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REVIEW ARTICLE

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Outbreaks of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in Comorbid Patients

Kaiser Jamil[1]*, Kavita Kumari Kakarala[1] and Ramesh Maturi[2]

[1]Genetics Department, Bhagwan Mahavir Medical Research Centre 10-1-1, Mahavir Marg, Masabtank, Hyderabad-500004, TS, INDIA

[2]Associate Professor of Surgical Oncology, MNJ Institute of Oncology, Regional Cancer Centre, Hyderabad. TS, India

ABSTRACT

The year 2020 has brought previously unseen challenges upon humankind. A new corona virus, spread at an unprecedented speed globally stormed the entire planet bringing life to almost a standstill with several months of lockdown. What is still sticking in our minds is –when will the pandemic end? or will it ever end? This article is a short review of COVID-19 patients who were already suffering from diseases such as diabetes, cardiovascular diseases, cancers and COPD and other respiratory diseases. We analyzed all articles which discuss the role of the comorbidities in predisposing people to coronavirus SARS- COV-2 and the associated fatalities. However, there are contradictory reports, and in a scenario where the mechanism of infection and resistance to infection and variation in the severity of infection is observed, the role of comorbidities must be evaluated with more data. This article presents an analysis of the fatalities and the role of comorbidities reported from the onset of SARS-COV-2 to present. Further, healthcare support system for the already suffering people was largely neglected during this period, as hospitals were overcrowded with COVID-19 patients. The aim of the article is also to appraise the neglect of primary health care during the COVID-19 pandemic which has been a concern globally and suggest methods to minimize such neglect in future.

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Introduction

The unexpected attack on humanity by the coronavirus is phenomenal. From the initial outbreak in China till today, the world has been jolted into action because the initial strides taken by governments to stop the spread of COVID-19 across the globe fell short, as the statistics have come to show. It is already twelve months since the world came to a standstill due to covid-19 pandemic. Looking at the losses of life, health, and livelihoods, it brought a scare among public. WHO Reports (17th-Jan-2021) that globally in the past week, over 4.7 million new COVID-19 cases and 93,000 deaths occurred. This brings the cumulative numbers to over 79 million reported cases and over 2 million deaths globally since the start of the pandemic

(www.who.int › docs › coronaviruse › situation-reports.)

SARS-CoV-2 is a highly contagious virus and it is transmitted aerially through the respiratory system, by droplets, secretions and direct contact. In most cases, especially in young subjects, the infection by SARS-CoV-2 causes a flu-like syndrome [1]. This corona virus is spherical structurally which is enveloped in a membrane, the envelope is studded with spike proteinsthat play an important role in attaching to the host [2]. The genomic structure of this corona virus (SARS-CoV-2) is organized as a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment of approximately 30 kb in length — the largest known RNA viruses — and with a 5'-cap structure and 3'-poly-A tail. The present global scenario of SARS-COV-2 infections is presented in Table-1.

Contact Kaiser Jamil ✉ Kaiser.jamil@gmail.com Genetics Department, Bhagwan Mahavir Medical Research Centre 10-1-1, Mahavir Marg, Masabtank, Hyderabad-500004, TS, INDIÁ.

Table 1: Showing COVID-19: Daily Dashboard

Global case count (as of February 17, 08:23 ET): **109,613,248** confirmed cases; **2,421,283** deaths (2.2%). The following are the 30 countries with the highest case counts as of February 17, 08:23 ET.

