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Linkage between HLA genotypes and COVID-19 susceptibility, severity and mortality-A Systematic Review

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Abstract

HLA is vital for effective immune responses against viruses. The virus responsible for COVID-19, SARS-CoV-2, highlights the significance of this immune response. The unpredictable nature of COVID-19 prompts investigation into how HLA, a component of host genetics, impacts disease susceptibility and outcomes. Understanding HLA variants' influence on COVID-19 susceptibility and severity can aid in identifying at-risk individuals. Significant HLAs that had been previously investigated for their association with COVID-19 were sought. Articles from January 2001 to February 2022 were reviewed in 2 databases: Science Direct and PubMed, employing the search terms "COVID-19" AND "HLA." Studies of genetic association measuring the severity or susceptibility to COVID-19 were analyzed in accordance with PRISMA guidelines. A total of 1326 studies related to the novel coronavirus and HLA conducted between the first month of 2001 and the second month of 2022 were identified in our search. Following the screening process, 15 relevant publications were selected. With the exception of one publication that did not demonstrate any connection, significant correlations between the incidence and mortality due to COVID-19 were found in all investigations. In severe cases, HLA class II, DRB113, was notably more prevalent. Among Black hospitalized patients positive for HLA-B53, there was an observed 7.4-fold higher risk of mortality, while HLA-B51:01 and HLA-A*26:01 were indicative of protective effects. HLAs play an essential role in immunological responses, potentially contributing to varying COVID-19 infection rates and outcomes across populations. These findings underscore the need for national networks to collect patient samples for HLA typing, identifying HLA genotypes associated with disease vulnerability.

INTRODUCTION

In December 2019, a newly identified variant of virus (nCoV) emerged in Wuhan, the capital city of Hubei Province, China (Naemi, Al-Adwani, et al., 2021b). The virus known as SARSCov2, which causes COVID-19, can lead to respiratory complications such as pneumonia, an excessive immune response (cytokine storm), severe lung inflammation (ARDS), failure of multiple organs, and can ultimately be deadly (Gutiérrez-Bautista et al., 2021). The HLA system, located on 6p21.3 of the human genome, is highly diverse genetically and is involved in immune response control (Lorente et al., 2021). An analysis of HLA alleles -A, -B, -DR, and -DQ in a sample of 90 individuals from China who tested positive for SARS through serological methods indicated a notable link between the development of SARS and presence of HLA -B*0703 and -DRB1*0301 alleles (Ng et al., 2004). Infections with SARS-coronavirus 2 can lead to mild or symptom-free cases, while some patients can develop severe and

potentially life-threatening COVID-19 infections (Khor et al., 2021; Vietzen et al., 2021). In 2019, it resulted in over 30 million cases of illness and caused more than 1 million deaths (Naemi, Al-Adwani, et al., 2021a, 2021b). Although death from severe illness is a major consequence, COVID-19 has a worldwide mortality rate of 5% (Naemi, Al-Adwani, Al-Nazawi, et al., 2021). At the onset of the outbreak of COVID-19, various factors have been identified as increasing the likelihood of severe illness from this infection including elderliness, being male, having pre-existing conditions such as respiratory or cardiovascular illnesses (Vietzen et al., 2021). Following outbreaks in East Asia and South Korea, Italy became one of the first countries in Europe who confronted the swift spread of COVID-19, starting with early cases in the province of Lodi (Littera et al., 2020). Connections between infectious diseases and distinct loci have been observed within the HLA complex, which encompasses over 250 active genes relevant to immunological systems (Astbury et al., 2022). Variations in the human leukocyte antigen (HLA) are frequently linked to infection susceptibility or resistance, including AIDS, HIV, hepatitis, malaria, dengue fever, leprosy and TB (Keicho et al., 2009).

The severity of each viral infection depends on how the virus engages with the immune defenses of its host (Naemi, Al-Adwani, Al-Nazawi, et al., 2021; Wang et al., 2020). The genetic background governing immune responses can influence the virus's capacity to infect and the host's ability to defend (Amoroso et al., 2021). It is studied that the disease's progress and transmission could be affected by changes in HLA genotypes (Tomita et al., 2020). The genes of MHC (Major Histocompatibility Complex), including both classes I and II of HLA are crucial components within the body's immune system. These genes encode molecules that help the host respond to viruses. Research has revealed that certain HLA variants and genetic patterns contribute to the intensity and advancement of various autoimmune and viral illnesses, such as HBV, HCV, HIV, and influenza (Alnaqbi et al., 2022). Historically, HLA has been linked with the infectious disease. Numerous studies have been reported on the linkage of specific HLA alleles and its susceptibility or resistance to various infectious diseases. It has been reported previously that HLA-B57 and HLA-B27 slower the progression of HIV disease and exhibited better control of viral replication.

HLA-A*02 is linked with better clearance of Hepatitis B virus, whereas the other alleles of HLA influence to chronic infection (Blackwell et al., 2009). Another study demonstrates the HLA-DRB1 gene plays a direct role in vaccination nonresponsiveness, but not in altered vulnerability to viral persistence. Furthermore, they offer a mechanistic interpretation of the predominant reaction to the HBV core protein throughout infection. HLA class II glycoproteins convey viral peptides to CD4 T cells and influence their responses. HLA-DRB1*1301/2 has been associated with viral clearance, whereas HLA-DRB1*0301 is linked to nonresponse to envelope protein immunization (Godkin et al., 2005). HLA alleles have also been linked to susceptibility and severity of tuberculosis. HLA-DR and KLRG1 have been associated with the progression of TB disease and can be considered as a potential predictive marker for clinical immune assessment.

