Investigation of the relationships between host genetics and COVID-19 disease progression among different ethnic groups in South Africa

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PREFACE

This project represents original work done by the author and others whose contribution has been acknowledged in the text. All experimental work mentioned in this dissertation was accomplished in the Infection and Control Laboratory, Howard College, University of Kwa-Zulu Natal, Durban, South Africa from 2021 to 2023, under the supervision of Prof. Veron Ramsuran and the assistance of Thilona Arumugam.

[redacted]____ 31 January 2024

Lisa Naidoo (Student) Date

DECLARATION

I, Lisa Naidoo, declare that:

The research reported in this study, except otherwise indicated, is my original work.

This study has not been submitted for any degree or examination at any other university.

This study does not contain other people's data, pictures, graphs, or other information unless specifically acknowledged as being sourced from other persons.

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Student name: Lisa Naidoo

Signature ___[redacted]____ Date 31 January 2024

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DEDICATION

I want to thank God first and foremost for making this milestone possible. I dedicate this qualification to family. To my parents, I deeply appreciate everything they have done for me, to mention a few, continual support, guidance, and motivation. I aspire to be successful, dedicated, and committed as you have shown and taught me to be. My dad, Vasuthevan, always wanted me to pursue a doctorate and work with infectious diseases. To my mum, Kanaga, who continually encourages me to pursue my dreams and goals and to never give up. To my grandmothers, I cannot thank you enough for the impact that you have left on my life, despite the generational changes, you both have supported my dreams. To my siblings, Kevin and Pragan, who always looked out for my best interest and cheered me on all the way. To my husband, Rishen, who through our courtship and marriage stood by me and took care of me through this journey. To Ace, you lit my life immensely and got me through the hardest times. To the rest of my family thank you for the advice and support, and finally, to the future, my nieces and nephews, and my future child, I look forward to what you aim to pursue, and I hope to inspire you.

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List of publications from the PhD project:

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Lisa Naidoo, Thilona Arumugam, Veron Ramsuran, Narrative Review Explaining the Role of HLA-A, -B, and -C Molecules in COVID-19 Disease in and around Africa (Published Infectious Disease Reports, /doi.org/10.3390/idr16020029)

Lisa Naidoo, Thilona Arumugam, Veron Ramsuran *HLA-B,* and *C* expression contribute towards COVID-19 disease severity within a South African cohort. (Published in Genes, DOI: 10.3390/genes15040522)

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LIST OF ABBREVIATIONS

SARS-CoV-2	Severe acquired respiratory syndrome-Corona virus 2
COVID-19	Corna virus disease
HLA-	Human Leucocytes Antigen
N	Number
PCR	Polymerase chain reaction
RT-PCR	Real-time PCR
WHO	World Health Organization
NK	Natural killer cell
NCD	Non-communicable diseases
VDR	Vitamin D receptor
MBL	Mannose-binding lectin
HAND	HIV-associated neurocognitive disorder
ICAM-1	Intercellular adhesion molecule-1
MHC	Major histocompatibility complex
CCR2	C-C motif chemokine receptor 2
CCR5	C-C motif chemokine receptor 5
CMI	Cell mediate immunity
CX3CR1	C-X-3 chemokine receptor 1
CXCR4	C-X-C motif chemokine receptor 4
CXCR6	C-X-C motif chemokine receptor 4
AIDS	Acquired immune deficiency syndrome
LTNP	Long-term non-progressors
TNF	Tumor necrosis factor

IFN	Interferon
HC	Healthy controls
LTB	Latent TB
CCL2	C-C motif ligand 2
CCL3	C-C motif ligand 3
CCL5	C-C motif ligand 5
SDF	Stromal cell-derived factor
DCS	Dendritic cells
RANTES	Regulated on activation normal T expressed and secreted
MIP	Macrophage inflammatory protein
CCL2	C-C motif ligand 2
CNV	Copy number variation
Th2	T helper 2
CSF	cerebrospinal fluid
ML	Mononuclear leukocyte
TBM	Tuberculosis meningitis
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-18	Interleukin-18
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4

TLR7	Toll-like receptor 7
TLR8	Toll-like receptor 8
MAF	Minor allele frequencies
NCBI	National Centre for Biotechnology Information
SNP	Single Nucleotide Polymorphism
HIV	Human Immunodeficiency Virus
TB	Tuberculosis

CHAPTER 1:

ABSTRACT

Human leukocyte antigens (HLA) are involved in presenting antigens to T cells, for pathogen identification. HLA genes are critical for the immune response and possibly for vaccine development. HLA has been shown to play a role in various diseases such as infectious, metabolic, and autoimmune diseases. It is, therefore, possible that HLA would play a role in SARS-CoV-2 disease progression. Studies showed that HLA alleles were associated with SARS-CoV-2 susceptibility and COVID-19 severity. HLA genetic variations might contribute substantially to the variation in the immune reaction to COVID-19 susceptibility and severity. HLA expression levels have not been analyzed for COVID-19 disease. Previous studies have linked expression levels of HLA with infectious diseases. In this study, we focused on the HLA class I genes, to examine the effect of HLA-A, HLA-B, and HLA-C mRNA expression levels on COVID-19 disease severity. Real-time PCR confirmed SARS-CoV-2 infected individuals, from South Africa with Black and Indian ethnicities, were used to measure the HLA-A HLA-B, and HLA-C expression at the mRNA level. The HLA mRNA expression levels were used to associate with a range of disease outcomes as well as other contributing factors such as gender, age, ethnicity, and comorbidities. Previous studies have highlighted the disparity among ethnic groups in COVID-19 disease progression. This study showed HLA-A mRNA expression levels associated with; differences in disease severity amongst COVID-19 infected individuals ($p=0.0005$), and differences between South African Black and South African Indian ethnic groups ($p<0.0001$). We also analyzed differences between severity, gender, comorbidities, and age. HLA-B mRNA expression levels were associated with differences in disease severity ($p<0.0001$). While HLA-C mRNA expression levels were not associated with COVID-19 disease severity. We observed that HLA-B and HLA-C mRNA expression levels were significantly different between South African Blacks and South African Indians ($p<0.0001$, $p<0.0001$). We observed HLA-B and HLA-C expression levels between severity, gender, comorbidities, and age. Our work is expected to strengthen the understanding of the relationship between HLA and COVID-19, by providing insights into HLA-A, B, and C expression levels across ethnic populations in South Africa among COVID-19 symptomatic and asymptomatic individuals. Our results highlight that HLA-A and HLA-B mRNA expression levels contribute to COVID-19 severity as well as variation in ethnicities associated with COVID-19. Further studies are needed to examine the effect of HLA expression levels

across various ethnic groups with contributing factors. These findings highlight the importance of HLA-A expression levels as previously demonstrated within HIV disease.

INTRODUCTION

Severe acute syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, which led to the most dreadful pandemic (1). Coronavirus is a respiratory virus that can cause symptoms as mild as a common cold and as severe as death (2). COVID-19 severity correlated with lymphopenia, cytokine storm (3), and exaggerated immune response (4). COVID-19 outcomes vary because of contributing factors such as; age, comorbidities, environment, viral genetics, genomics, blood groups (5, 6), and host genetics involved in immune response and pathogenesis (7, 8).

COVID-19 originated in China (9, 10), and spread around the world. In Africa, the reduced COVID-19 incidences have been attributed to the lack of COVID-19 testing, existing medical conditions in Africa, Africa's interventions, innate immune memory, population distribution in Africa, the genetic diversity among people within the African continent, and younger age (11). Despite Africa having high rates of infectious diseases, Africa was able to withstand COVID-19 better than other areas. Although Africa is a third world continent, Africa was able to implement additional public health guidelines because they had more preparation time for COVID-19 than other countries. and their experience with other infectious diseases such as malaria, TB, and HIV. Furthermore, Africa has a younger population compared to other populations, therefore allowing a better immune response to COVID-19 (11). This might have assisted with Africa's reduced COVID-19 incidence. Africa's response to COVID-19 needs to be understood.

The genetic diversity within African descent might be associated with the variation in SARS-CoV-2 susceptibility and COVID-19 severity between individuals and populations. There is increasing proof of host genetics playing a significant role in infectious diseases such as TB, HIV, malaria, and now COVID-19 (12). In addition, there is growing evidence that the difference in disease severity might be due to host genetics. Host genes might be involved in more than one infectious disease (12). This information is imperative when developing

therapeutic strategies for these diseases, especially for those infected with more than one disease. Therefore, studying host genetics is of utmost importance.

Human leukocyte antigens (HLA) genes are involved in presenting antigens to T cells, for pathogen identification. HLA genes are helpful for the immune response and vaccine development (13). It is imperative to determine the effect HLA has on human responses to SARS-CoV-2. Studies showed that genetic variants involved in immune activities were associated with SARS-CoV-2 susceptibility and COVID-19 severity (14, 15). HLA genetic variations might contribute substantially to the variation in the immune reaction to COVID-19 susceptibility and severity.

The HLA molecule is found on the cell surface of most cells and is critical in the adaptive immune response. It facilitates the killing of infected cells and antibody production. HLA-A, HLA-B, and HLA-C are HLA class I alleles. Nucleated cells express HLA class I molecules. Antigen-presenting cells, such as dendritic cells, macrophages, and mature B lymphocytes express HLA class II molecules. HLA is the most polymorphic human gene (16). These mutations encode for the peptide-binding groove and T-cell receptor interactions (17). Genetic variations affect HLA geometry, hydrophobicity, charge distribution, expression levels, and peptide interactions. Different HLA molecules may have unique peptide binding ability to B cell and T cell receptors. Variation in HLA among individuals might alter peptide presentation and immune responses (18). HLA genetic polymorphisms affect the disease severity of bacteria and RNA viruses (19-22). Therefore, analyzing HLA could be valuable in determining their contribution to severe COVID-19. The HLA class I genes are necessary for obtaining a specific immunological response to pathogens. HLA-A*68 was shown to be associated with prevention from COVID-19 severity and fatal outcomes (23). In this study, we will examine HLA class I gene expression from HLA-A, -B, and -C genes and COVID-19 disease progression.

The HLA region is an important target of COVID-19 therapeutics since it plays a key role in the immune response. Viral genetics have been studied intensively, however little is known about the host genetics, particularly HLA. (24, 25). Therapeutic development should include studies that focus on individuals who are affected and unaffected by the disease course. Studies have shown that different ethnicities with COVID-19 infection have varying outcomes and

states of disease (12). There are no studies on the relationship between HLA class-1 expression and disease outcome in COVID-19 infection, especially in Africa. HLA-I has been associated with disease progression of various infections and autoimmune diseases, however, it remains unknown whether HLA expression influences COVID-19 disease progression among different South African ethnicities and to what extent. HLA expression may be a key function for virus survival and persistence since it is involved in the immune response against COVID-19. Therefore, the first aim of this study was to investigate the relationship between the ability of HLA class I expression (gathered from a South African population of COVID-19 infected individuals) to alter disease progression.

In this study, we determined the HLA class I expression levels of COVID-19 infected individuals. We compared this with contributing factors such as age, gender, sex, and comorbidities. We used the SAPS cohort, this is a longitudinal study of SARS-CoV-2 infected individuals from South Africa. These aims were addressed by studying South African Blacks and South African Indians, these individuals were broken down into categories based on their presence or absence of clinical presentation; South African Black asymptomatic South African Black symptomatic South African Indian asymptomatic, and South African Indian symptomatic.

The main aims and objectives of this study are summarized below:
Specific aims:

To investigate the relationship between *HLA-A* expression levels and COVID-19 disease severity (asymptomatic and symptomatic) among different ethnic groups (Indian and Black) in South Africa

To understand the impact of *HLA-B* and *HLA-C* expression levels on COVID-19 disease progression (asymptomatic and symptomatic) among different ethnic groups (Indian and Black) in South Africa

To investigate the influence of ethnicity, gender, age, and comorbidities on the *HLA* class I expression.

To accomplish these aims the following objectives were fulfilled:

Measurement of *HLA-A, B,* and *C* expression, derived from patients infected with COVID-19 from Indian and Black South Africans to influence disease state through PCR.

Identify if factors such as ethnicities, comorbidities, age, and gender are associated with increased or decreased *HLA* class I expression through statistical analysis.

CHAPTER 2: LITERATURE REVIEW

Host genetics impact on infectious diseases among different ethnic groups, Advanced Genetics (Published by Advanced Genetics Journal Naidoo L, Arumugam T, Ramsuran V. *Host Genetic Impact on Infectious Diseases among Different Ethnic Groups* Advanced genetics (Hoboken, NJ). 2023,*4*(4),2300181.DOI: 10.1002/ggn2.202300181)

Title: Host genetic impact on infectious diseases among different ethnic groups

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Abstract

Infectious diseases such as malaria, tuberculosis (TB), human immunodeficiency virus (HIV), and the coronavirus disease of 2019 (COVID-19) are problematic globally, with high prevalence particularly in Africa, attributing to most of the death rates. There have been immense efforts toward developing effective preventative and therapeutic strategies for these pathogens globally, however, some remain uncured. Disease susceptibility and progression for malaria, TB, HIV, and COVID-19 varies among individuals and is attributed to precautionary measures, environment, host, and pathogen genetics. While studying individuals with similar attributes, it has been suggested that host genetics contributes to most of an individual's susceptibility to disease. Several host genes have been identified to associate with these pathogens. Interestingly, many of these genes and polymorphisms are common across diseases. This paper analyzes genes and genetic variations within host genes associated with HIV, TB, malaria, and COVID-19 among different ethnic groups. We review the differences in host-pathogen interaction among these groups, particularly of Caucasian and African descent, and which gene polymorphisms are prevalent in an African population that possesses protection or risk to disease. The information in this review could potentially help develop personalized treatment that could effectively combat the high disease burden in Africa.

Introduction

In 2019, the top ten causes of death were due to non-communicable diseases (NCDs) worldwide. The most common NCDs such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer make up 55% of deaths worldwide (1, 2). All NCDs are responsible for 41 million deaths a year, approximately 74% of all deaths (3). However, in 2019, in Africa, the 3 infectious/communicable diseases: TB, malaria, and HIV were the cause of the top 8 most common causes of death (4-7). In other continents of the world, communicable diseases are rarely among the top ten causes of death. In addition, the recent pandemic caused by SARS-CoV-2 has drastically impacted global death rates over the past few years. Europe had the highest COVID-19 cases of 273 666 626, followed by the Western Pacific and America. However, Africa had the lowest number of COVID-19 cases of 9,500 642. On November 18, 2022, there were 257,984 COVID-19 deaths in Africa (8). In Europe, on January 13, 2023, there were 2 169 191 COVID-19 deaths (9). In 2019, the death rate in Africa was 7.77 per 1000 people. In 2020, when the first case of COVID-19 was identified, the death rate reduced slightly to 7.62 deaths per 1000 (10). In Europe, the death rate was 9.97 in

2019 and increased to 11.1 in 2020 (10). This was also observed in North and South America (10). Despite Africa's COVID-19 data being underrepresented due to lower testing capacity (11), we noticed that the death rate reduced after COVID-19. This indicates that COVID-19 had a less severe impact on the African population as opposed to continents with a predominantly Caucasian population.

High levels of infectious disease cases in Africa have been attributed mainly to poor socioeconomic status resulting in a lack of basic needs and poor living conditions (12). Another contributing factor to the higher infection rates in Africa could be due to an ethnic-specific bias as the African population consists of 980 million black individuals (13). Previous studies showed that different populations react differently to infectious diseases based on their genetics (14-16). Africa, being the second largest continent with the second largest population, is known to have the greatest genetic diversity with 3000 different ethnic groups populating the continent. The high level of genetic diversity is a challenge and a prospect for Africa, as it is the least studied genome with one of the highest health burdens (17). Despite immense efforts toward developing effective preventative and therapeutic strategies for these pathogens, several uncured diseases with unsafe and resistant drugs are on the market. New treatment strategies that are affordable, harmless, and effective for Africans need to be developed for these infectious diseases. In this review, we determine the host genetic contributions to these diseases in the African population and whether the African population's genetics contribute to high rates of infectious diseases. The host genetics associated with these diseases need to be studied more in an African population.

Several host genes are associated with numerous infectious diseases, one of them being the vitamin D receptor (*VDR*). The *VDR* gene is a transcription factor that controls the expression of various genes involved in physiological processes (18), such as immunity and cell differentiation to target tissues (19). *VDR* was suggested to be important in malaria, TB, HIV, and SARS-CoV-2 susceptibility and COVID-19 severity in different populations (20-23). Polymorphisms within host genes, can alter the gene function and lead to anti or pro-disease activity (24-27). Several common host genes and gene polymorphisms play a role in infectious diseases.

Unraveling the host-virus and virus-virus interaction and identifying host factors that are important for pathogenesis will better equip us to understand the variability in pathogenesis

among different ethnic groups, particularly between Africans and Caucasians, and develop personalized treatments for these highly infectious diseases in Africa. This review will examine host genes overlapping with HIV, TB, malaria, and COVID-19. We will analyze the host gene functionality, genetic variations if any, and their effect, or whether it might confer protection or risk to infected individuals from different ethnicities and allele frequency among different ethnic groups.

Inclusion and Exclusion criteria for selected genes and SNPs

Host genes associated with HIV were identified using Google Scholar using the search words "host genes associated with HIV susceptibility, control, and progression" between 2007-2023 and sorted by relevance in the first phase. There were 19900 results on Google Scholar on 03/06/2023. We looked at all the titles in the second phase and found 25 relevant articles. In the third phase, we read all abstracts and selected 6 relevant articles. HIV-associated host genes from these relevant articles selected were used as a basis for the selection of host genes associated with TB, Malaria, and COVID-19 in phase four. The articles for these genes were found on PubMed using the infectious disease and the gene name. SNPs within the host genes that were associated with these infectious diseases were identified by these published scientific papers. There were multiple SNPs for each gene (VDR, n=6; *MBL*, n=4; *ICAM-1*, n=3, *CXCR6*, n=1, *CX3CR1*, n=0, *CCR2*, n=1, *CCR5*, *n=4*, *CXCR4*, n=0, *SDF-1*, n=0, *IFN*, n=0, *TNF*, n=0, *CCL3*, n=1, *CCL5*, n=1, *CCL2*, n=4, *IL-1*, n=7, *IL-4*, n=1, *IL-6*, n=10, *IL-8*, n=1, *IL-10*, n=3, *IL-18*, n=0, *TLR2*, n=0, *TLR4*, n=4, *TLR7*, n=0, *TLR8*, n=0, *TLR9*, n=6). The resulting SNPs were then ranked in order of minor allele frequencies (MAF) based on data from the National Centre for Biotechnology Information (NCBI dbSNP) (https://www.ncbi.nlm.nih.gov/) and SNPs characterised as being rare genetic variants among the African population (MAF < 2 or 1%) were removed (*VDR*, n=2; *MBL*, n=2; *ICAM-1*, n=2, *CXCR6*, n=1, *CX3CR1*, n=0, *CCR2*, n=0, *CCR5*, *n=2 CXCR4*, n=0, *SDF-1*, n=0, *IFN*, n=0, *TNF*, n=0, *CCL3*, n=0, *CCL5*, n=1, *CCL2*, n=1 *IL-1*, n=1, *IL-4*, n=1, *IL-6*, n=2 *IL-8*, n=1, *IL-10*, n=3, *IL-18*, n=0, *TLR2*, n=0, *TLR4*, n=0, *TLR7*, n=0, *TLR8*, n=0, *TLR9*, n=2). MAF, disease associations, and potential mechanisms of action for all eligible genes and SNPs were then summarized in **Figure 1**. Information regarding the gene function, genetic variation, and effect on disease has been summarized in **Table 1**.

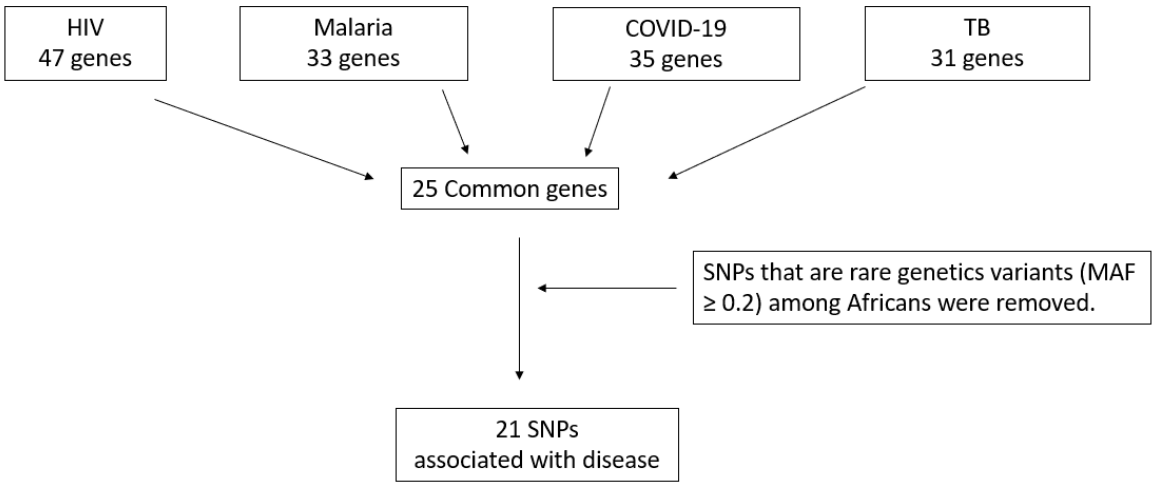

Figure 1: Flow diagram of the inclusion and exclusion criteria of genes and SNPs discussed in this review.

Table 1: Genes associated with infectious diseases.

Gene name	**Function**	**HIV**	**Malaria**	**COVID-19**	**TB**	**Genetic variation (>0.2)**	**Reference**
Chemokine receptors							
CCR2	Involved with the innate immune response.	Co-receptor of HIV, alters the cell surface location of the CCR5 and CXCR4 and regulates heterodimerization, reduces levels of CXCR4 in PBMCs from	CCR2-deficient mice have persistent parasitemia in malaria. CCR2 deficient mice inhibit inflammatory monocyte recruitment to the site of infection.	CCR2 is associated with the monocyte recruitment and infiltration of these cells in the lungs of COVID-19-infected individuals. CCR2 may	CCR2 contributes to the defense against MTB. This was shown in a study with CCR2-deficient mice.		(28-35)

		healthy donors and late disease		be protective in SARS-CoV-infected dendritic cells. CCR2 reduced viral load in SARS-CoV-2 infected mice.			
CCR5	Associated with cell activation and migration.	HIV receptor for HIV entry	*CCR5* was associated with adverse effects caused during pregnancy with malaria infection. *CCR5* deficiency increases maternal parasitemia.	CCR5 is expressed on macrophages and T cells acting as a co-receptor for SARS-Cov-2. CCR5 plays a role in COVID-19 severity.	CCR5 plays an essential role in cell activation and migration in immune responses against TB.	rs9845542 severe COVID-19 rs12639314 severe COVID-19	(27, 36-50).
CXCR4	Regulates and expresses T cell migration	CXCR4 s play a role as co-receptors for HIV, it is important at a	*CXCR4* increases calcium levels which influence	High levels of *CXCR4* direct cells to destroy lung tissue	*CXCR4* expression is higher among TB/HIV co-infected		(51-55)

		late stage of disease development	sporozoite transformation into exoerythrocytic forms which is necessary for parasite progression in the liver. Eliminating *CXCR4* inhibits the development of Plasmodium falciparum in the liver.	(51). fatal COVID-19 is associated with elevated *CXCR4* in bystander T cells.	individuals than HIV infected individuals Increased *CXCR4* expression is associated with TB in alveolar macrophages.		
CX3CR1	Involved with adhesion and migration.	Co-receptor for HIV infection, HIV-1 immune cell recruitment, infection expansion, signalling, and regulation of cell function.	High *CX3CR1* and *CCR2* on CD14 monocytes limit parasitic growth through antibody dependent cellular inhibition activity. Similarly, in another study, high *CX3CR1*	*CX3CR1* expression was impaired among individuals who had contrary artery disease and SARS-CoV2.	The *CX3CR1* expression levels on monocytes are elevated among latent TB infections.		(26, 56-60)

			expressing cells were associated with better survival.				
CXCL 12	Involved in a wide range of functions, one being the ability to control the trafficking of leukocytes	Ligand for CXCR4, which induces receptor internalization, and might restrict transmission of X4 viruses.	High *SDF-1* levels in African children were associated with acute malaria compared to healthy children.	*SDF-1* is upregulated in early post-SARS-CoV-2 infection.	*SDF-1* is a diagnostic marker for TB and correlates with severe TB		(61-63)
CCL2	Pro-inflammatory chemokine.	Granulomatous reaction in lung tissue	High levels of *CCL2* were observed in *P.vivax* infections (64). Similarly, elevated *CCL2* has been found in malaria-infected placentae (65).	The *CCL2* chemokine is involved in the migration of inflammatory monocytes. It is produced by alveolar macrophages, T cells, and endothelial	*CCL2* is associated with TB.	rs4586), resulting in a T>C allele change, affecting TB susceptibility	(32, 64-70)

				cells. In addition, *CCL2* chemokines were expressed at higher levels in lung macrophages of severe COVID-19 patients. *CCL2* was upregulated early post-SARS-CoV-2 infection.			
CCL3	Involved in the recruitment of neutrophils and monocytes, and the activation of inflammatory signalling.	Co-receptor of CCR5, internalizing and lessening the CCR5 levels on the cell surface, Cognate ligand for CCR6, Natural ligands of CCR5.	*CCL3L1* CNV and its association with disease susceptibility	The *CCL3* levels were increased in CM-infected mice (71). In addition, elevated levels of monocyte-attracting β-chemokines CCL3	*CCL3* is a leucocyte activating chemokine that is involved in TB restriction. High levels of *CCL3* were detected in PTB when compared to latent TB (LTB) and		(16, 65, 71-84)

		blocks HIV-1 infection		have been found in malaria-infected placentae.	healthy control (HC) patients.		
CCL5	Involved with the migration of macrophages and NK cells	The natural ligand of CCR5, blocks HIV infection, Reduces CD4 T cell depletion	Malaria outcomes are influenced by the role of *RANTES* in host immunity. Low levels of *RANTES* were associated with CM in Ugandan children. Bujarbaruah et al., observed similar results, showing low levels of *RANTES* were associated with severe malaria and high *RANTES* was associated with malaria recovery and	*CCL5* is upregulated in early post-SARS-CoV-2 infection. In addition, high levels of *CCL5* in found in critically ill COVID-19 patients.	*CCL5* plays a key role in co-stimulation of T cell proliferation a nd *RANTES* activation in anti-mycobacterial immunity. Studies have shown a significant relationship between *RANTES* polymorphisms and an increased TB risk.	(rs2107538) C>T increased PTB susceptibility.	(85-92)

			uncomplicated malaria.				
Toll-like receptors							
TLR2	TLR identifies motifs in pathogens.	Causing HIV-1 expression during opportunistic co-infections	*TLR2* helps the recognition of a wide range of ligands. Sporozoite activates *TLR2* and induces macrophages to release proinflammatory cytokines.	*TLR2 is* theoretically important in COVID-19 infection. There are beneficial and harmful effects of *TLR* in COVID-19 infection.	Several *TLR2* polymorphisms were found in tuberculosis patients. *TLR2* polymorphisms are a risk factor for tuberculosis infection. Yim et al. observed that TLR-2 deficiency makes patients more TB-susceptible. We suggest that genetic variations that result in TLR2 deficiency can be a risk factor for TB.		(93-102)
TLR4	Associated with activating gene expression and viral	Causing HIV-1 expression during opportunistic co-infections	, *TLR4* mediates the (lipopolysaccharides) LPS of gram-negative bacteria recognition	*TLR4 is* theoretically important in COVID-19 infection. There are	*TLR4* is associated with TB pathogenesis, this stems from the number of SNPs in *TLR4*		(93, 94, 99-104)

			(93). *TLR4* was expressed in correlation with the absolute neutrophil count	beneficial and harmful effects of *TLR* in COVID-19 infection.	and *TLR8* in TB infected individuals compared to healthy individuals. *TLR4* and *TLR8* heterodimer formation regulates MTB immune responses		
TLR7		Causing HIV-1 expression during opportunistic co-infections	*TLR7* and *TLR8* recognize plasmodium-derived RNA. *TLR8* has been associated with severe infected malaria in Mali children.	*TLR7* is expressed on dendritic cells and monocytes. *TLR7/8* mediates pro-inflammatory cytokine production (94). *TLR7* has been associated with SARS-CoV-2 pathogenesis. *TLR7/8*	*TLR7* has been suggested to provide MTB host cell immunity.		(94, 105-108)

				identify COVID-19. *TLR8* is present in the lungs, and *TLR7* and *TLR8* may lead to SARS-CoV-1 cytokine storms.			
TLR8		Causing HIV-1 expression during opportunistic co-infections	*TLR8* recognizes plasmodium-derived RNA. *TLR8* has been associated with severe infected malaria in Mali children.	*TLR8* mediates pro-inflammatory cytokine production. *TLR8* identify COVID-19. *TLR8* is present in the lungs, and *TLR8* may lead to SARS-CoV-1 cytokine storms.	*TLR4* and *TLR8* are associated with TB pathogenesis, this stems from the number of SNPs in *TLR4* and *TLR8* in TB infected individuals compared to healthy individuals. *TLR4* and *TLR8* heterodimer formation regulates MTB immune responses.		(94, 104, 107-111)

TLR9	Associated with activating gene expression and viral	Causing HIV-1 expression during opportunistic co-infections	*TLR9* facilitates recognition of the CpG motif in bacterial DNA	*TLR9 is* theoretically important in COVID-19 infection. There are beneficial and harmful effects of *TLR* in COVID-19 infection.	*TLR9* is a pattern recognition receptor that facilitates MTB recognition and controls MTB-specific T-cell responses.	(rs5743836) A>G malaria progression and susceptibility (rs352140) C>T high levels in highly active antiretroviral therapy (HAART)-naïve rapid progressors	(94, 112-116)
Cytokines							
IFN	Regulates cytokines and chemokines. It is involved in innate immunity.	Aberrant IFNG regulation	*IFN-γ* was higher among individuals who were parasitaemic than aparasitaemic. Reduced *IFN-α* levels were	Severe COVID-19 is associated with sustained *IFN* response. Severe	*IFN-α* expression levels are higher among TB patients than uninfected individuals. In-vitro *IFN-α* does not		(117-126).

			associated with severe malaria in Kenyan and Gabonese children. *IFN-α* regulates the immune response during human malarial infections. *IFN* has differing effects on infectious diseases.	COVID-19 patients had disrupted *IFN-α* and *IFN-β* production and downregulation of *IFN-simulated* genes. Mossel et al. did an *in vitro* study and showed that *IFN-α* and *IFN-γ* have a synergistic effect that inhibits SARS-CoV replication.	restrict MTB replication intracellularly. *IFN-γ* is associated with anti-mycobacterial activity. IFN-α compromised the activity of *IFN-γ*. *IFN-α* inhibited IL-1β production and induced the production of IL-10, which further reduced IL-1β. *IFN-α* enhances IFN-γ production. *IFN-α* and *IFN-γ* might be associated with MTB immune escape and disease progression.		