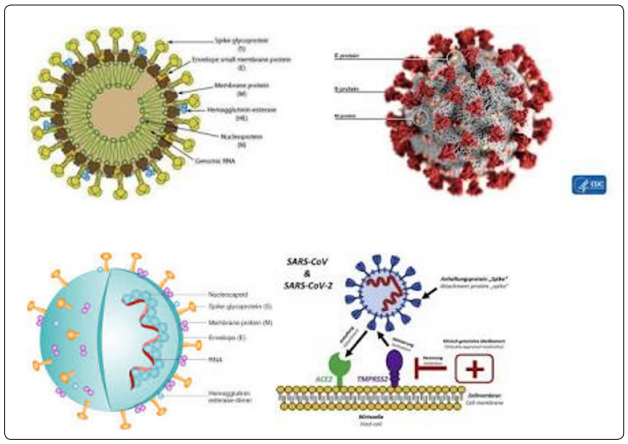
Country	Total confirmed cases	Total deaths	Total recovered	Confirmed cases per million population	Deaths per million population
US	27,757,609	488,103	NA	84,836	1,492
India	10,937,320	155,913	10,644,858	8,088	115
Brazil	9,921,981	240,940	8,847,264	47,366	1,150
United Kingdom	4,070,332	118,421	11,024	61,219	1,781
Russia	4,066,164	80,118	3,602,163	27,985	551
France	3,548,963	82,965	250,448	52,979	1,238
Spain	3,096,343	65,979	150,376	66,269	1,412
Italy	2,739,591	94,171	2,251,734	45,334	1,558
Turkey	2,602,034	27,652	2,489,624	31,608	336
Germany	2,356,966	66,251	2,161,116	28,240	794
Colombia	2,202,598	57,949	2,095,105	44,364	1,167
Argentina	2,033,060	50,432	1,838,291	45,691	1,133
Mexico	2,004,575	175,986	1,563,992	15,885	1,395
Poland	1,605,372	41,308	1,354,598	41,984	1,080
Iran	1,542,076	59,184	1,317,612	18,830	723
South Africa	1,494,119	48,313	1,396,951	25,860	836
Ukraine	1,326,891	26,017	1,169,314	29,560	580
Peru	1,244,729	44,056	1,155,956	38,755	1,372
Indonesia	1,243,646	33,788	1,047,676	4,619	126
Czechia	1,112,322	18,596	987,515	103,749	1,734
Netherlands	1,049,120	15,050	13,809	60,884	873
Canada	836,594	21,395	782,150	22,574	577
Portugal	788,561	15,522	677,719	76,697	1,510
Chile	782,039	19,644	740,465	41,753	1,049
Romania	768,785	19,588	714,709	39,354	1,003
Belgium	741,205	21,750	NA	64,892	1,904
Israel	737,644	5,463	678,906	82,703	612
Iraq	649,982	13,192	609,800	16,910	343
Sweden	622,102	12,569	NA	60,691	1,226
Pakistan	565,989	12,436	528,545	2,667	59

* data not available on the Johns Hopkins University COVID-19 Dashboard

Reference: https://coronavirus.jhu.edu/map.html

SOURCE: Johns Hopkins University CSSE

Images for covid 19 structure



Images -Source: Freely Available on the Internet

Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. The spike- receptor- binding domain allows the binding to the ACE2 receptor in the lungs and other tissues. The presence within the spike protein of an amino acid site (polybasic site) allows the functional processing of the same by the human enzyme furin (protease). This process allows the exposure of the fusion sequences and therefore the fusion of the viral and cell membranes, a necessary passage for the virus to enter the host cell.

How SARS-CoV-2 Enters our Cells

The first step of viral infection is the entry into the host cell. The spike glycoprotein on the corona virus envelope binds to specific receptors on the membrane of host cells. Previous studies have shown that ACE2 is a specific functional receptor for SARS-CoV, the receptor-binding domain of the spike glycoprotein binds to the tip of subdomain I of ACE2. Membrane fusion of the virus and the host cell is activated after binding, and viral RNA is subsequently released into the cytoplasm, establishing infection. ACE2 is a protein that sits on the outside of host cells and is normally involved in controlling blood pressure. However, the SARS-Cov-2 virus hijacks ACE2 by using it as a docking site that enables entry of the virus into a cell. The mechanism by which this happens is that the membrane bound Angiotensin converting enzyme (ACE2) coverts the Angiotensin -1 thus decreasing the level of Ang-II levels which then prevents vasoconstriction. ACE-II receptor has been postulated to be the entry point for SARS-Cov-2 into the host cells [3]. Once this happens, a flood of other reactions occur. In cases of community Transmission also same phenomena is observed, the SARS-CoV-2 virus makes its way into a host cell via a host protein known as ACE2, which is involved in a range of physiological functions in the body [4]. ACE2 receptors are also present on the cell walls of the heart, lungs, intestine and kidney cells.Researchers have demonstrated that when intestinal organoids are exposed to the virus, these cells became infected. (Figure 1 and 2)

