TOMUN KOUAGUI RICHARD

COMPARISON OF ANTIBODY LEVELS BETWEEN MALE AND FEMALE SUBJECTS AFTER RECEIVING CORONAVAC VACCINATION

MSc. THESIS

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TURKISH REPUBLIC OF NORTHERN CYPRUS
NEAR EAST UNIVERSITY
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Approval

We certify that we have read the thesis submitted by **TOMUN KOUAGUI RICHARD** entitled **"COMPARISON OF ANTIBODY LEVELS BETWEEN MALE AND FEMALE SUBJECTS AFTER RECEIVING CORONAVAC VACCINATION** and that in our combined opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science in Medical & Clinical Microbiology.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Prof. Dr. Emrah RUH	.....
Committee Member	Assoc. Prof. Dr. Mintaz ORAN	.....
Supervisor:	ASSOC. PROF.DR. UMUT GAZI	.....

Approved by the Head of the Department

.... /.... /2024
Prof. Dr. EMRAH RUH
Head of Department

Approved by the Institute of Graduate Studies

.... /.... /2024
Prof. Dr. Kemal Hüsnü Can Başer
Head of the Institute

Declaration

I hereby declare that all information, documents, analysis, and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

TOMUN KOUAGUI RICHARD

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Abstract

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TOMUN KOUAGUI RICHARD

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Aim: The purpose of this study is to determine if there is a variation in the levels of antibodies produced in response to the CORONAVAC vaccine between males and females.

Method: This study used the retrospective study design.

Results: The study found that the level of antibodies in females was identical compared to males.

Conclusion: The primary aim of this study was to compare the levels of antibodies after vaccination with CORONAVAC at two doses according to sex. This study showed that antibody levels in women 100 days after the second dose of CORONAVAC vaccination were identical to those detected in men. To better know the protector's antibody levels over time, additional large-scale studies are needed to assess immune levels over a wide period.

Key Words: Antibody, Gender, CORONAVAC, Vaccine, Vaccination, Northern Cyprus, SD.

ÖZET

Kuzey Kibris'ta Coronavac Aşisi Yaptirildiktan Sonra Erkek Ve Kadin Denekler Arasinda Antikor Düzeylerinin Karşilaştirilmasi

TOMUN KOUAGUI RICHARD

Yüksek Lisans, Klinik ve Tıbbi Mikrobiyoloji Anabilim Dalı

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Amaç: Bu çalışmanın amacı Kuzey Kıbrıs'ta erkek ve kadınlar arasında Coronavac aşısına yanıt olarak üretilen antikor düzeylerinde farklılık olup olmadığını tespit etmektir.

Yöntem: Bu çalışmada retrospektif çalışma tasarımı kullanılmıştır.

Sonuçlar: Çalışmada coronavac aşısının aşıyı alan nüfusun neredeyse tamamını koruduğu ortaya çıktı. Çalışmada ayrıca antikor düzeyinin kadın cinsiyette nispeten tatmin edici, erkek cinsiyette ise daha az olduğu ortaya çıktı.

Sonuç: Çalışma, conrovac aşısının kadınlarda yüksek bağışıklığa sahip olduğu, bunun da kadınlarda edinilen güçlü bağışıklığı, erkeklerde ise daha az sağlamlığı yansıttığı sonucuna varmıştır. Standart klinik tedavinin bir bileşeni olarak aşılamaya daha fazla önem verilmeli ve aşılamanın neden olduğu bağışıklığın süresini belirlemek için daha fazla araştırma yapılmalıdır.

Anahtar Kelimeler: Antikor, Cinsiyet, Coronavac, Aşı, Aşılama, Kuzey Kıbrıs

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List of Abbreviations

VLP: Virus-like Particles

PHEV: Virus that causes swine hemagglutinating encephalomyelitis primarily causes gastrointestinal illnesses.

TGEV: Transmissible gastroenteritis virus.

PEDV: Porcine epidemic diarrhea virus

PHEV: Porcine hemagglutinating encephalomyelitis virus

MHV: Murine hepatitis virus

SARS: Severe acute respiratory syndrome

FIP: Feline infectious peritonitis

MS: Multiple sclerosis

SARS: Severe acute respiratory syndrome

ACE2: Angiotensin-converting enzyme 2

MERS: Middle East respiratory syndrome-cov

DPP4: Dipeptidyl peptidase 4

RBD: Contains receptor binding domains.

Ro: Reproduction number

CDCs: Centers for Disease Control and Prevention

DS**:** shows the deviation in the data. It must be given in mean+- SD format

CHAPTER I

1.0 Introduction

The greatest-ever vaccination attempt has targeted the SARS-COV-2 virus, which causes COVID-19, in the hopes of conferring acquired protection. There were over 460 million confirmed cases of COVID-19 as of March 18, 2022, and over 6.06 million deaths because of the virus. Over 5 billion people have received a vaccination, and over 10.9 billion doses have been provided as of March 17, 2022 (WHO,2022). Vaccination was considered to be the most effective tool in stopping this epidemic. Various studies have found varying levels of vaccination effectiveness (Baden Lr et al., 2021). The vaccines BNT162b2 (Pfizer and BioNTech) and ChAdOx1 (University of Oxford and AstraZeneca) were found to have 95% and 70.4% effectiveness, respectively (Voysey M et al.,2021). In phase 3 clinical trials, the vaccines BNT162b2 (Pfizer and BioNTech) and ChAdOx1 (University of Oxford and AstraZeneca) demonstrated 95% and 70% effectiveness rates, respectively (Voysey M et al.,2021).

Vero cells, which are derived from the kidneys of an African green monkey that has been infected with the SARS-COV-2 (Cn02 strain), are used to make CORONAVAC, which is a whole virus COVID-19 vaccine that has been inactivated and mixed with aluminum hydroxide (Gao q et al., 2020). Sinovac Biotech, a Chinese pharmaceutical company, created the vaccine. The standard CORONAVAC vaccination schedule consists of two shots administered at an interval of two to four weeks (Zhang Y et al., 2021).

In June 2021, the World Health Organization (WHO) approved the use of the inactivated CORONAVAC vaccine, which was manufactured in Beijing by Sinovac, for emergency use. Also, Turkey claimed an 83.5% efficacy rate (Tanriover Md et al., 2021) for CoronaVac (Sinovac), whereas Chile reported a 65.9% efficacy (Jara A et al.,2021). The WHO approved the vaccine with an estimated efficacy of 51%. In addition, in Brazil, the efficacy for preventing symptomatic COVID-19 14 days or more after the second dosage was reported to be 50.7% (95% CI, 35.9%–62.0%), while in Indonesia, it was 65% (95% CI, 20%–85%) (Fadlyana E et al., 2021).

1.1 Research purpose.

The purpose of this research is to determine whether there is a variation in the levels of antibodies produced in response to the CORONAVAC vaccine between males and females.

1.2 Research significance.

This study has significant advantages because it can give useful information on a variety of public health issues, vaccination tactics and scientific knowledge. The development of more targeted immunization programs could benefit from a better understanding of gender equality in the antibody responses that this study explores. The results of this study could help determine how the CORONAVAC vaccine can be administered to as many people as

possible. Health researchers may find the results of the study useful in providing additional information on the need for prevention and vigilance.

1.3. Research questions.

- Are there notable variations in the antibody levels generated by the CORONAVAC vaccination according to gender differences?
- How do the antibody levels vary between genders less than 100 days and 100 days and more after receiving the CORONAVAC vaccine?

1.4. Limitation of study

The study's sample may have been biased because it was not 100% representative of the population. For instance, if a study solely examines a particular age range or healthcare setting, the findings might not apply to a wider population. The sensitivity and specificity of the diagnostic methods used to identify antibody levels may affect the accuracy of prevalence estimates. Results from different lab procedures may not always be consistent.

1.5. Definition of key term.

An **Antibody** is a large protein that is shaped like a y and is used by the body to identify and eliminate foreign substances such as viruses and dangerous bacteria. It is also often referred to as an immunoglobulin (IG).

CHAPTER II

Literature Review

2.1. Coronavirus

Many kinds of animals, including people, can be infected by coronaviruses, a large family of viruses (e.g. Cats, bats). Many people will at some point in their lives encounter these viruses. Infections of the upper respiratory tract (URTIs), much like the typical cold, are brought on by human coronaviruses. Extremely high fatality rates were initially attributed to SARS-COV-2 cases, especially in people with chronic illnesses including diabetes and heart disease (CDC, 2021).

Coronaviruses are positive-stranded RNA viruses with genomic sizes of around 30 kilobases (Goujon et al.,2021). Their genome includes genes that encode four structural proteins: membrane (M), nucleocapsid (N), spike (S), and envelope (E) (Docea et al., 2020). Coronaviruses belong to the order Nidovirales, the family Coronaviridae, and the subfamily Orthocoronavirinae (Cui et al., 2019). The Orthocoronavirinae subfamily has four genera: Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus (ICTV, 2011) (Cui et al., 2019). Alphacoronaviruses and betacoronaviruses exclusively infect animals, producing respiratory disease and gastroenteritis. Three types of betacoronaviruses cause serious respiratory illness in humans: SARS-CoV, MERS-CoV, and SARS-CoV-2.

