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Association of Human Abo and Rh Blood Group Systems With Covid-19 Infection Susceptibility in North West Amhara Region, Ethiopia

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BAHIR DAR UINVERSITY

COLLEGE OF SCIENCE

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BY:

WUBESHET MENGESHA

A THESIS SUBMITTED TO THE DEPARTMENT OF BIOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN BIOLOGY

ADVISOR: BIZUAYEHU KERISEW (PhD)

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APPROVAL SHEET OF THESIS

As the thesis advisor, I hereby certify that I have supervised, read, and evaluated this thesis entitled "**Association of Human ABO and Rh Blood Group Systems with COVID-19 Infection Susceptibility in North West Amhara Region, Ethiopia**" by Wubeshet Mengesha prepared under my guidance. I recommend that it can be submitted as fulfilling the thesis requirement.

Advisor's name Bizuayehu Kerisew, (PhD) Signature ---------- Date----------

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As a members of the Board of Examiners of the Msc, Thesis open Defense Examination, we certify that we have read and evaluated the thesis prepared by, **Wubeshet Mengesha** and examined the candidate. We recommended that the thesis be accepted as fulfilling the thesis requirement for the degree of Master of Science in Biology.

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DECLARATION

I declare that this Msc thesis is my original work that has not been presented to any University for the fulfillment of the Msc program, and all sources of materials used for this thesis have been duly acknowledged. This thesis is submitted in partial fulfillment of the requirements for the degree of Master of Science in biology at Bahir Dar University. It can be deposited in the University Library to be made available to borrowers under the rules of the Library. I solemnly declare that this thesis is not submitted to any other institution anywhere for the award of any academic degree, diploma, or certificate.

Candidate Wubeshet Mengesha Alebachew

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ABSTRACT

COVID -19 infections are a serious problem in the world, Africa, Ethiopia, and Amhara region. ABO blood types play a significant role in various illnesses like oncological, cardiovascular, and certain infectious and non-infectious diseases. Several types of research have been conducted to show the association between the human ABO and Rh blood group systems with COVID-19 infection susceptibility Therefore, this study was aimed to investigate the association of the ABO and Rh blood group systems with COVID-19 infection susceptibility from confirmed cases in referral hospitals of FHCSH and GURH in the Northwest Amhara Region, Ethiopia. A hospital-based case-control study was conducted. Data analysis of demographic and clinical variables was performed using SPSS version 25. Of the 410 (206 males and 204 females) study subjects, 204 were found to be COVID-19 positive (104 males (50.98%) and 100(49.02%) female) and 206 were COVID-19 negative (102 males (49.5%) and 104(50.5%) female). Of the 204 COVID-19 positive cases, 174 (86 male (42.2%) and 88 female (43.14%) recovered from COVID-19 infection diseases, while 30 (18 (8.8%) male and 12 (5.1%) female) died as a result of COVID-19 infection. In Chi-square analysis, the human ABO blood groups were significantly associated with deceased and recovery (P = 0.009) groups. There was also a statistically significant association between the severity of illness and COVID-19 infection with the ABO blood group systems (P = 0.000). However, sex, age, infectious and non-infectious diseases, and COVID-19 symptoms were not significantly associated with the recovery and deceased groups. In multivariate analysis, the odds of COVID-19 infection susceptibility were five times (AOR: 6.531[95%CI, (1.374-31.031)], p=0.018 higher in the study subjects whose age range were found between 51 and 60 years. The blood groups AB were significantly associated with COVID-19 infection (AOR: 0.192[95%CI, (0.054-0.683)], (P=0.011) and subjects who had infectious diseases of pneumonia were two times more likely to have COVID-19 infection susceptibility than those of infectious diseases (AOR: 3.807[95%CI, (1.021–14.200)], p=0.047) was statistically significant.

Keywords: - COVID-19 susceptibility, ABO blood groups, Rh blood groups, Northwest Ethiopia.

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LIST OF ABREVATIONS /ACRONYMES/

ABCA =ATP Binding Cassette

CAD = Coronary Artery Diseases

CDC=Center for Diseases Control and prevention

COPD =Chronic Obstructive Pulmonary Diseases

COVID -19 = Corona Virus Diseases 2019

CVD =Cardio Vascular Diseases

FDA =Food and Drug Administration

HHBGA =Human Histo Blood Group Antigen

IALP =Intestinal Alkaline Phosphate

IBV =Infectious Bronchitis Virus

IUGR =Intrauterine Growth Restriction

MERS =Middle East Respiratory Syndrome

MHV = Murine Hepatitis Virus

NCP =Novel Corona virus Pneumonia

SARS =Severe Acute Respiratory Syndrome

T2DM =Type two Diabetes Mellitus

TGEV =Transmissible Gastro Enteritis Virus

WHO=World Health Organization

1. INTRODUCTION

1.1 Background of the study

Coronavirus disease 2019 (COVID-19), also named novel coronavirus pneumonia (NCP), was first reported in China, Wuhan, in December 2019 and then gradually spread throughout the world. The pneumonia outbreak has become a serious public health event. The COVID-19 infections were caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is a new member of the coronavirus family (Gralinski *et al*., 2020).

There are currently seven known coronaviruses that can infect humans, such as the severe acute respiratory syndrome (SARS) coronavirus and the Middle East respiratory syndrome (MERS) coronavirus, Hcov-NL63 that usually mild respiratory illness, Hcov-229E, Hcov-oc43 and HKU1 coronavirus. Based on current epidemiological investigations, the incubation period is 1–14 days and typically 3–7 days, but there are also cases in which an incubation period of over 14 days is reported (Wang *et al.,* 2020). Individuals are contagious during the incubation period, and asymptomatic infection may also become the source of infection.

Respiratory droplets and close contact are the main transmission routes. COVID-19 infection is clinically characterized by fever, fatigue, and dry cough. In severe cases, affected individuals can undergo acute respiratory distress syndrome, septic shock, and even death (Chan, *et al.,* 2020).

ABO blood types play a significant role in various illnesses, like oncological, cardiovascular, and certain infectious and non-infectious diseases (Fan *et al.,* 2020). To name a few examples, studies have reported that blood group O substantially reduces the risk of hepatitis B. Simultaneously, rotavirus gastroenteritis was more common in patients with blood type A and less frequent in patients with blood type B (Mohammedali and Pourfathollah, 2014).

It was also observed that people with the AB blood type were 2.5 times more likely to experience dengue hemorrhagic fever than other blood types (Elnady *et al.,* 2017). Previous analyses of SARS-CoV-1 have identified a link between the chances of infection with the blood type, in which people with blood group O had a low risk of infection with SARS-CoV-1(Chen *et al.,* 2005). Another study reported that the presence of blood group O might significantly

decrease the risk of hepatitis B, and the distribution of Rh in HBV-infected individuals was higher between Rh-positive donors.

A study in Egypt found that rotavirus gastroenteritis was significantly more prevalent among those with blood type A and significantly less prevalent among those with blood type B (Elnady *et al.,* 2017). Another study carried out by (Degarege and colleagues, 2012) reported that malaria patients with blood group A had a higher risk of anemia than those with O and non-A phenotypes (Degarege *et al.,* 2012*).* Murugananthan and colleagues from Sri Lanka discovered that patients with AB blood had a risk of developing dengue hemorrhagic fever that was more than 2.5 times higher than those with other blood types (Murugananthan *et al.,* 2018).

In addition to this, a meta-analysis suggested that blood types A, B, and AB might not affect susceptibility to nor virus infection. However, those with blood type O appeared to be more susceptible to this infection (Lai *et al.,* 2020). Because SARS-CoV-2 is a completely new virus, it is unclear whether the ABO blood groups affect individuals' susceptibility to COVID-19 infection. In particular, the blood groups were recognized to influence susceptibility to certain viruses, including SARS-CoV-1 and norovirus.

Blood group A and B glycosyltransferases also affect glycosylation in a large number of cell types, including epithelial cells in the respiratory tract and shed viral particles. Recently, Zhao and colleagues found that ABO blood groups presented a different risk of contracting COVID-19 infection as a result of being exposed to SARS-CoV-2 (Zhao *et al.,* 2020) For the similar coronavirus SARS-CoV responsible for SARS, a study showed experimentally that for SARS-CoV synthesized by cells that expressed the A histo-blood group antigen, the interaction between S protein and its membrane receptor, ACE2, could be blocked by anti-A blood group antibody(Mahmud *et al.*, 2021).

Several types of research have been conducted to show the association between the human ABO and Rh blood group systems with COVID-19 infection susceptibility. Therefore, this study is aimed at ascertaining the association of the ABO and Rh blood groups systems with COVID-19 infection susceptibility from confirmed cases in referral hospitals in the Amhara Region (Felege Hiwot Comprehensive Specialized Hospital and Gondar University Referral Hospital),

Northwest Ethiopia. But the results were not consistent, and such a study has yet to be conducted in Ethiopia.

1.2 Statement of the problem

Evaluation of the association of the human ABO blood group system with COVID-19 infection susceptibility is necessary to prevent and control the disease. Now a day, COVID-19 infection is a crucial concern to a large extent in the world, especially in Africa, Ethiopia, and particularly in the Amhara region. The study was conducted at Felege Hiwot Comprehensive Specialized Hospital and Gondar University Referral Hospital in the Amhara region. Those hospitals are the biggest hospitals in the Amhara region that provide health services and serve as referral centers for other district hospitals in the region. The hospitals provide services for more than seven million people. Prevention and control methods of COVID-19 infection are important to decrease COVID-19 infection, the death of humans, and the development of the region.

1.3 Objectives of the Study

1.3.1 General objective

The general objective of this study was to investigate the association of human ABO and Rh blood group systems with COVID-19 infection susceptibility in the study area.

1.3.2 Specific objectives

The specific objectives of this study were:-

- To determine the distribution of ABO blood groups among COVID-19 positive cases in the study area.
- To determine the distribution of Rh blood groups among COVID-19 positive cases in the study area.
- To evaluate the association of human ABO blood group system with COVID-19 infection susceptibility in the study area.
- To evaluate the association of human Rh blood group system with COVID-19 infection susceptibility in the study area.
- To evaluate the association of other diseases and COVID-19 severity.

1.4 Significance of the study

Since COVID-19 infection is the main problem in the world, Africa, Ethiopia, and the Amhara region, assessing human ABO and Rh blood group systems with COVID-19 infection susceptibility would help to give alarming to communities and health workers towards feedback protection and control mechanisms to tackle COVID-19 infection. This study provides information for future studies and investigation into important other risk factors associated with COVID-19 infection susceptibility

In addition to this, the result of the study will be used as a source for other studies and for designing vaccination priorities.