TNF	Is associated with cell proliferation, death, survival, and differentiation	It is important for HIV pathogenesis. In addition, HIV uses TNF-α signalling pathways to expand its reservoir. HIV proteins act like and mediate the TNF signalling pathway.	TNF is known for malaria killing, however, it also is associated with severe malaria development.	When TNF was blocked in severe COVID-19 patients there was a reduction in lung damage and lower hospitalization. TNF was associated with severe COVID-19 pathogenesis and may have a role in cytokine storms.	TNF-α contributes to MTB host response. Inhibition of TNF-α is associated with an elevated risk of latent TB infection reactivation. TNF plays an important role in the host's immune response against TB.		(127-132)
Interleukins							
IL1	Inflammatory response	The *IL-1* family is primarily associated with innate immunity, manifested by inflammation		This IL-1 SNP is associated with disease severity.	*IL-1* accumulates in the acute phase response. Increased *IL-1β, IL-4*, and *IL-6* levels were	(rs16944) A>G was associated with severe influenza A/H1N1 and B.	(93, 133-143)

		, and functioning as a mechanism of host defense. *IL-1* triggers innate inflammation via IL-1 receptors. IL-1a also plays a role in acquired immunity as damage-associated molecular patterns (DAMPs). HIV inducive *IL-1* plays a role in HIV-1 disease progression. *IL-1α* and Interleukin-1 beta (*IL-1β)* are co-stimulatory cytokines for T helper cells that stimulate			associated with TBM		

		the maturation and clonal expansion of B cells.					
IL4		Anti-inflammatory cytokine with immune-regulating functions such as; downregulation of HIV co-receptors; CCR5 and upregulation of CXCR4, influence transcription of the cytokine, inhibits HIV-1 replication mostly for CXCR4			Increased *IL-4* levels were associated with TBM		(128, 139, 143-147)
IL6	Accumulates in acute response.	*IL-6* starts a signaling cascade associated with the Janus kinase/signal	The concentration of IL-6 has been associated with severe	Higher levels of inflammatory cytokines such as IL-6 in	The effect of CD4+ T cell response makes *IL-6* crucial in the protection against	Rs1800795 G>C	(42, 93, 133, 134, 138, 139, 141-143,

		transducer and activator of transcription (JAK-STAT) activation pathway, promoting the transcription of genes associated with cellular signaling processes. *IL-6* and the soluble form of the IL-6 receptor (sIL-6Rα) determine the change from acute to chronic inflammation by changing the nature of leucocyte infiltrate. *IL-6* stimulates the production of IL-1 receptor	malaria and death.	bronchoalveolar lavage fluids (BALFs) have been associated with severe COVID-19 infection compared to moderate infection.	murine *M. tuberculosis* infection. *IL-6* deficiency resulted in an altered Th1 response and raised bacterial loads. *M. tuberculosis*-infected macrophages secreted *IL-6* which overturned the responses of uninfected macrophages to interferon (IFN). Elevated *IL-6* in the lungs and increased concentrations of IL-1β correlated with TB progression. *IL-6* was shown to positively and negatively contribute to		148-164)

		antagonists, an anti-inflammatory mediator.			host control against *TB* infection.		
Il-8	*IL-8* has specificity to neutrophils, it attracts and activates them in inflammatory regions	The increase of *IL-8* in the peripheral blood and lymphoid tissue of HIV-infected individuals indicates that *IL-8* is important in HIV-1 pathogenesis. During early infection, *IL-8* decreased HIV-1 reverse transcription and viral integration.	The IL-8 receptor binds to *P.vivax* and is involved in inflammation.	Higher levels of inflammatory cytokines such as IL-8 in BALFs have been associated with severe COVID-19 infection.	*IL-8* is associated with TB.	rs4073 A>T increases TB susceptibility	(165-167).
IL10	Pro-inflammatory cytokine	Inhibits HIV-1 replication		*IL-10* is important in the COVID-19 host response.	*IL-10* is important in the TB host response, *it* increases the intracellular survival of mycobacterial		(144, 168-170)

					bacilli by inhibiting phagosomal maturation, reducing nitric oxide production, and blocking IFN-γ signaling in macrophages. Increased levels of *IL-10* are associated with MTB susceptibility.		
IL18	*IL-18* is associated with the activation of innate immune cells, and growing evidence in polarization of the adaptive immune system response.	IL18 induces IFN production in T cells and enhances NK cytotoxic activity	*IL-18* is a potent proinflammatory cytokine that induces IFN-γ production from Th1 cells, NK cells, and activated macrophages. *IL-18* induces production in various cells. *IL-18* induces severe malaria	In addition, *IL-18* correlates with severe COVID-19 and thus plays a role in inflammasome activation and pyroptosis.	A study showed an association between *IL-18* and TB among children. IL-18 was said to be involved in immune response and MTB control.		(171-174)

			through an elevating IFN-γ pathway.				
Other							
VDR	Transcription factor that binds to active vitamin D.	Vitamin D receptor mutation alters vitamin D's ability to alter immune regulation.	VDR has been associated with the severity of parasitemia and gametocytaemia clearance in plasmodium vivax (P. vivax) malaria infections. VDR plays a role in the malaria immune response.	Lack of vitamin D and inactivation of VDR have been associated with increased respiratory syndrome in COVID-19 individuals via a wounding response in stellate cells of the respiratory system.	Host gene polymorphisms are associated with TB resistance and susceptibility. Studies have implicated a link between vitamin D deficiency and TB susceptibility. An increase in vitamin D has shown benefits to cutaneous TB.	Rs11568820 Rs4516035	(4, 14, 18-23, 25, 175-182)
MBL	Involved in the innate immune system. Binds sugars and	Block the interaction between HIV and DC-SIGN In the innate immune	MBL-2 polymorphisms were associated with malaria disease severity.	*MBL* binds to the COVID-19 spike protein in a glycan-dependent	Increases phagocytosis activation of the cascade by binding to TB.	Rs1800450 C>T severe malaria susceptibility	(24, 183-188)

	inters with pathogens.	system, MBL attacks glycosylated gp120 of the virus		manner and inhibits SARS-CoV-2. Thereafter, *MBL* activates the lectin pathway of complement activation. *MBL* was predicted to recognize the Omicron variant of concern (VOC). of *MBL*,			
ICAM-1	Involved in inflammatory processes.	Enhances HIV-1 infectivity, and makes virions resistant to neutralization with gp120-specific antibodies	The *ICAM-1* kilifi genetic variation has a possible role in severe malaria and CM pathogenesis. ICAM-1 kilifi was associated with increased susceptibility to CM. *ICAM-*	high levels of *ICAM-1* are associated with severe COVID-19 and thus a predictor of severe COVID-19.	*ICAM-1* plays a role in host cell invasion as receptors or crucial accessory molecules in mycobacterium tuberculosis (*M. tuberculosis)*. *ICAM-1* was	Rs5498 A>G associated with severe malaria and TB susceptibility	(189-194)

			1 plays a role in host cell invasion as receptors or crucial accessory molecules in Plasmodium falciparum		increased in TB-infected individuals compared to uninfected individuals. Increased *ICAM-1* provides increased cell adhesion in TB-infected monolayers.		

VDR

The *VDR* gene is a transcription factor that binds to active vitamin D, $1,25(OH)_2D_3$, and controls the expression of nearly 900 genes that are involved in multiple physiological functions (18). Vitamin D is involved in calcium homeostasis, cell proliferation, immunity, and cell differentiation to target tissues (19). Most vitamin D activities are applied through the nuclear *VDR*-mediated control of target genes (175). There were 60 SNPs found in the *VDR* gene that have been associated with altered VDR function (4, 25). SNPs in the *VDR* gene have been associated with worse HIV susceptibility and disease progression. These polymorphisms may change the gene function and the role of 1,25 dihydroxy vitamin D. Some polymorphisms result in a shortened form of VDR protein or an abnormal receptor that interferes with signalling (176-178). VDR polymorphism is in strong linkage disequilibrium with other *VDR* polymorphisms. 3'UTR polymorphisms that are associated with HIV disease (21). It can be suggested that these polymorphisms might also play in HIV disease. Polymorphism Cdx (rs11568820) C>T is in the 5'UTR promoter region and is involved in transcriptional activity. Polymorphism rs11568820 C>T showed an association with HIV-1 protection (25). In Africans, the T allele frequency is 0.80, suggesting that there might be HIV protection among Africans. De la Torre et al., used multilocus logistic regression analysis to show haplotypes for rs11568820 and rs4516035 polymorphisms associated with protection against HIV-1 infection in 460 males who were HIV-1 exposed injection drug users, of which 335 were infected and

125 uninfected (P = .0025) (25). This is an indication of protective polymorphisms that individuals possess, despite their continual HIV exposure they remain HIV uninfected.

Host gene polymorphisms are associated with TB resistance and susceptibility. Studies have implicated a link between vitamin D deficiency and TB susceptibility. An increase in vitamin D has shown benefits to cutaneous TB (179, 180). Therefore, polymorphisms that reduce vitamin D levels are considered a risk factor for individuals with cutaneous TB. These genetic variations alter the innate and adaptive immune response and affect the *VDR* gene expression and VDR activity. 3'UTR polymorphisms had an association with TB in an Asian population. However, these polymorphisms were not associated with TB in the African and South American populations (14). This depicts that the effect of these polymorphisms varies among different ethnic groups. Therefore, targeting this gene for therapeutics will vary among ethnic groups and should be done with caution. In South Africa, the *VDR* polymorphisms, *Fok1*, *Bsm1*, *Apa1,* and *Taq1* resulted in the *F-b-A-T* haplotype, which was seen as a protective factor for TB (23). The *b-A-T* haplotype showed protection against HIV, while the *B-A-t* haplotype was associated with TB susceptibility in HIV-1-infected individuals (23, 181). This indicates that due to the linkage of these polymorphisms, any changes in one of these polymorphisms could alter disease outcomes.

Lack of vitamin D and inactivation of *VDR* have been associated with increased respiratory syndrome in COVID-19 individuals via a wounding response in stellate cells of the respiratory system (20). This suggests that genetic variations that reduce vitamin D levels are associated with increased COVID-19 risk.

VDR has been associated with the severity of parasitemia and gametocytaemia clearance in plasmodium vivax (*P. vivax)* malaria infections. *VDR* plays a role in the malaria immune response (22). We suggest that SNPs that affect the immune response might increase the risk of malaria. VDR has both positive and negative effects on malaria infected individuals. Therefore, targeting VDR as potential therapeutics for malaria might be challenging.

VDR gene expression is associated with disease and is dependent on ethnicity and the environment. VDR levels and activity differ among populations. Andrzej et al., 2013 showed that ethnicity had a significant effect on *VDR* expression and protein level. Caucasians had a higher *VDR* mRNA level, while Africans had significantly higher basal and control VDR

protein levels (182). There was an inverse relationship between gene expression and protein level. This indicated that there was differential post-transcriptional regulation between Africans and Caucasians, and the dynamics of *VDR* mRNA translation may differ among different populations (182). This is an indication of the differences across different ethnic groups. Despite vitamin D being important for VDR activity, there are multiple contributing factors to VDR-related disease susceptibility (182). We suggest that future studies should include such factors, along with different ethnic groups, particularly those of African descent where the disease burden is high. This gene might be targeted differently in different ethnic groups for a particular disease. More studies are required to identify VDR polymorphisms that are associated with malaria. This will help us better understand the relationship between host genetics and disease.

MBL

Mannose-binding lectin (*MBL*) is known as a pattern recognition molecule that participates in the innate immune system. *MBL* binds to a range of sugars, which allows interaction with various pathogens (183). *MBL* binds to HIV via glycosylated surface residues. It interacts with HIV by direct inactivation and opsonization, neutralization by complement activation, cytokine modulation, or inhibition of uptake by target cells. *MBL-2* promoter and *MBL-2* exon 1 genetic variations resulted in decreased protein levels and increased HIV susceptibility (184). Polymorphisms in the promoter region are likely to affect gene transcription and disrupt the normal functioning of the gene, resulting in increased disease susceptibility. In addition, polymorphisms in the exon region that code for the protein would have the same effect. *MBL-2* structural variants are located at the first exon at codons 52, 54, and 57. *MBL-2* 57AC (rs1800451) was associated with the risk of HIV-associated neurocognitive disorder (HAND) severity ($P = 0.0009$). *MBL-2* 57AC genotype and 57C alleles were linked with susceptibility to HAND ($P = 0.003$), and HIV disease severity **(**$P = 0.001$). Haplotype ACA which consists of *MBL-2* 52A, 54A, and 57C was significantly associated with HAND susceptibility and severity, and HIV-1 acquisition ($P = 0.005$) (24). The T allele frequency for rs1800451 among Africans is 0.22, while in Europeans it is 0.02 (24, 185). This genetic variation rarely occurs among Europeans, indicating that HIV-1 susceptibility and the risk of HAND are less likely among Europeans compared to Africans. This indicates that these structural mutations in the exon region play a very important role in HIV susceptibility and severity. We suggest that more research on the exon region is required to determine the importance of these gene polymorphisms in HIV disease.

MBL is a calcium-dependent serum lectin, that works with the immune system to enhance phagocytosis activation of the complement cascade, by effectively binding to mycobacteria. *MBL* deficiency results in amplified susceptibility to various infections caused by microorganisms and viruses. This indicates that genetic variations that reduce *MBL* will increase susceptibility to TB. However, another study showed that decreased *MBL* serum has been demonstrated in a *MBL* gene polymorphism at position 57 (rs1800541), which results in TB resistance (186). More research is necessary to establish the function and the impact of *MBL* polymorphisms on TB.

Furthermore, *MBL* binds to the SARS-CoV-2 spike protein in a glycan-dependent manner and inhibits SARS-CoV-2. Thereafter, *MBL* activates the lectin pathway of complement activation. *MBL* was predicted to recognize the Omicron variant of concern (VOC). This shows the importance of *MBL* in SARS-CoV-2 infection. Due to the importance of *MBL,* we suggest that further studies on MBL and MBL polymorphisms are required to determine which polymorphisms possess COVID-19 risk or protection.

MBL-2 polymorphisms were associated with malaria disease severity (187). Luty et al, (1998) showed a relationship between polymorphisms at codon 54 rs1800450 C>T, Glycine>Aspartic acid and codon 57 (rs1800451), C>T, Glycine>Glutamic acid and severe malaria susceptibility (188). We suggest that because the T allele frequency is almost absent among Europeans, malaria susceptibility and severity are lower in Europeans than in Africans.

ICAM-1

Intercellular adhesion molecule-1 *(ICAM-1)* is part of the immunoglobulin superfamily and is expressed on the vascular endothelium cell surface. *ICAM-1* is involved in the inflammatory processes and T-cell-mediated host defense. It is a costimulatory molecule located on antigen-presenting cells. They activate major histocompatibility complex (*MHC*) class II restricted T-cells that are associated with *MHC* class I to activate cytotoxic T-cells (189). *ICAM-1* expression levels are directly proportional to HIV disease progression. The *ICAM-1* cell surface influences HIV-mediated syncytia formation and virus spread. *ICAM-1* causes HIV to be more infectious and resistant to neutralization. We suggest that polymorphisms that reduce *ICAM-1* expression levels might have a protective effect against HIV. *ICAM-1* is a potential therapeutic

target in HIV-infected individuals (190). More research is required to evaluate *ICAM-1* as a potential therapeutic target for HIV and other diseases.

ICAM-1 plays a role in host cell invasion as receptors or crucial accessory molecules in mycobacterium tuberculosis (*M. tuberculosis)* and plasmodium falciparum (*P. falciparum),* respectively (191). *ICAM-1* was increased in TB-infected individuals compared to uninfected individuals. Increased *ICAM-1* provides increased cell adhesion in TB-infected monolayers (192). This indicates that polymorphisms associated with increased ICAM-1 increase TB susceptibility and severity. A similar effect is seen in HIV, therefore, we suggest this could be a potential therapeutic target for TB, as it is for HIV.

Similarly, high levels of *ICAM-1* are associated with severe COVID-19 and thus a predictor of severe COVID-19 (193). Increased *ICAM-1* is associated with all these infectious diseases. The Kilifi (rs5491) polymorphism is an A to T allele change at position 179, this results in a methionine to lysine amino acid change which may affect the function of the protein (194), and result in an altered response to disease.

The *ICAM-1* Kilifi polymorphism has been found in Kenyan children with severe malaria. This polymorphism has been associated with the risk of severe malaria in East Africa. However, this was not replicated in other populations in West and Central Africa such as Gambia and Malawi (195). This genetic variation has a possible role in severe malaria and CM pathogenesis. Another study showed that ICAM-1 Kilifi was associated with increased susceptibility to CM (196). This polymorphism is almost absent in the European population, while found at a 20% frequency in Africans. This might contribute to the highest malaria rate among Africans. This could be due to the genetic variation selection of population genetics (194). The Kilifi polymorphism may play a similar role in TB, HIV, malaria, and COVID-19. This polymorphism should be investigated in greater detail. Furthermore, a different *ICAM-1* SNP on exon6 (rs5498) A>G was associated with severe malaria susceptibility in Nigerians (194). Targeting this gene in therapeutic methods will be beneficial for all the diseases mentioned.

Chemokine receptor

CXCR6

Like $CD8^+$ T cells, C-X-C Motif chemokine receptor 6 *(CXCR6)* is involved in the maintenance of natural killer T cells (NKT) and the natural killer (NK) cell population (197, 198). Although, *CXCR6* does not alter the cell function (199). *CXCR6* is a secondary co-receptor for HIV that facilitates the fusion of HIV-1 dual-tropic strains and M-tropic to CD4+ T cells (79). The protective CXCR6 SNP (rs2234355) G>A has an added effect in viremic controllers. *CXCR6* expression levels were higher in viremic controls compared to healthy controllers and progressors (P_{bonf}<0.0001). Although, this *CXCR6* SNP had an association with HIV-1 disease control, it does not associate with elite controllers in black South Africans (200). This shows the different effects polymorphisms can have on different populations and at different points of disease progression. We suggest more studies with different ethnic groups are required to establish the role of this SNP and determine other SNPs that are associated with HIV. Precision medicine should be investigated when targeting this gene which is variable among different ethnic groups.

CXCR6 influences the inflammatory response mechanism. *CXCR6* deficiency results in increased *M. tuberculosis* control. In the lung, *CXCR6* is upregulated more on human bronchoalveolar lavage (BAL)-derived and lung T-lymphocytes than in the peripheral blood. Increased *CXCR6* expression on lung $CD8^+$ T-lymphocytes correlated with chronic obstructive pulmonary severity (201-203). This indicates that polymorphisms that affect CXCR6 function and decrease its expression will result in less severe TB and better TB control. Research on which polymorphisms lead to differential *CXCR6* expression levels will be beneficial for therapeutic strategies against TB.

CXCR6 regulates parts of lung memory CD8+ T cells during an unrelenting immune response to aero-pathogens, including other coronaviruses (204). *CXCR6* is a tissue-residence gene that is found in higher quantities in expanded CD8+ T cells compared to non-expanded cells in moderate SARS-CoV-2 infections (205). High amounts of total CD8+ T cells are found in moderate SARS-CoV-2 infection compared to severe infection. C-X-C motif ligand 16 (*CXCL16*), which produces a byproduct that binds *CXCR6*, was expressed more in moderate infection than in severe SARS-CoV-2 infection. The *CXCL16* chemokine and *CXCR6* receptors are associated with the migration and survival of NKT and innate lymphoid cells (ILC). They are elevated in hospitalized COVID-19 patients (206). *CXCR6* needs to be studied in greater detail to determine its role in COVID-19 infected individuals.

In addition, *CXCR6* is important in maintaining protective resident memory T cells in the liver following malaria infection in mice. *CXCR6* deficient CD8+ T cells decrease in the liver and prevent malaria inhibition (207, 208). Therefore, functional mutations in *CXCR6* will likely result in the risk of malaria severity over time. The frequency of SNPs and haplotypes differ significantly in different ethnic groups. This was observed in a South African population among Africans and Caucasians. Genetic studies with human subjects from Africa, with the greatest genetic diversity, are most beneficial to determine therapeutic targets for all infectious diseases.

CX3CR1

CX3C chemokine receptor 1 *(CX3CR1)* is likely to be a co-receptor for HIV-1 according to its functionality *in vitro*. *CX3CR1* is associated with cell adhesion and migration. Mutations that occur in some of these genes have shown an association with HIV disease progression. High levels of *CX3CR1* expression are associated with HIV infection (p=0.002) (26).

Like HIV, the *CX3CR1* expression levels on monocytes are elevated among latent TB infections (57). *CX3CR1* is vital for the development of atherosclerotic plaque because it assists with the recruiting of non-classical monocytes (56). Future studies with large cohorts and varying ethnicities on CX3CR1 are needed to determine its function in TB. Due to the similar effect observed in TB and HIV, it could be beneficial for the high rate of co-infection with TB and HIV in Africa and other countries.

CX3CR1 expression was impaired among individuals who had contrary artery disease and SARS-CoV2. *CX3CR1* mediates non-classical monocyte migration along with endothelial cells in the vascular system for antiviral immune response. *CX3CR1* is a candidate gene for COVID-19 severity and SARS-CoV-2 susceptibility. The role of polymorphisms in this gene is unknown (58). The gap in the research on the effect of these polymorphisms needs to be addressed as COVID-19 still exists globally. COVID-19 relationship with various other diseases and comorbidities makes it a challenging study.

High *CX3CR1* and *CCR2* on CD14 monocytes limit parasitic growth through antibody dependent cellular inhibition activity (59). Similarly, in another study, high *CX3CR1* expressing cells were associated with better survival (60). *CX3CR1* has differing effects on different infectious diseases. More studies are needed to unravel the roles of polymorphisms in *CX3CR1*.

CCR2

C-C motif chemokine receptor 2 (CCR2) is a G protein coupled receptor. The *CCR2* and *CCL2* interaction is important for inflammatory diseases and inflammation. It is also associated with innate immune response by recruiting monocytes into the inflammation site. *CCR2* alters the location of *CCR5* and *CXCR4* on the cell surface and regulates heterodimerization. Furthermore, the monoclonal antibody *CCR2-01* disrupts HIV replication by heterooligomerization induction of *CCR2* with *CXCR4* and *CCR5* co-receptors (28). They also form dimers with *CCR5* and *CXCR4* (29-31).

Studies show that *CCR2* contributes to the defense against M. tuberculosis (MTB). This was shown in a study with *CCR2*-deficient mice (33). Studies with human participants are required to determine the effect of CCR2 on TB. These studies should also include individuals of varying ethnicities to ensure that target genes are ethnic-specific to ensure an effective response.

CCR2 is associated with the monocyte recruitment and infiltration of these cells in the lungs of COVID-19 infected individuals. *CCR2* may be protective in SARS-CoV-infected dendritic cells. *CCR2* reduced viral load in SARS-CoV-2 infected mice (32). This suggests that mutations that reduce the *CCR2* expression and function might increase the viral load. More studies with human subjects are needed to unravel the function of CCR2 in COVID-19.

CCR2 deficient mice have persistent parasitemia in malaria (34). *CCR2* deficient mice inhibit inflammatory monocyte recruitment to the site of infection (35). *CCR2* has a protective effect on all four infectious diseases, therefore *CCR2* is an important gene to study in different populations, particularly in the African population. More mutations that influence *CCR2* need to be identified.

CCR5

C-C motif chemokine receptor 5 (CCR5) is located on *3p21.31*. CCR5 is upregulated by proinflammatory cytokines and is mainly expressed in memory T-cells, macrophages, and dendritic cells. CCR5 is the main coreceptor used by HIV-1 and HIV-2 responsible for viral transmission. CCR5 plays a vital role in HIV pathogenesis (36).

Additionally, CCR5 plays an essential role in cell activation and migration in immune responses against TB. A study that consisted of 450 TB patients and 306 healthy controls showed that *CCR5* promoter polymorphisms were found to be associated with pulmonary TB and TB progression in the Chinese Han population (37). *CCR5* is highly expressed on T helper (Th) 1 cells. Th1 responses play a critical role in TB immunity (38). There are elevated *CCR5* levels in Th cells in pulmonary TB patients (38, 39). *CCR5* expression is increased in individuals with active TB (40, 41). In addition, *CCR5* ligands are also increased during TB (39-42) and cell-mediated immunity (CMI) is a central determinant of TB resistance. The ligand of *CCR5* (43) influences CMI (44, 45). *CCR5*-HHD haplotype is found more in African ancestry. Further studies on its influence on HIV infection and TB susceptibility contributing to the growing burden of HIV and TB in Africa are necessary (44).

CCR5 is expressed in macrophages and T cells acting as a co-receptor for macrophage-tropic viruses and plays an important role in SARS-CoV-2 infection (46). The rs9845542 and rs12639314 variants of *CCR5* were associated with severe COVID-19 disease (27). *CCR5* plays a role in COVID-19 severity (47). The *CCR5Δ32* deletion leads to reduced expression, playing a protective role against SARS-CoV-2 infection (48, 49). This effect has also been observed in HIV (47). This suggests that reduced expression of *CCR5* is beneficial against TB, HIV, and COVID.

CCR5 was associated with adverse effects caused during pregnancy with malaria infection. *CCR5* deficiency increases maternal parasitemia. More information on the role of *CCR5* in malaria needs to be better understood (50). *CCR5* is a very important gene that plays an essential role in all the above diseases. Studies that focus on *CCR5* are required in an African population. There are various successful stories regarding targeting CCR5 in HIV infected individuals. While this is promising for future therapeutics targeting this gene is also associated with various other diseases, which makes it a good target for individuals who are infected with one or more of the other infectious diseases.

CXCR4

C-X-C motif chemokine receptor 4 (*CXCR4*) regulates and expresses T cell migration along gradients of *CXCL12*. CXCR4 is a chemokine coreceptor that allows X4 HIV viral strain entry

but reduces R5 viral entry. *CXCR4* expression is higher among TB/HIV co-infected individuals than HIV infected individuals Increased *CXCR4* expression is associated with TB in alveolar macrophages. (52).

High levels of *CXCR4* direct cells to destroy lung tissue (51). In a mixed cohort of Latins, Asians, and whites, fatal COVID-19 is associated with elevated *CXCR4* in bystander T cells (53). Interestingly, another study with Caucasian participants showed that low levels of *CXCR4* were associated with COVID-19 (54). Due to contradictory results, more studies are required to determine the function of CXCR4. This might also be variation among different ethnic groups.

CXCR4 increases calcium levels which influence sporozoite transformation into exoerythrocytic forms which is necessary for parasite progression in the liver. Eliminating *CXCR4* inhibits the development of Plasmodium falciparum in the liver (55). Increased *CXCR4* is detrimental to protection against these infectious diseases. Further studies should be performed among individuals of different ethnicities. Very few studies have evaluated the differences between cytokines across different ethnic groups. We are unable to highlight these differences with certainty.

Chemokine

SDF-1

Stromal cell-derived factor 1 (SDF-1) is a chemokine protein that has a wide range of functions, one being the ability to control the trafficking of leukocytes (61). *CXCL12/SDF-1* prevented the accumulation of newly reverse-transcribed HIV proviral DNA, required for productive infection. *SDF-1* did not inhibit viral replication (62). Furthermore, *SDF-1* is a diagnostic marker for TB and correlates with severe TB (61).

SDF-1 is upregulated in early post-SARS-CoV-2 infection. The SDF-1 chemokine and the CXCR4 receptor are responsible for bone marrow homing, it is upregulated and remains steady post-SARS-CoV-2 infection. More studies with a large cohort of varying ethnicities are necessary to determine the effects of *SDF-1* on COVID-19 disease.

Furthermore, high *SDF-1* levels in African children were associated with acute malaria compared to healthy children (63). There are different effects of *SDF-1* among these diseases.

Therefore, targeting this gene should be disease-specific and future and current disease exposures should be considered. There is a gap in the role of *SDF-1* and its polymorphisms in infectious diseases.