Human coronaviruses HCoV-NL63(alpha), HCoV-229E(alpha), HCoV-OC43(beta), and HKU1(beta) normally cause moderate upper respiratory disorders in immune-competent individuals but can cause serious infections in the elderly, newborns, and young children (Cui et al., 2019). SARS-CoV-1, HCoV-NL63, and SARS-CoV-2 typically infect ciliated bronchial epithelial cells (Cui et al., 2019) via angiotensin-converting enzyme 2 (ACE2), while MERS-CoV infects unciliated bronchial epithelial cells through dipeptidyl peptidase 4 (DPP4) (Cui et al., 2019). SARS-COV and SARS-COV-2 are beta coronavirus family as said before by (Lau et al., 2005). Two serotypes of human coronavirus, HCOV-229E and HCOV-OC43, were known to exist until 2002 (Fung Ts and Liu Dx, 2019).

HCOV-229E and HCOV-OC43 minor respiratory conditions that, in healthy individuals, heal relatively quickly. Two novel coronaviruses, HCOV-NL63 and HCOVHKU1, were discovered in 2004 and 2005 (Woo Pcy et al., 2005). These viruses also cause very mild flu-like diseases. Although they can cause more severe illness in newborns, the immunocompromised, and the elderly, 15–30% of common colds globally are likely caused by these four human coronaviruses each year (Van der Hoek L, 2007). Even though the four endemic coronavirus strains provide little to no risk to public health, coronavirus research has received much less funding and attention than it warrants. Upon its first appearance in southern China in November 2002, the world

changed forever due to the severe acute respiratory syndrome coronavirus (SARS-COV) (Zhong Ns et al., 2003).

By June 2003, there were over 8,000 verified instances of this viral respiratory illness across several nations (Fung Ts and Liu Dx,2019). After an incubation period ranging from 4 to 6 days, patients with SARS appeared to have symptoms like the flu in addition to pneumonia. Multiple organ infection by SARS-COV results in systemic illness, with symptoms that worsen as the virus is eradicated. Acute respiratory distress and fatal respiratory failure are the results of severe instances. It was discovered that the causing agent was a beta coronavirus that first infected horseshoe bats before developing to infect palm civets and eventually humans (Lau Skp et al., 2005). Years later, a productive pool of genes including coronaviruses linked to SARS in bats was found in a cave in Yunnan, China, suggesting the possibility of a future resurgence (Hu B et al., 2017)(a).

A second major coronavirus, MERS-COV, emerged in 2015 and caused massive epidemics in Saudi Arabia and South Korea. The first coronavirus, MERS-COV, emerged in June 2012 in Saudi Arabia (Zaki Am et al., 2012). Despite minimal human-to-human transmission, there were more than 2,000 documented cases worldwide, with a 35% fatality rate, primarily in patients who were elderly (Dawson P et al., 2019). Similar to the findings regarding SARS-COV, the origins of MERS-COV were found to be in bats. The virus first infected people through dromedary camels, acting as intermediate hosts (Adney Dr et al., 2014). Currently, neither the MERS-COV nor the SARS-COV vaccines have received approval (Fung Ts and Liu Dx, 2019). A novel human coronavirus caused the worst epidemic since 1918, seven years after MERS and seventeen years following SARS. Infection with SARS-COV-2 causes a new viral respiratory illness called COVID-19. In 2020, the results were released by the coronavirus study group of the International Committee on Taxonomy of Viruses.

The exponential rise in cases and deaths after the COVID-19 pandemic's announcement at the end of the year prompted the World Health Organization to declare a worldwide public health emergency (World Health Organization, 2020). The World Health Organization has linked the virus to sputum, saliva, throat, nasopharyngeal, and bronchoalveolar lavage (Wang W et al., 2020). Based on analyses and characterizations of the virus's genome that reveal mutation and recombination processes, scientists are only beginning to understand the SARS-COV-2 genome's evolution, emergence, and origins (Lu R et al., 2020).

2.1.1. Coronaviruses in animals

Over the past decades, several studies have shown that animals are the preferred targets of the coronavirus disease. Both domestic animals and livestock animals, including pigs, cows, chickens, dogs, and cats, are susceptible to diseases caused by these viruses, which are not only damaging but can cause major health issues in domestic

animals. The swine hemagglutinating encephalomyelitis virus, also known as (PHEV), is mostly recognized for its propensity to induce gastrointestinal illnesses in pigs.

However, it is also capable of infecting the neurological system, which may result in encephalitis, vomiting, and wasting. The feline infectious peritonitis virus, also known as (FIPV), is a more hazardous version of the feline enteric coronavirus, also known as (FCOV). This virus may induce infections in domestic cats that are either mild or present with symptoms. If the infection continues, the virus can evolve into potentially fatal feline infectious peritonitis (FIP). Nevertheless, further research is needed to validate this theory. The infectious bronchitis virus (IBV), rat COV, and bovine COV cause difficult health cases such as respiratory diseases in rats, chickens, and cattle, respectively.

In addition to causing significant losses for cattle farming, bovine COVID-19 has spread to infect a range of ruminants, such as camels, chickens, and deer. The virus not only causes severe respiratory illness but also diarrhea (sometimes known as "winter dysentery" and "shipping fever"), which can result in dehydration, depression, and weight loss (Perlman S et al., 2009). Certain γ-coronavirus strains, known as IBV, can also cause kidney illness in hens by affecting the urogenital tract. IBV infection of the reproductive system dramatically reduces egg production, resulting in yearly losses for the egg-producing business (Perlman S et al., 2009).

More recently, a dead beluga whale was found to have the new coronavirus known as SW1 (Mihindukulasuriya Ka et al., 2008). The liver of the dead whale, which had acute liver failure and respiratory illness, had a significant amount of virus particles. While studies unambiguously identified the virus tissue as a coronavirus, electron microscope images were insufficient to identify the virus as such. Also, the discovery of new bat coronaviruses has garnered significant attention since bats are believed to be the likely ancestors of MERS-COV and SARS-COV (He B et al., 2014).

Finally, recent studies have shown that the Nidoviruses of the Mesoniviridae family are the first infectious agents of host insects (Nga Pt al,2011). They have multiple differences from other Nidoviruses but have certain links with Roniviruses. At around 20 kilobase pairs, they fall in the middle of the size spectrum for Nidoviruses. It is suggested that these viruses may mark an evolutionary split between big and tiny Nidoviruses, or they may be the prototypical member of an entirely new family of Nidoviruses.

2.1.2. Coronaviruses in humans

Among the many human coronaviruses that may be cited are the Beta-Type HCOV-OC43 and HCOV-HKU1, as well as the ALPHA-TYPE HCOV-229E and HCOV-NL63. Although HCOV-229E and HCOV-OC43 have been known and tracked for fifty years, HCOV-NL63 and HCOV-HKU1 were only recently discovered after the COVID-19 pandemic (McIntosh K et al., 1967). These viruses cause 15–30% of respiratory tract illnesses in human populations. They disproportionately afflict the elderly, the young, and those with underlying medical issues: lower respiratory tract infections are more common in these groups. Additionally linked to acute laryngotracheitis (croup) (Van Der Hoek L et al 2005).

In China's Guangdong province, the 2002-2003 severe acute respiratory syndrome (SARS) outbreak was linked to the group 2b β-coronavirus or SARS-COV. It is the most serious coronavirus-related illness that affects humans. Approximately 8,098 cases and 774 deaths occurred during the 2002–2003 outbreak, yielding a 9% fatality rate. This rate was far higher among the elderly, with mortality rates for those over 60 surpassing 50%. The virus has repeatedly caused business closures in some countries such as South Asia and Toronto, Canada, resulting in a shortfall in the economy estimated at forty billion dollars. The outbreak started in a Hong Kong hotel and eventually spread to over twenty-two nations. Closely related viruses were recovered during the outbreak from several exotic animals, such as raccoon dogs and Himalayan palm civets (Guan Y et al., 2003).

It is generally noted that bats are the reservoirs of SARS-COV. Several Chinese horseshoe bats each have a source of COV that is linked to SARS and serological results have also shown a close affinity to previous COV infections. Thus, recent studies claim that the links between new coronaviruses (COV) and bat SARS are closer to SARSCOV. This confirms and shows that bald are the natural reservoir of SARSCOV (Ge Xy et al., 2013).

Before the outbreak, some people in animal sales locations (living in areas containing very little water) had indications of COVID-19 virus infection based on blood serum studies, but none of them exhibited symptoms (Guan Y et al., 2003). Therefore, several factors could have contributed to the presence of a roughly comparable virus on the premises of animals (living in areas containing very little water) for decades before it finally spread to the public.

Since the COVID-19 virus was only transmitted by direct contact with infected people after sickness started, transmission was rather inefficient. Apart from very rare situations in which a person was able to infect numerous contacts due to the significant abundance of the virus, the outbreak was largely mainly restricted to homes and hospital

settings (Peiris Js et al., 2003). Because of the comparatively slow spread of SARS-COV, quarantining was a useful tool in controlling the outbreak. After the outbreak had been contained by June 2003, very few new cases of SARS were reported.