The expression of HLA-DR and KLRG1 increases the cytotoxic potential and the secretion capacity of cytokine from CD3+ T cells in patients suffering from TB (Yang et al., 2024). HLA also plays a significant role in the immune response to COVID-19, influencing susceptibility and disease severity. The HLA -B*15 gene has been found to predict favorable outcomes in Egyptian individuals impacted by the coronavirus pandemic (Abdelhafiz et al., 2022). Infection and HLA connection with HLA- DQB1*06

(Poulton et al., 2020). HLA B53 has also been linked to a poor prognosis in black patients with the coronavirus disease, according to research (Norin et al., 2021). Furthermore, Studies exploring HLA associations in individuals affected by coronavirus-induced illness have found that *HLA -DQB1*06, -DRB1*15, -DRB1*10 and -A*26* alleles are positively linked. Conversely, *HLA -A*02, HLA -B*44, and HLA -C*05* showed negative associations. Additionally, higher frequencies of *HLA- B *15:27 and HLA -C*07:29* alleles were observed, indicating that *HLA -C*01 and HLA -B*44* may play an important part in the disease (Ebrahimi et al., 2021). The B22 serotype was found to have a substantial positive correlation with SARSCoV2 (Yung et al., 2021).

Among individuals diagnosed with coronavirus infection, elevated levels of soluble HLA-G were observed irrespective of the severity of the illness (Ad'hiah & Al-Bayatee, 2022). HLA alleles that predispose to infection with active symptoms by SARS-Coronavirus 2 are thought to be more common in individuals admitted in hospitals with positive coronavirus infection (Schindler et al., 2021). The modification of production of cytokines, plays the critical part in generating immunological reactions, may help explain how HLA polymorphism contributes to susceptibility to infection or the development of diseases. As previously reported, Specific HLA alleles have been linked with increased expression levels of Interleukin-10, -17, and Interferon-γ (Naemi, Al-Adwani, Al-Nazawi, et al., 2021). This article aims to examine various studies that investigate a link between HLA and COVID-19 using PICO criteria, where the conditions apply:

- Population (P): COVID-19 positive patients are focused population.
- Intervention (I): Analysis of every sample by RNA extraction, COVID 19 testing, DNA extraction and HLA Typing through PCR-sequence specific oligonucleotides.
- Comparison (C): Review different types of HLA sub types alleles and their linkage with COVID-19 in different ethnic groups.
- Outcomes (O): Correlation of HLA genotypes with COVID-19 positive population.

Keeping this in mind, material from published articles was focused on and analyzed to present a comprehensive and current overview of how HLA influences in predisposition, intensity and fatality of COVID-19 in this review article.

METHODOLOGY

Search strategy

The methodology used for the literature review in this article involved the following steps:

- Patients/population: Infected with SARS coronavirus 2.
- Comparison: various HLA alleles.
- Outcomes: COVID-19 predisposition, and intensity and progression of the disease.

LITERATURE SEARCH AND SELECTION CRITERIA

To ensure a comprehensive and systematic review, a meticulous search strategy was implemented using two primary databases: ScienceDirect and PubMed. The search phrases utilized included "COVID-19" AND "HLA," "SARS-CoV-2" AND "HLA genotypes," "COVID-19 susceptibility" AND "HLA alleles," "COVID-19 severity" AND "HLA polymorphisms," and "COVID-19 mortality" AND "HLA genetic variations." These combinations of relevant keywords and phrases were structured with Boolean

operators (AND, OR) to capture a wide array of studies examining the relationship between COVID-19 and HLA genotypes. The literature search was conducted on February 6th, 2022. Inclusion criteria specified that studies must involve patients infected with SARS-CoV-2, compare various HLA alleles, and report on COVID-19 predisposition, disease intensity, and progression. Only original research articles presenting primary data were considered, with a requirement that studies be published in English and involve human subjects. Eligible studies included cross-sectional, cohort, case-control, and quasi-experimental investigations, as well as brief communications containing primary data.

Exclusion criteria were equally stringent, omitting case reports, opinion papers, editorials, and preprint articles that had not undergone peer review. Additionally, studies involving patients with a history of other viral or bacterial infections or immunosuppressive conditions were excluded. To ensure consistency and accuracy, filters were applied to include only articles in English and involving human subjects. Filters were also set to exclude non-original research articles, focusing solely on those presenting primary data that had been peer-reviewed.

The screening process involved an initial review of titles and abstracts, selecting articles relevant to the topic for full-text review. Articles passing this initial screening were then assessed in detail based on the inclusion and exclusion criteria. The reference lists of all eligible full-text articles were also reviewed to identify additional relevant studies potentially missed during the initial search. To manage the extensive data, all database records were downloaded to a local computer and organized using EndNote WEB, facilitating a systematic review process. Following PRISMA guidelines, we examined studies on genetic links that assessed the severity of Covid19 or predisposition to SARSCoV2 infection. Full-text access was granted if the title and abstract aligned with the topic. Articles eligible after title and abstract screening were further assessed through full-text screening.

Disagreements regarding study inclusion at each step were resolved, and the reference lists of full-text articles were also reviewed for potential incorporation. All studies that explored the potential link between HLA genetic variations and associated polymorphisms and Covid19 predisposition, intensity, and progression were included. This study looked at primary data from cross-sectional, cohort, case-control and quasi-experimental investigations. Only when brief communications contained primary data were included. Only articles in the English language and involving human subjects were selected. This study focused exclusively on original research articles presenting primary data. We excluded case reports, opinion papers, editorials, and preprint articles that did not undergo peer review from our analysis. COVID-19 infected patients with no clinical restrictions ranging from symptom-free infection to mild and critical sickness were encompassed in this article. The definition of HLA followed guidelines from National Cancer Institute dictionary, encompassing all HLAs from Class I & II, both classical/non-classical, alongside alleles, haplotypes, and related characteristics (Deb et al., 2022).