CCL5

Regulated on activation, normal T expressed and secreted (*RANTES*)/ chemokine C-C motif ligand (*CCL5)* is a *CCR5* ligand that is involved in the migration of macrophages and NK cells as well as the T cell/ dendritic cells (DCs) interaction. *CCL5* inhibits *CCR5* HIV infections. Genetic variations in the *CCL5* promoter region are associated with more *CCL5* transcription, resulting in delayed HIV disease progression (85). Gonzalez et al., indicated a large amount of variation in the genotype frequencies between races, and different disease effects depending on ethnicity. The diverse spread of RANTES haplotypes (AC, GC, and AG) was associated with population-specific HIV-1 transmission and varied disease outcomes. Individuals with a homozygosity AC haplotype were associated with an increased risk of acquiring HIV-1 and disease progression in European Americans, but not in African Americans. Although, there was a higher prevalence of the AC haplotype in Africans compared to non-Africans (86). This indicates that the same haplotype can have differing effects on different populations. Therefore, taking ethnicity into account is of great importance. In a Japanese cohort, AG-containing RANTES haplotype pairs were associated with delayed HIV disease progression; however, the AG haplotype is infrequent in some of these populations (86).

CCL5 plays a key role in co-stimulation of T cell proliferation and *RANTES* activation in anti-mycobacterial immunity. Studies have shown a significant relationship between *RANTES* polymorphisms and an increased TB risk (87). *RANTES* expression was higher in PTB patients than in healthy individuals ($P < 0.05$). In the North central Indian tribe, Sahariya with high TB prevalence showed that the *CCL5* SNP (rs2107538) C>T resulted in reduced *CCL5* expression, and was found in PTB cases and therefore significantly associated with increased PTB susceptibility (88). These studies show that an increased and decreased CCL5 expression was associated with PTB. We suggest that the differing results could be ethnic-specific. More research is required to unravel the role of *CCL5* and *CCL5* polymorphisms and their impact on TB.

CCL5 is upregulated in early post-SARS-CoV-2 infection. In addition, high levels of *CCL5* in found in critically ill COVID-19 patients compared to healthy and moderately ill COVID-19

patients (89). However, Perez-Garcia et al., showed that high levels of SARS-CoV-2 viral load and low levels of *CCL5* were associated with ICU patients (90). This suggests that more information is needed to edify the role of CCL5 in COVID-19 disease. We suggest that the inconsistent *CCL5* level could be ethnic-specific or the patients. In addition, co-morbidities and various other factors needed to be accounted for when comparing these studies.

Malaria outcomes are influenced by the role of *RANTES* in host immunity. Low levels of *RANTES* were associated with CM in Ugandan children (91). Bujarbaruah et al., observed similar results, showing low levels of *RANTES* were associated with severe malaria and high *RANTES* was associated with malaria recovery and uncomplicated malaria (92). *RANTES* variations affect protein production and alter host immunity (92). We suggest that polymorphisms resulting in high expression levels of *RANTES* result in better immunity and could be beneficial to individuals with malaria. Further studies are required to identify *RANTES* polymorphisms that are associated with malaria.

CCL3

In the presence of a pathogen, macrophage inflammatory protein one alpha (*MIP-1a*)/ chemokine (C-C motif) ligand 3 (*CCL3*) is involved in the differentiation and migration of effector T cells resulting in inflammation (72). *CCL3* is involved in the recruitment of neutrophils and monocytes, and the activation of inflammatory signaling (73). CCL3 is a beta-chemokine that possesses anti-HIV-1 characteristics and thus is inversely associated with HIV disease progression (74). CCL3 is produced by CD8+ T cells. The *CCL3* gene duplication is known as chemokine (C-C motif) ligand three like 1 (*CCL3L1*) (75, 76). Gene duplication is referred to as copy number variation (CNV), this is when a portion of the gene is repeated. *CCL3L1* is the most effective inhibitor of *CCR5* and HIV-1 infection caused by the R5 strain (77). The copy number of *CCL3L1* varies among ethnic groups and is prevalent among the African population (78). Surprisingly, this genetic variation is prevalent among Africans where HIV prevalence is the highest. This indicates that multiple factors play a role in HIV acquisition. Low levels of CCL3L1 were demonstrated in acquired immune deficiency syndrome (AIDS) subjects, indicating that high levels of these chemokines are beneficial to the host. The copy number of *CCL3L1* influences HIV-1 susceptibility (79). *CCL3L1*, a *MIP-1* isoform, has the potential to block viral entry (80). Saha et al. demonstrated that high levels of MIP-1a and MIP-1b were produced in long-term nonprogressors (LTNPs) (81). The degree of *CCL3L1* expression can affect HIV infection by; internalizing *CCR5* receptors, subsiding

CCR5 expression levels on the cell surface, altering anti-viral responses via leukocyte trafficking, and preventing *CCR5* and HIV-1 gp120 binding (78, 82). Therefore, CNV is directly proportional to HIV disease. *CCL3* polymorphisms are associated with HIV resistance or susceptibility (83).

CCL3 is a leucocyte activating chemokine that is involved in TB restriction. High levels of *CCL3* were detected in PTB when compared to latent TB (LTB) and healthy control (HC) patients (84). As previously mentioned, CCL3L1 is more prevalent in the African population. We suggest that this might be attributed to the high TB prevalence in Africa.

Similarly, *CCL3* chemokines were expressed at higher levels in the lung macrophages of severe COVID-19 patients (73). This suggests that polymorphisms are associated with increased CCL3 levels. Therefore, increased CCL3 results in detrimental COVID-19 effects.

The *CCL3* levels were increased in CM-infected mice (71). In addition, elevated levels of monocyte-attracting β-chemokines CCL3 have been found in malaria-infected placentae (65). More research in humans is required to determine the function of *CCL3* and CNV in TB, malaria, and COVID-19. High levels of *CCL3* are harmful to malaria, COVID-19, and TB-infected individuals but beneficial for HIV-infected individuals.

Previous studies of *CCL3L1* CNV and its association with disease susceptibility have been found in various populations such as European, Japanese, African, and Korean. Copy number distribution differs among ethnic groups. Jamaluddin et al., suggested that ethnic groups influence genetic variation due to Malaysians having significantly different CCL3L1 copy numbers among different Malaysian populations. This was also seen in the African population (16).

CCL2

The chemokine (C-C motif) ligand 2 (*CCL2)* attaches to *CCR2*. *CCL2* is a pro-inflammatory chemokine, and *CCR2* plays a role in monocyte migration during inflammation. CCL2 drives the T helper 2 (Th2) immune response (66). This chemokine regulates immune cell movement to the site of HIV infection and cell activation; therefore, they are associated with HIV disease progression (67). Within the *CCL2* gene, the H7 haplotype (CCL2-CCL7-CCL11) has been found to reduce HIV susceptibility (68). The H7 haplotype was significantly elevated (P =

0.005–0.01) in uninfected exposed European-Americans (69). We suggest that genetic variations in haplotype 7 influence the risk of HIV-1 infection.

CCL2 is associated with TB. Genetic variations in this gene have shown an increase in TB susceptibility. Feng et al., found an association between *CCL2* SNP (rs4586), resulting in a T>C allele change, and pediatric TB in Han Chinese males, indicating that gender may affect TB susceptibility even in children (70). The homozygous T genotype associated with reduced cerebrospinal fluid (CSF) and mononuclear leukocyte (ML) count suggests significance, and potential to assist with tuberculosis meningitis (TBM) assessment in serious cases (70). This polymorphism is common among Africans, it might contribute to the high TB rates in Africa. This polymorphism should be studied in more detail in an African population.

The *CCL2* chemokine is involved in the migration of inflammatory monocytes. It is produced by alveolar macrophages, T cells, and endothelial cells. They also recruit mast cell progenitors and influence the accumulation of neutrophils and procollagen synthesis through fibroblasts (32). In addition, *CCL2* chemokines were expressed at higher levels in lung macrophages of severe COVID-19 patients. *CCL2* was upregulated early post-SARS-CoV-2 infection. Higher *CCL2* levels were detected in symptomatic individuals (32). We suggest that polymorphisms that decrease the levels of *CCL2* may be protective against COVID-19.

High levels of *CCL2* were observed in *P.vivax* infections (64). Similarly, elevated *CCL2* has been found in malaria-infected placentae (65). We suggest that decreased levels of CCL2 are beneficial to malaria-infected individuals. *CCL2* is involved in the immune response to HIV, TB, malaria, and COVID-19. It is important to consider and conduct research on CCL2 gene distribution in different ethnic groups.

Cytokines

TNF

Tumor necrosis factor (TNF) is a cytokine that has various roles such as cell proliferation, death, survival, and differentiation. TNF-α is important for HIV pathogenesis. In addition, HIV uses TNF-α signalling pathways to expand its reservoir. HIV proteins act like and mediate the TNF signalling pathway (127). This poses a risk factor for HIV.

TNF-α plays a vital contribution to MTB host response (128). Inhibition of TNF-α is associated with an elevated risk of latent TB infection reactivation (129). This indicates that TNF is important for the prevention of latent TB reactivation. This seems to be an important therapeutic target for TB. Future research should analyze the effect of this gene in detail to determine the effects on inhibition and which polymorphisms result in inhibition.

When TNF was blocked in severe COVID-19 patients there was a reduction in lung damage and lower hospitalization (130). TNF was associated with severe COVID-19 pathogenesis and may have a role in cytokine storms (131). TNF has a detrimental effect on COVID-19.

TNF is known for malaria killing; however, it also is associated with severe malaria development (132). TNF has differing effects on different diseases. TNF is beneficial to TB and malaria. However, it poses a detrimental effect on HIV and COVID-19. Targeting such a gene as a potential therapeutic for a particular disease such be done with caution of future and current exposure to other diseases.

IFN

IFN is made up of three groups, type I, type II, and type III. *IFN* regulates cytokines and chemokines. Type I IFN, *IFN*-α, and β are important for innate immunity against viruses and inhibit HIV-1 replication. *IFN* disrupts HIV infection and HIV disease progression (122). Type II *IFN-γ* inhibits HIV-1 entry into macrophages (117). In advanced stages of HIV infection when *IFN-γ* reduces, viral replication persists (118). IFN has a protective effect against HIV. Preventing the reduction of IFN might prevent advanced stages of HIV.

IFN-α expression levels are higher among TB patients than uninfected individuals. In-vitro *IFN-α* does not restrict MTB replication intracellularly. *IFN-γ* is associated with anti-mycobacterial activity. IFN-α compromised the activity of *IFN-γ* (123). *IFN-α* inhibited IL-1β production and induced the production of IL-10, which further reduced IL-1β. *IFN-α* enhances IFN-γ production. *IFN-α* and *IFN-γ* might be associated with MTB immune escape and disease progression (119).

Severe COVID-19 is associated with sustained *IFN* response. Severe COVID-19 patients had disrupted *IFN-α* and *β* production and downregulation of *IFN-simulated* genes (124). Mossel

et al. did an *in vitro* study and showed that *IFN-α* and *IFN-γ* have a synergistic effect that inhibits SARS-CoV replication (120).

IFN-γ was higher among individuals who were parasitaemic than aparasitaemic (121). Reduced *IFN-α* levels were associated with severe malaria in Kenyan and Gabonese children (125, 126). *IFN-α* regulates the immune response during human malarial infections (125). *IFN* has differing effects on infectious diseases. We suggest that *IFN* types I and II should be studied together on different ethnic groups.

Interleukin *(IL)* 1, 4, 6, 8, 10, 18

Cytokines are proteins produced by cells of the immune system that detect target cells and interact with them. This interaction triggers a specific response that maintains immune homeostasis. In response to infections and tissue damage, IL-6, a pleiotropic cytokine is produced (148). The IL-6 cytokine is produced by cells such as; mast cells, macrophages, dendritic cells, and T and B cells at the site of inflammation (149). Once specific receptors are targeted, *IL-6* starts a signaling cascade associated with the Janus kinase/signal transducer and activator of transcription (JAK-STAT) activation pathway (150), promoting the transcription of genes associated with cellular signaling processes (151). *IL-6* and the soluble form of the IL-6 receptor (sIL-6Rα) determine the change from acute to chronic inflammation by changing the nature of leucocyte infiltrate. *IL-6* stimulates the production of IL-1 receptor antagonists, an anti-inflammatory mediator (133, 134). *IL-1* shares similar functions to toll-like receptors (TLRs). The *IL-1* family is primarily associated with innate immunity, manifested by inflammation, and functioning as a mechanism of host defense. *IL-1* triggers innate inflammation via IL-1 receptors (135). IL-1a also plays a role in acquired immunity as damage-associated molecular patterns (DAMPs) (136). HIV inducive *IL-1* and *IL-6* play a role in HIV-1 disease progression. *IL-1α* and Interleukin-1 beta (*IL-1β)* are co-stimulatory cytokines for T helper cells that stimulate the maturation and clonal expansion of B cells (137). *IL-4* is a T helper cell type 2 (Th2) cytokine with co-stimulatory activity for T and B cells. It also upregulates *CCR5* and down-regulates *CXCR4,* although its impact on viral entry is unknown. *IL-4* presents stimulatory and anti-HIV activity (144). *IL-4*-dependent also prevents HIV-1 replication; however, this is cell-dependent and mostly affects X4-tropic strains. 589T/rs2243250 *IL-4* SNP impacts cytokine transcription and has been associated with disease progression in certain cohorts (145, 146). This mutation is prevalent in Europeans. Previous studies showed that the *IL-4* receptor, a chain gene has a significant association with disease

progression and susceptibility to HIV-1 infection. However, for HIV susceptibility it depends on the route of transmission (147). *IL-4* presents stimulatory and anti-HIV activity (144).
IL-8 is a chemoattractant cytokine produced by tissue and blood cells. *IL-8* has specificity to neutrophils, it attracts and activates them in inflammatory regions (165). The increase of *IL-8* in the peripheral blood and lymphoid tissue of HIV-infected individuals indicates that *IL-8* is important in HIV-1 pathogenesis. During early infection, *IL-8* decreased HIV-1 reverse transcription and viral integration (166). Polymorphisms that affect the normal functioning of *IL-8* can be considered a risk factor for HIV.

IL-10 is a powerful anti-inflammatory cytokine. *IL-10* 5'A is associated with decreased *IL-10* expression that limits infection and accelerates AIDS. Rs1800896, rs1800872, and rs2266590A have been associated with HIV disease (168), while rs2266590A is known to have a protective effect (169). In an Indonesia cohort, HIV-infected individuals heterozygous for rs1518111 and rs1800872 have been associated with decreased CD4+ T cell count (170). Rs1800896 and rs1800872 occur more frequently in Africans than in Europeans. In contrast, rs2266590A is less frequent among Africans. *IL-10* is a T helper cell type 2 (Th2) cytokine with co-stimulatory activity for T and B cells. It also upregulates *CCR5* and down-regulates *CXCR4*, although its impact on viral entry is unknown (144). *IL-18* is associated with the activation of innate immune cells, and growing evidence in polarization of the adaptive immune system response. In addition, it assists with the Th1 response and the IFNG secretion (171). Caspase-1 activation mediates the cleavage of the pro-IL-1B and pro-IL-18 molecules, resulting in an inflammatory process after HIV infection (172). IL-8 genetic variants were better immunological responses to HIV (173).

IL-6 and *IL-1* accumulate in the acute phase response (138). Increased *IL-1β, IL-4*, and *IL-6* levels were associated with TBM, however, *IL-4* and *IL-6* levels were not significantly different between TBM and individuals without meningitis and CNS infection (139). The effect of CD4+ T cell response makes *IL-6* crucial in the protection against murine *M. tuberculosis* infection (152). *IL-6* deficiency resulted in an altered Th1 response and raised bacterial loads (153). This indicates the importance of *IL-6* in the immune response against TB. Therefore, any polymorphism that results in *IL-6* deficiency will be a risk factor for TB-infected individuals. In a study, *M. tuberculosis*-infected macrophages secreted *IL-6* which overturned the responses of uninfected macrophages to interferon (IFN) (154). Elevated *IL-6* in the lungs and increased concentrations of IL-1β correlated with TB progression (42). *IL-6* was shown to positively and

negatively contribute to host control against *TB* infection (209). The reduced (interleukin 6 receptor) *IL-6R* expression in TB was associated with decreased T helper cell 17 (Th17) response. *IL-6/IL-6R* polymorphism has been associated with susceptibility and severity of a wide range of diseases (155). *IL-8* is associated with TB. The *IL-8* (rs4073) SNP, results in an A>T allele change at position 251, which increases TB susceptibility (167). This SNP is more common among Europeans than Africans. This could be due to the natural selection of protective genes in the African population due to the high rates of TB in Africa. *IL-10* is important in the COVID-19 and TB host response in diverse ways (128). Bonecini -Almeida et al., showed elevated *IL-10* in BAL lung samples of TB patients (210). A study showed an association between *IL-18* and TB among children. IL-18 participated in immune response and MTB control (173). *IL-10* is a human Cytokine Synthesis Inhibitory Factor (CSIF), that increases the intracellular survival of mycobacterial bacilli by inhibiting phagosomal maturation, reducing nitric oxide production, and blocking IFN-γ signalling in macrophages (211). Increased levels of *IL-10* are associated with MTB susceptibility (128).

Higher levels of inflammatory cytokines such as IL-8, IL-6, and IL-1β in bronchoalveolar lavage fluids (BALFs) have been associated with severe SARS-CoV-2 infection compared to moderate infection. In addition, *IL-1β* and *IL-6* were expressed at higher levels in lung macrophages of severe COVID-19 patients. *IL-1* and *IL-6* could be associated with cytokine storms and COVID-19 complications such as venous thrombosis. Similarly, *IL-4* and *IL-10* are found at higher levels in severe COVID-19 patients than in healthy individuals, especially during cytokine storms (128). In Iran, *IL-1 β* (HGNC:5992) (rs16944) A>G was associated with severe influenza A/H1N1 and B (140). This SNP is less frequent among Africans when compared to Europeans. This might be one possible contributing factor to the lower COVID-19 death and infection rate among Africans than Europeans. Another *IL-6* SNP (rs1800797) A>G at the promoter region along with previously mentioned polymorphisms (156) could be considered for studying COVID-19 disease progression. *IL-6* promoter activity reaches its highest level when the p65 and N proteins are present, these proteins have a synergetic effect on IL-6 activation. The nuclear factor kappa B (NF-κB) binding site polymorphism of the *IL-6* promoter (pIL6-luc-651ΔNF-κB) eliminates the effect of the p65 and N proteins on *IL-6* promoter activation (157, 158). In addition, *IL-18* correlates with severe COVID-19 and thus plays a role in inflammasome activation and pyroptosis (174).

Griffiths et al (141) showed that a cluster of genes containing *IL-6R*, and *IL-1R2* was expressed in correlation with the absolute neutrophil count. This gene region consisted of genes associated with mediators of innate and adaptive immunity (141). Differences in gene expression suggest that neutrophil response plays a role in acute malarial infection (142). Activation of the *TLR* pathways results in the secretion of pro-inflammatory cytokines, such as IL-1 and IL-6. The IL-8 receptor binds to *P.vivax* and is involved in inflammation (93). In malaria-infected adults, *IL-4* expression levels were reduced (143). The concentration of IL-6 has been associated with severe malaria and death. The *IL-6* rs1800795, resulting in a G>C allele change at position 174/176 was associated with increased *IL-6* expression in individuals with developing acute phase reactions (159-162). This SNP is more prevalent in the African population than the European population. We suggest that this SNP might contribute to the higher malaria rate in Africa than in Europe. In Mali, the frequency of *IL-6* CG/GG was higher than in non-Fulanis, who had increased malaria susceptibility, in symptomatic and asymptomatic malaria (163, 164). *IL-18* is a potent proinflammatory cytokine that induces IFN-γ production from Th1 cells, NK cells, and activated macrophages. *IL-18* induces *IL-4* and *IL-13* production in various cells. *IL-18* induces severe malaria through an elevating IFN-γ pathway (173).

Hick et al., 2013 showed an appreciable difference in gene expression levels of 300 genes among Caucasians, Africans, Hispanics, and Asians in the US. There was also an overlap in differential expression levels and patterns of gene expression among these ethnic groups (212). This indicates changes in cytokine levels across ethnic groups and highlights the specialized differences.

Receptors

Toll-like receptors *(TLRs) 2, 4, 7, 8, 9*

TLRs are involved in the innate immune response against pathogens by regulating the degree of viral replication (213, 214). *TLRs* identify motifs presented by pathogens and trigger inflammation (136). HIV directly activates *TLRs*, while opportunistic pathogens indirectly activate *TLRs,* impacting disease progression. Signals conciliated by pathogens can activate HIV transcription via cytokines, induce cell factor expression, and activate viral long terminal

repeats (213). *TLR2*, *TLR4*, and *TLR9* are associated with activating gene expression and viral replication during HIV infection and contribute to HIV severity through an antigenic group (Ag) and (5'-Cytosine-phosphate-Guanine-3') CpG induction (99-102). *TLR9* has been associated with modulating the extent of viral replication. *TLR9* SNP (rs352140) C>T is found at high levels in highly active antiretroviral therapy (HAART)-naïve rapid progressors compared to normal progressors (112). We suggest that this SNP is a risk factor for HIV-infected individuals. *TLR7* identifies guanosine (G) and uridine (U) rich single-stranded RNA (ssRNA) of HIV (105). The *TLR7* response to HIV is time-dependent. *TLR7* prevents HIV production and increases antiviral responses (106). *TLR8* also identifies HIV ssRNA (110). *TLR8* induces inflammatory responses that encourage HIV-1 replication and latency reversal (111).

TLRs consist of genes associated with mediators of innate and adaptive immunity [18]. *TLRs* play a role in recognizing viral particles. Activation of the *TLR* pathways results in the secretion of pro-inflammatory cytokines. *TLR* is associated with TB. Genetic variations in these genes have shown an increase in TB susceptibility. There were various *TLR2* polymorphisms found in tuberculosis patients. *TLR2* polymorphisms are a risk factor for tuberculosis infection (95-97). Yim et al. observed that TLR-2 deficiency makes patients more TB-susceptible (98). We suggest that genetic variations that result in TLR2 deficiency can be a risk factor for TB. TLR4 is involved in the induction of MTB immune responses and contributes to the suppression of infection (103). *TLR4* and *TLR8* are associated with TB pathogenesis, this stems from the number of SNPs in *TLR4* and *TLR8* in TB infected individuals compared to healthy individuals. Thada et al., hypothesised that *TLR4* and *TLR8* heterodimer formation regulates MTB immune responses (104). *TLR7* has been suggested to provide MTB host cell immunity. (94, 106, 107). *TLR9* is a pattern recognition receptor that facilitates MTB recognition and controls MTB-specific T-cell responses (113). We suggest that polymorphisms that affect the function of these genes will influence the TB outcome (104).

TLR2, *TLR4*, and *TLR9* are theoretically important in SARS-CoV-2 infection. There are beneficial and harmful effects of *TLR* in SARS-CoV-2 infection. *TLRs* are potential targets in controlling early infection and in a vaccine against SARS-CoV-2 (94). *TLR7* is expressed on dendritic cells and monocytes. *TLR7/8* mediates pro-inflammatory cytokine production (94). *TLR7* has been associated with SARS-CoV-2 pathogenesis. *TLR7/8* identify SARS-CoV-2 (94). *TLR8* is present in the lungs, and *TLR7* and *TLR8* may lead to SARS-CoV-1 cytokine

storms (107). More research is needed to elucidate the function of these *TLR* genes in COVID-19 disease.

Similarly, *TLRs* are involved in the innate immune response to malaria. *TLR9* facilitates recognition of the CpG motif in bacterial DNA, *TLR4* mediates the (lipopolysaccharides) LPS of gram-negative bacteria recognition and *TLR2* helps recognition of a wide range of ligands (93). Sporozoite activates *TLR2* and induces macrophages to release proinflammatory cytokines. *TLR4* was expressed in correlation with the absolute neutrophil count. Differences in *TLR4* gene expression suggested that neutrophil response plays a role in acute malarial infection. *TLR7* and *TLR8* recognize plasmodium-derived RNA (108). *TLR8* has been associated with severe infected malaria in Mali children (109). *TLR9* (rs5743836) A>G appears to affect malaria progression and susceptibility in specific populations (114-116). In Africa, the rs5743836 polymorphism is more common than in Europe. More research is required for *TLR* genes in all infectious diseases.

Conclusion and future recommendations

This review briefly discusses known host genes and gene variations that have been previously associated with HIV, TB, malaria, and COVID-19 disease progression. We did not mention Chromosome 3p21.31 (LZTFL1), a significant locus in COVID-19, due to the lack of association with HIV according to the literature, it focuses on genes with roles immune system.

We also touch on the prevalence of variation within these genes in certain ethnicities. The gene functionality, the effect of the gene variation, and gene frequency in different ethnicities need to be addressed for all infectious diseases. In summary, this review briefly shows how human genes are necessary for pathogenesis (215, 216). Disruption of host genes might slow down disease progression, eliminate the pathogen, or increase the chance of human survival from infections.

As we understand the host genetic impact on HIV, TB, malaria, and COVID-19, we can unravel their involvement in disease susceptibility, clinical outcomes, co-infection, and interindividual response. Gene association studies have contributed immensely to drug and therapeutic development for infectious diseases thus far. There are opportunities for future studies to replicate the studies mentioned above to identify host gene targets and do an in-depth analysis of the effect of host gene variation that is associated with malaria, TB, HIV, and COVID-19.

This is promising for the rapid development of safe and effective therapeutics (217) to target the common genes with similar effects on disease. Ultimately, this could be protective against more than one infection. Different populations have different responses to infectious diseases (14-16). Therefore, large-scale studies in different endemic regions, including various ethnic groups are required to better understand the host-pathogen interaction, pathogenesis, the epidemiological differences between gene expression, the clinical manifestation of infectious disease, why different populations might differ in their susceptibility and severity to HIV, TB, malaria, and SARS-CoV-2 infection, and which genes and genetic variations are associated with particular phenotypes that can be important drug targets. The host genetics associated with these diseases need to be studied more in an African population. New treatment strategies that are affordable, safe, and effective for Africans need to be developed for infectious diseases. In addition, this study could be carried out for various other diseases common in other populations and this will contribute to precision medicine based on the population's genetics.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. All authors have read and agreed to the published version of the manuscript.

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CHAPTER 3: Narrative Review Explaining the Role of HLA-A, -B, and -C Molecules in COVID-19 Disease in and around Africa (Published Infectious Disease Reports, /doi.org/10.3390/idr16020029)

Narrative Review Explaining the Role of HLA-A, -B, and -C Molecules in COVID-19 Disease in and around Africa

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Abstract: The coronavirus disease 2019 (COVID-19) has left a devasting effect on various regions globally. Africa has exceptionally high rates of other infectious diseases, such as tuberculosis (TB), human immunodeficiency virus (HIV), and malaria, and was not impacted by COVID-19 to the extent of other continents Globally, COVID-19 has caused approximately 7 million deaths and 700 million infections thus far. COVID-19 disease severity and susceptibility vary among individuals and populations, which could be attributed to various factors, including the viral strain, host ge-netics, environment, lifespan, and co-existing conditions. Host genetics play a substantial part in COVID-19 disease severity among individuals. Human leukocyte antigen (HLA) was previously been shown to be very important across host immune responses against viruses. HLA has been a widely studied gene region for various disease associations that have been identified. HLA proteins present peptides to the cytotoxic lymphocytes, which causes an immune response to kill infected cells. The HLA molecule serves as the central region for infectious disease association; therefore, we expect HLA disease association with COVID-19. Therefore, in this narrative review, we look at the HLA gene region, particularly, HLA class I, to understand its role in COVID-19 disease.

1. Introduction

Severe acute syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, which led to the most dreadful pandemic [1]. Coronavirus is a respiratory virus that can cause symptoms like the common cold and potentially lethal inflammation in ex-tra-pulmonary organs [2]. COVID-19 outcomes, severity, and symptoms vary due to age, comorbidities, living conditions, viral genetics, genomics, blood groups [3, 4], and host genetics involved in antiviral defense mechanisms and pathogenesis [5, 6]. COVID-19 severity correlates with lymphopenia, cytokine storm [7], and exaggerated immune response [8].

COVID-19 began in Wuhan, China [9, 10], and quickly reached Europe and the US [11, 12], followed by various other countries around the world. However, in Africa, with a population of more than 1.2 billion people, COVID-19 infections and deaths have been relatively low, especially in malaria-endemic regions [13]. The overall death rate in Africa reduced from 2019

to 2020 and 2020 to 2021. The lower COVID-19 incidences have been attributed to the lack of COVID-19 testing, early government interventions, population distribution, social distancing, habitation ecology, demographics, existing medical conditions, innate immune memory, genetics, and larger sociocultural dynamics [14]. This also includes Africa having a younger population, public support, a favorable climate, good healthcare systems, and quick action [15]. Despite Africa being a developing and poorer continent, it was suggested that Africa had implemented additional public health guidelines compared to other nations and that previous involvement with human HIV, Ebola, TB, etc., left them more equipped to deal with COVID-19. Africa might have also had more time to prepare and respond to COVID-19 with well-developed guidelines compared to other countries. Sub-Saharan Africa has one of the highest rates of endemic infectious diseases, suggesting an uncommon response to COVID-19 [14, 16, 17]. This requires the need to establish the basis of Africa's differential response during the pandemic. Host genetics could be the reason behind most of the SARS-CoV-2 susceptibility and COVID-19 severity variation between patients.

Human leukocyte antigens (HLAs) are major genes of the major histocompatibility complex (MHC), they play an integral part in presenting antigens to T cells, allowing the identification of foreign proteins from pathogens involved in various infectious diseases. HLA genes have been studied in various viral infections, they are beneficial to the immune response against viruses and related to vaccines [18]. It is crucial to understand the impact the HLA region has on individuals' or populations' responses to SARS-CoV-2. Genome-wide association studies, known as GWAS, showed genetic variants involved in immunological processes associated with SARS-CoV-2 susceptibility and COVID-19 severity [12, 19]. Therefore, HLA genetic variations might contribute significantly to the variation in the immunological reaction to COVID-19 and might be associated with cytokine storm and, in turn, the variation in SARS-CoV-2 susceptibility and COVID-19 severity.