The primary target of COVID-19 infections in the lung is epithelial cells. Although the virus can reach dendritic cells and macrophages, it only causes an unsuccessful infection (Peiris Js et al., 2003). Nevertheless, infection of these cell types may play a significant role in triggering proinflammatory cytokines, which could worsen the illness (Law Hk al., 2005). A potential immunopathological cause of the disease is suggested by the animals' decreased t-cell responses and elevated levels of protein inflammatory cytokines (Zhao J et al.,2010).

Even though the SARS-COV epidemic was contained in 2003 and the virus has not been seen since then, a new human coronavirus was discovered in the Middle East in 2012. It was discovered that Middle East respiratory syndrome (MERS-COV) was the cause of severe respiratory tract diseases in Saudi Arabia and other countries in the Middle East (Zaki Am et al.,2012). It was expected that the virus would produce a catastrophic pandemic because of the high initial mortality rate (less than fifty percent).

However, there was no acceleration of the outbreak in 2013, with only isolated cases persisting for the remainder of the year. There were concerns that the virus had changed and had become more capable of spreading from person to person after a spike of over 200 cases and nearly 40 deaths in April 2014. It was more likely that a seasonal rise in camel births along with enhanced techniques of identification and reporting contributed to the higher number of cases. According to the European Center for Disease Prevention and Control, the number of confirmed cases of MERS-COV reached 855 as of August 27, 2014. These cases resulted in 333 deaths, and the case fatality rate was about forty percent over this period.

Group 2c β-coronavirus MERS-COV shares strong similarities with two previously known bat coronaviruses, HKU4 and HKU5 (Van Boheemen S et al., 2012). Although bats are considered the virus's original hosts, the fact that humans seldom meet bats suggests that the virus probably had an intermediary host suggests that the virus probably had an intermediary host. Serological studies have shown the presence of MERS-COV antibodies in dromedary camels from the Middle East (Eckerle I et al., 2014). Additionally, camel cell lines have been proven to be permissive for MERS-COV replication (Eckerle I et al.,2014), suggesting that dromedary camels may be the natural host.

Recent tests have shown almost identical MERS-COVS in both humans and camels in Saudi Arabia (Memish Za et al., 2014) providing more compelling evidence for this theory. The number of MERS-COV cases caused by an intermediate host rather than

human-to-human transmission remains undetermined. The transmission of the virus from people to camels has also been proposed as a contributing factor behind the epidemic.

The MERS-COV receptor is dipeptidyl peptidase 4 (DPP4) (Raj Vs et al.,2013). The virus can only spread infection by using receptors from specific animals, including humans, camels, rabbits, horses, and bats. Unfortunately for researchers, the virus is unable to infect mouse cells due to differences in the structure of DPP4, making it difficult to evaluate potential vaccines or antivirals. The human DPP4 gene was recently introduced into the lungs of mice using an adenoviral vector to create a small animal model for MERS-COV (Zhao J et al., 2014). Any animal that is susceptible to adenoviral transductions can be used to test new vaccines and treatment interventions for MERS-COV thanks to this special approach.

2.2. The origin of SARS-CoV 2.

The first index patients of the SARS epidemic almost always had animal interaction before contracting the virus. After the SARS causative agent was discovered, masked palm civets and animal handlers at a marketplace tested positive for SARS-COV and/or anti-SARS-COV antibodies (Guan et al., 2003). Market civets tested positive for SARS-COV, but further research into wild-caught and reared civets revealed that these strains had been passed down from other species. While studying horseshoe bats (Genus Rhinolophus), two different research groups found coronaviruses like SARS in 2005 (Lau et al., 2005). These findings revealed that civets merely serve as hosts for SARS-COV. Subsequently, a significant number of coronaviruses from nations in southeast Asia and Europe, as well as bats from multiple Chinese provinces, were discovered to be connected to SARS-COV phylogenetically (SARSR-COVS) (Lau et al.,2005).

The only SARS-COV strains that match the ICTV requirements are those that have been found in Rhinolophus bats from Europe, Southeast Asia, and China. Those from African hippocampus bats should be classified as a unique coronavirus species as they are not as closely related to SARS-COV (Tong et al., 2009). These findings suggest that SARS-COVS are regionally widely distributed geographically and may have been common in bats for a very long period. In one cave in the Chinese region of Yunnan, a 5-year longitudinal research found that bat populations coexisted with a variety of SARS-COV (Ge et al., 2013). This region is a hotspot for SARSR-COVS diversification and possesses every genetic variety discovered in other regions of China.

Moreover, all the genetic components required for the development of SARS-COV are present in the viral strains exclusive to this region. Given the frequency of recombination in coronaviruses (Lai et al.,1997) and the fact that 15 years of research has not determined a direct progenitor of SARS-COV in bat populations, it is also possible that bat SARSR-COV recombination in this and other unidentified bat caverns

led to the recent evolution of SARS-COV. This notion is consistent with recent research suggesting that the SARS-COV's immediate ancestor existed before 2002 (Song et al., 2005). The recombination study also significantly validated the idea that the SARS-COV strain SZ3 in civets emerged from the crossing of WIV16 and RF4092, two previously existing bat strains (Hu b et al., 2017a).

Furthermore, the most plausible origin of WIV16, the closest known related of SARS-COV in bats, is the combination of two additional common SARS-COV in bats strains. Recombination breakpoints are most common in the f8 and s genes, which respectively code for auxiliary proteins and spike proteins containing the receptor-binding domain (RBD) (Hu et al., 2017a). The genetic diversity and prevalence of bat SARS-COVS, the frequent recombination of coronaviruses, and the tight coexistence of these viruses all point to the eventual appearance of further variations (Nagy et al., 1997).

In December 2019, an epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) expanded globally (Chan et al., 2020; Wang et al., 2020; Wu et al., 2020). The origin of SARS-CoV-2 was likely due to inter-species transmission between animals and humans, followed by human-to-human transmission (Xu et al., 2020a). Multiple research teams from China and other nations successfully isolated the virus and sequenced its whole genome (Wang et al. 2020). SARS-CoV-2 is classified as a β-coronavirus (Xu et al., 2020b), which provides a theoretical basis for epidemic prevention, control, and therapy. SARS-CoV-2 follows the normal genomic structure of β-coronaviruses. SARS-CoV-2 has been found in numerous animal species, including white-tailed deer (Odocoileus virginianus) (Martins et al.,2022) and the American mink (Neovison vison) (Oude Munnink et al., 2021). Vaccination against SARS-CoV-2 (and/or similar viruses) may be necessary due to the possibility of animal reservoirs and re-emergences, including potentially altered strains. Many emerging diseases originate in animal species (Jones et al., 2022), and close surveillance of these animals, potentially with one health preventive or therapeutic action (Mubareka et al., 2022), is essential, ideally before emergence.

2.3 Viral structure SARS-CoV 2.

The CoV is an encapsulated positive single-stranded RNA virus with the biggest known viral RNA genome, measuring 8.4-12 kDa (Van der Hoek L et al., 2004).

The viral genome consists of 5′ and 3′ terminals. The 5′ terminal of the genome contains open reading frames that encode viral replication proteins. The 3′ terminal houses five structural proteins: spike (S), membrane (M), nucleocapsid (N), envelope (E), and haemagglutinin-esterase (HE) (Beniac Dr et al., 2006).

The S protein facilitates viral attachment and fusion with the host cell membrane, as well as with infected and uninfected cells. They are the primary inducers for neutralizing antibodies in vaccines. The N protein joins RNA complexes to help in viral transcription and assembly. The M protein is the most abundant structural protein and determines the

structure of the viral envelope. The E protein is the most enigmatic and smallest of the key structural proteins, and it is extensively produced in the infected cell during viral replication. The HE protein is responsible for receptor binding and host specificity (Van Der Hoek L et al., 2004).

2.4. Pathogenesis SARS-CoV-2.

The distribution of ACE 2 receptors throughout tissues correlates with infection locations and patient symptoms. Non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms are caused by the virus's active proliferation in lung cells (Cevik M et al., 2020a). This causes transitory injury to the olfactory epithelium, leading to olfactory dysfunction as well as loss of taste and smell perceptions (Cevik M et al., 2020b). The presence of ACE 2 receptors in the gut, kidney, and endothelium contributes to gastrointestinal and cardiovascular problems. Post-mortem examinations of COVID-19 patients' lungs, hearts, kidneys, and liver revealed lymphocytic endothelium, hepatic necrosis, and myocardial infarction, indicating a direct effect on several organs (Monteil et al., 2020). Pathological alterations in the respiratory tract or endothelial dysfunction can be caused by viral infection, cytokine dysregulation, and coagulopathy (Varga Z et al., 2020).

2.5. Covid-19: what is it?

The severity of the respiratory illness known as COVID-19 may vary from moderate to severe. The primary methods of dissemination are airborne particles, droplets, and contact with contaminated surfaces. Two to fourteen days following exposure, symptoms can manifest as fever, coughing, dyspnea, sore throat, runny nose, or loss of taste or smell. Heart attacks, blood clots, respiratory failure, and other chronic issues are examples of complications. Many kinds of animals, including humans, are susceptible to infection by coronaviruses.