1.5 The limitation of the study

This study was focused only on Felege Hiwot Comprehensive Referral Hospital and Gondar University Referral Hospital. For financial, study period and security reasons, it was difficult to cover all comprehensive specialized hospitals in the Amhara region within the given time, financial and security reasons. As a result, the sample size and geographic coverage are limited.

2. LITERATURE REVIEW

2.1 Corona virus

Coronaviruses have repeatedly evolved during the past 1000 years (Forni *et al.,* 2017). The first recovery of coronaviruses involved the identification of illnesses in animals, followed by the isolation of infectious bronchitis virus (IBV) from chickens in 1937(Beaudette and Hudson, 1937) and murine hepatitis viruses (MHV) from mice in 1949 (Cheever *et al.,* 1949). Pigs were found to carry a transmissible gastroenteritis virus (TGEV) in the United States in 1946(Cheever and Daniels, 1949). Human coronaviruses were first characterized in the 1960s by respiratory tract infections (Kahn and Mcintoshk, 2005). The two first isolated viruses were B814 and 229E (Tyrrell and Byone, 1966). Since then, several other coronavirus strains have been isolated from humans using tissue culture (OC16 and OC43) (Tyrrell *et al.,* 1975). The number of identified coronaviruses has continued to increase significantly to include viruses of several additional animal species such as calves, dogs, cats, bats, sparrows, rabbits, and turkeys (Lai *et al.,* 2020).

In 2002–2003, SARS-CoV caused a disease outbreak with deaths in 29 countries, most of them being in China and Hong Kong. Based on the genome sequence, SARS-CoV appeared to be very closely related to another virus from Himalayan palm civets, from which it may have emerged (Guan *et al.,* 2003). Later, civets were considered an intermediate host for SARS-CoV, with bats as the natural host (Cui *et al.,* 2019). (Hu *et al*., 2020) conducted a five-year surveillance study of SARS-related coronaviruses isolated from horseshoe bats in Yunnan province, China, where eleven SARS-like CoVs were identified. Genome comparisons revealed high genetic diversity among these viruses in several genes, including *S*, *ORF3*, and *ORF8*. Despite the differences in S protein sequences, all eleven SARS-like CoVs are still able to use the same human angiotensin-converting enzyme-2 (hACE2) receptor, demonstrating a close relationship with SARS-CoV. Therefore, SARS-CoV likely emerged through the recombination of bat SARS-like CoVs before infecting civets, from which the recombinant virus spread to humans, causing the SARS epidemic (Cui *et al.,* 2019). Ten years later, MERS-CoV emerged in Middle Eastern countries where the virus was transmitted to humans by dromedary camels (Zaki *et al.,* 2012). As of January 2020, MERS-CoV has resulted in 2519 laboratory-confirmed cases and 866 deaths (34.3% fatality rate), with more than 80% of the cases reported from Saudi Arabia (WHO,

2020). The human and camel MERS-CoV strains share more than 99% identity with variations (substitutions) located in the *S, ORF3,* and *ORF4b* genes (Chu *et al.*, 2018).

Phylogenetically, MERS-CoV is very close to bat coronaviruses HKU4 and HKU5 (Lau *et al.,* 2013). A comprehensive analysis of the evolutionary relationships indicated that MERS-CoV may have originated from bats as a result of recombination events within *ORF1ab* and *S* genes (Dudas and Wang, 2015). To gain access to the cell, MERS-CoV uses the human dipeptidyl peptidase 4(DPP4) receptor (Raj *et al.,* 2013). This is also the case for MERS-related CoVs isolated from bats in China, whose spike proteins can bind to the same receptor as MERS-CoV, confirming the possibility of a bat origin for MERS-CoV (Luo *et al.,* 2018).In December 2019, SARS-CoV-2 emerged in Wuhan City, China, causing severe respiratory illness and mortality. Early studies reported that it may have evolved from bats, as revealed by phylogenetic analysis (Zhou *et al.,* 2020) and its high identity (96.3%) with the bat coronavirus RaTG13.

2.2 Corona virus Taxonomy

Corona viruses are enveloped, icosahedral symmetric particles, approximately 80–220 nm in diameter containing a non-segmented, single-strand, positive-sense RNA genome of about 26–32 kb in size (Weiss,2020).Corona viruses (CoVs) are one of the largest groups of viruses that belong to the order *Nidovirales*, suborder *Cornidovirineae*, and family *Coronaviridae*. *Coronaviridae* is classified into two subfamilies, namely, *Letovirinae* and *Orthocoronavirinae*. *Letovirinae* includes the *Alphaletovirus* genus, while *Orthocoronaviridae* is further classified on the basis of phylogenetic analysis and genome structure into four genera: *Alphacoronavirus* (αCoV), *Betacoronavirus* (βCoV), *Gammacoronavirus* (γCoV), and *Deltacoronavirus* (δCoV), which contain 17, 12, 2, and 7unique species, respectively (ICTV, 2018).

2.3 Genetic Diversity of SARS-CoV-2

The assessment of genetic diversity among 86 complete or semi-complete genomes of SARS-CoV-2 viruses revealed three deletions in the genome of isolates from Japan, USA, and Australia in addition to many other substitution mutations. The deletion mutations were in the *ORF1ab* gene (3-nucleotide and 24-nucleotide deletion) and at the end of the genome (10-nucleotide deletion). Of the 93 substitution mutations, 42 changed the amino acid sequence of

structural and non-structural proteins (Paraskevis *et al.,* 2020).The 3- and 24-nucleotide deletions in *ORF1ab* were expected to reduce the protein sequence by 1 and 8 amino acid residues, respectively, without changing the reading frame, but the functional effects have yet to be investigated. The alignment of SARS-CoV-2 reference S protein gene against all SARS-CoV-2 sequenced genomes from China, USA, Japan, Australia, and Taiwan revealed 99.97–100% identity, with 100% query coverage (also confirmed by our phylogenetic analysis, while the identity and coverage for SARS-CoV S protein gene were 74.5% and 91%, respectively. Also, the S protein gene from bat SARS and SARS-like coronavirus isolates shared 76.5 % – 83% identity with that of SARS-CoV-2(Paraskevis *et al.,* 2020).

2.4 Source of Infection and Evolution of SARS-CoV-2

The origins of more than 75% of coronavirus infections are considered zoonotic, i.e., animals are the main source of the outbreaks. For example, SARS-CoV was transmitted from palm civets to humans and MERS-CoV from dromedary camels to humans. Bats are currently considered a reservoir for all human coronaviruses, as mentioned above (Cui and Shi 2019). Many coronaviruses are circulating in animals but have not yet infected humans.

The type of animal that SARS-CoV-2 originated from is still unclear. At the beginning of the outbreak in Wuhan, China, many patients were linked to the Huanan Seafood Wholesale Market, suggesting animal-to-person spread. After retrospectively studying case reports, the number of patients that did not have exposure to animal markets has risen, indicating person-to-person spread was also occurring at that time (CDC,2020). SARS-CoV-2 is closely related to bat coronaviruses and SARS-CoV (Huang *et al.,* 2020). A group of researchers reported early in the outbreak that the novel SARS-CoV-2 has the highest similarity of codon usage bias among snakes (Ji *et al.,* 2020). However, this method of determining initial host origins is dubious. Interestingly, researchers also reported one amino acid difference in the receptor-binding domain of the S protein of Pangolin-CoV compared to that of SARS-CoV-2, suggesting that pangolins might play a role as an intermediate host. There was speculation that SARS-CoV-2 is a laboratory-engineered CoV that leaked directly from a laboratory in Wuhan, where a bat CoV (RTG13) was recently reported. However, there is no evidence to support this allegation (Liu *et al.,* 2020). Recently, a group of researchers found that SARS-CoV-2 replicates poorly in dogs,

pigs, chickens, and ducks but efficiently in ferrets and cats (Shi, 2020). Scientists are still trying to find the main source of the disease outbreak and identify the definitive intermediate hosts.

2.5 Mode of SARS-CoV-2 Transmission to Humans

Both established (SARS-CoV, MERS-CoV) and novel (SARS-CoV-2) coronaviruses have been reported to spread from an infected person to a non-infected person through direct or indirect contact. Like most respiratory viruses, SARS-CoV-2 infection was reported to be transmitted directly from person to person through close contact with an infected person or through respiratory droplets (aerosol) produced when an infected person coughs or sneezes. These droplets can be inhaled to reach the lungs. The virus can be indirectly transmitted by touching a surface or an object that was previously contaminated with the virus and then touching the face, eyes, or mouth (CDC, 2019).And possibly via the fecal-oral route (Lai *et al.*, 2019). Asymptomatic carriers (during the incubation period of the virus) and patients after recovery from the acute form of the disease are also considered potential sources of virus transmission to healthy persons (Liao *et al.,* 2020). Interestingly human coronaviruses can survive on steel, metal, wood, aluminum, paper, glass, plastic, ceramic, disposable gowns, and surgical gloves for 2–9 days. High temperature (≥30 °C) can reduce the persistence period, while low temperature (4 °C) increases the persistence time up to 28 days (Kamp *et al.,* 2020). Transmission of the virus vertically from mother to fetus or via breast milk has not been confirmed yet (Chen *et al.*, 2019). The transmission cycle of the corona virus among animals and humans is shown in figure 1. (Helmy *et al.*, 2017). The transmission cycle of coronaviruses includes MERS-CoV, SARS-CoV, and SARS-CoV-2. The transmission of the virus to humans occurs by direct contact with infected animals.