The 02HLA genes are located on the short arm of chromosome 6 (p21.3) [20]. The HLA molecule is found on the cell surface of most cells. HLA molecules are important in the adaptive immune response. It mediates specific attacks on infected cells and antibody production. HLA classical class I molecules are made up of HLA-A, HLA-B, and HLA-C, and they comprise two noncovalently bound polypeptide chains. Nucleated cells express HLA class I molecules [21]. The HLA gene codes for the polymorphic alpha chain, while chromosome 15 includes the nonpolymorphic beta-2 microglobulin chain gene. HLA class I molecules have endogenic peptides, comprising those that are virus-originated [22]. Class I antigens present

foreign peptides that are identified by CD8 T cells [20, 23]. HLA class II is categorized into three groups, HLA-DR, HLA-DQ, and HLA-DP. They are heterodimers made up of α and β chains, and display peptides produced in endosomes from presenting cells to CD4 T cells [20]. Antigen-presenting cells, such as macrophages, dendritic cells, and mature B lymphocytes, express HLA class II molecules. Intestine and lung epithelial cell surfaces also express HLA class II molecules [24]. HLA is the most polymorphic human gene [25]. There are more than 30,000 HLA alleles that have been identified, which code for approximately 18,000 different proteins [26]. However, there have been various database updates according to Rigen et al., 2023, such as removals and additions of new papers [27]. Most of the HLA mutations occur in the exons. These mutations encode for the peptide-binding groove and T-cell receptor interactions [28]. Genetic variations affect HLA geometry, hydrophobicity, charge distribution, and peptide interactions. Different HLA molecules may have unique peptide binding abilities to B-cell and T-cell receptors, known as immunoglobulins. Varying genotypes of HLAs in individuals might deviate in pep-tide presentation and immune responses [29]. HLA genetic polymorphisms affect the disease severity of RNA and DNA viruses, for example, influenza H1N1 [30], Hantaan [31], SARS-CoV-1 [32], HCV, HBV, HIV, hepatocellular carcinoma, liver cirrhosis [21, 33], and bacterial infections such as tuberculosis [34]. Therefore, HLA studies could be valuable in determining which genes contribute to severe COVID-19 in patients. The HLA class I genes are required in developing a specific immunological response to viral infections. HLA-A*68 was shown to be associated with protection against COVID-19 severity and fatal outcomes [35]. In this narrative literature review, we will look at HLA class I genes that are COVID-19-associated. We will also discuss poly-morphisms in this region that impact the COVID-19 disease outcome.

2. Selection Criteria

Articles were selected using the following criteria for our literature review. In the first phase, on 14 January 2024, we searched the terms “HLA class I AND COVID” on PubMed and excluded all articles before 2019. We found 283 results. In the second phase of the selection, we analyzed the titles and abstracts of all the articles and found 18 articles that focused on HLA class I and COVID-19. We retrieved information from the 36 articles and their referenced articles. This is summarized in Figure 1 below. Information regarding the gene, gene effect, ethnicity, no. of samples, and the p-value used in each study reviewed in this article are summarized in Table 1.

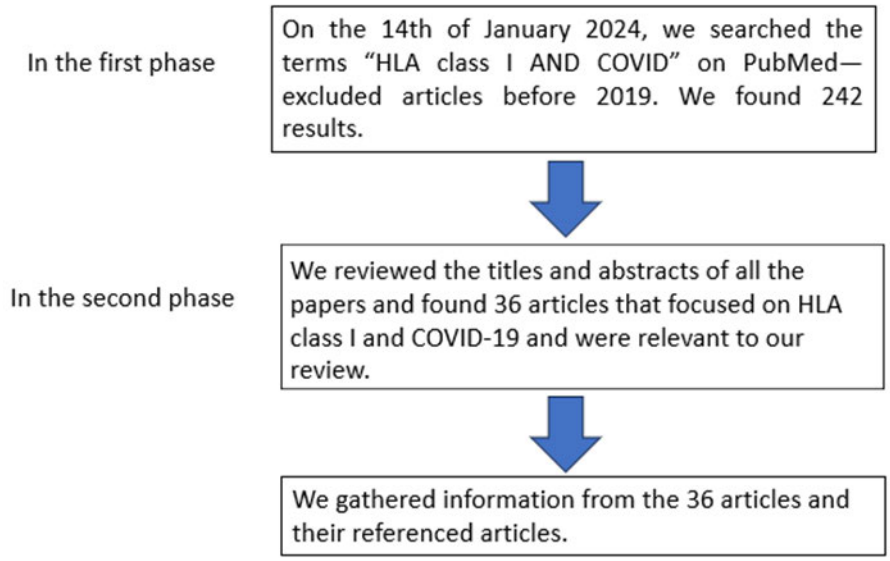

Figure 1. Flow diagram of the selection criteria of the article.

Table 1: HLA class I genes associated with COVID-19

Table 1. HLA class I genes associated with COVID-19.

Gene	**Ethnicity**	**Effect/Association**	**No. of Samples**	**p Value**	**Reference**
HLA-A					
HLA-A*01	Mexican	Risk of fatal COVID-19	146 111 COVID-19-infected individuals and 35 controls	Pc = 0.03	[35]

	Spain	Associated with higher mortality	3886	Apache p = 0.04 or sofa p = 0.02	[36]
	West Indian	Prevalent in controls than COVID-19 patients	228 controls, 235 COVID-19 patients	p = 0.011	[37]
HLA-A*01:01	Russian	Protective against severe COVID-19	100 pneumonia caused by COVID-19 patients and 100 controls	p = 0.009	[38]
HLA-A*02	UK (Manchester and Leeds)	Might cause a protective effect or effective immune response against COVID-19 Protective against susceptibility and mortality	80 COVID-19-infected individuals 308 wait-listed renal transplants 10,000 deceased	p = 0.0179 Insignificant after correction	[39]

	West Indian	Prevalent among COVID-19-infected individuals of varying severity	228 controls, 235 COVID-19 patients	$p < 0.001$	[37]
HLA-A*02:01	German	Associated with symptomatic COVID-19	6919 COVID-19-infected individuals	$p = 0.03$	[40]
	Japanese	Low COVID-19 risk.	1336		[41]
	19 countries	Increased risk of COVID susceptibility and mortality.		$p = 0.20$	[42]
HLA-A*02:05	German	Associated with the risk of severe respiratory infection	6919 COVID-19-infected individuals	$p = 0.04$	[40]
HLA-A*26	Manchester and Leeds	Increased in patients than in controls	80 COVID-19-infected individuals, 308	$p = 0.0049$	[39]

			wait-listed renal transplants, 10,000 deceased donors		
HLA-A*02:06	Asia, North America, Europe, Oceania		6421 sequences		[41]
HLA-A*03	Prevalent in COVID-19 patients.		p = 0.047		
	Iranian	Associated with risk	142 COVID-19-infected individuals and 143 controls	p = 0.0025	[43]
HLA-A*03:01		Low COVID-19 risk			[44]
HLA-A*11	Spain	Higher mortality Increased frequency in	3886	SOFA (p = 0.04) APACHE (p = 0.02) p = 0.051	[36]

		deceased than in survivors			
	Chinese	Possibly confers susceptibility in SARS-Cov-2 infection.	332 patients	$p = 8.5 \times 10^{-3}$	[45]
HLA-A*11:01	Japanese	Severe disease, hospitalization, and mortality COVID-19 severity Protective against COVID-19 susceptibility and mortality	190	$p = 3.34 \times 10^{-3}$ $p = 0.013$ $p = 0.0078$	[46]
	Albany, USA	Increased risk of hospitalization	100 hospitalized COVID-19 patients and 26 controls	$p = 0.0078$	[47]
	Spanish	COVID-19 severity	5943 controls	$p = 0.033$	[48]

			9373 COVID-19-infected individuals		
HLA-A*23:01	Brazilian	Protection against COVID-19			[49]
HLA-A*24	Iranian		48 severe COVID-19 cases	p = 0.003	
HLA-A*24:02	Brazilian	Protection against COVID-19			[49]
	Ecuadorians	Protection against severe COVID-19			[50]
HLA-A*24:02:01	Chinese	Susceptibility	5		[51]
HLA-A*24:02	Japanese	Worse COVID-19 outcomes	1336		[41]
HLA-A*26:01	Russian	Worse COVID-19 outcome	111 COVID-19-infected individuals and	p = 0.0459	[44]

			428 controls		
	South Han Chinese	Associated with diabetes a risk factor for COVID-19	5		[51]
	Russian		111	0.0400	
HLA-A*30:02	African American	Increased COVID-19 susceptibility	234 COVID-19 cases and 22,000 controls	p = 0.01	[52]
	Albany, USA	Enriched in COVID-19-positive individuals	100 hospitalized COVID-19-infected individuals and 26 controls	(Exact test) p = 0.0417	[47]
	Brazilian	Protection against COVID-19			[49]
HLA-A*31:01	Brazilian	Protection against COVID-19			[49]

HLA-A*32	Spain	Higher in healthy controls than COVID-19 patients	3886	(p = 0.004)	[36]
	Iranian	Protection against COVID-19	143 controls and 142 COVID-19-infected individuals	p = 0.0388	[43]
HLA-A*68	Iranian	Prevalent in COVID-19	48 severe COVID-19 and 500 controls	p = 0.001	[53]
	Mexican	Protective against severe COVID-19	146 111 COVID-19-infected individuals and 35 controls	PC = 0.03	[35]
HLA-A*68:01	Brazilian	Protection against COVID-19			[49]
HLA-B					

HLA-B*07	74 countries	Risk of mortality		p = 0.00081 Insignificant after multivariable regression	[54]
HLA-B*07:03	Hong Kong	Disease	90	p = 0.00072	[55]
HLA-B*08	Italians	Increased COVID-19 and death rate		HLA−A*01:01g−B*08:01g−C*07:01g−DRB1*03:01gG (p = 0.00042, p = 0.013)	[56]
HLA-B*08:01	74 countries	Increased COVID-19 and death rate	104,135	p = 0.047 (insignificant after multivariate regression with backward elimination)	[54]
HLA-B*08:01	209 populations		420 HLA-B alleles	<0.0001	[57]
HLA-B*14	Italians	Inversely associated with COVID-19	370,000	p < 0.0001	[58]
HLA-B*14:02	Chinese	Patients entering the severe stage.	332	$p = 3 \times 10^{-3}$	[59]
HLA-B*15	West Indian	Protection against COVID-19	228 controls, 235 COVID-19 patients	p = 0.008	[37]
	Egyptian	Protection	69	p < 0.001	[60]

HLA-B*15:03		Protective against COVID-19			[61]
HLA-B*15:01	805 district populations from 101 countries	Positively associated with COVID-19			[62]
		Asymptomatic SARS-CoV-2			[63]
HLA-B1527	Chinese	More frequent in COVID19-infected individuals than in healthy controls	82	p = 0.001	[59]
HLA-B*18	Italians	Inversely associated with COVID-19	370,000 and additional 120,926 individuals	p < 0.0001	[58]
HLA-B*18:01	Italian	Protects against COVID-19 incidence and mortality		HLA-A*02.01g-B*18.01g-C*07.01g-DRB1*11.04g (p = 0.0053, p = 0.034)	[56]

	Brazilian	Protection against COVID-19			[49]
HLA-B*22	Chinese	SARS-CoV-2 susceptibility	190 COVID-19-infected individuals and 294 controls	p = 0.032	[64]
HLA-B*27	Chinese	More prevalent among controls than COVID-19 patients Susceptibility and resistance to all SARS-CoV-2 strains	190 COVID-19-infected individuals and 294 controls	p = 0.068	[64]
HLA-B*35	United Arab Emirates (15 nationalities)	Severe COVID-19	92 patients	p = 0.0051	[65]
	South Asian	Severe COVID-19			

HLA-B*37:01	Russia	Associated with deceased COVID-19 individuals	111 COVID-19-infected individuals and 428 controls	p = 0.0331	[44]
HLA-B*38	Iranian	Disease susceptibility	48 severe cases of COVID-19	p < 0.001	[53]
HLA-B*39	Spain	Higher COVID-19 rates	72 infected out of 3886	p = 0.02	[62]
	Ecuadorian	Associated with COVID-19 risk	52 COVID-19-infected individuals and 87 controls		[50]
HLA-B*41	Egyptian	Associated with severe COVID-19	69		[60]
HLA-B*44	Italian	High risk for COVID-19 susceptibility, severity, and mortality in	182 patients, 619 controls	p = 0.175	[66]

		population-based studies.			
	74 countries	Risk of mortality		p = 0.0022 (insignificant after multivariable regression)	[54]
	UK (Manchester and Leeds)	Protective effect	10,000 deceased donors, 308 wait-listed renal patients, and 80 COVID-19-infected individuals	p = 0.0052 (did not remain significant after correction).	[39]
HLA-B*44:02	60 countries 209 populations	High risk for COVID-19 susceptibility, severity, and mortality in population-based studies.	420 Hla-b alleles	0.0003	[57]
	Brazilian	Protection against COVID-19			[49]
	German	Associated with the risk of	6919 COVID-19-infected	p = 0.008	

		hospitalization	individuals		
HLA-B*46:01	Chinese, Vietnamese, Taiwan, Singaporean	Increased COVID-19 susceptibility			[67]
		Prevalent in mild COVID-19			[68]
HLA-B*49	Italians	Inversely associated with COVID-19	370,000 and additional 120,926 individuals	$p < 0.0001$	[58]
HLA-B*51	South Asian	Fatal COVID-19			[69]
HLA-B*52:01	African, European, Asian, Australian, Oceanian, American.		158 and 374 typed samples		[70]
HLA-B*54:01	Six areas (Asia, North America, South America, Europe,	SARS-CoV-2 susceptibility	158 and 374 typed samples		[70]
		Protection against	12,343 SARS-CoV-2	$p = 0.017$ (insignificant after adjusted $p = 0.45$)	[71]

	Oceania, and Africa)	COVID-19 infection			
HLA-B*55	Iranian	Protection	142 COVID-19 patients and 143 controls	p = 0.0033	[43]
HLA-B*55:01	African, European, Asian, Australian, Oceanian, American.	SARS-CoV-2 susceptibility	158 and 374 typed samples		[70]
HLA-B*55:07	African, European, Asian, Australian, Oceanian, American.	SARS-CoV-2 susceptibility	158 and 374 typed samples		[70]
HLA-B*55:12	African, European, Asian, Australian, Oceanian, American.	SARS-CoV-2 susceptibility	158 and 374 typed samples		[70]
HLA-B*51:01	Chinese	Severe COVID-19	332 patients	p = 0.007	[45]

	Brazilian	Protection against COVID-19			[49]
HLA-B*56:01	African, European, Asian, Australian, Oceania, American.	SARS-CoV-2 susceptibility	158 and 374 typed samples		[70]
	Hong Kong Chinese	Associated with COVID-19	190 COVID-19 cases	p = 0.045	[64]
HLA-B*56:04	Hong Kong Chinese	Associated with COVID-19	190 COVID-19 cases	p = 0.029	[64]
HLA-B*58	Iranian	Protection	143 controls and 142 COVID-19-infected individuals	p = 0.0376	[43]
	74 countries	Risk of death		p = 0.0089 (insignificant after adjustment).	[54]
HLA-B*58:01	209 populations	High risk for COVID-19 susceptibility, severity, and mortality in		0.0062	[57]

		population-based studies.			
	Italian	Positively associated with COVID-19	99 patients	p = 0.01317	[72]
HLA-C					
HLA-C*01		Prevalent in mild COVID-19 infection compared to severe COVID-19	228 controls, 235 COVID-19 patients	p = 0.004	[37]
	Italian	Permissive to SARS-CoV-2. More prevalent in the deceased than in survivors.		p = 0.09	[36, 58]
HLA-C*03	Italian	Positively associated with the incidence of SARS-CoV-2 infection	370,000 individuals and an additional 120,926 individuals	p > 0.0001	[58]
	Saudi	Increased COVID-19 severity	136 COVID-	p = 0.047	[69]

			19 patients		
HLA-C*04:01	Germany, Spain, Switzerland, and the United States	Severe COVID-19	435	p = 0.0074	[73]
	Europeans	Severe COVID-19	619 controls and 182 infected individuals.		[74]
	Russian	Associated with COVID-19 susceptibility.	12,139		[75]
	Sardinian	Susceptibility to SARS-CoV-2 infection	619 controls, 182 SARS-CoV-2 patients	p = 0.001	[66]
		Increased risk of COVID-19		p = 0.005	[76]
	Albany, USA	Severe COVID-19	100 hospitalized COVID-19	p = 0.0087	[47]

			infections and 26 controls		
		Increased risk of hospitalization measured by days with ventilation		p = 0.0023	
	United Arab Emirates (15 nationalities)	COVID-19 severity	92 COVID-19-infected individuals	p = 0.0077	[65]
HLA-C*05	Spain	Severe COVID-19	9373 COVID-19-infected individuals and 5943 controls	p = 0.045	[48]
	74 countries	Risk of COVID-19 death		p = 0.000027	[54]
HLA-C*05:01	Brazilian	COVID-19 protection			[49]
HLA-C*06:02	Manchester and Leeds	Worse COVID-19	80 infected		[39]

		disease outcome	out of 308		
HLA-C*7	Egyptian	Associated with protection from death	69 COVID-19 patients	p = 0.001	[60]
HLA-C*07:01	Sardinian	Negatively correlates with SARS-CoV-2 susceptibility and mortality	619 controls, 182 SARS-CoV-2 patients	p = 0.0406	[66]
	Brazilian	COVID-19 protection			[49, 77]
	German	Decreased risk of symptomatic COVID-19	6919 COVID-19-infected individuals	p = 0.001	[40]
HLA-C*07:29	Chinese	Higher expression in COVID-19 patients than controls.	82	p = 0.001	[59]
HLA-C*08:02	Sardinian	Increased susceptibility SARS-CoV-1	619 controls, 182 SARS-	HLA-A*30:02, HLA-B*14:02, and HLA-C*08:02 haplotypes (p = 0.0008)	[66]

			CoV-2 patients		
	Brazilian	COVID-19 protection			[49]
	Spanish Mediterranean Caucasian	Mild COVID-19		p = 0.0014	[48]
	Spanish	Reduced risk of COVID-19	9373 COVID-19-positive cases and 5943 controls	p = 0.024	[48]
HLA-C*12	Manchester and Leeds	Prevalent in the control population	80 COVID-19-infected, 308 wait-listed renal transplants (control), and 10,000 deceased donors (control)	p = 0.0286	[39]

	Egyptian	Protection from death	69 COVID-19 patients	p = 0.008	[60]
HLA-C*12:02	Han	High response against COVID-19	5		[51]
HLA-C*12:03	Spanish Mediterranean Caucasian	Mild COVID-19 compared to critical COVID-19	72 individuals, 24 COVID-19-infected individuals, and 48 hospitalized	p = 0.0001	[78]
HLA-C*14:02	Chinese	Severe COVID-19	332	p = 0.003	[45]
HLA-C*15:02	Brazilian	COVID-19 protection			[49]
HLA-C*16	Egyptian	COVID-19 severity	69 COVID-19 patients		[60]
	Spain	Increased COVID-19 infection	3886	p = 0.02	[36]

HLA-C*16:01	Spanish Mediterranean Caucasian population	Associated more with mild COVID-19 when compared to critical than severe	72 individuals, 24 COVID-19-infected individuals, and 48 hospitalized	p = 0.0014	[78]
HLA-C*17	Egyptian	COVID-19 severity	69 COVID-19 patients		[60]
HLA-C*17:01	Brazilian	Associated with COVID-19 protection			[49, 77]

*• The asterisk allows for differentiation between variants within the same HLA gene group

3. The Role of HLA in COVID-19

HLA antigens could be a valuable contributing factor in SARS-CoV-2 outcomes [79, 80]. Studies have shown specific HLA alleles correlated with the risk of SARS-CoV-2 infectivity, COVID-19 disease progression, and vaccine responses. Individuals with different HLA profiles but the same antigen may result in unique T-cell-mediated immune responses because they have contrasting numbers of specific HLA antigen-derived epitopes. Some studies distinguish the viral antigens presented by specific HLAs [79-81]. Understanding how T-cell reactivity and antigen presentation are associated with HLA, and the immune mechanisms responsible for different host immune reactions to SARS-CoV-2, may assist researchers to

develop strategies to alleviate COVID-19 [82]. The HLA variations determine the antigen presentation [82]. Studies have shown the importance of peptide magnitude, specificity, and the quality of cellular and humoral immune responses. In silico research, analysis has been conducted on the binding ability among peptides of SARS-CoV-2 and diverse genotypes of HLA class I [42, 47, 61, 83]. HLA studies have shown insight into viral susceptibility in different populations. Hence, studies have uncovered HLA alleles that contributed to susceptibility or resistance to COVID-19 in different ethnic groups. While other studies did not show a relationship between HLA polymorphism or haplotypes and COVID-19 susceptibility and resistance [68]. Therefore, it is important to further analyze these HLA alleles that could be targeted in therapeutic strategies to alleviate the COVID-19 disease and be aware that this might vary between ethnicities.

3.1. HLA-A

Hernandez-Dono et al., 2022, studied the relationship between HLA alleles and severe COVID-19 in Tapachula, Mexico. This study consisted of 146 Mexicans. The patients were categorized according to their outcome (deceased or recovered) and severity (moderate or severe), and exposed uninfected participants were included. This study showed that the HLA-A*68 allele protected against severe COVID-19 and fatal outcomes. COVID-19 severity and fatal outcomes in Tapachula, Chiapas, were pre-dominantly dependent on the absence of resistance than HLA susceptibility alleles. There was a significant statistical difference in HLA-A*68 among COVID-19-infected individuals and exposed uninfected individuals, and severely infected COVID-19 individuals and exposed uninfected individuals. HLA-A*68 was absent among severe COVID-19 and COVID-19 patients. In carriers, this allele conferred 2.4 times more severe SARS-CoV-2 infection resistance. It also protected against deadly SARS-CoV-2 outcomes 3.3 times more in Tapachula, Chiapas, and mestizo participants [35]. In the same study, HLA-A*01 was associated with the risk of COVID-19 fatal outcomes. There was a significant statistical difference between deceased patients and recovered patients [35]. This study showed two different HLA-A genes that had different associations with COVID-19. A western Indian population showed HLA-A*01 was more prevalent in controls than COVID-19-infected individuals ($p = 0.011$), while HLA-A*02 was prevalent with COVID-19-infected individuals of varying severity ($p < 0.001$) [37]. Similarly, HLA-A*01 was associated with low ferritin, which was associated with low severity ($p = 0.016$) [69]. In Russia, HLA-A*01:01 was expressed at lower in severe pneumonia and indicated a protective factor for severe COVID-19 [38]. HLA-A*02:01 was associated with the risk of symptomatic COVID-19 ($p = 0.03$), and

HLA-A*02:05 was linked to severe respiratory infection risk (p = 0.04) [40]. These genes need to be further studied in other populations to determine if their effect varies.

A bioinformatics analysis screened for possible SARS-CoV-2 epitope sequences for HLA. This study identified two epitopes that are nonstructural proteins in the open reading frame (ORF) that displayed a compelling binding affinity for HLA-A*24:02, HLA-A*02:06, and HLA-A*02:01 in a Japanese cohort. These epitopes had the highest population coverage at 83%. Therefore, they were regularly accessible and applicable to a bigger population [41]. Regrettably, this study's mathematical estimates need to be better defined with regard to immunogenetic traits and clinical and experimental estimates [46].

HLA-A*11:01 was associated with severe disease in a Japanese cohort, OR = 3.41 and p = 0.003 [46]. A study with 190 individuals from Japan with moderate to severe COVID-19 observed an association between HLA-A*11:01 and COVID-19 severity (OR = 2.26) (p = 0.013) [46]. HLA-A*11:01 significantly correlated with COVID-19 severity, hospital admission, and fatality after adjusting for sequential organ failure assessment (SOFA) or acute physiology and chronic health evaluation II (APACHE-II) when compared with mildly infected COVID-19 patients [36, 45-47, 71]. SOFA is a score used to anticipate mortality in septic patients, while APACHE II is a score of the disease severity categorization taken during the initial 24 hours after hospital admission. Similarly, another study using logistic regression analysis showed that HLA-A*11 was linked with increased mortality, after regulating for APACHE-II (p = 0.02) or SOFA (p = 0.04). They found an increased frequency of HLA-A*11 (p = 0.051) in the deceased than in survivors [34]. Toyoshima et al. showed that HLA-A*11:01 was defensive against SARS-CoV-2 susceptibility and COVID-19 fatality when compared to the global database for allele rate, infection, or death [71], which were inconsistent with research that compared allele incidence and effect at an individual level [45-47]. Analysis of inferences from bioinformatics and practical applications should be undertaken with caution because different methods may result in differing and incomparable results. HLA-A*11 was associated with weak evolution in other infectious diseases [34, 84]. The HLA allele data from next-generation sequencing (NGS) of 332 patients from China who were admitted to a hospital showed the difference between allele frequency among individuals severely and moderately infected with COVID-19 (p = 0.009) [45]. HLA-A*11:01 allele could protect against infection [71]. Another study with 73,000 Israeli individuals, including 6,413 SARS-CoV-2-infected individuals and 181 COVID-19-hospitalized individuals, showed no significant association with common HLA alleles [85]. HLA-A*11:01 had a significantly negative association with

SARS-CoV-2 susceptibility and mortality in 21 countries. However, this was insignificant for the death rate when modified for the S 614G variant. Studies of HLA-A*11:01 were conflicting regarding SARS-CoV-2 susceptibility. HLA-A*11 possibly confers SARS-CoV-2 susceptibility in different populations, such as Chinese, Indian, and Asian individuals born in the United Kingdom; Hispanic; and Black [39, 47]. In the Spanish population of 5943 controls and 9373 COVID-19-infected individuals, HLA-A*11:01 was associated with COVID-19 severity ($p = 0.033$) [48]. These studies suggest that HLA-A*11:01 could have varying effects on COVID-19 in different ethnicities. HLA-A*11:01 might be a possible therapeutic target in some populations.

HLA-A*02:01 positively correlated with increased risk of COVID susceptibility and mortality [42], due to its low SARS-CoV-2 antigen presentation ability. However, HLA-A*02 showed protection against susceptibility and death [39]. Shkurnikov et al. (2021) showed that HLA-A*02:01 and HLA-A*03:01 were associated with low COVID-19 risk [44]. HLA-A*02:01 showed contrasting results between these studies. Therefore, more research is required on this allele to understand its role in COVID-19 disease. Haplotype HLA-A*02:01g~B*18:01g~C*07:01g~DRB1*11:04g negatively correlated with COVID-19 and, therefore, might also be protective against infection [56]. HLA-A*24:02:01 was associated with SARS-CoV-2 susceptibility and severity among Chinese [45, 51]. The HLA-A*1 allele was found in four out of five South Han Chinese COVID-19 patients. This allele has been associated with diabetes, a risk factor for COVID-19 [51]. HLA-A*24:02 and HLA-A*26:01 [44] may worsen the COVID-19 outcome. Contrastingly, in Ecuador and Madrid, HLA-A*24:02 was linked to protection from severe COVID-19 [50]. A study with a Brazilian population showed that HLA-A*23:01, HLA-A*24:02, HLA-A*26:01, HLA-A*30:02, HLA-A*31:01, and HLA-A*68:01 were associated with protection against COVID-19 [49, 77]. HLA-A*30:02 alleles among African Americans [52] were more significantly susceptible to SARS-CoV-2 infection. HLA-A*30:02 is prevalent in Africa and Sardinia [66, 86, 87]. Larger sample sizes are required to validate the role of these HLA-A alleles on COVID-19.

An HLA-A-genotyping study was performed with 72 COVID-19-infected individuals and 3886 well individuals in the control group. The frequency of HLA-A*32 ($p = 0.004$) was higher in the control group when compared to the COVID-19-infected individuals, and HLA-A*03 ($p = 0.047$), HLA-B*39 ($p = 0.02$), and HLA-C*16 ($p = 0.02$) alleles were more prevalent in COVID-19-infected participants compared to healthy individuals; but, after multiple assessments modification, the p-values were insignificant. This might be attributed to the small

COVID-19-positive cohort. In another study, HLA-A*03 was associated with risk, and HLA-A*32 was associated with protection. After correction, only HLA-A*03 remained significant [43]. A study with a Brazilian population showed that HLA-A*01:01, HLA-A*02:01, and HLA-A*03:01 were associated with protection against COVID-19 [49, 77].

HLA class I molecules have varied reactivity to cytotoxic T lymphocytes. Another study showed that weak HLA-A and B haplotypes are associated with deaths and COVID-19 severity [88]. Additional studies are required to authenticate the impact of these HLA-A alleles between healthy and infected individuals.

3.2. HLA-B

HLA-B*08:01 and HLA-B*08 correlated with raised COVID-19 risk and mortality [54, 56, 57, 71]. Pisanti et al. suggested that HLA-B*18:01 and haplotype HLA-A*02.01g-B*18.01g-C*07.01g-DRB1*11.04g protect against COVID-19 occurrence and mortality [56]. HLA-B*18:01, HLA-B*35:03, HLA-38:01, HLA-B*44:02, and HLA-B*51:01 were associated with protection against COVID-19 among the Brazilian population [49, 77]; whereas HLA-B*44, HLA-B*44:02, and HLA-B*58:01 were associated with greater risk in population reports for SARS-CoV-2 susceptibility, COVID-19 severity, and death. However, this was not reflected in laboratory studies [39, 54, 57, 58, 66, 72]. In another study, HLA-B*44:02 was associated with a risk of respiratory hospitalization ($p = 0.008$) [40]. Varying study designs should be compared with caution, and other contributing factors should be taken into account.