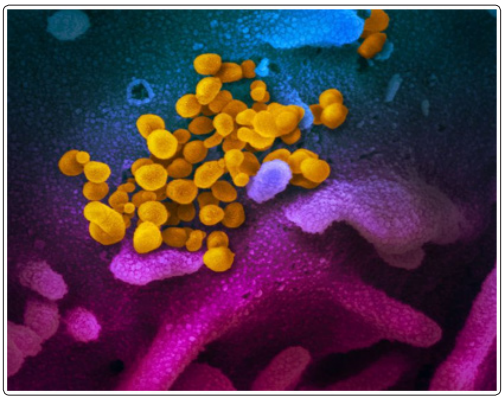


Figure 1: Source: This scanning electron microscope image shows SARS-CoV-2 (yellow)-also known as 2019-nCoV, the virus that causes COVID-19-isolated from a patient in the U.S., emerging from the surface of cells (blue/pink) cultured in the lab. Image captured and colorized at NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana. Credit: NIAID

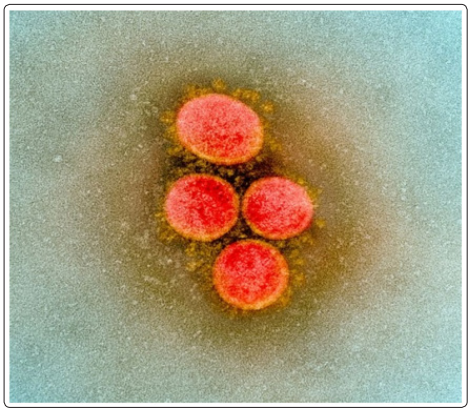


Figure 2: Source: Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. / Credit: NIAID

Cytokine Storm Syndrome in COVID-19

The virus then starts multiplying in the body of the affected patient, which thenleads to a high production of pro-inflammatory cytokines, which is the body's natural response to the foreign agent. These cytokines [5] were identified as interleukins such as –IL-6, IL-1 ,and TNF-α, further, excessiveinfiltration of pro-inflammatory cells, mainly involving macrophages and T-helper cells, have been found in lung tissues of patients with COVID-19 by postmortem examination. Various studies indicate thatSARS-Cov-2 selectively induces a high level of IL-6 which results in the exhaustion of lymphocytes, and this "cytokine storm" may contribute to the mortality of COVID-19 patients especially when they are immune-compromised [6]. High levels of the cytokine proteins interleukin (IL)-6 and tumor necrosis factor (TNF)-α on admission to hospital with COVID-19 predicted a worse outcome than having lower levels [7]. Levels of the interleukin proteins were considered high if 2-3 times higher than the upper limit of normal levels, whereas the cutoff for TNF-α being high was at the 99th percentile of normal levels.This finding was reported to be independent of age, gender and underlying medical conditions, among other factors, although levels of two other cytokines—IL-1β and IL-8—did not significantly impact patient outcomes.

How our Immune System Responds to SARS-Cov-2

Our immune system is instrumental in protecting us from external in vaders of every shape and size. If it isn't part of us, our immune system will fight it, or at least try to destroy it. When a virus appears, the T cells quickly multiply to attack the virus and recruit B cells to produce antibodies that potentially provide protection against future infection [8]. An important characteristic about T cells is that they can "remember" past infections and kill pathogens if they reappear. This is significant because antibody signals for SARS-CoV-2 have been reported by many researchers to decline over time. Additionally, recent research has shown that the T-cell response can persist even when antibodies wane.

SARS-CoV-2 contains a receptor-binding domain (RBD) that recognizes angiotensin-converting enzyme 2 (ACE2) as its receptor with a higher binding affinity compared to SARS-CoV-1[9].

Interestingly the SARS-CoV-2 infection decreases with the decrease in availability of ACE2 receptor on cell membranes resulting in the loss of membrane bound catalytic activityand increasing Ang II levels. The high levels of Ang II might be responsible for the increased pulmonary inflammation and coagulation. Understanding the impact of ACE2 deficiency and finding strategies to prevent binding of S-protein to the ACE2 is therefore critical.