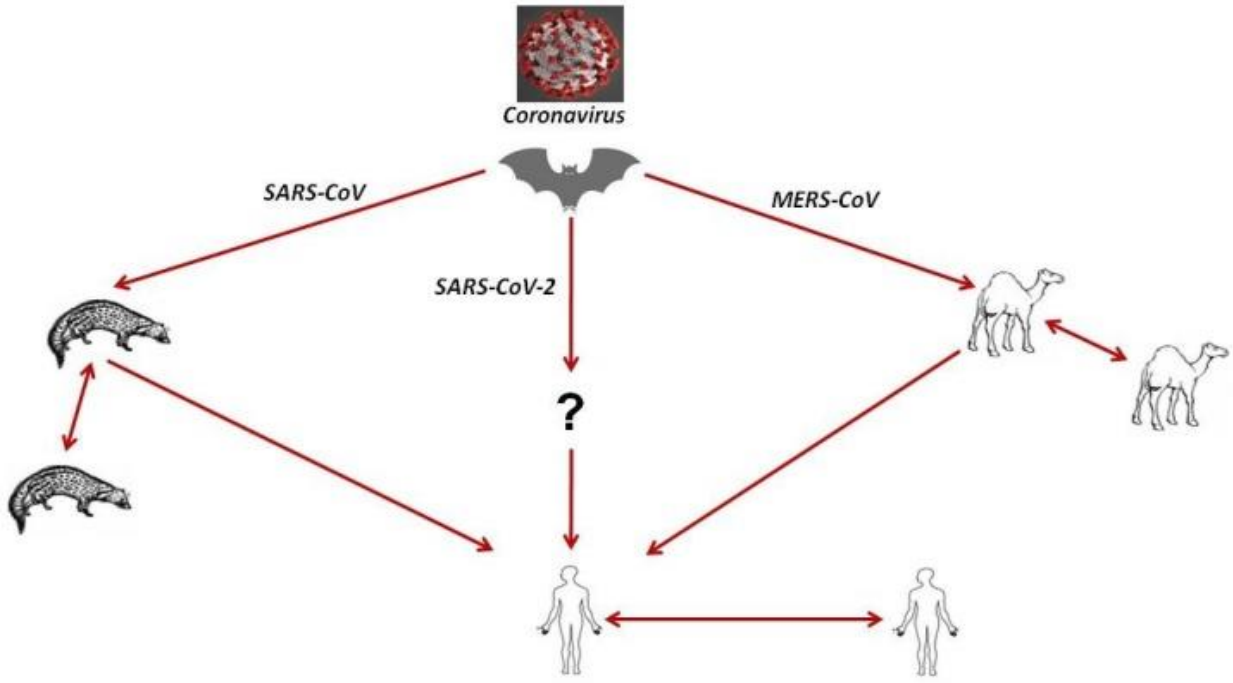

Figure 1 . *The transmission cycle of corona viruses among animals and humans* (Helmy *et al.*, Adawy and Abdelwhab, 2017) .The transmission cycle of corona viruses including MERS-CoV, SARS-CoV, and SARSCoV-2. The transmission of the virus to humans occurs by direct contact with infected animals.

2.6 Prevention Methods of COVID-19 infection

The U.S. Food and Drug Administration (FDA) have given emergency use authorization to some COVID-19 infection vaccines in the U.S. The FDA has approved the Pfizer-BioNTech COVID-19 vaccine, now called Comirnaty, to prevent COVID-19 in people age 16 and older. A vaccine can prevent you from getting the COVID-19 virus or prevent you from becoming seriously ill if you get the COVID-19 virus. In addition, COVID-19 vaccination might offer better protection than getting sick with COVID-19. (WHO, 2020) A recent study showed that unvaccinated people who already had COVID-19 are more than twice as likely to get re-infected with COVID-19 as fully vaccinated people. Also, if you are fully vaccinated, you can return to many activities you may not have been able to do because of the pandemic, including not wearing a mask or social distancing (except where required by a rule or law). However, if you are in an area with a high number of new COVID-19 cases in the last week, the CDC recommends wearing a mask

indoors in public and outdoors in crowded areas or when you are in close contact with unvaccinated people. If you are fully vaccinated and have a condition or are taking medications that weaken your immune system, you may need to keep wearing a mask.

There are more vaccine candidates simultaneously in the pipeline for COVID-19 than ever before for an infectious disease. All of them are trying to achieve the same thing – immunity to the virus, and some might also be able to stop transmission. They do so by stimulating an immune response to an antigen, a molecule found on the virus. In the case of COVID-19, the antigen is typically the characteristic spike protein found on the surface of the virus, which it normally uses to help it invade human cells. There are four categories of vaccines in clinical trials: whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA). Some of them try to smuggle the antigen into the body, others use the body's own cells to make the viral antigen. (WHO, 2020**)**

2.7 Association of ABO Blood Groups and Diseases

2.7.1 Infectious Diseases

According to Anstee, (2010), ABO polymorphism has been associated with certain infectious diseases. The presence or absence of A/B antigens and the correspondent absence or presence of anti-A/B antibodies provides strong or weak defensive lines against infection. Many vertebrate species uphold the ABO gene and hence benefit from it. However, having both functional A and B genes in common within species may not be important because they may lose anti-A and B antibodies in the long run. But frequent gene conversion of A/B specificity producing amino acid substitutions or recombination with nonfunctional partial genes may have conferred an adaptation against microbial attacks (Yamamoto *et al.,* 2015). Glycoconjugated red cell surfaces are used effectively by parasites, bacteria, and viruses as receptors for attachment (Yamamoto *et al.,* 2012). Because infectious agents often use cell surface glycoconjugates as receptors for attachment, glycosylation polymorphisms in the ABO blood type may affect host-pathogen connections and result in vulnerability (Yamamoto 2012). The difference among individuals with diverse glycosylation profiles (Yamamoto *et al.,* 2012) is striking. It should be recalled that certain microbial parasites share blood group antigens with their hosts (molecular mimicry).

Early etiological studies (Yamamoto *et al.*, 2012) identified an association between ABO and infectious diseases like cholera.

According to the study of Mourant *et al.,* (1976), the major variations observed in ABO blood groups in different parts of the world were due to the epidemics that have occurred in the past. Reports showed that once a person is infected with cholera (*Vibrio cholerae* strains O1 El Tor and O139), the O blood types had a greater frequency of severe infections than the non-O blood types (Anstee, 2010). Patients of blood type O were more vulnerable to infections like gastrointestinal outbreaks caused by *Escherichia coli* O157 in Scotland in 1996, and a total of 87.5% of blood type O patients died. According to the study of (Garratty, 2000),blood type O was also associated with increased incidence of cholera, plague, tuberculosis infections, and mumps, whereas blood type A was associated with increased incidence of smallpox and *Pseudomonas aeruginosa* infection; blood type B is also associated with increased incidence of gonorrhea, tuberculosis, and *Streptococcus pneumoniae*, *E. coli*, and salmonella infections; and blood type AB is associated with increased incidence of smallpox and *E. coli* and salmonella infections.

2.7.1.1 Malaria

The connection between the ABO blood type and malaria was suggested by Abdulganiyu and Athreya (2016); they indicate that type B provides a selective advantage to malarial disease. In 1978, a noticeable number of type A patients were known from combined data analysis as compared to types B and O. According to the ABO phenotype, there are some variations in Lewis antigen levels among A, B, and AB blood types, since these blood types carry fewer Lewis antigens than O types, because their corresponding transferases use similar precursors (Abdulganiyu, 2016). The first implies the formation of masses of diseased RBCs and normal RBCs or platelets. The second implies the course whereby *P. falciparum*-infected RBCs move on and stick to the microvascular endothelium and then are removed from the circulation (Yamamoto *et al.*, 2012). The microcirculatory blockade by cut adhesion can decrease oxygen and substrate supplies (Yamamoto *et al.*, 2012). The complement receptor type 1 (CR1) is a rosetting receptor in RBCs, and CR1 seems to carry the Knops blood type antigens with the S1 (a) phenotype, creating fewer rosettes (Rowe *et al.*, 1997). Identification of a carbohydrate structure found in glycophorin A or B that consists of sialic acid and galactose is the major

requisite for the entrance of *Plasmodium falciparum* merozoites into human RBCs (Cartoron *et al.,* 1983). Sialic acid is common to some pathways that use glycophorins as ligands and has also been related to the ABO phenotype.

2.7.2 Non- Infectious Diseases

2.7.2.1 Cancer

Even though the association between the ABO blood type and cancer was the subject of rigorous investigation in the mid-1900s, there has been improved attention after the contemporary publication of reports establishing a connotation between the ABO blood type and pancreatic cancer (Wolpin *et al*., 2009). Blood type antigens play a role in tumor genesis, metastasis, and prognosis and probably take part in cell recognition, cell signaling, and cell adhesion (Weisbord *et al*., 2013). Expression of ABH and related antigens differs during cellular development, aging, and differentiation; this is mainly realistic during carcinogenesis and pathological phenomena ABH antigens can be found in the epithelial tissues of the gastrointestinal tract, breast, uterine cervix, mouth, lung, bladder, and prostate. But these antigens are missing from glycol lipids and glycol proteins of malignant tissues in these areas (Daniels, 1999). For example, it is thought that DNA methylation in the promoter region for the blood group A gene may inhibit transcription of the associated enzyme and therefore loss of the A antigen, but different mechanisms for the reduction of mRNA have been found in A tumors, which appear to be specific to each tumor cell line (Hakomori, 1999).

Loss of A and B antigens leads to metastasis, resulting from downregulated transcription of ABO with related loss of A or B transferase activity, and upsurges the buildup of other antigens which act as ligands for selections and facilitate the metastatic process (Daniels, 1999). Some non-A blood type people have tumors with real A antigens or with "A-like" antigens that have very similar properties to A antigens; in these people, the tumor antigens would be seen as foreign and would interact with anti-A antibodies, resulting in an attack of the tumor (Ewald and Sumner,2016). This explains why a greater incidence of cancer is common in blood type A people than in blood type O people; the A+ or "A-like" properties of these tumor antigens are not recognized as foreign in blood type A people (Garratty, 2000).

2.7.2.2 Leukemia and Lymphoma

In patients with acute leukemia and aplastic anemia, the antigens usually decreased till they were untraceable in patients with acute leukemia and aplastic anemia; as the patient's condition improves, the antigens increase again to their former levels (Garratty, 1999). However, the loss of antigens may be due to an inhibitory factor related to antigen-antibody binding or an abnormal distribution or density of antigen sites in the RBC membrane, but not a deficiency in transferase synthesis or activity (Ewald and Sumner, 2016). Expression of A, B, or H antigens in leukemia patients was significantly lower between 17% and 37% when compared to healthy controls of A, B, or AB. Patients with myeloid malignancies had reduced expression of A or B antigens. Blood type O patients had reduced H antigens by 55% and 21% when compared with healthy controls of the same ABO genotype (Daniels *et al.,* 2000).

In non-Hodgkin's lymphoma (Ewald *et al*., 2016), primary central nervous system lymphoma (PCNSL) begins in and characteristically remains limited to the central nervous system (CNS) in non-Hodgkin's lymphoma (Ewald *et al.,* 2016), while secondary central nervous system lymphoma (SCNSL) characteristically does not originate from the CNS but may later take part in the CNS in up to 10% to 30% of cases (Ewald *et al.,*2016). A study of 36 patients with PCNSL occurrence reported 8.3% in blood type A, 27.8% in blood type B, 55.6% in blood type O, and 8.3% in blood type AB (Gharouni *et al., 2008),* whereas another study that assessed 202 patients with secondary central nervous system lymphoma (SCNSL) indicated that the occurrence was 5.0% in blood type A, 61.9% in blood type B, 29.7% in blood type O, and 3.5% in blood type AB. The same populations of healthy controls were also used for both studies; the shared blood type percentages were 22.2% in blood type B, 37.1% in blood type A, 6.1% in blood type AB, and 35.6% in blood type C (Gharouni *et al*., 2008).