Nguyen et al. (2020) showed that HLA-B*15:03 was protective against COVID-19 by efficiently presenting conserved peptides of SARS-CoV-2 to T cells, and found it had one of the highest binding affinities to SARS-CoV-2 peptides [61]. In this study, mathematical predictions required experimental and clinical evaluation and participants with immunogenetic characteristics. HLA-B frequency data were acquired from the Allele Frequency Net Database [89] for 805 different populations from 101 countries. There was a robust linkage disequilibrium between HLA-B*15:01 and HLA-DRB1*04:01; this correlated considerably with infected European individuals who presented no symptoms [62]. In a western Indian population, HLA-B*15 was associated with protection against COVID-19 ($p = 0.008$), while HLA-B*40 was associated with mild COVID-19 infections ($Pc = 0.03$) [37]. Similarly, in an Egyptian population, HLA-B*15 was significantly associated with protection ($p < 0.001$) [60]. In a study consisting of 82 COVID-19-infected individuals from China, the frequencies of HLA-B*15:27 and HLA-B*40:06 were statistically higher in COVID-19-infected individuals

than in healthy controls [59]. However, this study did not have enough power to find a substantial association between HLA polymorphism and COVID-19 susceptibility. Studies with higher power and a bigger cohort are required to decipher the role of HLA-B alleles in COVID-19 disease. Cheranev et al. (2023) showed that statistically significant alleles joined into haplotypes HLA-B*27:02:01G and HLA-C*02:02:02G, and HLA-B*14:02:01G and HLA-C*08:02:01G were prevalent in deceased patients and survivors, due to linkage disequilibrium, respectively [90]. In Spain, HLA-B*14:02 was associated with a reduced risk of COVID-19 ($p = 0.006$) [48].

In Egypt, a study with 69 COVID-19 patients showed that HLA-B*41 and HLA-B*42 were associated with severe COVID-19 [60]. HLA-B* 46:01 was associated with SARS-CoV-1 severity in an Asian population and SARS risk [32]. HLA-B*46:01 has a low binding affinity to SARS-CoV-2 peptides, indicating that individuals with HLA-B*46:01 might have increased COVID-19 susceptibility [61]. HLA-B*46:01 [61] and HLA-B*07 displayed a role in susceptibility among a cohort consisting of multiple ethnicities [54]. These estimates were not evaluated clinically and by experimentation and had insufficient immunogenetic traits. Similarly, HLA-B*46:01 was associated with SARS-CoV-2 severity [32, 61, 91]. HLA-B*46:01 is uncommon in the United States (US), Switzerland, and Spain [91]. HLA-B*46:01 was absent in the data comprising Europeans. Analyses established that most of the allele frequencies in the German cohort were comparable in cohorts from Switzerland, the US, and Spain. The SARS-CoV-1 outbreak revealed that HLA-B*46:01 [32] and HLA-B*07:03 were associated with disease [55]. HLA-B*46:01 is significantly associated with SARS-CoV-2 susceptibility among Singaporeans, Chinese, Vietnamese, and Taiwanese, except for children of mixed ethnicities [32]. Wang et al. and Gutierrez-Bautista et al. (2022) showed that HLA-B*46:01 is prevalent in mild COVID-19 compared to severe COVID-19, and it does not present SARS-CoV-2 peptides well [68]. SARS-CoV-2 is approximately 77% similar to the SARS-CoV-1 genome [92], so it is typically acceptable to assume similarities in the host immune reaction to the SARS-CoV viruses.

The HLA-B*22 serotype is a possible marker for SARS-CoV-2 risk [64]. Barquera et al. (2020) showed five HLA-B*22 alleles (HLA-B*54:01, HLA-B*55:01, HLA-B*55:07, HLA-B*55:12, and HLA-B*56:01) possessed the lowest binding ability to SARS-CoV-2, indicating that HLA-B*22 is associated with SARS-CoV-2 susceptibility [70]. In another study, HLA-B*55 and HLA-B*58 were associated with protection; however, after multiple corrections, this was insignificant [43]. HLA-B*54:01, HLA-B*56:01, and HLA-B*56:04 were associated with

COVID-19 patients when compared to Hong Kong Chinese Cord Blood Registry controls ($p > 0.05$) [93]. The HLA-B*27 serotype might regulate SARS-CoV-2 infection [64] and is linked with infectivity and protection against all strains of SARS-CoV-2 [94]. The change in immune homeostasis could be involved in coronavirus pathogenesis. Yung et al. (2020) performed a study with 190 Chinese participants with COVID-19. They showed a correlation between the HLA-B*22 serotype and SARS-CoV-2 infection ($p = 0.032$, OR = 1.71) [64]. Epitopes of SARS-CoV-2 and HLA-A*02:06, HLA-B*52:01, and HLA-C*12:02 shared high binding affinity. Binding affinity studies highlight and put into perspective the impact of these HLA alleles on COVID-19.

COVID-19 patients in a Chinese cohort showed HLA-B*51:01 alleles were significantly associated with severe COVID-19 [45]. This allele had quite reduced SARS-CoV-2 antigen presentation ability compared to other HLA class I molecules [42]. HLA-B*54:01 alleles might be responsible for protecting against COVID-19 infection [71]. HLA-B*15:01 was significantly associated with asymptomatic SARS-CoV-2 [63]. In Italy, HLA class I alleles could play a role in the differences in the extent of SARS-CoV-2 infection between North and South Italy. HLA allele frequency from a bone marrow donor registrar in Italy and the prevalence of SARS-CoV-2 infection in various districts were assessed. HLA-B*08, HLA-B*15:01, HLA-B*44, and HLA-B*51 pos-itively correlated with COVID-19. However, HLA-B*14, HLA-B*18, and HLA-B*49 were inversely associated with COVID-19. HLA-B*44 alleles were found at a higher incidence in Italians from the north and were positively associated with COVID-19, after multiple regression models [58]. This epidemiological analysis shed light on specific HLA class I alleles that are not capable of presenting adequate virus-derived epitope peptides to initiate an acceptable SARS-CoV-2 immune response to offset infection. HLA-B*44 alleles are tolerant to SARS-CoV-2 infection in Italians [95, 96]. HLA-B*44 inheritance is the cause of recurrent sinopulmonary infection susceptibility [97]. The analysis of HLA allele data from NGS of 332 hospitalized Chinese patients detected variations among mild and severe COVID-19 infections in individuals with HLA-B*51:01 ($p = 0.007$) [45]. Similarly, HLA-B*51 was associated with fatal COVID-19 in a South Asian population [69]. HLA-B*37:01 was associated with deceased COVID-19 individuals ($p = 0.0331$); therefore, it might be involved in severe COVID-19 disease outcomes [44, 98]. Poulton et al. (2020) showed that HLA-B*44 might have a protective effect against SARS-CoV-2 infection when compared to controls. HLA-A*02, HLA-B*44, and HLA-C*05 are

usually inherited together. This might cause a protective effect or effective immune response against COVID-19 [39].

Seven HLA haplotypes or alleles were identified as defensive against SARS-CoV-2 infection. In addition, five haplotypes or alleles correlated with enhanced susceptibility to SARS-CoV-2. HLA-A*30:02, HLA-B*14:02 and HLA-C*08:02 three-loci haplotypes were statistically significant after p-values were corrected. There was a strong correlation observed between this haplotype and COVID-19 disease severity [66]. Geographical epidemiology analysis showed significant variances in the incidence of two of the prevalent HLA haplotypes in Italians between North, Central, and South Italy, with HLA-A*01:01g (change in expression)-B*08:01g-C*07:01g-DRB1*03:01g (prevalent haplotype countrywide) showing a declining incidence gradient, and HLA-A*02:01g-B*18:01g-C*07:01g-DRB1*11:04g (second prevalent haplotype) showing a cumulative incidence gradient from Northern to Southern Italy. The haplotype division correlates with COVID-19 in Italians. HLA-A*01:01g-B*08:01g-C*07:01g-DRB1*03:01 is indicative of COVID-19 susceptibility, while HLA-A*02:01g-B*18:01g-C*07:01g-DRB1*11:04g might be associated with COVID-19 protection [56].

HLA-B*35 was significantly associated with severe COVID-19 in a study with 92 patients of 15 nationalities from the United Arab Emirates ($p = 0.0051$) [65]. Similarly, HLA-B*35 was more significantly associated with mild than severe COVID-19 in a South Asian population [69]. Farahani et al. (2021) and Shekarkar et al. (2020) observed a significant association between HLA-B*38 and disease susceptibility in the Iranian population [53]. In Spain, a study, conducted with patients from six ICUs observed higher COVID-19 infection rates among individuals with HLA-B*39, but these p-values were insignificant after multiple comparisons correction [62]. A total of 3886 healthy individuals and 72 COVID-19-infected individuals were genotyped for HLA-B. HLA-B*39 ($p = 0.02$) alleles were found more in COVID-19-infected individuals than in healthy individuals; yet, the p-values were insignificant after being adjusted for multiple comparisons. These studies included a small COVID-19 population, which might be the reason for the absence of significant differences. In an Ecuadorian population made up of 52 COVID-19-infected individuals and 87 controls, HLA-B*39 was associated with a risk of COVID-19 development [50].

3.3. HLA-C

High binding affinity was observed between epitopes of SARS-CoV-2 and HLA-C*12:02, which suggests a high immune response against COVID-19 [41]. A study with 82 COVID-19-

infected Han individuals from Zhejiang found a statistically significant difference between HLA-C*07:29 in COVID-19 patients compared to controls; this allele was prevalent in COVID-19 patients [59]. All these individuals had moderate or severe COVID-19, had no critical conditions, donated plasma after recovery, and were aged between 20 to 54. However, only one COVID-19-infected individual possessed a HLA-C*07:29, and none of the controls [59]. These findings should be proven in studies with greater sample sizes. A study with Chinese individuals showed that HLA-C*14:02 significantly correlated with severe COVID-19 [45]. HLA-C*03 was associated with high ferritin, which was associated with increased COVID-19 severity in the Saudi population [69]. Another study showed that HLA-C*01 and HLA-C*03 were positively related to the prevalence of SARS-CoV-2 infection. After multiple regression models, only HLA-C*01 alleles, which are common in northern Italy, were positively associated with COVID-19. This was established by a diverse provincial sub-analysis in Italy [58]. In this study, they genotyped HLA-C in 72 COVID-19-infected individuals and 3886 healthy individuals. HLA-C*01 alleles might be permissive to SARS-CoV-2 infection among Italians [58]. HLA-C*01 was more prevalent ($p = 0.09$) in the deceased than in survivors. In addition, the allele HLA-C*01 was associated with a higher death rate after modulating for SOFA ($p = 0.04$) or APACHE-II ($p = 0.02$) [36]. HLA-C*01 was formerly associated with the risk of other infectious diseases [99]. Tripathy et al. (2023) showed that HLA-C*01 was associated with mild COVID-19 infection ($p = 0.004$) [37]. There were more HLA-C*16 alleles ($p = 0.02$) found in COVID-19 patients compared to controls; nonetheless, all the p-values were insignificant after multiple comparisons adjustment [36]. HLA-C*05:01 was significantly associated with the risk of COVID-19 death [54]. HLA-C*05:01, HLA-C*07:01, HLA-C*08:02, HLA-C*15:02, and HLA-C*17:01 were associated with COVID-19 protection [49, 77]. Among 69 COVID-19 patients from Egypt, HLA-C*16 and HLA-C*17 were associated with COVID-19 severity, while HLA-C*7 and HLA-C*12 were associated with protection from death [60]. HLA-C*08:02, HLA-C*12:03 and HLA-C*16:01 were more prevalent in mild COVID-19 than severe COVID-19 ($p = 0.0014$) in a Spanish Mediterranean Caucasian population [78]. In another Spanish population, HLA-C*08:02 was associated with a reduced risk of COVID-19 ($p = 0.024$) [48]. In Spain, a study consisting of ICU patients observed increased COVID-19 infection rates in individuals with HLA-C*16, but the p-values were insignificant after multiple comparisons correction. The small COVID-19 population in these studies could justify the insignificance [36].

Shkurnikov et al. (2021) observed that HLA-C*06:02 significantly correlated with COVID-19 mortality; therefore, it may be related to more severe COVID-19 outcomes [39]. On the contrary, HLA-C*05 was found more frequently among controls and, therefore, protects against SARS-CoV-2 infection. Although, this was not significant after multiple test corrections [39]. Additional studies are imperative to understand the role of HLA-C*05 in COVID-19.

HLA allele data from the NGS of 332 individuals from the Shenzhen Third People' Hospital, China revealed that HLA-C*14:02 was significantly prominent in severe compared to mild COVID-19 cases ($p = 0.003$) [45]. Further research will determine if this allele could be a potential target for therapeutics in a Chinese population.

In Europeans, HLA-C*04:01 has been shown to influence severe COVID-19. Carriers of HLA-C*04:01 have two times the risk of needing automatic ventilation [82]. In addition, HLA-C*04:01 could be related to COVID-19 susceptibility. This was further assessed by genotyping of 12,139 Russian individuals from another cohort [75]. HLA-C*07:01 had a significant negative correlation with SARS-CoV-2 susceptibility and death rate [66, 74], while HLA-C*01 and HLA-C*04:01 were positively associated with SARS-CoV-2 infectivity, severity, and death rate [47, 58, 100, 101] Weiner [76] et al. noticed that HLA-C*04:01 is prevalent among British and Russians, but uncommon among the Taiwanese population [83]. In another study, HLA-C*07:01 was linked to a decreased risk of symptomatic COVID-19 [40]. The increased risk of hospitalization suggests that the HLA-C*04:01 allele increased the risk of COVID-19 severity. COVID-19-infected individuals with HLA-C*04:01, whose disease diagnosis was determined by days with the ventilator, were statistically significant to increased risk of COVID-19 after Bonferroni's correction ($p = 0.0023$) [47]. In addition, another study with 92 COVID-19-infected individuals of 15 different nationalities with varying severity from the United Arab Emirates also observed a significant association between HLA-C*04 and COVID-19 severity ($p = 0.0077$) [65]. A study with 9373 COVID-19-infected individuals and 5943 controls in Spain showed that HLA-C*04:01 was linked with severe COVID-19 ($p = 0.045$) [48].

In a study, with 435 mild to severely symptomatic individuals from Spain ($n = 133$), Germany ($n = 135$), Switzerland ($n = 20$), and the US ($n = 147$), HLA-C*04:01 has been shown to have a potential association with severe COVID-19. SARS-CoV-2-infected HLA-C*04:01 carriers had two times more intubation risk (adjusted p-value = 0.0074). This could be due to other

HLA alleles having more SARS-CoV-2 peptide binding sites than HLA-C*04:01. HLA-C*04:01 carriers are linked to SARS-CoV-2 severity, suggesting that HLA class I is involved in SARS-CoV-2 immune defense [76]. HLA-C*04:01 was higher in COVID-19-infected individuals than in healthy individuals [66]. The frequency of HLA-C*04:01 was about 13% in Germans, 15% in Spain, 19% in Germans with Turkish ancestry, and 16% in Switzerland [73]. The relationship between severe COVID-19 and HLA-C*04:01 remained when ethnicity was a covariate, and the effect of homogeneous populations was calculated [76]. Intubation was associated with HLA-C*04:01 (adjusted p-value = 0.0074) when applying age, gender, and ethnicity as covariates. An association was observed between intubation and HLA-C*04:01, with the exclusion of additional covariates (OR = 2.9), (adjusted p-value = 0.02) [76]. There was a chance that the correlation between COVID-19 severity and HLA-C*04:01 was a statistical artifact in one of their datasets. For individual ethnicities, an association between HLA-C*04:01 and severe COVID-19 was presented in every group. This association was insignificant, except for Caucasians, because of the small sample size. However, African Americans, Hispanics, and Caucasians who were HLA-C*04:01 carriers were admitted to the intensive care, and all Hispanics, African Americans, and 66% of Caucasians who were HLA-C*04:01 carriers underwent intubation [76]. The HLA-C*04:01 allele was recognized as a severe COVID-19 risk factor among 2113 individuals who disclosed that they were COVID-19-infected, and 10,026 individuals were controls from the cohort, Genotek. HLA-C*04:01 accounted for 13% of the allele frequency. HLA-C*04:01 enhanced the COVID-19 risk significantly in an association analysis with age, gender, and body mass index (BMI) as covariates (p-value = 0.005). The comprehensive effect of HLA-C*04:01 on severe COVID-19 was depicted by the odds ratio of 1.1 (p-value = $5.8 \times 10{-}4$) [76]. Weiner et al. (2021) showed that the HLA alleles could affect disease severity via unusual binding affinity between HLA and peptides of SARS-CoV-2. Following the Iturrieta-Zuazo approach, [102] showed the amount of SARS-CoV-2 peptides that “strongly” (at <50 mM) or “weakly” (at <500 mM) bound to the HLA allele. HLA-C*04:01 had one of the ten lowest HLA allele bind-ing abilities to SARS-CoV-2 peptides. The late immune response triggered by low HLA binding affinity may be the reason for the severe COVID-19 in individuals with HLA-C*04:01 [76]. In addition, HLA-C*04:01 was linked with increased amounts of C-reactive protein (CRP) as an alternative for pervasive inflammation (Wilcoxon test, p = 0.021); however, the result was trivial (r = 0.2). Between ICU patients and non-ICU patients ($p < 10{-}5$) and intubation and non-intubation patients ($p < 10{-}5$), the CRP was significantly different [76]. HLA-C*04:01 could cause more dreadful consequences via more severe inflammation [103, 104]. HLA-

C*04:01 is a potential risk allele that was associated with double the intubation risk when one allele was present. These results were replicated in a COVID-19 shared dataset at Albany Medical Center, US [105], and data from the University of California, San Francisco, and the US. There was a strong association between HLA-C*04:01 and intubation. Furthermore, KIR2DS4 polymorphisms and HLA-C*04:01 increased the SARS-CoV-2 viral quantity and led to severe COVID-19 in individuals co-infected with HIV [106]. KIR2DS4f and HLA-C*04:01 combined were detected in four individuals, one of which was KIR2DS4-homozygous. This individual had severe COVID-19, had high troponin T hs, and was intubated [76]. There was no association between HLA-C*04:01 and the initial measure of viral load from patients during hospital admission [107]. It might be likely that patients' viral load with HLA-C*04:01 might be increased throughout the initial stage of infection [108], but patients start to develop symptoms after 7 days [109-111]; this period may have been skipped to determine the relationship with SARS-CoV-2 viral loads and HLA-C*04:01 when recorded at the beginning of infection. Overall, no particular HLA allele correlated with the initially recorded viral load [76]. The HLA-C*04:01 allele had a significant association with COVID-19 susceptibility in the independent cohort. In these analyses, certain research could not find a correlation between HLA-C*04:01 and COVID-19 [76]. rs143334143 (CCHCR1) showed a significant association with COVID-19 severity. In the 1KG European cohort, HLA-C*04:01 was in linkage disequilibrium with the rs143334143 variant. Although, in another analysis [112], other SNPs in the same linkage disequilibrium category as HLA-C*04:01 and rs143334143 did not have the same effect. Conversely, there was significant heterogeneity between research papers in this analysis (p-value = $3.2 \times 10{-}3$) [76]. In an Armenian population of 299 COVID-19-infected individuals, HLA-C*04 was associated with a risk of hospitalization [113]. HLA-C*04:01 has been studied extensively in various populations and has shown some significant impact on COVID-19 disease and should be analyzed further as a potential therapeutic target.

4. Discussion

Differentiation in HLA expression levels has been formerly shown to be associated with infectious and autoimmune diseases, such as HIV, Parkinson's, Crohn's disease, and cancer [114], but there is a wealth of knowledge to be discovered about the relationship between HLA and COVID-19 [115-117], particularly HLA class I. This relationship should be analyzed in the future, as a similar trend could be detected with COVID-19.

SARS-CoV-2 variations can impact the course of infection, antigen presentation, and HLA binding [118]. An HLA allotype might present the most frequent peptide effectively, but a mutant strain differently. NetMHCpan tools are trained on binding affinity data [119, 120]. Nersisyan et al. created tools to trace the SARS-CoV-2 mutation effect on HLA binding [119]. Delta, reported to be one of the most contagious viral strains, while Omicron, is a highly genetically altered, infective, and transmissible viral strain, is the most prevalent SARS-CoV-2 variant. [121, 122]. In spite of the results not directly correlating with T-cell responses, the data allow further research to hypothesize about these mutations. Genetic variations in the virus and HLA regions contribute to the effect of the presentation of antigens to T cells and ultimately affect the immune response and COVID-19 disease outcomes. While some polymorphisms might affect others more, it is important to identify such genetic variations in therapeutics for current and future coronaviruses. While the viruses continue to mutate rapidly, it is more promising to put more focus on the host genetics to find effective and longer-lasting therapeutics. In addition, results might not correlate directly with the T-cell response because various other factors and genes contribute to disease outcomes. Related genes should be analyzed together with HLA to gather a more holistic view of COVID-19 pathogenesis.

Prugnolle et al. indicated that approximately 39% of HLA class I diversity is a consequence of human migration and is possibly pathogen-driven [123]. Thus, HLA diversity is known to increase with higher pathogen exposure [124]. As previously mentioned, Africa has one of the highest disease burden rates. Therefore, HLA diversity decreases outside of Africa. Hence, HLA types that are present in Africa are different than other countries or among other ethnicities [124]. TB in Western Europe and malaria in Africa have been shown to drive some of these pressures of diversity on immune-associated genes [125]. HLA-C diversity is unlikely to be due to viral pathogens. The most protective HLA class I is HLA-B*57. HLA-B*57:01 and HLA-B*57:03 are the most widespread subtypes in Caucasian and African populations, presenting protection against HIV disease progression [126, 127]. This highlights the HLA allele differences and its effect on infectious diseases among different ethnicities. The genetic diversity in Africa is not fully understood. HLA-specific studies are imperative to fully understand the relationship between HLA and COVID-19 particularly in Africa.

The HLA molecule's role is not fully understood, and more HLA-based studies are required. HLA and COVID-19 studies' inconclusiveness and irreproducibility depend on the study groups, sample sizes, genetic variation, separation in phenotype definitions of selected alleles, HLA typing methods, and what type of studies are compared [36, 45, 46, 64, 72, 102]. The

different allele frequencies in studies vary between regions. Risk or protection alleles in certain findings have no relevance in other populations, because of their absence [89]. HLA and COVID-19 studies require bigger cohorts. Another limitation of these studies is that it is hard to determine the value of HLA in parallel with other disease risk considerations, like lifespan and co-existing conditions [128, 129].

Evidence suggests that including HLA in clinical trials and joining COVID-19 testing with HLA typing to determine which factors are associated with disease severity in different populations. However, some consistent patterns between HLA and SARS-CoV-2 relationships can contribute to explaining antigen presentation in related studies. The forecasts from immunoinformatics show the binding affinity of the pep-tide of SARS-CoV-2 to HLA-A and in silico investigations have shown the relevance of HLA in the risk of SARS-CoV-2 and its importance in vaccine targets [42, 47, 61, 83].

Despite Africa being highly burdened with infectious diseases, it has not been severely impacted by COVID-19 compared to other regions; researchers need to identify the host genetics in this region. In addition, the African population is the most genetically diverse among humankind [130]. Therefore, it is of utmost importance to focus on the impact of human genetics on infectious diseases in Africa.

5. Conclusions

GWAS results from large populations reported COVID-19 severity associations [131-133], but more studies in an African population are required. These findings may provide new insights into the SARS-CoV-2 pathogenesis, identify high-risk individuals, and decrease mortality and morbidity. Identifying individuals at high risk of SARS-CoV-2 could assist with averting viral spread and reduce the health burden.

Identifying alleles involved in protection will increase the discovery of SARS-CoV-2 target epitopes, which will support forthcoming vaccine research [134]. Regrettably, the data from advanced countries may not be relevant to other regions. Research needs to focus on HLA allele frequency and SARS-CoV-2 mutation data globally to unravel this pandemic efficiently and prevent future pandemics.

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CHAPTER 4 HLA-A expression contributes to COVID-19 disease severity within a South African cohort (Unpublished)

HLA-A expression contributes to COVID-19 disease severity within a South African cohort

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Abstract

SARS-CoV-2 had a devasting impact on the world thus far. There has been extraordinary research built on existing knowledge to rapidly develop vaccines. The Human Leukocyte Antigen (HLA) alleles have been previously demonstrated to be associated with COVID-19 severity. However, the *HLA* expression level's contribution towards COVID-19 is yet to be understood. Previous studies have shown that expression of *HLA* is associated with HIV, Parkinson's, Crohn's, and graft versus host disease. Within the *HLA* class I genes, *HLA-A* expression levels were found to be elevated in individuals who progress with HIV disease, while *HLA-C* demonstrated the converse. In this study, we focused our attention on the *HLA-A* gene, with the aim of examining the effect of *HLA-A* mRNA expression levels on COVID-19 disease severity. Real-time PCR confirmed SARS-CoV-2 infected individuals, from South Africa with Black and Indian ethnicities, were used to measure the *HLA-A* expression at the mRNA level. The *HLA-A* mRNA expression levels were used to associate with a range of disease outcomes as well as other contributing factors such as gender, age, ethnicity, and comorbidities. Furthermore, studies have highlighted the disparity among ethnic groups in COVID-19 disease progression. Therefore, in our study, we examined the contribution of *HLA-A* expression levels on COVID-19 across South African Blacks and South African Indians. Results from this study showed *HLA-A* mRNA expression levels associated with; (1) differences in disease severity amongst symptomatic and asymptomatic COVID-19 infected individuals (p=0.0005). (2) Significant differences between South African Black and South

African Indian ethnic groups ($p<0.0001$). (3) Males were significantly higher than females ($p=0.0041$). (4) Individuals with comorbidities demonstrated lower mRNA expression levels than individuals without comorbidities ($p=0.0020$). Amongst the comorbidities, noncommunicable diseases against no comorbidities demonstrated differences ($p=0.0158$). (5) Finally, the age of participants was also associated with *HLA-A* mRNA expression levels ($p=0.0353$). This study provides the first evidence demonstrating *HLA-A* mRNA expression levels are associated with COVID-19 disease. These findings highlight the importance of *HLA-A* expression levels as previously demonstrated within HIV disease.

Keywords: COVID-19, *HLA-A*, disease severity

Introduction

SARS-CoV-2 led to the COVID-19 pandemic (365) that started in China and dispersed to the rest of the world (366). Despite 175,475 deaths being reported within the entire African continent since the start of the pandemic, COVID-19 did not affect Africa as severely as other countries (367). This might be due to improved protocols, previous diseases, co-morbidities, age, and genetics. It has been almost five years ago, yet COVID-19 continues to infect individuals globally. COVID-19 pathogenesis research has been conducted with vigour and is quite extensive. Regardless of efforts, host factors involved in SARS-CoV-2 susceptibility and disease progression need to be properly understood. SARS-CoV-2 has a comparable genomic mutation rate to other RNA viruses (368-370), and studies show that COVID-19 mortality rates may be associated with the virus mutation rate (291). COVID-19 symptoms range from asymptomatic to severe infection, respiratory and organ failure, and death (332, 371). Furthermore, age and pre-existing conditions increase the risk of severe COVID-19 (366). The differences in COVID-19 susceptibility and severity between ethnicities are dependent on various factors such as genetics and lifestyle are important for pathogenesis.

Host genetics could be the key factor affecting disease susceptibility (372) and disease outcome diversity (21). The *HLA* system encoded by the Major Histocompatibility Complex (MHC) is responsible for pathogen detection and neutralization. *HLA* has been associated with COVID-19 infection and outcomes in different populations (267, 295, 329). *HLA* class I and II, vary significantly among ethnicities. The outcome depends on the presentation of viral peptides to killer T-cells (373, 374). An immune response to pathogens relies on their inherited

complement of *HLA*, influencing the effectiveness of an immune response (259, 375). *HLA* may be responsible for the variations in COVID-19 susceptibility and severity due to the polymorphisms in *HLA*. Other infectious diseases and autoimmune disorders outcomes have been correlated with host genetics that impact the immune response to SARS-CoV-2. *HLA* polymorphisms have influenced outcomes of other RNA viruses (305, 366).

HLA expression levels play a role in HIV. *HLA* class I molecule diversity determines peptide-binding specificity and has a vital influence on human disease pathogenesis. Deviation in certain *HLA* allele expression levels has also been associated with disease outcomes (376-381), emphasizing the importance of *HLA*. The greatly polymorphic *HLA* encodes cell surface proteins that are necessary for immunity. *HLA-A* expression levels change in an allotype-specific manner (382) but have many unique features. *HLA-A* is expressed at high levels on the cell surface (383). Transcriptional regulation mechanisms for the allele are also definite under good circumstances (382, 384, 385). These and other differences may affect how *HLA* affects human disease. *HLA-A* is associated with HIV disease. Ramsuran et al. showed that higher *HLA-A* levels lead to faster progression of HIV in a study with 9763 HIV-infected individuals from 21 cohorts (386). Increased *HLA-A* expression increases the *HLA-A* signal peptide levels that bind and regulate *HLA-E* expression levels, it is an inhibitory NKG2A natural killer (NK) cell receptor ligand. Therefore, inhibited HIV infected cell death. *HLA* expression was also associated with other diseases, such as Crohn's (387), cancer (388), Graft vs. Host disease (379), and Parkinson's (389).

In this paper, we investigated the contribution *HLA-A* expression levels have on COVID-19 disease severity and whether these variations are likely to influence the state of COVID-19 infection in an ethnic group. Furthermore, this is one of the first studies to show an association between *HLA-A* expression levels and COVID-19 disease and also shows to vary amongst race groups within South Africa.

