was then estimated using Monte Carlo sampling for the WT and altered structures at pH 7 using multiconformation continuum electrostatics. For single and double mutant structures, as well as the wild type, the electrostatic and van der Waals contributions to the interaction energies of SARS-CoV-2/ACE2 were estimated[10].

The research type of SARS-CoV-2 included both wild type and mutation-free SARS-CoV-2. *In silico* mutation assignment was by PyMol (PyMol, version 2.4). The variants studied are: (1) Beta (K417N, E484K, and N501Y assigned mutations); (2) Delta (T478K, P681R, and L452R assigned mutations); and (3) Omicron (K417N, E484K, and N501Y assigned mutations) (A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F assigned mutations).

The overall electrostatic interactions value for wild type was derived from the previously mentioned bioinformatic procedure. The already described molecular changes were used for simulation to get the overall electrostatic interactions value for each specific variant. We then calculated the effects of the aforementioned mutations and compared our findings to those of the wild type (native) protein. In brief, the effect of variant on electrostatic interactions was calculated based on a direct comparison to the baseline electrostatic interactions value in wild type. For calculation, the derived overall electrostatic interactions for wild type and each SARS-CoV-2 variant were used as basic parameters. For each type, the change of electrostatic interactions compared to wild type was calculated by the formula "change of electrostatic interactions comparing to wild type = 100 x (electrostatic interactions in that type/ electrostatic interactions of wild type)" and presented in percentage.

## RESULTS

The electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor for wild type, beta variant, delta variant, and omicron variant SARS-CoV-2 are presented in Figure 1. The values are equal to -39.38, -41.26, -163.82, and -643.71 kcal/mol, respectively.

There were differences in electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor among the variants studied. The most change was detected in the omicron variant, followed by delta variant and beta variant (Table 1).

## DISCUSSION

In clinical genetics, a genetic change may occur, which may result in a new clinical condition. The clinical problem caused by the pathogen's genetic variation has already been noticed in COVID-19[4,5]. In clinical virology, a mutation in the SARS-CoV-2 virus could occur, and the new variety could be clinically significant. SARS-CoV-2 variations have been reported in a number of places. The changes occur at the receptor-binding region of the spike glycoprotein, which is critical for binding to the ACE2 receptor. The interaction between receptor and SARS-CoV-2 is a significant factor of sickness, according to pathophysiology.

Basically, several alterations have been discovered in the omicron variant's molecular structure. The mutations could lead to a shift in molecular pathogenesis. A key feature, electrostatic interaction with receptor, was evaluated in this study. The ability of SARS-CoV-2 to bind to a receptor is a critical factor in its transmission. There is no doubt that the new variant spreads quickly[7], which can be explained by the change in electrostatic interactions between receptor and SARS-CoV-2.

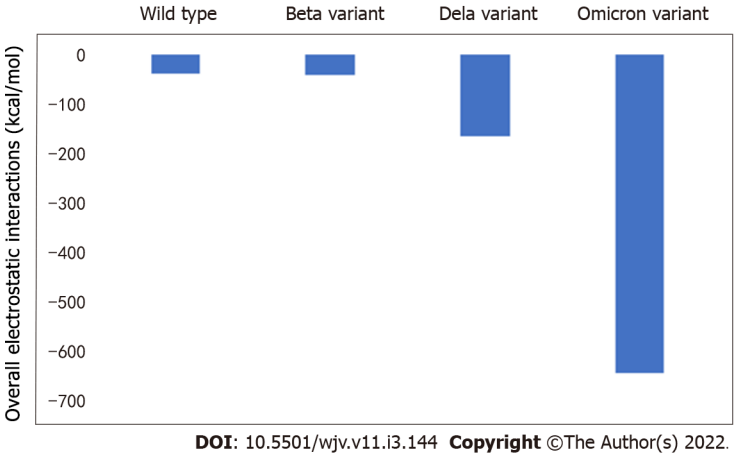
As a result, measuring changes in virus-receptor electrostatic interactions can help researchers better understand disease pathogenesis. According to this study, there has been a significant change in electrostatic interactions. The change of electrostatic interaction has been well described in the delta variant [10], and a change was also observed in the omicron variant. In delta variant, a replacement due to mutation resulted in electrostatic interaction change, and the increased magnitude of electrostatic interactions corresponded to the increased transmissibility of the virus[14].

According to this study, there is a different change of electrostatic interactions between receptor binding domain of SARS-CoV-2 and the ACE2 receptor due to different SARS-CoV-2 variants. The most change was detected in omicron variant, followed by delta variant and beta variant. According to Table 1, the greatest percentage of change compared to wild type was detected in omicron variant. The greatest degree of change indicates the most changes in electrostatic interactions, which can also indicate major changes in clinical features. When compared to wild type, the omicron variant poses around 16 times more electrostatic interactions, implying a significantly stronger connection between the virus and its receptor.

This finding can support the clinical observation that the omicron variant has an increased transmissibility compared to the wild type and other variants. The data from this preliminary study are useful for explaining the pathogenesis of the omicron variant. Further studies on the detailed flexibility of

**Table 1 Change of electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 and the angiotensin-converting enzyme 2 receptor**

| Types | Mutations | Electrostatic interactions | |
|---|---|---|---|
| | | Overall, kcal/mol | Change compared to wild type, % |
| Wild type | No | -39.38 | 0 |
| Beta variant | T478K, P681R, and L452R | -41.26 | 104.8 |
| Dela variant | T478K, P681R, L452R, and K417N | -163.82 | 416.0 |
| Omicron variant | A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F | -634.71 | 1611.8 |




**DOI**: 10.5501/wjv.v11.i3.144 

**Figure 1 Graphical result showing electrostatic interactions between receptor binding domain of severe acute respiratory syndrome coronavirus 2 and the angiotensin-converting enzyme 2 receptor.**

molecular binding, molecular mass change, and immunological epitope change will add to our understanding of the virological properties of the variant.

## CONCLUSION

Each studied variant affects the electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor, according to this study. The omicron form demonstrated the greatest change, followed by the delta and beta variants. These results could support the clinical finding that the omicron variant is more contagious than the wild type and other SARS-CoV-2 variants.

## ARTICLE HIGHLIGHTS

### *Research background*

According to this study, each investigated variant altered the electrostatic interactions between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor binding domain and the angiotensin-converting enzyme 2 (ACE2) receptor. The omicron variant showed the biggest alteration, followed by the delta and beta variants. This finding could back up the clinical observation that the omicron variant is more transmissible than the wild type and other SARS-CoV-2 variants.

### *Research motivation*

Each studied variant affected the electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor. The omicron form, followed by the delta and beta variants, displays the most change. This could support the clinical finding that the omicron variant is more contagious than

the wild type and other SARS-CoV-2 variants.

### *Research objectives*

The authors conducted a study to see how mutations are associated with alterations of electrostatic interactions between receptor binding domain of SARS-CoV-2 with the ACE2 receptor.

### *Research methods*

The researchers investigated how mutations affect electrostatic interactions between the SARS-CoV-2 receptor binding domain and the ACE2 receptor. In this report, three important coronavirus disease 2019 variants, beta, delta, and omicron, were investigated.

### *Research results*

There was a change of electrostatic interactions between the receptor binding domain of SARS-CoV-2 with the ACE2 receptor due to each studied variant compared to wild type. The most change was detected for the omicron variant, followed by delta variant and beta variant.

### *Research conclusions*

Our findings can support the clinical observation that the omicron variant has an increased transmissibility comparable to the wild type and other variants.

### *Research perspectives*

Our findings are consistent with the clinical observation that the omicron variation is more transmissible than the wild type and other variants.

## FOOTNOTES

**Author contributions:** Mungmunpuntipantip R and Wiwanitkit V contributed to study conception and design, acquisition of data, and analysis and interpretation of data; Mungmunpuntipantip R drafted the article, revised it critically for important intellectual content, and approved the version of the article to be published

**Conflict-of-interest statement:** All authors declare that there are no conflicts of interest.



**Country/Territory of origin:** Thailand

**ORCID number:** Rujittika Mungmunpuntipantip 0000-0003-0078-7897; Viroj Wiwanitkit 0000-0003-1039-3728.

**S-Editor:** Ma YJ
**L-Editor:** Filipodia
**P-Editor:** Ma YJ

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World Journal of Virology

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*World J Virol* 2022 May 25; 11(3): 150-169

DOI: 10.5501/wjv.v11.i3.150

ISSN 2220-3249 (online)

ORIGINAL ARTICLE

Observational Study

# Educational, psychosocial, and clinical impact of SARS-CoV-2 (COVID-19) pandemic on medical students in the United States

Veronica Frank, Anjali Doshi, Natalie L Demirjian, Brandon K K Fields, Catherine Song, Xiaomeng Lei, Sravanthi Reddy, Bhushan Desai, Drayton C Harvey, Steven Cen, Ali Gholamrezanezhad

**Specialty type:** Virology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Khosravi M, Iran; Liu XQ, China; Mohammadi S, Iran

**Received:** December 17, 2021
**Peer-review started:** December 17, 2021
**First decision:** February 21, 2022
**Revised:** March 10, 2022
**Accepted:** April 22, 2022
**Article in press:** April 22, 2022
**Published online:** May 25, 2022

**Veronica Frank,** Semmelweis University Faculty of Medicine, Semmelweis University Faculty of Medicine, Budapest 1085, Hungary

**Anjali Doshi, Brandon K K Fields, Catherine Song, Drayton C Harvey,** Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

**Natalie L Demirjian,** Department of Integrative Anatomical Sciences, Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

**Xiaomeng Lei, Sravanthi Reddy, Bhushan Desai, Steven Cen, Ali Gholamrezanezhad,** Department of Radiology, Keck School of Medicine of University of Southern California, Los Angeles, CA 90033, United States

**Corresponding author:** Ali Gholamrezanezhad, MD, Associate Professor, Department of Radiology, Keck School of Medicine of University of Southern California, 1500 San Pablo Street, Los Angeles, CA 90033, United States. a.gholamrezanezhad@yahoo.com

## Abstract

***BACKGROUND***

The coronavirus disease 2019 (COVID-19) pandemic altered education, exams, and residency applications for United States medical students.

