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وزارة التعليـم العالـي والبحـث العلمـي

Ministère de l'Enseignement Supérieur et de la Recherche Scientifique

No Réf ……

Centre Universitaire Abd El Hafid Boussouf- Mila

Institut des Sciences et de la Technologie
Département des sciences de nature et de la vie

Mémoire préparé en vue de l'obtention du diplôme de Master

Domaine : Sciences de la Nature et de la Vie

Filière : Sciences Biologiques

Spécialité : Biochimie Appliquée

THÈME:

Étude épidémiologique de coronavirus dans la wilaya de Mila

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Soutenue devant le jury :

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Examinateur : BAKLI Sabrina	**MCB / Centre Universitaire de Mila**
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Abstract

COVID-19 is an infectious disease recently emerged in Wuhan City, Hubei Province, China. This infection was then linked to SARS-CoV-2 virus which is a non-segmented positive sense RNA virus. Typically, fever, cough and tiredness are some of the most frequent symptoms. Infected patients may also exhibit severed shortness of breath, low blood oxygen, lung damage as the infection progress. Our retrospective epidemiological study, conducted in Mila district, was based on clinical data analysis from 957 hospitalized patients that were admitted to both 'Meghloui brother's' and 'Tobal brothers' hospitals. Our findings showed that there was a correlation between number of coronavirus-infected individuals and the population density. Men are more susceptible to COVID-19 infection than women and this seems due to the high expression level of ACE2 SARS-CoV-2 receptor. Furthermore, COVID-19 severity was generally associated with coexisting chronic diseases. Our results showed that Omicron variant infected frequently younger individuals then older ones due to development of patients immune system during the three first waves.

Key words: COVID-19, SARS-CoV-2, Mila District, Virus, Infection, ACE2, Patients.

Résumé

Le COVID-19 est une maladie infectieuse récemment apparue dans la ville de Wuhan, dans la province de Hubei, en Chine. Cette infection a ensuite été liée au virus SRAS-CoV-2 qui est un virus à ARN à sens positif non segmenté. En général, la fièvre, la toux et la fatigue font partie des symptômes les plus fréquents. Les patients infectés peuvent également présenter un essoufflement sévère, un faible taux d'oxygène dans le sang et des lésions pulmonaires à mesure que l'infection progresse. Notre étude épidémiologique rétrospective, menée dans le district de Mila, était basée sur l'analyse des données cliniques de 957 patients hospitalisés dans les hôpitaux des frères Meghloui et des frères Tobal. Nos résultats ont montré qu'il existait une corrélation entre le nombre de personnes infectées par le coronavirus et la densité de la population. Les hommes sont plus sensibles à l'infection par le COVID-19 que les femmes et cela semble dû au niveau d'expression élevé du récepteur ACE2 SARS-CoV-2. En outre, la gravité de l'infection par COVID-19 était généralement associée à des maladies chroniques coexistantes. Nos résultats montrent que le variante Omicron a infecté plus fréquemment les individus plus jeunes que les plus âgés en raison du développement du système immunitaire des patients au cours des trois premières vagues.

Mots clés : COVID-19, SARS-CoV-2, District de Mila, Virus, Infection, ACE2, Patients.

ملخص

فيروس كورونا هو مرض معد ظهر مؤخرًا في مدينة ووهان ، مقاطعة هوبي ، الصين. تم ربط هذه العدوى لاحقًا بفيروس SARS-CoV-2 وهو فيروس RNA غير إيجابي الحس. بشكل عام ، تعتبر الحمى والسعال والتعب من أكثر الأعراض شيوعًا. قد يعاني المرضى المصابون أيضًا من ضيق شديد في التنفس ، وانخفاض مستويات الأكسجين في الدم ، وتلف الرئة مع تقدم العدوى. استندت دراستنا الوبائية بأثر رجعي ، التي أجريت في منطقة ميلة ، إلى تحليل البيانات السريرية من 957 مريضًا في المستشفيات في مستشفيات الأخوين مغلوي والأخوين توبال. أظهرت نتائجنا وجود علاقة ارتباط بين عدد المصابين بفيروس كورونا وكثافة السكان. الرجال أكثر عرضة للإصابة بعدوى COVID-19 من النساء ويبدو أن هذا يرجع إلى مستوى التعبير العالي لمستقبلات SARS-CoV-2 ACE2. علاوة على ذلك ، ارتبطت شدة الإصابة بـ COVID-19 بشكل عام بالأمراض المزمنة. تظهر نتائجنا أن متغير Omicron أصاب الأفراد الأصغر سنًا بشكل متكرر أكثر من كبار السن بسبب تطور أجهزة المناعة لدى المرضى خلال الموجات الثلاث الأولى.

الكلمات الأساسية: COVID-19، SARS-CoV-2 ، منطقة ميلة ، فيروس ، عدوى ، ACE2 ، مرضى.

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First and foremost, we would like to thank God for his blessing and mercy given to us throughout all the challenging moments in completing this work. We are truly grateful for His unconditional and endless love, mercy, and grace.

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At the end of this work, we would like to express our deep gratitude to all those who have contributed in any way to the realization of this work.

DEDICATION

I would like to dedicate this work to my great beloving parents whose always give me the support, gaudiness, motivation, encouragement, as well as for all of their sacrifices.

I also dedicate this work to my two beautiful sisters Amina and Fedoua who have supported me throughout the process. I will always appreciate all they have done, especially their encouragements.

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Hadjar

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I dedicate this work to my dear parents who have provided me with their encouragement understanding and love.

To my brothers for their whole-hearted support.

A special thanks to my friends Hadjar Abir Maroua Douaa and Fayssal for their help and encouragement.

Nahla

DEDICATION

This study is wholeheartedly dedicated to my beloved parents, who have been my source of inspiration and gave me strength when I thought of giving up, who continually provide their moral, spiritual, emotional, and financial support.

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I also dedicated this study to the best lovely brother ever Mohamed.

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Abir

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List of Abbreviations

Covs	Coronaviruses
229^{E}, HKU1, NL63, OC4	Human coronavirus virion
MERS	Middle East respiratory syndrome
SARS-CoV	Severe Acute Respiratory Syndrome-Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
MERS-CoV	Middle East Respiratory Syndrome-Coronavirus
WHO	World health organization
Covid-19	Coronavirus disease 2019
Nm	Nano Meter
kb	Kilobase
ORFs	Opening reading frames
S	Spike protein
N	Nucleocapsid protein
M	Membrane protein
E	Envelope protein
AA	Amino Acid
2019-nCoV	Coronavirus disease 2019
ARDS	Acute Respiratory Distress Syndrome
HCov	Human Coronavirus
RBD	Receptor Binding Domain
ACE2	Angiotensin -converting enzyme 2
RAS	Renin- Angiotensin system
ACE	Angiotensin-converting-enzyme
TMPRSS2	Transmembrane protease, serine 2
Nsps	Nonstructural proteins
RTC	Replicase-transcriptase complex
RdRp	RNA-dependent RNA polymerase
Sg	Subgenomic
ER	Endoplasmic Reticulum
ERGIC	Endoplasmic Reticulum-Golgi Intermediate Compartment
VLPs	Virus-like particules

UTR	Untranslated regions
pp1a	Polypeptides 1a
kDa	Kilodalton
NTD	The N-terminal domain
FP	Fusion Peptide
HR	Heptad repeat
CH	Central Helix
CD	Connector Domain
TM	Transmembrane domain
CT	Cytoplasmic tail
N-terminus	NH_2-terminus
C-terminus	COOH-terminus
CTD	C-terminal domain
HE	Hemagglutinin-esterase
NF	Nutritic factor
JNK	C-Jeun N terminal kinase
INF	Interferon
IL-8	Interlukine-8
MAP	Mitogen-activated protein kinase
VOC	Variants of concern
VOIs	Variants of interest
B.1.1.7	Alpha variant
B.1.3.5.1	Beta variant
P.1	Gamma variant
B.1.6.1.7.2	Delta variant
B.1.1529	Omicron variant
PRRA	Four Amino Acid Residues
SpO2	Spot Oxygen Saturation
FDA	Food and Drug Administration
CDC	Centers for Disease Control
R	Effective reproductive number
AU	African Union

CFRs	Case fatality rate
CT scan	Computed tomography scan
PCR	Polymerase chain reaction
SD	Standard deviation
CVD	Cardiovascular diseases
HTN	Hypertension
IDDM	Insulin dependent diabetes mellitues
NIDD	Non-insulin dependent diabetes
P-value	Probability value
DSF	Pharmaceutical and Pharmacological Sciences
CD4/CD8	Cluster differentiation
ARBs	Angiotensin receptor blockers
ARDS	Acute Respiratory Distress Syndrome

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Introduction

Introduction:

In the two last years, the world has experienced a real tragedy due to coronavirus outbreak and particularly its ability to spread quickly and it claimed a huge number of lives worldwide. Also, its high rate of mortality that passed six million, which terrified peoples around the world.

Facing the unexpected massive number of patients with COVID-19 disease, the World Health Organization on March 2020 has declared the novel coronavirus COVID-19 as a global outbreak, where the SARS-Cov-2 virus was discovered for the first time in Wuhan, China in 2019, then this outbreak spread around the world (Marino *et al*., 2021).

Algeria was among the first African countries affected by COVID-19 on February 2020 after that the infection has propagated to all its regions (Wilayas).

This COVID-19 outbreak is a viral infection that causes common symptoms such as cough, fever, tiredness, anosmia, loss of taste and smell as well as serious symptoms such as difficulty of breath, chest pain and also shortness of breath. These symptoms may differ from a person to another in severity depending on their age, sex and their antecedents. Moreover, some persons could be asymptomatic. However, the matter did not end in this point, but also it passed to the development of SARS-Cov-2 to new variants where the global has witnessed several mutations from its first apparition. As consequence, several variants have been reported such as Alpha, Beta, Gamma, Delta, and finally Omicron.

Considering that COVID-19 is a novel disease in the process of research and investigation with new reports and new clinical data, the epidemiological profile enabled to set approximately the health characteristics of patients.

In the present work, we first began by a theoretical part in which we exposed the most important bibliographic reports in the field of infectious diseases and particularly coronavirus infection and the epidemiological situation through the world especially in Algeria. We thus investigated latest reports about SARS-Cov-2 infection in general, its symptoms and its pathophysiology. Then we performed a more descriptive study of the SARS-Cov-2 virus in which we exhaustively detailed its morphological structure, its genomic organization, its

variants and its phylogenetic by seeing the possible origin of this virus. We then exposed the most important preventive actions in order to prevent the propagation of the infection.

As a second part, we conducted an epidemiological study in which we collected clinical data from SARS COV 2 hospitalized patients admitted to both ‘Meghloui’ and ‘Tobal’ brothers’ hospitals during the four waves of the outbreak. This study allows us to identify and better study the clinical differences among patients depending on age, sex and mortality outcomes, as well as the possible variations in symptoms in function of coronavirus variant. We also tried to better identify possible risk factors associated with the infection.

For our knowledges, the present work is the first epidemiological study of coronavirus infection in the north eastern regions of Algeria, that was conducted in Mila district, allowing to understand which profile of Algerian individuals is most affected by this pandemic and the feature of this infection on their patients to better understand and face this outbreak.

Part one

Bibliographic Synthesis

Chapter one

Generalities of infectious diseases

1.1 Generalities of Infectious diseases related to coronavirus

An infectious disease is described as a disorder caused by a pathogenic microorganism or its harmful substance (Van Seventer *et al*., 2017), such as viruses, bacteria, parasites, and fungus, which are responsible for the majority of contagious diseases. In most cases, they're innocuous or even beneficial. However, under specific conditions, some microorganisms might cause infection. Infectious diseases, unlike other diseases, may spread rapidly across populations in a very short period of time, posing a threat to public health and possibly the economy (Chen *et al*., 2019). Some infectious diseases are transmitted to a vulnerable host by an infected person, an infected animal, or a contaminated inanimate object (Van Seventer *et al*., 2017). Concerning the symptoms fever and malaise are common signs that vary depending on the organism that is causing the illness. Mild infections may be treated with rest and home remedies, although more serious infections may necessitate hospitalization. Infectious pathogens are projected to affect more than half of the world's population, making them one of the most significant risks to mankind (Van Seventer *et al*., 2017).

Infectious disorders also include emerging infectious diseases, which are diseases that have recently emerged (e.g., Middle East Respiratory Syndrome) or have existed but are quickly expanding in incidence or geographic range (Van Seventer *et al*., 2017). Simply put, new infections might occur as a result of changes or evolution in existing organisms, and old diseases can resurface due to antibiotic resistance in preexisting agents. Or a breakdown in public health measures, previously unknown infections emerging in ecologically transformed areas, or known infections spreading to new geographic areas or populations. Infectious pathogens that are transferred from animals to people by direct contact, food, water, or the environment are known as zoonotic infections and account for 61% of all infectious organisms that cause disease. 7,8 zoonotic diseases are classified into five phases based on their capacity to transmit among people, ranging from simply spreading among animals (stage 1) to total human infections (stage 5) (Behler *et al*., 2019). In the modern world, the first report of the virus causing respiratory infections in children and adults dates from the 1960s.

Coronaviruses (COVs) are re-emerging infections that have caused major issues in humans and animals (Made Artika *et al*., 2020). Human pathogenic coronaviruses (CoV) are seven viruses that mostly cause respiratory illnesses in humans. 229E, HKU1, NL63, and OC43 are the four most prevalent coronaviruses (Saib *et al*., 2021), in most cases, these virus types only cause minor respiratory infections. Severe cases are unusual, and they are more likely to occur in immunodeficient people. MERS (Middle East respiratory syndrome) and SARS-CoV (severe acute respiratory syndrome) are two more strains that often cause mild upper respiratory infections, with severe illnesses occurring in babies, young children, and the elderly on rare occasions (Corman *et al*., 2019). The third form is SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), with variable clinical severity featuring respiratory and extra-respiratory manifestations. This last form of the virus that has emerged has spread around the world, resulting in a pandemic with a mortality toll in excess of 3 million (Saib *et al*., 2021).

1.2 Coronavirus infections

1.2.1 History of coronavirus

Coronaviruses are a huge virus family that infects a wide range of mammalian and avian species, including cattle and companion animals. The first coronavirus discovered was the avian infectious bronchitis virus (iBv) in 1931 (V'kovski *et al*.,2020).

In the 1960s, zoonotic coronaviruses were found Since then, a dangerous human coronaviruses have been discovered and rapidly spread starting with. The 229E, OC43, NL63, and HKU1 (Malik 2020).

From 1986 to 2001, the research in this period was between the first complete genome sequenced, target recombination, polyprotein processing, full length revers genetic clones. Which was essentially to the creation a milestone that greatly contributed to coronavirus knowledge (V'kovski *et al*.,2020).

The appearance of the severe acute respiratory syndrome coronavirus (SARS -CoV) and the resulting SARS outbreak starts in southern China in the winter of 2002 claimed the lives of 10% of the afflicted individuals. The virus has been quickly spreading over the world, particularly in Asia, before being brought under control in July 2003 (Yesudhas *et al*., 2020)

In 2012 it was the emergence of a new coronavirus family in middle east called (MERS-CoV) which is second deadly zoonotic coronavirus, has resulted over than 2,500 cases, and it caused lung damage and severe clinical symptoms (with a 36% case fatality rate). MERS-CoV was also derived from bats, and it developed a reservoir in dromedary camels (V'kovski *et al*.,2020).

Since 2019 until present people around the world affected by SARS -CoV2 which came from Wuhan China, it characterized by the rapidly spread and its serious clinical manifestation in human causing more than 6million deaths from the first emerge and over than 500 million cases around the world (According to WHO organization).

That what make the World Health Organization (WHO) and the governments around the world tried to keep the COVID-19 Pandemic under control by a severe prevention to stopping the spread of this virus and save the human life. Figure 01 present the important events of coronaviruses.

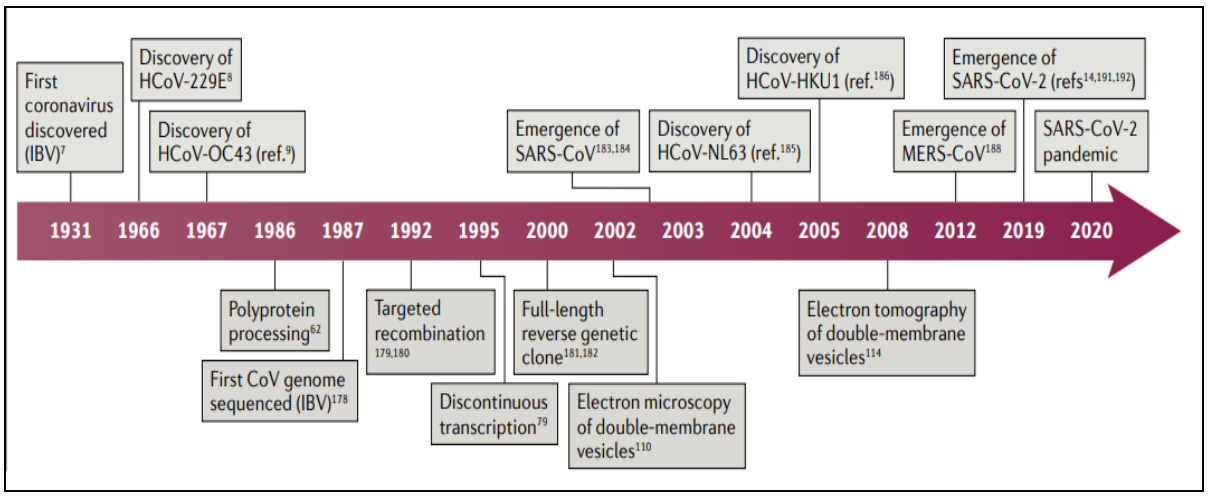

Figure 01: Dates representing the milestones of coronaviruses (V'kovski *et al*.,2020).

1.2.2 Symptoms

The four endemic CoVs (229E, HKU1, NL63, and OC43) as well as the worldwide common CoV cause mild to moderate infections of the upper Airways with symptoms similar to a cold or flu infection (Corman *et al*., 2019*)*. More recent studies of coronaviruses it showed other new common symptoms like Cough, sore throat, fever, muscular pain, and trouble breathing in human's coronavirus. Anosmia, chest discomfort, and stroke are among symptoms that some patients may experience. SARS -CoV, MERS-CoV, and SARS-CoV-2 are three extremely contagious diseases that have developed in humans in the last two decades (Made Artika *et al*., 2020). Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and coronavirus disease (COVID-19) are examples of symptoms that can range from moderate to deadly (Prabhakar *et al*., 2020). Also, Coronaviruses can affect various organs in the body, including the gastrointestinal tract, liver, kidney, and brain in both humans and animals, in addition to the respiratory tract (Made Artika *et al*., 2020). Almost everyone will be infected with one of these CoV types at some point in their lives. Reinfections of the same kind are prevalent due to just one transitory immunity (Corman *et al*., 2019*)* symptoms of the coronaviruses is presented in table 01 (Made Artika *et al*., 2020).

Table 01: Human pathogenic coronaviruses (Made Artika *et al*.,2020).

Virus	Genus	Natural Host	Symptoms
HCoV-229E	α-coronavirus	Bats	Mild respiratory tract infections
HCoV-NL63	α-coronavirus	Bats	Mild respiratory tract infections
HCoV-OC43	β-coronavirus	Rodents	Mild respiratory tract infections
HCoV-HKU1	β-coronavirus	Rodents	Pneumonia
SARS-CoV	β-coronavirus	Bats	Severe acute respiratory syndrome, 10% fatality rate
MERS-CoV	β-coronavirus	Bats	Middle East respiratory syndrome , 37% fatality rate
SARS-CoV-2	β-coronavirus	Bats	Severe acute respiratory syndrome, 3.7% fatality rate

HCoV, Human coronavirus; SARS-CoV, sever acute HCoV, Human coronavirus; SARS-CoV, sever acute respiratory syndrome coronavirus; MERS-CoV, Middle east respiratory syndrome coronavirus; SARS-CoV-2, Sever acute respiratory syndrome coronavirus.

1.2.3 Structure

Coronaviruses are enclosed viruses with non-segmented, single-stranded, positive-sense RNA genomes and crown-like spikes that protrude from the helical symmetry capsid. They have an RNA genome that is unusually lengthy, as well as a unique replication technique (Sanctis 2021). The term "corona" comes from the Latin word "corona," which meaning "crown or wreath." June Almeida and David Tyrrell, who first noticed and investigated human coronaviruses, established the term “coronavirus” (Prabhakar 2020).

These viruses are spherical in shape, with an average diameter of 80–120 nanometers. Their surface spikes protrude around 17–20 nm from the virus particle’s surface and are described as club-like, pear-shaped, or petal-shaped, with a narrow base that expands to a width of roughly 10 nm at the distal extremity. The inner component of the coronavirus was investigated using virions that burst spontaneously and discharged their content, or virions that were treated with detergents, and it was discovered that the viruses had helically symmetric nucleocapsids with a diameter of 14–16 nm. In side of the nucleocapsid It is stored the gene of this viruses.

Coronavirus genome RNA (+ssRNA), it has 5'caps and 3 poly-adenine tails, which is typical to the most eukaryotic mRNAs. The coronavirus genome is notable for its very enormous size, ranging from 26 to 32 kb. It contains different ORFs that express a stable range of structural (S, N, E, M) present in table 02 (Seah *et al*., 2020) (Made Artika *et al*., 2020) and nonstructural proteins, as well as a range of accessory proteins that vary in quantity and sequence. Among the structural proteins expressed by coronaviruses: The spike (S) protein, the nucleocapsid (N) protein, the membrane (M) protein, and the envelope (E) protein are the four main structural proteins encoded by the coronavirus genome. A schematic visualization of the coronavirus particle shown in (Figure 02) (Made Artika *et al*., 2020). Each one of these proteins plays a key role in the structure of the virus particle as well as other aspects of the viral replication cycle (Made Artika *et al*., 2020).

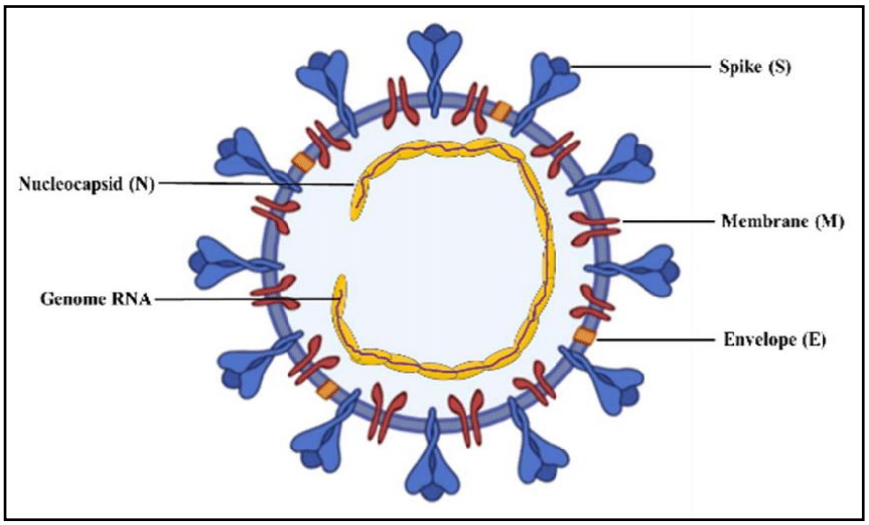

Figure 02: A schematic representation of coronaviruses virion (Okpara *et al*., 2020).

Table 02: coronaviruses structural proteins characteristics (Seah et al., 2020) (Made Artika et al., 2020).

Structural Protein	Amino acid Residues	Molecular Masse (Kd)	Function of protein
Nucleocapsid Protein (N)	phosphoprotein of 422 AA residues	Between 43-46 Kd	Bound to RNA genome to make up nucleocapsid.
Spike protein (S)	Glycosylated protein with 1162-1452 AA	150-200Kd	Critical for binding of host cell receptors to facilitate the entry of host cell.
Envelope Protein (E)	Polypeptide ranging from 76-109 AA	8.4-12Kd	Interacts with protein M to form viral envelope
Membrane Protein (M)	217-230AA	25-30 Kd	Central organizer of CoV assembly. Determines shape of viral envelope

Kd, kilodalton; AA, amino acid; CoV, Coronavirus.

1.3 SARS-CoV-2 infections

1.3.1 History of SARS-CoV-2

Since the late 60s, when human coronaviruses were first identified, coronavirus infections were thought to be harmless to humans (Yesudhas *et al*., 2021). Until the first pneumonia case of unknown cause was reported in Wuhan City, Hubei Province, China, on December 31, 2019, the outcome of an uncertain etiology of the patient were initially linked to a local wet market (seafood markets, live animal markets), which is a frequent commercial source of food in China. Concerns about animal-to-human transfer and, eventually, human-to-human spread of disease have long been linked to these wet markets, including SARS. A variety of potential etiological agents, including the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle-East respiratory syndrome coronavirus (MERS-CoV), avian influenza virus, and other common respiratory infections, were ruled out in order to establish the etiology. Finally, the organism responsible for infection has been identified as a novel coronavirus, now known as 2019-nCoV and later renamed to SARS-CoV-2, (Li *et al*., 2020) that is the seventh member of the coronavirus family that infects humans, which is not similar to MERS-CoV or SARS-CoV (Yesudhas *et al*., 2020). The World Health Organization (WHO) announced it on 12January 2020. 41 pneumonia cases had been diagnosed as of January 11, 2020, with seven severe cases and one mortality. According to the scientific literature at the time, there was no indication of person-to-person transmission. The initial "super-spreading" incident became a defining feature of the disease's epidemiology. In epidemiological studies on January 20, 2020, two local infections in patients infected with 2019-nCoV without physical visit to Wuhan were detected in Guangdong Province, confirming the presence of human-to-human transmission (Li *et al*., 2020).

The human-to-human transmission was then verified by 14 medical workers infected with 2019-nCoV from patients. The World Health Organization (WHO) declared on January 21, 2020 that 2019-nCoV may have been sustained through human-to-human transmission, and advised the public to take self-protection measures. This virus was quickly found to generate an epidemic in the first of many cases. Due to the high transmissibility of 2019-nCoV, the Chinese government acted quickly and implemented a variety of steps to combat the pandemic, attempting to contain the outbreak and cure patients. Researchers have been studying several medications to screen for successful therapy while trying to understand

the genesis and pathophysiology of this unique coronavirus. Until February 6, 2020, confirmed 2019-nCoV pneumonia cases in China were spreading at an alarming rate. As of February 5th, mainland China had confirmed 24,377 cases, including 492 fatalities, 3219 severe cases, and 901 treated cases. Figure 03 summarizes the significant occurrences of the 2019-nCoV outbreak. China's national and local governments have taken a variety of extreme steps to combat the 2019-nCoV pandemic (Li *et al*., 2020).