Pathology of Corona Virus (SARS-CoV-2) – Current Understanding

The reason for the deaths of COVID-19 patients is suspected to be due to the "cytokine storm" [also called "cytokine storm syndrome" (CSS)]. Cron and Behrens [6] bring the current knowledge of CSS. They define that "cytokine storm" is an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to different triggers. The triggers involved infections, malignancy, rheumatic disorders [6], etc. Another scholar described that cytokine storm is a systemic inflammatory response to infections and drugs that leads to excessive activation of immune cells and the generation of pro-inflammatory cytokines. A similar entity is termed "cytokine release syndrome" (CRS), which is not defined in the CSS. CRS is an acute systemic inflammatory syndrome characterized by multiple-organ dysfunction (MOD). It has been reported that chimeric antigen receptor (CAR)-T-cell therapy could help to distinguish CRS from a cytokine storm. Of note, is the criteria of CSS based on hemophagocytic lymphohistiocytosis (HLH) and secondary HLH (sHLH) associated with rheumatic disorders, such as macrophage activation syndrome (MAS).The triggers for immune thrombocytopenia, or CSS for COVID-19 patients compared to other diseasesor to comorbid patients could be different hence the sequence of events that follow will also differ (CSS vs CRC) [9-11]. The question remains whether comorbid conditions can modulate the severity of the disease outcome or cause COVID-19 infections. The pandemic of COVID-19, a disease caused by a novel coronavirus SARS-CoV-2, is associated with significant morbidity and mortality. Recent data showed that hypertension, diabetes mellitus, cardiovascular diseases, and chronic obstructive pulmonary disease were the most prevalent comorbidities in COVID-19 patients. Additionally, data indicate that hypertension, diabetes, and cardiovascular diseases are important risk factors for progression and unfavorable outcome in COVID-19 patients. Early hematological abnormalities in COVID-19 have been described in the literature which is directly linked to mortality in these patients [12]. Increased expression of ACE2 is reported in diabetic, hypertensive, and obese patients [13]. ACE2 receptor is commonly identified in the epithelial cells of the lungs, intestine, kidney, and blood vessel [14].

The Vasoprotective Axes of the Renin-Angiotensin System

Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases [15]. Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients [16].Consequently, the increase expression of ACE receptors may lead to higher internalization of virus and resultant conditions which vary in people according to the response initiated. Surprisingly, there were reports where continued use of the drugs used in Diabetes and Hypertensionhas resulted in reducing the severity of disease. Interestingly obesity alone was also related to morbidity in Covid 19 patients [17]. However, physiological factors in obese individuals, such as a decline in the types of anti-inflammatory cells and an increase in proinflammatory cells, a shift in the integrity of the immune system, an increase in insulin and leptin resistance,(insulin and leptin are important for regulation of both innate and adaptive response regulated host defense against infection) and higher levels of prothrombin factors, are some of the conditions that can increase the severity of disease-related outcomes[18]Interestingly, there are many reports which have not been able to establish the mortality in obesepatients [19]. Highlighting the need for further studies and SARS-COVID specific complication in obese patients needs to be focused rather than deriving a common phenomenon for all the diseases. Moreover, due to insufficient genetic data, the existence of coronavirus S-protein binding resistant towards ACE2 still a mystery. Interestingly, age is independently not a the risk factors as there are reports It has been reported that people in their teens or twenties may develop a severe form of the disease, may require intensive care and may die as well [20,21]. Nevertheless, age related conditions like higher levels of inflammatory activity evidenced by elevated levels (TNF-alpha, IL-6, cytokine antagonists, etc [22], could add to the inflammatory response due to virus infection.