The study encompassed a range of sample sizes, which included both cases and controls. The specific sample sizes varied across the included studies, with some involving smaller cohorts and others examining larger populations. Detailed documentation of the sample size for each study was maintained, noting the number of COVID-19 cases confirmed through laboratory testing and the corresponding control groups. The selection criteria ensured that only studies with clearly defined sample sizes and adequately powered analyses were included, thereby allowing for

meaningful comparisons and reliable conclusions. A variety of study designs were considered to provide a comprehensive understanding of the linkage between HLA genotypes and COVID-19 susceptibility, severity, and mortality. The primary types of study designs included cross-sectional studies, which provided a snapshot of the prevalence of specific HLA alleles in COVID-19 patients at a single point in time, allowing for an assessment of associations between HLA types and disease outcomes. Longitudinal cohort studies followed groups of individuals over time to observe the incidence of COVID-19 and its progression in relation to their HLA genotypes, enabling an understanding of causality and disease progression. Case-control studies compared HLA genotypes between COVID-19 patients (cases) and non-infected individuals or those with mild symptoms (controls) to identify potential genetic factors influencing susceptibility and severity. Additionally, some studies employed quasi-experimental designs, leveraging naturally occurring variations in HLA genotypes to examine their impact on COVID-19 outcomes.

In assessing the risk of bias in the included studies, particular attention was given to selection and performance bias to ensure the reliability of the findings. Selection bias was scrutinized by evaluating the representativeness of participant samples and recruitment methods, with a preference for studies using clear inclusion criteria and random sampling techniques, as these are more likely to provide a representative sample of the population. Performance bias was examined by ensuring that study groups were managed uniformly or that any treatment variations were appropriately accounted for, ensuring that differences in outcomes could be attributed to HLA genotypes rather than inconsistencies in study protocols. Differences in study designs, such as cross-sectional, cohort, case-control, and quasi-experimental studies, complicate direct comparisons and integration of findings. Population diversity, including age, sex, ethnicity, and geographic location, affects the generalizability of results, as certain HLA genotypes may be more prevalent in specific ethnic groups, influencing observed associations.

Methodological differences in HLA typing, ranging from molecular techniques like PCR to computational approaches, lead to inconsistencies in allele identification and classification. Variability in COVID-19 outcome measures, such as susceptibility, severity, and mortality, further complicates the evaluation of HLA genotype impacts. Diverse statistical methods used in data analysis also affect the robustness and validity of reported associations. Underlying reasons for this heterogeneity include differing research objectives, geographic and population differences, technological and methodological advancements, resource availability, and the evolving understanding of COVID-19. Addressing heterogeneity involves using strategies like subgroup and sensitivity analyses and narrative synthesis to provide a balanced interpretation of the evidence. This approach acknowledges the complexity of researching HLA genotypes and COVID-19 outcomes while aiming to draw reliable and meaningful conclusions.

Data extraction and quality assessment

Cases of COVID-19 verified from laboratories were the primary outcome, with severity and death linked with COVID-19 as secondary outcomes. On a worksheet, an improvised method for extracting and synthesizing information was established. The following data was gathered independently from the included articles: any pre-existing health conditions or comorbidities, blood group of individual, specific HLA alleles, variants or mutations of SARS Coronavirus 2, where the HLA alleles were sourced from (whether from dry lab or wet lab settings), the sizes of samples for both

cases and controls, the study designs employed, demographic details of the study participants such as elderliness, sex, and ethnicity, the duration of the study, the prevalence of HLA alleles observed, and the statistical analysis for SARSCoV-2 and outcome. For HLA typing, data obtained through computational and experimental approaches were considered. Molecular HLA typing investigations utilized PCR methods using sequence-specific primers and oligonucleotides.

HLA TYPING

The identification and characterization of HLA alleles were crucial components of the study. Data on HLA typing were obtained through both computational and experimental approaches. Molecular HLA typing was the most commonly used technique, primarily involving Polymerase Chain Reaction (PCR). This method utilized sequence-specific primers (SSP) and sequence-specific oligonucleotides (SSO) to amplify and detect specific HLA alleles, allowing for high precision and sensitivity in identifying HLA genotypes. The SSP technique involved designing primers that bind specifically to the target HLA alleles, facilitating their amplification and subsequent detection. SSP-PCR was particularly useful for distinguishing between closely related HLA alleles. The SSO method involved hybridizing oligonucleotide probes to PCR-amplified DNA, enabling the detection of specific HLA alleles through complementary base pairing and providing a robust approach for typing multiple HLA loci simultaneously. In addition to experimental methods, computational approaches were utilized to analyze genomic data and predict HLA genotypes. Bioinformatics tools and databases facilitated the identification of HLA alleles from whole-genome sequencing data and other high-throughput genomic technologies. By incorporating both molecular and computational methods, the study ensured comprehensive and accurate HLA typing, enabling a robust analysis of the relationship between HLA genotypes and COVID-19 outcomes.

Data synthesis and summary measures

The information was compiled and provided in the form of percentage and frequency. Similar HLAs were grouped together based on their effects, and the data was unified. The study used a narrative synthesis to illustrate how HLA factors are linked to COVID-19 predisposition, intensity, and fatality. Due to the diversity in data sources, study methodologies, and variables among the publications examined, a meta-analysis was not possible.

RESULTS

A thorough review of two databases turned up 1326 probable COVID-19 and HLA-related publications published between January 2001 and February 2022. The remaining 654 records underwent screening based on their titles and abstracts after 672 duplicate records were discarded. 28 records were subjected to full-text review based on the defined criteria for inclusion and exclusion. After reviewing the full texts, 627 papers were eliminated, not linked to COVID-19 or HLA, replication, review; 13 articles were eliminated because they were unrelated to COVID predisposition, severity, or fatality; 3 articles were not relevant to HLA; and 4 articles focused on HLA but were not linked to COVID19; and 4 articles did not pertain to COVID19. One record was eliminated because it was conference abstract, while one article's entire text was found to be in Russian, despite the abstract being in English. As a result, for data extraction and analysis, 15 publications in all were chosen. Figure 1 depicts an

in-depth overview of the systematic literature search process, following the PRISMA standards.