There are very few studies on the association between ABO blood types and children with leukemia and lymphoma. A study of pediatric victims with acute myeloid leukemia (AML;), acute lymphoblastic leukemia (ALL;), Hodgkin's lymphoma and non-Hodgkin's lymphoma exhibited an important variation in the overall dissemination of blood groups when compared to the source population for all but the AML victims (Ewald *et al.,*2016). This study stated that the occurrence of Hodgkin's lymphoma was 45.6% greater in blood type B victims and 56.5% lesser

in blood type A patients; the occurrence of non-Hodgkin's lymphoma was 52.9% lesser in blood type A patients; the occurrence of ALL was 14.3% greater in blood type O victims; but there was no variation in the dissemination of blood types in victims with AML (Ewald *et al.,* 2016).

A distinct multicenter pediatric study of 682 victims with ALL and 224 victims with AML stated that the occurrence of ALL was 56.5% greater in blood type O victims, 35.8% lesser in blood type A victims, and 26.9% lower in blood type B victims, while the occurrence of AML was 28.8% greater in blood type A victims (Ewald and Sumner, 2016).

2.7.2. 3 Hypertension

It can have several causes; thus, it is not surprising that different studies have found various links between blood type and hypertension. Some investigations indicate that the rate of hypertension in blood type B was maximum, followed by blood type A and blood type AB which had the lowest rate of hypertension (El-Sayed and Amin, 2015). Another study also reported that there was a link between blood type A and systolic blood pressure in Caucasians but not in Blacks (Ewald and Greenwell,2016).In hypertension due to abnormal red cells' lithium-sodium counter transport, no connection was found with the MNS blood type polymorphism (Tournoy,1996).

2.7.2. 4 Hyper lipidemia

Investigators have also studied the relationship between ABO blood type antigens and hyperlipidemia. A few studies stated that LDL cholesterol, total cholesterol, and triglycerides were higher while HDL cholesterol was lower in blood types A and B. However, blood type AB was protective against hyperlipidemia (El-Sayed and Amin, 2015). Other studies also indicated that blood type A was linked with LDL cholesterol and higher total cholesterol, but there was no relation with HDL cholesterol (Ewald and Greenwell, 1997). The most exciting discovery was the relationship of ABO and secretor blood types with serum levels of intestinal alkaline phosphatase (I-ALP) and apo lipoprotein B-48 (apo B-48); I-ALP is necessary for the passage of chylomicrons from the bowels to the circulation and is thus an indicator for chylomicron absorption, whereas apo B-48 is a protein that strengthens the chylomicron membrane and is thus an indicator for chylomicron fabrication (Ewald *et al.,* 2016). There are important variations in serum I-ALP and apo B-48 between blood type O and B secretors and all other blood types; the O and B secretors have very high serum levels of these indicators relative to blood type A/AB

secretors and nonsecretors of all blood types (Ewald *et al.,* 2016). ABO nonsecretors alone have about 20% of the serum I-ALP of secretors, and among secretors, blood type A has very low activity compared to blood types B and O respectively (Ewald and Sumner, 2016).

It is believed that I-ALP is linked with ABO antigens on RBCs of nonsecretors and is also accumulated by the A antigens of secretors, thus being quickly removed from circulation in these persons, while the soluble circulating antigens of O and B secretors favorably link with I-ALP and protect its removal in these persons (Nakano *et al.,*2006). Blood type A persons also have lesser serum apo B-48 levels, which can be due to a genetic down-regulation of I-ALP activity in their intestines, subsequently lower chylomicron secretion (Ewald *et al.,* 2016), and possibly lesser serum cholesterol levels.

2.7.2. 5 Diabetes Mellitus (DM)

Individuals with blood type O show a lowermost risk of T2DM, whereas those with blood type B were at the uppermost risk, followed by type AB and type A individuals; nevertheless, the risk for type AB people did not have statistical implication (Fagherazzi *et al*., 2015). When Rh and ABO types were assessed together, blood type B+ persons showed the uppermost risk, followed by type AB+, A–, and A+ persons, but a similar risk was seen for the other types (Fagherazzi *et al*., 2015). Findings also indicated inconsistent results: a study in Yemen indicated that the maximum arbitrary blood sugar and insulin levels were found in blood type A, whereas blood type AB showed a defensive effect (El-Sayed and Amin, 2015). Research in Iraqi persons indicated greater blood glucose, total cholesterol, and blood pressure in blood type O persons, followed by lesser risk in type A, B, and AB persons, who showed the bottommost risk (Ewald and Fagherazzi, 2015).

2.7.2.6 Asthma and COVID-19

People with asthma (PWA) generally are considered at higher risk from respiratory infections, as is seen annually with influenza. At the outset of the COVID-19 pandemic, PWA was widely assumed to be at increased risk from COVID-19. However, as data emerged throughout 2020, the association between asthma and COVID-19 appeared less clear (Hartmann *et al.,* 2020) rapid systematic review was undertaken to inform this scientific brief. The review set out to assess the available peer-reviewed literature regarding whether PWA is at increased risk of infection with

the virus that causes COVID-19, and/or of experiencing complications or death. (Silamlak Birhanu Abegaz, 2021).

2.7.2.7 Association of ABO Blood Groups and COVID-19 Infection

The ABO blood group is the most important blood group system in humans and includes four blood types, namely, A, AB, B, and O. The human ABO blood group is located on chromosome 9 (9q34.2) (Melzer *et al*., 2008). Many studies have found that the ABO blood group plays an important role in various human diseases, such as cardiovascular, oncological, and some infectious and non-infectious diseases (Wolpin *et al*., 2010). Meanwhile, the system can play a direct role in infection by serving as receptors or co-receptors for microorganisms, parasites, and viruses.

The ABO blood group has been previously found to contribute to the risk of multiple infectious diseases in a series of studies. Mohammadali *et al. (*2014) reported that the presence of blood group O might significantly decrease the risk of hepatitis B, and the distribution of Rh in HBV-infected individuals was higher among Rh-positive donors (Mohammadali and Pourfathollah, 2014), (Elnady *et al*., 2017). It was found that rotavirus gastroenteritis was significantly more prevalent among those with blood type A and significantly less prevalent among those with blood type B (Elnady *et al.,* 2017). Another recent study carried out by Degarege *et al. (*2012) reported that malaria patients with blood group A had a higher risk of anemia than those with O and non-A phenotypes (Degarege *et al*., 2012). Among dengue virus-infected patients (Murugananthan et al., 2018), It was found that patients with AB blood had a risk that was more than 2.5 times higher of developing dengue hemorrhagic fever than did those with other blood types (Murugananthan *et al.,* 2018). In addition, a meta-analysis suggested that blood types A, B, and AB might not affect susceptibility to norovirus infection. However, those with blood type O appeared to be more susceptible to this infection (Liao *et al.,* 2020).

2.7.2.8 Association between the Rh Group and the COVID-19 Susceptibility

Blood group antigens are genetically coded, and these antigens can be susceptibility factors for some diseases and resistance factors for others. In studies, the ABO blood group system has been shown to be associated with rheumatologic diseases and viral diseases such as Norwalk virus and

Hepatitis B (Zhao *et al*., 2020). It has also been found that the rate of being infected with the SARS coronavirus is less than in the blood group of O**.** The Rh (Rhesus) blood group system is the most complex of known human blood group polymorphisms. Expression of their antigens is controlled by a two-component genetic system consisting of RH and RHAG locus encoding Rh30 polypeptides and Rh50 glycoprotein, respectively.(Huang *et al.,* 2000).West Nile virus infection is more common in Rh-negative individuals, a hypothesis posits that glycosylated structures expressed differently on the surface of erythrocytes will facilitate virus binding or serve as receptors/ co-receptors through glycan-glycan or lectin-glycan interactions in a Velcro-like interaction.(Kaidaro *et al.,* 2016)However, natural antibodies can block or opsonize the entry of viral particles leading to complement-mediated neutralization. (Neli *et al.,* 2005). It has also recently been shown that natural antibodies can aid the formation of cytotoxicity T cells against the pathogen. (Durrbach *et al*., 2007).

2.7.2.9 Associations of ABO and Rh blood groups in susceptibility, severity and deceased of COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged from Wuhan, China in December 2019 has posed a great threat to global public health. It causes coronavirus disease 2019 (COVID-19) (Long *et al*., 2020; Wang *et a*l., 2021). COVID-19 affects people in different ways. It has a wide range of symptoms like fever, dry cough, and shortness of breath, muscle pain, fatigue, sore throat, ageusia, and anosmia. However, a large proportion of infected patients remain asymptomatic (Lovato *et al.,* 2020; Rodriguez-Morales *et al.,* 2020). COVID-19 has an incubation period of 1–14 days, but typically, it takes 3–7 days to present symptoms. There are many cases where the COVID-19 infection has taken more than 14 days to present any symptoms (Fan *et al.,* 2020; Huang *et al*., 2020).

The knowledge of blood group types and their association with COVID-19 may help in disease management and treatment. Out of 34 blood group types that the International Society of Blood Transfusion (ISBT) recognizes, ABO and Rh blood types are the most investigated, studied, and clinically applied. The antigenic structure present on the surface of erythrocytes determines the ABO blood group and also, whether there is an antigenic structure present or not, determines the Rh system (Sayli, 2020).

Previous studies have found an association between rheumatological diseases, cancers, cardiovascular diseases, infectious and non-infectious diseases, bacterial and viral diseases, and the ABO blood group. Previous studies have shown susceptibility of ABO blood groups to viruses such as Middle East Respiratory Syndrome (MERS), hepatitis B, human immunodeficiency virus, norawalk virus, rotavirus, dengue virus, and SARS coronavirus (Mehta, 2009; Wolpin *et al.*, 2010). Degarege *et al*., 2012; Chen et al., 2016; Batool *et al.,* 2017and Murugananthan *et al.,* 2018.

Recent studies from China and other parts of the world have reported that there is an association of ABO and Rh blood groups with SARS-CoV-2 infection. Blood group A has a high risk of infection, whereas blood group O appears to have a lower risk of infection and severity. Rh (D) positive blood group is also linked to an increased risk of COVID-19 infection (Goker *et al.,* 2020; Noor *et al.,* 2020; Zietz *et al.,* 2020; Zhao *et al.,* 2021). Several theories have been proposed to elaborate on the mechanism of this association. Genetically encoded blood group antigens might be a predisposing factor for SARS-CoV-2 infection. The human ABO blood group is located on chromosome 9 (9q34.1-34.2) (Amundadottir *et al.,* 2009; Wiggins *et al.,* 2009; Vasan *et al.,* 2016). The ABO blood groups are associated with several bacteria, parasites, and virus infections and also have shown major role as a receptor and co receptor. ABO blood groups represent a polymorphic trait that has histo-blood group antigens (HBGAs), which are present on the outer surface of red blood cells(RBCs).The expression of HBGAs can decrease or increase the susceptibility of disease (Singh *et al.,* 2016; Liu *et al.,* 2018).