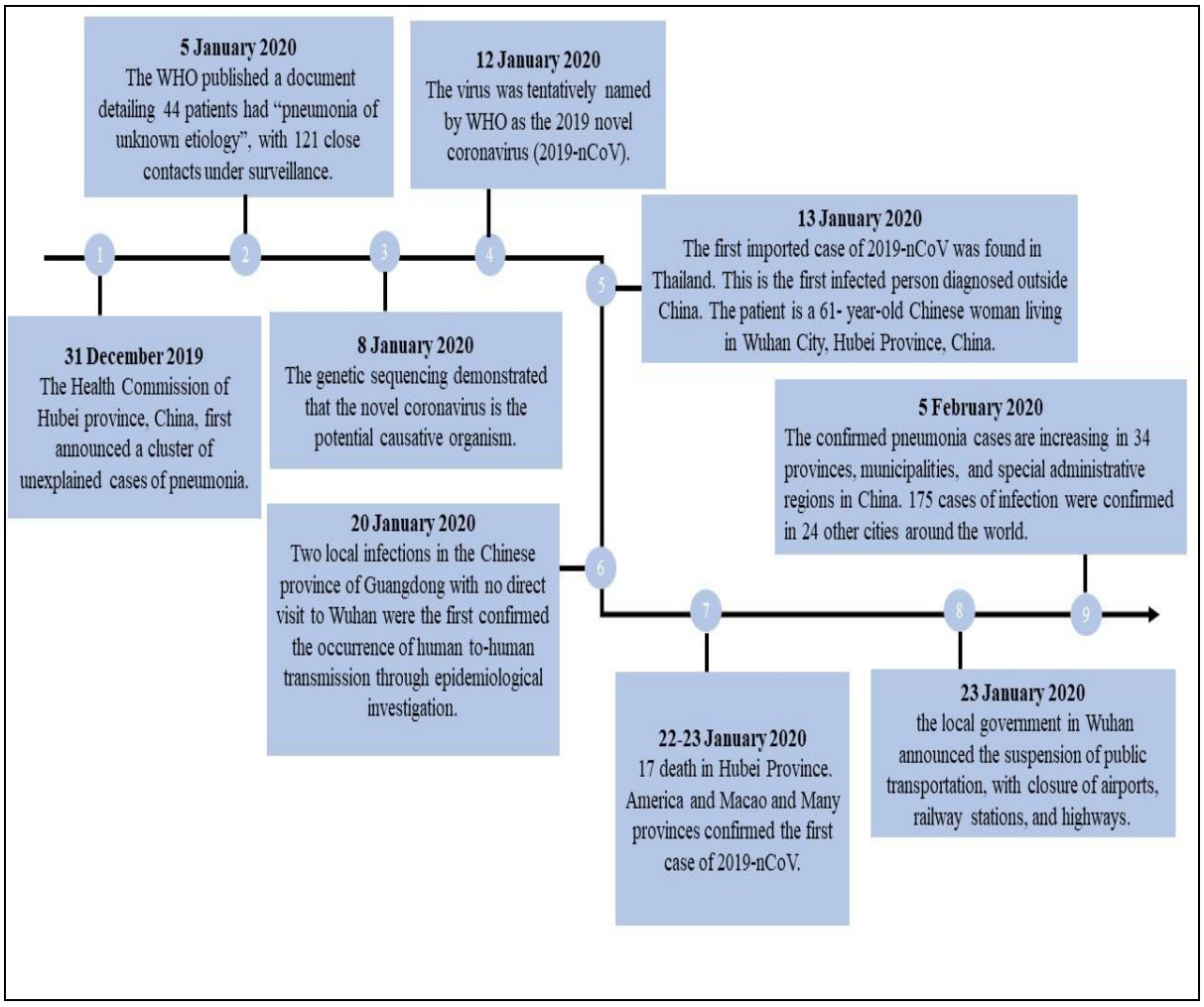

Figure 03: The significant events during the current SARS-CoV-2 outbreak, from 31 December 2019 to 5 February 2020 (Li *et al*.,2020).

1.3.2 Infection

The SARS-CoV-2 generally it's a viral infection known as acute upper and lower respiratory tract infection that can be worsened by interstitial and alveolar pneumonia it can also touch Multiple additional tissues, including the heart, kidneys, digestive tract, blood, and neurological system (Marino *et al*., 2021). It resembles past CoV infections that caused severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Yapasert *et al*., 2021). SARS-CoV-2 infection now it's one of the fastest spread infections among all the previous infections, inhaling an aerosol of respiratory droplets released by someone with COVID-19 coughing, sneezing, talking, and breathing without a face mask, or fomite infection of the surfaces of items, is the primary route by which individuals become infected with Sars-CoV-2. The mechanics of transmission is determined by fluid dynamics and thermodynamics, which may be altered by wind, temperature, and humidity (Hartig *et al*., 2021).

1.3.3 Symptoms

Each disease has its own set of symptoms; yet, some diseases share similar symptoms, which can lead to confusion when it comes to diagnosing the sickness. Coronavirus disease has symptoms that are nearly identical to those of influenza. Symptoms can change from person to person, as well as between age groups and variants. Typically, fever, dry cough, and weariness are some of the most frequent COVID-19 infection symptoms in the early stages. Nasal congestion, conjunctivitis, headache, several forms of skin rashes, diarrhea, shivering, and dizziness are some of the less prevalent symptoms. The patient will have severe shortness of breath, low blood oxygen (hypoxia), lungs damage, and many organs failure as the condition progresses. Stroke, encephalitis, psychosis, and nerve damage are among the most serious and uncommon neurological consequences of COVID-19 disease. The major cause of induced death is acute respiratory distress syndrome (ARDS). Also, it might be asymptomatic in certain cases, (SalahShoori *et al*., 2021). Most frequent symptoms are presented in the figure 04 below.

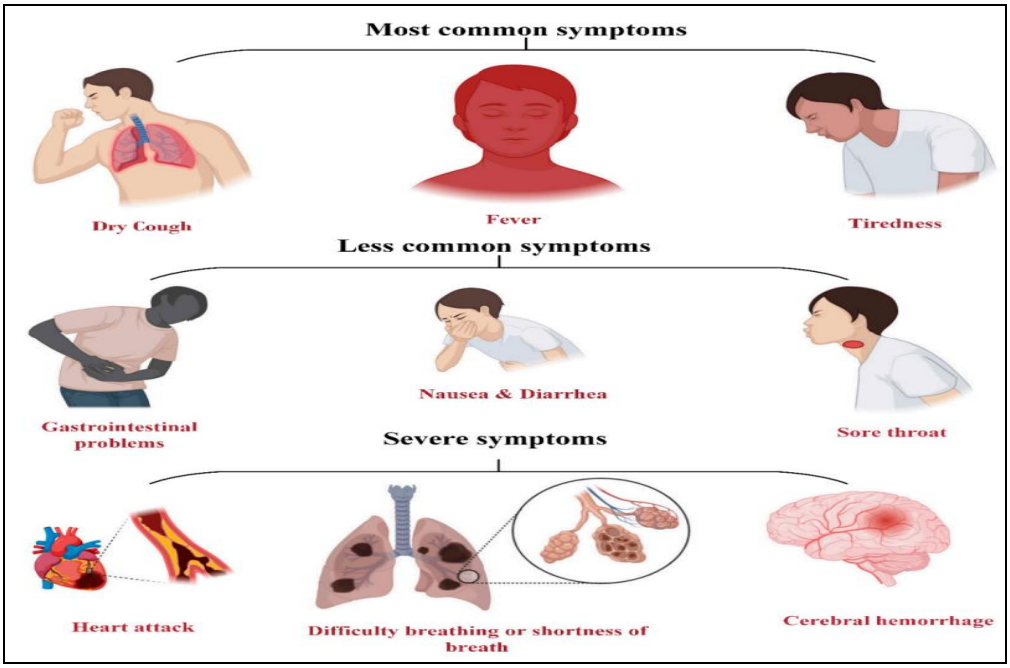

Figure 04: The most minor and major symptoms of COVID-19 (SalahShoori *et al*., 2021).

According to the figure 05, people of all ages are vulnerable to SARS-CoV-2 infection, with the median age of illness being about 50 years. Clinical signs, on the other hand, vary with age. Most young adults and children have relatively minor illnesses (non-pneumonia or mild pneumonia) or are asymptomatic, but elderly men (>60 years old) with co-morbidities are more prone to develop serious respiratory disease that necessitates hospitalization or even death. Fever, tiredness, and a dry cough are the most frequent signs of infection. The majority of people acquired symptoms of infections after an incubation period of 1–14 days (most typically around 5 days), while dyspnea and pneumonia occurred after a median of 8 days of illness onset (Hu *et al*., 2021).

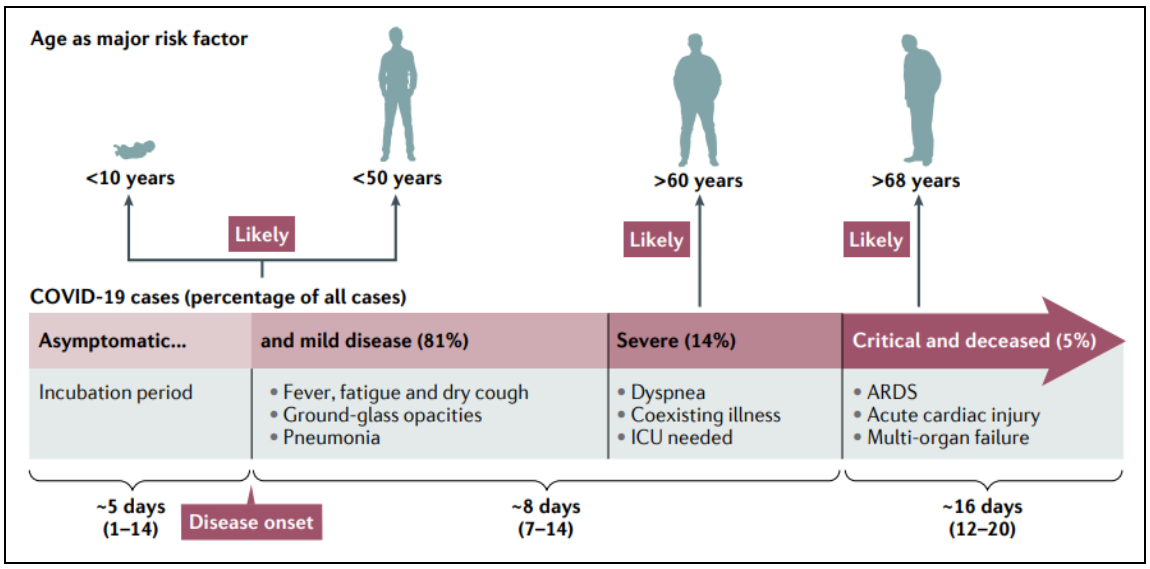

Figure 05: Clinical features of COVID-19 (Hu *et al.*,2020).

1.3.4 Pathophysiology

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has cost the lives of over 1.45 million people throughout the world as of November 30, 2020 (Trougakos *et al.*, 2021) While SARS-CoV-2 is a novel virus with limited antiviral medicines that have been repurposed for COVID-19 therapy, understanding the fundamental pathophysiology of COVID-19 is critical for developing preventative and/or therapeutic measures. Following infection in a host cell, all SARS-like CoVs show typical strategy for replication and translation. This section summarizes the SARS-CoV-2 lifecycle in the host cell, which begins with viral attachment to the receptor on the host cell and ends with the liberation of newly generated progeny from infected cells (Kirtipal *et al.*, 2020).

1.3.4.1 Attachment and entry

The initial step in viral infection is HCoV binding to the host-cell receptor, which determines the severity of infection and pathogenesis. A better understanding of the relationship between viral structural proteins and the targeted receptor on host cells, as well as other involved proteins like host protease, can aid in the prediction of zoonotic CoVs infection in humans (Kirtipa *et al.*, 2020). The infection starts with densely glycosylated S protein, a trimeric class I fusion protein with two major subunits; a receptor binding domain

(S1; also known as RBD) and a second domain (S2) that mediates viral fusion with the host cell membrane. When the S1 domain attaches to the host-cell receptor, the viral membrane fuses with the host-cell membrane (Kirtipal *et al*., 2020). The angiotensin-converting enzymes (ACE2) is the specific receptor of SARS-CoV-2, serve as S-spike protein recipients, allowing endogenous viral RNA genetic material to enter host cells (Salahshoori *et al*., 2021).

The renin-angitonsin system (RAS) (is a critical complicated mechanism in the human body that ensures survival by maintaining vascular tone, controlling extracellular fluid, and arterial pressure.) one of the most important functions of angiotensin-converting enzymes (ACE2) (Salahshoori *et al*., 2021). The ACE2 can be found in the lungs, kidneys, and heart, among other organs. Furthermore, the disruption of the ACE/ACE2 balance and activation of RAS by SARS-CoV-2 is one of the reasons for the development of COVID-19, particularly in patients with underlying cardiovascular disease, hypertension, and diabetes (Salahshoori *et al*.,2021).

Table 03 present ACE2 receptor detection in different tissues (Abbasi Pashaki *et al*., 2020) This enzyme expression is much higher in alveolar epithelial cells types 1 and 2 in the human lung than in other parts of the body. In addition, males' trend to have much higher levels of ACE2 expression in alveolar cells than female, according to researches (Salahshoori *et al*., 2021). Even so, receptor binding is required for coronavirus infection of host cells. Virus entrance into the cell has been decoded via two alternative pathways dependent on the availability of host cell protease to activate receptor-attached spike protein. CoVs entered the host cell as an endosome in the first route, which is mediated by clathrin-dependent and clathrin-independent endocytosis. This caused conformational changes in viral particles, causing the viral envelope to merge with the endosomal wall. In a second pathway, virus particles are directly invaded into host cells via proteolytic cleavage of receptor-attached spike protein on the cell surface by the host's transmembrane serine protease 2 (TMPRSS2) or transmembrane serine protease 11D (TMPRSS11D) represented in figure 06 (Kirtipal *et al*., 2020).

Table 03: ACE2 receptor detection in different tissues (Abbasi Pashaki *et al*., 2020).

SARS-CoV receptor ACE2	
Detectable	**Undetectable**
Stomach	Spleen
Pancreas	Esophagus
Small intestine	Lymph node
Lung	Ovary
Renal Tubule	Thyroid
Liver	Testis
Parathyroid	Bone narrow
Adrenal gland	Uterus
Sweat gland	Aorta And muscle

ACE2, angiotensin-converting enzyme 2.

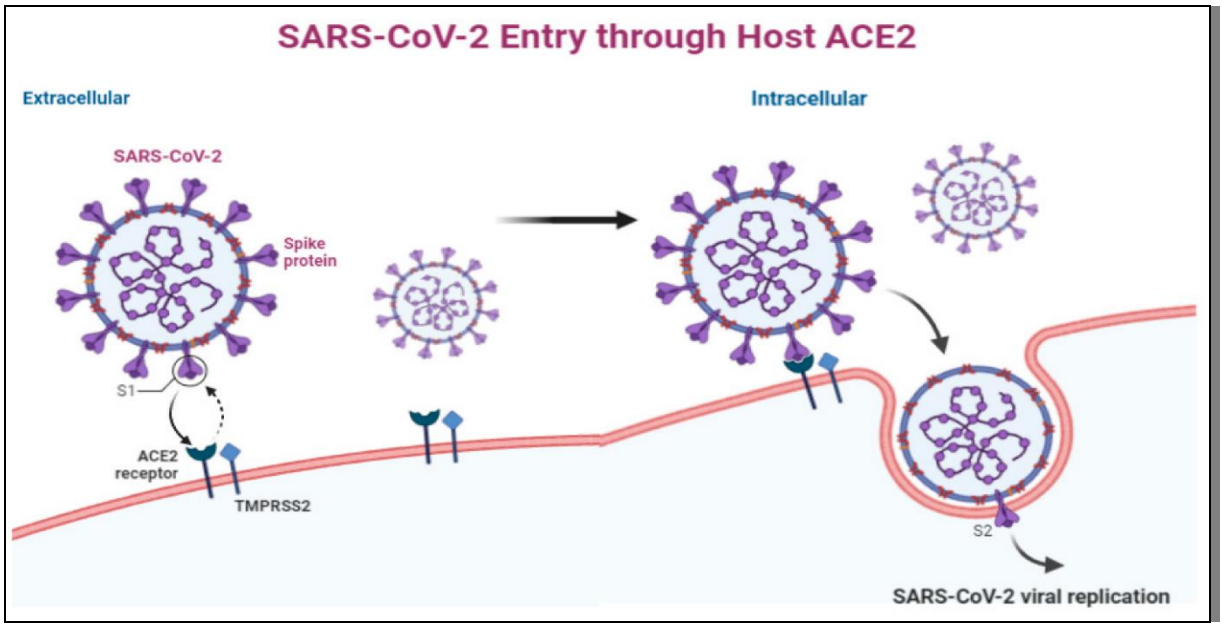

Figure 06: SARS-CoV-2 enters the infected cell by targeting the ACE2 receptor (Salahshoori *et al*., 2021).

1.3.4.2 Genome translation

Following viral-host cell membrane fusion, the virus released nucleocapsid packed genomic RNA into the cellular cytoplasm as a result of induced structural conformation changes (Kirtipal *et al*., 2020). The translation of the replicase gene from the virion genomic RNA is the next stage in the coronavirus lifecycle. Coronaviruses have two or three proteases that break the polyproteins that make up the replicase. Many nonstructural proteins (nsps) then combine into the replicase-transcriptase complex (RTC) to produce an RNA-synthesis-friendly environment, and are ultimately responsible for RNA replication and transcription of sub-genomic RNAs (Malik 2020).

1.3.4.3 Replication and Transcription

The majority of newly translated nsps, along with the structural protein. N protein, formed the multi-protein replicase-transcriptase complex (RTC), which carried out viral genome replication and transcription. The RTC complex contained RdRp as the main replicase transcriptase protein for the synthesis of negative-sense subgenomic (sg) RNA strands from viral RNA and transcription of negative-sense subgenomic RNA molecules from corresponding positive-sense mRNAs at the site of replicative organelles. The new created minus strands of genomic and sgRNAs are then used as templates for the production of positive sense strands (mRNAs), specifically in the creation of genomic and sg mRNAs (transcription). These newly manufactured RNA strands served as the genome for new viral progeny to be formed. Several smaller mRNAs are also created from the viral final third of genome, which follow reading frames ORF1a and ORF1b, which are interpreted into viral four structural proteins (S, E, M, and N) and become part of viral progeny, along with supplementary proteins (ORF3a through ORF9b). Other nsps in the RTC complex also help in viral replication and transcription (Kirtipal *et al*., 2020) in RNA replication, for example, the nsp15 protein, a 3'-5' exoribonuclease, added fidelity to the RTC complex through its proofreading role, Because CoVs have a comparatively large RNA genome in compared to other RNA viruses, this improved fidelity and processivity are generally necessary during RNA synthesis (Kirtipal *et al*., 2020).

1.3.4.4 Assembly and Release

Following replication and subgenomic RNA production, the S, E, and M proteins are translated and placed into the endoplasmic reticulum (ER). These proteins make their way into the endoplasmic reticulum-Golgi intermediate compartment through the secretory route (ERGIC). The viral genomes encapsidated by the N protein will bud into the membrane in the compartment, leading in the creation of the mature virus. Most of the protein interactions essential for coronavirus assembly are directed by the M protein. However, virus-like particles (VLPs) can only be generated when M and E proteins are both expressed. Other functions of the E protein include generating membrane curvature and blocking M protein aggregation. Virions are assembled and transported to the cell surface in vesicles, where they are discharged by exocytosis. A schematic visualization of the SARS-CoV-2 life cycle is shown in figure 07.

Novel strains of coronaviruses will continue to evolve, emerge, and create new outbreaks due to their capacity to recombine, mutate, and infect a wide range of species (Malik 2020).

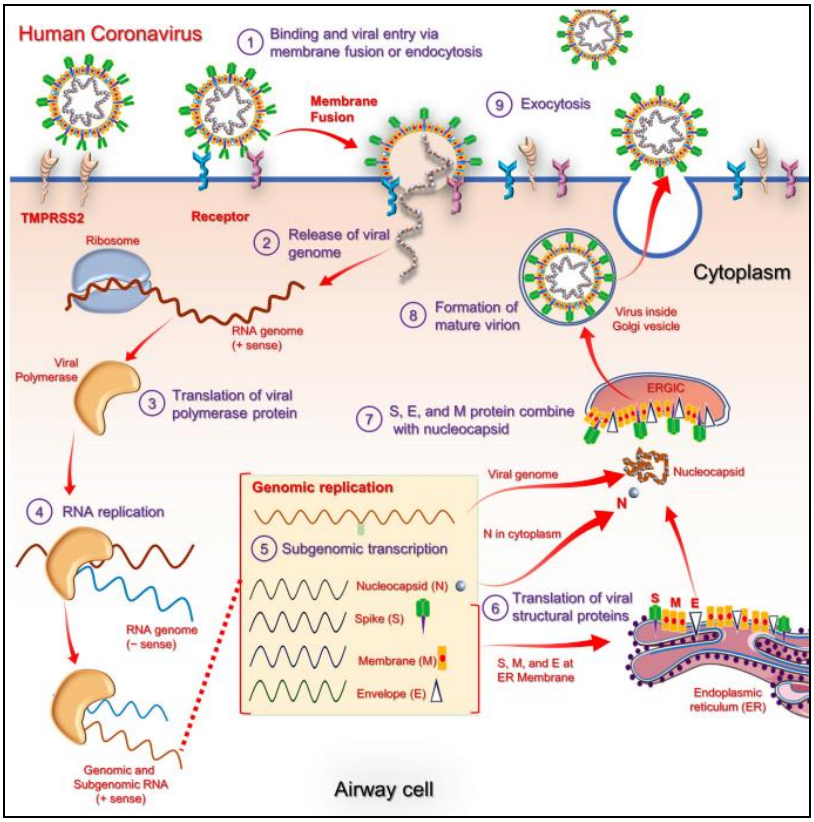

Figure 07: The coronavirus (SARS-CoV-2) virion and life cycle (Kirtipal *et al.*, 2020).

1.3.4.5 SARS-CoV-2 in lungs

SARS-CoV-2 enters the body through the mouth or nose and travels to the lungs, where it infects alveolar cells with its unique spike proteins. In reaction, the immune system targets the contaminated region, resulting in the death of healthy alveolar cells. Reduced or severely hampered gas exchange is caused by reduced surfactant from alveolar epithelial type II cells, as well as fluid accumulation due to cell destruction in the alveoli.

When cytokines are activated repeatedly without a pause, however, the cells' reactions to the cytokines might be harmed, and the organs' function can be disrupted. This is referred to as a cytokine storm, and it is responsible for the transmission of serious diseases such as COVID-19.

The following stages show how a cytokine storm develops in the lungs figure 08.

- COVID-19 infection of lung cells.
- Production of cytokines as a result of immune cells detecting viruses (macrophages).
- Using the cytokine phenomenon to create a cycle of inflammation in lung cells by increasing the absorption of immune cells (white blood cells).
- Fibrin production and worsening of the condition.
- Infiltration of fluids into weak blood arteries, resulting in lung cavity filling and respiratory dysfunction (Salahshoori *et al*., 2021).

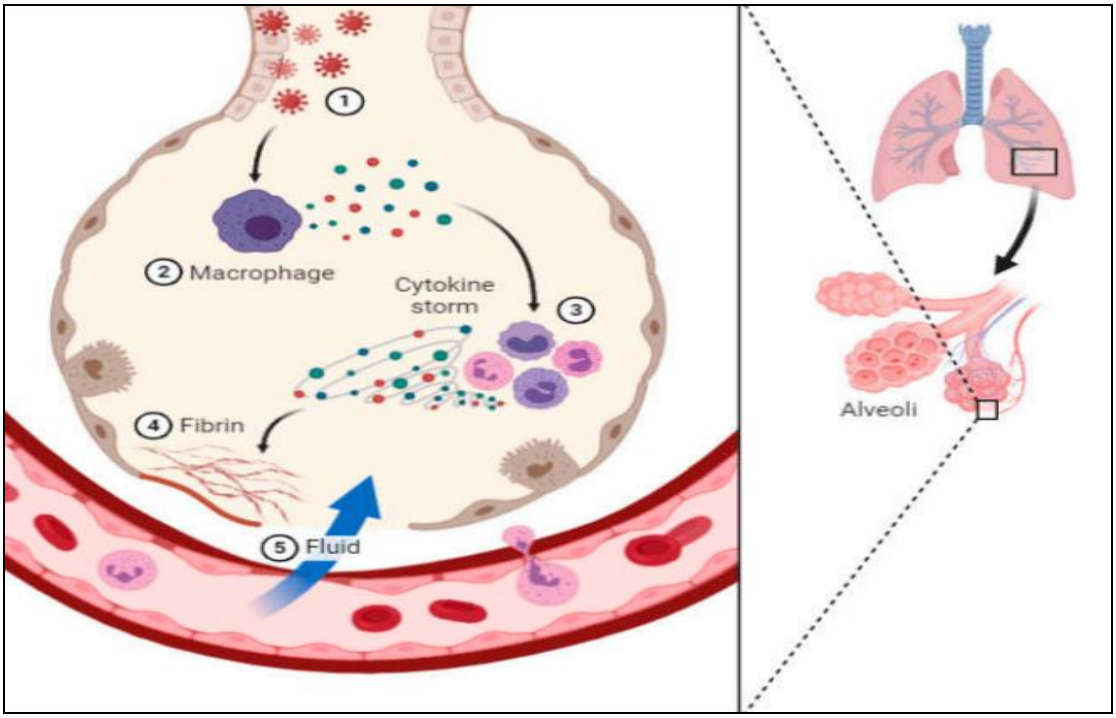

Figure 08: A cytokine storm in the lungs due to COVID-19 disease (Salahshoori *et al*., 2021).

1.4 SARS-CoV-2 virus

1.4.1 Definition

The SARS-CoV-2 causes the COVID-19 infection, which are tiny infectious particles that have emerged as one of the world's top causes of mortality, making it one of the most serious public health crises in recent decades (Rehman *et al*., 2021). Causing acute respiratory syndromes According to the phylogenic tree, it belongs to the coronavirus family. SARS-CoV-2, like most viruses, has a protective envelope and a genome. The RNA virus encodes four structural proteins as well as a number of other proteins (accessory proteins). SARS-CoV-2 is distinguished by the presence of a polybasic cleavage site, which boosts its pathogenicity it’s the main character furthermore the ability to spread quickly contrary to SARS and MERS viruses. this transmissibility of SARS-CoV-2 is thought to be due to its genetic variation (Saleem *et al*., 2021).

1.4.2 Structure

Understanding the viral genome and protein structure of SARS-CoV2 is critical for preventing the virus from spreading. The RNA sequence of the coronavirus (SARS-CoV-2) genome is 30,000 bases long and features a particular polybasic cleavage site, according to high throughput sequencing technology. The SARS-CoV-2 virion structure is 50–200 nanometers in diameter and is made up of four structural proteins: S (spike), E (envelope), M (membrane), and N (nonstructural protein) (nucleocapsid). The N protein is involved in the construction of the viral envelope, whereas the other proteins are involved in the synthesis of the RNA genome (Saleem *et al*.,2021). SARS-CoV-2 structure represented in figure 08.

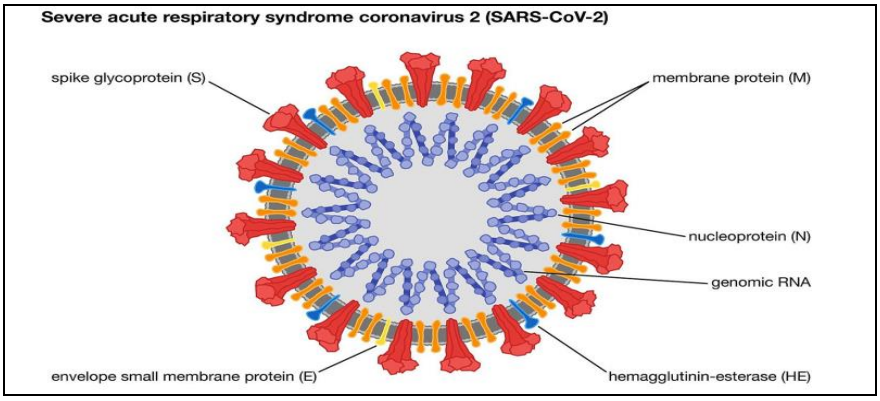

Figure 09: Structure of SARS-CoV-2 (Shaikh *et al*., 2020)

1.4.2.1 Organization of the Genome

Coronaviruses (SARS-CoV-2) are non-segmented positive-sense RNA viruses with a genome size of 30 kb and a nucleotide and amino acid sequence of 29899 and 9860. Their genomic RNA has a 5′ cap and a 3′ poly (A) tail, making it suitable for replication polyprotein translation (Saleem *et al*., 2021). The genome of SARS-CoV-2 is comparable to that of other CoVs and comprises at least 10 open reading frames (ORFs) presented in table 04 (Yoshimoto *et al*., 2020). The ordered structure begins with a 5' UTR leader-replicase (Saleem *et al*., 2021), the replicase-transcriptase complex is made up of two big polyproteins encoded by the 5'-terminal two-thirds of the genome ORF1a/b (Malik 2020) ORF1a and ORF1b are open reading frames (ORFs) that translate polypeptides with molecular weights of 440-500kDa (pp1a) and 740-810kDa (pp1ab), respectively (Saleem *et al*., 2021). The remaining SARS-CoV-2 ORFs encode the same four primary structural proteins: spike (S),

envelope (E), nucleocapsid (N), and membrane (M), as well as many auxiliary proteins with unknown functions that do not engage in viral replication (Malik., 2020). The UTR region at the 3′ end, on the other hand, contains RNA structures that are essential for viral RNA replication and synthesis (Saleem *et al*., 2021). Figure 10 depicts the entire genetic arrangement, including ORF regions at polyproteins.