***AIM***

To determine the specific impact of the pandemic on US medical students and its correlation to their anxiety levels.

***METHODS***

An 81-question survey was distributed *via* email, Facebook and social media groups using REDCap™. To investigate risk factors associated with elevated anxiety level, we dichotomized the 1-10 anxiety score into low (≤ 5) and high (≥ 6). This cut point represents the 25$^{th}$ percentile. There were 90 (29%) shown as low anxiety and 219 (71%) as high anxiety. For descriptive analyses, we used contingency tables by anxiety categories for categorical measurements with chi square test, or mean ± STD for continuous measurements followed by *t*-test or Wilcoxson rank sum test depending on data normality. Least Absolute Shrinkage and Selection Operator was used to select important predictors for the final multivariate model. Hierarchical Poisson regression model was used to fit the

final multivariate model by considering the nested data structure of students clustered within State.

***RESULTS***

397 medical students from 29 states were analyzed. Approximately half of respondents reported feeling depressed since the pandemic onset. 62% of participants rated 7 or higher out of 10 when asked about anxiety levels. Stressors correlated with higher anxiety scores included "concern about being unable to complete exams or rotations if contracting COVID-19" (RR 1.34; 95%CI: 1.05-1.72, $P$ = 0.02) and the use of mental health services such as a "psychiatrist" (RR 1.18; 95%CI: 1.01-1.3, $P$ = 0.04). However, those students living in cities that limited restaurant operations to exclusively takeout or delivery as the only measure of implementing social distancing (RR 0.64; 95%CI: 0.49-0.82, $P$ < 0.01) and those who selected "does not apply" for financial assistance available if needed (RR 0.83; 95%CI: 0.66-0.98, $P$ = 0.03) were less likely to have a high anxiety.

***CONCLUSION***

COVID-19 significantly impacted medical students in numerous ways. Medical student education and clinical readiness were reduced, and anxiety levels increased. It is vital that medical students receive support as they become physicians. Further research should be conducted on training medical students in telemedicine to better prepare students in the future for pandemic planning and virtual healthcare.

**Key Words:** Medical student; SARS-CoV-2; Anxiety; Stress; Psychological; Impact clinical



**Core Tip:** The severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019) pandemic resulted in a significant impact on medical student education. Education was switched to on-line, examinations were changed, and students' faced dismissal from hospital wards. In this study we analyzed the unique stressors that resulted in higher anxiety levels in medical students. From the results, we can agree that the development of medical school curricula for public health and mass casualty planning as well as providing further mental health support for medical students is necessary and should be further studied.

**Citation:** Frank V, Doshi A, Demirjian NL, Fields BKK, Song C, Lei X, Reddy S, Desai B, Harvey DC, Cen S, Gholamrezanezhad A. Educational, psychosocial, and clinical impact of SARS-CoV-2 (COVID-19) pandemic on medical students in the United States. *World J Virol* 2022; 11(3): 150-169
**URL:** https://www.wjgnet.com/2220-3249/full/v11/i3/150.htm
**DOI:** https://dx.doi.org/10.5501/wjv.v11.i3.150

## INTRODUCTION

In March 2020, the World Health Organization (WHO) declared the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a worldwide pandemic. Starting in China, SARS-CoV-2 [coronavirus disease 2019 (COVID-19)] went on to globally infect more than 426 million people and affect their community healthcare systems, calling on healthcare workers to work overtime to cover the exceeding demand for care[1]. American hospitals faced tremendous difficulty in not only providing enough hospital beds and ventilators for critically ill COVID-19 patients, but also in maintaining the care of existing critically ill patients recovering from a prolonged hospital course. Moreover, hospitals nationwide have faced a severe shortage of personal protective equipment (PPE) for front-line workers and healthcare workers in general[2]. These shortages with the necessity for slowing the rate of infection resulted in several isolation measures, including the temporary dismissal of many medical students from the hospital wards. Medical students amid their clinical training were placed in a particularly difficult spot; neither physicians, nurses, nor local public health departments were able to come to a consensus on whether or not medical students were to be considered "essential workers" amid the pandemic[3]. As a result, medical schools across the US varied in their placement of medical students during this time, either pulling medical students off the wards and away from progressing through their clinical training or fast-tracking their graduations to allow for additional assistance in hospitals and emergency departments with an overabundance of ill patients[4].

Classes were switched to online education to abide by local public health laws mandating stay-at-home orders. Students faced closures of their medical schools as well as postponements, cancellations,

or changes to their National Board of Medical Examiners (NBME) board and shelf exam[1] dates. In addition clinical rotation NBME shelf exams were switched from in-person proctored exams to online [5]. The United States Medical Licensing Examination (USMLE) Step series of board exams continued to be administered at Prometric and other official testing centers, but with far fewer available spots, causing many students to go without any test date. To address this problem, the USMLE had designated specific medical schools as eligible testing centers for board exam administration in late May[5]. Additionally, there had been modifications to the residency application cycle, calling for the suspension of all in-person interviews in favor of virtual interviews. This presents significant challenges in allowing institutions and students to get to know each other on the only personal, in person, level that was possible for a typical residency application cycle[6].

Clearly, COVID-19 has had a significant impact on medical students, perhaps with lasting consequences that may affect their future careers. We aim to understand the extent to which COVID-19 has affected medical students by focusing on educational impact and clinical outcome with corresponding levels of anxiety. More specifically, our goal is to qualitatively evaluate the cancellation of academic activities, USMLE exam planning and preparation, or change of school year end date due to COVID-19 as well as psychological and financial impacts of the pandemic on the medical students. By knowing how global health crises affect future physicians, healthcare systems, national organizations and medical institutions can take steps to best prepare medical students while ensuring a stable trajectory towards training as well as healthy personal well-being and morale.

## MATERIALS AND METHODS

The online survey was designed to be anonymous to more accurately understand the impact of COVID-19 on medical students. A subset of questions were adapted from a survey studying the impact of COVID-19 on spine surgeons[7]. Only less than 30% of the questions were adopted from the survey on spine surgeons and the majority of questions were specifically designed for medical students. The questions went through several rounds of review and revision by the attendings of the medical school to verify they reliably assess the impact of COVID-19 on students. The Institutional Review Board of USC determined this study to be exempt from review (application number UP-20-00314).