People with rheumatic disease are immune-compromised due to increased use of immunosuppressive drugs making them respond to infection with severity. However, despite having high prevalence, obesity was not associated with mortality in COVID-19 patients [18]. The mechanism for coronavirus S-protein binding to ACE2 is enigmatic because of insufficient genetic evidence [23]. To improve clinical outcomes, a deeper understanding of the different ways in which endocrine status and endocrine treatments affect COVID-19 and vice versa wil**l help.**

Non-Corona Patients Suffered Neglect Due To Unpreparedness of Health Care System in India and Worldwide

While the severity of COVID-19 cannot be debated, but the

health care for non-COVID-19 patients suffering with serious illness like cancer, kidney ailments cardiovascular complications, etc., was badly hit and resulted in suffering for them and made them susceptible to COVID-19 infection. While the world was focusing on COVID-19 the people with existing complications had no information or facility for specific treatment as the healthcare system underwent tremendous pressure to cater to an alarming situation for healthcare workers and doctors. For many non-coronavirus patients, both communicable and non-communicable, restricted access to both outpatient and hospitalization facilities proved fatal. However, despite chronic underfunding and general neglect, broadly speaking, the Indian public health system has been able to handle the pandemic in a highly successful way. Nevertheless, there are many lessons which should get a place in revising the health care policy in India and worldwide as world might witness more severe pandemics in future. Although there is an urgent need for dedicated centers and ancillary centers to develop a disaster management program along with trained health care personnel to deal with the system, the government should ensure that non-covid patients who need medical facilities are not victimized or have to pay the price. By scaling up health care facilities, specialized centers for the health care of non-covid patients should also be opened. Further, for understanding the evolution of viral pathogens and monitoring for improvements in transmissibility, virulence, and disease pathology, global epidemiological surveillance is essential. Global monitoring, as such, plays a vital role in the effective control of pathogens. Without a comprehensive, organized, universal effort to recognize and classify emerging variants, communities are at risk of suffering major health and economic setbacks.

COVID-19: Higher Viral Load in Asymptomatic Patients

Epidemiological updates reveal that people infected with the SARS-CoV-2 virus experience mild to moderate respiratory illness and may recover without requiring special treatment. However, older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. In a study of over 200 patients with SARS-CoV-2 virus, carried out in Telangana, revealed that there is a greater association between higher viral load and asymptomatic COVID-19 patients. Viral load is the amount of virus present in the bodily fluid of an infected person. The scientists, including those from the CDFD, Hyderabad, suggested screening of asymptomatic primary and secondary contacts of the COVID-19 patients. The silent spreaders of SARS-CoV-2 virus are those who appear asymptomatic, pre-symptomatic or mildly symptomatic. also reported by South Korean Scientists.

SARS-CoV-2 Fatal In Comorbid / Immune-Compromised Patients

The presence of more than one disorder in an individual is known as Comorbidity. These disorders can exist independently or can be interlinked to other similar causes. According to a study published in the Lancet journal SARS-CoV-2 infection can be more fatal in patients who are already suffering from diabetes, hypertension, heart disease or cancer. Hence it is a doctor's dilemma to deal with such cases, especially when such patients are already immuno-compromised and mortality is inevitable. The lancet report says that in India there are about 8 crore hypertensive patients and 72.96 crore diabetic patients [24]. No such figure is yet available for cancer patients. Similarly, people who have a stent implanted in their arteries may be more vulnerable to COVID-19 infection, as the virus can cause tears in a patient's blood vessels. Few doctors have stated that: "When people with diabetes develop a viral infection, it is often difficult to treat them due to fluctuations in their blood glucose levels and the presence of diabetes complications. Their immune system is compromised," Dr Mahesh DM, a consultant for endocrinology at Bengaluru's Aster CMI Hospital. Further - "Influenza virus is already known as a propellant for heart attacks. The patients who are on blood-thinning medications, their chances of bleeding from lungs become high in case of coughing, such as in the case of coronavirus infection, as reported by Y.K. Mishra, head of cardiac sciences at Manipal Hospital in Delhi,

An electronic literature review search showed that patients with COVID-19 disease who have comorbidities, such as hypertension or diabetes mellitus, are more likely to develop a more severe course and progression of the disease. Furthermore, older patients, especially those 65 years old and above who have comorbidities and are infected, have an increased admission rate into the intensive care unit (ICU) and mortality from the COVID-19 disease.

Co-morbidities include other illness like HBP, Diabetes, Cardiovascular diseases, or Cancers or COPD, Rhinitis, Allergies etc. Here the body's immune system is weak and cannot destroy the heavy viral load and hence mortality / death occurs. The chances of dying are much higher (50%) for people who are suffering from comorbidities. JAMA medidata was the first one to publish a 60% reduction in Oncology trials globally during the first wave of COVID-19 pandemic this was an effort by the health professionals to stop the virus spread, save lives and reduce pressure on hospitals.