2.7.3 Association of COVID-19 with other diseases

2.7.3.1 HIV and COVID -19 Infections

HIV causes immune depression by depleting CD4 cells, thus reducing the capacity of the organism to defend against bacterial, fungal, parasitic, and viral infections such as COVID-19. This vulnerability to infection is greater when the immune depression is severe and the patient is not on ART making the patient at risk of opportunistic infections. The presence of 38 million people worldwide with HIV during this period of COVID-19 could therefore be challenging for health systems worldwide as more aggressive preventive and therapeutic measures might be needed for this population. It is, therefore, necessary for programmatic purposes, optimal

allocation of public health interventions, and prioritization of care in a context of scarce resources due to the pandemic to know whether, given the state of the art, people living with HIV are proportionally more affected than people without the disease, and whether they are at greater risk of the pejorative outcome when affected by COVID-19 (WHO, 2020).

3. MATERIALS AND METHODS

3.1 Description of the study area

The Amhara regional state is located between 8 degree 45N latitude and 35 degree 46 E to 40 degree 25 longitudes, the study area were located particularly 11º39'30"N longitudinal and 36º31'0" E latitudinal. It has an elevation ranging from 500 to 3500 meter above sea level and cover about 170, 752 sq .Km with populations 21.1 million in 2017.among this 89.3% comprise the rural populations. Amhara region is the second most populous region (making up 22.4 percent of the Ethiopian population. It covers west and East Gojjam zone with populations of 4.4million and North Gondar with populations of 2.9 million (CSA in 2007) .The studies was conducted at Felege Hiwot Compressive Specialized Hospital and Gondar University Referral Hospitals in Amhara regional state, Northwest Ethiopia. Those hospitals are the biggest hospitals in the Amhara region which provide health services and serve as the referral centers for other district hospitals in the region.

Map of the study area

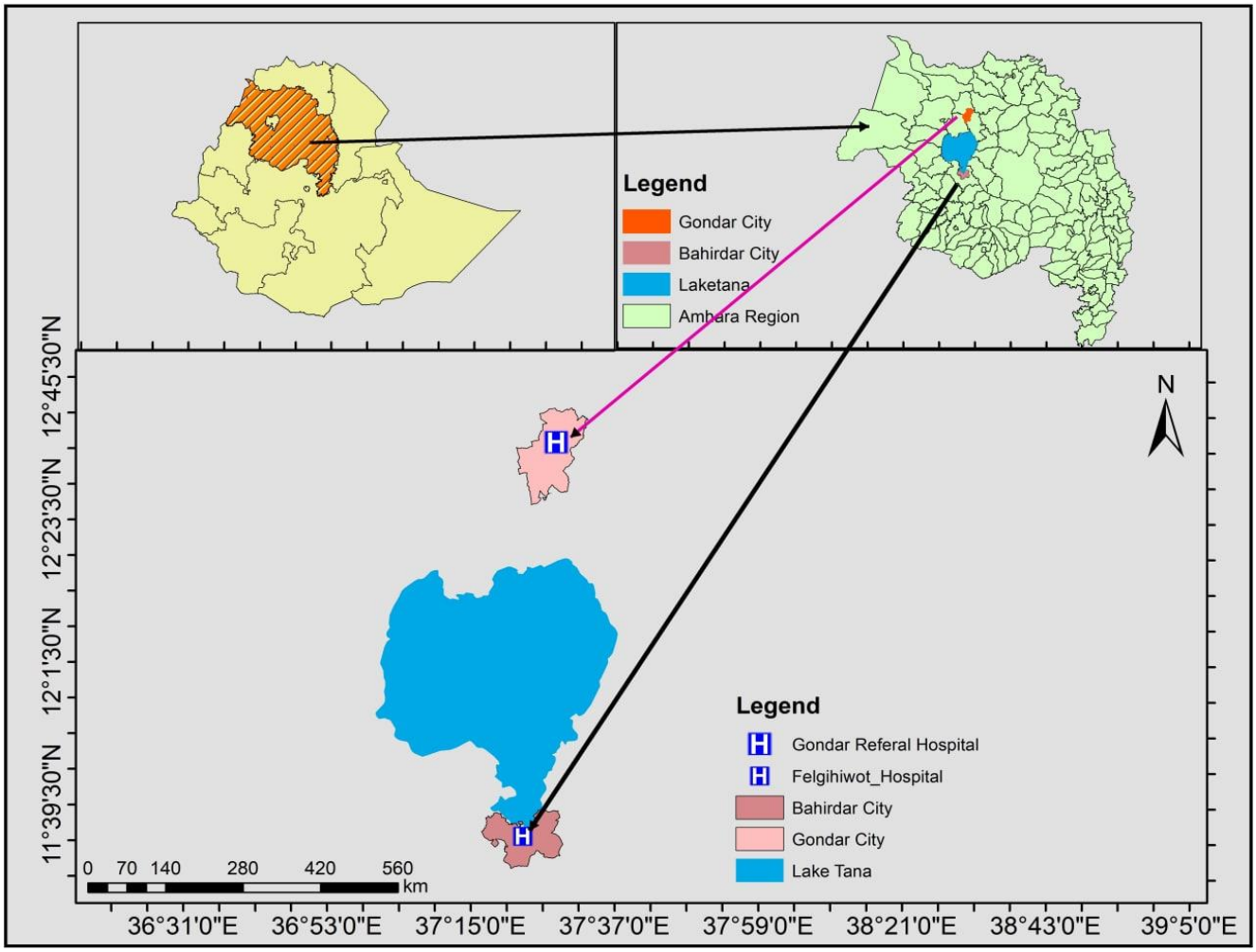

Figure 2. *Map of Administrative Zones of Amhara Region and Referral Hospital (2022)*

3.2 Study Design and Period

A hospital-based case-control (longitudinal) study was conducted to assess the association of human ABO and Rh blood group system with COVID -19 infection susceptibility in Amhara region. This study was initiated to the association between blood group and risk of COVID-19 infection and susceptibility of both positive and negative cases for the diseases in the study area.

To study effect of blood group on susceptibility of COVID-19 infection, the distribution of blood types among a sample of confirmed COVID-19 infected individuals in FHCSH and GURH.

3.3 Source Population and Study population

3.3.1 Source of Population

The source population was taken from all individuals who came to the two referral hospitals for COVID-19 diagnosis.

3.3.2 Study population

All COVID-19 positive and negative individuals were randomly selected during the study period.

3.4 Sample Size Determination

The study was case-dependent and all COVID-19 positive cases under treatment/recovery/and death group and matching number of negative cases from the two referral hospitals. COVID-19 treatment centers register log book documents were carefully recorded and used in the study.

3.5 Data Collection

Data of medical records from all COVID-19 confirmed positive and negative cases in the referral hospitals were collected using COVID-19 treatment center register log book charts by medical personnel selected from the respective referral hospitals. The study of individuals was subjected to demographics, such as, sex, age, blood group, presence of infectious and non- infectious diseases. The severities of illness COVID-19 were classified into, mild, moderate and critical according the Centers for Diseases Control (CDC) guidelines. Individuals who were have various signs and symptoms of COVID-19 infection such as, fever, cough, sore throat and shortness of breath also listed.

Demographic and clinical data were collected with the semi structured pretested COVID-19 test request/report/form by trained nurses or blood typing from the study area.

3.6 Data Analysis

After collecting data, a Statistical Package for Social Sciences (SPSS) version 25 was used to analyze the collected data. Descriptive statistics were used for presenting Demographic

variables, Chi-square ($\chi 2$) test, was performed to compare the proportion of blood groups, ABO and Rh blood groups, age group, and sex, severity of illness, infectious and non- infectious diseases and symptoms of COVID-19 infection between the recovered and deceased groups.

Univarate and multivariate logistic regressions analyses were also used to assess the association of human ABO and Rh blood group systems with COVID -19 infection susceptibility. In the Wald test from logistic regressions and a p- value cut-off point of 0.25 were used. Variables which have a p-value of less than 0.25 in the Univarate analysis were selected to be used in the multivariate analysis.

3.7 Ethical Clearance

The protocol of the study was reviewed and approved by the Ethical Review Committee of the College of Science, Bahir Dar University and an ethical clearance was obtained from the same. The study subjects were informed about the objective of the study and, the advantages and importance of the study were communicated.

3.8 Study variables

The study consisted of dependent and independent variables.

Dependent Variables: - COVID-19 infection susceptibility (COVID-19 positive cases and negative cases or control group) recovery group, death group, and severity of illness were the dependent variable.

Independent Variables: -The independent variables of the study include: sex, age, infectious and non-infectious diseases, human ABO, and Rh blood group were the independent variables.

4. RESULTS

4.1 Demographic characteristics

Of the 410 total COVID-19 positive and negative cases, 206 (50.2%) were males and 204(49.8%) were females. From this, 204 were COVID-19 positive, with 104 (25.4%) males and 100(24.4%) females. From 206 COVID-19 negative cases (102 male (24.9%) and 104(25.4%) female). From the total 204 COVID-19 positive cases, 174(male 86, 42.2%) and female 88, 43%) were in the recovery group from COVID-19 infection, and 30 male (18, 8.8%) and female (12, 5.8%) subjects died due to COVID-19 infection. The highest COVID-19 positive cases were observed in the age category above 61, at 45 (22%), and lower COVID-19 positive cases were observed in the age category 0-10, at 12(5.1%). In COVID-19 negative cases, higher negative cases were observed in the category of 21-30, 42(20.4%) and lower COVID-19 negative cases were observed in the age category of 0-10, 16(7.8%). (Table1).

Table 1: The demographic characteristic of COVID -19 positive and negative study subjects

Characte rs tics	Group	COVID-19 Positive cases and Negative cases							
		Positive		Negative		Recovered		Deceased	
		N	%	N	%	N	%	N	%
Sex	Male	104	25.4	102	24.9	86	42.2	18	8.8
	Female	100	24.4	104	25.4	88	43	12	5.8
	Total	204	49.8	206	50.2	174	85.3	30	14.7
Age	0 -10	12	5.9	16	7.8	9	4.4	3	1.5
	11-20	19	9.3	38	18.4	16	7.8	3	1.5
	21-30	26	12.7	42	20.4	23	11.2	3	1.5
	31-40	29	14.2	41	19.9	26	12.2	3	1.5
	41-50	32	15.7	29	14	29	13.7	3	1.5
	51-60	41	20	22	10.6	37	18	4	2
	> 61	45	22	18	8.7	34	16.7	12	5.9

4.2 COVID-19 Positive subjects and COVID -19 Negative subjects with Age and Sex

Among the COVID-19 positive subjects, the age group above 60 years (11%) had the highest COVID-19 positive infection susceptibility, while the age group from 0–10 years (2.9%) had less COVID-19 infection susceptibility. Similarly, in the other age groups, among the COVID-19 negative cases, the age group of 21–30, 42(10.2%) had the highest COVID-19 negative cases, while the lowest COVID-19 negative cases were observed in the age group of 0–10, 16(3.9%) (Table 2).