2.5.1. History of Covid-19.

COVID-19 is a highly contagious illness caused by SARS-CoV-2, a new coronavirus (WHO, 2021). In late December 2019, groups of individuals with pneumonia from unknown causes were discovered in Wuhan, China. SARS-CoV-2, a novel coronavirus, was discovered as the cause of Coronavirus Disease 2019 (COVID-19) (Hu B et al., 2021b) .

China's national authorities informed the WHO of 44 individuals with pneumonia of unknown cause detected between December 31, 2019, and January 3, 2020. No causal agent was found throughout this reporting period. Resultantly, the National Health Commission of China provided the World Health Organization with more information on January 11 and 12, 2020. This information revealed that one of the seafood markets in the city of Wuhan was connected to the occurrence. China discovered and isolated a novel coronavirus on January 7, 2020, allowing other nations to create customized diagnostic tools. China released the unique coronavirus genomic sequence on January 12, 2020 (Lu et al., 2020).

The first case of the newly discovered coronavirus (2019-nCoV) was verified by the Ministry of Public Health of Thailand on January 13, 2020. The case originated from Wuhan, which is in Hubei province, China. A case of 2019-novel coronavirus (2019-nCoV) was confirmed to have come from the same source as a previous case on January 15, 2020, according to the Ministry of Health, Labor, and Welfare of Japan (MHLW) (World Health Organization. Novel coronavirus – Japan (ex-China); 2020).

The first instance of the new coronavirus, originating in Wuhan, China, was officially communicated to the National IHR Focal Point (NFP) for the Republic of Korea on January 20, 2020 (Park Wb et al., 2020). Covid-19 cases were first documented in Turkey on March 10, 2020. After one month, there were 47,029 cases and 1,006 deaths had been reported. By April 10, 2020, there were 1,727,602 confirmed instances of SARS-CoV-2 infections and 105,728 deaths recorded across more than 210 countries (World Meter, 2020).

2. 5.2. Covid-19 epidemiology.

Initially, it was believed that COVID-19 was a zoonotic illness that originated in bats and may have seen many cross-species transmissions, initially from bats to pangolins and then to humans. The Wuhan wet market appears to have been the source of one or more zoonotic transmission events that led to the outbreak (Mackenzie Js and Dw S,2020). Initially, it was believed that the main way in which SARS-COV-2 spread was by interaction with intermediary host animals or the consumption of wild animals. The development of several verified instances of severe respiratory distress, each of which had a unique radiological pattern (e.g., early chest imaging), was the first evidence that its epidemiological relationship was related to severe respiratory distress showing consolidation in 70–80% of patients with coronavirus infection and multifocal airspace opacities (Hosseiny M et al., 2020).

2. 5.3. Transmission mechanisms

When determining the transmissibility of an illness, the basic reproduction number **(**Ro**)** is used. A number that is greater than one indicates that the transmission of the virus from one individual to another is continuing and maintained (Atkins P et al.,2020). One of the factors that contribute to the rapid spread of SARS-COV-2 is the method of transmission of the viral agent. To obtain important insights into the epidemiologic spread, the execution of epidemic containment methods, and the evaluation of the efficiency of such initiatives, it is essential to develop a solid understanding of the transmission dynamics of infectious dispersion (Atkins P et al., 2020). There is a significant similarity between the transmission characteristics of SARS-COV-2 and those of SARS-COV and pandemic influenza. According to the findings of Riou J and

Althaus CL (2020), this was an indication of both the potential for global spread and the likelihood of human-to-human transmission over an extended period.

Recent research found that the average Ro value ranged from 2.24 to 3.58 (Zhao S et al., 2019). With a transmissibility level that was equivalent to that of SARS-COV, pandemic influenza, and HIV, but far lower than that of measles and chickenpox, SARS-COV-2 constituted a substantial infectious hazard that ranged from mild to severe (Riou J and Althaus Cl, 2020). A publication by (Chan Jf et al., 2020) presented the first evidence of the possibility of transmission from person to person. They investigated the spread of the illness among many family members who had recently returned from a trip to Wuhan. Even though they stayed at the same hotel throughout the trip, they had no prior contact with markets, animals, or the consumption of game meat. This was the first indication that the virus could be transmitted from person to person without the participation of animals. Subsequent data increasingly confirmed the continuing spread of the virus from person to person (Riou J and Althaus Cl,2020). SARS-COV-2 predominantly spreads via the respiratory tract and utilizes the ACE2 receptor, which is also used by SARS-COV (Zhou P et al., 2020). The virus is mainly spread via droplets, respiratory secretions, and direct contact because it is an infectious disease of the respiratory system (Li Q et al., 2020).

Nevertheless, viral particles have also been detected in blood and fecal swabs, suggesting several different channels for transmission (Zhang Y et al., 2020). It is important to note that enterocytes in the small intestine also express the ACE2 protein (Hamming I et al., 2004). There is no evidence that the virus can spread vertically by blood products or the fecal-oral route, according to other Chinese findings (Zhang Y et al., 2020). Nonetheless, a modest incidence of vertical transmission caused by COVID-19 has been established by some recent investigations conducted in the UK and other nations (Kalyan Sundaram S et al., 2020).

2. 5.4. The incubation periods.

Although incubation times may range from 1–14 days, the typical range is 3–7 days. Several days before the onset of symptoms, SARS-COV-2 may be found in the nasal passages and throat. It is interesting to note that participants who exhibit no symptoms at all could have virus loads comparable to those of those who do (Zou L et al., 2020). Familiar symptoms, including fever, coughing, and malaise, are experienced by patients after the incubation period has already passed. Furthermore, only a small proportion of those experiencing gastrointestinal side effects such as nausea, vomiting, and diarrhea also experience these symptoms. Consequences such as acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation failure can manifest quickly in patients who have underlying illnesses or the elderly. Fatalities and multiple organ failures are possible outcomes of these diseases (Hy et al., 2020).

2. 5.5. Pathology

SARS-COV-2 spreads by contact droplets and fomites from an infected individual, affecting the respiratory system. Symptoms may or may not be present in the infected person (Jefferson T et al.,2021). Virus incubation is characterized by a gradual response from the lungs. The primary mechanism by which SARS-COV-2 causes respiratory symptoms is via the invasion of alveolar epithelial cells (Yi Y et al., 2020).

Both endocytosis and direct fusion with the viral envelope are common entry routes for coronaviruses into host cell membranes. After internalization, the viral particle sheds its coating and releases its genome into the host cell's cytoplasm. The coronavirus can directly synthesize its proteins from its RNA genome and bind to the host ribosomes in the cytoplasm to generate new genomes (Astute I and Ysrafil, 2020). Within the host cell, ribosomes are responsible for the transcription of viral RNA into proteins that function as RNA polymerase. The positive strand is then read once again by this RNA polymerase, resulting in the formation of single-stranded (SS) RNA strands, which are used by RNA polymerase as a template to produce more strands of SSRNA copies. Through the process of reading the short strands of RNA, the ribosomes of the host in the endoplasmic reticulum are responsible for making the structural components of the virus.

The Golgi apparatus assembles new virion particles from nucleocapsids that have SSRNA+ genomes. As the virus replicates in alveolar cells, the host cell releases these offspring viruses via secretory vesicle-mediated exocytosis, causing tissue damage and an inflammatory reaction. The virus elicits an inflammatory response via the recruitment of helper T-cells that produce interferon (IFN)-gamma (IFN- γ), interleukin (IL)-2, and IL-12 (Liu J et al., 2020). The subsequent surge of more inflammatory cells initiates a "cytokine storm," which can accelerate damage to organs and failure of numerous organs that are hallmarks of serious illness (Liu J et al., 2020)

When alveolar cells sustain damage, they release cytokines, which are recognized and addressed by the alveolar macrophages. In response, cytokines and chemokines are secreted by alveolar macrophages (Hu G and Christ Man Jw, 2019). Inflammation of the lung parenchyma stimulates the cough reflex nerve endings, which explains why people often present with an early dry cough (Hu G and Christ Man Jw, 2019). The synthesis of adhesion molecules is increased, vascular permeability is widened, and more immune cells like monocytes and neutrophils are attracted by proinflammatory cytokines including tumor necrosis factor (TNF)-α and Il-1β. They attach surface adhesion proteins on injured tissue, allowing them entry (Fahey E and Doyle Si, 2019). Neutrophils are drawn to IL-8, but monocytes are recruited by other chemokines (CXC, CC, CX3C, and C.) (Moore Bb and Kunkel Sl, 2019). Fluid seeping into the interstitial space and alveoli because of an increase in vascular permeability is the cause of interstitial and pulmonary edema. This could lead to various symptoms including dyspnea, hypoxemia, or reduced oxygenation. The clinicopathological characteristics of coronavirus are shown in Figure 1.