Characteristics of the study

Despite all the studies analysed being cross-sectional, there was significant diversity in the research populations, HLA allele identification methods, and methods for analyzing the pertinent data as shown in table 1. The selected papers studied 3408 cases in total and 4219 controls, omitting three articles that correlated HLA frequency to the infection incidence of specific country and/or mortality rates without providing information on the total sample size Data came from different nations, 2 were from Saudi Arabia and USA each, and UK, UAE, Iran, Iraq, Spain, Italy, Egypt appearing in only one study each. All 15 studies found a link between the HLA allele and COVID. Although these studies included people of many nationalities, the linkage between Covid19 and HLA variations, and ethnicity was not solely investigated.

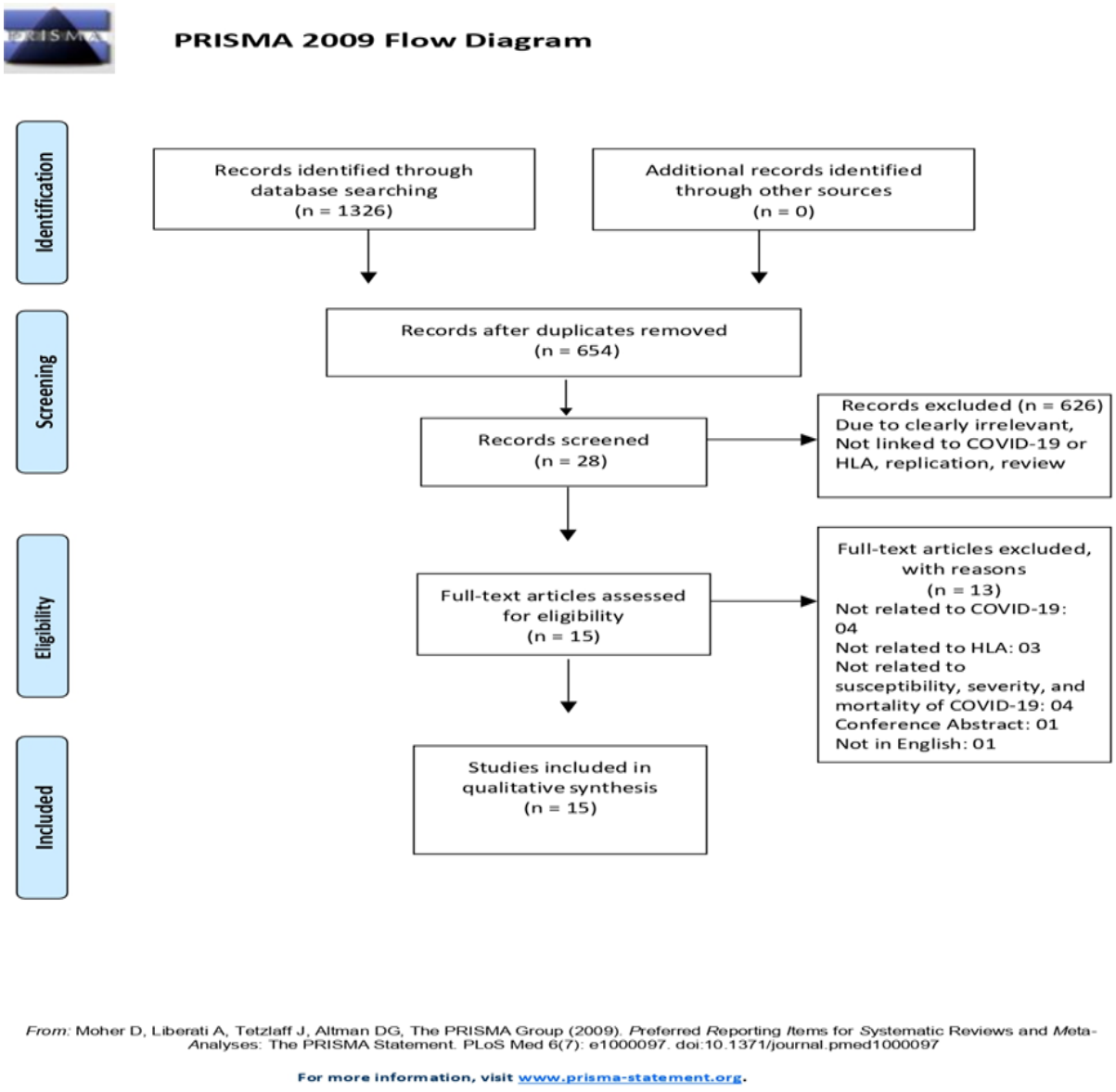

Figure 1.
HLA class I & II allele frequencies in COVID-19 affected individuals and their association with disease severity and mortality

The prevalence of HLA -B*51 markedly exceeded that of patients who experienced fatal outcomes. In the group with less severe infections, the frequency of HLA -B*35 was substantially greater compared to those with fatal outcomes. Additionally, in fatal infections, HLA -DRB1*13 showed a significantly elevated presence compared to those with mild infections (Norin et al., 2021). Black COVID-19 patients who tested positive for HLA-B*53 and were hospitalized had a 7.4 times greater likelihood of death (Abdelhafiz et al., 2022). In contrast, HLA A*26:01 and -B*51:01 have been found to indicate protective effects, whereas HLA -A*03:01, -DRB1*15:01, and B44 supertype were linked to the severity of Covid19 (Tomita et al., 2020).

A study reported that in individuals with mild infection, the prevalent HLA-A allele was A*02 while ICU-admitted subjects had A*11. In individuals experiencing mild infections, the predominant allele observed from HLA-B was B*35 while ICU patients showed B*15 and B*35. Across all groups, the predominant HLA-C allele was C*07 (Naemi, Al-Adwani, et al., 2021a). Notably, alleles B*41 and -B*42 from HLA-B, and -C*16, and -C*17 from HLA-C were identified as linked with serious coronavirus infection. HLA-B*15 exhibited a significant association with protection against mortality, similar to the findings for HLA -C*07 & -C*12. Another study uncovered suspected risk factors for active infection of coronavirus with signs and symptoms among different demographic groups. Specifically, in Hispanics, HLA -DRB1*08:02 emerged as a potential susceptibility marker, while HLA-A*30:02 showed a similar association in younger African Americans when compared to their respective population controls (Schindler et al., 2021).