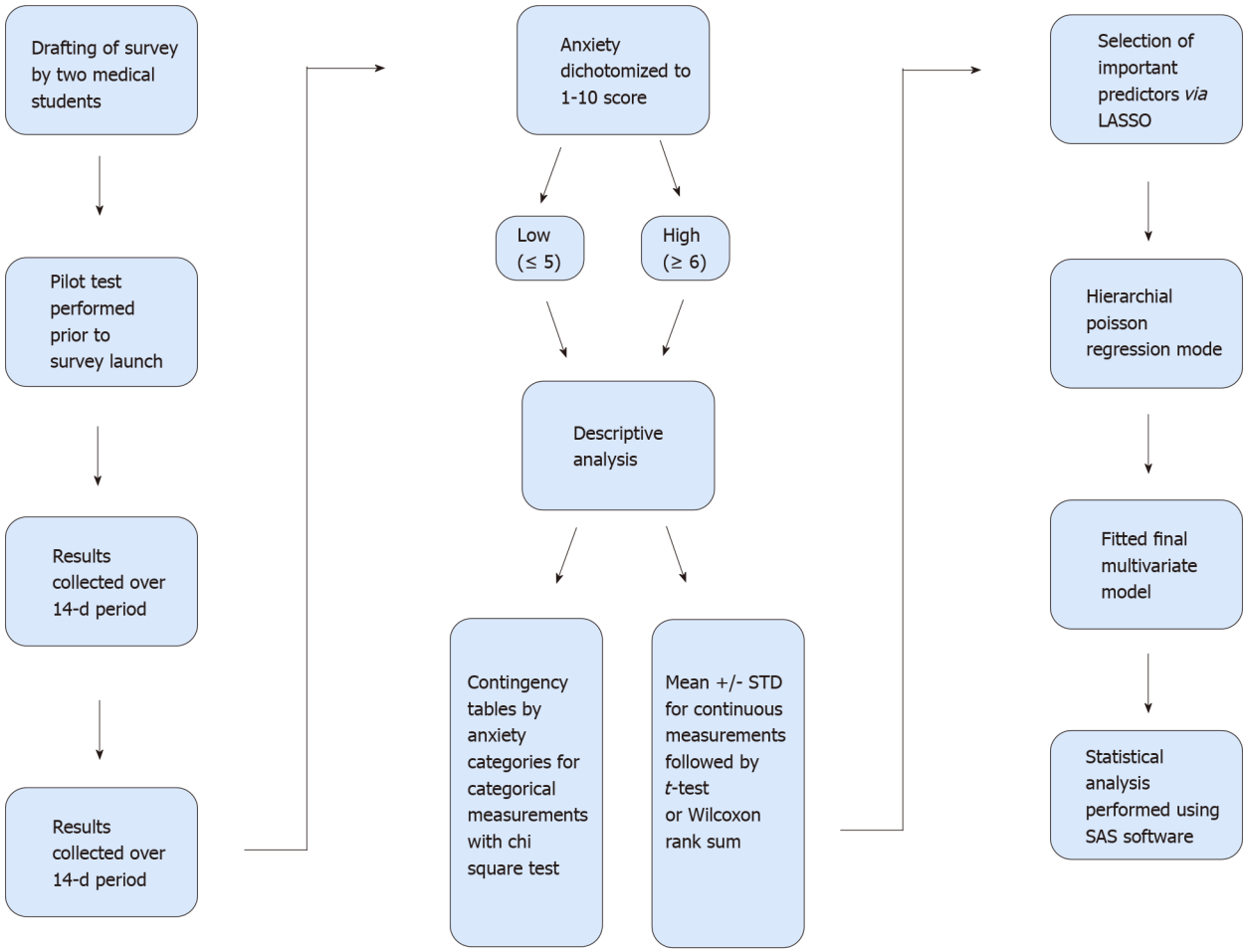
### *Study design and survey*

A list of medical school contacts, including medical students and presidents from medical student associations, were compiled from 51 medical schools within the US through the students contributing to this survey. The survey was distributed using a secure web-based platform, REDCap™ (Research Electronic Data Capture), provided by our institution[8,9]. All invitations were sent *via* email or an online social networking platform with a short explanation of the study. Participants included medical students located in the United States in their pre-clinical, clinical, and research years. Participants were also encouraged to share the survey with their fellow medical students to expand the response rate. Due to the urgency of pandemic, we did not use any sampling strategy such as clustered sample or stratified sample. Instead, a broadcasting email went out to reach as many students as possible in a short period of time.

Two medical students drafted the survey questions, which were reviewed by a team that included medical students, research personnel, and physicians, and a pilot test was run prior to launch of the survey (Figure 1). A total of 81 questions were included in the survey with a 10-min estimated duration time. The survey analyzed the general demographics of participants including age, sex, medical school year, and the state in which medical school is located. The survey data included the following groupings on the impact of COVID-19: General impact, educational duties, medical school preparedness, exams and residency application impact, volunteering, working during the pandemic, financial, and psychological impact. For example, participants were asked about their local government restrictions, educational impact with closure of in-person medical schools, and how well their medical schools adapted. Further questions included changes made to exams, process of applying to residency changes, and levels of anxiety elicited by these changes and the uncertainty of the pandemic. The response options included: binary (yes/no), "non-applicable" and "I don't know"; use of Likert scales on rating participants agreement on provided statements, and selection of items from a list also including text boxes for further elaboration.

### *Data collection*

The survey was distributed on May 6, 2020 *via* email and online social networking platforms using a secure web-based platform, REDCap™. To protect the identity of the participants, no personal identifiers were saved such as IP address tracking, browser activities, read receipts, email activity, or similar data. Participants were encouraged to complete the survey on their own time and in a private environment. Results were collected over a 14-d period and the survey was closed on May 20, 2020. After the survey closure, the collected results were downloaded from REDCap™ and data analysis was initiated.




**DOI**: 10.5501/wjv.v11.i3.150 

**Figure 1 Flowchart of the study process.** LASSO: Least Absolute Shrinkage and Selection Operator.

### *Data analysis*

Mean age, response distribution percentage, Chi-squared test for categorical data, and independent t-tests for continuous measurements were used for descriptive analysis. To investigate risk factors associated with elevated anxiety level, we dichotomized the 1-10 anxiety score into low (≤ 5) and high (≥ 6). This cut point represents the 25$^{th}$ percentile of the original scale. We dichotomized items in order to maximize the number of cases and improve statistical power based on a recent study[10].

For descriptive analyses, we used contingency tables by anxiety categories for categorical measurements with chi square test, or mean ± STD for continuous measurements followed by *t*-test or Wilcoxon rank sum test depending on data normality. Least Absolute Shrinkage and Selection Operator (LASSO) was used to select important predictors for the final multivariate model[11]. Hierarchical Poisson regression model was used to fit the final multivariate model by considering the nested data structure of students clustered within State. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States).

## RESULTS

### *Participant characteristics*

397 medical students (61.17% women, overall participant mean age = 26 ± 2.43 years) who responded to the survey from 29 states were included in the analysis. The distribution across the United States is shown in Table 1, and the demographics of the respondents is demonstrated in Table 2. Of the respondents, 33% were in their first year, 22% second years, 25% third years, and 18% in their fourth year. The remaining 2% were either MD/PhD track students or in their research year. The results of the survey are presented below.

### *Anxiety assessment*

The anxiety scale (1-10) had a distribution of 6.8 ± 2.4, with median of 7, Q1-Q3 of 5-9. When

**Table 1 Respondent distribution across the United States**

| State | N = 397 (%) |
|---|---|
| Missouri | 139 (35.0) |
| California | 68 (17.13) |
| Pennsylvania | 39 (9.82) |
| Massachusetts | 33 (8.31) |
| Washington | 28 (7.05) |
| Florida | 25 (6.3) |
| Texas | 17 (4.28) |
| Nebraska | 8 (2.02) |
| Illinois | 5 (1.26) |
| New York | 4 (1.01) |
| Wisconsin | 4 (1.01) |
| New Jersey | 3 (0.76) |
| Colorado | 3 (0.76) |
| Ohio | 3 (0.76) |
| Minnesota | 2 (0.50) |
| Alabama | 2 (0.50) |
| Nevada | 2 (0.50) |
| Michigan | 1 (0.25) |
| Arizona | 1 (0.25) |
| North Carolina | 1 (0.25) |
| Virginia | 1 (0.25) |
| Maine | 1 (0.25) |
| Georgia | 1 (0.25) |
| Washington DC | 1 (0.25) |
| Louisiana | 1 (0.25) |
| South Carolina | 1 (0.25) |
| North Dakota | 1 (0.25) |
| Kansas | 1 (0.25) |
| Idaho | 1 (0.25) |

dichotomized by Q1, there were 90 (29%) shown as low anxiety and 219 (71%) as high anxiety.

### *General impact of COVID-19*

When asked in the survey about medical students' usual living situation during the school year, prior to the pandemic, 87% of participants selected "off-campus housing apartment-home" (Table 3). Approximately 39% of respondents noted a change in living situation due to the pandemic. Almost all participants (99%) selected "no" when asked if they currently feel sick with symptoms of COVID-19. The vast majority (95%) had not been tested for COVID-19. Notably, only 27% of respondents had a close relative or friend test positive for COVID-19. When asked to select all resources used to educate oneself about COVID-19 the top two were the World Health Organization (WHO)/the Center for Disease Control and Prevention (CDC) (86%) and reading publications (76%). It was important to understand which resources medical students utilized to receive information and how these sources affected their anxiety level. Medical students who educated themselves with reliable resources, such as WHO/CDC and medical publications, exhibited a lower anxiety level compared to those who relied on information seen on social media. Furthermore, more than half of respondents (75%) did not know what personal protective equipment their medical school or center provided, while 15% noted "none."

**Table 2 Sample population characteristics**

| Characteristics | N = 309 (%) |
|---|---|
| Age (years)[1] | 26 (2.43) |
| Gender | |
| Male | 119 (38.51) |
| Female | 189 (61.17) |
| Prefer not to say | 1 (0.32) |
| Current year of medical school | |
| 1 | 101 (32.79) |
| 2 | 68 (22.08) |
| 3 | 77 (25) |
| 4 | 56 (18.18) |
| MD | 3 (0.97) |
| Research year | 2 (0.65) |
| Other | 1 (0.32) |

[1]Reported as mean ± SD. All data are presented as numerators and denominators with percentages in parentheses unless otherwise specified.

### *Educational impact*

When asked if their current academic activity (clinical rotations, in-person class, *etc.*) was cancelled and had not moved online, 73% of participants responded with "no" (Table 4). This implies that students who were removed from campuses and hospitals continued their medical education and training through online supplementation. 44% of participants also reported cancellation of their future academic activities. For those who answered "yes" to cancellation of academic activities, 33% noted a 2-6-mo cancellation, while 30% answered with "I am not sure." Almost all participants (94%) had information being supplemented through distance or online learning. When asked how their overall workload was affected by the pandemic, more than half of the participants (54%) noted a decrease, while 14% had an increase in overall workload. 29% of participants also noted a decrease in research productivity. It is important to note that 45% of participants selected "does not apply," meaning they were not involved in research.

Out of the respondents, 80% agreed there was no change in the school year end date and 54% also noted no change in school exam dates. 41% of participants who stated they were taking the USMLE exams noted a postponement in the exam dates. Medical students spend months preparing for the USMLE exams, a requirement for applying to residency, and any uncertainty regarding the exam can cause an increased anxiety level. Half of the participants (51%) strongly agreed to being concerned how the pandemic would affect their continuing semesters or residency positions, if it were to extend past August.

### *Psychosocial impact*

Respondents were asked using a Likert scale to rate their agreement with the statement "I am worried about the COVID-19 pandemic in general" (Table 5). 40% of participants strongly agreed and 43% agreed with the statement. Respondents were asked to rate their level of stress and anxiety using a scale from 1-10, with mean 6.7 ± 2.4 IQR (5, 8). The self-reported use of mental health resources compared to their previous experiences showed 59% remained unchanged, however there was an increase amongst some participants (17%). We asked to rate the accessibility to mental health services (psychologist, psychiatrist, 24-h emergency hotline, other) on a scale of 1 to 10. An average of 6.78 (SD = 2.33) was self-reported by the respondents. Half of the respondents (50%) reported experiencing an episode of depression during this time. The stressors which were most common amongst participants were waiting for campuses and clinical sites to reopen to students (51%), family well-being (46%), and personal well-being (41%). The self-care activities reported which were the most helpful to respondents were talking to friends (84%), television (81%), and exercise (77%).