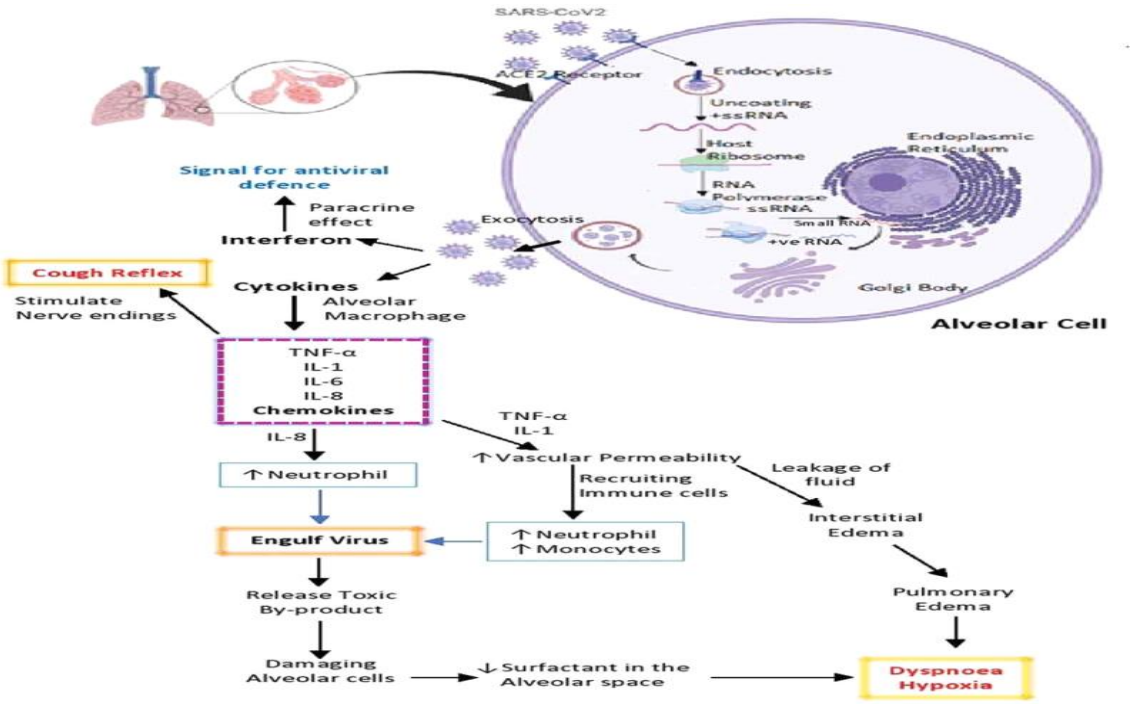

Figure 1: SARS-COV-2 virus replication in alveolar cells.

Neutrophils can injure surrounding tissue by releasing chemical by-products when they consume viruses and detritus (Felsenstein S et al., 2020). Consequently, less surfactant is produced when there is widespread injury to alveolar cells. Collapse of the alveoli is a known risk factor for hypoxemia, or decreased oxygenation (Gonzales Jn et al., 2015) (Figure 1). Additional inflammatory mediators, such as leukotrienes and prostaglandins, which are metabolites of arachidonic acid, are released by injured endothelium cells and white blood cells (WBCs). According to (Abdul Khaleq LA et al. (2018)), leukotrienes cause airways to become constricted, which in turn makes breathing difficult and leads to hypoxemia. The most prominent manifestation of COVID-19 is fever, which is triggered by prostaglandins, interleukin1, interleukin-6, and (TNF-α) (Robb Ct et al., 2020).

When there is an insufficient amount of oxygen in the blood, chemoreceptors in the cardiopulmonary system of the brain act and send a signal to the heart to pump blood more rapidly, which in turn elevates blood oxygen levels (Brinkman Je and Sharma S, 2020). Patients with hypoxemia typically have tachycardia and tachypnea as a result (Marshall Jm,1998). Some people may only have moderate symptoms such as a cough, shortness of breath, and a low-grade fever, or they may show no symptoms at all due to their immune system managing the virus. Alveolar macrophages use TLR-4 receptors to recognize viruses and phagocytize them (Cascella M al., 2020)

Interferons are believed to be the reason for the prevalent occurrence of lymphoma in COVID-19 (Jafarzadeh A. et al.,2020). Hepatocytes are stimulated by IL-6 to create acute phase reactants, which include fibrinogen, hepcidin, and C-reactive protein (CRP) (Effenberger M et al.,2020). Elevated CRP levels in the bloodstream suggest the presence of inflammation and serve as a valuable marker for inflammation (Chen Ld et al.,2020). ARDS in COVID-19 is primarily caused by damaged alveolar tissue, fluid buildup, ventilation/perfusion mismatch, and hypoxemia, all of which are not connected to cardiac function and are believed to be the main factors leading to death (Bansal H and Mittal R, 2020).

2. 5.6. Clinical signs and symptoms.

Eighty percent of COVID-19 patients had mild infections, with varied degrees of severity (Michelen M et al., 2021). About 15% of patients experience severe illness, which is characterized by dyspnea, hypoxia, and abnormalities in the lungs on imaging. Of these, 5% have respiratory failure due to acute respiratory distress syndrome (ARDS), shock, and/or multi-organ dysfunction (Yang X et al., 2020). ACE2 is present in several tissues such as the heart, pancreas, intestines, kidneys, and blood vessels. This suggests that SARS-CoV-2 might potentially invade and damage these tissues, resulting in multiple organ dysfunction syndrome (MODS) (Chai X et al., 2020). Immune-mediated damage is promoted in COVID-19 patients by increased pro-inflammatory mediators and excessive lymphocyte activation. This process leads to a single organ involvement developing into MODS and a moderate disease becoming more severe. Severe cases of the illness may result in coagulation malfunction, ARDS, septic shock, metabolic acidosis, and MODS. Severe infections are more likely to occur in elderly people with comorbidities and lowered immunity (Xie P et al., 2020).

As the patient's condition deteriorates, critical care may be required as patients with ARDS may contract pneumonia. Children often have symptoms that are either extremely minor or nonexistent. Although both males and females are equally susceptible to infection, male patients have a greater chance of suffering less favorable outcomes or potentially dying (Jin Jm et al., 2020). A high fever, fatigue, dry cough, weakness, lack of appetite, muscular soreness, trouble breathing, and the production of phlegm are some of the symptoms that may be experienced (Singhal Ta, 2020).

Both sociodemographic variables and comorbid diseases, which include diabetes, heart disease, chronic renal disease, chronic lung disease, and other conditions, contributed to an increase in the death rate. Another factor that was discovered is that those who have specific comorbidities, such as hypertension (27-30%), diabetes (19%), and coronary heart disease (6-8%), are more likely to be infected with SARS-COV-2 (Zhou F et al., 2020). Additionally, research has shown that individuals with severe COVID-19 experienced the

development of acute renal injury (28.9%), aberrant hepatic function (28.9%), cardiac injury (23.1%), and ARDS (67.3%) (Yang X et al., 2020).

2. 5.7. Methods for diagnosing COVID-19

It is now essential that COVID-19 is detected quickly and accurately to respond effectively and stop the virus from spreading to huge populations. It has also been demonstrated that contact tracking is crucial, as it has made it possible for governments to safeguard public health without totally closing their economies by enabling the methodical encapsulation of caseload rise hotspots. The Centers for Disease Control and Prevention (CDC) has mostly used real-time polymerase chain reaction (PCR) techniques for identifying SARS-CoV-2 since its discovery (Lab Corp, 2021).

The COVID-19 PCR can only determine whether a person has this specific coronavirus infection at this time. However, it may omit individuals who have recovered from the illness and cleared the infection, as well as information on other illnesses or symptoms (Tang Yw et al., 2020). Additionally, serology tests are crucial because they can monitor the disease's course, evaluate the immunological response (Peeling Rw et al., 2020), and determine how long a patient's immune protection lasts after recovering from COVID-19 (Anawa Biomedical Services and Products. SARS-COV-2 (Covid-19, 2021).

The serologic test uses an enzyme-linked immunosorbent assay (ELISA) to identify SARS-COV-2 antibodies, namely IgG and IgM, in blood or plasma. The CDC uses pure SARS-COV-2 S protein, devoid of active virus, as an antigen in their ELISA test (Freeman B et al., 2020). Serologic testing has a limitation in that it cannot completely exclude the possibility of cross-reactivity with antibodies generated by other coronaviruses (Freeman B et al., 2020).

2. 5.8. Treatment and preventive measures

Treatment is symptomatic in the absence of clinically established options; supportive care and infection prevention and control measures are currently part of clinical management (WHO, 2020). Therapeutic medications that are currently on the market include corticosteroids, IL-6 antagonists, vitamin C, azithromycin, Remdesivir, and chloroquine, among other antiviral and supportive medications (CDC, 2023.). Creating a COVID-19 vaccination that works because of a global research priority (WHO,2021). The regulatory bodies authorized several vaccinations to prevent COVID-19 (FDA, 2021).