Table 04: SARS-CoV-2 genes (Yoshimoto *et al*., 2020).

Gene	Gene ID	Location	Protein	Locus
ORF1ab	43,740,578	266-21,555	ORF1a Polyprotein	[BCB15089.1/BCB97900.1]
ORF1a	43,740,578	26613,483	ORF1a Polyprotein	[YP_009725295.1]
ORF2	43,740,568	21,56325,384	S Protein	[BCA87361.1]
ORF3a	43,740,569	25,393-26,220	3a Protein	[BCA87362.1]
ORF4	43,740,570	26,245-26,472	E Protein	[BCA87363.1]
ORF5	43,740,571	26,523-27,191	M Protein	[BCA87364.1]
ORF6	43,740,572	27,202-27,387	ORF6 Protein	[BCA87365.1]
ORF7a	43,740,573	27,394-27,759	ORF7a Protein	[BCA87366.1]
ORF7b	43,740,574	27,756-27,887	ORF7b Protein	[BCB15096.1]
ORF8	43,740,577	27,894-28,259	ORF8Protein	[BCA87367.1]
ORF9	43,740.575	28,247-29,533	N Protein	[BCA87368.1]
ORF10	43,740,567	29,558-29,674	ORF10 Protein	[BCA87369.1]

ORF, opening reading frame.

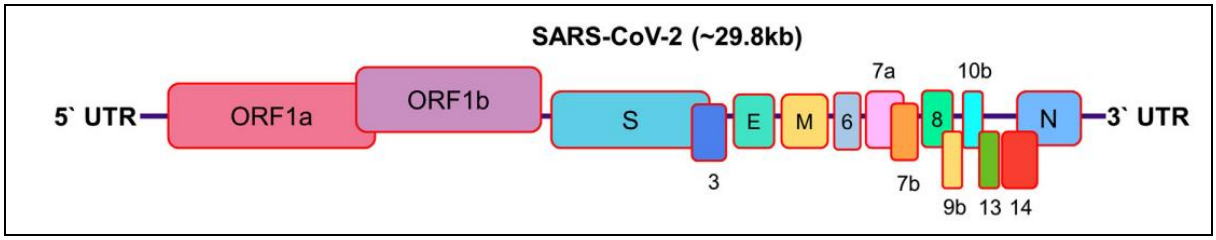

Figure 10: Genome organization of SARS-CoV-2 (Kirtipal *et al*., 2020).

1.4.2.2 Coronaviruses Proteins

The protein composition of coronaviruses is split into structural and nonstructural proteins. Represented in figure 11 (Saleem *et al*.,2021).

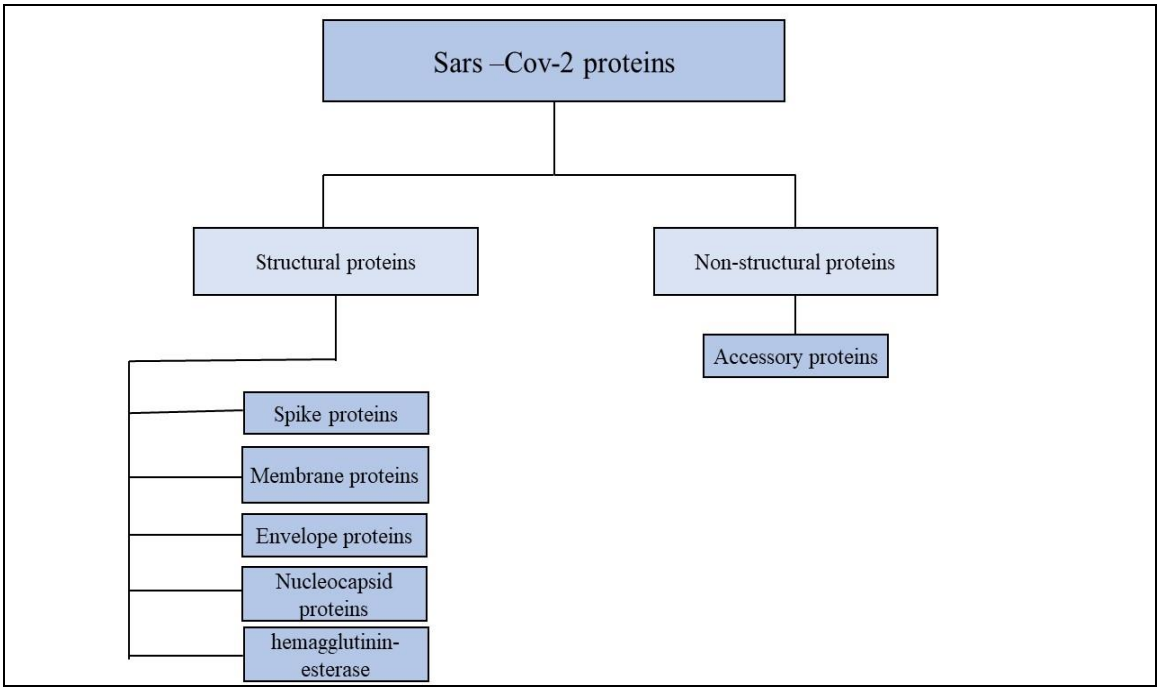

Figure 11 : SARS-CoV-2 proteins (Saleem *et al*., 2021).

1.4.2.2.1 Structural Proteins

The nucleocapsid (N) protein, the transmembrane (M) protein, the envelope (E) protein, and the spike (S) protein are the four major structural proteins found in the virion (Hasöksüz *et al*., 2020).

- **Spike Glycoprotein**

Spike protein (S protein) is a 150 kDa protein with a glycosylated N-terminal signal region required for ER (endoplasmic reticulum) entrance. S protein has 1255 amino acids and 23 potential N-linked glycosylation sites (Saleem *et al*., 2021).

The homotrimers of transmembrane spike glycoproteins protrude from the viral surface. Because the spike glycoprotein is required for coronavirus entrance, it is a potential antiviral target. The S1 and S2 subunits make up the S protein, which is made up of two functional subunits. The N-terminal domain (NTD) and receptor binding domain (RBD) make up the S1 subunit (RBD). The S1 subunit's role is to attach to the receptor on the host cell. Fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), transmembrane domain (TM), and cytoplasmic tail (CT) are all found in the S2 subunit (CT). The S2 component is responsible for fusing the membranes of viruses and

host cells. The S1/S2 protease cleavage site is located on the junction between the S1 and S2 subunits. Host proteases cleave the spike glycoprotein at the S2' cleavage site to activate the proteins, which are required to fuse the membranes of viruses and host cells via irreversible conformational changes in all coronaviruses (Wang *et al*.,2020) Figure 12 and 13 summarizes the genetic architecture of spike proteins as well as their sub-structures.

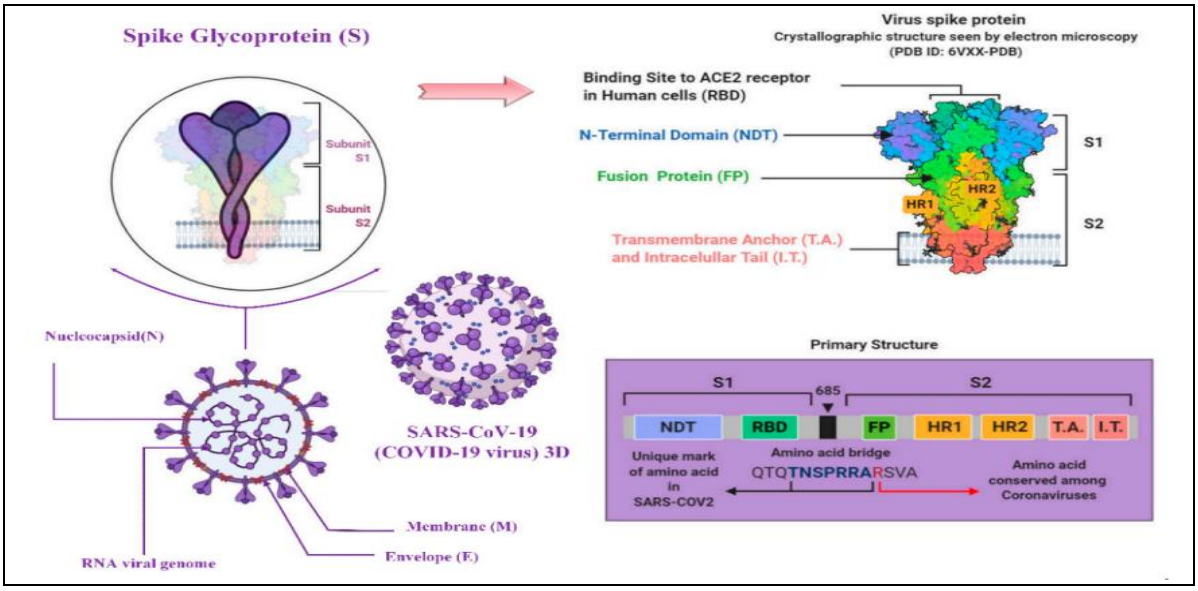

Figure 12: A detailed examination of the SARS-CoV-2 Spike Glycoprotein (Salahshoori *et al*., 2021).

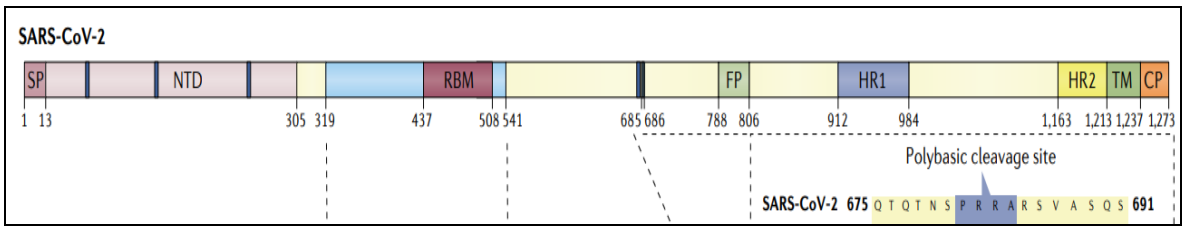

Figure 13: The spike protein of SARS-CoV-2(Hu *et al*., 2021).

- **Envelope Protein**

The envelope protein is a tiny integral membrane protein that may oligomerize and form an ion channel (Yoshimoto *et al*., 2020). The virion includes a little quantity of the 8–12 kDa envelope protein. A transmembrane protein containing an ectodomain at the N-terminus and an endodomain at the C-terminus is known as envelope polypeptide. It facilitates in the virus's assembly and release, as well as a range of other functions.

The ion channel subunit is not required for SARS-CoV2 replication, but it is required for disease transmission (Saleem *et al*., 2021).

- **Membrane Protein**

The most prevalent structural protein is the M protein (25–30 kDa) with three transmembrane domains, which determines the structure of the viral envelope. It features a short glycosylated ectodomain at the N-terminus and a considerably bigger endodomain at the C-terminus that extends 6–8 nm within the viral particle. The M protein exists as a dimer and may assume two alternative conformations, allowing it to increase membrane curvature and attach to the nucleocapsid, according to research. S-M protein interaction is essential for S retention in the ER-Golgi intermediate compartment (ERGIC)/ Golgi complex and integration into new virions, but not for the assembly process (Malik 2020)

Binding of M to N protein helps complete viral assembly by stabilizing the nucleocapsid (N protein-RNA complex) as well as the internal core of virions. The viral envelope is made up of M and E proteins, and their interaction is enough to produce and discharge virus-like particles (VLPs) (Malik 2020).

- **Nucleocapsid Protein**

The only protein that binds to the RNA genome is N. 51 The protein has two domains: an N-terminal domain (NTD) and a C-terminal domain (CTD). It has been suggested that both of these domains are required for optimal RNA binding. It also plays a role in viral assembly and budding, which leads to virion generation (Malik 2020)

- **Hemagglutinin-esterase**

An additional membrane protein present in a subgroup of group 2 coronaviruses is the hemagglutinin-esterase (HE) protein. This non-essential protein's major function is to assist viral entrance and pathogenesis in vivo. It creates short projections that bind to N-glycolylneuraminic acid or Nacetyl-9-O-acetlyneuraminic acid and exhibit esterase activity (Shaikh *et al*., 2020).

1.4.2.2.2 Non-structural Proteins

Several genes produce proteins that are required for viral replication, transcription, and assembly. The translation of two important open reading frames 1a and 1b (ORF1ab) produces these non-structural proteins Summarized in table 05 (Yoshimoto *et al*., 2020). These proteins play an important role in the replication and transcription of viral RNA genomes. Other than structural and accessory proteins, there are some genes known as "group-specific or accessory genes" that are present. These proteins are required for viral survival in the natural environment of the infected host (Saleem *et al*., 2021)

Table 05: Nonstructural proteins (NSPs) identified in SARS-CoV-2 polyprotein (Yoshimoto et al., 2020).

Name	Accession	Amino acide	Proposed function
NSP1	YP_009725297.1	180 amino acids	Induce host mRNA (leader protein) cleavage
NSP2	YP_009725298.1	638 amino acids	Binds to PHBs 1, 2
NSP3	YP_009725299.1	1945 amino acids	Release NSPs 1, 2, 3 (Papain like proteinase)
NSP4	YP_009725300.1	500 amino acids	Membrane rearrangement
NSP5	YP_009725301.1	306 amino acids	Cleaves at 11 sites of (3C-like proteinase) NSP polyprotein
NSP6	YP_009725302.1	290 amino acids	Generates autophagosomes
NSP7	YP_009725303.1	83 amino acids	Dimerizes with NSP8
NSP8	YP_009725304.1	198 amino acids	Stimulates NSP12
NSP9	YP_009725305.1	113 amino acids	Binds to helicase(?)
NSP10	YP_009725306.1	139 amino acids	Stimulates NSP16(?
NSP11	YP_009725312.1	13 amino acids	Unknown
NSP12	YP_009725307.1	932 amino acids	Copies viral RNA (RNA polymerase) methylation (guanine)
NSP13	YP_009725308.1	601 amino acids	Unwinds duplex RNA (Helicase
NSP14	YP_009725309.1	601 amino acids	5′-cap RNA (3′ to 5′ exonuclease, guanine N7-methyltransferase)

NSP15	YP_009725310.1	346 amino acids	Degrade RNA to (endoRNAse/endoribonuclease) evade host defense
NSP16	YP_009725311.1	298 amino acids	5′-cap RNA (2′-O-ribose-methyltransferase—potential antiviral drug target) methylation (adenine)

NSP, non structural proteins.

- **Accessory proteins**

A number of auxiliary genes can be found at the genome's 3′ end. Other accessory or group-specific genes are also widely distributed across the genome, including two genes located between S and E genes (ORFs 3a and 3b), five genes located between M and N genes (6, 7a, 7b, 8a, and 8b), and one gene within the N gene (9b) (Saleem *et al*., 2021). Table 06 summarized accessory proteins (Saleem *et al*., 2021).

Table 06: SARS-CoV-2 accessory proteins (Saleem *et al*., 2021).

Accessory proteins	**Incorporation into viruses**	**Functions**
3a	Yes	NF↑, JNK ↑, IL-8 ↑, RANTES ↑ Ion Channel activity, apoptosis induction and cell cycle arrest.
3b	Unknown	Type 1 INF production and signaling inhibition, apoptosis induction and cell cycle arrest
ORF6	Yes	Type 1INF production and signaling inhibition
7a	Yes	NF↑, JNK ↑, IL-8 ↑, p38 MAP knase, host translation inhibition, apoptosis induction and cell cycle arrest
7b	Yes	No known function

8a	Unknown	No known function
8b	Unknown	No known function
9b	Unknown	No known function

ORF, opening reading frame; NF, nutritic factor; JNK,c-Jeun N terminal kinase ;INF, interferon ;IL-8,interlukine-8 ; MAP, mitogen-activated protein kinase.

Each protein type is related with a distinct role in the overall life of this virus. Figure 14 demonstrate the general genomic arrangement of coronaviruses as well as SARS-CoV-2.

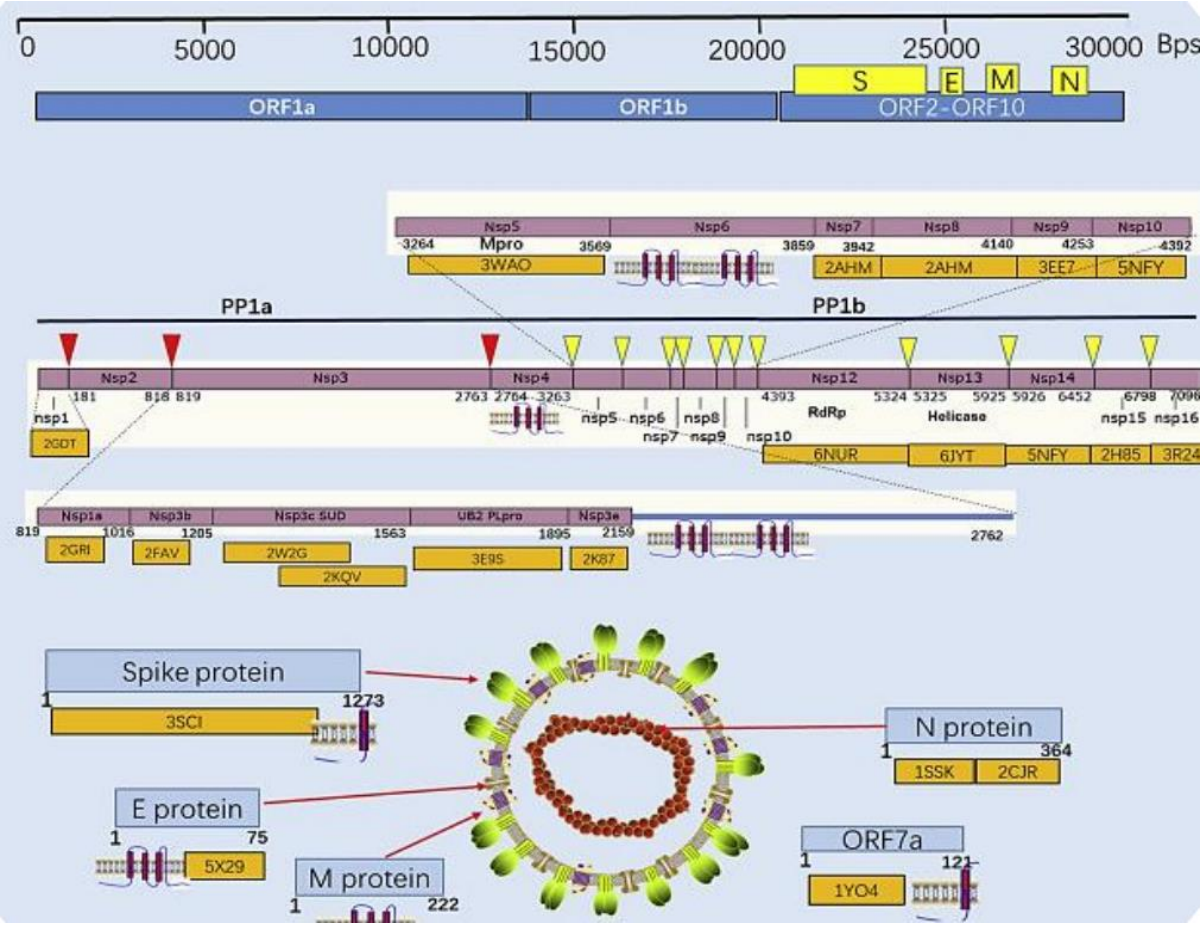

Figure 14: SARS-CoV2 Genome and Protein Analysis in General (Saleem *et al*., 2021).

1.4.3 SARS-CoV-2 variants

The ongoing evolution of mutations in the genome of SARS-CoV-2 causing the current pandemic, results in the emergence of variations of the original Wuhan strain of the virus with minor genetic alterations that may have a greater or lesser influence on the virus's functional activity. There are mutations in the virus's genome that, depending on their position or character, may increase the virus's transmissibility (Cantón *et al*., 2021).

SARS-CoV-2 variants or lineages have mutations in their genome that cause differences in their phenotype, such as different antigens, alterations in transmissibility, or virulence. Many of the documented variations have a competitive edge over their forerunners and, in many cases, are dominant. The polymorphisms changing the spike regions have gotten the greatest scientific and clinical interest, because here is where the binding to ACE2 receptors takes place, and it can change their clinical impact, as well as their capacity to colonize the respiratory tract and the probability of transmission. They are also significant for public health for all of these reasons. In terms of the names given to the variations, they have adopted the names of the countries or geographical areas in which they've been reported in the majority of cases. According to risk analysis, the numerous variations of SARS-CoV-2 are divided into three groups in terms of public health. The variants of interest the variants of concern and the variants of high consequence (Cantón *et al*., 2021).

Recently in COVID-19 case and according to the WHO all the variants of SARS-CoV-2 are classified as variants of concern (VOC) (WHO., 2022).

1.4.3.1 Variants of public health importance or concern (VOC):

Are often more infectious and virulent than VOIs, since they can result in more severe infection, more hospitalizations, and higher death. They have the potential to impair therapeutic effectiveness and can evade the action of antibodies acquired through natural infection with past variations or through vaccination. Finally, the evidence of an augmentation in transmissibility (Cantón *et al*., 2021). The four variants as the last classification as shown in table 07 (Yong Choi *et al*., 2021, Konings *et al*.,2021).

1.4.3.1.1 Alpha variant (B.1.1.7)

Primitive determination was in September 2020 in United Kingdom the spike protein of this category was changed by 7 mutations in: N501Y, A570D, D614G, P68H, T716I, S982A, D1118II.and 2 deletionsH69-V70dcl, YI44dcl this causing a lot of problems the first and the main one is the increasing of transmission also the infection severity (Mohammadi *et al*., 2021)

1.4.3.1.2 Beta variant (B.1.3.5.1)

The origin of this variant was in South Africa in October 2020 the Beta spike protein undergoes mutation in L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V with one deletion LAL242-244dcl the possibility problems that caused the raising of transmission and the reinfection rats (Mohammadi *et al*., 2021).

1.4.3.1.3 Gamma variant (P.1)

In Brazil and Japan, it was in January 2021with a 12 mutation in spike protein: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027, V1176F the gamma variants have the same possibility problem as beta variants (Mohammadi *et al*., 2021).

1.4.3.1.4 Delta variant (B.1.6.1.7.2)

The last one before the Omicron is Delta variants of concern in India. The S protein mutated in E484Q, L452R, add to these 17 mutations: T19R, (V70F*), T95I, G142D, E156-F157 R158G, (A222V*), (W258L*), (K417N*), L452R, T478K, D614G, P68IR, D950N, E484Q, L452R (Mohammadi *et al*., 2021).

1.4.3.1.5 Omicron variant (B.1.1529)

Is the new SARS-CoV-2 strain, identified as a variant of concern by WHO in November 26th, 2021 South Africa it characterized by the spike mutation G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H. The impact of this mutations/deletions/insertion on the spike portion gene leads to a different structure of spike protein which Increased rates of infectivity and re-infection

of pure or vaccinated individuals and the morbidity levels could be dramatically increased (Papanikolaou *et al*., 2021).

Table 07: Characteristics of the SARS-CoV-2 variants of concern (Yong Choi et al., 2021, Konings et al.,2021).

Who label	Lineage additional mutations	Country of origin	Date of designation	Mutation in spike protein
Alpha	(B1.1.7)	United Kingdom	18 December 2020	N501Y,A570D,D614G,P68H,T716I,S982A,D1118II,H69-v70dcl,YI44dcl
Beta	(B.1.351)	South Africa	18 December 2020	L18F,D80A,D215G,R246I,K417N,E484K,N501Y,D614G,A701V ,LAL242-244dcl
Gamma	(P.1)	Brazil	11 January 2021	L18F,T20N,P26S,D138Y,R190S,K417T,E484K,N501Y,D614G,H655Y,T1027,V1176F
Delta	(B.1.617.2)	India	4 April 2021 (VOI); 11 May 2021 (VOC)	E484Q,L452R, T19R, (V70F*), T95I, G142D, E156-F157-R158G,(A222V*),(W258L*),(K417N*),L452R,T478K,D614G,P68IR,D950N, E484Q,L452R
Omicron	(B.1.1529)	South Africa	November 2021	A67V, del69-70, T95I, del142-144, Y145D, del211, L212I, ins214epe, 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, L981F

B.1.1.7, Alpha variant; B.1.3.5.1, Beta variant; P.1, Gamma variant; B.1.6.1.7.2, Delta variant; B.1.1529, Omicron variant.

1.4.4 Phylogeny

The genome sequencing and phylogenetic study of the new coronavirus SARS-CoV-2 revealed that it is genetically related to the previously known coronavirus SARS-CoV, and so belongs to the Coronaviridae family. Coronavirus' genetic material is positive sense single-stranded RNA (+ve ssRNA) (Shaikh et al., 2020). Coronavirinae is further split into four genera: alpha, beta, gamma, and delta-coronavirus. Viruses that have the potential to infect humans are classified as alpha-CoV and beta-CoV (SARS-CoV and MERS-CoV), while viruses in the gamma-CoV and delta -CoV genera are largely known to infect pigs and avians. As shown in figure 15. Sars-CoV-2 is a novel coronavirus that belongs to the genus beta-CoV, as it shares 88 percent sequence identity with SARS-CoV-like coronaviruses (derived from bats), but only 79 percent sequence identity with SARS-CoV and 50 percent similarity with MERS-CoV (Kumar *et al*., 2020).

The majority of the proteins encoded by SARS-CoV-2 are comparable in length to those encoded by SARS-CoV. Except for the S gene, which diverges, SARS-CoV-2 shares more than 90% amino acid identity with SARS-CoV of the four structural genes. The replicase gene encodes a big polyprotein (pp1ab), which is proteolytically broken into 16 non-structural proteins involved in transcription and viral replication. The majority of these non-structural SARS-CoV-2 proteins share more than 85% of their amino acid sequence with SARS-CoV (Hu *et al*., 2021). SARS-CoV-2 appears to be related to SARS-CoV and SARS-related coronaviruses (SARSs-CoVs) found in bats, according to a whole-genome phylogenetic analysis. SARS-CoV-2 belongs to a distinct lineage with four horseshoe bat coronavirus isolates (RaTG13, RmYN02, ZC45, and ZXC21) and novel coronaviruses recently found in pangolins, which group with SARS-CoV and other SARSs-CoVs as shown in figure 16 (Hu *et al*., 2021).