Hierarchical Poisson regression model showed students who experienced episodes of depression during this time was a strong risk of high anxiety level (RR 1.6; 95%CI: 1.38–1.85, $P < 0.01$). However, those participants who selected "Participated in volunteer activities for child care for health care workers" (RR 0.68; 95%CI: 0.49–0.93, $P = 0.02$); "USMLE exams or equivalent state exams NOT postponed" (RR 0.87; 95%CI: 0.76–0.99, $P = 0.03$); "Experienced support from school administration and

**Table 3 Univariate analysis on sample population general impact of coronavirus disease 2019**

| General impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| Usual living situation during the school year (*i.e.* before the pandemic) | | | | 0.97 |
| Home with family | 8 (30.77) | 18 (69.23) | 26 (8.41) | |
| Off-campus housing Apartment- House | 78 (28.89) | 192 (71.11) | 270 (87.38) | |
| Campus housing – School dormitory or apartment | 4 (30.77) | 9 (69.23) | 13 (4.21) | |
| Change in living situation during the pandemic | | | | 0.04 |
| No | 63 (33.33) | 126 (66.67) | 189 (61.17) | |
| Yes | 27 (22.5) | 93 (77.5) | 120 (38.83) | |
| Currently living with | | | | 0.54 |
| Alone | 13 (28.89) | 32 (71.11) | 45 (14.56) | |
| With spouse partner | 36 (34.29) | 69 (65.71) | 105 (33.98) | |
| With family | 27 (25.47) | 79 (74.53) | 106 (34.3) | |
| With roommates | 14 (29.17) | 34 (70.83) | 48 (15.53) | |
| Temporarily staying with friends or couch surfing | 0 (0) | 3 (100) | 3 (0.97) | |
| Other | 0 (0) | 2 (100) | 2(0.65) | |
| I have easy access to testing for COVID-19 through my medical school/center if needed | | | | 0.23 |
| 1 = Strongly disagree | 9 (21.95) | 32 (78.05) | 41 (13.27) | |
| 2 = Disagree | 18 (22.5) | 62 (77.5) | 80 (25.89) | |
| 3 = Neutral | 26 (31.71) | 56 (68.29) | 82 (26.54) | |
| 4 = Agree | 22 (31.88) | 47 (68.12) | 69 (22.33) | |
| 5 = Strongly agree | 15 (40.54) | 22 (59.46) | 37 (11.97) | |
| Do you currently feel sick with symptoms of COVID-19? | | | | 0.36 |
| No | 90 (29.32) | 217 (70.68) | 307 (99.35) | |
| Yes | 0 (0) | 2 (100) | 2 (0.65) | |
| Have you been tested for COVID-19 | | | | 0.82 |
| No | 86 (29.35) | 207 (70.65) | 293 (95.13) | |
| Yes, awaiting test result | 1 (25) | 3 (75) | 4 (1.3) | |
| Yes, result was negative | 3 (33.33) | 6 (66.67) | 9 (2.92) | |
| Yes, result was positive | 0 (0) | 2 (100) | 2 (0.65) | |
| Has a close relative or friend tested positive for COVID-19? | | | | 0.2 |
| No | 70 (31.25) | 154 (68.75) | 224 (72.73) | |
| Yes | 20 (23.81) | 64 (76.19) | 84 (27.27) | |
| Resources used to educate about COVID-19-WHO CDC? | | | | 0.67 |
| No | 14 (31.82) | 30 (68.18) | 44 (14.24) | |
| Yes | 76 (28.68) | 189 (71.32) | 265 (85.76) | |
| Resources used to educate about COVID-19-Reading publications? | | | | 0.9 |
| No | 22 (29.73) | 52 (70.27) | 74 (23.95) | |
| Yes | 68 (28.94) | 167 (71.06) | 235 (76.05) | |
| Resources used to educate about COVID-19-Lectures educational resources from school? | | | | 0.52 |
| No | 27 (76.73) | 74 (73.27) | 101 (32.69) | |

| | | | | |
|---|---|---|---|---|
| Yes | 63 (30.29) | 145 (69.71) | 208 (67.31) | |
| Resources used to educate about COVID-19-Social media? | | | | 0.17 |
| No | 40 (33.61) | 79 (66.39) | 119 (38.51) | |
| Yes | 50 (26.32) | 140 (73.68) | 190 (61.49) | |
| Medical school or center providing adequate access to PPE: Gowns | | | | 0.27 |
| No | 81 (28.32) | 205 (71.68) | 286 (92.56) | |
| Yes | 9 (39.13) | 14 (60.87) | 23 (7.44) | |
| Medical school or center providing adequate access to PPE: Gloves | | | | 0.35 |
| No | 81 (28.42) | 204 (71.58) | 285 (92.23) | |
| Yes | 9 (37.5) | 15 (62.5) | 24 (7.77) | |
| Medical school or center providing adequate access to PPE: Face shield or eye protection | | | | 0.21 |
| No | 81 (28.22) | 206 (71.78) | 287 (92.88) | |
| Yes | 9 (40.91) | 13 (59.09) | 22 (7.12) | |
| Medical school or center providing adequate access to PPE: Surgical mask | | | | 0.35 |
| No | 81 (28.42) | 204 (71.58) | 285 (92.23) | |
| Yes | 9 (37.5) | 15 (62.5) | 24 (7.77) | |
| Medical school or center providing adequate access to PPE: N95 or FF3 masks | | | | 0.14 |
| No | 82 (28.18) | 209 (71.82) | 291 (94.17) | |
| Yes | 8 (44.44) | 10 (55.56) | 18 (5.83) | |
| Medical school or center providing adequate access to PPE: None | | | | < 0.01 |
| No | 85 (32.2) | 179 (67.8) | 264 (85.44) | |
| Yes | 5 (11.11) | 40 (88.89) | 45 (14.56) | |
| Medical school or center providing adequate access to PPE: I do not know | | | | 0.02 |
| No | 14 (18.42) | 62 (81.58) | 76 (24.6) | |
| Yes | 76 (32.62) | 157 (67.38) | 233 (75.4) | |

COVID-19: Coronavirus disease 2019; CDC: The Center for Disease Control and Prevention; PPE: Personal protective equipment; WHO: World Health Organization.

faculty regarding COVID-19" (RR 0.75; 95%CI: 0.65–0.87, $P < 0.01$); and "Less concerned about being unable to complete exams or rotations if I contract COVID-19" (RR 0.77; 95%CI: 0.62–0.96, $P = 0.02$) were less likely having high anxiety (Table 6). Therefore, these would propose a protective effect on the level of anxiety experienced.

### *Clinical impact*

Respondents were asked to rate their level of agreement with the statement "COVID-19 has increased the community perception of physicians and healthcare workers as heroes" (Table 7). 23% strongly agreed with the statement and 19% were neutral regarding it. Most of the respondents (96%) were not assisting in the healthcare system at the time of the survey due to restraints caused by COVID-19. Respondents were asked to rate their level of preparedness working with COVID-19 patients on a scale of 1-5. It was important to know if medical students felt ready to care for patients, especially if they were required to volunteer. A lack of preparedness can further increase the anxiety and stress level medical students may already be experiencing. Approximately 45% felt not prepared at all, while 32% gave a rating of 2. When asked if they have the option to volunteer in the hospital for COVID-19, many students responded with no (78%). Out of the respondents, 49% would like to volunteer, however a portion were unable to volunteer due to external factors. The greatest external factor were respondents living or helping with family and/or friends and they did not want to risk exposure. It should be noted that medical students in their pre-clinical years are more likely to feel less prepared to volunteer in the hospital, compared to those students in their clinical and post-graduate years who have more experience on the hospital wards.