Table 2: COVID-19 positive subjects and COVID -19 negative subjects with age and sex

	Range	Male	Female	Frequency	Percentage
Characteristics	0 -10	5	7	**12**	**2.9**
Age with	11-20	9	10	19	4.6
COVID-19	21-30	12	14	26	6.3
positive cases	31-40	15	14	29	7
	41-50	12	20	32	7.8
	51-60	22	19	41	10
	>61	29	16	45	11
	Total	**104**	**100**	**204**	**49.8**
Age with	0 -10	3	13	16	3.9
COVID-19	11-20	20	18	38	9.2
negative cases	2 1-30	23	19	42	10.2
	31-40	12	29	41	10
	41-50	23	6	29	7
	51-60	**11**	**11**	**22**	**5.4**
	>61	**10**	**8**	**18**	**4.4**
	Total	**102**	**104**	**206**	**50.2**

4.3 Association with blood type and Recovery and Deceased

As indicated in table 3, of the total (204) COVID-19 positive group, 174 (86 (42.2%)) males and 88(43%) females were found in the recovery group. From this, thirty (18(8.8%)) male and

12(5.8%) female) subjects were in the deceased group. Among the ABO and Rh blood group systems, blood group O (54(26.5%)) was observed to have a shorter recovery time, while blood group AB 18(8.8%) had a longer recovery time.

In this study, subjects with blood group A (10(4.9%)) were observed to be in the highest death group, and those with blood group B were least represented among the age group deceased, with 4(1.9%).

On the other hand, 204 Rh blood groups (142(69.6%)) individuals that had Rh positive blood were highly susceptible to COVID-19 infection, while individuals who were Rh negative (32(15.7%)) were less susceptible (Table 3).

Table 3: Distributions of human ABO and Rh blood group system between deceased and recovered group due to COVID-19 infection

Characteristics	Group	Recovered				Deceased			
		Male N	Female N	Total N	Percentage %	Male N	Female N	Total N	Percentage %
Human ABO blood group	A	34	33	67	32.8	6	4	10	4.9
	B	14	21	35	17.2	3	1	4	1.9
	AB	8	10	18	8.8	5	4	9	4.4
	O	30	24	54	26.5	4	3	7	3.4
Rh factor system	Rh +	69	73	142	69.6	11	10	21	10.3
	Rh-	17	15	32	15.7	7	2	9	4.4

4.4 Human ABO and Rh Blood Group System Distribution with COVID -19 Positive and Negative cases

In this study, the overall distribution of ABO blood group COVID-19 positive infection susceptibility was observed in the descending order AB 28(13.7%) B 39(19.11%) O 61(29.9%) A 76(37.3%).

Likewise, the distribution of the ABO blood group COVID-19 negative cases in the descending order was AB 33(16.01%) < B 48(23.3%) < A 62(30.09%) O 63(30.58%). In this case, blood group O had less COVID-19 infection susceptibility and blood group AB was observed to have the highest COVID-19 infection susceptibility. On the other hand, the distribution of Rh blood groups showed that individuals who were Rh positive (162(79.4%)) were highly susceptible while individuals who were Rh negative (42(20.6%)) were less susceptible (Table 4).

Table 4**: Human ABO and Rh blood group system distribution with COVID -19 positive and negative cases**

Characteristics	**Categories**	**Sex**			
	Blood group	Male **Frequency**	Female **Frequency**	Total **Frequency**	Percentage
ABO blood group With COVID-19 Positive Cases	A	40	36	76	37.3
	B	17	22	39	19.11
	AB	13	15	28	13.7
	O	34	27	61	29.9
Positive cases Rh type	Rh +	80	82	162	79.4
	Rh-	24	18	42	20.6
ABO blood group With COVID-19 Negative Cases	A	31	31	62	30.09
	B	28	20	48	23.3
	AB	13	20	33	16.01
	O	30	33	63	30.58
Negative cases Rh type	Rh+	79	82	161	78.16
	Rh-	23	22	45	21.84

4.5 Association of ABO blood groups among COVID-19 positive cases from infectious and non-infectious diseases

Among the COVID-19 positive cases, the infectious diseases of pneumonia 39.3% were associated with blood group AB, which had the highest COVID-19 infection, while HIV/AIDS 15.4% were associated with blood group, B which had less COVID-19 infection susceptibility.
In non-infectious diseases, chronic respiratory diseases were associated with blood group AB, highly susceptible to COVID-19 infection, and among individuals with asthma, 3.6% were less susceptible to COVID-19 infections (Table 5).

Table 5: **Association of ABO blood groups among COVID-19 positive cases with infectious and non-infectious diseases**

Characteristics	**Categories**	**Blood group**			
		A N (%)	B N (%)	AB N (%)	O N (%)
Infectious diseases	HIV	13(17.1)	6(15.4)	6(21.4)	15(24.6)
	Tuberculosis	21(27.6)	11(28.2)	11(18.0)	11(18.0)
	Malaria	22(28.9)	7(17.9)	6(21.4)	22(36.1)
	Pneumonia	20(26.3)	15(38.5)	11(39.3)	13(21.3)
Non-infectious diseases	Dm	15(19.7)	8(20.5)	5(17.9)	11(18.0)
	Hypertension	23(30.3)	15(38.5)	10(35.7)	18(29.5)
	CRD	24(31.6)	12(30.8)	12(42.9)	20(32.8)
	Asthmas	14(18.4)	4(10.3)	1(3.6)	12(19.7)

From the above table DM=Diabetes mellitus, CRD=Chronic Respiratory Diseases

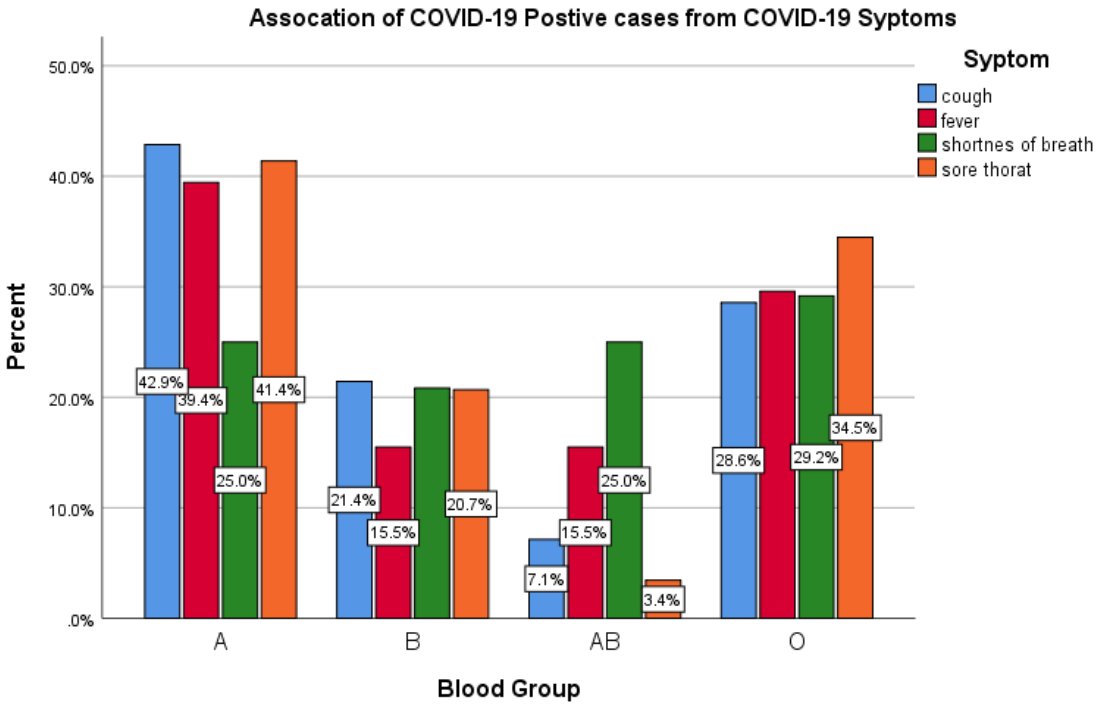

Figure 3. Association of COVID-19 from COVID-19 Diseases symptoms

4.6 Chi-square (X^2) Association of ABO, sex ,age and other diseases with Deceased and Recovery between COVID -19 Positive cases

In Chi-square analysis, the associations of the human ABO and Rh blood group with COVID-19 positive infection were significantly associated with death and recovery (P = 0.009). There was also a statistically significant association between the severity of illness and COVID-19 infection susceptibility from the ABO blood group (P = 0.000). However, sex, age, infectious, non-infectious diseases, and COVID-19 symptoms were not statistically significant with regard to the recovery and deceased. Their P-values were (P = 0.285), (P = 0.359), (P = 0.157), (P = 0.255) and (P = 0.142) respectively.

Table **6**: **Chi-square (X^2) Association of ABO, Rh, sex, age and other diseases with Deceased and Recovery between COVID -19 Positive cases**

Variables	Categories	COVID-19 Infection Positive cases			$\chi 2$ Value	P-value
		Recovery	Deceased	Total		

		N (%)	N (%)	N (%)		
Sex	Male	86(42.2%)	18(8.8%)	104(50.98%)	1.145	0.285
	Female	88(43%)	12(5.8%)	100(49.02%)		
Age	0 -10	9(4.4%)	**3(1.5%)**	**12(5.9%)**	6.608	0.359
	11-20	16(7.8%)	**3(1.5%)**	**19(9.3%)**		
	21-30	23(11.2%)	**3(1.5%)**	**26(12.7%)**		
	31-40	26(12.2%)	**3(1.5%)**	**29(12.2%)**		
	41-50	29(13.7%)	**3(1.5%)**	**32(15.7%)**		
	51-60	**37(18%)**	**4(2%)**	**41(20.09%)**		
	Above 61	**34(16.7%**	**12(5.9)**	**46(22.5%)**		
ABO blood group	A	67(32.8%)	9(4.4%)	76(37.3%)	11.472	0.009
	B	35((17.2%)	4(1.96%)	39(19.1%)		
	AB	18(8.8%)	10(4.9%)	28(13.7%)		
	O	54(26.5%)	7(3.4%)	61(29.9%)		
Rh factor	Positive	142(69.6%)	20(9.8%)	164(80%)	3.494	0.062
	Negative	32(15.7%)	10(4.9%)	42(20%)		
Infectious diseases	HIV/AIDS	6(2.9%)	34(16.6%)	40(19.5%)	5.215	0.157
	Tuberculosis	7(3.4%)	41(20.1%)	48(23.5%)		
	Malaria	4(1.96%)	53(26%)	57(27.9%)		
	Pneumonia	13(6.4%)	46(22.5%)	59(28.9%)		
Non-infectious diseases	DM	9(4.4%)	30(14.7%)	39(19.1%)	4.061	0.255
	Hypertension	11(5.4%)	55(27%)	66(32.4%)		
	CRD	7(3.4%)	61(29.9%)	68(33.3%)		
	Asthmas	3(1.47%)	28(13.7%)	31(15.2%0		
Severity of	Moderate	174(85.3%)	0(0%)	174(85.3%)	204	0.000

illness	Critical	0(0 %)	30(2.9%)	30(14.7%)		
COVID-19 Symptoms	Cough	6(2.9%)	50(24.5%)	56(27.5%)	5.449	0.142
	Fever	7(3.4%)	64(31.4%)	71((34.8%)		
	Shortness of breath	11(5.4%)	37(18.1%)	48(23.5%)		
	Sore throat	6(2.9%)	23(11.3%)	29(14.2%)		

*Significant at P< 0.05

4.7 Univarate and Multivariate Analysis of ABO and Rh Blood Groups System with COVID-19 Infections Susceptibility

In this study, the univarate and multivariate analysis, sex, age, ABO blood groups, Rh type, infectious diseases, non-infectious diseases, and COVID-19 symptoms were listed. The variables that had a p-value of less than 0.25 in the univarate analysis were selected to be used in the multivariate analysis. From this, the odds of COVID-19 infection s age were five times (AOR: 6.531 [95%CI, (1.374-31.031]), p=0.018) higher in the study subjects whose age ranged between 51-60 years, which was statistically significantly associated.