The full size of the SARS-CoV-2 S protein is 1,273 amino acids, which is longer than Sars-Cov (1,255 amino acids) and known bat SARSr-CoVs (1,245–1,269 amino acids). It differs from the S proteins within most members of the subgenus Sarbecovirus, sharing amino acid sequence similarities of 76.7–77.0% with SARS-CoVs from civets and humans, 75–97.7%

with bat coronaviruses in the same subgenus, and 90.7–92.6% with pangolin coronaviruses. The amino acid similarity between SARS-CoV-2 and SARS-CoV is only 73 percent in the S protein's receptor-binding domain (RBD). Another distinctive genetic characteristic of SARS

CoV-2 is the insertion of four amino acid residues (PRRA) at the junction of S protein subunits S1 and S2 (Hu *et al*., 2021).

However, phylogenetic comparisons to other coronavirus strains and previously identified coronavirus recombination events show that SARS-CoV-2 experienced complicated recombination events during its development (Singh et Yi., 2021).

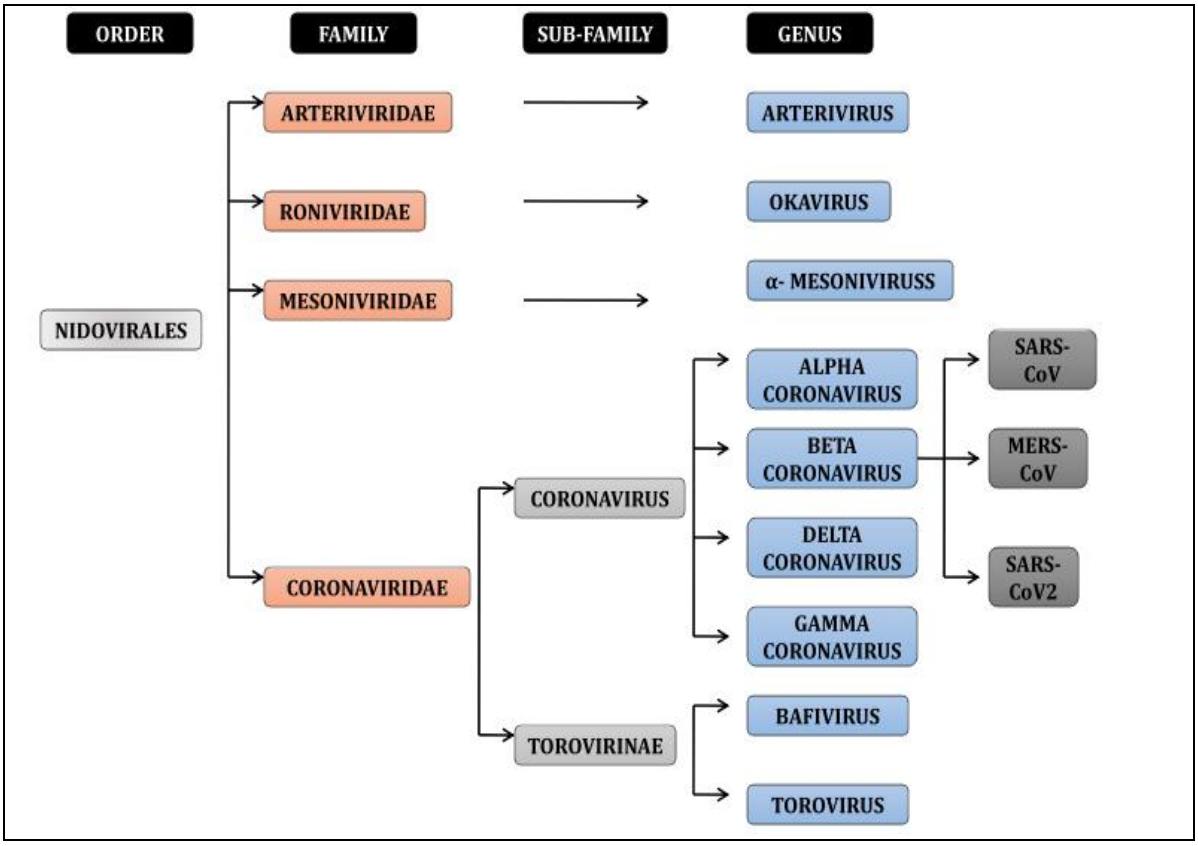

Figure 15: Classification of Human Coronaviruses (Shaikh *et al*., 2020).

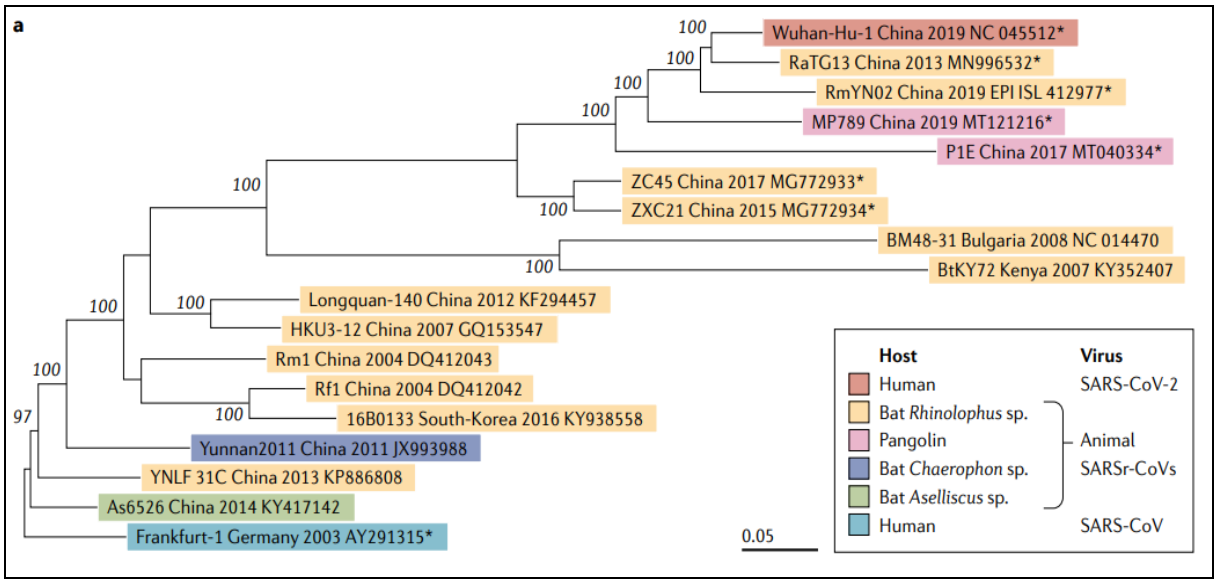

Figure 16: Phylogenetic tree of Human and animal coronaviruses full length genomic sequences (Hu *et al*., 2021).

1.5 Treatment and prevention methods

1.5.1 Treatment

The treatments available for COVID-19 patients are based on their symptoms, and there is no effective treatment for complete recovery in COVID-19 patients. COVID-19 patients are receiving proper treatment due to the efforts of researchers and physicians. Antiviral medicines, immunosuppressants, monoclonal antibodies, and vaccines are among the treatments being tested by researchers. The patient's immune system is challenged in the early stages of the disease to prevent SARS-CoV-2 viral multiplication; nevertheless, in the acute phases, tissue damage may occur owing to significant immunological/inflammatory responses (Salahshoori *et al*., 2021). In the last two years since the beginning of the SARS-CoV-2 pandemic, therapies have been divided into three categories: general treatments, oxygen therapy (which is used more frequently in severe cases of infection), and medications to speed up recovery and strengthen the body's immunity (Salahshoori *et al*., 2021).

1.5.1.1 General therapy

General treatment including more health care as the bed rest the prevention of the inner body by ensuring sufficient intake of, fluids, and electrolytes, inhaling more oxygen from the

air correctly by walking for 30mn daily in the morning. All this can keep any person away of the severe symptoms. (Shaikh *et al*., 2020)

1.5.1.2 Oxygen therapy

The SARS-CoV-2 touch the lungs so keeping attention to the patient's oxygen level it cortical especially for those who suffer of some blocked breathing, shock, coma, or convulsions require oxygen treatment and airway control, with a goal of a SpO2 of higher than 94 percent. If the patients are in critical condition, use a face mask with a reservoir bag (10–15 L/min) titrated to reach the target. Once stabilized, the goal for non-pregnant individuals is 90% SpO2 and 95% for pregnant adults. In young children, nasal prongs or a nasal cannula are used because they may be more tolerated (Shaikh *et al*., 2020).

1.5.1.3 Drugs

Dexamethasone and Remdesivir were authorized by the US Food and Drug Administration (FDA). It is advised for hospitalized patients who require more oxygen. Remdesivir is an adenosine analogue-derived intravenous nucleotide medication. Figure 17 depicts Remdesivir's pathway of action against the SARS-CoV-2 virus. Remdesivir binds to RNA dependent RNA polymerase and limits viral replication by prematurely terminating RNA transcription, as seen in Figure 16. Dexamethasone, a corticosteroid, has a considerable impact on patients' recovery during the acute phase of the condition, when they require an ventilator (Salahshoori *et al*., 2021). Table 08 lists some of the COVID-19 medications that have been suggested (Salahshoori *et al*., 2021).

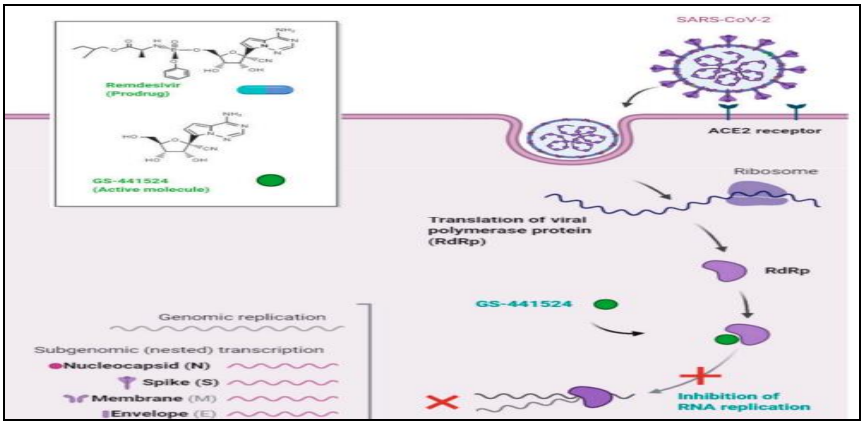

Figure 17: The potential mechanism of remidsiver (Salahshoori *et al*., 2021).

Table 08: Suggested medicaments against COVID-19 (Salahshoori *et al*., 2021).

Properties	Types	Description
Drug treatments	Remdesivir	▪ Due to its ability to inhibit SARS-CoV-2, one of the promising drugs for SARS-19. ▪ Increased transaminase levels, increased prothrombin time and hypersensitivity reactions.
	Favipiravir	▪ Favipiravir is a promising drug for COVID-19 that decreases hospital stay and the need for mechanical ventilation.
	Lopinavir/ritonavir	▪ Prevent severe acute respiratory syndrome-associated coronavirus (SARS-CoV-2) IN VITRO condition.
Anti-SARS-CoV-2 Antibody Products	bamlanivimab	▪ The bamlanivimab plus etesevimab combination blocks SARS-CoV-2 entry into host cells and is being evaluated for the treatment of COVID-19
Corticosteroids	Dexamethasone	▪ In hospitalized patients with severe Covid-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline.
	Hydrocortisone	▪ Hydrocortisone is commonly used to manage septic shock in patients with COVID-19
Immune-Based Therapy	Immunomodulatory therapies	▪ Use of drugs to treat immune and/or inflammatory syndromes such as corticosteroids. ▪ Targeted anti-inflammatory treatments such as interleukin inhibitors, interferons, kinase inhibitors
	Baricitinib	▪ Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating clinical status improvement among patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation

Adjunctive Therapy	Zinc	▪ There are insufficient data to recommend either for or against the use of zinc to treat COVID-19. ▪ Evaluation in clinical trials of zinc supplement alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19. ▪ The potential designation of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19.
	Vitamin C	▪ hydroxychloroquine for the prevention and treatment of COVID-19. ▪ The potential designation of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19.
	Vitamin D	▪ Increased risk of pneumonia in patients with low levels of vitamin D. ▪ Use of vitamin D supplementation to protect against acute respiratory tract infection.
		▪ Not used for non-hospitalized patients with COVID-19. Prohibition of oral anticoagulants with direct action.

1.5.2 prevention methods

To avoid the spread of COVID-19 the preventive interventions are the last ways especially in the lack of a clear cure. At the public health level, several prophylactic interventions have been implemented to prevent or postpone the spread of COVID-19 (SalahShoori *et al*., 2021). These preventive ways including these:

- Quarantine of the infected person
- Identification and monitoring of contacts.
- Environmental disinfection.

and the use of personal protective equipment, as well as social/physical distancing, orders such as stay-at-home orders, the closure of non-essential businesses, and school closures, and bans on public gatherings. Figure 18 below demonstrates different safety information about the COVID-19 infectious disease caused by the SARS-CoV-2 virus (SalahShoori *et al*., 2021). Also, the table 09 below reports the CDC (Centers for Disease Control) recommendations for avoiding the outbreak of COVID-19 (SalahShoori *et al*., 2021).

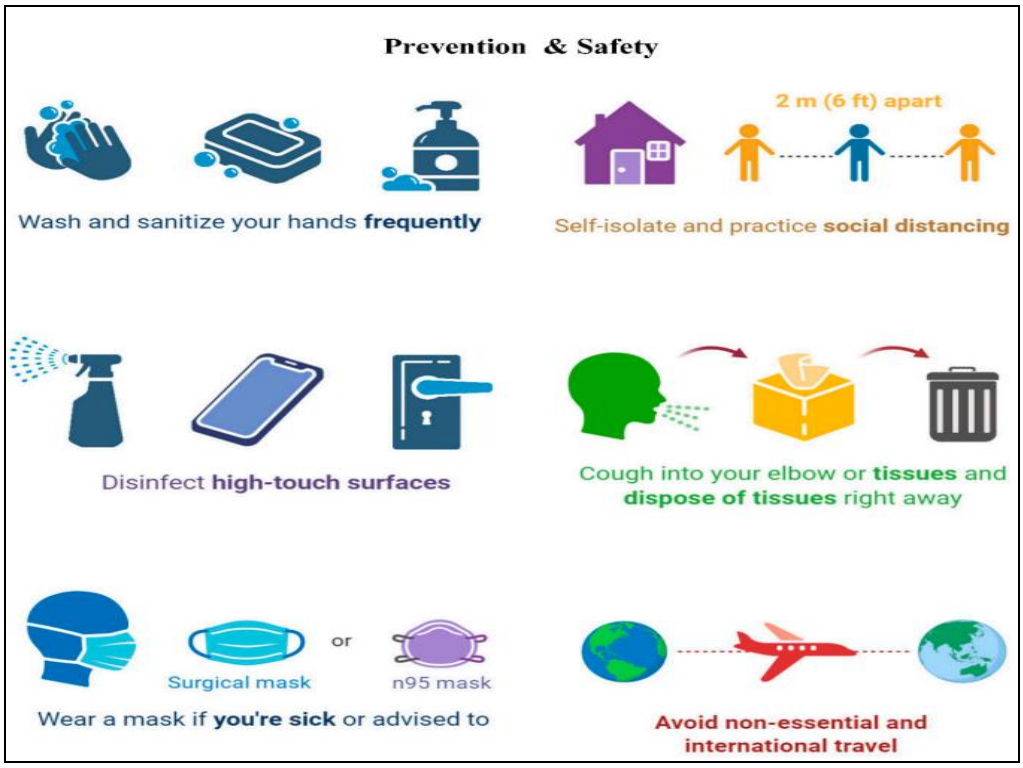

Figure 18: Infographic of various safety information about the COVID-19 infectious disease caused by the SARS-CoV-2 virus (SalahShoori *et al*., 2021).

Table 09: The CDC recommendations for preventing the spread of COVID-19 (SalahShoori *et al*., 2021).

Everyone should	Description
Wash your hands	▪ Washing hands for at least 20 s with soap and water ✓ When you leave a public place ✓ After coughing, blowing your nose, and sneezing ✓ Posterior to touching your mask ✓ When caring for a sick person ✓ Posterior to handling pets and animals ▪ Use hand sanitizer (at least 60% alcohol) if the soap is not available
Stay away from close contact	▪ Indoors: prevent close contact with sick people and maintain a distance of 6 feet between the patient and other members of the home. ▪ Outdoors: Maintain a 6-foot distance between yourself and people. ▪ Warning: Asymptomatic disease vectors spread the virus.
Cover coughs and sneezes	▪ Everyone should cover their mouth and nose with a handkerchief or hand when coughing or sneezing, and refrain from spitting in public places. ▪ Never leave used napkins in public places and be sure to put them in the trash bin.
Clean and disinfect	▪ Clean dirty surfaces with detergent or soap and water before disinfecting. ▪ Use a household disinfectant as much as possible.
Monitor Your Health Daily	▪ Check your symptoms regularly, such as fever, cough, shortness of breath, or other symptoms of COVID-19, especially when travelling to high-risk areas. ▪ If your symptoms develop, check your body temperature regularly. Be careful not to check your body temperature within 30 min of exercising or after taking fever medications.

Protect Your Health This Flu Season	▪ The importance of influenza vaccination in winter and autumn months in 2020–2021 for the following reasons: ✓ Reduction of the risk of influenza, hospitalization, and mortality. ✓ Saving health resources to care for patients with COVID-19.
The necessity of using masks to cover the mouth and nose in the face of others	▪ The necessity of wearing masks in public areas and around people in society due to the difficulty of observing social distancing. ▪ Do not use masks for employees of health centers and hospitals due to the importance of surgical masks and N95 respirators to prevent disease in staff. ▪ Everyone should maintain social distancing in society because masks are not a suitable alternative to social distancing.

Chapter two

Epidemiology of coronavirus

2.1 Generalities of epidemiological study

Infectious diseases have been a severe danger to human survival for ages, and they can destroy entire societies (Srivastava *et al.*, 2020), accounted for almost one-third of all mortality and were the leading cause of death (Philipson 2000). One of the methods of improving public health is to study the epidemiology, which is applied in a variety of ways (Bonita et al., 2006). Epidemiology is a vast field that has developed in response to public changes and the appearance of new diseases. As a result of this change, epidemiology has remained a useful and relevant tool for bringing infections and health events to light and interpreting them (Frérot *et al.*, 2018). WHO defines epidemiology «as the study of the distribution and determinants of health-related states or occurrences (including infection), and the application of this knowledge to disease control and other health problems. Epidemiological investigations can be carried out using a variety of methods: surveillance and descriptive studies can be used to study distribution, while analytical studies can be used to study determinants» (Srivastava *et al.*, 2020).

Epidemiologists are interested in more than just mortality, disease, and disability; they are also interested in more positive states and, most importantly, ways to enhance health (Bonita *et al*., 2006). In the last 100 years, the human species has faced a number of epidemic diseases, that are mostly caused by viruses (Srivastava *et al*., 2020). The leading agent of the current worldwide pandemic COVID-19 with a rising mortality rate is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (provisionally called 2019-nCoV). The World Health Organization has classified it as a worldwide public health emergency (Muralidar *et al*., 2020).

The main issue is regulating and establishing efficient treatments for these outbreaks, as well as closely monitoring the viruses and other bacteria for mutations and cross-genetic translation (Srivastava *et al*., 2020).

2.2 Methodology of epidemiological study

Epidemiology is the study of disease distribution patterns and the factors that can affect these patterns. These studies are frequently carried out within a conceptual or philosophical perspective. As a result, epidemiology can be thought of as an eclectic integrative discipline that draws on a variety of disciplines such as biology, biostatistics, economics, genetics, medicine, psychology, and sociology.

Epidemiology is, at its base, a "comparative" science. That is, most epidemiological studies compare diseases and probable causes connected to these diseases across diverse groups, time periods, and locations. The initial stage in this procedure is to evaluate the strength of the statistical link between a factor and disease, after which biological conclusions may be drawn from the statistical correlations (Wilson et Burden., 2009).

The information gathered during these investigations is used in a variety of ways, including:

1. To completely comprehend the pathogenesis of an illness or a collection of disorders
2. To see if epidemiologic data matches up with etiological ideas based on clinical or laboratory observations.
3. To provide a basis for developing consistent preventive procedures, public health policies and public health practices (Wilson et Burden., 2009).

The three basic epidemiologic methods are:

1. Descriptive, which organizes data by time, location, and person.
2. Analytic, which includes a case-control or cohort study.
3. Experimental (Baron 1996).

Although all three methods may be used to investigate disease incidence, descriptive epidemiology is the most commonly utilized. After a disease's fundamental epidemiology has been identified, particular analytic tools may be utilized to further investigate the disease, and a specific experimental methodology can be devised to test a theory (Baron 1996).

2.2.1 Descriptive Epidemiology

Data that characterize the incidence of the illness are collected from all relevant sources using various approaches in descriptive epidemiology. The information's are then organized by time, location, and individual. The epidemiology data is described using four-time trends.

The secular trend explains the prevalence of illness over a long period of time, generally years; it is impacted by the population's level of immunity as well as nonspecific factors such as increased socioeconomic and dietary levels. The periodic trend is the second time trend. The periodic trend is a sudden variation in the general secular trend that may reflect a change in the antigenic features of the disease agent.

The third time trend is the seasonal trend. This pattern represents variability in disease incidence as a result of changes in environmental factors that improve the agent's capacity to reproduce or spread.

The epidemic incidence of sickness is the fourth time trend. An epidemic is a rapid increase in the occurrence of a disease caused by common circumstances that accelerate transmission.

A description of epidemiologic data by location must address three distinct sites: where the individual was when the disease occurred, where the individual was when the source infected him or her, and where the source was infected with the etiologic agent.

The characteristics of the epidemic should be obvious enough once the descriptive epidemiologic data has been reviewed those further areas for investigation should become accessible (Baron 1996).

2.2.2 Analytic Epidemiology

Analytic epidemiology investigates disease determinants for probable causal relationships. The case-control (or case-comparison) technique and the cohort method are the two basics analytic methodologies. The case-control technique begins with the consequence (illness) and explores the cause that led to the effect retrospectively.

The case group is made up of people who have the disease, while the comparison group is made up of people who are similar to the case group but don't have the disease. These two groups are then compared to see if there are any changes that might explain the disease's occurrence.

The cohort technique is the second analytic approach, which investigates two groups prospectively: one that has had interaction with the suspected causative factor under research and a comparable group that has not. The influence of the factor should be recognizable when both groups are monitored (Baron 1996).

A cross-sectional study is another analytic approach in which a population is surveyed over a short period of time to establish the association between a disease and variables occurring at the same time that can impact its incidence (Baron 1996).

2.2.3 Experimental Epidemiology

An experimental model is built in which one or more selected parameters are modified, and a hypothesis is developed. The outcome of the experiment will either prove or reject the hypothesis (Baron 1996).

2.3 Epidemiology of SARS-CoV-2 in the world

For the first time On December 31st 2019, instances of pneumonia with an unknown origin were reported in Wuhan, China, and a novel strain of coronavirus was discovered as the cause of those pneumonia cases later in January 2020. The infection was given the official name COVID-19 (short for coronavirus disease 2019) by the World Health Organization (WHO), and the virus was given the name SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the WHO. In the epidemiology of this developing illness, a pattern comparable to Sars and Middle East Respiratory Syndrome (MERS) coronaviruses has been seen (Nikpouraghdam *et al*., 2020).

The World Health Organization announced in March 11, 2020 that the epidemic may be uncontrollable and that COVID-19 should be classified as a pandemic. COVID-19 had been

reported in 649,604 cases in over 177 countries and regions as of March 28th, 2020, with 30,249 confirmed fatalities. On the same day, Italy was the world's second-worst-affected nation in the pandemic, with 92,472 cases and 10,023, based on the ratio of persons tested positive to the COVID-19 over population. These statistics, on the other hand, are updated on a regular basis by worldwide data providers (Abenavoli *et al.*, 2020). Figure19 presenting reported cases of the worst-affected nations (from January21, 2020, to March 24, 2020).

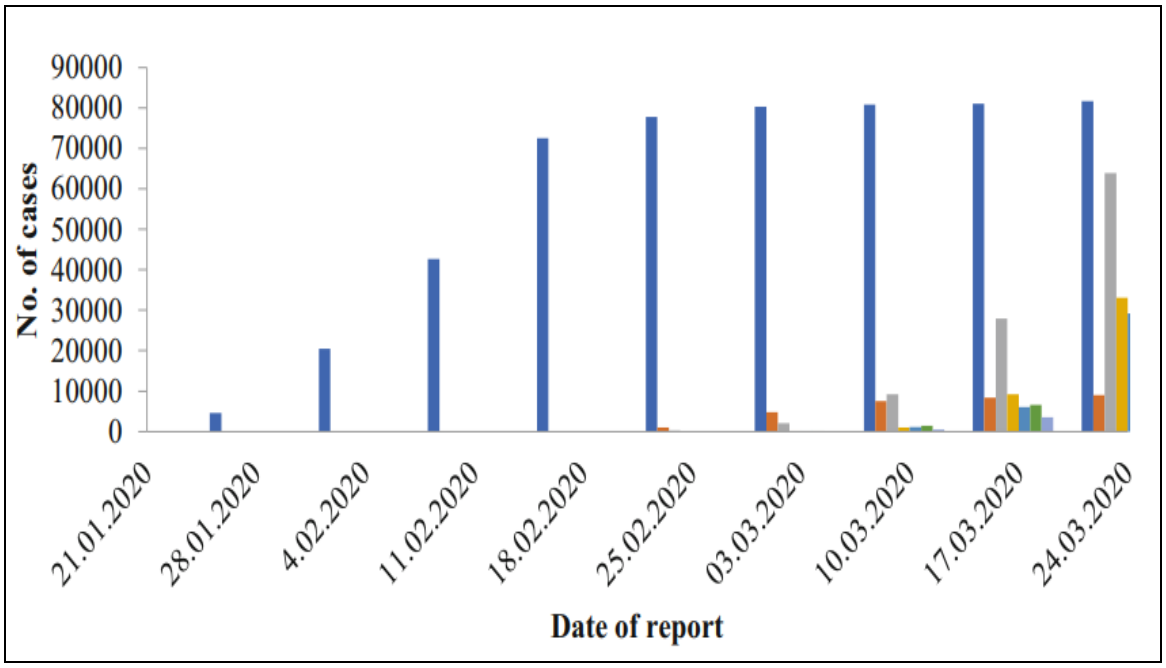

Figure 19: Data of reported cases by week in some of the worst-affected nations (from January21, 2020, to March 24, 2020) (Srivastava *et al.*, 2020).

As of April 29, 2020, there has been a total of 3,061,615 COVID-19 cases documented in at least 170 nations and territories, with a 7% death rate (213,577/3,061,615). A previous review of 72,314 confirmed, probable, and asymptomatic COVID-19 cases from China found numerous key epidemiological aspects of the virus. The majority of patients were between the ages of 35 and 55, with children and newborns being less affected. According to a study on the dynamics of early viral transmission, the median age of patients was 59 years, with a range of 15 to 89 years, and the majority of patients (59%) were men. People with a weak immune system, particularly the elderly, as well as those with renal and hepatic disease, were at threat.

SARS-CoV2 was shown to have greater rates of transmissibility and pandemic risk than SARS-CoV, with a worldwide effective reproductive number (R) of 2.9, which is much higher than SARS's R. (1.77). SARS-CoV-2 has been found to be between 2.6 to 4.71 in another investigation. SARS-CoV-2 has a 4–8day incubation period following infection (*Zhou et al*., 2021). As of May 13, 2020, a total of 4,170,424 confirmed COVID-19 cases (with 287,399 fatalities) have been recorded in more than 210 countries (WHO Situation Report 114) as it shown in figure 20. Initially, China was the center of the Sars-Cov-2 pandemic, with 84,458 laboratory-confirmed cases and 4,644 fatalities recorded as of May 13, 2020. Apart from China, confirmed SARS-CoV-2 cases have been recorded in more than 210 countries (WHO Situation Report 114) as of May 13, 2020. Except for Antarctica, COVID-19 has been reported on every continent. Italy was the center of attention for several weeks due to the enormous number of cases, with 221,216 cases and 30,911 fatalities, but later the United States has the most instances, with 1,322,054 cases and 79,634 deaths. As it shown in figure 21 (Dhama *et al*., 2020).