Methods

A cohort of SARS-CoV-2 positive individuals of South African Black and South African Indian ethnicity were included in this study. SARS-CoV-2 diagnosis was agreed upon by using the TaqPath COVID-19 RT-PCR kit (Thermo Fisher Scientific) and the QuantStudio 5 Real-Time PCR system (Applied Biosystems, Woburn, MA, USA), as per the manufacturer's guidelines. SAP (SARS-CoV-2 Antibody Prevalence Study) is a longitudinal cohort. SARS-

CoV-2 infected individuals were recruited, after gaining informed consent from all individuals. Buffy coat samples were collected 6, 12, and 24 weeks post-infection between 2021 and 2022. The 6 weeks post-infection time point was used in this study (n=258). All demographic, clinical data, and personal information such as; age, race, gender, and symptoms, was obtained and samples were allocated unique identifiers. The ethnic groups were Black (n=147), and Indian (n=111) individuals within South Africa. Patients were grouped according to their infection severity including asymptomatic and symptomatic and then divided into ethnicity. Symptomatic participants presented at least one of the following symptoms: oxygen required, hospitalization, pneumonia, confusion, sore throat, loss of taste/smell, shortness of breath, nausea/vomiting, headache, body aches, fatigue, cough, fever, and chills. At the same time, asymptomatic participants did not present any of the following symptoms. Our study consisted of South African Blacks (n=147) and South African Indians (n=111), these individuals were broken down into categories based on their presence or absence of clinical presentation; South African Black asymptomatic (n=35) South African Black symptomatic (n=112) South African Indian asymptomatic (n=10) and South African Indian symptomatic (n=101).

Buffy coat samples and SARS-CoV-2-positive nasopharyngeal swabs (n=117) were obtained in this study.

Comorbidities were grouped into non-communicable (obesity, anemia hypertension, cardiovascular, asthma, diabetes, and cancer) and communicable disease (HIV).

For this study Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal, protocol reference number: BREC/ 00002648/2021.

We extracted nucleic acid from buffy coat samples as per the supplier's instructions; the extracted RNA was stored at 20ºC. Subsequently, cDNA was made using the iscript cDNA synthesis kit (BioRad) according to the company guidelines and then kept at -20 ºC. The *HLA-A* mRNA expression levels were obtained using a Real-Time PCR (RT-PCR) procedure (Thermo Fisher Scientific) on the QuantStudio 5 instrument as per the manufacturer's guidelines. In brief, the PowerUp SYBR Green Master Mix (ThermoFisher Scientific) was made as per manufacturer recommendations, and RT-PCR was performed. RT-PCR cycling

Conditions and catalogue numbers for *HLA-A* are accessible upon request. The conditions and primers used are as previously published (382).

Statistical and Bioinformatics Analysis

For our analysis was used GraphPad Prism 8 software. T-tests were used to compare variables; categorical variables were analyzed using Fisher's exact tests. We also used a one-way ANOVA T-test Bonferroni to test to correct for multiple testing. A p-value of less than 0.05 was considered statistically significant.

To test whether *HLA-A* mRNA expression levels are associated with COVID-19, we examined COVID-19-infected individuals of different ethnicities recruited from South Africa, in which the estimated effect of disease severity, race, gender, ethnicity, comorbidities, and age on *HLA-A* among COVID-19 infected individuals. We included South African Indians and South African Blacks in this study. We determine the *HLA-A* mRNA expression levels in South African Indians and South African Blacks.

Results

***HLA-A* mRNA expression levels across different disease severity**

We investigated the effect of *HLA-A* mRNA expression levels on COVID-19 severity in positive COVID-19 individuals. The *HLA-A* mRNA expression levels mean and p-values are presented in the figures. For all individuals, *HLA-A* mRNA expression levels are significantly lower in symptomatic individuals, suggesting its protection against COVID-19 (95% CI -21.56 to-6.466; asymptomatic mean=19.48; symptomatic mean=5.461; p=0.0005, Figure 1).

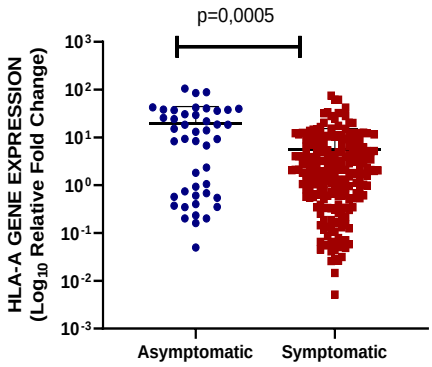
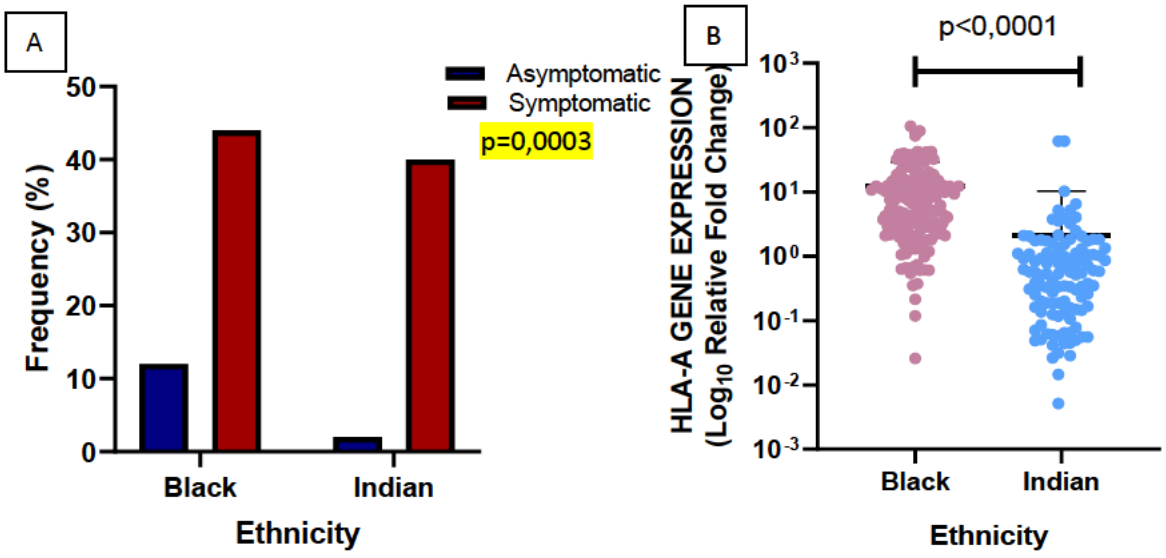


Figure 1: *HLA-A* mRNA expression levels measured within symptomatic and asymptomatic COVID-19 infected individuals. We compared *HLA-A* mRNA expression levels among symptomatic and asymptomatic individuals from South Africa. There was a significant association between asymptomatic (blue dots) and symptomatic (red squares) (p=0.0005).

HLA-A mRNA expression levels across different ethnic groups

We first, looked at the relationship between ethnicity and disease severity, we then analyzed the effect on *HLA-A* mRNA expression levels among different ethnic groups. We found a significant difference between COVID-19 infected South African Blacks and South African Indians who were asymptomatic and symptomatic (p=0.003; Figure 2A). This indicates that COVID-19 severity is associated with ethnicity. South African Black individuals have higher *HLA-A* mRNA expression levels than South African Indian individuals (95% CI -13.34 TO -7.079; South African Black mean=12.30, South African Indian mean 2.089; p<0.0001, figure 2B). There is a significant difference between symptomatic and asymptomatic South African Blacks (p=0.0013). Similarly, there is a significant difference between symptomatic and asymptomatic South African Indians (p=0.0464) (Figure 2C). *HLA-A* mRNA expression levels are higher among South African Black asymptomatic and symptomatic individuals than among South African Indian asymptomatic and symptomatic individuals (p>0.0001; p>0.0001) respectively, suggesting significant protection in South African Black individuals (mean asymptomatic South African Black =24.9; mean symptomatic South African Black =8.36; mean asymptomatic South African Indian=0.493; mean symptomatic South African Indian=0.553; Figure 2C).



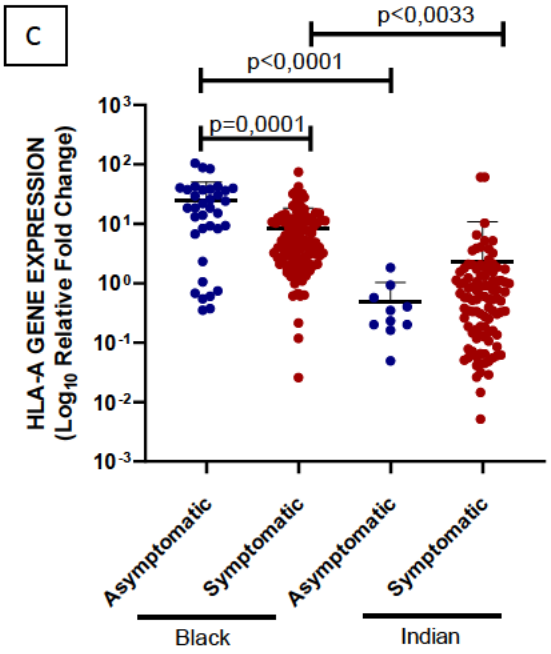


Figure 2: (A) The frequency of South African Black and South African Indian individuals that are asymptomatic and symptomatic. There was a significant difference between ethnicity and disease severity (p=0.0003) (B) *HLA* mRNA expression levels among COVID-19 infected South African Black and South African Indian individuals. South African Black individuals (red dots) had significantly higher *HLA-A* mRNA expression levels than South African Indian individuals (blue dots) (p<0.0001). (C) *HLA-A* mRNA expression levels among COVID-19 infected symptomatic and asymptomatic South African Blacks and South African Indians. There is a significant association between *HLA-A* in South African Black asymptomatic (blue dots) and South African Black symptomatic (red dots) (p<0.0001). Similarly, this was also observed among South African Indian asymptomatic (blue dots) and South African Indian symptomatic (red dots) (p>0.9999). South African Indian asymptomatic individuals were higher than symptomatic individuals, this could be due to the small sample size. In addition, we observed significantly higher *HLA-A* mRNA expression levels between asymptomatic South African Black and asymptomatic South African Indians, and symptomatic South African Black and symptomatic South African Indian respectively, (p<0.0001) (p<0.0033).

HLA-A mRNA expression levels across different genders

We analyzed the relationship between gender and COVID-19 disease severity. We did not find an association between ethnicity and COVID-19 disease severity (p=0.1088, Figure 3A). We then observed the effect of gender on *HLA-A* mRNA expression levels. Males had significantly higher *HLA-A* mRNA expression levels than females (Females means=5.556, males

mean=11.50; p=0.0041). *HLA-A* mRNA expression levels of males asymptomatic were higher than asymptomatic females (p=0.1399; Figure 3B). However, the difference was not significant. *HLA-A* mRNA expression levels were significantly different between asymptomatic males and symptomatic males (p=0.0144). (Male asymptomatic mean=27.6; male symptomatic mean=6.97; female asymptomatic=12.0; female symptomatic=4.55, Figure 3C).

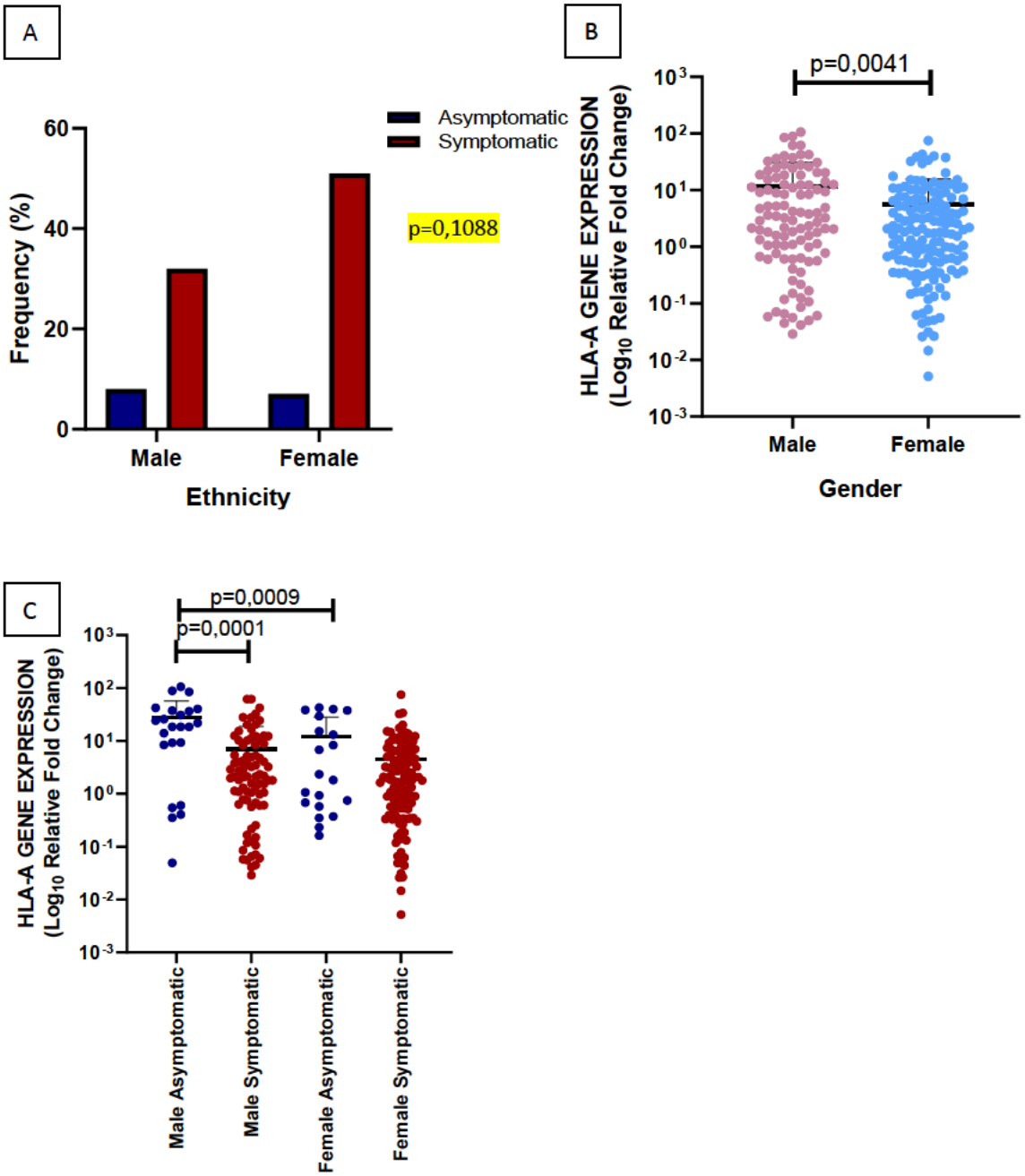


Figure 3: (A) The frequency of males and females that are asymptomatic and symptomatic. There was no significant difference between asymptomatic males and females and

symptomatic males and females (p=0.1088). (B) *HLA-A* mRNA expression levels of infected COVID-19 South Africans among different genders. A comparison of *HLA-A* mRNA expression levels between COVID-19 infected South Africans of different genders. There is a significant difference between *HLA-A* mRNA expression levels in males (red dots) and females (blue dots) (p=0.0041). Males had significantly higher *HLA-A* expression levels than females. (C) *HLA-A* mRNA expression levels among different genders and clinical presentations. A comparison between symptomatic and asymptomatic males, and symptomatic, and asymptomatic females. *HLA-A* is significantly higher in asymptomatic males (blue dots) than in symptomatic males (red dots) (p<0.0001). Similarly, *HLA-A* expression levels were higher in asymptomatic females (blue dots) than in symptomatic females (red dots) (p=0.1198). However, the difference was not significant. Asymptomatic males (blue dots) and asymptomatic females (red dots) were significantly different (p=0.0009). *HLA-A* expression levels between symptomatic males (blue dots) were not significantly higher than symptomatic females (red dots) (p>0.9999).

HLA-A mRNA expression levels across existing comorbidities

In addition, we analyzed the relationship between COVID-19 severity and comorbidities. We found an association between COVID-19 severity and existing comorbidities (p=0.0528, Figure 4A). The effect of comorbidities on *HLA-A* expression. There is a significant association between *HLA-A* mRNA expression levels among COVID-19 infected individuals with (blue dots) and without comorbidities (red dots) (95% CI= -8.556 to -1.932; no comorbidities mean=9.835, comorbidities mean=4.591; p=0.0020, Figure 4B). We then divided the comorbidities into communicable and non-communicable diseases. We observed a significant difference between no comorbidities and communicable diseases (p=0.0158; no comorbidities mean=10.1, communicable disease mean=5.65, noncommunicable disease=4.63, Figure 4C). We further divided the communicable and non-communicable diseases (no comorbidities mean=9.83, HIV mean=5.65, hypertension mean=5.05, asthma mean=5.43, anemia mean=2.49, cardiovascular disease mean=2.55, diabetes mean=0.877). There was a significant difference between no comorbidities and cardiovascular disease, as well as no comorbidities and diabetes respectively (p=0.0456; p<0,0001; Figure 4D).

A

B

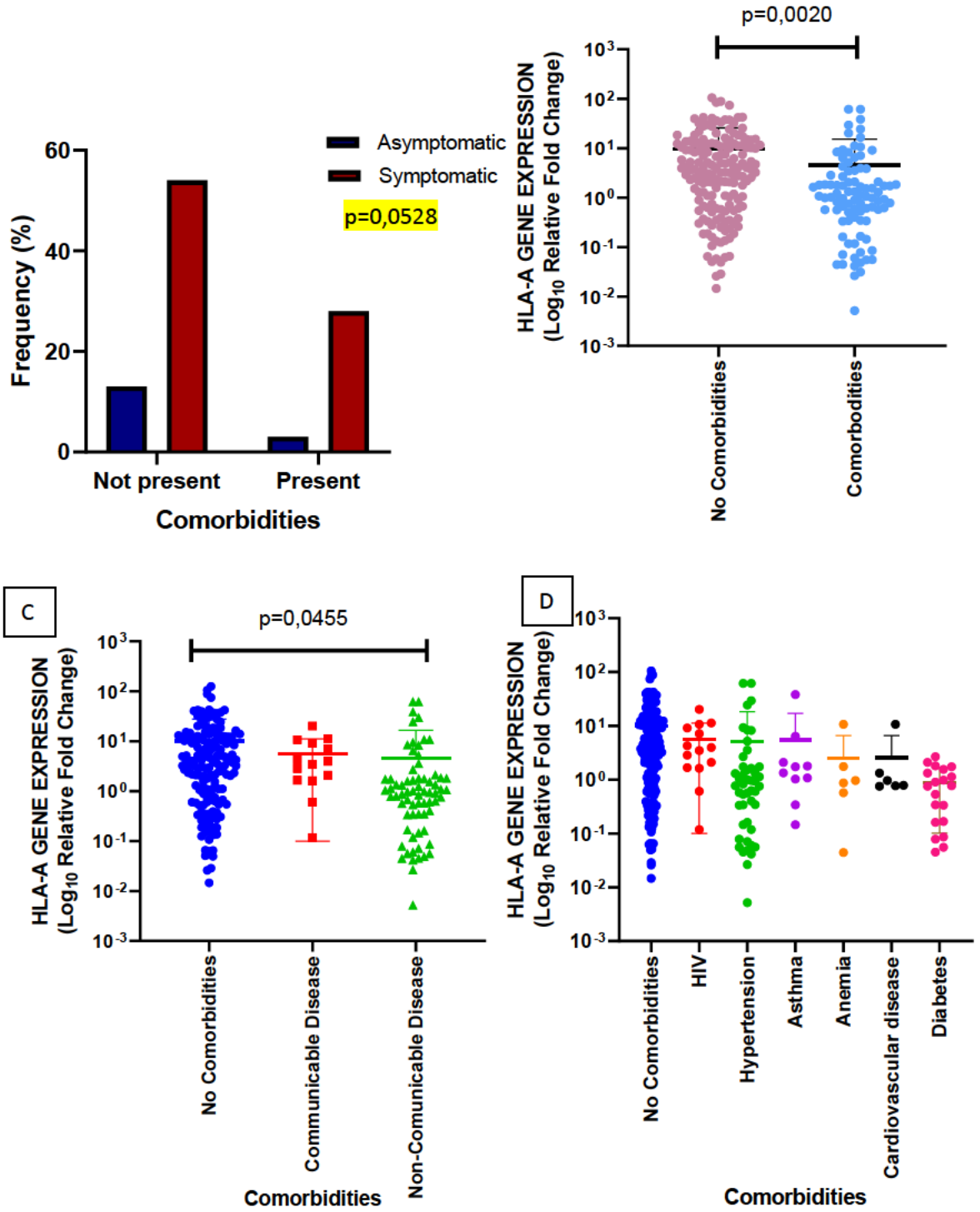


Figure 4: (A) The frequency of individuals that did or did not present with comorbidities that are asymptomatic or symptomatic. There was no significant difference between asymptomatic (blue) and symptomatic (red) individuals who did and did not present comorbidities (p=0.0528). (B) *HLA-A* mRNA expression levels between COVID-19-infected individuals within South Africa with and without comorbidities. A comparison between *HLA-A* among COVID-19 infected individuals with or without comorbidities. There is a significant

association between *HLA-A* mRNA expression levels among COVID-19 infected individuals with (blue dots) and without comorbidities (red dots) (p=0.0020). (C) *HLA-A* mRNA expression levels among individuals with communicable disease, non-communicable disease, and no comorbidities. There was no significant difference between communicable disease (red squares) and no comorbidities (blue dots). Individuals with no comorbidities were significantly higher than individuals with non-communicable diseases (p=0.0455). (D) There were no significant differences between any of the comorbidity categories.

HLA mRNA expression levels across different age groups

Finally, we examined the relationship between age and disease severity. We did not find an association between age and COVID-19 disease severity (p=0.6709, Figure 4A). Thereafter, we determined the effect of age groups on *HLA-A* mRNA expression levels in COVID-19 infected individuals. Previously, COVID-19 disease was associated with age. We observed that ages 18-25 were significantly higher than 45-55, and over 65 respectively (p=0.0446, p=0.0353). In addition, we also observed that 26-35 years was significantly higher than over 65 (p=0.0413, Figure 4B).

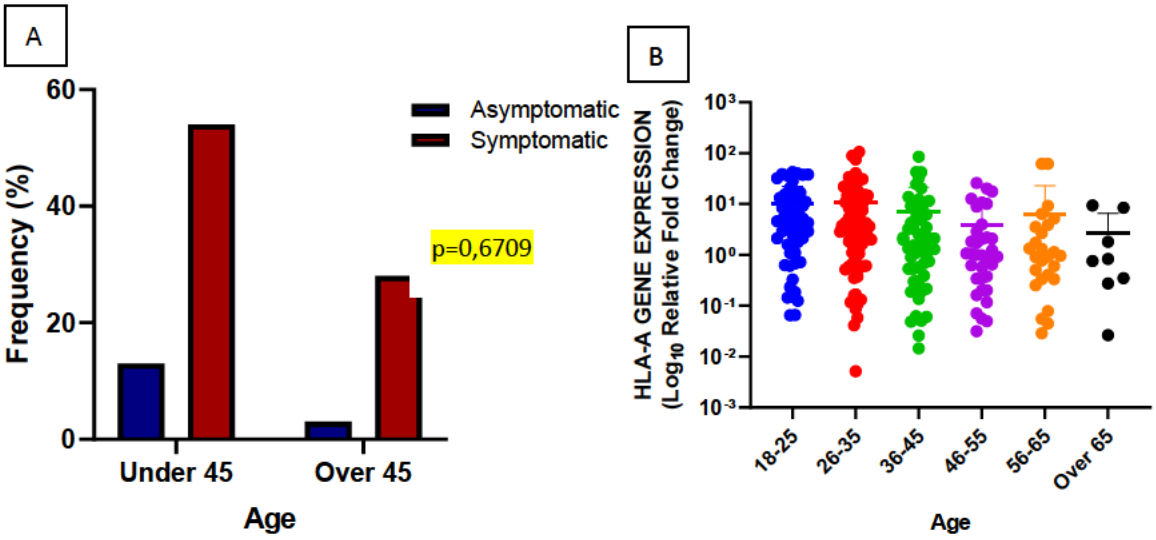


Figure 5: The frequency of individuals who are under and over 45 years that are asymptomatic and symptomatic. Asymptomatic (blue) Symptomatic (red). There is no significant difference between disease severity and ages below and above 45 (p=0.4249). (B) *HLA-A* mRNA expression levels and age among COVID-19 infected individuals within South Africa. A comparison between *HLA-A* among COVID-19 infected individuals and age. 18-25 (blue dots), 25-35 (red dots), 35-45 (green dots), 45-55 (purple dots), 55-65 (orange dots), >65 (black dots). We observed no significant difference between any of the age groups.

Discussion

This study aimed to determine the effects of *HLA-A* mRNA expression levels on COVID-19. Ramsuran et al. showed that higher *HLA-A* levels lead to faster progression of HIV (386). Increased *HLA-A* expression increases the *HLA-A*–derived signal peptide levels that bind and regulate *HLA-E* expression levels. Opposite to the HIV analysis among sub-Saharan Africans, elevated *HLA-A* mRNA expression levels were significantly associated with asymptomatic infection. COVID-19 uses the antigen presentation cell pathway rather than the NK cells mechanism. HIV-1 is primarily within T cells, while COVID-19 is within monocytes. The function of NK cells is weakened in COVID-19 infected individuals. They are unable to kill infected cells and prevent the virus from spreading (390). As previously mentioned, *HLA* class I molecule diversity determines peptide-binding specificity and has a critical impact on pathogenesis.

Ethnicity, gender, comorbidities, and age have been previously associated with COVID-19 outcomes. These contributing factors are analyzed in this study. We suggest that *HLA-A* mRNA expression level plays a role in COVID-19 pathogenesis and the expression level might be influenced by these contributing factors.

We observed a significant difference between South African Blacks and South African Indians and their disease severity ($p=0.0003$). Mackey et al showed disparities in COVID-19 among African American/Black and Hispanic and non-Hispanic white populations. In this study, they observed higher COVID-19 rates in African Americans compared to the White population (391). Other studies showed a similar trend, in the USA the minority groups were more prone to hospitalization and death than the white populations. In 2021, Latinx made up 27% of the COVID-19 infections, while the Black population made up for 12% of all infections (392). There is limited knowledge regarding disparities among South African ethnicities. This indicates that ethnicity plays a role in COVID-19 outcomes. Symptomatic individuals had significantly lower *HLA-A* mRNA expression levels than asymptomatic individuals. This was expected as COVID-19 uses a different identification mechanism compared to HIV. South African Black asymptomatic and symptomatic individuals ($p=0.0001$) had a significant difference compared to South African Indians ($p=0.9999$). Asymptomatic South African Indians and South African Blacks showed a significant difference ($p<0.0001$). These results suggest that South African Black individuals might be less symptomatic or susceptible to

disease. There was no significant difference between symptomatic South African Indians and asymptomatic South African Indians. This could be due to the sample size of asymptomatic South African Indians. Naidoo et al. 2023, reviewed the differences observed between ethnic groups are expected as this is observed in various other diseases (12). This explains the reason for the variation in severity and effect across different ethnic groups globally.

We did not observe a significant difference between the frequency of males and females and disease severity (p=0.1088). Interestingly, (p=0.0041) males had higher *HLA-A* mRNA expression levels compared to females. This might suggest that females are more susceptible to COVID-19 and have more symptomatic infection. *HLA-A* is significantly higher in asymptomatic males than in symptomatic males (p=0.0001). Similarly, *HLA-A* mRNA expression levels were higher in asymptomatic females than in symptomatic females (p=0.1198). However, the difference was not significant. Asymptomatic males and asymptomatic females were significantly different (p=0.0009). *HLA-A* mRNA expression levels between symptomatic males were not significantly higher than symptomatic females (p>0.9999). Some studies showed an association between *HLA* class I alleles and gender (310, 393) while others did not (394).

There was a marginally significant difference observed between disease severity and comorbidities (p=0.0528). However, this might be due to the smaller sample size among the asymptomatic individuals, since the results are trending towards significance. Therefore, unclear whether the higher HLA-A expression also found in people without comorbidities is related to a lower risk of developing symptoms. Comorbidities might play a role in COVID-19 outcomes. In addition, we observed a significant association between *HLA-A* mRNA expression levels among COVID-19 infected individuals with and without comorbidities (p=0.0020). We then divided the comorbidities into communicable and non-communicable diseases. We observed a significant difference between no comorbidities and communicable diseases (p=0.0455). There was a significant difference between any of the medical conditions, comorbidities, and no comorbidities. Comorbidities are associated with *HLA-A* mRNA expression levels in COVID-19 infected individuals. Indicating that noncommunicable diseases such as diabetes and cardiovascular disease play an important role in COVID-19 disease severity. This is in line with previous studies, HLA-A*11:01:01:01, and type 2 diabetes was significantly associated with COVID-19 severity (p=0.0014) (310). In addition, WHO reported that diabetes and cardiac disease were associated with the risk of severe COVID-

19(395). However, communicable diseases are not associated with *HLA-A* mRNA expression levels among COVID-19 infected individuals.

HLA-A mRNA expression levels vary across ethnicities, states of disease, comorbidities, and age indicating that together determine the mRNA expression level. COVID-19 deaths in Lusaka and Zambia occurred regardless of age and it has been stated that COVID-19 was the prominent reason for death through the peak of infection caused by the Beta and Delta SARS-CoV-2 variants, approximately, 90% of late individuals were SARS-COV-2 positive (396). Among the African populations, COVID-19 has been less severe and fatal compared to other regions. Age has been previously associated with increased or worse disease progression (310, 393). There is no significant difference between age frequency and disease severity (p=0.6709). There was no significant difference observed between any of the age groups, which may be because all types of symptoms, including chills and sore throat, were compared with asymptomatic rather than severe vs mild COVID-19 or severe illness vs asymptomatic.