2. 5.9. Preventive measures

Measures aimed at stopping the spread of COVID-19 were centered around public health and preventative approaches, including personal hygiene, social distancing, testing, case tracing, and isolation (Wilder-Smith A and Freedman DO,2020). It is essential to

prioritize hand cleanliness, personal protection equipment (PPE), avoiding crowds, practicing social distancing, isolating when necessary, closing workplaces and schools, quarantining, and adhering to travel restrictions (Güner R et al.,2020). After community transmission was confirmed, a Singaporean study recommended the use of quarantine measures, strict social distancing in the workplace, and the closure of schools to contain the epidemic (Koo Jr et al.,2020).

It was also discovered that taking these steps lowered mortality, infection rates, and intensive care unit (ICU) hospitalizations (Rodriguez-Morales Aj et al., 2020). Social separation functions effectively in stopping community transmission and lessens interpersonal contacts (Wilder-Smith A and Freedman Do, 2020). It was highly recommended that individuals who may be asymptomatic or pre-symptomatic wear face masks to prevent the spread of COVID-19 (European Centre for Disease Prevention and Control, 2021).

Face masks effectively reduced the transmission of SARS-COV-2 in heavily affected areas of Italy and New York City (Zhang R et al., 2020). SARS-CoV-2 affects people of all ages, but the elderly and those with past health difficulties are more likely to die (Daoust, 2020). (Daoust et al. 2020) found that elderly people are more prone to COVID-19 and are disproportionately impacted. To lower the risk of SARS-COV-2 infection, the elderly were advised to limit their contact with others and remain at home (CDC,2020).

Global advisories were developed to limit the spread of the new coronavirus, including special travel precautions. Airports set up screening booths to identify sick travelers (Guardian Staff and Agencies. Coronavirus:2020). Some nations, such as Japan, implemented quarantine checks at airports and other entrance points (The Japan Times, 2020). Airlines issued precautionary measures for passengers entering and leaving China (China Airlines, 2020). Quilty et al. (2020) researched the efficiency of airport screening in detecting COVID-19-infected travelers. Many nations imposed lockdowns and mobility controls to protect the public from possible COVID-19 carriers (New Straits Times. Covid-19: 2020).

Studies showed that wearing a surgical mask may decrease virus exposure for infected individuals by an average of six times, with a range from 1.1 to 55 times (Booth Cm et al., 2013). Healthcare personnel were required to comply with WHO guidelines for personal protective equipment (PPE) by using medical/surgical masks, gowns, gloves, and face shields while interacting with infected patients or collecting samples (WHO. 2019). It was discovered that quarantine was the most successful strategy for lowering death rates and the number of infected cases (Bavli L et al., 2020).

Quarantine was found to be capable of reducing the number of infection cases from 81% to 44% and decreasing the mortality rate from 61% to 31%, as reported in a study of

29 COVID-19-related studies (Nussbaumer-Streit B et al.,2020). Early in the pandemic, travel restrictions and lockdowns in Australia (Costantino V et al., 2020) and China (Wilder-Smith A et al., 2020) substantially reduced the rate of transmission. In countries including South Korea, Singapore, Taiwan, and Hong Kong, testing, isolation, and contact tracking were effective in limiting the spread of the virus (Salathe M et al., 2020). On the other hand, Italy saw more extensive impacts since the nation did not implement such preventive measures in the early stages of the pandemic (Boccia S et al., 2020).

2. 5.10. Treatment

Significant work has been conducted to find antiviral therapies for COVID-19. Patients hospitalized with COVID-19 who participated in the Adaptive COVID-19 treatment trial (ACTT-1) provided preliminary results. There were 60 trial sites in the double-blind randomized control trial (RCT), with 13 subsites located in the following countries: the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1). There was evidence of lower respiratory tract infection, and the findings showed that remdesivir was associated with a shorter median recovery time (11 vs. 15 days) compared to placebo (Beigel Jh et al., 2023).

2. 5.10.1. Remdesivir.

Despite the lack of statistical significance, a Chinese study that was prematurely halted due to remdesivir side effects found that Covid-19 patients whose symptoms lasted at least 10 days healed faster than the placebo group (Wang Y et al., 2020). In a trial conducted in the US, Europe, and Canada, 36 out of 53 patients (68%) patients with severe COVID-19 who were hospitalized showed clinical improvement in after receiving compassionate use of remdesivir (Grein J et al.,2020). Another randomized controlled trial (RCT) found that 584 patients with mild COVID-19 at 105 institutions in the US, EU, and Asia had a statistically superior result with a 5-day treatment of Remdesivir compared to usual management (Spinner Cd et al.,2020).

Overall mortality, ventilation requirement, and duration of hospital stay were found to be either minimally or not affected by Remdesivir (containing hydroxychloroquine, lopinavir/ritonavir, and interferon), according to the WHO Solidarity Trial, which took place in thirty different countries (WHO, 2020). The UK recovery trial found that lopinavir/ritonavir did not enhance survival rates, affect clinical progression, or shorten the length of hospitalization (University of Oxford, 2020). After an interim analysis showed that hospitalized COVID-19 patients did not exhibit significantly reduced mortality relative to the standard of therapy, the lopinavir/ritonavir arms of the WHO solidarity and UK recovery trials were halted (WHO, 2021).

The Food and Drug Administration (FDA) initially authorized remdesivir under the brand name Valkyr, "for the treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg" (Food and Drug Administration, 2021). On July 3, 2020, the European Commission granted remdesivir conditional marketing permission to treat Covid-19 patients (European Commission. Daily News, 2020). Oseltamivir (Wang Z et al., 2020) and Arbidol (Wang X et al., 2020) are two anti-flu medications that have been used to treat Covid-19 patients and have shown some degree of success.

2.5.10. 2.Corticosteroids

Corticosteroids have attracted significant interest in the COVID-19 therapeutic field (WHO, 2020) and have been shown to help treat several COVID-19-related illnesses, including pneumonia, sepsis, and ARDS (Annane D et al., 2019). In the recovery trial, dexamethasone was shown to decrease death in severely sick COVID-19 patients by a third (Ledford H, 2020). People who required more oxygen or were on a ventilator benefited the most from the medicine; however, people with milder symptoms showed no improvement.

Other research, however, reported contradictory findings; some (Kolilekas L al., 2020) showed advantages, while others (Yuan M et al.,2020) showed possible harm. A meta-analysis of 15 trials (Yang Z et al.,2020) found that among COVID-19, SARS, and MERS patients, using corticosteroids could increase the risk of death and multi-organ failure, but there was no mortality benefit. Systemic corticosteroids may have increased mortality in less severe cases of COVID-19, but they likely reduced 28-day mortality in individuals with severe cases, according to new research from the World Health Organization (European Commission. Daily News, 2020).

2.5.10.3. Immunomodulatory/antiviral medications

Chloroquine and hydroxychloroquine are frequently utilized as immunomodulatory treatments. Both medications are now approved by the FDA for the treatment and prevention of malaria. Under an emergency use authorization (EUA), the Food and Drug Administration has approved chloroquine and hydroxychloroquine for the treatment of COVID-19 in hospitalized patients in cases when access to or participation in clinical studies is not feasible (US-FDA, 2021). As of September 3, 2020, 38 chloroquine trials (Randomized trials) and 212 hydroxychloroquine trials (Randomized trials) were registered on ClinicalTrials.gov (Clinical Trials.Gov, 2021).

However, the outcomes of using 500 mg of chloroquine every 12 hours with hydroxychloroquine, were not positive. The recovery study found that hydroxychloroquine did not reduce 28-day mortality compared to the standard of therapy. Patients given hydroxychloroquine were more likely to die or need intrusive artificial breathing than

patients given the gold standard of treatment; they also had a longer median hospital stay (Horby P et al., 2020). Treatment with hydroxychloroquine or azithromycin alone or in combination failed to alleviate symptoms in a Brazilian multicenter, randomized, open-label, three-group controlled trial including hospitalized patients with mild to severe COVID-19 (Cavalcanti Ab et al., 2020). Compared to patients who did not receive either medication, individuals who received hydroxychloroquine or hydroxychloroquine plus azithromycin experienced an increased frequency of adverse events (such as elevated liver enzyme levels and prolonged QTc intervals) (Cavalcanti Ab et al., 2020).

Hospitalized patients in Brazil with moderate to severe COVID-19 were included in a randomized, open-label, three-group controlled trial. The results showed that neither azithromycin nor hydroxychloroquine alleviated symptoms (Furtado Rhm et al., 2020). There was no evidence that hydroxychloroquine, either in combination with azithromycin or alone, was beneficial in large-scale retrospective observational studies conducted on hospitalized COVID-19 patients (Geleris J et al., 2020). One large retrospective observational research in the United States found that therapy with hydroxychloroquine alone or in combination with azithromycin decreased COVID-19-related mortality (Arshad S et al., 2020).

Several randomized trials including COVID-19 patients who were not hospitalized were unable to show a therapeutic benefit from hydroxychloroquine treatment (Skipper Cp et al., 2020). There are significant toxicities associated with treating COVID-19 with high doses of chloroquine, including increased mortality and QTc prolongation, according to the US National Institutes of Health, COVID-19 Treatment Guidelines (National Institutes of Health (NIH,2021). Caution has been advised regarding the usage of azithromycin and hydroxychloroquine together since it has been linked to QTc prolongation in COVID-19 individuals (Institute for Safe Medication Practices, 2020).