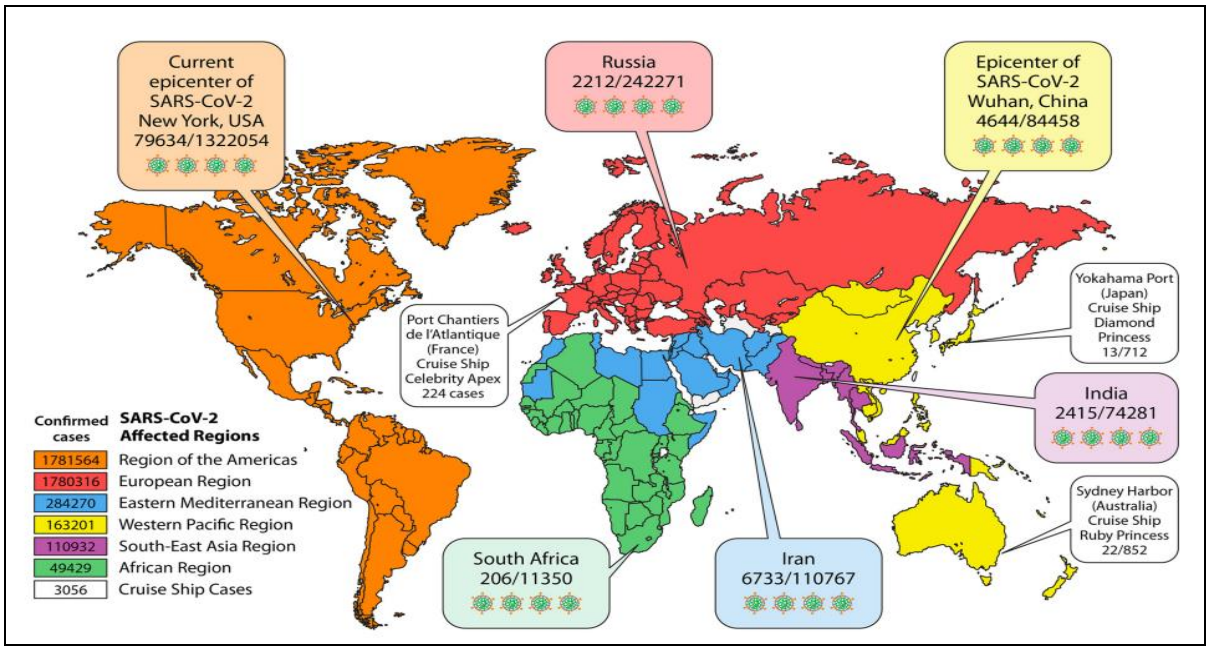

Figure 20: World map depicting the current scenario of COVID-19. Shown are countries, territories, or regions with reported confirmed cases of SARS-CoV-2 as of 13 May 2020 (Dhama *et al*., 2020).

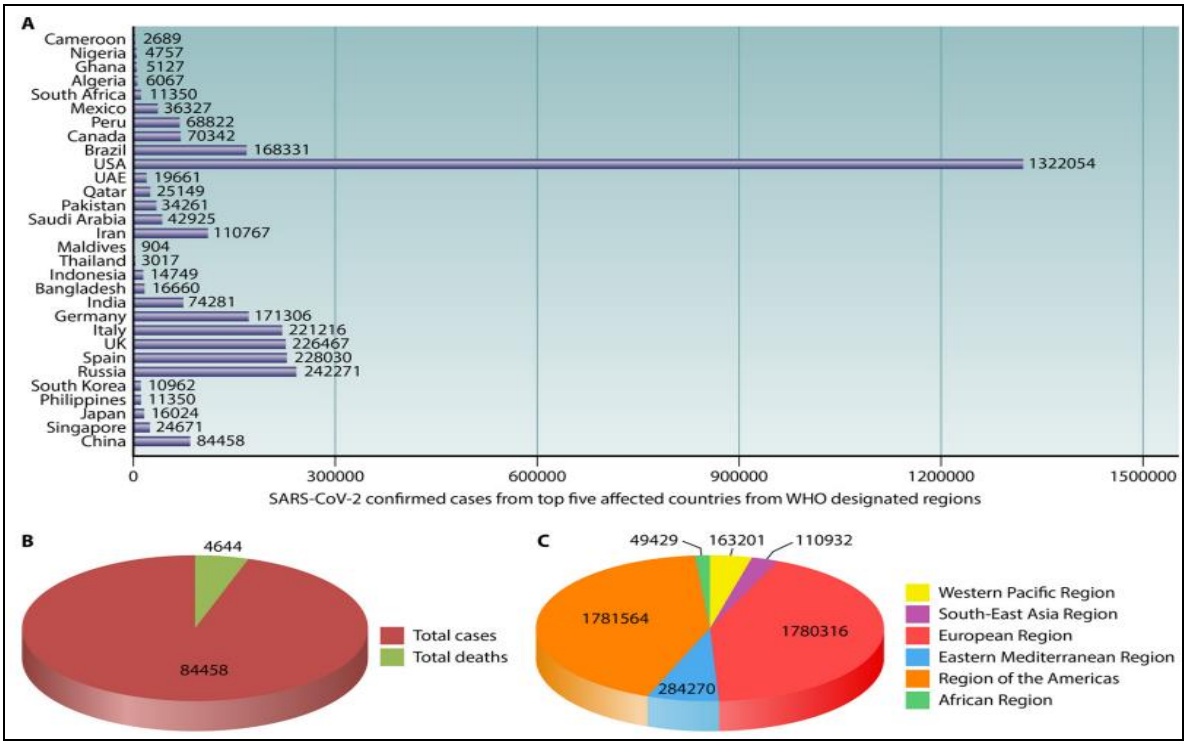

Figure 21: (A) SARS-CoV-2 confirmed cases in the top five affected countries from each WHO designated region, where maximum casualties were reported to WHO until 13 May 2020. **(B)** Total numbers of deaths and cases in China only. **(C)** Total number of cases worldwide by region (Dhama *et al*., 2020).

Within 210 days (30 weeks), this extremely infectious virus has killed over 761,779 people throughout the world, and the death count is still rising on a daily basis representing in figure 22. As a result, strategic preparedness and comprehensive public health measures are seen as the most critical need for containing this worldwide pandemic (Muralidar *et al*., 2020).

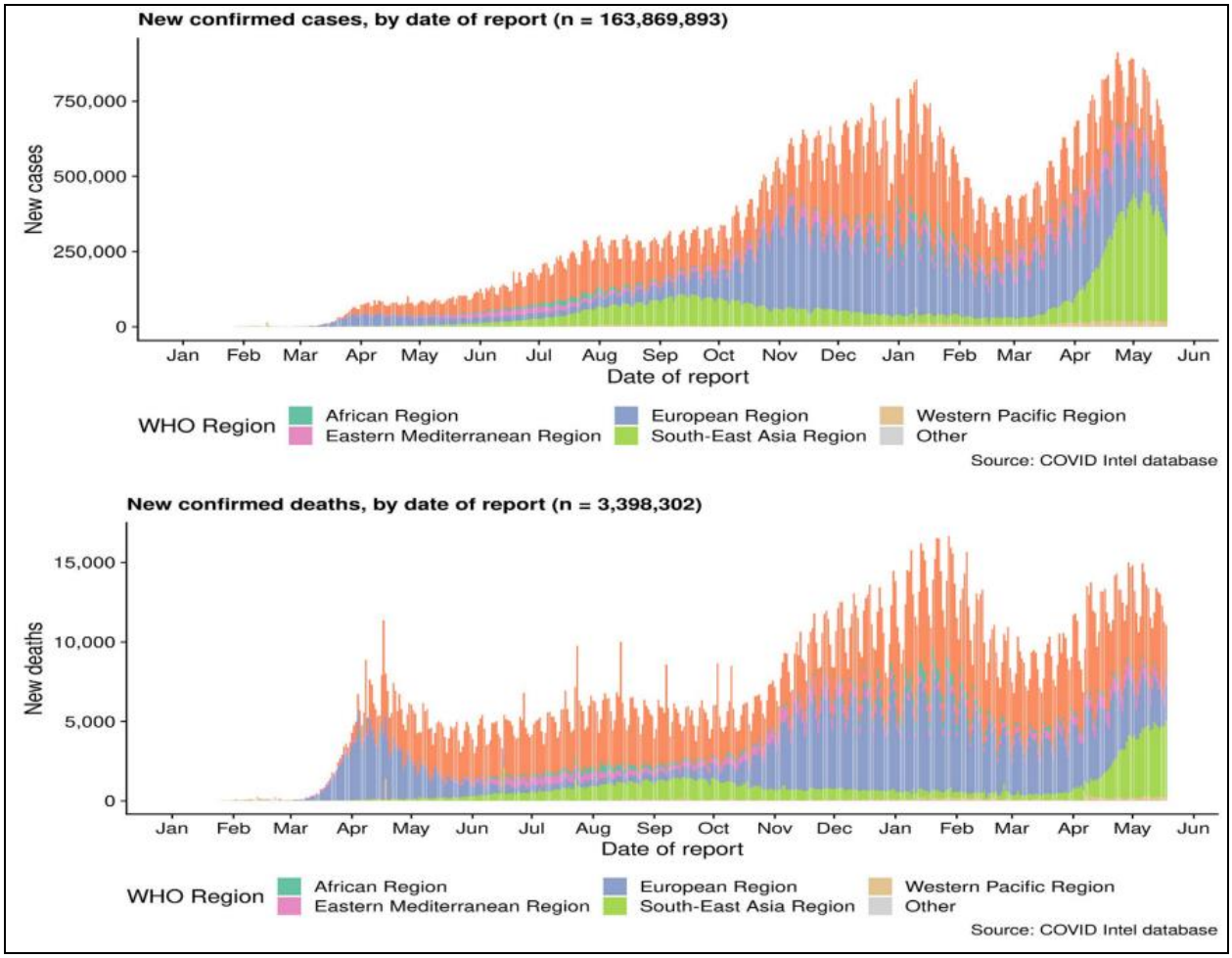

Figure 22: COVID-19 confirmed cases and fatality cases in total. The World Health Organization provided the data (Zhou *et al*., 2021).

2.3.1 Variants

A VOC is defined as a SARS-CoV-2 variation that satisfies the definition of a VOI and has been linked to one or more of the following modifications with worldwide public health implications: an increase in transmissibility or a negative shift in COVID-19 epidemiology; an increase in virulence or a change in clinical symptom presentation; or a decrease in the efficacy of current diagnostics, vaccines, and treatments. The WHO has recognized four VOCs (alpha, beta, gamma, and delta) as of August 30, 2021.

According to the WHO epidemiological report, the alpha, beta, gamma, and delta variants have spread to 193, 141, 91, and 170 nations, respectively, as of August 31, 2021(Choi *et al*., 2021) Presented in figure 23 (Choi *et al*., 2021).

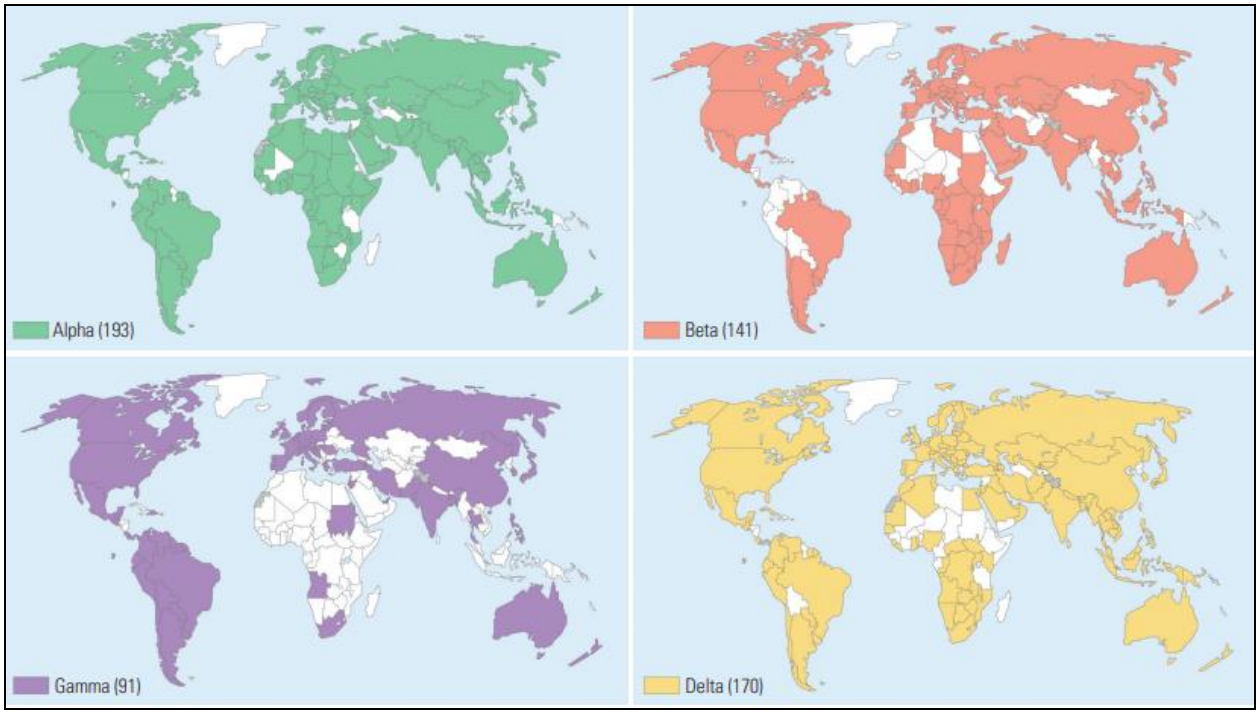

Figure 23: Areas where there have been reports of variations of concern (as of August 31, 2021) (Choi *et al*., 2021).

On November 24, a new variant of the severe acute respiratory syndrome coronavirus 2 was shown in the south of Africa, and it's called the omicron variant of concern (VOC) (B.1.1 529) (Poudel *et al*., 2022). The Omicron was initially discovered in Botswana and South Africa, and it is rapidly spreading throughout South Africa and the world. As of December 16, 2021, it was found on five continents: Europe, North America, Asia, South America, Africa, and Oceania, with at least 77 countries reporting Omicron cases, including the United States, the United Kingdom, France, Germany, Australia, Japan, and China. At least 44 nations have imposed travel restrictions on and out of South Africa. Many nations and areas throughout the world are alarmed, creating fear and uncertainty in the global fight against the COVID-19 pandemic (Ren *et al*., 2022). Figure 24 present the region affected with omicron variant.

Figure 24: Regions where the omicron variant has been reported (Corum et Zimmer., 2022).

2.4 Epidemiology of SARS-CoV-2 in Africa

The population of Africa is around 1.3 billion people. Due to their strong relations with China and other afflicted nations, African countries began anticipating the virus's entry to the continent after reports of coronavirus (COVID-19) appeared in Wuhan, China, in December 2019. On the continent, health professionals feared and predicted a public health and economic disaster. Social lifestyle, weak healthcare systems, frail infrastructure, low availability of skilled employees, insufficient financing, improper data transmission, and limited access to medical supplies and equipment throughout the continent all contributed to the projections. Interestingly, Africa was the last and least afflicted region. Early in January 2020, the Ivory Coast, followed by other African countries, began working to limit COVID-19 imports and contain onward transmission within countries.

On February 14, 2020, Egypt announced the first COVID-19 case in Africa. It was followed chronologically by Algeria, which reported its first incidence on February 25, 2020, and Nigeria on February 27, 2020, South Africa, Ghana, and Morocco are among the rest of Africa's countries.

The majority of the early cases were imported from Europe, which was the epicenter of COVID-19 by March 13, 2020. This resulted in an increase in the number of cases in Africa, with 52 African nations reporting 19,895 confirmed cases as of April 18, 2020, and just two countries (Comoros and Lesotho) remaining virus-free. With the exception of Western Sahara, 54 of the 55 African Union Member States have reported an increase in coronavirus infection by the end of May 2020, with nearly 100,000 cases documented. Most nations had dealt with imported cases and community transmission COVID-19 instances in Africa had topped 200,000 by the second week of June, and had risen to 400,000 by the 6th of July. South Africa and Egypt accounted for half of the 500,000 cases documented on the continent. At this point, the World Health Organization expressed concern about the pandemic's expansion in Africa in July 2020, warning that the rising numbers in South Africa might be a prelude to following outbreaks across the continent as shown in figure 25 (Dufailu *et al*., 2021). All this was at the beginning of the pandemic with many attempts to reduce the spread of COVID-19 by preventive precautions and measures and temporarily disrupting flights, social distancing, and, in addition the masks. After the first phase in Africa, like in other continents, there was an increase in the number of deaths and cases (Dufailu *et al*.,2021).

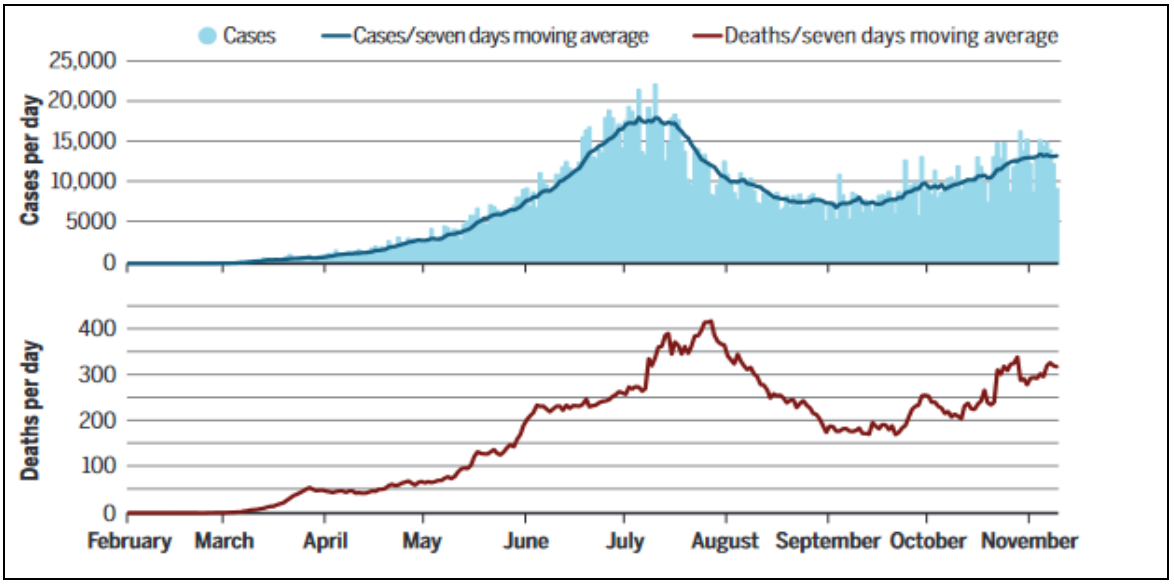

Figure 25: The evolution of daily reported COVID-19 cases across the African continent from February to November 2020 (Maeda *et al.*,2021).

2.4.1 Waves

According to the number of fatalities and cases recorded by the WHO in Africa. The first wave of the Covid-19 outbreak began in July 2020. The first wave of COVID-19 cases peaked in August 2020, followed by a gradual reduction between September and November. The second wave began in December 2020 and ended in January 2021, with a gradual reduction in Covid-19 cases between February and June. The third wave of the COVID-19 pandemic began at the end of June, followed by the fourth wave, which began at the end of November and peaked on December 27th as shown in figure 26 (Ilesanmi *et al.*, 2021).

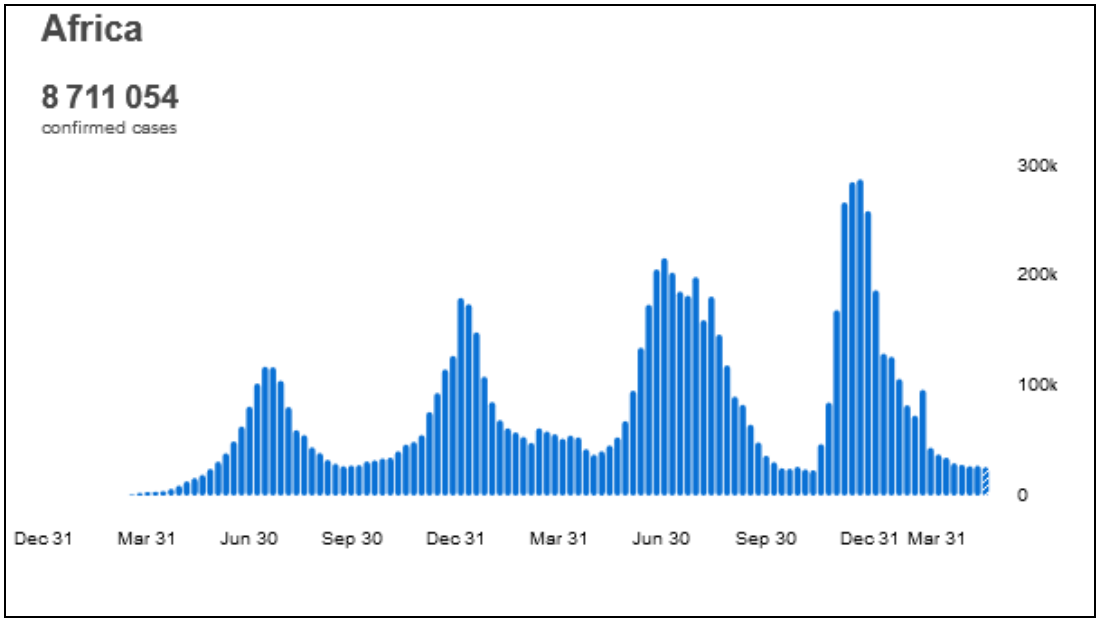

Figure 26: A represented diagram of COVID-19 cases in Africa representing of the four waves over the last 2 years per month (WHO., 2022)

2.4.1.1 First wave

The first wave of the COVID-19 pandemic spread more slowly in Africa than in the rest of the world, peaking in July 2020, with an average daily number of new cases of 18 273, and proportions of cumulative cases and deaths varying across the five AU regions: 43 percent of cases and 46% of deaths in the Southern region, 12 % of cases and %percent of deaths in the Eastern region, 34% of cases and 37 % of deaths in the Northern region, In the Central region, 3% of cases and 2% of fatalities occurred, whereas in the Western reon, 9% of cases and 5% of deaths occurred, as shown in figure 27.

The Southern area reported more instances than the other regions, where 9 countries accounted for 2 283 613 cases, 82.6% of the COVID-19 cases recorded in Africa: South Africa (38.3%), Morocco (15.9%), Tunisia (5.1%), Egypt (5.0%), Ethiopia (4.5%), Libya (3.6%), Algeria (3.6%), Kenya (3.5%), and Nigeria (3.2%), The remaining 46 nations each reported 34 to 55000 cases. The greatest cumulative incidence of cases per 100 000 population was recorded in Cabo Verde (1973•3), South Africa (1819•6), Libya (1526•4), Morocco (1200•0), and Tunisia (1191•2).

Where the largest prevalence was found in the Southern area. Moreover, South Africa, Egypt, Morocco, Tunisia, and Algeria each recorded 65 602 deaths. As of August 25, 2020, 17 nations reported CFRs higher than the continental and worldwide CFRs of 22%, out of 53 (96%) countries actively reporting, and reporting more than 100 COVID-19 cases: Sudan (6•1%), Egypt (5•5%), Chad (4•9%), Liberia (4•6%), Mali (3•8), Tunisia (3•4%), Democratic Republic of Congo (3•3%), Niger (3•1%), Malawi (2•9%), Sierra Leone (2•9%), Algeria (2•8%), Somalia (2•8%),The Gambia (3•3%), South Africa (2•7%), Zimbabwe (2•6%), Mauritania (2•3%), and Angola (2•3%).The Southern area had the most fatalities (30 453 (46•4%)), whereas the Northern and Southern regions had the highest regional CFRs. (Salyer *et al*., 2021)

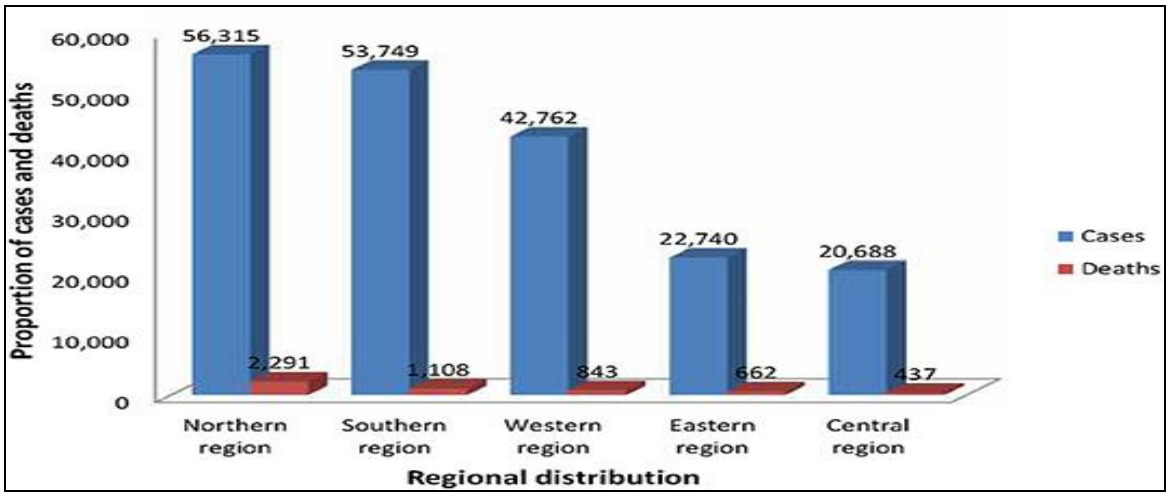

Figure 27: A represented diagram of regional distribution of COVID-19 cases and deaths in Africa based on data from Africa Center for Disease Control (June 2020) (Hagan *et al*.,2020)

2.4.1.2 Second wave

The pandemic's second wave began from November 2020 through February 2021.South Africa recorded 52.9 % of instances (n = 781996 out of 1.47 million), Nigeria (6.1 percent; n = 90989), and Zambia (4.1 percent; n = 60052) during this period.

The greatest incidence rates were found in Seychelles (24665.8 cases per million), South Africa (13354.2 cases per million), and Cape Verde (11 579.6). Throughout this time, the Seychelles and Eritrea recorded 14 deaths out of 2408 cases and seven deaths out of 2326 deaths, respectively. The median CFR was 1.3%, with a range of 0 to 5%. On February 24, 2021, the pandemic trajectory indicated a declining or plateauing tendency in 35 nations (76.1%) and an ascending trend in 11 countries (23.9%). Benin, Burundi, Cameroon, Chad, Equatorial Guinea, Ethiopia, Gabon, Guinea, Madagascar, Namibia, and South Sudan all had an increase in cases over the four weeks (28 January–24 February 2021) (Salyer *et al*., 2021).

In 11 additional countries (Botswana, DRC, Ghana, Guinea-Bissau, Kenya, Liberia, Mauritius, Mozambique, Sao Tome and Principe, Senegal, and Seychelles), the epidemic trajectory fluctuated or plateaued over this 4-week period (28 January–24 February 2021). In the 24 remaining African nations, observed a declining trend during the 4 -week period leading up to the conclusion of the pandemic's first year (Impouma *et al*., 2021). This wave came with it a daily influx of aggressive fatality cases, with an estimated total of 23,790 new cases every epidemiological week as represented in figure28 (Salyer *et al*., 2021).