**Table 4 Univariate analysis on sample population educational impact of coronavirus disease 2019**

| Educational impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| Was your current academic activity (for example clinical rotations, in-personal class, *etc.*) cancelled, and not moved online? | | | | 0.29 |
| Yes | 20 (24.39) | 62 (75.61) | 82 (26.62) | |
| No | 69 (30.53) | 157 (69.47) | 226 (73.38) | |
| Were your future academic activities cancelled? | | | | 0.02 |
| Yes | 31 (22.63) | 106 (77.37) | 137 (44.34) | |
| No | 59 (34.3) | 113 (65.7) | 172 (55.66) | |
| Is information being supplemented through distance/online learning? | | | | < 0.01 |
| No | 0 (0) | 17 (100) | 17 (5.52) | |
| Yes | 89 (30.58) | 202 (69.42) | 291 (94.48) | |
| How has your overall workload been affected? | | | | < 0.01 |
| Increased | 5 (11.36) | 39 (88.64) | 44 (14.24) | |
| Decreased | 60 (36.14) | 106 (63.86) | 166 (53.72) | |
| Unchanged | 25 (26.6) | 69 (73.4) | 94 (30.42) | |
| Does not apply | 0 (0) | 5 (100) | 5 (1.62) | |
| How has your research productivity been affected? | | | | < 0.01 |
| Increased | 15 (38.46) | 24 (61.54) | 39 (12.62) | |
| Decreased | 23 (25.56) | 67 (74.44) | 90 (29.13) | |
| Unchanged | 20 (50) | 20 (50) | 40 (12.94) | |
| Does not apply | 32 (22.86) | 108 (77.14) | 140 (45.31) | |
| Has the school year end date been: | | | | 0.04 |
| Cancelled | 1 (14.29) | 6 (85.71) | 7 (2.27) | |
| Postponed | 0 (0) | 8 (100) | 8 (2.59) | |
| Unchanged | 76 (30.89) | 170 (69.11) | 246 (79.61) | |
| Moved forward | 2 (16.67) | 10 (83.33) | 12 (3.88) | |
| Does not apply | 8 (53.33) | 7 (46.67) | 15 (4.85) | |
| I don't know | 3 (14.29) | 18 (85.71) | 21 (6.8) | |
| Has graduation been: | | | | 0.24 |
| Cancelled | 15 (23.08) | 50 (76.92) | 65 (21.1) | |
| Postponed | 3 (60) | 2 (40) | 5 (1.62) | |
| Unchanged | 44 (32.59) | 91 (67.41) | 135 (43.83) | |
| Moved forward | 0 (0) | 5 (100) | 5 (1.62) | |
| Does not apply | 21 (30.43) | 48 (69.57) | 69 (22.4) | |
| I don't know | 7 (24.14) | 22 (75.86) | 29 (9.42) | |
| If applicable have your USMLE exams or equivalent state exams been postponed? | | | | < 0.01 |
| Yes | 25 (19.84) | 101 (80.16) | 126 (40.78) | |
| No | 11 (36.67) | 19 (63.33) | 30 (9.71) | |
| Does not apply | 53 (38.41) | 85 (61.59) | 138 (44.66) | |

| | | | | |
|---|---|---|---|---|
| Not sure | 1 (6.67) | 14 (93.33) | 15 (4.85) | |
| If the COVID-19 pandemic extends until or past August, I am concerned it will have a major effect on my continuing semesters or residency position | | | | < 0.01 |
| 1 = Strongly disagree | 3 (100) | 0 (0) | 3 (0.97) | |
| 2 = Disagree | 12 (70.59) | 5 (29.41) | 17 (5.5) | |
| 3 = Neutral | 6 (26.09) | 17 (73.91) | 23 (7.44) | |
| 4 = Agree | 34 (41.98) | 47 (58.02) | 81 (26.21) | |
| 5 = Strongly agree | 27 (17.2) | 130 (82.8) | 157 (50.81) | |
| Does not apply | 8 (28.57) | 20 (71.43) | 28 (9.06) | |
| How effectively have your medical school leadership been managing this outbreak? | | | | < 0.01 |
| Inadequate | 11 (13.58) | 70 (86.42) | 81 (26.47) | |
| Appropriate | 79 (36.07) | 140 (63.93) | 219 (71.57) | |
| Excessive | 0 (0) | 6 (100) | 6 (1.96) | |
| Which of the following best describes your medical school communication efforts to students? | | | | < 0.01 |
| Overly frequent updates | 8 (33.33) | 16 (66.67) | 24 (7.79) | |
| Adequately frequent updates | 69 (35.38) | 126 (64.62) | 195 (63.31) | |
| Infrequent updates | 11 (14.47) | 65 (85.53) | 76 (24.68) | |
| No regular updates | 2 (15.38) | 11 (84.62) | 13 (4.22) | |

COVID-19: Coronavirus disease 2019; USMLE: The United States Medical Licensing Examination.

### *Financial impact*

When presented with the statement "has the pandemic affected you financially," participants were asked to respond in a Likert scale format (Table 8) in which 21% agreed with the statement. Financial assistance availability was present for 34% of respondents, and 41% did not know if any was present. When asked which available emergency funds were accessible the highest response rate (19.2%) was through the school financial aid office.

### *Future impact*

The anticipation of having similar outbreaks in the future was presented with a Likert scale and respondents were asked to rate the statement in which 51% agreed with the statement (Table 9). Respondents were asked to rate on a scale of 1-5 their fear of how future public health crises will be handled. 48% of participants agreed, and 22% strongly agreed, that the lessons learned from this outbreak will help us cope with future crises. The need for medical school curricula in local mass casualty planning was addressed in a Likert scale, in which 50% of respondents agreed and 22% strongly agreed with the statement.

## DISCUSSION

Currently, there is minimal literature on medical students experiencing a pandemic and how a public health crisis may affect medical education. In our study, we have used a 1-10 scale to quality anxiety level, then dichotomized base one Q1 value of 5 into "At least some anxiety (≥ 6) " or "low to no anxiety (≤ 5)". By treating the anxiety measurements as a continuous scale, it is more likely to dilute important information. The difference between a scoring of 1 *vs* 3, 4 *vs* 6, or 7 *vs* 9 is the same, however a scoring of 1 and 3 or 7 and 9 will belong to the same level of anxiety. Dichotomizing a continuous anxiety/stress scale has been used in literature. In most cases, studies would like to detect high risk populations who had higher anxiety/stress level and the risk factors associated with the elevated anxiety level. The benefit of dichotomizing includes providing more clinical meaningful result and better statistical power compared to the modeling approach using outcome with multiple categories[12,13].

Our study was designed to rapidly respond to a worldwide pandemic. To maintain data accuracy, we used the QC procedure to examine any missing data. 19.6% of our survey results were returned with some missing data. Among those, only four participants with more than four missing items were found, from a total of 308 survey questions. The sensitivity analysis was conducted with and without the

**Table 5 Univariate analysis on sample population psychosocial impact of coronavirus disease 2019**

| Psychosocial impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| I am worried about COVID-19 pandemic in general | | | | < 0.01 |
| 1 = Strongly disagree | 3 (75) | 1 (25) | 4 (1.29) | |
| 2 = Disagree | 11 (68.75) | 5 (31.25) | 16 (5.18) | |
| 3 = Neutral | 15 (48.39) | 16 (51.61) | 31 (10.03) | |
| 4 = Agree | 46 (34.59) | 87 (65.41) | 133 (43.04) | |
| 5 = Strongly Agree | 15 (12) | 110 (88) | 125 (40.45) | |
| I am worried about contracting COVID-19 | | | | < 0.01 |
| 1 = Strongly disagree | 11 (55) | 9 (45) | 20 (6.47) | |
| 2 = Disagree | 25 (39.06) | 39 (60.94) | 64 (20.71) | |
| 3 = Neutral | 31 (34.44) | 59 (65.56) | 90 (29.13) | |
| 4 = Agree | 21 (18.92) | 90 (81.08) | 111 (35.92) | |
| 5 = Strongly agree | 2 (8.33) | 22 (91.67) | 24 (7.77) | |
| If applicable, how has your utilization of mental health resources changed? | | | | < 0.01 |
| Increased | 9 (17.31) | 43 (82.69) | 52 (16.83) | |
| Decreased | 2 (7.41) | 25 (92.59) | 27 (8.74) | |
| Unchanged | 59 (32.07) | 125 (67.93) | 184 (59.55) | |
| Does not apply | 20 (43.48) | 26 (56.52) | 46 (14.89) | |
| Mental health services the university provides: Psychologist | | | | 0.29 |
| No | 31 (33.33) | 62 (66.67) | 93 (30.1) | |
| Yes | 59 (27.31) | 157 (72.69) | 216 (69.9) | |
| Mental health services the university provides: Psychiatrist | | | | 0.84 |
| No | 59 (29.5) | 141 (70.5) | 200 (64.72) | |
| Yes | 31 (28.44) | 78 (71.56) | 109 (35.28) | |
| Mental health services the university provides: 24 hour emergency hotline | | | | 0.7 |
| No | 41 (28.08) | 105 (71.92) | 146 (47.25) | |
| Yes | 49 (30.06) | 114 (69.94) | 163 (52.75) | |
| Mental health services the university provides: Does not apply | | | | 0.02 |
| No | 73 (26.84) | 199 (73.16) | 272 (88.03) | |
| Yes | 17 (45.95) | 20 (54.05) | 37 (11.97) | |
| On a scale of 1-10, how accessible do you find mental health services? | | | | 0.21 |
| 1 | 3 (33.33) | 6 (66.67) | 9 (2.95) | |
| 2 | 0 (0) | 5 (100) | 5 (1.64) | |
| 3 | 4 (21.05) | 15 (78.95) | 19 (6.23) | |
| 4 | 1 (11.11) | 8 (88.89) | 9 (2.95) | |
| 5 | 10 (19.23) | 42 (80.77) | 52 (17.05) | |
| 6 | 8 (25.81) | 23 (74.19) | 31 (10.16) | |
| 7 | 17 (32.08) | 36 (67.92) | 53 (17.38) | |
| 8 | 20 (36.36) | 35 (63.64) | 55 (18.03) | |

| | | | | |
|---|---|---|---|---|
| 9 | 4 (19.05) | 17 (80.95) | 21 (6.89) | |
| 10 | 20 (39.22) | 31 (60.78) | 51 (16.72) | |
| Most Stress: Residency applications | | | | 0.03 |
| No | 68 (33.01) | 138 (66.99) | 206 (66.67) | |
| Yes | 22 (21.36) | 81 (78.64) | 103 (33.33) | |
| Most Stress: Community well-being | | | | 0.12 |
| No | 56 (26.42) | 156 (73.58) | 212 (68.61) | |
| Yes | 34 (35.05) | 63 (64.95) | 97 (31.39) | |
| Most Stress: Personal well-being | | | | 0.31 |
| No | 57 (31.32) | 125 (68.68) | 182 (58.9) | |
| Yes | 33 (25.98) | 94 (74.02) | 127 (51.1) | |
| Most Stress: Family well-being | | | | 0.08 |
| No | 56 (33.33) | 112 (66.67) | 168 (54.37) | |
| Yes | 34 (24.11) | 107 (75.89) | 141 (45.63) | |
| Most Stress: Clinical education related to COVID-19 | | | | 0.05 |
| No | 70 (32.41) | 146 (67.59) | 216 (69.9) | |
| Yes | 20 (21.51) | 73 (78.49) | 93 (30.1) | |
| Most Stress: Limited to only essential activities | | | | 0.04 |
| No | 47 (24.87) | 142 (75.13) | 189 (61.17) | |
| Yes | 43 (35.83) | 77 (64.17) | 120 (38.83) | |

COVID-19: Coronavirus disease 2019.

missing data. The findings between the two data sets were consistent. Therefore, we have concluded that this minimal amount of missing data did not influence our findings from the study.