In the Iranian population, COVID-19 patients with non-severe symptoms exhibited higher prevalence of HLA-DRB1*04 genotype (Ebrahimi et al., 2021). Furthermore, one study indicated a notable rise in prevalence of A*03 and C*06 among affected individuals who died compared to those who did not die from the disease. Regarding HLA class II, the study also highlighted that HLA -DRB1*04 was notably prevalent in the control sample compared to those who contracted the infection, whereas HLA -DRB1*08 showed a distinctly elevated frequency in infected individuals compared to controls (Naemi, Al-Adwani, et al., 2021b). According to a study, individuals carrying HLA-DRB1*13:02 are linked to a heightened susceptibility to symptomatic disease after infection (Astbury et al., 2022). Whereas one study showed that there was no observed connection between variations in HLA and vulnerability or immunity against Covid19 (Gutiérrez-Bautista et al., 2021).

One study investigated how specific genetic variations influence the likelihood of contracting Covid19. Compared to patients having A*02 allele, those with A*01 had a significantly increased risk of infection. Patients carrying B*56 were nearly twice as likely to become infected compared to those with B*51. Conversely, individuals carrying the C*16 allele had notably reduced infection risk compared to those with C*07. Meanwhile, those with HLA-DRB1*08 were more susceptible to contracting SARSCoV2 compared to those with DRB1*04 (Naemi, Al-Adwani, et al., 2021b).

Comparison of HLA class I & II allele frequencies in COVID-19 affected Saudi Arabian versus South Asian populations

Figure 2 illustrates "HLA-A" alleles frequency among South Asian and Saudis with Covid19. HLA -A*02 showed a significant link with South Asians, whereas HLA -A*02 & HLA -A*24 were found to be the more common alleles in Saudi Arabians. Whereas Figure 3 showcases the prevalence of "HLA-B" alleles. HLA-B*51 demonstrated a

robust correlation with Saudi Arabians, while HLA-B*35 was predominant among South Asians.

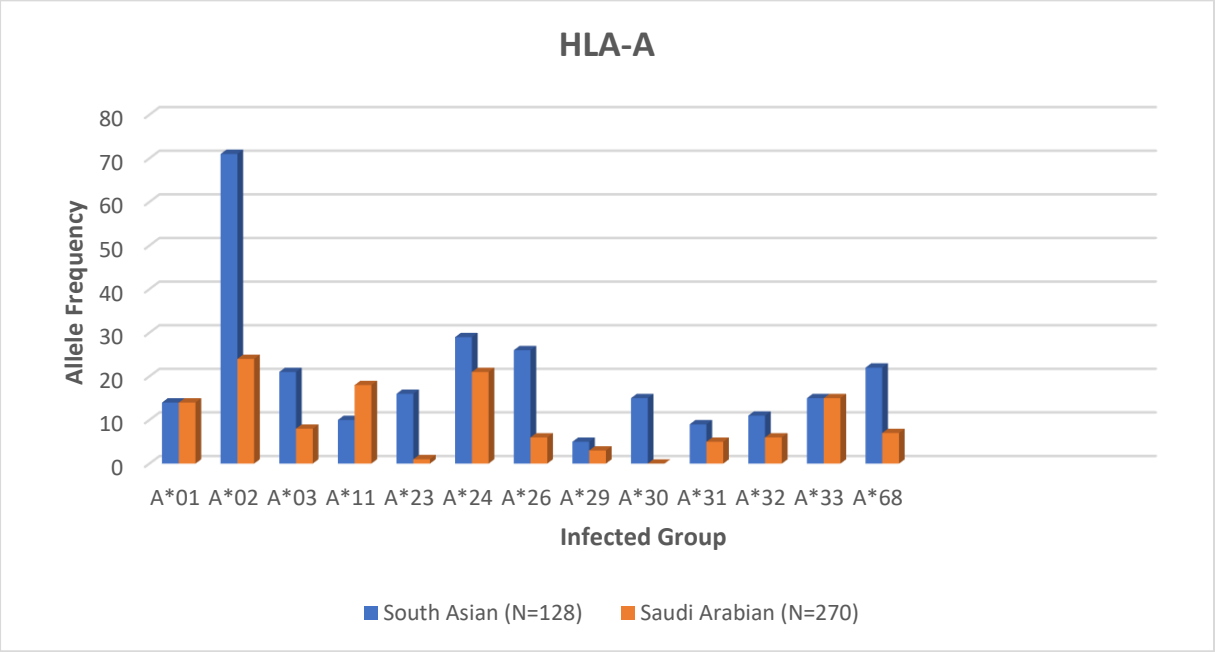

Figure 2.
the occurrence of HLA-A alleles in South Asians and Saudis affected with coronavirus infection.