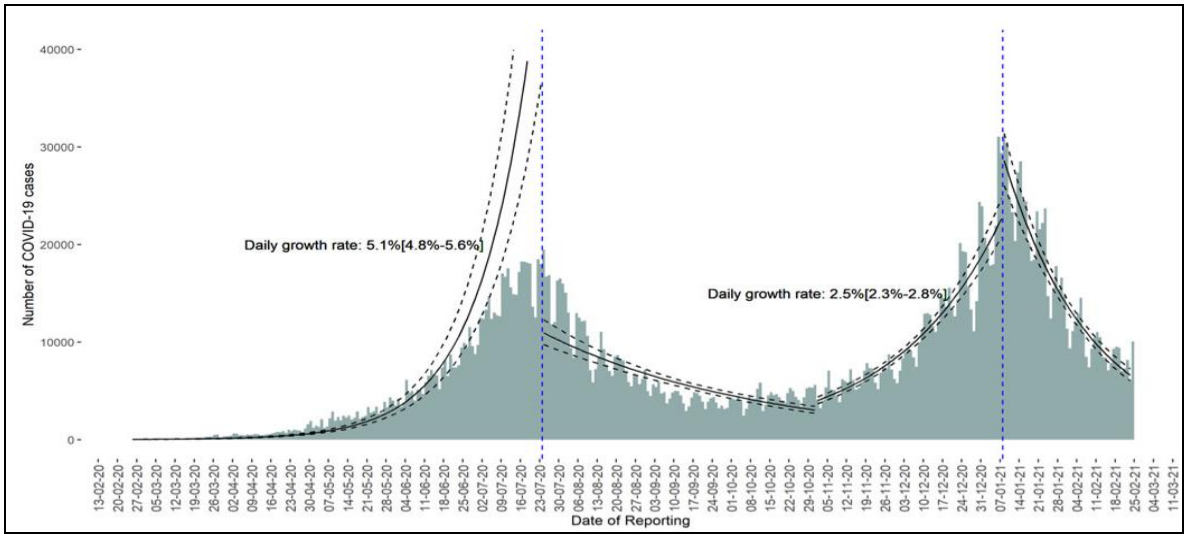

Figure 28: Distribution of COVID-19 cases by the reporting date and log-linear fit in the African region (data as of 24 February 2021) (Impouma *et al*.,2021).

2.4.1.3 Third wave:

After many jurisdictions around the world relaxed their COVID-19 pandemic restrictions, the third wave of COVID-19 emerged. In mid-June 2021, World Health Organization Regional Director Matshidiso Moeti reported that COVID-19 incidence and death rates in Africa had increased by over 30% and 15%, respectively ,with Seychelles (25.1%, n = 160244/638232), Mayotte (10.9% n = 69460/638232),Cape Verde (9.1% n = 58122/638232), Tunisia (5.7 n = 36238/638232), Namibia (5.6% n = 35901/638232), Reunion(5.3% n = 33917/638232), South Africa (5.3% n = 33633/638232), Botswana (4.7% n =29781/638232), Libya (4.4% n =27901/638232) and Eswatini (2.6% n = 16281/638232) accounted for almost 78.6% (n = 501477/638232) of the total number of verified COVID-19 cases per million of the population in early July 2021 (Kangbai *et al*., 2021). As shown in figure 29. As of July 18, 2021, there have been 6,288,605 COVID-19 cases and 158,354 Covid-19-related fatalities (Ilesanmi *et al*., 2021).

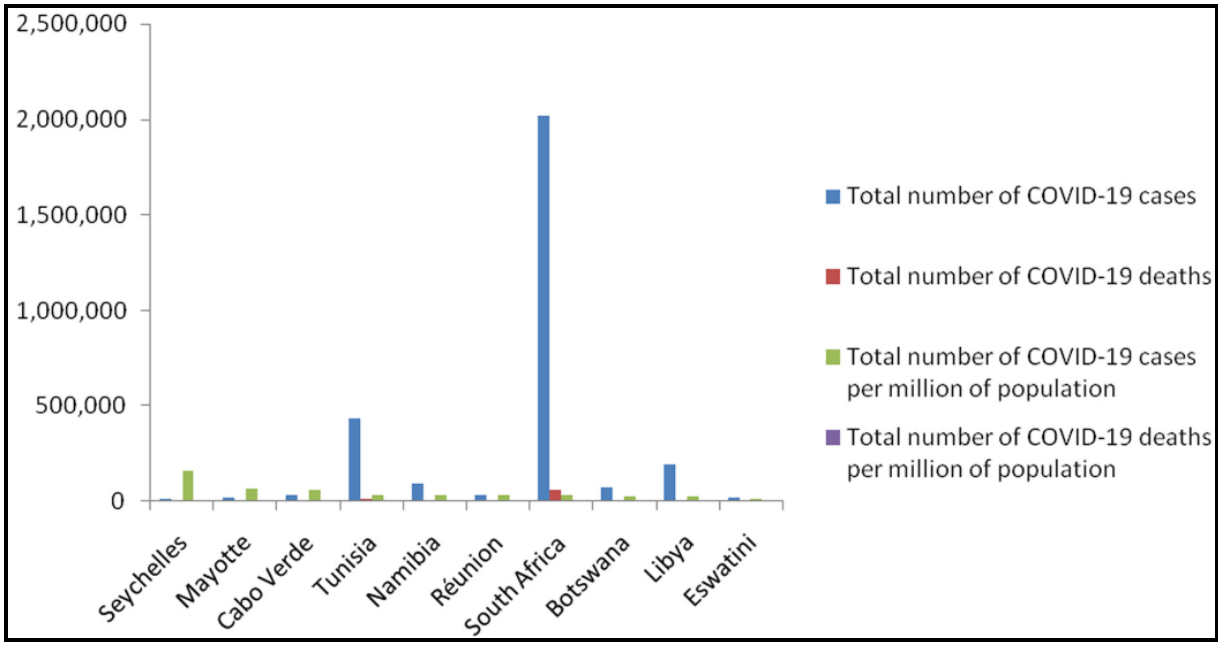

Figure 29: Total number of Covid -19 cases and fatalities per million people for the 12 most impacted African nations as of the first week of July 2021 (Kangbai *et al*.,2021).

2.4.1.4 Fourth wave

In November 2021, South African and Botswana genomic surveillance teams discovered a novel SARS-CoV-2 variant linked to a fast upsurge of illnesses in Gauteng province, South Africa, the World Health Organization recognized the first genome as a variation of concern (Omicron, B.1.1.529) just three days after it was posted. By the first week of December 2021Omicron had caused a dramatic and continuous rise in cases in South Africa and Botswana by the first week of December 2021.

By the 16th of December 2021, Omicron had been discovered in 87 countries, both in samples from travelers coming from southern Africa, and by the 1st of January 2022, over 100,000 genomes had been produced from over 100 countries, and Omicron had established itself as the world's dominant VOC (Viana *et al*., 2022). It was characterized by a high number of confirmed cases but a low number of deaths per week, as reported by WHO, with 1001 deaths at the end of December, indicating a 436-weekly increase, in addition to the 285630 confirmed cases, which represented a massive number of cases per week, estimated at 186547 weekly increases (WHO., 2022).

2.5 Epidemiology of SARS-CoV-2 in Algeria

Algeria, like the rest of the globe, has been affected by the pandemic respiratory disease. Algeria, along with Egypt and South Africa, was considered one of the three African nations with the highest danger of COVID-19 importation from China prior to the arrival of COVID-19 in the country. Furthermore, it was one of the World Health Organization's 13 highest priority nations for travel to China, based on direct ties and amount of travel. However, much like in Morocco's border country, the initial cases were all from Europe (Especially from France, Italy and Spain). The first case was recorded on February 25 in the department of Ouargla, when an Italian citizen tested positive for COVID-19. On March 1st, the genuine start of the pandemic was reported in the district of Blida, and the first fatality was documented on March 12th, 2020. We predict that the basic reproduction number for the epidemic in Algeria is 2.09 when no control measures are in place; the number of new cases in Algeria would peak around late May to early June, and up to 82 percent of the Algerian population will likely get the coronavirus.

Notably, Algeria has adopted the Chloroquine (Hydroxychloroquine)/Azithromycin strategy for the treatment of COVID-19 patients since March 23. The medication was first advised for "certain instances," but it was made universal on April 6 for all COVID-19 positive individuals. The treatment consists of the administration of Chloroquine (500mg) twice a day for 5 to 7 days or hydroxychloroquine (200mg) three times/ day for 10 days; in association with azithromycin (500mg) twice a day for 5 days. Alternatively, Lopinavir/Ritonavier (200/50mg) could be administrated twice/day for 5 to 7 days for patients with chloroquine contraindications. Since May 1st, all the 48 departments of Algeria were affected with a number varying from 2 to 865 of positive cases (Lounis., 2020). COVID-19 has the greatest impact in Algeria on people aged 25 to 49 years (42.1%) and those over 60 years (34.3%). Patients under the age of 25 account for 5.3 percent, while those between the ages of 50 and 59 account for 18.3 percent. Men (54.2%) appear to be more impacted than women (45.8%) as shown in figure 30.

Even if the exact number of severe cases and deaths is unknown, the current data show that 75 percent of all deaths in the country occurred in adults over the age of 60 (Lounis 2021).

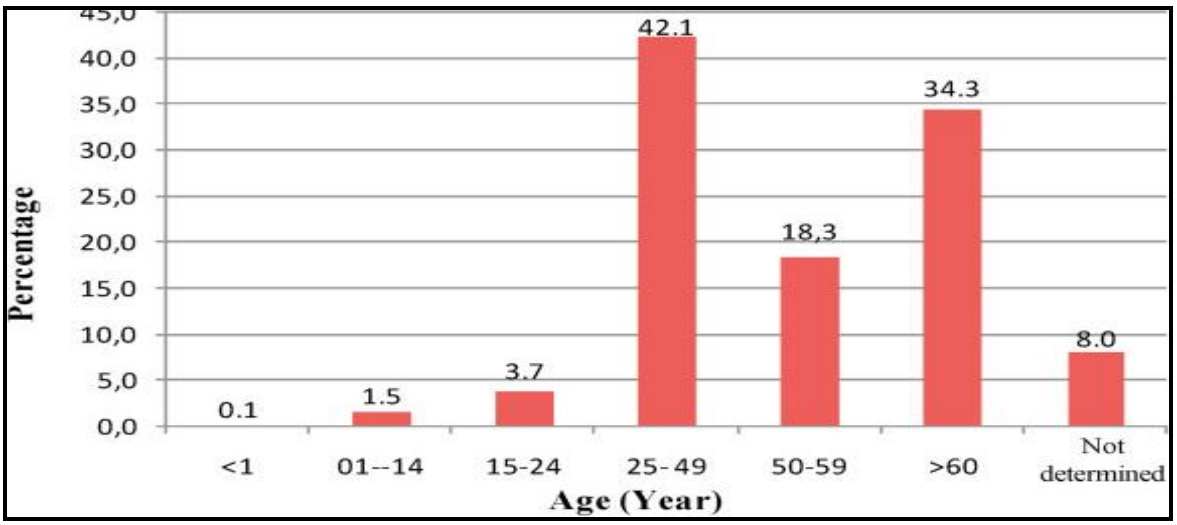

Figure 30: Distribution of COVID-19 positive patients according to their age (Lounis 2021).

The number of infected patients increased from one confirmed case on February 25, 2020 to 265 754 confirmed cases and 6875 deaths on April 24, 2022 as shown in figure 31 below (WHO., 2022).

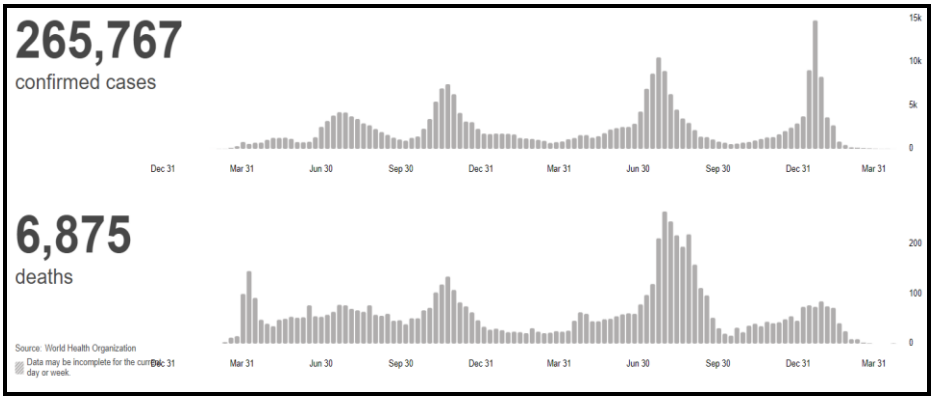

Figure 31: COVID-19-Algeria situation (confirmed cases/deaths) (WHO., 2022).

2.5.1 Waves

2.5.1.1 First wave:

Since the first case, reported on 25 February 2020, the number of confirmed cases has increased. The true starting outbreak in the department of Blida on 1 March 2020 of two national citizens who came from France. Those who have been confirmed affected of the Alpha variant. The Algerian government has begun to undertake a series of preventive measures to increase social distance and restrict the spread of the virus quickly after the first cases were discovered. These measures include the cancellation of travel and isolation of repatriated citizens, as well as the restriction of all public gatherings through the closure of schools, universities, and all educational institutions, as well as the closure of mosques and cult sites and the suspension of collective prayers. All private and public common transportation, as well as rail service, has been suspended (Lounis 2020). On May 23, 2020, the government declared mask wearing mandatory in all public and work locations, as well as all public closed and open spaces, including public enterprises and administrations, for all people and in all circumstances. Since late May, the number of cases seemed to increase until the highest daily number (675 cases) reported on 24 July 2020 (Lounis 2021).

The department of Blida had recorded the highest nu mbers until 16 July 2020.Currently, the most affected departments are Algiers (4501), Oran (3407), Blida (3209) and Setif (2903). The least impacted departments include Saïda (63), Relizane (189), and Chlef (194) in the west, and Illizi (124), Tamenrasset (194), and Tindouf (195) in the south. The highest numbers of deaths were reported in the departments of Algiers (234), Blida (147) and Setif (120) while Saida had not recorded any deaths (Lounis., 2021). The national mortality rate is at 32 per million of population, with the highest rates in Blida (113.4 per million), Setif (69.6 per million), and Algiers (66.5 per million). The national case fatality rate is about 3.5% as shown in figure 32.

Since 3 August, Algerian authorities have taken a second step toward loosening control strategies by reopening beaches, religious and public areas in conjunction with a curfew reduction. On 15 August, it was decided to reopen mosques (with more than 1000 people), cafés, restaurants, and other commercial activities in conjunction with targeted containment for certain most affected territories. Lastly, it has recorded 42 619 infected cases, making it one of the most affected countries in Africa and 29 886 persons have recovered from this disease, representing a rate of recovery of 70.1% on 25 August 2020, it is also the third country in terms of deaths, with 1465 deaths (Lounis 2021).

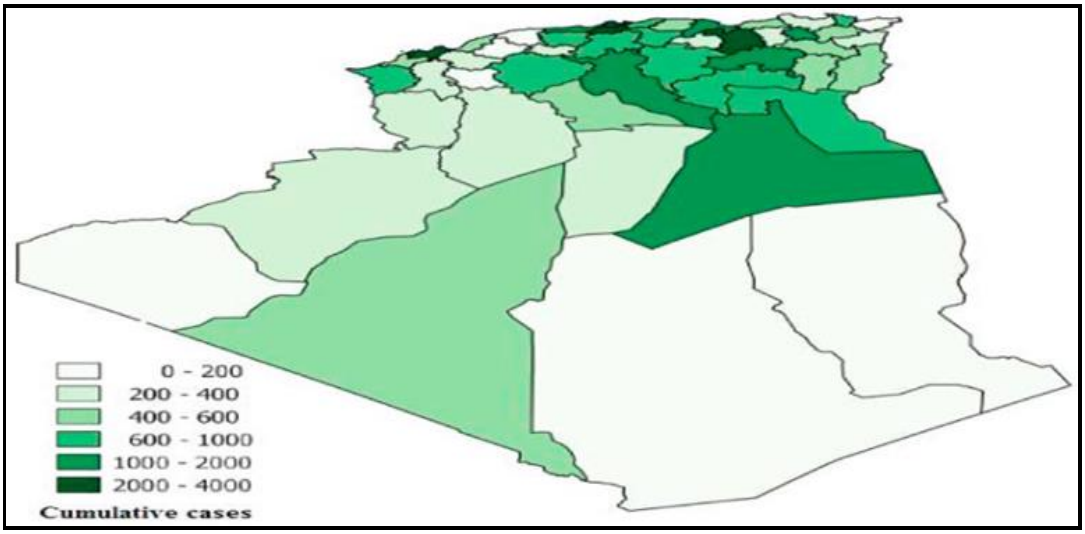

Figure 32: Geographic repartition of COVID-19 cases in Algeria (Lounis 2021).

2.5.1.2 Second wave

After few months a new variant has appeared which is Beta variant, the number of infected cases has increased from October until the end of 2020, there were 16,411 new cases in the end of December, taking the total number of confirmed cases to 99 610. The death toll rose to 2,756. The number of recovered patients increased to 67 127. Algeria officially started the vaccination campaign at the end of January 2021 (WHO., 2022).

2.5.1.3 Third wave

Since May 3, 2021 another new variant is detected which is the Delta variant (VOC).

Since June 1, 2021, the partial reopening of air borders has been effective. Travelers must present a negative RT-PCR Covid test dated less than 36 hours on boarding and will have to carry out an antigen test at their own expense on arrival. However, land and sea borders remain closed (WHO., 2022). On September 13, 2021, the Government decided, under the health crisis management system linked to the COVID-19 pandemic, to rearrange the hours of partial confinement at home from 10 pm. to 5am.At the end of this month the total number of confirmed cases increased to 202 574. The death toll rose to 5767. The number of recovered patients increased to 138 737 (WHO., 2022).

2.5.1.4 Fourth wave

On December 15,2021, Algerian health authorities confirmed the detection of the first case of the Omicron COVID-19 variant, it dominated by rapid spread, reputed to be more contagious but less dangerous than Delta (WHO., 2020).

In January, there were 32 342 new cases. The Algerian authorities have had to close schools and universities since January 20 due to the spread of the pandemic. Decided for a period of 10 days, the measure has been extended until February 7(WHO., 2022).

The total number of confirmed cases increased to 265 671. The death toll rose to 6874. The number of recovered patients increased to 178,288, leaving 80,509 active cases at the end of March (WHO., 2022).

Part two

Practical part

Chapter three

Materiel and Method

3.1 Hospitals location

Patients included in the present study were admitted to 'Meghlaoui brother's' and 'Tobal brother's' hospitals. Their corresponding data has been archived in preventative facility in 'Sennaoua polyclinic' (Figure 33).

Figure 33: Meghlaoui brothers and Tobal brothers hospitals locations.

3.1.1 Tobal brother's hospital presentation

The public healthcare institution "Brothers Tobal" was established under the executive decree No 140-07 dated on the 2nd of Jumada 1, 1428 that corresponds to May,19 2007, which includes the establishment, management and organization of public health institutions and local public health establishments according to Articles 02 to 05 of this decree. As for its management and organization, according to articles 10 to 33. This establishment is located in the chief of the Wilaya next to the court. The hospital covers an area of 26531 m^2 of which 1783 m2 is built.

The Tobal Brothers Hospital Institution contains 106 equipped beds for the year 2021 (Figure 34).

Figure 34: Tobal brothers hospital

The hospital includes two departments: Hospital facilities (Figure 35), and administrative department (Figure 36).

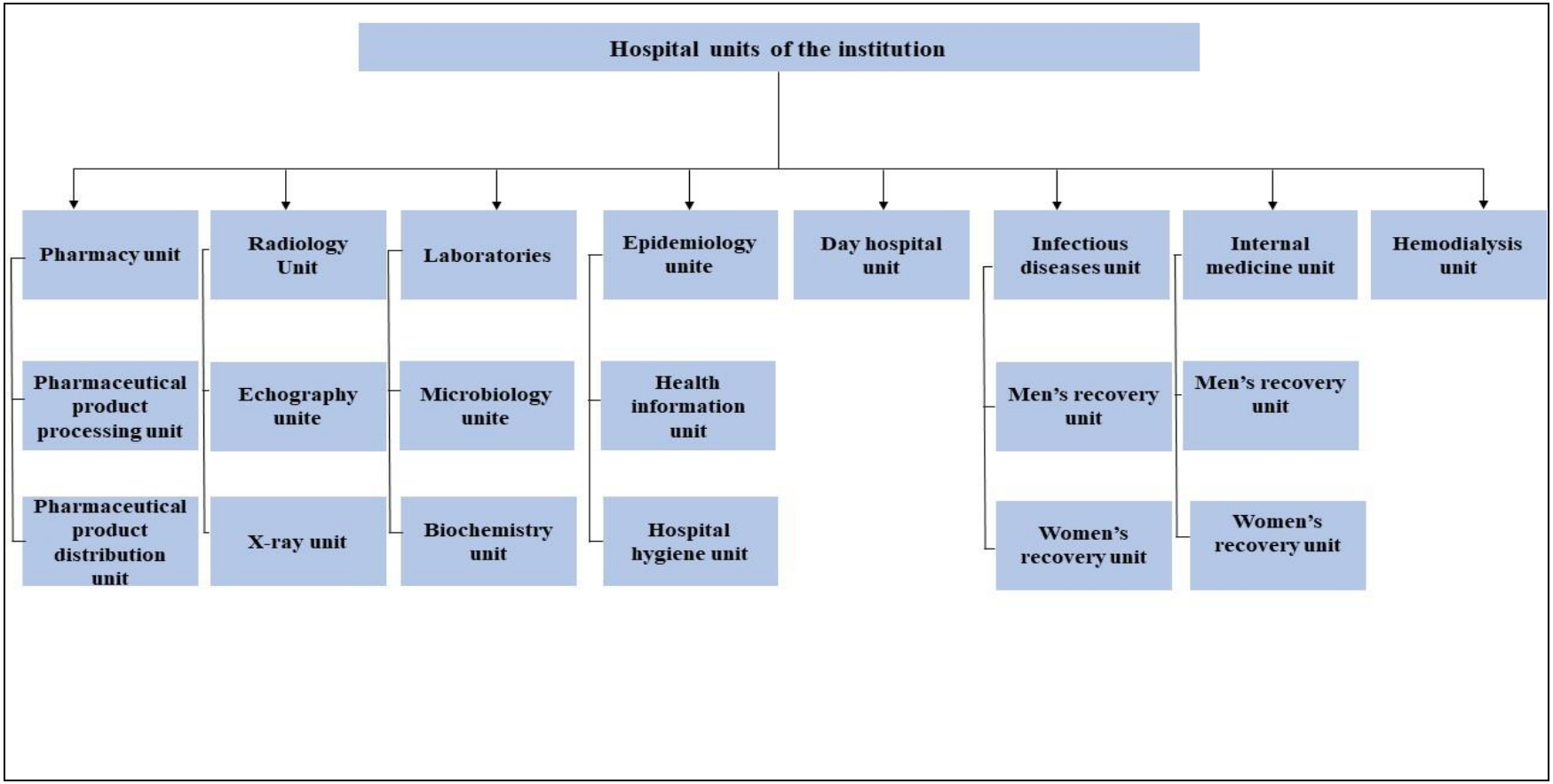

Figure 35: Tobal brothers hospital units.

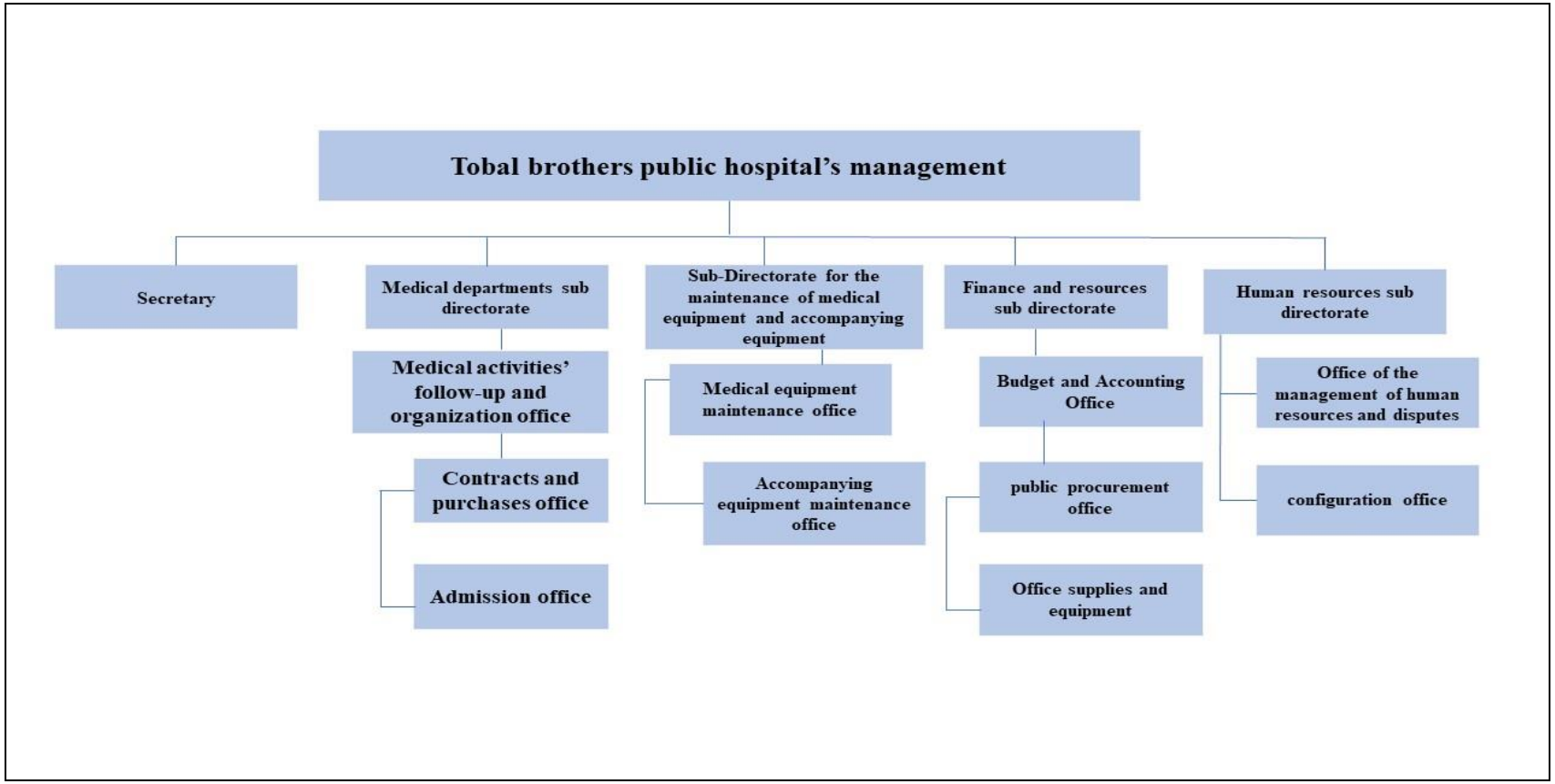

Figure 36: Tobal brothers hospital management.