From our study, we have found that COVID-19 has significantly impacted medical students across the United States. 54.87% of respondents were first- and second-year medical students and 43.18% were third-year medical students, most of whom were suddenly disrupted during the peak of their clinical education. Regardless of their progress through medical school, nearly all students have faced abrupt changes in medical education and clinical training, resulting in concern and uncertainty with regard to their paths towards residency programs. Most students noted restrictions in their cities, including medical school closure, shelter or safer-at-home measures, social distancing, limited restaurant operations, and mandates to keep only essential businesses open. The majority of respondents reported that their current academic activities had been cancelled and moved online to a distance learning curriculum, predominantly *via* Zoom, and approximately half felt it was not beneficial to them. Of these respondents, decreased motivation with online learning and an inadequate quality of virtual curriculum were cited as the biggest issues. Due to the unforeseen nature of the pandemic, schools were not prepared to teach medical students remotely. This consequentially resulted in decreased medical student workloads. Restrictions from going on campus and to corresponding medical centers may have contributed to a decrease in students' research productivity as well.

Of those facing postponements in their USMLE or equivalent state exams, almost half of respondents felt very or extremely concerned about the impact of COVID-19 on the residency application process. With this year's residency application deadline looming at the end of October 2020, it is worrisome for students to consider submitting an incomplete application to a system that is already extremely competitive. In an effort to reduce unnecessary exposure and further viral spread, virtual residency interviews will be held for the 2021 Match. It is expected to cause many difficulties in the application process and perhaps negatively impact the applicant even further. It is anticipated that applicants will accept more interviews because of the reduced cost and time needed to travel to each institution, adding to the already growing hyperinflation in the application process. With these changes, programs will ultimately spend less money and time on each applicant. This begs the question if there will be an increase in the number of interview invites. Medical students may anticipate saving money with these adjustments as well, thus being more likely to apply to an increased number of residency programs. While this may seem like a positive result of the pandemic, with more competitive medical students overapplying, less competitive students may consequentially have more difficulty securing a virtual

**Table 6 Multivariate analyses of anxiety association factors after Least Absolute Shrinkage and Selection Operator**

| Survey questions | Rate ratio | Confidence interval | Sig. |
|---|---|---|---|
| I feel disenchanted with the healthcare system due to inadequate response, lack of PPE, lack of testing, *etc.* | | | |
| Disagree (2) *vs* Strongly disagree (1) | 0.93 | 0.5-1.72 | 0.81 |
| Neutral (3) *vs* Strongly disagree (1) | 1.39 | 0.85-2.27 | 0.19 |
| Agree (4) *vs* Strongly disagree (1) | 1.48 | 0.95-2.31 | 0.09 |
| Strongly agree (5) *vs* Strongly disagree(1) | 1.39 | 0.86-2.25 | 0.18 |
| Does not apply *vs* Strongly disagree (1) | 0.93 | 0.5-1.72 | 0.81 |
| Volunteer Activities - Child care for health care workers: Yes *vs* No | 0.68 | 0.49-0.93 | 0.02 |
| Is the distance learning beneficial to you? | | | |
| Agree *vs* Strongly agree | 0.87 | 0.6-1.27 | 0.47 |
| Neutral *vs* Strongly agree | 0.93 | 0.62-1.37 | 0.7 |
| Disagree *vs* Strongly agree | 0.98 | 0.66-1.46 | 0.93 |
| Strongly disagree *vs* Strongly agree | 0.84 | 0.57-1.23 | 0.36 |
| If applicable, have your USMLE exams or equivalent state exams been postponed? | | | |
| No *vs* Yes | 0.87 | 0.76-0.99 | 0.03 |
| Does not apply *vs* Yes | 1.01 | 0.87-1.18 | 0.85 |
| Not sure *vs* Yes | 1.19 | 0.96-1.48 | 0.12 |
| How concerned are you that COVID-19 will affect the residency application process? | | | |
| Slightly concerned (2) *vs* Not concerned (1) | 1.3 | 0.79-2.13 | 0.3 |
| Moderately concerned (3) *vs* Not concerned (1) | 1.22 | 0.79-1.88 | 0.36 |
| Very concerned (4) *vs* Not concerned (1) | 0.86 | 0.58-1.26 | 0.43 |
| Extremely concerned (5) *vs* Not concerned (1) | 1 | 0.6-1.68 | 1 |
| Does not apply *vs* Not concerned (1) | 1.3 | 0.79-2.13 | 0.3 |
| On a scale of 1-5 how supportive have school administration and faculty been regarding COVID-19? | | | |
| 2 *vs* Not supportive | 0.81 | 0.63-1.04 | 0.1 |
| Moderately supportive *vs* Not supportive | 0.75 | 0.65-0.87 | < 0.01[1] |
| 4 *vs* Not supportive | 0.79 | 0.6-1.03 | 0.09 |
| Extremely supportive *vs* Not supportive | 0.89 | 0.78-1.02 | 0.11 |
| Have you experienced episodes of depression during this time? | 1.6 | 1.38-1.85 | < 0.01[1] |
| I am concerned about being unable to complete exams or rotations if I contract COVID-19 | | | |
| Strongly disagree (1) *vs* Strongly agree (5) | 0.66 | 0.26-1.7 | 0.39 |
| Disagree (2) *vs* Strongly agree (5) | 0.77 | 0.62-0.96 | 0.02 |
| Neutral (3) *vs* Strongly agree (5) | 1.11 | 0.95-1.3 | 0.2 |
| Agree (4) *vs* Strongly agree (5) | 1.05 | 0.84-1.31 | 0.68 |
| Does not apply *vs* Strongly agree (5) | 0.88 | 0.69-1.14 | 0.34 |

[1]These covariates were significant using a cut-off *P* value of < 0.01. COVID-19: Coronavirus disease 2019.

interview. To avoid this issue, a fifteen-interview limit per applicant, per specialty, could allow below-average applicants an equal opportunity, but there is no guarantee that AAMC will implement such a regulation[6].

Less than half of medical student respondents indicated wanting to volunteer during the pandemic, perhaps because none reported previous or current infection. Based on survey respondent comments, many based this on their attempt to preserve their own health and the health of family members and friends. Additionally, this finding may emphasize that medical students feel vastly ill-prepared to work

**Table 7 Univariate analysis on sample population clinical impact of coronavirus disease 2019**

| Clinical, future, and financial impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| COVID-19 has increased the community perception of physicians and healthcare workers | | | | 0.1 |
| 1 = Strongly disagree | 1 (25) | 3 (75) | 4 (1.29) | |
| 2 = Disagree | 7 (26.92) | 19 (73.08) | 26 (8.41) | |
| 3 = Neutral | 11 (18.64) | 48 (81.36) | 59 (19.09) | |
| 4 = Agree | 44 (30.14) | 102 (69.86) | 146 (47.25) | |
| 5 = Strongly agree | 25 (34.72) | 47 (65.28) | 72 (23.3) | |
| Does not apply | 2 (100) | 0 (0) | 2 (0.65) | |
| Are you required to assist in the healthcare system currently due to COVID-19? | | | | 0.06 |
| Yes I am being put to work wherever I a needed | 0 (0) | 3 (100) | 3 (0.97) | |
| Yes I am continuing to work in the same clinical role that I was in pre-pandemic | 0 (0) | 10 (100) | 10 (3.24) | |
| No | 90 (30.41) | 206 (69.59) | 296 (95.79) | |
| Do you have the option to volunteer to work in the hospital for COVID-19? | | | | 0.31 |
| No | 66 (27.5) | 174 (72.5) | 240 (77.92) | |
| Yes | 23 (33.82) | 45 (66.18) | 68 (22.08) | |
| Would you like to volunteer? | | | | 0.34 |
| Yes | 46 (30.26) | 106 (69.74) | 152 (49.35) | |
| No | 28 (32.94) | 57 (67.06) | 85 (27.6) | |
| Cannot due to external factors | 16 (22.54) | 55 (77.46) | 71 (23.05) | |
| Cannot volunteer due to external factors: I live or help out with family and or friends who I do not want to risk exposure | | | | 0.1 |
| No | 81 (30.92) | 181 (69.08) | 262 (84.79) | |
| Yes | 9 (19.15) | 38 (80.85) | 47 (15.21) | |
| Cannot volunteer due to external factors: I am concerned about my own safety | | | | 0.56 |
| No | 88 (29.63) | 209 (70.37) | 297 (96.12) | |
| Yes | 2 (16.67) | 10 (83.33) | 12 (3.88) | |
| Cannot volunteer due to external factors: I have to work elsewhere for financial reasons | | | | 0.11 |
| No | 90 (29.7) | 213 (70.3) | 303 (98.06) | |
| Yes | 0 (0) | 6 (100) | 6 (1.94) | |
| Volunteer activities: Fundraising or obtaining PPE for hospitals | | | | 0.52 |
| No | 81 (29.89) | 190 (70.11) | 271 (87.7) | |
| Yes | 3 (21.43) | 29 (76.32) | 38 (12.3) | |
| Volunteer Activities: Helping answer COVID-19 phone lines | | | | 0.41 |
| No | 84 (29.79) | 198 (70.21) | 282 (91.26) | |
| Yes | 6 (22.22) | 21 (77.78) | 27 (8.74) | |
| Volunteer Activities: Child care for healthcare workers | | | | 0.02 |
| No | 78 (27.37) | 207 (72.63) | 285 (92.33) | |
| Yes | 12 (50) | 12 (50) | 24 (7.77) | |
| On a scale of 1-5, how prepared to you feel to work with COVID-19 patients? | | | | 0.38 |
| 1 = Not at all prepared | 37 (72.79) | 99 (72.79) | 136 (44.16) | |
| 2 | 26 (26.26) | 73 (73.74) | 99 (32.14) | |