Patients with comorbidities should take all necessary precautions to avoid getting infected with SARS CoV-2, as they usually have the worst prognosis, as SARS-CoV-2 primarily attacks alveolar epithelial cells, producing respiratory distress. These cases illustrate that in the current times, any co-morbid patient presenting with vaso-occlusive crisis (VOC) or acute chest syndrome (ACS) should be tested for SARS-CoV-2 and treating physicians should have a low threshold for exchange transfusion.

Conditions Caused by COVID-19

Common symptoms of COVID-19 are well-documented. Patients often experience fever, dry cough, difficulty breathing, fatigue, and other symptoms. Many of these symptoms persist for months after patients recover.Though the COVID-19 virus primarily impacts the lungs, it also affects the heart and the brain. COVID-19 patients often have permanent damage to their heart muscles, which can increase the risk of CVD. Scar tissue in the lungs can lead to lasting breathing issues.For COVID-19 patients of all ages, the virus can cause seizures and strokes. Some researchers believe COVID-19 may also increase patient

risk of developing neurological disorders such as Parkinson's or Alzheimer's disease.

Understanding comorbidities allows us to identify the communities at the highest risk of contracting the virus. Such data can also inform population health initiatives, like drive-through testing. This will be especially important as States continue to reopen perhaps leading to another rise in COVID-19 cases. Also it is important to get access to medical claims data of patients to identify comorbidities associated with Covid-19. As the pathophysiology and complications associated with COVID-19 continue to unfold, further basic sciences research in areas of pathophysiology and randomized control trials for successful management of this pandemic are needed.

Conclusion and Perspective

One of the reasons for COVID-19 deathsbeing underreported across India, could be due to patients succumbing to complications of comorbidities and are reported as death due to CVD or heart attach –also a heart-attack death could also be erroneously attributed to COVID-19. Because of the high global prevalence of arterial hypertension Covid-19 infection aggravates its condition and increases mortality. Similar could be the case with cancer patients though much information is not available on cancer-covid deaths.

Consistent monitoring and management of blood pressure can help avoid broad BP fluctuations, which are associated with a higher risk of developing targeted (i.e., lung) or multiple organ failure. The exact cellular mechanisms, through which CVDs, including AH and Cancers aggravate COVID-19 prognosis, are still being investigated.

One important aspect which requires extensive studies is the genetic predisposition linking ACE2 polymorphism associated with AH. However, we also need to address a number of questions such as - does preexisting AH increase the risk of SARS-CoV-2 infection and/or worsen the course of COVID-19? Is the degree of AH related to high expression levels of ACE2, the SARS-CoV-2 receptor, in the heart and blood vessel endothelium? How the imbalances of the immune system caused by COVID-19 increase the severity of AH? Can modulation of the immune response in COVID-19 patients reduce the severity of AH and hypertensive damage to the target organs? What are the optimal AH ranges and therapies that can ensure a protective effect against COVID-19 and improve its clinical outcomes? With the increase in our scientific knowledge and understanding on COVID-19 our outlook has changed and we are more capable of dealing with this pandemic with the new Norms. From the beginning of the pandemic, one notable difference between severe and mild-moderate cases of COVID-19 is the onset of excessive inflammation or a 'cytokine storm' in severe patients leading to multiple organ damage and a high mortality rate [25]. It is therefore suggested that more research is needed on the impact of treating patients with drugs to lower the levels of these enzyme proteins. For example, remdesivir was shown to be beneficial for COVID19 patients as it lowers IL-6 levels.It is through our determination and commitment to further our knowledge through research that we give hope and healing to the world.

Ultimately, neglected Public Health Aspects globally have been exposed to COVID-19 pandemic asa greater number of deaths were associated to disease conditions most of which could be avoided if good healthcare policies were available in various countries where the mortality rate is high. To provide an improved understanding of potential changes in population-wide genetic predispositions, the fundamental pathophysiological mode of action between COVID-19 and the role of comorbidities, further research is urgently needed.

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