The risk of COVID-19 infection in ABO blood group individuals with blood group AB (AOR: 0.192[95%CI, (0.054-0.683)], P=0.011) was significantly associated with COVID-19 infection.

The risk of COVID -19 infections of pneumonia were (AOR: 3.807[95%CI, (1.021–14.200)], p=0.047 was statistically significantly associated**.**

Table **7**: **Univarate and Multivariate analysis of ABO and Rh blood groups system with COVID -19 infections susceptibility (October 2021 to March 2022)**

Risk factor	**Categories'**	**Cases N**	**COR (95%/ CI)**	**P value**	**AOR(95%CI)**	**P value**
Sex	Male	104	0.652(0.296-1.434)	0.000	0.720(0.301-1.719)	0.459
	Female	100	1(Ref)		1(Ref)	

Age	0-10	12	1(Ref)		1(Ref)	-
	11-20	19	1.778(0.295-10.719)		0.886(0.158-4.957)	0.890
	21-30	26	2.556 (0.433-15.096)	0.001	1.916(0.411-8.936)	0.408
	31-40	29	2.889 (0.492-16.937)		1.988(0.444-8.907)	0.369
	41-50	32	3.222(0.551-18.850)		3.856(0.836-17.788)	0.084
	51-60	41	3.083(0.83-16.294)		6.531(1.374-31.031)	0.018
	>61	45	1.030(0.236-4.494		3.129(0.825-11.874	0.094
ABO Blood group	A	76	0.965(0.337-2.760)		0.971(0.323-2.918)	0.958
	B	39	1.134(0.309-4.162)	0.000	1.373(0.349-5.402)	0.650
	AB	28	0.233 (0.077-0.703)		0.192(0.054-0.683)	0.011
	O	61	1(Ref		1(Ref)	-
Rh type	Rh +	162	2.219(0.948-5.194)	0.000	2.198(0.895-5.399)	0.086
	Rh -	42	1(Ref)		1(Ref)	-
Infectious diseases	HIV/AIDS	40	1(Ref)		1(Ref	-
	Tuberculosis	48	1.034(0.317-3.368)		1.631(0.461-5.776)	0.448
	Malaria	57	2.338 (0.614-8.898)	0.000	1.447(0.458-4.574)	0.530
	Pneumonia	59	0.624(0.215-1.810		3.807(1.021-14.200)	0.047
Non-Infectious diseases	D/ mellitus	39	0.357 (0.088-1.445)		0.538(0.134-2.171)	0.384
	Hypertension	66	0.536(0.138-2.077)	0.000	0.823(0.216-3.140)	0.775
	CRD	68	0.934(0.225-3.880)		1.553(0.354-6.806)	0.560
	Asthma	31	1(Ref)		1(Ref)	-
COVID-19 Symptoms	Cough	56	2.174(0.632-7.472)		2.336(0.625-8.730)	0.207
	Fever	71	2.385 (0.726-7.840)	0.003	3.272(0.959-11.160)	0.058
	S/ breath	48	0.877 (0.286-2.696)		1.391(0.375-5.165)	0.622
	Sore throat	29	1(Ref)		1(Ref)	-

From the above table COR =Crude Odd Ratio, AOR=Adjusted Odd Ratio, Ref= Reference

5. Discussion

Coronavirus disease 2019 (COVID-19), also named novel coronavirus pneumonia (NCP), was first reported in China, Wuhan, in December 2019 and then gradually spread throughout the world. The COVID-19 infection was caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is a new member of the coronavirus family. ABO blood types play a significant role in various illnesses, like oncological, cardiovascular, and certain infectious and non-infectious diseases (Fan *et al.,* 2020).

The present study showed that COVID-19 infection susceptibility in males and females (50.98 % and 49.02% respectively) was almost similar. However, other findings from Pakistan showed that males were more prone to COVID-19 infection than females (67.55% vs. 32.45%) Zietz and Tatonetti (2020). The most probable reason for this difference seems to be the more exposure of male individuals as compared to female individuals as in Pakistan, females mostly live in villages and are restricted at home while in Ethiopia there is almost equal chance of exposure.

In the present study, the highest COVID-19 positive cases were observed in the age category above 61, at 22%, and lower COVID-19 positive cases were observed in the age category 0–10, at 5.1%. The number of COVID-19 positive cases and deaths gradually increased with age, so the number of deceased was higher in the age group over 60 years. These results agree with the study of Sadamadizadeh *et al.,* (2021), which might be expected because aging tends to have a higher prevalence of co-morbidities such as diabetes, heart disease, hypertension, and chronic respiratory diseases and they have a reduced immune response.

The findings of this study showed that the overall distribution of ABO blood group against COVID-19 infection susceptibility showed that blood group A (37.3%) was the most susceptible to COVID-19 infections, and blood group O (30.58%) was the least susceptible to COVID-19 infections. This result agrees with a study done in China (Zhao *et al*., 2020) which showed that individuals with blood group A were at a higher risk of acquiring COVID-19 infection (37.75%), while individuals with blood group O were at a lower risk of acquiring COVID-19 infection (25.80%). Similarly, agreeing result was also reported by Ray *et al*. (2020), Kim *et al*. (2021), Zhang *et al*., 2021, Fan *et al*. (2020), Wu *et al*. (2020), and Li *et al*. (2020). To this end, certain biological reasons have been forwarded why blood group O is least susceptible. Gerard *et al.*

(2020) described that blood group O is not susceptible to the COVID-19 infection due to its protective nature (protective effect of anti-A from blood type O).

The impact of infectious and non-infectious diseases on COVID-19 infection susceptibility was also investigated in this study. Our result showed that among 204 COVID-19 positive subjects, 59 (28.9%) were found to have pneumonia as an infectious disease while 68 (33.3%) had chronic respiratory disease (CRD) as a non-infectious disease. This result agrees with the reports of Boren and Chan *et al*, .2020). On the other hand, among the non-infectious diseases, the rate of hypertension was seen to be higher in COVID -19 positive individuals who have blood group B (38.5%) than other blood groups. This result agrees with El-Sayed and Amin (2015).

This immune response fact has been explained in different studies. Chromosome 9 in human DNA (9q34.2) and many studies have demonstrated a vital role for the ABO blood group in some infectious and non-infectious diseases. Histo-blood group antigens (HBGAs) are one of the main antigens expressed on human red blood cells, and differences in blood group antigens can alter host susceptibility to many infections. HBAs are postulated to decrease the spread of infections through antibodies.

In this study, the severity of illness also showed the highest association with blood groups A (38.5%) than other blood groups. This finding agrees with the reports of Ishag *et al*. (2021) studied in Pakistan (33.7%). The degree of death was also associated with blood group A (4.9%) which agrees with the study done in Pakistan (13.9%) by Ishag *et al*. (2021).

In the current study, COVID-19-infected individuals with blood group AB showed higher symptoms of fever (39.3%) than other symptoms. This finding is in agreement with the previous reports from Komal *et al*., (2021) and explained that COVID-19-infected individuals with blood group AB showed a deviated clinical spectrum of signs and symptoms as subjects with the AB blood group demonstrated slightly higher chances of fever.

In Chi-square analysis, the ABO blood group were significantly associated with death and recovery ($P<0.005$). There was also a statistically significant association between the severity of illness and COVID-19 infection from the ABO blood group ($P<0.005$). These agree with the reports of Ray *et al*. (2020).

In the multivariate logistic regressions analyses, this study showed that the odds of being COVID-19 infected is six times (AOR: 6.531[95%CI, (1.374-31.031)], p<0.005 higher in age group 51 to 60 years than other age groups. Similarly, the risk of COVID-19 infection susceptibility in ABO blood group individuals with blood group AB (AOR: 0.192[95%CI, (0.054-0.683)], P<0.005) was statistically significantly associated with COVID-19 infection. This result agrees with the reports of other studies by Rana *et al*. (2019), who found that patients with the AB blood group had a 0.66-times higher risk of COVID-19 than any other blood type. In our study, subjects who had infectious diseases of pneumonia were two times more likely to have COVID-19 infection than those with other infectious diseases (AOR: 3.807[95%CI, (1.021-14.200)], p<0.005 was statistically significantly associated.

6. Conclusions and Recommendation

6.1 Conclusion

This study provides an important insight into the association of the human ABO and Rh blood group systems with COVID-19 infection susceptibility in FHCSH and GURH. Our frequency distribution results showed that COVID-19 infection susceptibility was higher in the age category of over 60 years old, while the least was in the age category of 0–10 years. Blood group A was the most susceptible to COVID-19 infection, while blood group O had the least susceptibility in the study population. The Rh positive blood group had the highest COVID-19 infection susceptibility, while the Rh negative blood group was less susceptible; on the other hand blood group AB had a higher death frequency. This study agrees with many published data, blood group A was more susceptible to COVID-19 infection, while individuals with blood group O had a higher rate of negative cases that had less COVID-19 infection or protective. In Chi-square analysis, the ABO blood group and severity of illness were significantly associated with death and recovery ($P<0.005$) while this study did not find a significant association between COVID-19 positive cases from sex, age, Rh type, infectious and non-infectious diseases, and COVID-19 disease symptoms. In the multivariate analysis, this study found that the risk of COVID-19 infection susceptibility in the ABO blood group, blood AB was significantly associated with COVID-19 infection.