| | | | | |
|---|---|---|---|---|
| 3 = Adequately prepared | 14 (42.42) | 19 (57.58) | 33 (10.71) | |
| 4 | 5 (27.78) | 13 (72.22) | 18 (5.84) | |
| 5 = Extremely well prepared | 0 (0) | 3 (100) | 3 (0.97) | |
| Does not apply | 7 (36.84) | 12 (63.16) | 19 (6.17) | |
| On a scale of 1-5, how prepared to you feel to work in the general healthcare system (caring for internal medicine patients, surgical patients, *etc.*)? | | | | 0.5 |
| 1 = Not at all prepared | 17 (34) | 33 (66) | 50 (16.18) | |
| 2 | 25 (28.74) | 62 (71.26) | 87 (28.16) | |
| 3 = Adequately prepared | 23 (25.27) | 68 (74.73) | 91 (29.46) | |
| 4 | 17 (33.33) | 34 (66.67) | 51 (16.5) | |
| 5 = Extremely well prepared | 2 (13.33) | 13 (86.67) | 15 (4.85) | |
| Does not apply | 6 (40) | 9 (60) | 15 (4.85) | |

COVID-19: Coronavirus disease 2019; PPE: Personal protective equipment.

**Table 8 Univariate analysis on sample population financial impact of coronavirus disease 2019**

| Financial impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| Has the pandemic affected you financially? | | | | < 0.01 |
| Strongly Agree | 1 (5.56) | 17 (94.44) | 18 (5.83) | |
| Agree | 13 (20.31) | 51 (79.69) | 64 (20.71) | |
| Neutral | 25 (22.73) | 85 (77.27) | 110 (35.6) | |
| Disagree | 36 (39.56) | 55 (60.44) | 91 (29.45) | |
| Is financial assistance available to you if needed? | | | | 0.3 |
| Yes | 37 (35.24) | 68 (64.76) | 105 (33.98) | |
| No | 10 (20.83) | 38 (79.17) | 48 (15.53) | |
| I do not know | 35 (27.34) | 93 (72.66) | 128 (41.42) | |
| Does not apply | 8 (28.57) | 20 (71.43) | 28 (9.06) | |

in a pandemic environment. It is difficult for medical students to feel prepared and secure if they do not see this reflected in their own institution. A majority of students did not have adequate or any access to PPE gowns, N-95 or FF3 masks during this time. In light of the lack of preparative measures to protect healthcare workers, and by extension medical students, in a pandemic or public health crisis, it is no surprise that more than half of respondents believe their medical school should offer curricula in national mass casualty planning[14]. In order for medical schools to be prepared for future public health crises, we now know that measures must be in place to allow for the continuation of quality medical school education regardless of outbreak or mass casualty status. In addition to the evident need for better PPE preparation across the US, a preparation that should include all students working in a clinical setting, there is concern over how the COVID-19 pandemic, and possible future public health crises, will affect medical students' ability to work clinically and prevent early burnout. Based on our results, medical students already feel disenchanted with the US healthcare system with an overarching sense of worry for the current state of affairs and what is to come with future health crises. In a career path previously touted as stable, nothing seems predictable now. Almost half of respondents have been most stressed by their inability to go to campus or clinical sites. These destinations are not only a source of education for students, but also a source of community. As our data shows, this disruption has caused a predictable increase in anxiety. The additional stress of being limited to essential activities and worrying about residency applications also does not bode well for mental health outcomes in these future physicians. This crisis has exacerbated existing medical student mental health issues in addition to instilling fear for the future, which an overwhelming majority of respondents indicated experiencing.

Clearly, medical students and residency program applications care about hands-on education. However, given the current situation, an effort to teach future physicians how to practice non-traditionally is needed, which may include telemedicine and tele-education. Recent research into remote and virtual medical education may prove to be a solution for future needs. Some studies have even

**Table 9 Univariate analysis on sample population future impact of coronavirus disease 2019**

| Future impact | Low anxiety, N = 90 (%) | High anxiety, N = 219 (%) | Total, N = 309 (%) | Sig. |
|---|---|---|---|---|
| I anticipate having similar outbreaks in the future | | | | 0.35 |
| 1 = Strongly disagree | 1 (100) | 0 (0) | 1 (0.32) | |
| 2 = Disagree | 6 (46.15) | 7 (53.85) | 13 (4.22) | |
| 3 = Neutral | 11 (31.43) | 24 (68.57) | 35 (11.36) | |
| 4 = Agree | 46 (29.3) | 111 (70.7) | 157 (50.97) | |
| 5 = Strongly agree | 25 (25) | 75 (75) | 100 (32.47) | |
| Does not apply | 1 (50) | 1 (50) | 2 (0.65) | |
| I am fearful of how future public health crises will be handled? | | | | < 0.01 |
| 1 = Strongly disagree | 2 (100) | 0 (0) | 2 (0.65) | |
| 2 = Disagree | 15 (65.22) | 8 (34.78) | 23 (7.52) | |
| 3 = Neutral | 16 (43.24) | 21 (56.76) | 37 (12.09) | |
| 4 = Agree | 31 (24.8) | 94 (75.2) | 125 (40.85) | |
| 5 = Strongly agree | 25 (21.19) | 93 (78.81) | 118 (38.56) | |
| Does not apply | 1 (100) | 0 (0) | 1 (0.33) | |
| I think the lessons we learn from this outbreak will help us cope with future crises? | | | | 0.04 |
| 1 = Strongly disagree | 3 (37.5) | 5 (62.5) | 8 (2.59) | |
| 2 = Disagree | 11 (34.38) | 21 (65.63) | 32 (10.36) | |
| 3 = Neutral | 9 (17.65) | 42 (82.35) | 51 (16.5) | |
| 4 = Agree | 38 (25.68) | 110 (74.32) | 148 (47.9) | |
| 5 = Strongly agree | 28 (40.58) | 41 (59.42) | 69 (22.33) | |
| Does not apply | 1 (100) | 0 (0) | 1 (0.32) | |
| I think we need medical school curricula in national mass casualty planning? | | | | 0.13 |
| 1 = Strongly disagree | 0 (0) | 4 (100) | 4 (1.3) | |
| 2 = Disagree | 7 (41.18) | 10 (58.82) | 17 (5.52) | |
| 3 = Neutral | 22 (28.21) | 56 (71.79) | 78 (25.32) | |
| 4 = Agree | 49 (33.56) | 97 (66.44) | 146 (47.4) | |
| 5 = Strongly agree | 11 (17.74) | 51 (82.26) | 62 (20.13) | |
| Does not apply | 0 (0) | 1 (100) | 1 (0.32) | |

shown virtual reality to be a useful tool for both learning motivation and learning competency in medical students[15]. With the AAMC recommendation to remove students from the wards to conserve PPE, new modalities of clinical education have already been put into place, such as remote grand rounds *via* Zoom, virtual reality cadaver dissections, and case discussions through online curriculum platforms such as Aquifer[16]. We recommend more research into these methods, as well as medical student exposure to participating in clinical care *via* telemedicine. These changes, understandably, bring feelings of uncertainty and instability to not only educators, but also medical students. In addition to the changes brought about by the pandemic, medical students face uncertainty with what to expect this school year and perhaps beyond graduation. We found that 74.6% feel concerned about the pandemic affecting continuing semesters or their residency position were the pandemic to extend past August 2020. 55.6% indicated concern over being unable to complete rotations and/or exams were they to be infected with COVID-19. Medical students make an immense investment by committing to medical school, both financially and mentally, and many cite the job's stability and satisfaction as primary factors for choosing to go into medicine in the first place. It is understandable that lacking the clear path towards a career so often cited as a stable and predictable journey has stirred up discomfort for the

entire medical community. For medical students in particular, anxiety had already been on the rise, and now further exacerbated by the pandemic[17].

We conducted our multivariate analysis to specifically look at the effect of these educational and clinical changes on the anxiety of medical students. The level of anxiety of the participant, or lack of, may impact the response rate to those survey questions dealing with anxiety. It is not uncommon to have a high percentage of "no response" rate. The missing data is not necessarily problematic in every instance. Participants may not report on one variable because of the anxiety exhibited from it or because of it. For example, a study which examined the tobacco use of adolescent smokers who smoked heavily found that the number of cigarettes smoked per day was not reported. It is assumed that due to the illegality of smoking for these individuals, many participants may have experienced fear of repercussions, thus limiting their response rate[18]. This concept seen in adolescent smokers can provide a valuable explanation on the "no response" rate seen on those questions using anxiety as its variable in this study. Thus, we grouped non-respondents and high-level of anxiety respondents *vs* low-level of anxiety respondents in the multivariate analysis, which looked at educational impact and clinical outcome as the main variables causing an effect on anxiety.