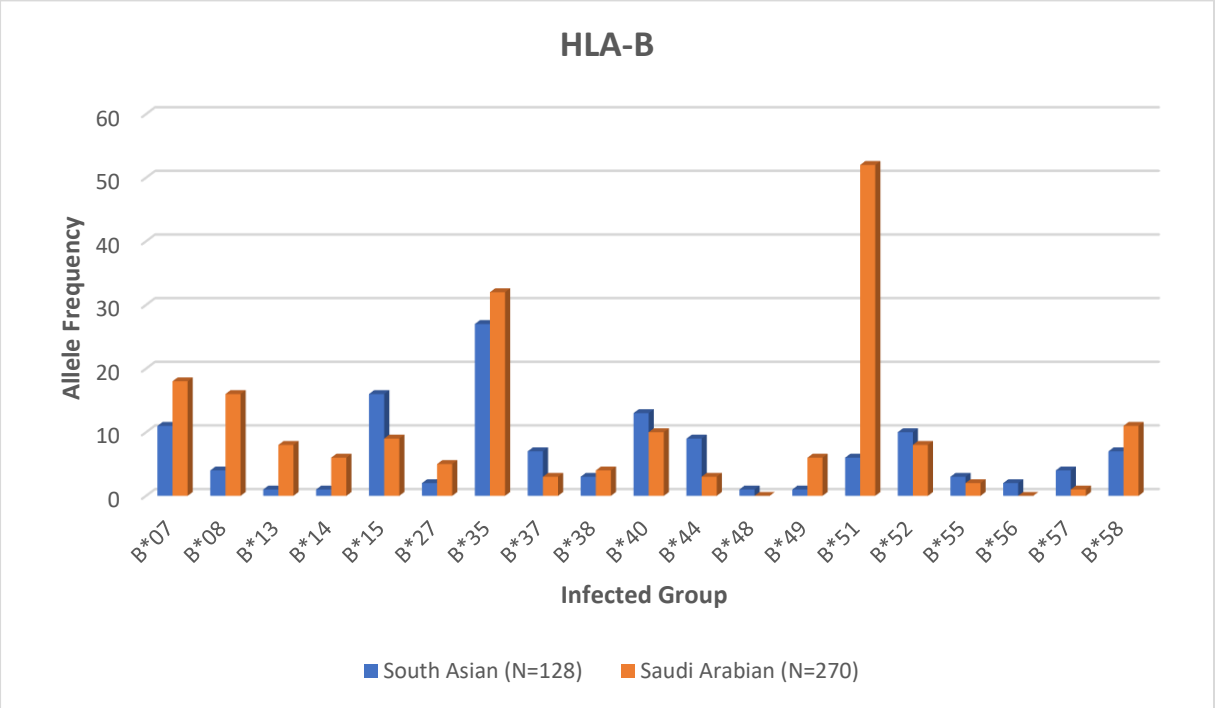

Figure 3.
The occurrence of HLA-B alleles in South Asians and Saudis affected with coronavirus infection.

In Figure 4, the prevalence of "HLA-C" alleles is depicted among COVID-19-infected individuals in both populations, particularly prominent among Saudi Arabians. *HLA -C*04, -C*06,* & *-C*07* exhibited pronounced associations among Saudi Arabians, while *HLA -C*04* & *-C*07* were more prevalent among South Asians. HLA-DRB1*04 exhibited

a notable association with Saudi Arabians, and HLA-DRB1*03 also showed significant association among them, whereas Figure 5 presented that HLA-DRB1*15 was more prevalent in the South Asian population (Naemi, Al-Adwani, et al., 2021a) (Naemi, Al-Adwani, et al., 2021b).

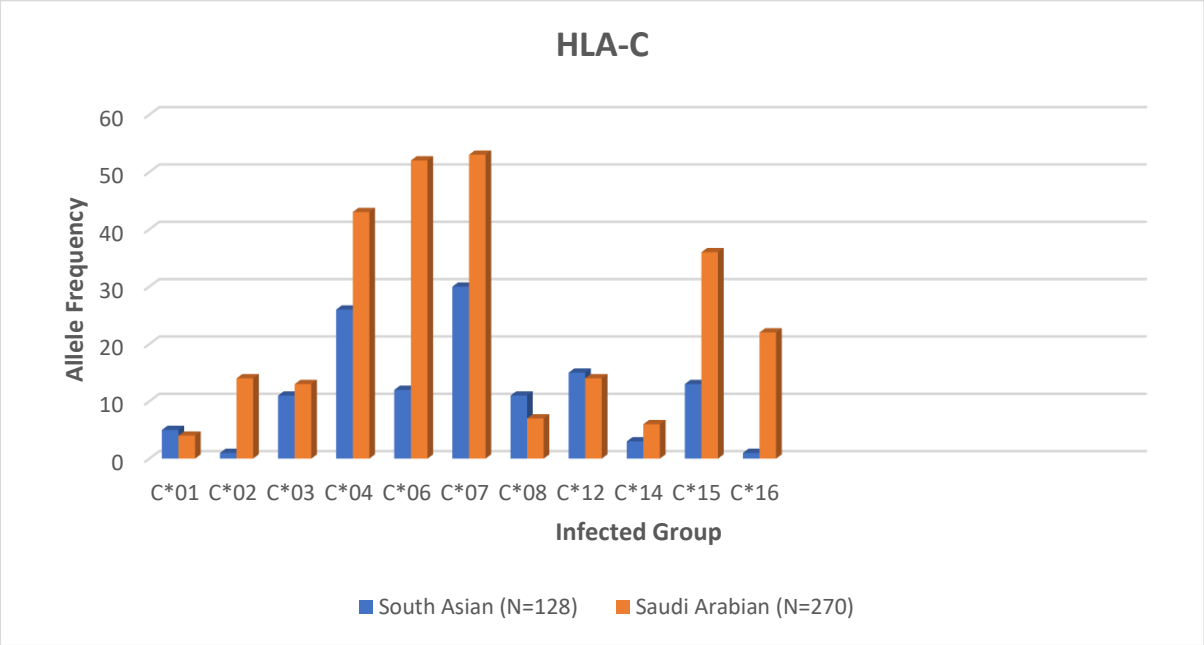

Figure 4.
The occurrence of HLA-C alleles in South Asians and Saudis affected with coronavirus infection.