In this study, subjects who had infectious diseases of pneumonia were two times more likely to have COVID-19 infection susceptibility than those with infectious diseases (AOR: 3.807[95%CI, (1.021–14.200)], p 0.005 was statistically significantly associated.

Results from this study, and the limited reports in this field, reveal a variety of findings concluding an association between blood type and COVID-19infection susceptibility.

6.2 Recommendation

Based on the findings of this study, the following recommendations were provided:

- Providing COVID-19 mRNA vaccination technology had been a game changer in the management to develop immune system.

  Follow up WHO and CDC manifests, using different precaution for avoiding exposure to the virus infection and to get medical care(WHO,2020) that will be reduce COVID-19 infection .

- All concerned governmental and Non-governmental bodies shall focus on creating public awareness programs about COVID -19 infections and blood group association.
- As blood groups have different degree of susceptibility to COVID-19 infection, stakeholders shall design a criteria for vaccination priorities whenever there is resource limitation.
- More studies with more sample size, different methodologies and wider areas are recommended.
- Avoid the negative attitudes of COVID-19 vaccination program.

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8. APPENDICES

BAHIR DAR UINVERSITY

COLLEGE OF SCIENCE

DEPARTMENT OF BIOLOGY

COVID-19 Test Request/Report/ Form

Code--

Dear respondents, the main aim of this forms/charts is to gather data from COVID-19 causes/patient/ documents to find out some relevant information about **the association of human ABO and Rh blood group system with COVID-19 infection susceptibility in Amhara region**. **Then circle or tick mark (√) and write numerics for the case and events of COVID -19** infections documents in front of each information.

COVID-19 Test Request/Report/ Form

Part A. personal background data

1. Sex Male ☐ Female ☐
2. Age A/ 0 - 15 years B/ 16 - 31 years C/ 32 - 46 years D/ 47 - 61 years E/ 61 above
3. Educational status A/ No formal B/Adult education C/Primary education D/ Secondary education E/ Above
4. Marital status A/ Single B/ Married C/ Divorced
5. Specimen ID/ Barcode No----------

Part B Clinical/ other information

1. Symptom on set date----------/----------/----------
2. Symptom of compatible with COVID-19
   A/Cough B/Fever C/Shortness of breath D/ Sore throat E/ Headache F/ Other

3. Do the patient /client have any other chronic diseases **Circle yes or No?** if yes choose below A/ Diabetes mellitus /DM/ B/ HIV C/ Malaria D/ Hypertension E/Cancer F/ Pneumonia G/ TB H/ Chronic respiratory diseases I/Pregnant J/ Others
4. Severity of illness A/Low B/ Medium C/High D/Very high
5. Reason for Testing A/suspect B/ Contact of confirmed case C/New D/ Follow up D/ Travel
6. Laboratory method A/RT-PCR B/ RDT C/ Other
7. Laboratory result A/Positive ☐ B/ Negative ☐
8. Status of COVID -19 A/ case group ☐ B/Recovery group ☐ C/ Death group ☐

Part C Blood group type of COVID-19 cases tick mark (√) below

A+	**A-**	**B+**	**B-**	**AB+**	**AB-**	**O+**	**O-**

Thank you for your co-operation in advance

- **For any information Researchers name:- Wubeshet Mengesha**

  E-mail-wubeshetmengesha@gmail.com .phone number -09-18-28-01-72

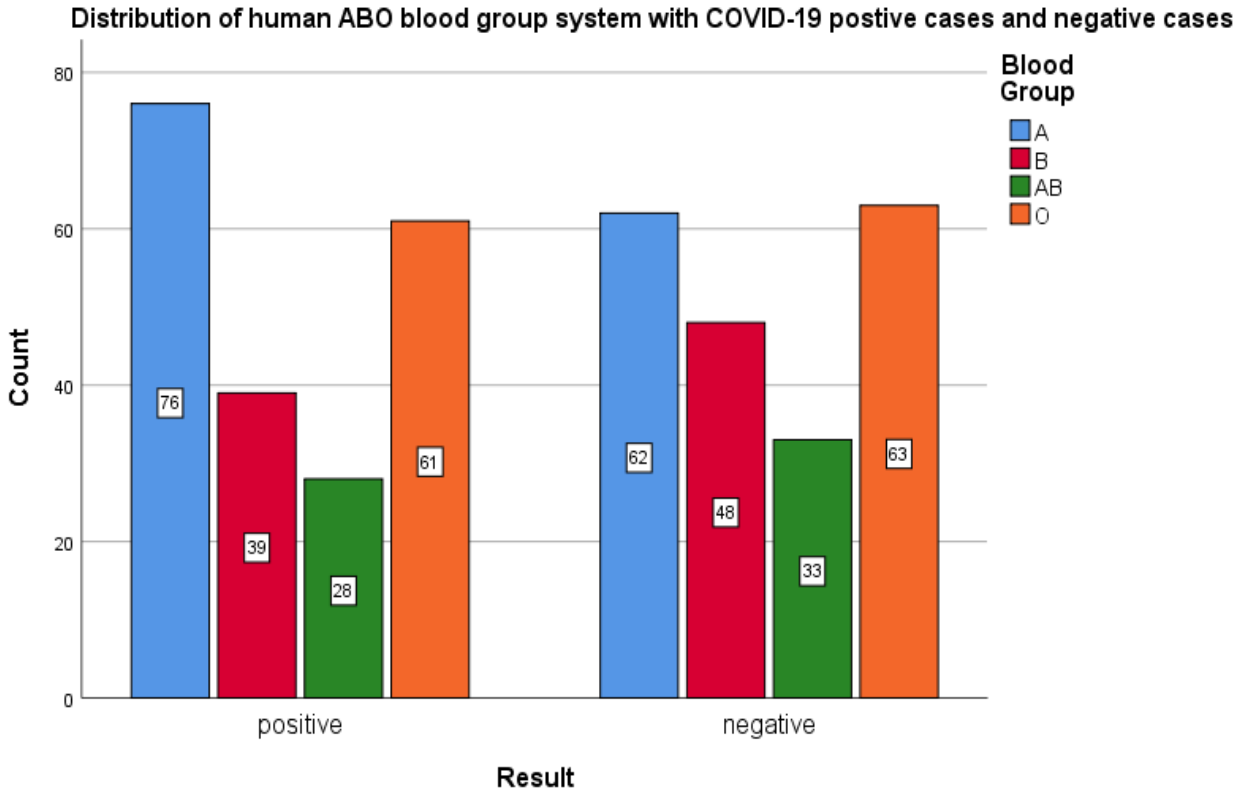

Figure 4. Distrubtion of human ABO blood group system with COVID 19 postive and negative cases

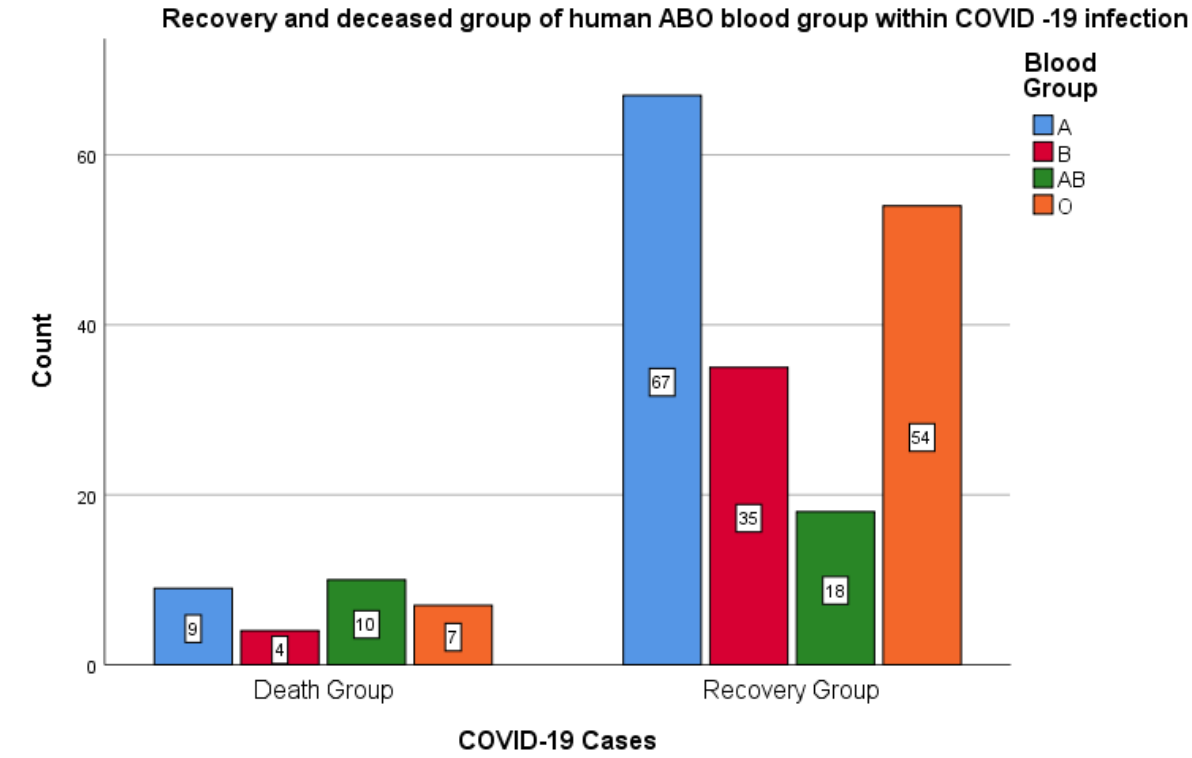

Figure 5. Recovery and deceased group of human ABO blood group within COVID- 19 Infection

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Ref.No PRCSVD/284/2014

Date 14 Feb. 2022

Ethical Clearance Approval Form

Applicant's Name: Wubeshet Mengesha

Research Title	Association of human ABO and Rh blood group system with COVID-19 infection susceptibility in Amhara Region
Researcher (s) Name (s)	Wubeshet Mengesha

Thank you for submitting your application for ethical clearance, which was considered at the College of Science Research Ethics Committee meeting on 14 February 2022. The committee has reviewed your ethical application, issues pertaining to participants, consent form, debriefing, and relevant questionnaires.

The researcher should keep the confidentiality of the identity of research participants and data that will be obtained from them. Any serious adverse events or significant changes which occur in connection with this study and /or which may alter its ethical consideration must be reported immediately to the committee for a possible ethical amendment.

We are therefore pleased to inform you that the College's Ethical Clearance Committee has approved your study from an ethical point of view.

With kind regards

Tsegaye Kassa (PhD)
The Graduate, Research and Community Services V/Dean
College of Science

Office of Research & Community Services Bahir Dar University College of Science

CC //

- Dean office
- The Graduate, Research and Community Services V/Dean
- Department of Biology

College of Science