Elderly individuals, male sex and comorbidities are known risk factors for COVID-19, an association of these factors with the clinical presentation should be expected but was shown for sex and comorbidities. The low sample size might be the reason for these findings, The analysis could be improved by analyzing more extreme severities, such as severe COVID-19 vs. asymptomatic. The detailed metadata available is a strong point of the study, as is the availability of infected but asymptomatic controls instead of population controls.

HLA-E Expression is reliant on secure binding signal peptides from *HLA-A* (13, 14). These results reinforce that enhanced *HLA-A* expression levels are beneficial for COVID-19. Our data and these previous studies indicate that variation in expression level contributes to the complexity of the relationship between *HLA* and COVID-19 disease, a trend noticed for class I in other species (29). The antibody monalizumab is a therapeutic strategy that is in trials for the therapy of rheumatoid arthritis, stem-cell transplantation, and cancer, because of the HLA-E–mediated immunosuppression role in these disorders (30, 31). These statistics indicate that antagonizing HLA-E/NKG2A relations, will not be beneficial in COVID-19 disease. Therapeutics that aim to increase the HLA-A mRNA expression levels will be beneficial for COVID-19 infected individuals. The shortcoming of this study was the small cohort size. Our study consisted mainly of middle-aged individuals. Furthermore, our age groups started from 18 years and above. The results from this study do not include post-transcription effects.

More research is essential to conclude the effect of *HLA-A* expression on COVID-19 and how other contributing factors contribute to *HLA-A* expression, especially in Africa. Due, to the multiple ethnicities found in South Africa, our study reflects the genetic diversity. Individuals at a higher risk of a particular disease should be prioritized, this will impact the ultimate spread of a pathogen. We will be able to determine high-risk individuals through genetic impact on disease outcomes.

Conclusion

Africa was a major concern at the arrival of COVID-19, due to the high infectious disease rate and being a third-world continent. However, to everyone's surprise, Africa was not as drastically affected. In this study, we show *HLA* expression levels differ among different ethnic groups in South Africa. In addition, we observed that *HLA-A* expression levels are associated with COVID-19. We observed that South African Blacks have higher *HLA* mRNA expression levels than South African Indians. We also showed that comorbidities are associated with COVID-19 and *HLA* mRNA expression levels. This study provides substantial evidence that COVID-19 disease states are dependent on host genetics.

Author Contributions

Conceptualization, V.R.; Data curation, review & edit; Writing—original draft, L.N. (Lisa Naidoo); Writing—review & editing, T.A. (Thilona Arumugam). All authors have read and agreed to the published version of the manuscript.

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Informed consent was obtained from all subjects involved in the study.

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CHAPTER 5 HLA-B and C expression contribute towards COVID-19 disease severity within a South African cohort. (Published in Genes, DOI: 10.3390/genes15040522).

HLA-B and *C* expression contribute towards COVID-19 disease severity within a South African cohort.

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Abstract

Globally, SARS-CoV-2 has negatively impacted many lives and industries. SARS-CoV-2 disease severity varies among different populations. Host genetics have been associated with various diseases, and their ability to alter disease susceptibility and severity. In addition, Human Leukocyte Antigen (*HLA*) expression levels and alleles vary significantly among ethnic groups, which might impact the host's response to SARS-CoV-2. Our previous study has highlighted that *HLA-A* might have an effect on COVID-19 disease severity across ethnicities.

Therefore, in this study, we aim to examine the effect of *HLA-B* and *C* expression levels on COVID-19 disease severity. To do this, we used Real-time PCR to measure the *HLA* mRNA expression levels of SARS-CoV-2 infected individuals from a South African cohort and compared them across ethnic groups, disease outcomes, gender, comorbidities, and age. Our results show (1) that the effect of *HLA-B* mRNA expression levels was associated with differences in disease severity when we compare symptomatic vs asymptomatic ($p<0.0001$). While *HLA-C* mRNA expression levels were not associated with COVID-19 disease severity. (2) In addition, we observed that *HLA-B* and *HLA-C* mRNA expression levels were significantly different between South African Blacks and South African Indians ($p<0.0001$, $p<0.0001$). *HLA-B* mRNA expression levels among symptomatic South African Blacks were significantly higher than symptomatic South African Indians ($p<0.0001$). This was also seen in asymptomatic South African Blacks and asymptomatic South African Indians ($p<0.0001$). In addition, the *HLA-B* mRNA expression levels of symptomatic South African Blacks were significantly higher than asymptomatic South Blacks, and, symptomatic South African Indians were significantly higher than asymptomatic Indians, respectively ($p>0.0001$, $p>0.0001$). *HLA-C* mRNA expression levels among symptomatic South African Blacks were significantly higher than among symptomatic South African Indians ($p=0.0034$). This was also seen in asymptomatic South African Blacks and asymptomatic South African Indians ($p=0.006$). In addition, the *HLA-C* mRNA expression levels of symptomatic Indians were significantly higher than asymptomatic Indians ($p<0.0001$) (3) *HLA-B* mRNA expression levels were only significantly different between symptomatic and asymptomatic females ($p<0.0001$). However, *HLA-C* expression levels were significantly different between males and females ($p=0.0052$). (4) *HLA-B* expression levels were significantly different between individuals with and without comorbidities ($p=0.0009$). In addition, we observed a significant difference between individuals with no comorbidities and non-communicable diseases ($p=0.0001$), in particular, diabetes ($p=0.0002$) and hypertension ($p=0.0011$). *HLA-C* expression levels were only significantly different between no comorbidities and anemia ($p=0.0003$) and cardiovascular disease ($p=0.0246$). (5) *HLA-B* expression levels were significantly different between individuals between the ages 18-26 and 56-65 years ($p=0.009$), as well as 26-35 and 56-65 years ($p=0.0018$). Our work is expected to strengthen the understanding of the relationship between *HLA* and COVID-19, by providing insights into *HLA-B* and *C* expression levels across ethnic populations in South Africa among COVID-19 symptomatic and asymptomatic individuals. Our results highlight that *HLA-B* mRNA expression levels contribute to COVID-19 severity as well as variation in ethnicities associated with COVID-19. Further studies are

needed to examine the effect of *HLA* expression levels across various ethnic groups with contributing factors.

Keywords: COVID-19, *HLA-B, HLA-C,* disease severity

Introduction

COVID-19, a serious health burden, has severely and quickly disrupted the world in various ways (366). SARS-CoV-2, the cause of COVID-19, will continue to mutate and escape the human immune response and human therapeutics for years to come until serious innovations to eliminate the virus are implemented. Since viral genetics changes rapidly, it would be more beneficial if we focus our attention on host genetics. More research on host genetic factors and their role in SARS-CoV2 susceptibility and disease progression is required. COVID-19 severity rates have been associated with viral mutations (291). COVID-19 has been associated with a range of symptoms from asymptomatic, and mildly symptomatic to severe infection, and death (332, 371). The varying severity experienced during COVID-19 could be attributed to host genetics. Africa was not as severely affected, due to contributing factors such as; other infectious diseases, co-morbidities, age, and genetics. Elder individuals and individuals with comorbidities are at risk for severe COVID-19 (366). Identifying host genes associated with these contributing factors and lower COVID-19 severity among the African population is imperative. The disparities in COVID-19 outcomes are multifactorial. Therefore, it is important to include these factors in research.

Host genetics has been shown to have a significant impact on disease outcomes (21, 372). The *HLA* system is the first line of defense and it is imperative for the identification of foreign particles and immune response. An effective immune response is dependent on the presentation of the virus to the host cell surface (259, 373-375). Other infectious diseases and disorders have been associated with *HLA*. *HLA* polymorphisms have impacted the severity of other RNA viruses like SARS-CoV-2 (305, 366). Therefore, other studies have analyzed *HLA* and shown the growing evidence of its importance in COVID-19 pathogenesis (267, 295, 329). Varying *HLA* alleles and expression levels may lead to different peptide presentations, which may lead to different individuals having varying COVID-19 susceptibility and severity. *HLA* has been suggested as a potential genetic host factor that influences individual immune responses to SARS-CoV-2. Our previous study showed that *HLA* class I, *HLA-A,* a highly polymorphic gene, varies significantly among different ethnicities and is associated with COVID-19 disease

severity (397). *HLA-B* and *C* were associated with COVID-19 disease in other populations such as Brazilian, Western Indian, Egyptian, Spanish, Asian, European, Chinese, Vietnamese, Taiwanese, Hong Kong Chinese, Italian, and Ecuadorians. Increased *HLA-C* expression was associated with protection against HIV-1 (356). *HLA-C* is responsible for acting as a ligand for natural killers and immunoglobulin receptors (398). Some *HLA* alleles have been associated with mild COVID-19 when compared to severe COVID-19 (297). *HLA-B* expression has also been associated with Behçet's disease (399). *HLA-B* plays a role in peptide presentation. *HLA-B* alleles have been associated with COVID-19 (21, 285). In addition, *HLA-B* expression has been associated with SARS-CoV-2 infected human lung cells (400).

In this paper, we investigated the *HLA-B* and *C* expression levels across South African ethnicities, and whether these expression level variations influence COVID-19 severity in a different ethnic group. Real-time PCR was used to identify the *HLA* expression levels. To our knowledge, this was the first study to analyze the relationship between *HLA-B* and *HLA-C* mRNA expression levels and COVID-19 severity in different South African ethnicities.

Methods

In this study, we used a cohort of SARS-CoV-2 positive individuals (SARS-CoV-2 Antibody Prevalence Study (SAP; n =591)). These individuals were South African Blacks and South African Indians. SARS-CoV-2 diagnosis was performed by using the TaqPath COVID-19 RT-PCR kit (Thermo Fisher Scientific) and the QuantStudio 5 Real-Time PCR system (Applied Biosystems, Woburn, MA, USA), as per the manufacturer's directions. This was a longitudinal cohort of SARS-CoV-2 infected individuals. In 2021 and 2022 buffy coat samples (n =560) were gathered at 6 weeks post infection. SARS-CoV-2-positive nasopharyngeal swabs (n =117) were also obtained. All samples along with the necessary information such as; demographic, clinical data, personal information (age, gender, race), and informed consent were obtained. The ethnic groups analyzed were South African Black (n =147), and South African Indian (n =111) individuals. We grouped patients into two groups according to their infection severity, which included South African Black asymptomatic (n=35), South African Black symptomatic (n=112), South African Indian asymptomatic (n=10), and South African Indian symptomatic (n=101).

Symptomatic participants presented at least one of the following symptoms: oxygen required, hospitalization, pneumonia, confusion, sore throat, loss of taste/smell, nausea/vomiting,

headache, shortness of breath, body aches, fatigue, cough, fever, or chills. Asymptomatic participants did not present any symptoms. We grouped comorbidities into non-communicable (obesity, anemia, hypertension, cardiovascular, asthma, diabetes, and cancer) and communicable disease (HIV).

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal, protocol reference number: BREC/00002648/2021

To test whether *HLA-B* and *C* mRNA expression levels were associated with COVID-19, and their contributing factors such as age, gender, comorbidities, disease severity, and ethnicity, we examined COVID-19-infected individuals of different ethnicities recruited from South Africa, in which the estimated effect of each *HLA* allele on COVID-19 and its contributing factors were reported.

Nucleic acid was extracted from buffy coat samples as per the manufacturer's directions; the RNA extraction was stored at 20ºC. Thereafter, cDNA was prepared using the iscript cDNA synthesis kit (BioRad) according to manufacturer guidelines and then stored at 20ºC. The *HLA-B* and *HLA-C* mRNA expression levels were obtained using a Real-Time PCR (RT-PCR) protocol (Thermo Fisher Scientific) on the QuantStudio 5 instrument as per the manufacturer's guidelines. PowerUp SYBR Green Master Mix (ThermoFisher Scientific) was prepared as per manufacturer guidelines, and RT-PCR was performed. RT-PCR cycling conditions and catalogue numbers for *HLA-B* and *HLA-C* are available on request. The RT-PCR conditions and primers used are as previously published (382).

Statistical and Bioinformatics Analysis

GraphPad Prism 8 software was used for analysis. The T-test was used to compare variables; categorical variables were analyzed using Fisher's exact tests. A p-value of less than 0.05 was considered statistically significant.

Results

***HLA-B* and *C* mRNA expression levels across different COVID-19 disease severity**

In this study, we investigated the effect of *HLA-B* and *HLA-C* mRNA expression levels on COVID-19 severity in positive COVID-19 individuals. The *HLA-B* mRNA expression levels

mean and p-values are summarized in the figures. For all individuals, *HLA-B* mRNA expression levels were significantly lower in symptomatic individuals, suggesting protection against COVID-19 (95% CI 0.4463 to 1.052; asymptomatic mean=0.6389; symptomatic mean=1.388; p=0.0001, Figure 1).

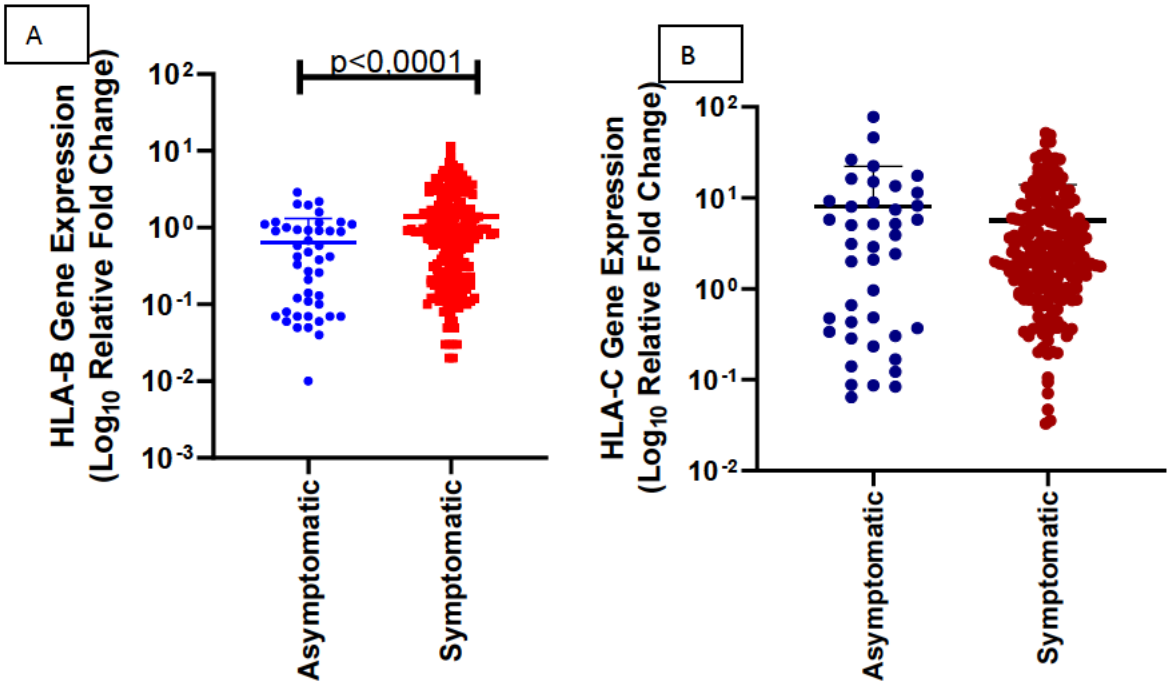


Figure 1: *HLA-B* mRNA expression levels among symptomatic and asymptomatic COVID-19-infected individuals. There was a significant difference between symptomatic (red squares) and asymptomatic (blue dots) individuals. Asymptomatic individuals were significantly lower than symptomatic individuals (p=0.0001, Figure 1A). *HLA-C* mRNA expression levels among COVID-19-infected individuals of different disease severity. There is no significant difference between asymptomatic (blue) and symptomatic individuals (red) (p=0.2914, Figure 1B).

HLA-B and *HLA-C* mRNA expression levels across different ethnic groups

We first, looked at the relationship between ethnicity and disease severity We saw an association with disease severity and ethnicity (p=0.0003, Table 1). (A) We then analyzed the relationship between *HLA-B* mRNA expression levels and different ethnic groups. South African Black individuals have significantly higher *HLA-B* mRNA expression levels than South African Indian individuals (95% CI -1.835 to -1.225; South African Black mean=1.914, South African Indian mean 0.3837; p<0.0001, Figure 2A). (B) In addition, we look at the *HLA-B* mRNA expression levels between ethnicity and disease severity. There is a significant difference between symptomatic and asymptomatic South African Blacks (p<0.0001).

Similarly, there is a significant difference between symptomatic and asymptomatic South African Indians ($p<0.0001$). *HLA-B* mRNA expression levels are higher among asymptomatic South African Black than asymptomatic South African Indian individuals, and symptomatic South African Black individuals and symptomatic South African Indian individuals ($p<0.0001$; $p<0.0001$) respectively, suggesting significant protection in South African Black individuals (mean asymptomatic South African Black=0.799; mean symptomatic South African Black=2.26; mean asymptomatic South African Indian=0.0838; mean symptomatic South African Indian=0.414; Figure 2B). (B) We also observed the effect of ethnicity on *HLA-C* mRNA expression levels. South African Black individuals have significantly higher *HLA-C* mRNA expression levels than South African Indians (95% CI -6.636 to -2.497, South African Black mean=7.969, South African Indian mean=3.403, $p=0.0001$, Figure 2C). (D) In addition, we looked at the *HLA-C* mRNA expression levels between ethnicity and disease severity. (South African Black asymptomatic mean=9.99, South African Black symptomatic mean=7.38, South African Indian asymptomatic mean=0.290, South African Indian symptomatic mean=3.65; Figure 2D). *HLA-C* mRNA expression levels were significantly higher in South African Black symptomatic than in South African Indian symptomatic individuals ($p<0.0034$). The *HLA-C* mRNA expression levels of asymptomatic South African Black individuals were significantly higher than asymptomatic South African Indians ($p<0.006$). Symptomatic South African Indians *HLA-C* mRNA expression levels were significantly higher than asymptomatic South African Indians ($p<0.0001$).

Table 1: The frequency of South African Black and South African Indian individuals who are asymptomatic and symptomatic.

Ethnicity	**Asymptomatic**	**Symptomatic**	**Total**	**p-value**
South African Black	33	115	148	
South African Indian	7	106	113	
Total	40	221	261	0.0003

There was a significant difference between ethnicity and disease severity ($p=0.0003$)

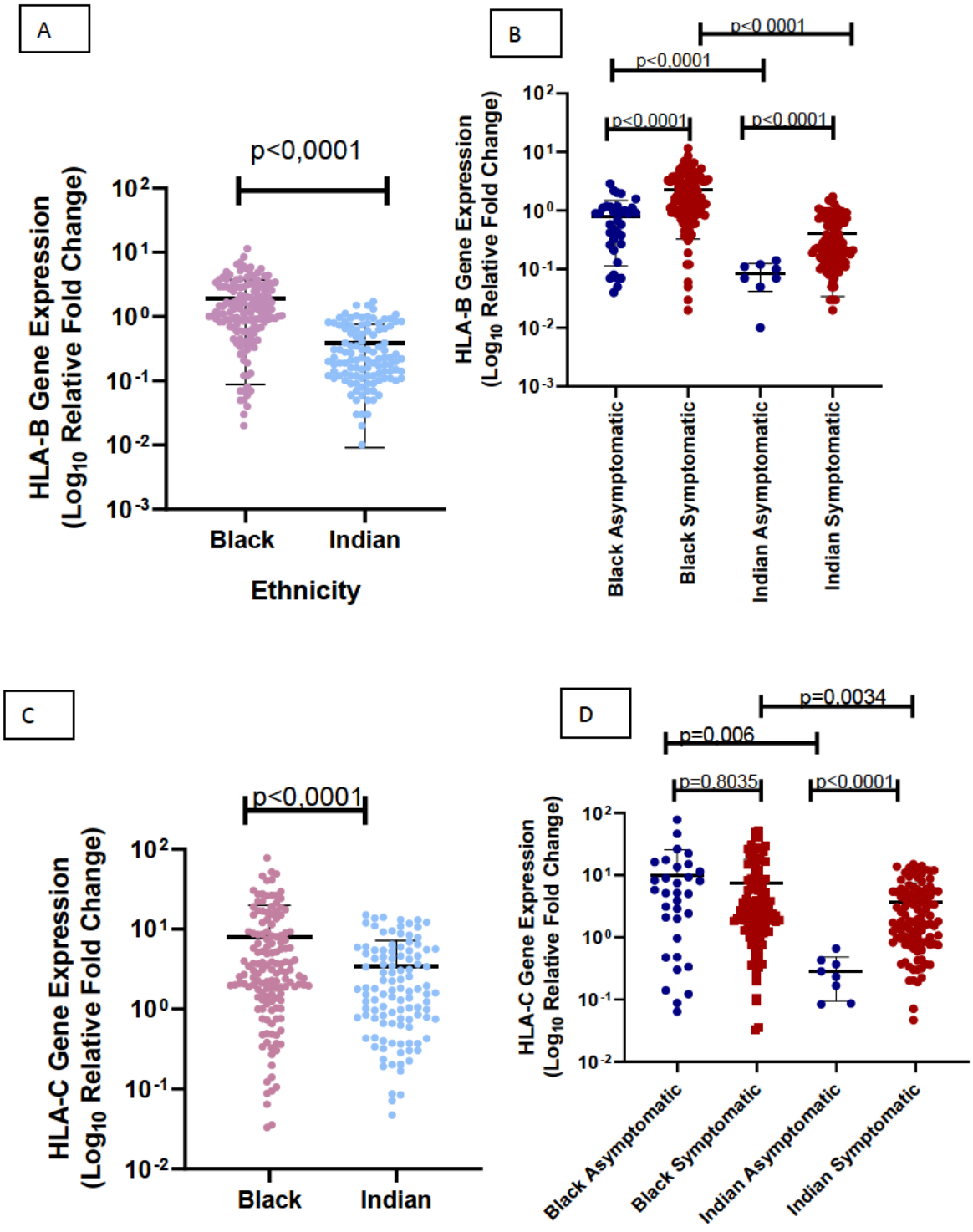


Figure 2: (A) *HLA-B* mRNA expression levels among different ethnic groups. We found that South African Black individuals' *HLA-B* mRNA expression levels are significantly higher than South African Indians' (p=0.0001). (B) *HLA-B* mRNA expression levels among symptomatic and asymptomatic individuals of South African ethnicity. A comparison between South African Black symptomatic, South African Black asymptomatic, South African Indian symptomatic, and South African Indian asymptomatic. There is a significant association

between *HLA-B* in South African Black symptomatic (red dots) and South African Black asymptomatic (blue dots) ($p<0.0001$). *HLA-B* mRNA expression levels were significantly higher in South African Black symptomatic (red dots) than in South African Indian symptomatic (red dots) individuals ($p<0.0001$). The *HLA-B* mRNA expression of asymptomatic South African Black (blue dots) individuals was significantly higher than asymptomatic South African Indian (blue dots) ($p<0.0001$). Symptomatic South African Indians (red dots) *HLA-B* mRNA expression levels were significantly higher than asymptomatic South African Indians (blue dots) ($p<0.0001$). (C) *HLA-C* mRNA expression levels among different ethnic groups. We found that South African Black individuals' had significantly higher *HLA-C* mRNA expression levels than South African Indians' $p<0.0001$. (D) *HLA-C* mRNA expression levels among symptomatic and asymptomatic individuals from South African ethnicities. A comparison between South African Black symptomatic, South African Black asymptomatic, South African Indian symptomatic, and South African Indian asymptomatic. We did not observe a significant difference between *HLA-C* mRNA expression levels in South African Black symptomatic (red dots) and South African Black asymptomatic (blue dots) ($p<0.8035$). *HLA-C* mRNA expression levels were significantly higher in South African Black symptomatic (red dots) than in South African Indian symptomatic (red dots) individuals ($p<0.0034$). The *HLA-C* mRNA expression levels of asymptomatic South African Black (blue dots) individuals were significantly higher than asymptomatic South African Indians (blue dots) ($p<0.006$). Symptomatic South African Indians (red dots) *HLA-C* mRNA expression levels were significantly higher than asymptomatic South African Indians (blue dots) ($p<0.0001$).

HLA-B and *HLA-C* mRNA expression levels across different genders

We analyzed the relationship between gender and COVID-19 disease severity. There was no significant association between gender and COVID-19 severity (Table 2, $p=0.1088$). (A) We then analyzed the effect of gender on *HLA-B* mRNA expression levels. There was no significant difference between *HLA-B* mRNA expression levels of males and females (Females means=1.281, males mean=1.315; $p=0.8680$, Figure 3A). (B) We did not observe a significant difference between the *HLA-B* mRNA expression of asymptomatic males and symptomatic males ($p=0.2407$; Figure 3B). We also did not observe a significant difference between symptomatic males and females ($p=0.9944$). *HLA-B* mRNA expression levels were not significantly different between asymptomatic males and asymptomatic females ($p=0.1390$). *HLA-B* mRNA expression levels were significantly different between asymptomatic females

and symptomatic females (p<0.0001). (Male asymptomatic mean=0.899; male symptomatic mean=1.35; female asymptomatic=0.446; female symptomatic=1.41). (C) We then analyzed the effect of gender on *HLA-C* mRNA expression levels. There was a significant difference between *HLA-C* mRNA expression levels of males and females (Females means=0.04701, males mean=0.03294; p=0.0052, Figure 3C). (D) We did not observe a significant difference between the *HLA-C* mRNA expression levels of asymptomatic males and symptomatic males (p=0.6810; Figure 3D). We also did not observe a significant difference between symptomatic males and females (p=0.1352). *HLA-C* mRNA expression levels were not significantly different between asymptomatic males and asymptomatic females (p=0.2624, Figure 3D). *HLA-C* mRNA expression levels were not significantly different between asymptomatic females and symptomatic females (p=0.9740). (Male asymptomatic mean=12.0; male symptomatic mean=7.31; female asymptomatic=3.95; female symptomatic=4.59).

Table 2: The frequency of males and females that are asymptomatic and symptomatic.

Gender	**Asymptomatic**	**Symptomatic**	**Total**	**p-value**
Male	22	86	108	
Female	20	134	154	
Total	42	220	262	0.1088

There was no significant difference between asymptomatic males and females and symptomatic males and females (p=0.1088).

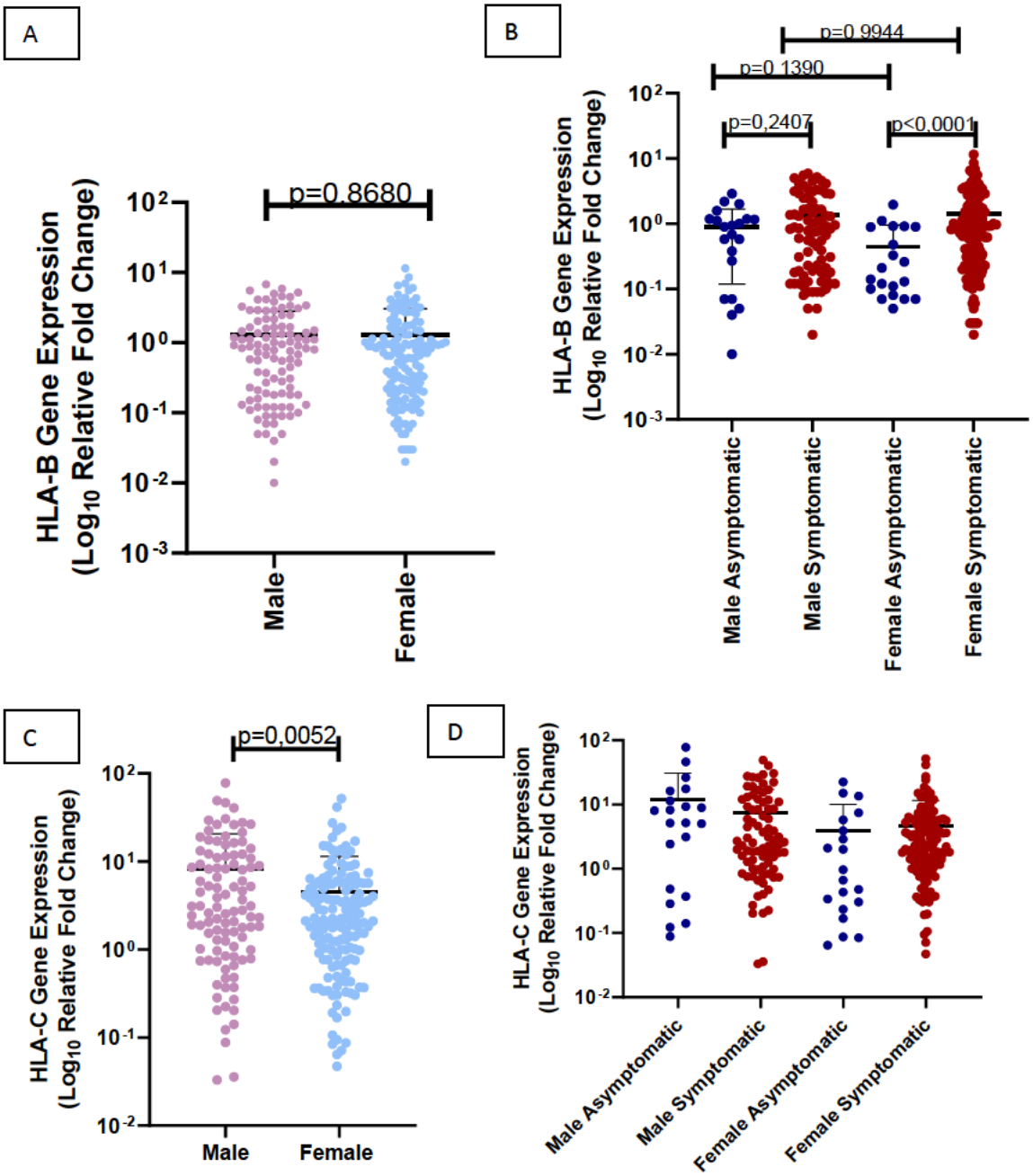


Figure 3: (A) *HLA-B* mRNA expression levels of COVID-19 infected South Africans among different genders. A comparison of *HLA-B* mRNA expression levels between infected COVID-19 South Africans and gender. There is no significant difference between *HLA-B* mRNA expression levels in males (blue dots) and females (red dots) (p=0.8680). (B) *HLA-B* mRNA expression levels among symptomatic and asymptomatic COVID-19-infected males and females. A comparison between *HLA-B* among symptomatic males (red dots), females (blue dots) asymptomatic males (blue dots), and females (red dots). There is a significant association with *HLA-B* in females symptomatic (red dots) and asymptomatic females (blue dots)

(p=0.0001). *HLA-B* was significantly different between male symptomatic (red dots) and asymptomatic males (blue dots) (p=0.2407). There was no significant association with *HLA-B* in males symptomatic (red dots) and symptomatic females (red dots) (p=0.9944). There is a significant association with *HLA-B* in males asymptomatic (blue dots) and asymptomatic females (blue dots) (p=0.1390). (C) *HLA-C* mRNA expression levels of infected COVID-19 South Africans among different genders. A comparison of *HLA-B* mRNA expression levels between infected COVID-19 South Africans and gender. There is a significant difference between *HLA-C* mRNA expression levels in males (blue dots) and females (red dots) (p=0.0052). (D) *HLA-C* mRNA expression levels among symptomatic and asymptomatic COVID-19-infected males and females. A comparison between *HLA-C* among symptomatic males (red dots), and females (blue dots), asymptomatic males (blue dots), and females (red dots). There was no significant difference between *HLA-C* in females symptomatic (red dots) and asymptomatic females (blue dots) (p=0.9740). *HLA-C* was no significant difference between male symptomatic (red dots) and asymptomatic males (blue dots) (p=0.6810). There was no significant association with *HLA-B* in males symptomatic (red dots) and symptomatic females (red dots) (p=0.1352). There was no significant difference between *HLA-C* in males asymptomatic (blue dots) and asymptomatic females (blue dots) (p=0.2624).