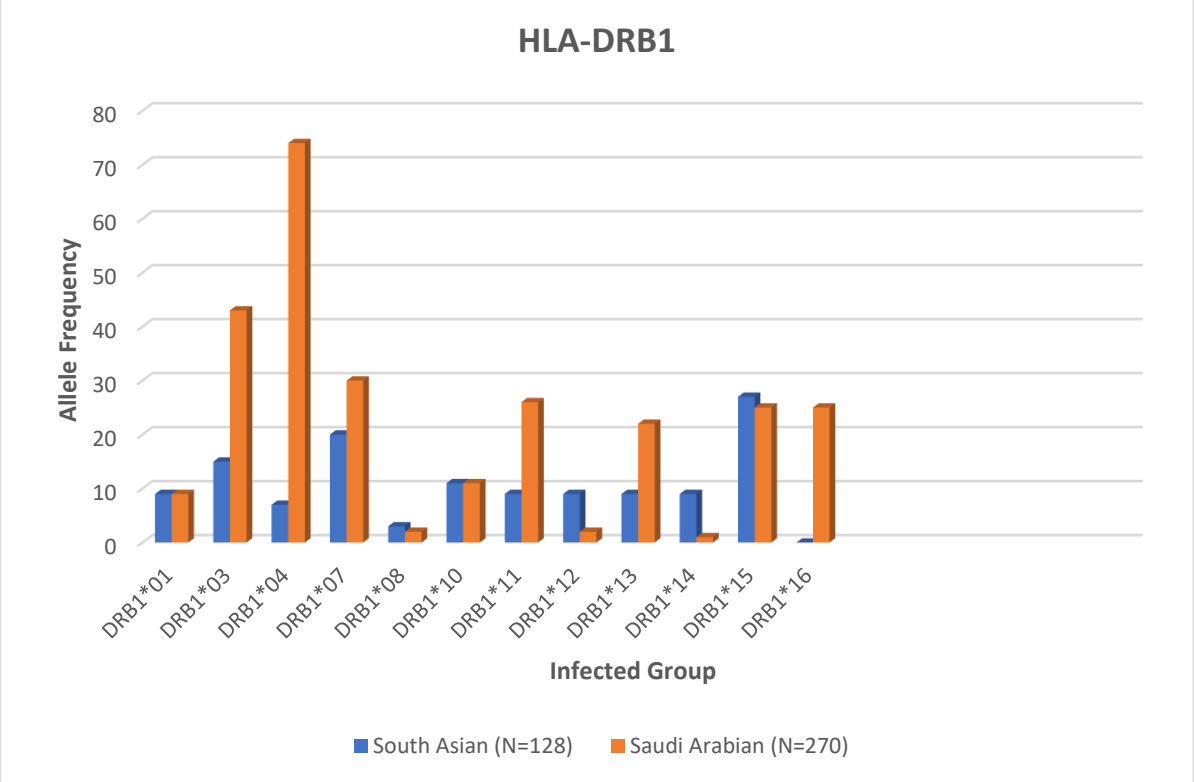

Figure 5.
The occurrence of HLA-DRB1 alleles in South Asians and Saudis affected with coronavirus infection.

Table 1.
Summary Table

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
Fatmah M. A. Naemi, 2021	Ferritin levels and HLA genotype in COVID-19 patients	Saudi Arabia/ 160,-/ Male and Female	(Cross-Sectional Study)	Saudi	Nasopharyngeal Swab/ RT-PCR	Blood/EZ1 Advanced-XL (Qiagen, USA) instrument/rPCR-SSO technique	May be affection of HLA, Increasing in Ferritin level, high rate of increasing in covid infection.	An increase in infection severity is linked to a high serum ferritin level. This preliminary study found a link, but further research is needed before it can be used in clinical practise.
Fatmah M. A. Naemi, 2021	The correlation between South Asians' HLA genotype and Covid19 infection outcomes	Asians (Bangladeshis, Indians, & Pakistanis)/ 95,-/ Male and Female	(Cross-Sectional Study)	Bangladeshis, Indians, and Pakistanis	Nasopharyngeal Swab/ RT-PCR	Blood/ EZ1 Advanced XL (Qiagen, USA) instrument/ PCR-rSSO	The frequency of HLAB*51 and -DRB1*13 were substantially greater in the patients lying in fatal group. While the patients in the group with mild infection had a substantially greater frequency of HLAB*35 compared to the patients lying in the group with fatal infection.	-
Ali H. Ad'hia, 2022	The relationship between the deletion/insertion of 14 bp in HLA-G polymorphism and the likelihood	Iraq/ 209,198/ Male and Female	(Cohort study)	Iraqi	Nasopharyngeal Swab/ RT-PCR	Blood/Promega, USA/ReliaPrep Blood gDNA Miniprep System kit/ELISA	In COVID19 patients, regardless of illness severity, sHLA-G levels were elevated. Furthermore, the	-

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
	of contracting COVID-19						deletion/insertion of 14 bp in HLA-G polymorphism has been linked with COVID-19 risk.	
Allen J. Norin, 2021	HLA B53 association with black COVID-19 patients	USA/ -,-/ Male and Female	(Cross-Sectional Study)	Black	-	Plasma/ ELISA/ -	Hospitalized Black COVID-19 patients who tested positive for HLA B*53 showed a 7.4-times increased likelihood of mortality compared to Black individuals tested negative for B*53, according to multivariate analyses. HLA B53 positive Black COVID19 individuals should be considered for faster immunisation and treatment.	-
Ashley Otter, 2022	Polymorphism of HLA-DR in infection with SARS-Coronavirus 2	UK/ 1364, -/ Male and Female	(Cross-Sectional Study)	-	-	Plasma/ ELISA/ -	Anti-spike protein antibody titers and DRB1 alleles did not interact following two coronavirus vaccination doses.	-