2.5.10.4. Immune-based treatment

Human blood-derived products and immunomodulatory therapy are two of the drugs that are employed in the treatment of COVID-19 levels that range from moderate to critical. The immune response is regulated by these agent substances. Additionally, immunoglobulin products and convalescent plasma are acquired from persons who have recovered from COVID-19 infection. Other products produced from human blood are also obtained from these patients (Wang X et al., 2020). COVID-19 patients may also be treated with additional medications, such as corticosteroids (e.g., glucocorticoids) (Horby P et al., 2020), interleukin inhibitors (Shakoory B et al., 2016), interferons (Zhou Q et al., 2020), and kinase inhibitors (Cao Y et al.,2020), which have been licensed to treat various immunological and/or inflammatory syndromes.

Convalescent plasma has been proposed as a potential aid in both viral suppression and modifying the inflammatory response (Wang X et al., 2020). Reviewing data from more than 70,000 patients who were given COVID-19 convalescent plasma, researchers from the FDA and the Mayo Clinic in the US found that high-titer antibody plasma may have better effects than low-titer plasma in patients who are not intubated (Food and Drug Administration, 2021).

Furthermore, 20,000 inpatients who were given convalescent plasma for COVID-19 were evaluated by the FDA. Overall, the study found a minimal frequency of severe adverse events (SAEs), indicating that transfusion is safe for COVID-19 patients (Joyner Mj et al., 2020). It is important to note that on August 23, 2020, the FDA approved an EUA for the use of convalescent plasma in hospitalized COVID-19 patients (Food and Drug Administration, 2021).

It was discovered that interferon β works well against coronaviruses (Sallard E et al., 2020). Interferon was found to have little to no effect on overall mortality, ventilation demand, and length of hospital stay in the WHO Solidarity Trial (WHO et al., 2020). There was a substantial increase in the likelihood of both quick recovery and clinical improvement for hospitalized SARS-CoV-2 patients who were given inhaled nebulized interferon β-1a, according to the WHO ordinal scale for clinical improvement (Peiffer-Smadja N et al., 2020).

2.6. 0 Vaccine.

The WHO launched the COVID-19 Solidarity vaccination experiment on May 28, 2020. This worldwide, randomized controlled phase III trial evaluated many vaccine candidates (WHO. What we know about COVID-19 vaccine development 2021). This experiment, one of the largest, included about 280,000 patients from 470 hospital locations across 34 nations (WHO. What we know about COVID-19 vaccine development 2021). The experiment intended to evaluate the efficacy of numerous vaccinations within a short time of introduction to avoid the use of ineffective vaccines to treat COVID-19 patients (Krause P et al., 2020).

By October 2020, 42 COVID-19 vaccine candidates were in clinical testing, with 10 in phase 3 trials (Ophinni et al., 2020). There were 151 vaccine candidates for preclinical testing (WHO. What we know about COVID-19 vaccine development, 2021). Four vaccinations were deemed to be effective in preventing COVID-19: Pfizer/BioNtech, Moderna, Oxford, and Sputnik V. (Ophinni et al., 2020). The first two vaccinations gained emergency clearance for COVID-19 prevention (FDA. Moderna COVID-19 Vaccine.2021). However, further research was needed to determine the efficacy of these vaccinations against newly detected SARS-CoV-2 strains in the UK and other countries.

2.6.1. The CORONAVAC vaccine's efficacy

2.6.1.1. Clinical trial efficacy

The percentage of a disease that is reduced in those who receive vaccinations during a clinical trial is known as vaccine efficacy (WHO, 2021). Three phase 3 clinical trials of CORONAVAC have been reported. One involved 10,214 persons between the ages of 18 and 59 and was conducted at 24 sites in Turkey between September 2020 and January 2021 (before the development of variations of concern). A placebo or two doses of CoronaVac were given to participants at random (vaccinations were spaced 14 days apart) (Tanriover Md et al., 2021).

Before the appearance of variants of concern, a second study was carried out at 16 sites in Brazil between July 21 and December 16, 2020, involving 12,396 healthcare personnel who were aged between 18 and 59 and 60 years of age or older (≥14 days apart) (Palacios R et al.,2021). The third study, which took place in Indonesia between August 11, 2020, and October 21, 2020 (before the discovery of variations of concern), involved 1620 healthy volunteers between the ages of 18 and 59 who were spaced 14 days apart (Fadlyana E et al., 2023).

The efficacy in preventing symptomatic COVID-19 in Turkey (Tanriover Md et al.,2021) was 83.5% (95% CI, 65.4% to 92.1%), Brazil reported a rate of 50.7% (95% CI, 35.9%-62.0%), and Indonesia achieved 65% (95% CI, 20% to 85%) (Fadlyana E et al., 2021). Researchers generated a pooled value using inverse variance-weighted random effect models and log-transformed impact size estimates from each phase 3 experiment. The combined effectiveness for preventing symptomatic COVID-19 was determined to be 67.7% (95% CI, 35.9% to 83.7%). In other words, when compared to placebo users, two doses of CoronaVac reduced COVID-19 risk by 67.7%. The effectiveness in terms of prevention of COVID-19-related hospitalization (in Turkey), cases needing help, and moderate/severe cases (in Brazil) were 100.0% (95% CI, 20.4% to 100.0%), 83.7% (95% CI, 58.0% to 93.7%), and 100.0% (95% CI, 56.4% to 100.0%), respectively (Palacios R et al., 2021). CoronaVac is therefore clearly more successful at preventing severe COVID-19 outcomes than it is at preventing SARS-CoV-2 infections.

2.6. 1.2. Effectiveness against non-variants of concern

The treatment included two doses of CORONAVAC, with a 28-day interval between each. Testing the vaccination's efficacy fourteen days or more following the second dose revealed success rates of 65.9% (95%CI, 65.2%-66.6%), 87.5% (95%CI, 86.7%-88.2%), 90.3% (95%CI, 89.1%-91.4%), and 86.3% (95%CI, 84.5%-87.9%) in preventing covid-19, hospitalization, intensive care unit admission, and fatalities associated with the virus. respectively. The efficacy of these was substantially greater as compared to the effectiveness that occurred after the first dose (Jara A et al., 2021). According to the

subgroup data, persons over 60 years old had lower efficiency from two doses in reducing hospitalization and ICU admission than adults between the ages of 16 and 59 (Jara A et al., 2021).

2.6.1.3. Effectiveness against concerning SARS-CoV-2 variants.

Concerning SARS-CoV-2 variations are more contagious or have changed negatively from the original virus. According to estimates, the Alpha variant (B.1.1.7) is 1.4–1.9 times more transmissible than the wild-type SARS-CoV-2. Between March 1, 2021, and May 31, 2021, retrospective cohort research involving 4,067 healthcare workers in Turkey was carried out, during the time in which the Alpha variant was prevalent. Following the second treatment, the follow-up duration was 104 days on average. The effectiveness of two doses of CORONAVAC in preventing Alpha variant infection was 39% (95% CI, 20%-64%) (Can G et al.,2022).

The early 2021 discovery of the Gamma variant (P.1) in Manaus revealed that it was 1.7–2.4 times more transmissible than the parent virus (Faria Nr et al., 2021). Between January 17 and April 29, 2021, a matched, test-negative case-control real-world investigation involving 22,177 people over the age of 70 who received two doses of immunization (spaced 28 days apart) across 645 cities was carried out in Brazil. Giving a second dose at least 14 days after the first one reduced the risk of hospitalization by 46.8% (95% CI, 38.7% to 53.8%), deaths from COVID-19 by 55.5% (95% CI, 46.5% to 62.9%), and symptomatic COVID-19 by 61.2% (95% CI, 48.9% to 70.5%). This occurred in a population that had high rates of the gamma version of the virus (Ranzani Ot et al., 2021). A retrospective longitudinal study of over 25 million CoronaVac vaccines in Brazil from January 18 to July 24, 2021 (P.1) found that adults over 60 had lower rates of hospitalization, ICU admission, and death 14 days after the second dose compared to those under 60 years old (Cerqueira-Silva T et al., 2021).

The Delta (B.1.617.2) variant was shown to be 60% more transmissible than the Alpha form (Shiehzadegan S et al., 2021). From September 1, 2021, to September 30, 2021, researchers in Malaysia tracked 9.92 million people infected with SARS-COV-2, and the dominant strain was found to be the Delta variant. Vaccine efficacy against COVID-19 reduced from 74.5% (95% CI, 70.6% to 78.0%) at 1-2 months to 30.4% (95% CI, 18.8% to 40.3%) at 3-5 months following the second dose in those aged ≥15 years. Additionally, the efficacy against ICU admission fell from 56.0% (95% CI, 51.2% to 60.2%) to 28.7% (95% CI, 12.2% to 42.1%). Effectiveness against death was steady (Suah Jl et al.,2022).