HLA-B and *HLA-C* mRNA expression levels across existing conditions

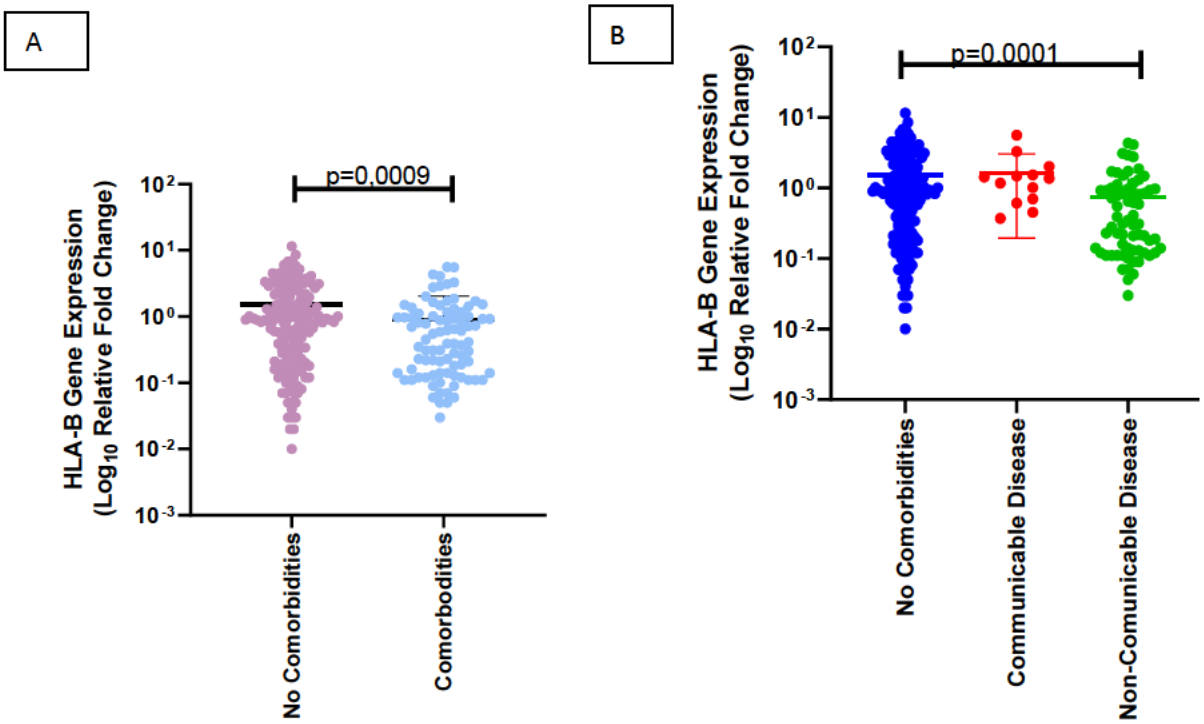
In addition, we analyzed the relationship between COVID-19 severity and comorbidities There was a significant difference between COVID-19 severity and the presence of comorbidities (Table 3, p=0.0528). (A) We also analyzed the effect of comorbidities on *HLA-B* mRNA expression levels. There is a significant association between *HLA-B* mRNA expression levels among COVID-19-infected individuals with and without comorbidities (95% CI= -0.9944 to -0.2584; no comorbidities mean=1.513, comorbidities mean=0.8867; p=0.0009 Figure 4A). (B) We then divided the comorbidities into communicable and non-communicable diseases. We observed a significant difference between no comorbidities and communicable diseases (p=0.0001; no comorbidities mean=1.51, communicable disease mean=1.62, noncommunicable disease=0.747, Figure 4B). (C) We further divided the communicable and non-communicable diseases (no comorbidities mean=1.51, HIV mean=1.70, hypertension mean=0.703, asthma mean=1.04, anemia mean=0.632, cardiovascular disease mean=0.638, diabetes mean=0.597, Figure C). There was a significant difference between no comorbidities and hypertension, as well as no comorbidities and diabetes respectively (p=0.0011; p=0,0002; Figure 4C). (D) In addition, we analyzed the effect of comorbidities on *HLA-C* mRNA

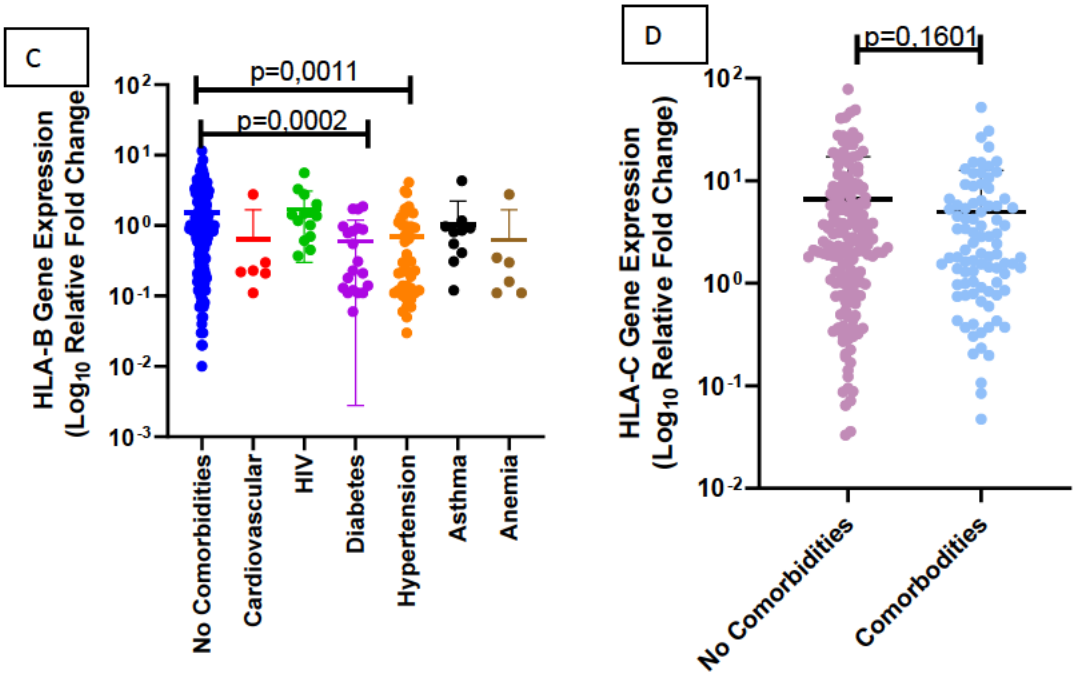
expression levels. There is a significant association between *HLA-C* mRNA expression levels among COVID-19-infected individuals with and without comorbidities (95% CI= -3.883 to 0.6446; no comorbidities mean=6.602, comorbidities mean=4.983; p=0.1601 Figure 4D). (E) We then divided the comorbidities into communicable and non-communicable diseases. We observed no significant difference between all three categories (p=0.9952, p=0.1867, p=0.8249; no comorbidities mean=6.60, communicable disease mean=6.97, noncommunicable disease=4.64, Figure 4E). (F) We further divided the communicable and non-communicable diseases (no comorbidities mean=6.60, HIV mean=6.97, hypertension mean=5.19, asthma mean=4.74, anemia mean=1.99, cardiovascular disease mean=2.41, diabetes mean=4.24, Figure 4F). There was a significant difference between no comorbidities and cardiovascular disease, as well as no comorbidities and anemia respectively (p=0.0246; p=0,0003; Figure 4F).

Table 3: The frequency of individuals who did or did not present with comorbidities that are asymptomatic or symptomatic.

Comorbidities	Asymptomatic	Symptomatic	Total	p-value
Not present	34	138	172	
Present	8	72	80	
Total	42	210	252	0.0528

There was no significant difference between asymptomatic and symptomatic individuals who did and did not present comorbidities (p=0.0528).




C
p=0,0011
p=0,0002
HLA-B Gene Expression
(Log10 Relative Fold Change
10^2
10^1
10^0
10^-1
10^-2
10^-3
No Comorbidities
Cardiovascular
HIV
Diabetes
Hypertension
Asthma
Anemia
D
p=0,1601
HLA-C Gene Expression
(Log10 Relative Fold Change)
10^2
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No Comorbidities
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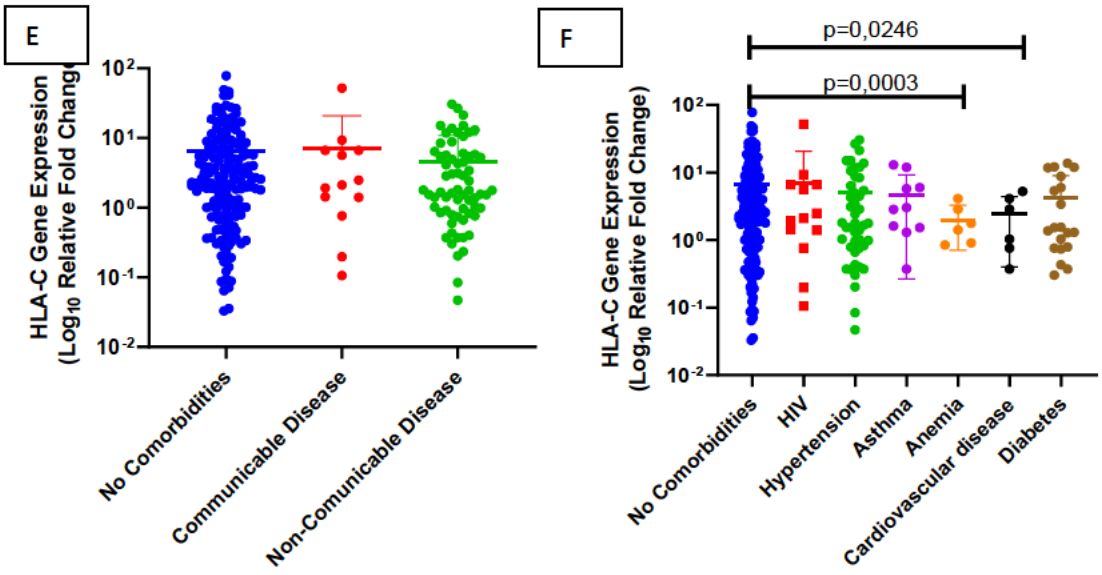

Figure 4: (A) *HLA-B* mRNA expression levels and presence and absence of comorbidities among COVID-19-infected individuals. We compared *HLA-B* mRNA expression levels among COVID-19-infected individuals with or without comorbidities. There is a significant association between *HLA-B* mRNA expression levels among COVID-19-infected individuals with (blue dots) and without comorbidities (red dots) (p=0.0009, Figure 4A). (B) *HLA-B* mRNA expression levels among COVID-19 infected individuals with communicable, noncommunicable, or no comorbidities. No comorbidities (blue dots), communicable disease (red dots), or non-communicable (green dots). Significant differences were observed between no comorbidities and non-communicable diseases (p=0.0001, Figure 4B). Individuals with no comorbidities had significantly higher *HLA-B* mRNA expression levels than those with non-communicable diseases. (C) We then analyzed the relationship between *HLA-B* expression levels among different types of comorbidities among COVID-19-infected individuals. We compared no comorbidities (blue dots), with different types of diseases such as cardiovascular disease (red dots), HIV (green dots), Diabetes (purple dots), hypertension (orange dots), asthma (black dots), and anemia (brown dots). There is only a significant difference between no comorbidities and diabetes (p=0.0002), and no comorbidities and hypertension (p=0.0011, Figure 4C). (D) The effect of comorbidities on *HLA-C* mRNA expression levels. There is a significant association between *HLA-C* mRNA expression levels among COVID-19 infected individuals with (blue dots) and without comorbidities (red dots) (95% CI= -3.883 to 0.6446; no comorbidities mean=6.602, comorbidities mean=4.983; p=0.1601 Figure 4D). (E) We then divided the comorbidities into communicable and non-communicable diseases. We observed

no significant difference between all three categories (p=0.9952, p=0.1867, p=0.8249; no comorbidities mean=6.60, communicable disease mean=6.97, noncommunicable disease=4.64, Figure 4E). (F) We further divided the communicable and non-communicable diseases. (no comorbidities mean=6.60, HIV mean=6.97, hypertension mean=5.19, asthma mean=4.74, anemia mean=1.99, cardiovascular disease mean=2.41, diabetes mean=4.24, Figure 4F). There was a significant difference between no comorbidities (blue dots) and cardiovascular disease (black dots), as well as no comorbidities (blue dots) and anemia (orange dots) respectively (p=0.0246; p=0,0003; Figure 4F).

HLA-B and *C* mRNA expression levels across different age groups

Finally, we examined the relationship between age and disease severity. We did not find an association between age and disease severity (p=0.6709). then determined the effect of age groups on *HLA-A* mRNA expression levels in COVID-19-infected individuals (Figure 5). We determined the effect of age groups on *HLA-B* mRNA expression levels in COVID-19-infected individuals. (18-23 mean=1.53, 26-35 mean=1.52, 36-45 mean=1.21, 46-55 mean=1.20, 56-65 mean=0.549, over 65 mean=0.930, Figure 5.1). Previously, COVID-19 disease was associated with age. We observed that ages 18-25 were significantly higher than 56-65 (p=0.0099). We also observed a significant difference between 26-35 and 56-65 years (p=0.0018). We determined the effect of age groups on *HLA-C* mRNA expression levels in COVID-19-infected individuals. (18-23 mean=7.28, 26-35 mean=5.74, 36-45 mean=5.08, 46-55 mean=7.76, 56-65 mean=3.43, over 65 mean=5.12, Figure 5.2) Previously, COVID-19 disease was associated with age. We did not observe a significant difference between any of the age groups and *HLA-C* mRNA expression levels.

Table 4: The frequency of individuals who are under and over 45 years that are asymptomatic and symptomatic.

Age (Years)	**Asymptomatic**	**Symptomatic**	**Total**	**p-value**
Under 45	31	160	191	
Over 45	10	61	71	
Total	41	221	262	0.6709

There is no significant difference between disease severity and ages below and above 45 (p=0.6709).

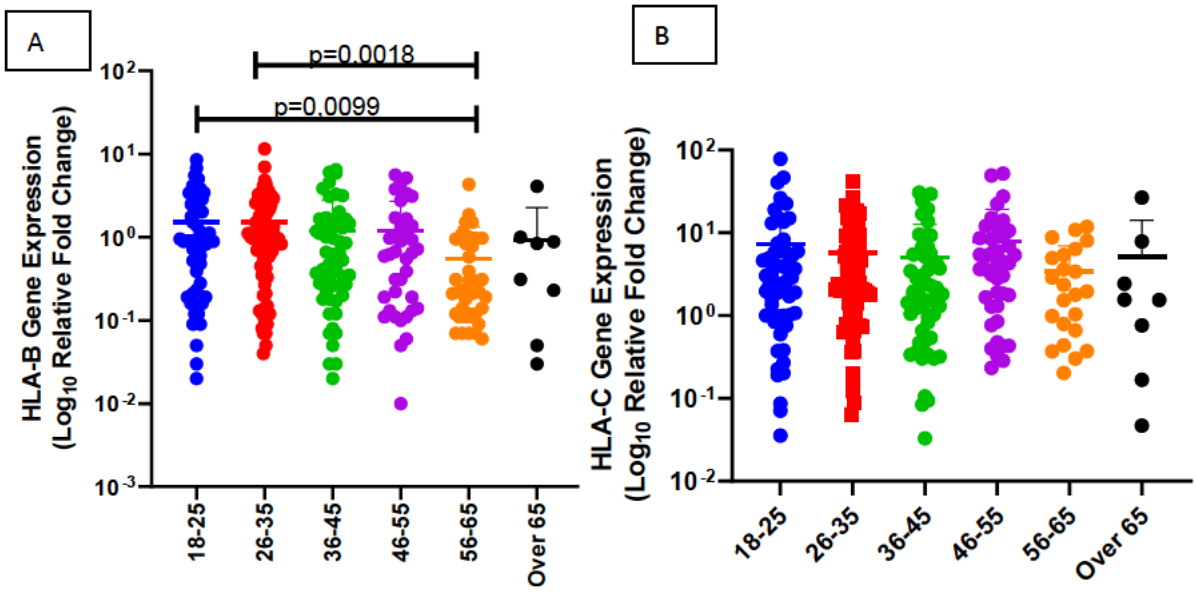

Figure 5: *HLA-B* mRNA expression levels and age among COVID-19 infected individuals South Africans. A comparison between *HLA-B* among COVID-19 infected individuals and age. 18-25 (blue dots), 26-35 (red dots), 36-45 (green dots), 46-55 (purple dots), 56-65 (orange dots), >65 (black dots). We observed that ages 18-25 had significantly higher *HLA-B* mRNA expression levels than 56-65 (p=0.0099). We also observed a significant difference between 26-35 and 56-65 years (p=0.0018, Figure 5A). There is no significant association between *HLA-B* mRNA expression levels among COVID-19-infected individuals and any of the other age groups. (B) *HLA-C* mRNA expression levels and age among COVID-19 infected individuals. A comparison between *HLA-C* mRNA expression levels among COVID-19 infected individuals and age. 18-25 (blue dots), 26-35 (red dots), 36-45 (green dots), 46-55 (purple dots), 56-65 (orange dots), >65 (black dots). There is no significant association between *HLA-C* mRNA expression levels among COVID-19-infected individuals and any of the age groups (Figure 5B).

Discussion

We aimed to determine the effects of *HLA-C* and *HLA-B* mRNA expression levels on disease severity, age, ethnic groups, gender, and comorbidities in COVID-19-infected individuals. We compared *HLA-B* and *HLA-C* mRNA expression levels within the South African COVID-19 cohort.

Previous studies have shown that disease severity varies across ethnicities. There have been less severe outcomes among the African populations and COVID-19 has been less deadly in Africa compared to other continents (396). We observed that *HLA-B* and *HLA-C* mRNA expression levels were both significantly higher in South African Blacks than in South African Indians ($p<0.0001$).

Various studies analyzed the association of *HLA-B* and *HLA-C* with other infectious diseases (356, 399). These studies have confirmed the importance of *HLA* alleles in disease severity. These results strengthen the significance of the role of *HLA* in COVID-19. In this study, we observed that symptomatic COVID-19-infected individuals had a significantly higher *HLA-B* mRNA expression than asymptomatic individuals. However, *HLA-C* mRNA expression levels showed no significant difference between symptomatic and asymptomatic individuals. This suggests that *HLA-B* mRNA expression levels are associated with increased disease severity, while *HLA-C* expression might not play a significant role in COVID-19 disease severity. Furthermore, we showed a significant difference in *HLA-B* mRNA expression levels among South African Black asymptomatic and symptomatic individuals ($p<0.0001$) as well as South African Indian asymptomatic and symptomatic ($p<0.0001$). In addition, asymptomatic South African Indians and South African Blacks also showed a significant difference ($p>0.0001$). These results suggest that *HLA-B* is associated with worse disease outcomes regardless of ethnicity. *HLA-C* was not significantly different between symptomatic South African Blacks and asymptomatic South African Blacks. However, there was a significant difference between symptomatic South African Indians and asymptomatic South African Indians ($p<0.0001$). This could be due to the small sample size of asymptomatic South African Indians. *HLA-C* mRNA expression was significantly higher in asymptomatic South African Blacks than in asymptomatic South African Indians ($p>0.006$). *HLA-C* mRNA expression levels were significantly higher in symptomatic South African Blacks than in symptomatic South African Indians ($p>0.0034$). Some of these findings are consistent with studies that confirm an association between disease severity and ethnicity (12).

Males had significantly higher *HLA-C* mRNA expression levels compared to females ($p=0.0052$). However, there was no significant difference between the *HLA-B* mRNA expression levels and gender ($p=0.8680$). More studies are required to determine the effect of gender on COVID-19, if any. Interestingly, only *HLA-B* mRNA expression levels among asymptomatic and symptomatic females showed a significant difference. As expected,

symptomatic females were higher than asymptomatic females. Naemi et al. showed that there was no relationship between gender and COVID-19 severity in the South Asian population (309).

Increased age has been previously associated with increased or worse disease progression, however, we did not see an association between age and COVID-19 severity. Our results showed that *HLA-B* mRNA expression levels among ages 18-25 and 56-65 were significantly different (p=0.0099). In addition, ages 26-35 were significantly higher than 56-65 (p=0.0018). However, there was no significant association between age and *HLA-C* mRNA expression levels in COVID-19-infected individuals. Surprisingly, *HLA-B* mRNA expression was higher in younger individuals than older individuals, therefore *HLA-B* might play a role in COVID-19 disease severity among younger individuals. There are controversial results on the effect of age on *HLA* alleles. Izaks et al. did not find an association between *HLA* and death after 85 years. Another study showed that *HLA* class I expression was reduced in lymphocytes and monocytes of the elderly (401). The *HLA* mRNA level was increased in PBL for *HLA-B* than *HLA-A*. This suggests *HLA* class-I molecules expressed on the cell surface are associated with specific mRNA levels. *HLA* class-I locus expression is cell type dependent. This cellular differential expression of *HLA* class-I loci could act on the immune response by preferentially presenting distinct peptides to T cells. There was a significant decrease in the amounts of *HLA-A* and *HLA-B* transcripts with increasing age (402). In a South Asian population, patients who were admitted into ICU were significantly older than those with mild COVID-19 ($p<0.001$) (309).

We observed that *HLA-B* mRNA expression levels were significantly higher in individuals who had no comorbidities than comorbidities (p=0.0009). We did not observe a significant difference between comorbidities and no comorbidities for *HLA-C* mRNA expression levels (p=0.1601). We further divided comorbidities and did not see a difference between the different comorbidities. *HLA-B* mRNA expression was significantly different between noncommunicable diseases and no comorbidities (p=0.0001). However, there is no significant difference between comorbidities and communicable or non-communicable diseases for *HLA-C* mRNA expression levels. Comorbidities contribute to the disease state and are associated with *HLA-B* mRNA expression levels. However, HLA-B mRNA expression levels were significantly higher in individuals with no comorbidities and diabetes and no comorbidities and hypertension. *HLA-C* mRNA expression levels were higher in no comorbidities than in anemia

and cardiovascular disease. This suggests that *HLA-B* mRNA expression levels have a relationship with diabetes and hypertension in COVID-19-infected individuals, while *HLA-C* is associated with anemia and cardiovascular disease in COVID-19-infected individuals. COVID-19-infected individuals over 65, predominantly males, with comorbidities or organ-associated pathologies are at increased risk of developing severe, critical COVID-19 and death (403). Type I diabetes mellitus was associated with severe SARS-CoV-2 infection. Hypertension and cardiovascular disease are also increasing the risk of worse COVID-19 (404). More research within an African population is required to unravel the role of *HLA* expression level in COVID-19 and other factors and diseases. Researchers should include individuals of different ethnicities and a big sample size. The limiting factor of this study was the sample size of the asymptomatic individuals. In addition, the age groups were limited in this study. Genetic studies are important to develop specific therapeutics to elevate disease among specific populations. *HLA* studies are significant because they are involved in host response to pathogens.

Conclusion

In Africa, the impact of COVID-19 compared to the rest of the world came as an astonishment. The reason behind the effect of COVID-19 on Africa is yet to be unraveled. We showed that *HLA* expression levels differ among different South African ethnic groups. In addition, comorbidities are associated with COVID-19 and *HLA-B* expression levels. This is evidence that COVID-19 disease severity is dependent on host genetics.

Author Contributions

Conceptualization, V.R.; Data curation; Writing—original draft, L.N. (Lisa Naidoo); Writing—review & editing, T.A. (Thilona Arumugam). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal, protocol reference number: BREC/00002648/2021.

Informed Consent Statement:

Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest: The authors declare no conflict of interest.

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CHAPTER 6 – DISCUSSION/SYNTHESIS

Host genetics is important in pathogenesis, and it contributes significantly to disease severity. Initially, we reviewed the impact of host genetics on three infectious diseases that are prevalent in Africa, and the recently emerged COVID-19. We found that HIV, malaria, TB, and COVID-19 are associated with common host genes (12). Some of these host genes play a similar role in pathogenesis, while others have differing effects. Understanding their roles could contribute to developing a single therapeutic for multiple diseases and high-risk individuals.

HLA alleles have been shown to be associated with various other diseases and autoimmune disorders (387) (379, 388, 389). Naidoo et al (unpublished)., our second review paper underlines the impact of *HLA* class I alleles on COVID-19 in different populations around the world (405). It shows that different ethnic groups respond differently to COVID-19 and have

varying *HLA* profiles. *HLA* class I is an integral target for COVID-19 therapeutics since it contributes to COVID-19 immune response. However, each allele plays a different role in the immune response, and all the roles are not fully understood.

For our research study, we decided to investigate the relationship between class I *HLA* region and COVID-19. We measured the mRNA expression levels of *HLA-A*, B, and C from the buffy coats of COVID-19 infected individuals of South African Indian and South African Black ethnicity, using real-time PCR and compared the *HLA* gene expression with COVID-19 disease progression. We also investigated the impact of ethnicity, gender, age, and comorbidities on the *HLA* class I expression, through statistical analysis (397).

HLA-A expression correlated with symptomatic COVID-19. This was also seen in different ethnic groups with varying disease severity. This disparity was observed in other studies all over the world. (391, 392). We found an association between *HLA-A* expression and gender, particularly, between asymptomatic and symptomatic males. More research is required to unravel the impact and cause of this relationship. We observed an association between comorbidities and disease progression. In addition, we found an association between *HLA-A* expression levels between no comorbidities and non-communicable disease particularly in those with anemia, cardiovascular, and diabetes. This is in line with previous studies and the WHO guidelines(395). The *HLA-A* expression levels are associated with certain age groups. However, there was no association between age and disease severity. *HLA-A* increases *HLA-E* expression which is involved in NK cells inhibition (386). In HIV-1 increased *HLA-A* expression correlates with detrimental effects (386). However, the opposite is seen with COVID-19. Increased *HLA-A* is associated with symptomatic COVID-19. This could be due to a hyperactive immune response seen during COVID-19.

HLA-B expression was associated with disease severity. While *HLA-C* expression was not significantly associated with COVID-19 severity. *HLA-B* and *HLA-C* expression was significantly different between race groups, as well as race groups with varying disease severity. *HLA-B* expression was not associated with genders but there were significant differences between female asymptomatic and female symptomatic. However, *HLA-C* was significantly different between genders. *HLA-B* expression levels were significantly different

between those with and without comorbidities. This indicates that *HLA-B* might be associated with comorbidities. We finally observed significant differences between certain age groups in HLA-B expression. Our study was limited to the number of samples and the variety of samples (405).

Our study contributes to the gap in knowledge regarding the impact of *HLA* class I alleles on COVID-19 and their contributing factors. We showed the effect of *HLA* class I expression levels on age, gender, comorbidities, and ethnicity among COVID-19 infected individuals. We also showed the effect of these contributing factors on COVID-19 within a South African cohort. *HLA* alleles are of great importance to various diseases and the immune response. Therefore, future studies must analyze the impact of *HLA* alleles. Africa, with one of the highest infectious rates and the greatest genetic diversity, is required to determine the impact of host genetics on COVID-19 disease, as well as other infectious diseases. Therefore, studies in Africa are of great importance. This information could be used as biomarkers in future outbreaks, where vaccine supply might be limited. Studying host genetics gives insight into which individuals are at higher risk of infections. These individuals should be prioritized in vaccine distribution. This information could also be used as multitargeted therapeutics. More research with large cohorts is recommended with varying ages, comorbidities, and ethnicities to determine the true impact of each gene. *HLA* expression has been shown to play a significant role in COVID-19 disease, and other infectious diseases. These therapeutics will help eliminate the disease burden in Africa and work specifically according to their genetic targets.

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