Uncertainty has been one of the main drivers of anxiety among medical students. We found that those who were unsure whether their USMLE or equivalent state exams would be postponed were more likely to have a higher level of anxiety. Those who primarily used the WHO and CDC websites as a source of their education regarding COVID-19 were less likely to have high levels of anxiety. Those who reported experiencing episodes of depression during this time were more likely to have high levels of anxiety. Those who indicated being worried about contracting COVID-19 were more likely to have high levels of anxiety as well. Medical schools have made attempts to better wellness programs for their students and to make mental health resources more available, and perhaps the accessibility of these resources is indeed reaching students in need. We found that those who selected or knew their school offered a psychiatrist were more likely to have high levels of anxiety. We can interpret that because of their anxiety, they have contemplated seeking or have sought the aid of a psychiatrist, and thus were knowledgeable about their school having this resource available.

The need for mental health resource accessibility for medical students remains clear; approximately 33% of medical students worldwide have anxiety, a significantly greater prevalence than the general population[19]. This anxiety does not stop after medical school graduation. The anxiety, stress, and susceptibility to depression continues throughout residency and into attending life if help-seeking behaviors are not encouraged early on in the work environment[20]. Availability of mental health resources for medical students has a lasting effect, helping future physicians develop healthy stress-reducing habits early on in their careers. Adequate mental health should not only be a concern for physicians-in-training and physicians, but also for patients. Studies have found that physicians are less likely to make medical errors when less stressed[20]. Now more than ever, there need to be adequate mental health programs in place. The pandemic has only further exacerbated psychosocial issues that were already problems for student doctors and physicians[21]. Undeniably, the best way to improve health outcomes and patient care is to support our doctors and doctors-in training, and this includes doctors supporting each other. Without this, we risk a devastating mental health crisis that would affect all[21].

There is minimal information regarding the effects of the COVID-19 pandemic on medical students. The study of Harries *et al*[22] shows that more than two third of medical students believe the pandemic has significantly disrupted their education. More than half of the students expressed desire to return to their normal clinical rotations, accepting the risk of infection with COVID-19. In another study by Alsoufi *et al*[23] more than 85% of the participating medical students reported suspended educational programs, lectures, and clinical rotations during the pandemic. However, the reported studies suffer from significant limitations, such as limited survey response rate (although the students were directly contacted from their medical school leadership), and therefore, further studies in this field were recommended.

Perhaps this surreal time in our lives has indicated we need to conduct medical education differently. The pandemic has revealed the flaws in medical education when curriculum is devoted entirely or predominantly towards in-person learning. We need to incorporate nontraditional learning into medical education. This may include educating and preparing medical students for practicing in nontraditional ways, such as *via* telemedicine. We have found that clinic visits can be conducted successfully over a remote interface, posing the question if follow-up in-person visits are actually essential to quality medical care. In fact, the pandemic has highlighted much of what is truly essential in healthcare, and a closer look at what has been emphasized and successfully conducted during this time can guide medical school curriculum committees on where to emphasize their medical education efforts.

There are several limitations to this study. The sample population was largely composed of medical students with access to social media, neglecting those who may limit their social media presence. Furthermore, survey responses were dependent upon the point in time in which respondents filled out the survey, as responses would surely vary at different times during the pandemic. Most of the studied subjects were from California, Florida, Massachusetts, Missouri, Pennsylvania, and Washington. However, we may say that those six states with the highest participants are from West, Central, and East of the USA, which somehow can represent a sample of the entire nation's students. These states are

also very popular to receive students from other states, which again helps in generalizability of the results to the entire country. Additionally, our survey may not ask all pertinent questions assessing the holistic impact of COVID-19 on medical students. The majority of students participating in the survey were in their beginning four years of their studies. This highlights an additional limitation as the final two years are the clinical training years and students faced dismissal from the hospital wards. Lastly, our survey was voluntary, potentially biasing our results to respondents who may have felt strongly about sharing their experiences. Although our study has some limitations, it focuses on some aspects of the medical student education, such as preparation and planning for USMLE exams and school year end date, that have not been assessed in the published reports. More importantly, respondent distribution across the United States in our study is geographically different from the limited available reports, which is another important advantage of our study. Given the fact that the geographic distribution of COVID-19 is not uniform, its psychosocial effects on the population is also not homogeneous. More specifically, different medical schools have implemented different strategies to respond to the pandemic, which certainly result in different effects on their medical students. As research on the impact of pandemics on medical students is limited, adding to the pool of these reports and data could positively improve our understanding about how pandemics affect medical schools, which areas of educational programs are more vulnerable, and which supporting strategies are important to employ to subdue the effects of pandemics effectively and safely on the education.

## CONCLUSION

This study provides insight and important information about how medical students have experienced and been affected by the pandemic. Ultimately, we found that medical students have been significantly impacted in numerous ways. From our results, we now know that amid a public health crisis, medical student education and clinical readiness were reduced, with predictably negative outcomes on medical student anxiety and presumably, residency applications. As no prior research has been done on the effect of a global pandemic on medical students and medical education, we recommend that efforts be placed in healthcare system readiness for public health crises[24], the development of medical school curricula for public health and mass casualty planning, and further mental health support that starts with changing physician culture and stigma and encouraging mental health resource utilization. Furthermore, we encourage research on medical student education that is focused on what has been found to be critically essential. This includes training students in telemedicine and virtual care where applicable. We hope that the results of this study will initiate a restructuring of medical education that will consider medical students' experiences and the potential consequences of future challenges as well as training in non-traditional ways.

## ARTICLE HIGHLIGHTS

### *Research background*

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic prompted abrupt closures of medical schools affecting education, exams, and residency applications for United States medical students.

### *Research motivation*

The survey was drafted by two medical students who faced on-campus closure's of their medical schools and the uncertainty of it's impact on medical education. We wanted to determine potential outcomes caused by the SARS-CoV-2 pandemic on medical students and examine what measures should be taken in the future to better prepare students for pandemics.

### *Research objectives*

The aim of the study was to determine what specific factors impacted medical students, their anxiety, and the effect on medical education. It is important to examine these factors and determine what can be done in the future to prevent similar outcomes.

### *Research methods*

The survey was drafted by two medical students, revised by multiple attending physicians, and a pilot test was performed prior to the survey launch. Anxiety scores were dichotomized to a 1-10 score and for descriptive analysis contingency tables by anxiety categories for categorical measurements and mean ± STD for continuous measurements followed by t-test or Wilcoxson rank were performed. Least Absolute Shrinkage and Selection Operator was utilized to select important predictors for the final multivariate model. The final model was fitted by Hierarchical Poisson regression model.

### *Research results*

The SARS-CoV-2 pandemic greatly impacted medical students' anxiety levels. There was a strong educational and clinical impact and students were faced with many uncertainties, driving up their anxiety levels. It has become evident the need for mental health resource accessibility for medical students is crucial. We still need to better understand the long term effects the pandemic will have on these students as they transition into becoming doctors and how medical schools can better prepare students for future pandemics or global health crises.

### *Research conclusions*

This study provides insight on important information about how medical students have experienced and been affected by the pandemic. We recommend that efforts be placed in the healthcare system readiness for public health crisis, the development of medical school curricular for public health and mass casualty planning, along with further mental health support. We encourage research on medical education that is focused on what has been found to be critically essential: training students in tele-medicine and virtual care.

### *Research perspectives*

Further research should be focused on the long-term effects of the pandemic on medical students, especially as they transition into residency. Research should also be conducted on training students in virtual care and preparedness for future public health crises.

## FOOTNOTES

**Author contributions:** Doshi A and Frank V drafted the survey for the present study; Doshi A managed the survey edits, coding the survey, and submission; Desai B obtained IRB approval; Demirjian NL, Fields BKK, and Song C assisted in survey question editing rephrasing; Desai B, Reddy S, and Gholamrezanezhad A reviewed study documents, survey modifications, and provided input; Doshi A, Frank V, Demirjian NL, Fields BKK, Harvey DC facilitated network outreach; Lei X and Cen S performed statistical analysis on the data; Doshi A and Frank V drafted the manuscript. Prior to submission all authors provided edits; Doshi A and Frank V equally contributed to the work.

**Institutional review board statement:** The Institutional Review Board of USC determined this study to be exempt from review (application number UP-20-00314).

**Informed consent statement:** The study was a survey, for which informed consent was waived by IRB, as no clinical or identifying information from the participants were recorded.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.



**Country/Territory of origin:** United States

**ORCID number:** Veronica Frank 0000-0001-7096-8138; Anjali Doshi 0000-0001-9486-7657; Natalie L Demirjian 0000-0002-1368-1568; Brandon K K Fields 0000-0002-1727-2091; Catherine Song 0000-0003-3096-1251; Xiaomeng Lei 0000-0001-8899-5177; Sravanthi Reddy 0000-0002-6007-4429; Bhushan Desai 0000-0001-9998-0536; Drayton C Harvey 0000-0002-6571-312X; Steven Cen 0000-0002-7859-8909; Ali Gholamrezanezhad 0000-0001-6930-4246.

**S-Editor:** Liu JH
**L-Editor:** A
**P-Editor:** Liu JH

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