The Omicron (B.1.1.529) variation proliferated approximately 70-fold quicker than the Delta version in the bronchi (Harvard Medical School, 2022). Ecological research assessing the effectiveness of vaccinations was conducted in Hong Kong, China, from December 31, 2021, to March 8, 2022, during an Omicron variant-associated COVID-19

epidemic. 14,861 patients between the ages of 20 and 69 who tested positive for SARS-CoV-2 were studied. The research revealed that CORONAVAC was effective after only one dose and offered protection against severe or catastrophic outcomes from Omicron infection. Two doses offered superior protection against severe illness or death compared to a single dosage (McMenamin Me,2022).

Chapter III

3.0 Materials and Methods

3.1 Introduction

The study objectives, demographics, participant selection, and data collection and analysis procedures are all outlined in this section.

3.2. Data and sample collection periods.

The data and information available have been collected from the database of the nearby university hospital. According to this information, a total of 591 volunteers from Northern Cyprus, including 283 men and 308 women, received two doses of the CORONAVAC vaccine. The age of the participants varied between 4 and 95 years, and the time interval between the first and the second dose was between 1 and 5 months. Volunteers gave their consent for their samples to be analyzed at the NEU micro-bacteriology lab 100 days or more after the second dose of the CORONAVAC vaccine,

3.3. Materials and Equipment Used.

The data and information available were collected from the database of Near East University Hospital.

3.4. Methods

3.4.1 Serum anti-RBD IgG antibody assay.

Venous blood samples collected were separated after centrifugation of blood samples at 4,500 rpm for ten minutes. The anti-RBD IgG levels in the serum samples were quantitatively measured by chemiluminescent microparticle immunoassay (CMIA) using a commercially available Abbott SARS-CoV-2 IgG II Quant ELISA assay kit (Abbott Diagnostics, Abbott Park, IL, USA) and automated immunoassay analyzer Abbott Architect ci4100.

CHAPTER IV

RESULTS.

According to the results of our study, on the one hand, the best growth of antibody levels as a function of time was detected. On the other hand, the equality of antibody levels at the maximum threshold in general between the female and male sex was identified (Fig. 2). By comparing individually, according to each sex, the antibody levels as a function of time, it was detected that from 100 days or more, the antibody levels were higher than those observed from less than 100 days (Table 1). In addition, the time intervals before the antibody test were slightly higher in women than in men (Figure 2). Furthermore, we observed an inequality of DS values as a function of time, which remained significantly higher in favor of the male sex compared to the female sex (Table 1). Also, the antibody levels below the maximum threshold remained identical between the female and male sex (Table 2). Finally, beyond the maximum thresholds, the antibody level remained constant.

	Less than 100 days			100 days or more		
GENRES	Mean	SD	N	Mean	SD	N
MALES	1426.63261	2996.69611	230	8809.15094	14317.2171	53
FEMALE	1622.77615	2915.00142	260	9651.95625	12779.5968	48

TABLE 1: Comparison of antibody levels.

GENRES	Less than 100 days	100 days or more	Below threshold?	Summary	Adjusted P Value
MALES	-7383	-9502 to -5263	Yes	****	<0.0001
FEMALE	-8029	-10214 to -5844	Yes	****	<0.0001

TABLE 2: Comparison antibody level

DS**:** shows the deviation in the data. It must be given in mean+- SD format

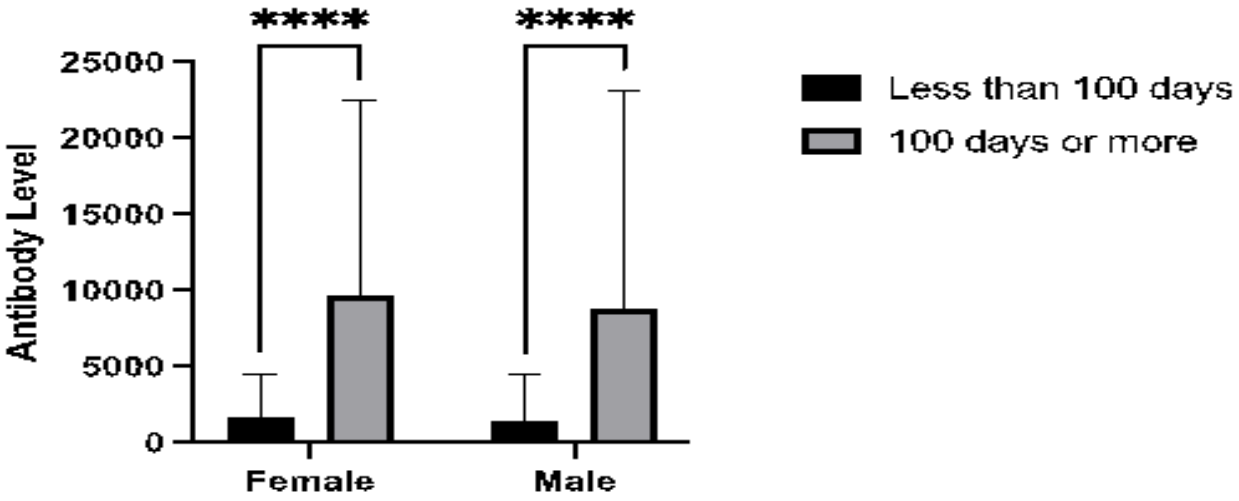

Figure2: Graph showing antibody rate versus time.

CHAPTER V

DISCUSSION.

The vaccination campaign against SARS-CoV-2 was an effective method of stopping the progression of the COVID-19 pandemic. This study demonstrated the beneficial results of CORONAVAC in women and men. The results have shown that two doses of CORONAVAC 'significantly stimulated the increase and the stability' of the antibody levels in the populations vaccinated with CORONAVAC. During this period, the antibody status in the population may indicate acquired immunity to exposure to SARS-COV-2.

After 100 days, a significant increase in the antibody level was detected, contrary to some study results. This is the case of research conducted in Brazil which examined the antibody response of the CORONAVAC vaccine against SARS-CoV-2 in 1237 health workers after the first (1D) and second (2D). The result of this etude showed a decrease in antibody levels 6 months after vaccination with the coronavirus vaccine. According to these researchers, the degradation of antibodies should decrease because not all the plasmablasts generated by vaccination develop into long-term memory plasma cells (Maber P et al.,2021). Thus, the success of the vaccine depends on the generation and maintenance of immunological memory (Palm AE and Henry C, 2019).

Then, this study showed that the females had antibody levels identical to those observed in men after vaccination with the CORONAVAC vaccine. This not the case with the results of some studies showing the inequality of the level of antibodies after CORONAVAC vaccination in the population. For example, the study conducted in Brazil where females had much greater antibody-positive rates and titers, according to the study. Antibody responses differ between men and women, affecting susceptibility to infectious illnesses and vaccination responses (Klein SL and Flanagan KL, 2016). Sex-based immunological differences may explain male-biased COVID-19 mortality (Jin JM et al., 2020) and the stronger female immune response to COVID-19 vaccinations, as described in the literature (Bayram A et al.,2021).

In our study, there was also a large variation in antibodies from two-time differences (less than 100 days and times more than 100 days) in both men and women. In addition, the antibody response is, in fact, significantly higher after a hundred or more days in each sex. This significant increase can be explained either by the time it takes for antibody levels to reach their maximum after the second dose. Either due to the functioning of our immune system. Vaccination requires two types of B lymphocytes, white blood cells responsible for producing antibodies. "The first ones will immediately produce antibodies. The second, called memory B lymphocytes, will keep in memory the manufacturing plan of these antibodies and will be stored in the bone marrow for later. After having been requested for the first time by the first injection, our body knows well the antigen presented to it by the

booster dose. "He will directly solicit these memory cells. These B lymphocytes, sensitized by the first injection, will mobilize very quickly and produce very large quantities of antibodies.

The seroprevalence of anti-SARS-CoV-2 antibodies in the population of Northern Cyprus before vaccination was not evaluated, which is one of the limitations of this research. A definition of the seroconversion (from IgM to IgG) rate has not been established as a result. In addition, there were no particular risk categories that were considered, such as pregnant women or persons who were unwell. Moreover, given that the male group was underrepresented, it is necessary to do more research before drawing any conclusions on gender differences in vaccine response. Furthermore, neither the neutralizing antibody activity nor the T-cell responses were examined throughout the study. Additionally, it was not possible to compare the effectiveness, safety, and immunogenicity of CORONAVAC with other potential vaccine candidates. Nevertheless, our assessment of CORONAVAC has the potential to provide a scientific foundation for the optimization of vaccination tactics on a worldwide scale.

CHAPTER VI

6.0 CONCLUSION AND RECOMMENDATIONS.

6.1 CONCLUSION

The primary aim of this study was to compare the levels of antibodies after vaccination with CORONAVAC at two doses according to sex. This study showed that antibody levels in women after vaccination with CORONAVAC vaccines were identical to those detected in men. To better understand the protector's antibody levels over time, additional large-scale studies are needed to assess immune levels over a longer period.

6.2 RECOMMENDATION

The study should be extended to compare the antibody levels of the CORONAVAC vaccine with other types of vaccines to determine which will be most effective in the coming years. Furthermore, the study can be expanded to determine the average time after vaccination that the antibody levels will be maintained at high levels before decreasing.

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