3.1.2 Meghlaoui Brothers Hospital

Meghloui Brothers hospital was established on January, 1st 2008 after the health sector's reorganization according to the new health map and the executive decree Nº140/07 dated on Mai, 19 2007, regarding the establishment, organization and management of public hospital institutions and local public health establishment. This hospital was the center of the health sector for 8 municipalities. It employs 421 persons and contains 146 equipped beds. Its main mission is providing medical treatment for several diseases in addition to emergency care and general surgery. In order to accomplish these tasks, many medical and administrative facilities were established (Figure 37, 38).

Figure 37: Meghlaoui brothers hospital.

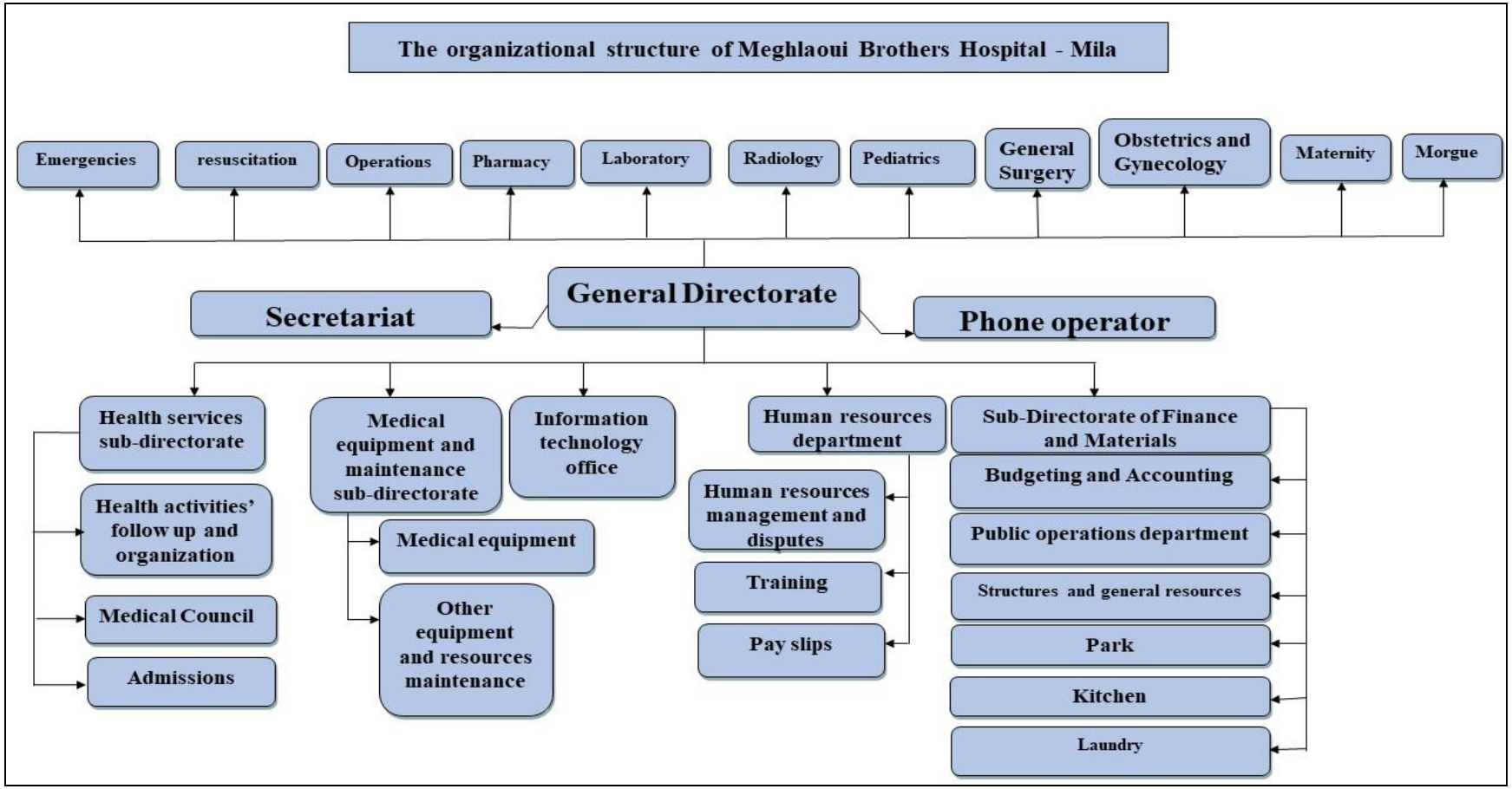

Figure 38: organization of Meghlaoui brothers medical and administrative units.

3.2.1 Investigation

Our retrospective study aimed to investigate coronavirus epidemiology in Mila district - north east of Algeria. The study relied on gathering and analyzing clinical data of patients that were admitted to both 'Meghlaoui brother's' and 'Tobal brother's' hospitals. During the four waves of coronavirus outbreak these two Hospitals received 3175 of confirmed cases (Tobal brother's' hospital received 1575 cases, whereas Meghloui Brothers' Hospital received about 1600 cases). During our training period, we examined medical files that were archived in preventative facility in 'Sennaoua polyclinic'. This study focused on hospitalized patients that were confirmed to be infected by coronavirus by a computed tomography scan (CT scan), a polymerase chain reaction (PCR), or a rapid antigen test. Basically, our study is a descriptive and analytic epidemiological study of the spread of coronavirus outbreak in north east of Algeria, as well as its development and factors affecting state of health of Algerian population. During our two months training period we analyzed clinical data of patients hospitalized from march 2020 (when the first case was reported) to February 2022. Clinical data we analyzed were: age, sex, symptoms such as fever, cough, asthenia, dehydration, shortness of breath and dyspnea, antecedent, patient's tests, hospital stay, region, vaccinated patients or not and mortality as advised by the Ministry of Health and Population which provide instructions to follow for suspected patients in hospitals (Annex 1).

3.3 Patients

We retrieved clinical data from 957 patients that were admitted to the two hospitals during the four waves of coronavirus outbreak. Hospital admission decision was based on clinical data of patients with symptoms that predicted a coronavirus infection such as fever, low oxygen, clinical state, old age or a positive test showed by the patient. These patients required to stay in the hospital for medical follow-up. However, patients with moderate symptoms were returned to home confinement due to the lack of medical equipments and beds.

These patients were daily followed by phone during their confinement period and for whom an adequate treatment was proposed to ensure the improvement of their health. A psychological cell was created for their family members in order to improve their mental health.

3.4 Clinical and statistical data analysis

Clinical data were summarized into excel sheets to create our work database that used for result`s deduction and interpretation. Clinical data were first analyzed globally, and then compared depending on age, sex, coronavirus variant type and mortality.

Statistical data analysis was performed using graph pad (https://www.graphpad.com). We provide descriptive statistics as frequencies, mean ±SD. We compared categorical variables by using $\chi 2$, Fischer exact test or t-student test when possible. We considered p value<0.05 statistically significant.

Chapter four

Results

4.1 Distribution of COVID-19 cases

In this retrospective study, 957 cases were confirmed in 16 communes. It's indicated that the spread of COVID-19 was relatively quick. The confirmed cases were geographically localized as follows: Mila city (365; 38%), Grarem Gouga (290; 33%), Sidi Merouane (124; 13%), Zeghaia (79;8%), Chigara (35; 4%), Hamala (25; 3%), Ain Tinne (18; 2%), Azzaba and Sidi Khelifa respectively (6,5; 1%), Amira Arres, Ahmed Rachdi, Beinan, Redjas, Tassala, Zarza, Ferdjioua are the remaining cities with the fewest cases (Figure 39).

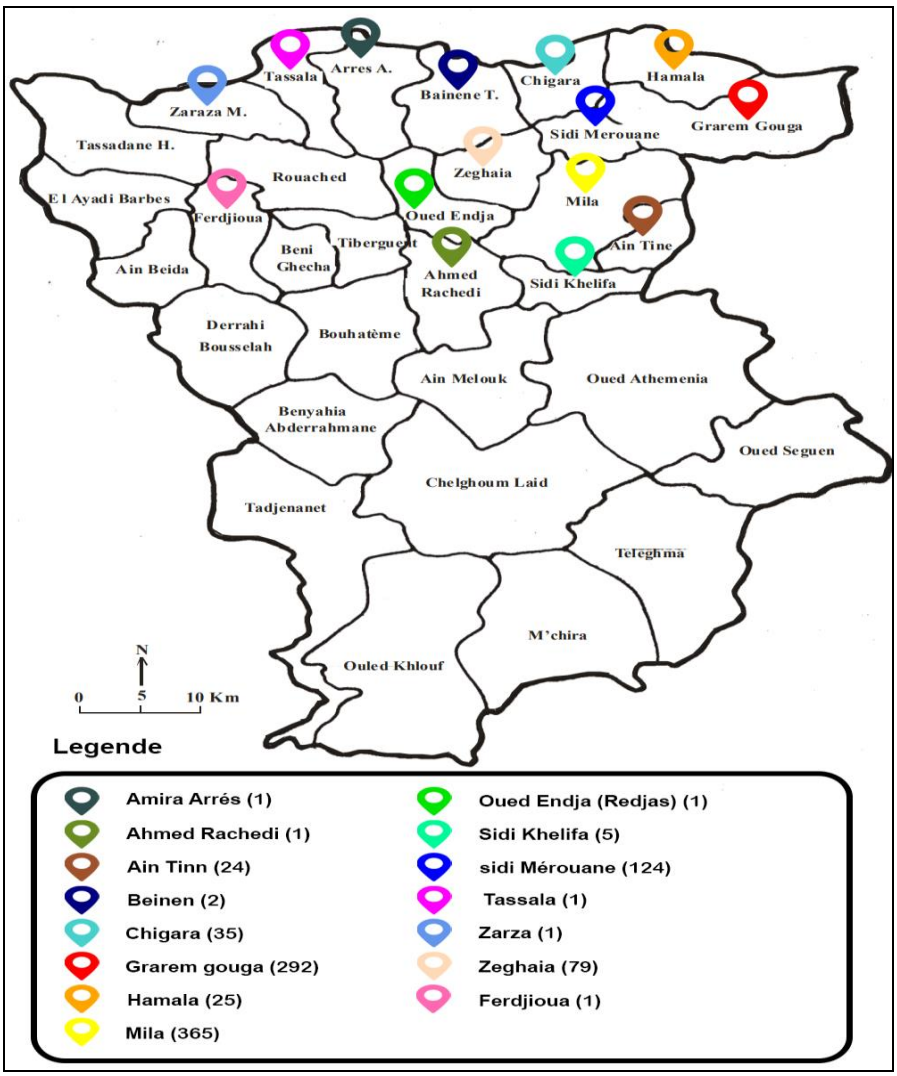

Figure 39: Distribution of COVID-19 cases in Mila district.

4.2 General clinical data analysis

First, we globally analyzed clinical data of all patients to determine their frequencies. Then these clinical data were studied between men and women, between age ranged cohorts (18-65; >65), between survivors and dead and finally among wave's cohorts patients. These clinical data are significant indicators of health stat of patients (severe, moderate). The frequencies of different clinical data are represented in tables and graphs below. Clinical data are provided as symptom frequency or as mean plus or minus the standard deviation (mean ± SD) to facilitate the interpretation of the results.

In our epidemiological research, clinical data from 957 COVID-19 patients was studied. Of whom, 440 (46%) were women and 517 (54%) were men (Figure 40).

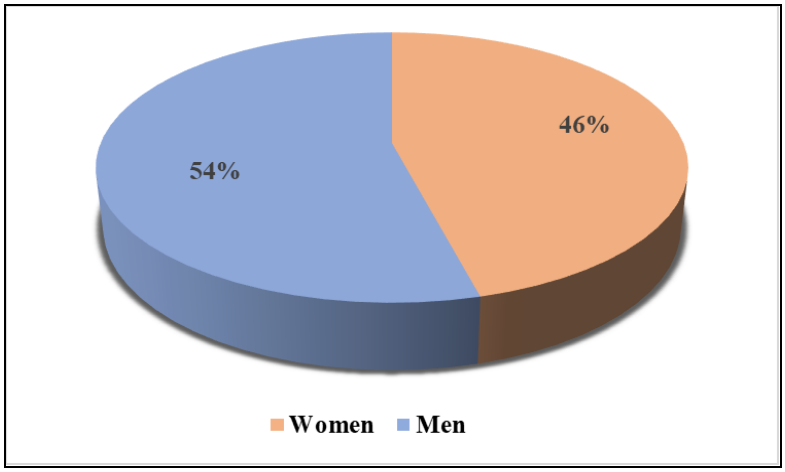

Figure 40: Coronavirus number of cases in Mila district by gender.

In addition, patients included in the present study seem to be elderly with a median age of 58 ±18 (range 1-111 years). Moreover, most coronavirus symptoms that were frequently observed among our patients were as follow: fever (649, 68%), cough (482, 50%), asthenia (667, 70%), headache (203, 21%), dyspnea (451,47%), oxygen deficiency (254, 27%) and shortness of breath (66, 7%).

As predicted, such symptoms are highly previously reported to be associated to coronavirus infection. Otherwise, other symptoms such as muscular pain (106, 11%); diarrhea and anosmia (54, 6%), anorexia (28, 3%) and abdominal pain (51, 5%) were observed as the less prevalent symptoms. Otherwise, coexisting diseases are known to be an important risk factors of mortality. In our study, frequency of coexisting diseases was as follow: cardiovascular disease (96, 10%), hypertension (251, 26%), insulin dependent diabetes mellitues (193, 20%), non- insulin dependent diabetes (67, 7%) and breathing illness (30, 3%). Additionally, hospitalization period was known as drastic impact on hospital budget. In our study, the mean of hospital stay was 11±SD4 (3-30 days). Finally, mortality rate seems to be high among our hospitalized patients and reach 9% (table10).

Table 10: clinical data of coronavirus cases (march 2020-februry 2022).

Clinical Data	Frequency, n (%)
Patients total number, N	957
Age (mean ±SD)	58 ± 18
Fever (> 38°C)	649 (68%)
Cough	482 (50%)
Headache	203 (21%)
Asthenia	667 (70%)
Sore Throat	15 (2%)
Shortness of breath	66 (7%)
Dyspnea	451(47%)
Oxygen Deficiency (< 90 %)	254 (27%)
Muscular Pain	106 (11%)
Diarrhea	54 (6%)
Anosmia	54 (6%)
Anorexia	28 (3%)
Abdominal Pain	51 (5%)
Dehydration	10 (1%)
Vomiting	25 (3%)
HTN	251 (26%)
Other CVD	96 (10%)
IDDM	193 (20%)
NIDD	67 (7%)
Breathing Illness	30 (3%)
Hospital admitted patients	782 (80%)
Positive PCR test	258 (27%)

Positive CT scan	665 (69%)
Rapid antigen test	247 (26%)
Vaccinated	6 (2%)
Hospital stay	11±4
Mortality	86 (9%)

N, Patients total number; n (%), Clinical data frequencies; SD, standard deviation; CVD, Cardiovascular diseases; HTN, Hypertension; IDDM, Insulin dependent diabetes mellitues; NIDD, Non-insulin dependent diabetes PCR, Polymerase chain reaction; CT scan, Computed tomography scan.

4.3 Clinical data analysis depending on sex

In our study, as previously showed, Men (54%) constituted a higher proportion of COVID-19 cases than women (46%) (Table 11). our results showed that the mean age was significantly higher among men (60 ±17) compared to women (56 ± 19); P=0.0006. Among men, frequent symptoms including fever (69%), asthenia (70%), shortness of breath (9%), dyspnea (50%) and oxygen deficiency (30%) were frequently than among women. Of them, shortness of breath (P=0.0016), oxygen deficiency (P=0.0171) and dyspnea (P=0.0460) were statistically significant.

In inverse, symptoms that was more likely observed among women were, headache (25%), muscular pain (13%), anosmia (8%), abdominal pain (7%) and sort throat (2%). Whitin theme, headache (P=0.0129), anosmia (P=0.0216), muscular pain (P=0.0555) and abdominal pain (P=0.0135) were statistically significant.

In addition, the severity of the coronavirus infection was more likely to be associated with certain coexisting chronic diseases, which appeared among women respectively as follow: hypertension (29%) and insulin dependent diabetes mellitues (23%). In contrary non-insulin dependent diabetes was highly appeared among men (8%) comparing to women (5%), except for cardiovascular disease it was equal in both women and men cohorts. Concerning our patients mean of hospitalization period, it was equal in the two cohorts (11 days). Finally, the case mortality rate was seeming to be higher in men cohort (10%) compared to women (8%), although it was not statistically significant.

Table 11: Epidemiological characteristics of coronavirus patients by sex.

Clinical Data	Frequency, n (%)		P -value
sex	Female	Male	
Patients total number, N	440(46%)	517(54%)	**0.0004**
Age (mean ±SD)	56 ± 19	60 ±17	**0.0006**
Fever (> 38°C)	293 (67%)	356 (69%)	0.3523
Cough	230 (52%)	252 (49%)	0.2764
Headache	109 (25%)	94 (18%)	**0.0129**
Asthenia	303 (69%)	364 (70%)	0.6048
Sore Throat	9 (2%)	6 (1%)	0.2720
Shortness of breath	18 (4%)	48 (9%)	**0.0016**
Dyspnea	192 (44%)	259 (50%)	**0.0460**
Oxygen Deficiency (< 90 %)	98 (22%)	156 (30%)	**0.0171**
Muscular Pain	58 (13%)	48 (9%)	**0.0555**
Diarrhea	25 (6%)	29 (6%)	0.9613
Anosmia	33 (8%)	21 (4%)	**0.0216**
Anorexia	14 (3%)	14 (3%)	0.6646
Abdominal Pain	32 (7%)	19 (4%)	**0.0135**
Dehydration	6 (1%)	4 (0.7%)	0.3711
Vomiting	16 (4%)	9 (2%)	0.0669
HTN	127 (29%)	124 (24%)	0.1820
Other CVD	46 (10%)	50 (10%)	0.6877
IDDM	100 (23%)	93 (18%)	0.0686
NIDD	24 (5%)	43 (8%)	0.0837
Breathing Illness	16 (4%)	14 (3%)	0.4114
Hospital admitted patients	342 (78%)	440 (85%)	**0.0032**
Positive PCR test	98 (22%)	160 (30%)	**0.0026**
Positive CT scan	290 (66%)	375 (73%)	**0.0265**
Rapid antigen test	128 (29%)	119 (23%)	**0.0324**
Hospital stay	11± 3	11± 4	1.000
Mortality	36 (8%)	51 (10%)	0.3031

N, Patients total number; n (%), Clinical data frequencies; SD, standard deviation; CVD, Cardiovascular diseases; HTN, Hypertension; IDDM, Insulin dependent diabetes mellitues; NIDD, Non-insulin dependent diabetes PCR, Polymerase chain reaction; CT scan, Computed tomography scan; P-value, Probability value.

4.4 Clinical data analysis depending on age range

To evaluate a probable effect of the age on the severity of the infection we separated our coronavirus patients into two cohorts based on their age. The first cohort included these aged from 18 to 65 years while the second one included these aged more than 65 years. Among our 957 patients studied herein, 563 were aged from 18 and 65 years, and 379 were over 65 years (Figure 41). In both cohorts' men were dominated women (289 men vs 274 women in the first cohort, while in the second, 219 were men and 160 were women) (Figure 42).

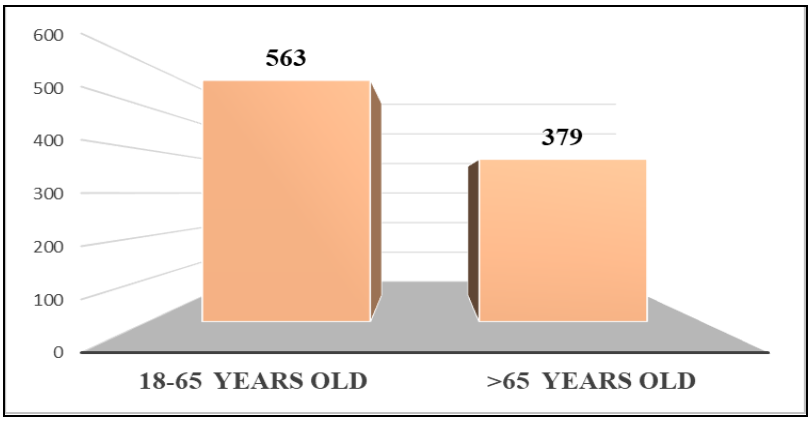

Figure 41: Patients distrubution in the two cohorts depending on age.

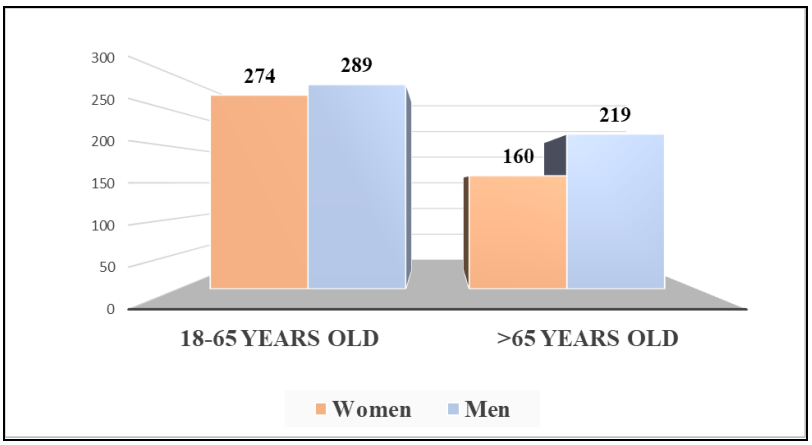

Figure 42: Patients distribution in the two cohorts depending on age by gender.

Clinical data of patients in both cohorts are sumarized in Table 12. In more detail, our results showed that symtoms such as fever, cough, headeach, muscular pain and abdominal pain were significatly more frequently observed in the first cohort than in patients over 65 years (Table12). Otherwise, while the difference was not statistically significant, asthenia anosmia were slightly more frequent in the first cohort than in the second.

In the opposite, dyspnea and oxygen deficiency were statistically more frequent in elderly patients (second cohort) compared to those under 65 years (first cohort). Likely, elderly patients seem to be significantly suffered from chronic diseases such as cardiovascular diseases, hypertension and insulin dependent diabetes mellitues than those aged under 65 years (P=0.0250,

P=0.001, P=0.0001). Finally, as predicted, our results showed that hospital stay and mortality rate seem to be higher among elderly patients.

Table 12: Clinical data distribution by age range.

Clinical Data	**Age range (Number of cases)**		**P- value**
Patients total number, (N)	**18-65 (563)**	**>65 (379)**	
Age (mean ±SD)	48±12	76±9	-
Fever (> 38°C)	397 (71%)	240 (63%)	**0.0481**
Cough	315 (56%)	161 (42%)	**0.0001**
Headache	154 (27%)	43 (11%)	**0.0001**
Asthenia	405 (71%)	254 (67%)	0.1064
Sore Throat	10 (2%)	3 (1%)	0.2040
Shortness of breath	34 (6%)	32 (8%)	0.1563
Dyspnea	238 (42%)	211 (56%)	**0.0001**
Oxygen Deficiency (< 90 %)	120 (21%)	134 (36%)	**0.0001**
Muscular Pain	75 (13%)	27 (7%)	**0.0027**
Diarrhea	30 (5%)	23 (6%)	0.6289
Anosmia	38 (7%)	15 (4%)	0.0682
Anorexia	16 (3%)	12 (3%)	0.7738
Abdominal Pain	37 (7%)	11 (3%)	**0.0120**
Dehydration	5 (1%)	4 (1%)	0.7957
Vomiting	13 (2%)	11 (3%)	0.5709
HTN	93 (17%)	158 (42%)	**0.0001**

Other CVD	29 (5%)	66 (18%)	**0.0250**
IDDM	86 (15%)	107 (28%)	**0.0001**
NIDD	44 (8%)	23 (6%)	0.3064
Breathing Illness	17 (3%)	13 (3%)	0.7249
Hospital admitted patients	416 (74%)	249 (66%)	**0.0068**
Positive PCR test	140 (25%)	136 (36%)	**0.0003**
Positive CT scan	349 (62%)	237 (63%)	0.8660
Rapid antigen test	177 (31%)	80 (21%)	**0.0005**
Vaccinated	1 (0.2%)	5 (1%)	**0.0308**
Hospital stay	10± 4	11± 4	**0.0002**
Mortality	44 (8%)	44 (12%)	**0.0497**

N, Patients total number; n (%), Clinical data frequencies; SD, Standard deviation; CVD, Cardiovascular diseases; HTN, Hypertension; IDDM, Insulin dependent diabetes mellitues; NIDD, Non-insulin dependent diabetes PCR, Polymerase chain reaction; CT scan, Computed tomography scan; P-value, Probability value.

4.5 Clinical data comparison between dead and survivors

To demonstrate the influence of age, common coronavirus symptoms and coexisting diseases on mortality rate we analyzed clinical data from coronavirus dead patients and compared to those from survivors. In our study, mortality rate was 9% (86 patients, of whom 36 (8%) were women and 51(10%) were men) (Figure 43).

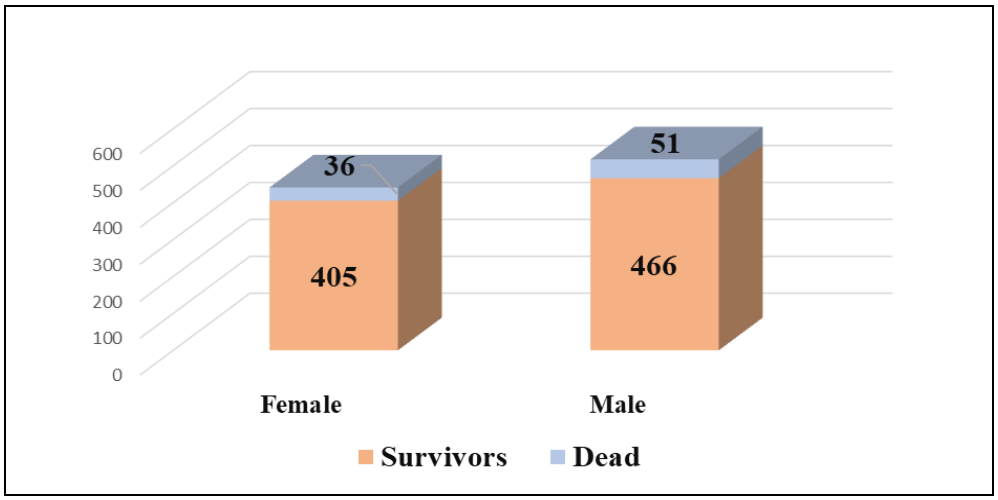

Figure 43: coronavirus mortality by sex.

Clinical data from both survivors and dead patients are summarized in table13. Our results showed that dead patients were significantly older than survivors with mean age that was 67 ±16 compared to survivors for whom the mean age was 58±18. Such result showed that late age may clearly increase the mortality risk. In addition to elder age, dead patient exhibited dyspnea and oxygen deficiency they were statistically more frequent in dead patients compared to survivors (P=0.0001). Moreover, dead patients seem to be significantly suffered from chronic diseases such as hypertension and insulin dependent diabetes mellitues. In contrast, symptoms such as cough, asthenia, shortness of breath and muscular pain were significantly more frequent amog survivors than among dead patients (Table 13). Otherwise, for other common coronavirus symptoms such as fever and headach, no significant adifference was observed.

Finally, our results showed that the mean of hospital stay of dead patients was significantly shorten compared to that of survivors (P=0.0001).

Table 13: Coronavirus clinical data distribution by age range.

Clinical Data	**Frequency, n (%)**		**p-value**
Patients total number, N	**Survivor (871)**	**Dead (86)**	
Age (mean ±SD)	58± 18	67±16	**0.0001**
Fever (> 38°C)	593 (68%)	56 (65%)	0.5743
Cough	452 (52%)	30 (35%)	**0.0026**
Headache	58 (7%)	8 (9%)	0.3561
Asthenia	617 (71%)	50 (58%)	**0.0145**
Sore Throat	14 (2%)	1 (1%)	0.7515
Shortness of breath	438 (50%)	13 (5%)	**0.0001**
Dyspnea	212 (24%)	42 (49%)	**0.0001**
Oxygen Deficiency (< 90 %)	80 (9%)	26 (30%)	**0.0001**
Muscular Pain	199 (23%)	4 (5%)	**0.0001**
Diarrhea	49 (6%)	5 (6%)	0.9425
Anosmia	51 (6%)	3 (3%)	0.3641
Anorexia	26 (3%)	2 (2%)	0.7292
Abdominal Pain	47 (5%)	4 (5%)	0.7692
Dehydration	10 (1%)	0 (0%)	0.3178
Vomiting	23 (3%)	2 (2%)	0.8613

HTN	218 (25%)	33 (38%)	**0.0073**
Other CVD	86 (10%)	10 (12%)	0.6054
IDDM	161 (18%)	32 (37%)	**0.0001**
NIDD	62 (7%)	5 (6%)	0.6511
Breathing Illness	25 (3%)	5 (6%)	0.1350
Hospital admitted patients	702 (81%)	80 (93%)	**0.0045**
Positive PCR test	232 (27%)	26 (30%)	0.4733
Positive CT scan	602 (69%)	63 (73%)	0.4264
Rapid antigen test	237 (27%)	10 (12%)	**0.0016**
Vaccinated	4 (0.4%)	2 (2%)	**0.0364**
Hospital stay	11± 3	7±7	**0.0001**

N, Patients total number; n (%), Clinical data frequencies; SD, standard of deviation; CVD, Cardiovascular diseases; HTN, Hypertension; IDDM, Insulin dependent diabetes mellitues; NIDD, Non-insulin dependent diabetes PCR, Polymerase chain reaction; CT scan, Computed tomography scan; P-value, Probability value.

4.6 Clinical data analysis depending in coronavirus variants

From its discovery, SARS-CoV-2 had developed several mutations. Some mutations did not have a great impact neither on the health of patients nor on mortality rate. However, there were some others mutations that have been caused concerns. To clarify knowledge about how novel coronavirus variants impact our patients, clinical data from the four precedent coronavirus waves were analyzed separately (Figure 44). In the present study, first wave included 382 patients (145 women and 237men), the second included 11 patients (3 women and 8 men), the third included 237 patients (132 women and 105 men) and the fourth one included 327 patients (160 women and 167men) (Figure 45).

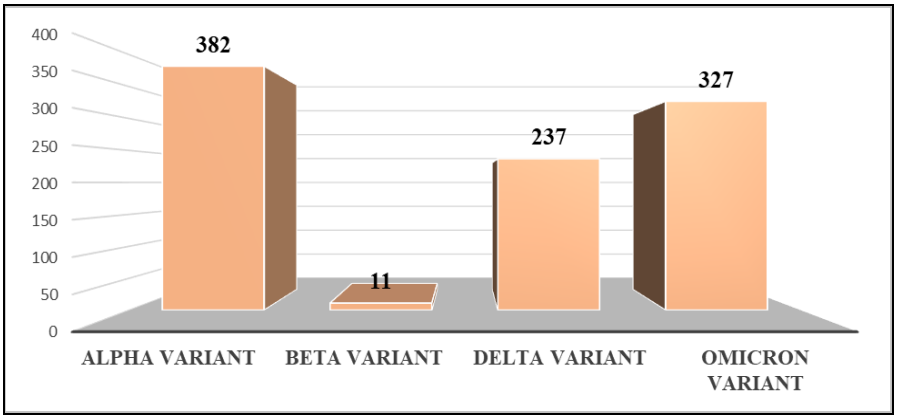

Figure 44 : Coronavirus number of cases by variant.

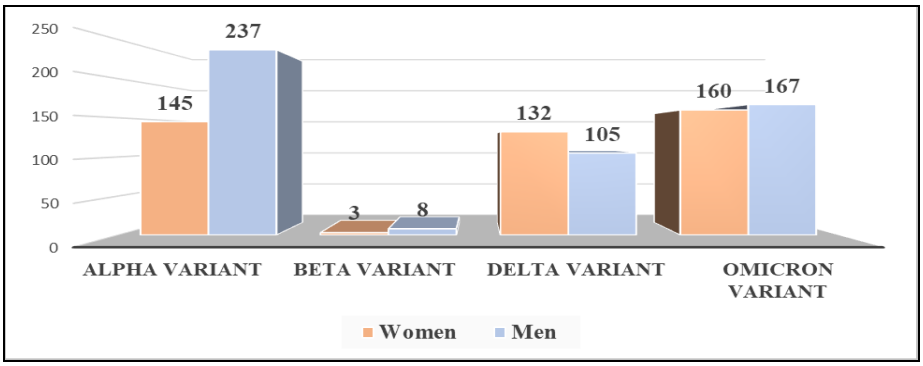

Figure 45: Coronavirus number of cases by sex in each wave.

Clinical data from the four waves are presented in table 14. In more detail, patients median age was considered as one of the important factors of hospitalization, it seems that patients from the three first waves were elderly compared to omicron variant wave.

In addition, coronavirus most common symptoms such as fever, asthenia and cough were more frequent when patients were infected by Alpha and Beta variants rather than in Delta and Omicron episodes (Table14). Other common symptoms such as headache and shortness of breath seem to be more frequent when infection by Omicron and Alpha variants was occurred respectively.

Unlikely, oxygen deficiency and muscular pain were particularly more frequently observed from second wave patients (beta variant infection) to the last wave (Omicron variant infection).

Concerning coexisting diseases, our results showed that hypertension (45%), insulin dependent diabetes (36%) and other cardiovascular disease (27%) were more frequent in the beta wave variant compared to the three others variants. Unlikely, non-insulin dependent diabetes was more frequent among alpha variant-infected patients.

Finally, for hospital stay, our study showed that prolonged hospital stay was particularly observed among patients from the first wave of coronavirus infection (alpha variant). Concerning mortality rate, it was highly more frequent among patients from the second wave (patients infected with beta variant). However, this mortality rate in the second wave may not be representative due the low number of patients included in this wave.

Table 14: Clinical data of patients in the four waves.

Wave number	wave one (Alpha variant)	wave two (Beta variant)	wave three (Delta variant)	wave four (Omicron variant)
Patients total number, N	382 (40%)	11 (1%)	237 (25%)	327 (34%)
Age (mean ±SD)	61±52	59 ± 11	59 ±20	54±20
Fever (> 38°C)	326 (85%)	8 (73%)	129 (54%)	186 (57%)
Cough	239 (63%)	6 (55%)	87 (37%)	150 (46%)
Headache	60 (16%)	1 (9%)	47 (20%)	95 (29%)
Asthenia	318 (83%)	8 (73%)	146 (62%)	195 (60%)
Sore Throat	11 (3%)	0 (0%)	2 (1%)	2 (1%)
Shortness of breath	60 (16%)	0 (0%)	6 (3%)	0 (0%)
Dyspnea	195 (51%)	7 (64%)	111 (47%)	138 (42%)
Oxygen Deficiency (< 90 %)	69 (18%)	4 (36%)	106 (45%)	75 (23%)
Muscular Pain	27 (7%)	2 (18%)	31 (13%)	46 (14%)
Diarrhea	18 (5%)	0 (0%)	20 (8%)	16 (5%)

Anosmia	27 (7%)	0 (0%)	12 (5%)	15 (6%)
Anorexia	17 (4%)	1 (9%)	7 (3%)	3 (1%)
Abdominal Pain	14 (4%)	0 (0%)	18 (8%)	19 (6%)
Dehydration	3 (1%)	1 (9%)	5 (2%)	1 (0,3%)
Vomiting	11 (3%)	0 (0%)	11 (5%)	3 (1%)
HTN	118 (31%)	5 (45%)	70 (30%)	58 (18%)
Other CVD	46 (12%)	3 (27%)	30 (13%)	17 (5%)
IDDM	88 (23%)	4 (36%)	61 (26%)	40 (12%)
NIDD	51 (13%)	1 (9%)	3 (1%)	12 (4%)
Breathing Illness	20 (5%)	0 (0%)	4 (2%)	6 (2%)
Hospital admitted patients	365 (96%)	11 (100%)	204 (86%)	202 (62%)
Positive PCR test	175 (46%)	5 (45%)	28 (12%)	50 (15%)
Positive CT scan	342 (90%)	9 (82%)	155 (65%)	159 (49%)
Rapid antigen test	2 (1%)	0 (0%)	75 (32%)	170 (52%)
Vaccinated	0 (0%)	0 (0%)	0 (0%)	6 (2%)
Hospital stay	13±4	9±2	10 ± 2	8±2
Mortality	43 (12%)	3 (27%)	26 (11%)	14 (4%)

N, Patients total number; n (%), Clinical data frequencies; SD, standard of deviation; CVD, Cardiovascular diseases; HTN, Hypertension; IDDM, Insulin dependent diabetes mellitues; NIDD, Non-insulin dependent diabetes PCR, Polymerase chain reaction; CT scan, Computed tomography scan.

Chapter five

Discussion

5. Discussion

The coronavirus disease 19 (COVID-19) is a highly contagious and pathogenic viral infection caused by the SARS-Coronavirus-2 (SARS-CoV-2). It may cause several symptoms that variate from moderate to severe. Our epidemiological study based on 957 COVID-19 cases, provided clinical characteristics of coronavirus patients who were leaving in Mila district and admitted to "Meghlaoui and Tobal brothers hospitals".

First of all, we studied the frequency of coronavirus clinical data exhibited by our patients particularly common symptoms, coexisting diseases, hospital stay and mortality rate among others. Then we conducted a comparative analysis to show the variation of these clinical data depending on sex, on age range, between dead and survivors and depending on coronavirus variants.

As primary outcome, our study showed a strict correlation between number of coronavirus-infected individuals and the population density in different regions of Mila districts (Figure 38), considering the impact of the population density on the spread of COVID-19. This result seems to be in concordance with what had been demonstrated previously by Arif and Sengupta in 2021 who clearly showed that the number of confirmed cases increased in high-density regions, and decreased in medium to low density areas (Arif and Sengupta., 2021).

Concerning coronavirus symptoms, SARS-CoV-2-infected individuals ranged from mild non-specific symptoms to severe pneumonia with organs-failed functions. In the present study, fever, cough, asthenia, headache, dyspnea and oxygen deficiency were more frequently observed among our patients. These symptoms are frequently reported as prevalent symptoms (Ge *et al*., 2020). Others less common such as sore throat, rhinorrhea, chest discomfort, hemoptysis, conjunctival congestion, diarrhea, nausea, myalgia, sputum production and vomiting were also reported (Ge *et al*., 2020).

In addition, concerning the effect of gender on the COVID-19 propagation, our epidemiological results showed that men (54%) are more susceptible to COVID-19 infection compared to women (46%).

Similarly, the mortality rate was higher among men compared to women (Table 11). At the beginning of the coronavirus outbreak, and according to a study conducted by the department of Pharmaceutical and Pharmacological Sciences (DSF), University of Padova, Italy in 2020, the cause of this difference between genders was unclear. The authors associated these results to differences in sex hormones and living styles that are thought to have a role in the patient's sensitivity to severe SARS-CoV-2 outcomes (Froldi et Dorigo., 2020). Infectivity studies by Zhou and colleagues revealed that ACE2 was required for SARS-CoV-2 to penetrate Cells (Zhao *et al*., 2020). These results indicate that ACE2 is the SARS-CoV-2 receptor. This showed that an organism with high ACE2 protein expression has an easier way causing coronavirus pathogenesis, according to the results, Asian males showed more levels of ACE 2 expression than Asian females. Furthermore, there was evidence of heterogeneity in ACE 2 expression between ethnicities (Cao *et al*., 2020). Finally, there are biological variations in men and women's immune systems that may affect our ability to fight infections like SARS-CoV-2. Females are generally more resistant to infections than men, and this may be mediated by a number of variables, including sex hormones and high expression of coronavirus receptors (ACE 2) in men, as well as lifestyle factors, such as smoking and drinking at higher rates in men than in women even more, women are more responsible than men when it comes to the COVID-19 epidemic (Bwire 2020).

Concerning age range distribution, our results showed that coronavirus affect younger adult (563, aged 18-65 years) than old adult (379, aged more than 65 years) (Table 12). In contrast, however, the mortality rate was higher among older adults (Table 13). There are various scientific explanations for why COVID-19 was more harmful with high mortality rates in older individuals (Crimmins., 2020). Different studies showed that the capacity of the host immune response to control viral infections declines with age. Impaired innate and adaptive immune responses may enhance virus susceptibility as getting older due to the fact that COVID-19 was a novel virus that had never been seen before, and thus having more immune cells available to combat it is essential (Channappanavar et Perlman., 2020). Furthermore, the availability of native T cells and the ratio of CD4/CD8 T cells to recognize any new pathogen declines as people get older, and this depletion has been linked to poor COVID-19 responses.

Discussion

Low CD4/CD8 counts were frequently used as an indicator of immunosenescence (Crimmins., 2020). Besides, human coronavirus infection causes an early rise of IFN-I and IL-12 responses, as well as regulated proinflammatory cytokine/chemokine production, in young adult, resulting in efficient adaptive

immunity and viral clearance (Channappanavar et Perlman., 2020). Additionally, old adults may develop diminished and delayed IFN-I and IL-12 responses, as well as excessive proinflammatory cytokine/chemokine responses resulting in excessive inflammation, a slowed adaptive immune response and deadly pneumonia (Channappanavar et Perlman., 2020).

Moreover, severity of COVID-19 in older people was that they are more likely to have underlying diseases such as heart disease, hypertension, diabetes, and lung disease, and COVID-19 mortality was increased in individuals with underlying conditions. These diseases might be related to COVID-19 because they're linked to higher levels of angiotensin-converting enzyme 2, even more, increased levels of inflammation are connected to these diseases. In addition to what was mentioned previously, differences in social contact and living circumstances affect the age structure of who becomes infected (Crimmins., 2020).

Furthermore, our study demonstrated that headaches was more prevalent among younger adults. In a previous study by Al-Hashel and colleges showed that COVID-19-related headaches significantly increased in younger persons with main headache illnesses. In the same study, male gender, younger age, and moderate COVID-19 infection were all linked to high pain severity (Al-Hashel *et al*., 2021).

Otherwise, this study found that adult younger patients were more likely to develop fever than adult old patients. A study by Mori and colleagues who compared symptoms from young patients to these from elderly patients revealed that the most common symptom among the young group was fever (41 in elderly group (47.1%) compared to 77 (77%) in young group, $p < 0.0001$) (Mori *et al*., 2021). These findings suggest that there may be variations in disease development and progression between younger and older individuals. One proposed theory is that in severely sick COVID-19 patients, cellular hyperfunctions of older individuals were more likely to convert to cellular depletion, resulting in function loss in the late stages (Tan *et al*., 2020).

Moreover, our study clearly confirms results from previous similar studies who showed that mortality rate highly increased among the elderly coronavirus-infected individuals with pre-existing comorbidities, such as diabetes, hypertension and other cardiovascular diseases. In the light of our statistics, diabetic patients were more susceptible to COVID-19 infection and developed a more severe form of the infection as a result. This might be due in part to the metabolic syndrome's systemic inflammatory state and prothrombotic environment (Gangadharan *et al*.,2021). Individuals with type 2 diabetes as part of a metabolic syndrome have increased renin angiotensin system (RAS) activation, which leads to the development of diabetic complications such as micro and macrovascular diseases. In the other hand, RAS and its regulator ACE2 enhance the entrance of SARS-CoV-2 into the human body. RAS and ACE2 play critical roles in the physiological function of the kidneys, heart, and lungs (Gangadharan *et al*., 2021).

In addition, hypertension is frequently observed in the elderly, and older persons tend to be of high risk of developing severe COVID-19 symptoms. Hypertension was related with an increased risk of infection who may lead to severe lung damages. However, considering that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were frequently used to treat hypertension and other kinds of cardiovascular disorders, both of which were common in COVID-19 patients, and that SARS-Cov-2, the virus that causes COVID-19, attaches to ACE2 in the lung to enter cells, doubts have been raised regarding whether these treatments are useful or really damaging to patients who are taking them. It has previously been demonstrated that ACE inhibitors and ARBs may raise ACE2 expression, which might possibly increase SARS-CoV-2 lung binding, resulting in increased lung damage (Schiffrin *et al*., 2020). However, actually, there is no evidence that hypertension is linked to COVID-19 outcomes, or that using an ACE inhibitor or an ARBs during the COVID-19 pandemic is unadvised. The use of these drugs for blood pressure regulation should be maintained, and they should not be discontinued, at least not based on current data (Schiffrin *et al*., 2020).

We also previously considered patients suffering from diabetes, hypertension, and heart disease mostly their conditions develop and become severely infected (severe COVID-19 infection).

Discussion

One of indicators of coronavirus infection severity was acute respiratory distress syndrome (ARDS). Although COVID-19 targets primarily lung cells (as ACE2 is abundantly expressed in type II lung alveolar cells), which may lead to alterations in cellular junctions in alveolar tissue, increasing vascular permeability and eventually alveolar fluid leaks. As a result of these cellular alterations, ARDS patients develop pulmonary edema, which may furtherly lead to an increase in dysregulated epithelial cell remodeling, which might contribute to pulmonary fibrosis that is a significant cause of death among ARDS patients (Pollard *et al*., 2020 and Perrotta *et al*., 2020).

Otherwise, our results showed different patterns of infection depending on coronavirus variants. In fact, our study showed that patients from the alpha, beta and delta variants were elderly compared to omicron variant wave which seems to affected preferentially younger individuals (Table 14). Also, omicron-infected patients seem to have shorter lengths of hospital stay and reduced mortality rate.

Additionally, although beta variant infected individuals were significantly lower compared to alpha variant patients (P=0.0001), fever, cough and asthenia were frequent among both alpha and beta infected patients. In contrast, severity and high mortality rate were observed among beta-infected patients. According to a study by Zhao and colleges, it was showed that alpha lineage, which was one of variants of concern, was the most widely disseminated variant. Also, the spatial distribution of the alpha variant demonstrates that countries near the originate of the variant were heavily affected than other countries (Zhao *et al*., 2022). Indeed, in a Qatari study that investigated the severity of alpha and beta variants, infections with beta variant had 24% greater risk to develop severe disease, 49% higher risk to develop critical disease and 57% higher risk of COVID-19–related mortality when compared to the Alpha variant (Abu-Raddad *et al*., 2021). In the same study, unlike the alpha lineage, the number of beta lineage infected individuals was not as high, especially in the worst-affected countries. For this concern, the results of our study seem to be in accord with what had previously been demonstrated (Zhao *et al*., 2022).

In our study, omicron variant seems to significantly infect more peoples than delta variant (P=0.0001) while, in contrast, common symptoms, comorbidities and mortality rate seem to be highly observed among delta variant patients than omicron ones.

Discussion

According to the World Health Organization, the extremely infectious Delta variation (B.1.617.2) was the fastest and fittest coronavirus strain currently, infecting the most susceptible persons, particularly in places with low COVID-19 immunization rates (Roy *et al*., 2021). Moreover, a study by Shiehzadegan And colleges mentioned that the delta variant spreads twice as quickly as the alpha variant. In addition, fever, cough, shortness of breath, vomiting, diarrhea, sore throat, and headache were some of the most common symptoms of the delta variant. Myalgias, loss of taste, loss of smell, weariness, and rhinorrhea were some of the other symptoms (Shiehzadegan *et al*., 2021).

Finally, various studies reported that, during omicron wave, the number of individuals aged 20 and older admitted to hospitals with SARS-CoV-2 was significantly lower than previous waves, resulting in decrease of patients consultations in health-care systems. As delta variant infections were particularly severe, the delta-driven third wave led to a significant increase in seroprevalence. Thus, a previous infection with the delta variant supplies some T-cell immunity that protects against severe illness from omicron infection, this might explain why the omicron driven fourth wave of infections was less severe (Jassat *et al*., 2022).

Conclusion

Sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also called COVID-19, is an infectious disease that emerged for the first time in 2019 in Wuhan, Hubei province, China. Then, the virus has been propagated worldwide and was declared as an epidemic in 2020. In Algeria, epidemiological studies concerning this pandemic are rarely conducted. This study was an entry of analyzing clinical data from northeast Algerian individuals who suffered from SARS-COV-2 infection in order to study its pattern of transmission. Future more detailed epidemiological studies are highly required to understand the transmission of the outbreak and thus adequate preventive actions should be taken consequently. Findings from our study showed that high incidence of SARS-COV-2 episodes is directly linked to high density areas and decreased in medium to low density regions. In this region of concern, the infection seemed to mainly affect men, resulting, by the way in a mortality rate that was higher in men than in women. These findings might be due to several factors such as higher levels of ACE2 receptor among men, as well as difference in sexual hormones and living styles. Furthermore, the infection appears to change from person to another depending on several data particularly age and coexisting comorbidities like diabetes, hypertension and other cardiovascular diseases that may affect the immune system. In contrast, patients without preexisting disease, have more ability to fight the infection.

In addition, in our studied population, patients from the three first waves were older than those infected with the omicron variant with a decrease in severity and mortality rate. This may be due to the fact that older peoples acquired immunity more than younger ones during the first three waves due to the fact they were the ones mostly affected at first. However, while this virus and its variants seem to decrease in severity with time, Precautionary measures must constantly be maintained as a form of precaution to reduce the transmission of the disease, as well as minimizing the mortality rate.

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Annex 01

Date de notification: /__/__//__/__//__/__/__/__/ Identifiant du cas : I___I___I___II___I___I

Médecin déclarant : _____

Etablissement déclarant :

1- CHU ☐ 2- EHU ☐ 3- EHS ☐ 4- EPH ☐ 5- EPSP ☐ 6- Clinique privée ☐ 7- Cabinet privé ☐ 8- Autres ☐

Nom de l'établissement : _____ Wilaya : _____

Détecté au point d'entrée : Oui ☐ Non ☐ Inconnu ☐

Si oui, date /__/__//__/__//__/__/__/__/

Partie 1 : Identification du patient

Nom :_____ Prénom :_____

Date de naissance :/__/__//__/__//__/__/__/__/ ou âge : /__/__/__/en année

si < 1 an, /__/__/en mois ou si < 1 mois, /__/__/ en jour

Sexe : Masculin ☐ Féminin ☐

Adresse exact du patient : _____

Partie 2 : Information clinique

Date d'apparition des 1ers symptômes : /__/__//__/__//__/__/__/__/

Date de consultation du patient : /__/__//__/__//__/__/__/__/

Lieu de prise en charge initiale du patient : 1- CHU ☐ 2- EHU ☐ 3- EHS ☐ 4- EPH ☐ 5- Polyclinique ☐
6- Salle de soins ☐ 7- Clinique privée ☐ 8- Cabinet privé ☐ 9- Autres ☐

Date d'hospitalisation : /__/__//__/__//__/__/__/__/

Service d'hospitalisation : 1- UMC ☐ 2- Soins intensifs ☐ 3- Réanimation ☐ 4- Autres ☐
Si Autres, préciser .....

Mode d'admission : 1- Evacuation ☐ 2- Urgence ☐ 3- Consultation ☐

Si Par évacuation, préciser : .....

Date d'isolement : /__/__//__/__//__/__/__/__/

Symptômes du patient : Cocher tous les symptômes rapportés

1- Fièvre ☐	6- Essoufflement ☐	11- Douleur articulaire ☐
2- Asthénie ☐	7- Diarrhée ☐	12- Douleur abdominale ☐
3-Toux ☐	8- Nausée/vomissement ☐	13- Irritabilité ☐
4-Maux de gorge ☐	9- Céphalées ☐	14- Confusion mentale ☐
5-Ecoulement nasal ☐	10- Douleur musculaire ☐	15- Autres ☐

Si Autres (précisez) : _____

Examen clinique du patient : Cochez tous les signes observés :

1- Température: /__/__/__/°C
2- Exsudat pharyngé ☐
3- Injection conjonctivale ☐
4- Auscultation pulmonaire anormale ☐
5- Coma ☐
6- Dyspnée / tachypnée ☐
7- Résultats anormaux de radiographie pulmonaire ☐
8- Convulsion ☐
9- Autres ☐, précisez : _____

Conditions sous-jacentes et comorbidité : Cochez tous ceux qui sont applicables

1-Grossesse ☐ (trimestre: _____)
2- Maladie cardiovasculaire ☐
3- HTA ☐
4- Diabète ☐
5- Maladie du foie ☐
6- Maladie neurologique ou neuromusculaire chronique ☐
7- Post-partum (< 6 semaines) ☐
8- Immunodépression (VIH inclus) ☐
9- Maladie rénale ☐
10- Maladie chronique des poumons ☐
11- Cancer ☐
12- Autres ☐, préciser_____

Evolution clinique du patient

Le patient a-t-il été ventilé : Oui ☐ Non ☐ Inconnu ☐
Si Oui, précisez le type de ventilation :_____

Evolution : en cours ☐ guérison ☐ décès ☐
Date de décès ou de sortie de l'hôpital : /__ /__//__ /__//__ /__/__ /__/

Partie 3 : Notion d'exposition et /ou voyages dans les 14 jours précédant l'apparition des symptômes

Profession : Cochez tous ceux qui sont applicables

Etudiant ☐ Professionnel de santé ☐ Autres ☐ (à spécifier): _____

Travailleur en contact avec les animaux ☐ Professionnel de laboratoire ☐

Le patient a-t-il **voyagé** au cours des 14 jours précédant l'apparition des symptômes ?

Non ☐ Oui ☐ Inconnu ☐ Si oui, préciser les endroits où le patient a voyagé :

Pays _____ Ville_____Date de départ de la localité /__ /__//__ /__//__ /__/__ /__/

Pays _____ Ville_____ Date de départ de la localité /__ /__//__ /__//__ /__/__ /__/

Pays _____ Ville_____ Date de départ de la localité /__ /__//__ /__//__ /__/__ /

Le patient a-t-il visité des **établissements de soins de santé** au cours des 14 jours précédant l'apparition des symptômes ? Oui ☐ Non ☐ Inconnu ☐

Le patient a-t-il eu **un contact étroit** avec une personne atteinte d'une infection respiratoire aiguë au cours des 14 jours précédant l'apparition des symptômes ?

Oui ☐ Non ☐ Inconnu ☐

Si oui, précisez le lieu de contact (cochez tous ceux qui sont applicables):

Structure de santé ☐ Cadre familial ☐ Lieu de travail ☐ Autres (à spécifier): _____

Le patient a-t-il été en contact avec **un cas suspect ou confirmé** au cours des 14 jours précédant l'apparition des symptômes? Oui ☐ Non ☐ Inconnu ☐

Si oui, énumérez tous les cas suspects ou confirmés :

Cas 1 : Nom et prénom : _____ Age : /__/__/

Sexe : Masculin ☐ Féminin ☐ Adresse exact : _____

Cas 2 : Nom et prénom : _____ Age : /__/__/

Sexe : Masculin ☐ Féminin ☐ Adresse exact : _____

Cas 3 : Nom et prénom : _____ Age : /__/__/

Sexe : Masculin ☐ Féminin ☐ Adresse exact : _____

Si oui, précisez le lieu de contact (cochez tous ceux qui sont applicables):

Structure de santé ☐ Cadre familial ☐ Lieu de travail ☐ Autres (à spécifier): _____

Si oui, lieu/ville/pays d'exposition : _____

Partie 4 : Information de laboratoire

Nom du laboratoire de confirmation : _____

Le test utilisé : _____

Classification du cas : Cas suspect ☐ Cas confirmé ☐ Cas exclu ☐

Si cas confirmé :

Date de confirmation par le laboratoire /__/__//__/__//__/__/__/__/

Signature du médecin déclarant