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
Ahmed Samir Abdelhafiz, 2021	Survival of HLA-B*15 in Egyptian individuals positive for Covid 19	Egypt/ 69,-/ Male and Female	(Cross-Sectional Study)	Egyptian	Nasopharyngeal Swab/ RT-PCR	Blood/Qiagen/QIAamp DNA small extraction kit/ LAB Type SSO typing kits	The higher the levels of creatinine, serum ferritin, and TLC, the lesser the rate of survival. More Studies require to understand relation of class I HLAs & Covid 19.	HLA-DP, -DR, & -DQ, might also influence predisposition to SARSCov2 & the progression to critical infection. However, additional research is needed to validate these findings in different populations
Chang Liu, 2021	HLA genetic polymorphism in covid 19	USA/ 234,-/ Male and Female	(Population-Based Case–Control Study)	-	Nasopharyngeal Swab/ RT-PCR	Blood/EZ1 (Qiagen) DNA Blood 350 µl Kit /NGS LR kit (One Lambda)	There is a chance that some HLA alleles may predispose or protect against covid 19.	Confirming and expanding these results will need future collaborative investigations of pooled cases and controls.
L. Lorente, 2020	Prognosis of covid 19 individuals and HLA genetic variants	Spain/ 72,3886/ Male and Female	(Cross-Sectional Study)	-	Nasopharyngeal Swab/ RT-PCR	Blood/Maxwell® RSC Device/PCR-SSO	The HLA genetic variation may have an impact on the mortality risk of Covid 19.	-

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
Habiba S. Alsafar, 2021	HLA profiles of infected individuals from the UAE with SARSCov2	UAE/ 115,-/ Male and Female	(Cross-Sectional Study)	UAE National	Nasopharyngeal Swab/ RT-PCR	Blood/Zinexts, Taiwan's MagPurix system/Omixon, Budapest, HLA-96/11 library kit, Hungary's Holotype	HLA A*26:01 and -B*51:01 have been found to indicate protective effects, whereas HLA -A*03:01, -DRB1*15:01, and B44 supertype were linked to the severity of Covid19.	To fully understand the function of HLA in coronavirus infection, more research with a bigger cohort and various populations is required. This will aid in the development of specialised vaccinations and the personalization of therapies.
Ghasem Solgi, 2021	The linkage between HLA-DRB1*04 and the severity of covid19 in Iranian individuals	Iran/ 144,-/ Male and Female	(Cross-Sectional Study)	Iranian	Nasopharyngeal Swab/ RT-PCR	Blood/ Modified salting out methods/PCR	HLA class II was found to have a significant connection with the Covid19 outcomes and clinical characteristics	As the result, new information on future vaccine tactics and clinical care of this viral infection may become available.
Yusuke Tomita, 2020	Variations in the HLA gene and covid 19 related mortality	-/ -,-/ Male and Female	(Cross-Sectional Study)	-	Nasopharyngeal Swab/ RT-PCR	In Silico Analysis	T-Cell antiviral response generation in genotypes HLA-A*11:01, -A*24:02 are more rapidly as compared to HLA-A*02:01.	-

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
Antonio Amoroso, 2020	The impact of HLA and AB0 variations on Covid19 infection and disease seriousness	Italy/ -,-/ Male and Female	(Cohort study)	Italian	Nasopharyngeal Swab/ RT-PCR	In Silico Analysis	Influence of HLA antigen played a significant role in COVID-19 clinical evolutions.	Other patient groups will need to be studied to corroborate these findings, as well as to see HLA-C, -DQ, and -DP, have a role in coronavirus infection and evolution.
Fatmah M.A. Naemi, 2021	Prevalence of HLA gene variants among individuals who have contracted Covid19	Saudi Arabia/ 135,135/ Male and Female	(Cross-Sectional Study)	Saudi	Nasopharyngeal Swab/ RT-PCR	Blood/EZ1 Advanced XL (Qiagen, USA) instrument/SSO PCR method	HLA genotypes help in determining the risk and effect of infection with covid 19.	-
Elisabeth Puchhammer-Stöckl, 2021	KLRC2 gene-encoding NKG2C receptor deletion and variations in HLA-E as significant contributor to covid19	-/ 361,-/ Male and Female	(Cohort study)	-	Nasopharyngeal Swab/ RT-PCR	Respiratory swab/ NucliSens EasyMag extractor (Biomereius)/ Taqman assay and touchdown PCR	The occurrence of severe SARS coronavirus 2 infections is significantly influenced NKG2C+ /HLA -E genetic variation, which may also be useful in identifying patients who are at severity for covid 19.	Furthermore, investigations in separate and larger research groups may indicate if these disparities in HLA-E variations are attributable to an overshadowing effect on a genome-wide scale through cross-replicating connections.

Author, Year	Objective	Country of study/ Cases,Controls/ Genders	Study design	Ethnicity	Method for Covid 19 (RNA Extraction Sample/ Amplification)	Method for HLA (Sample/ DNA Extraction/ HLA typing)	Conclusion/ Outcomes	Future Direction
Juan Francisco Gutie´rrez-Bautista, 2021	Analysis of HLA class I & II polymorphisms in covid19 infected individuals	-/ 450,-/ Male and Female	(Cohort study)	-	Nasopharyngeal Swab/ RT-PCR (cobas 6800 system)	Blood/QIAMP DNA (Qiagen, Germany) Blood short Kit/(One Lambda, California, USA) sequence-specific oligo-nucleotide typing/PCR with sequence specific primers	There is no correlation between HLA variations in predisposition or protection to Covid19.	The effect of polymorphisms of HLA on Covid19 result (risk/protection) may be partially hidden by current patient care advances. To find answers to these crucial problems, more research is required.

DISCUSSION

HLA Biomarker discovery may present an effective chance to forecast outcomes and gain a deeper understanding of disease biology, ultimately leading to enhanced human health and lower expenditures on health care (Ferreira de Araújo et al., 2022). Despite a multitude of studies targeted at understanding the link among HLA variations, SARSCov2 infection, and COVID-19 outcome, findings are still relatively dispersed and contradictory (Deb et al., 2022). Several studies have discovered substantial links involving particular HLA alleles and the predisposition and outcomes of certain viral illnesses. Table 2 summarizes the HLA haplotypes and variants identified as pivotal in SARS coronavirus 2 infection. HLA refers to a vast group of genes that regulate and activate the immune system in response to viruses. In this context, it is yet unknown how SARS coronavirus 2 infection and HLA genotype are related, with just a few research in this area focusing on identifying specific susceptibility alleles (Iturrieta-Zuazo et al., 2020). While this research has identified numerous genes that are linked to the prognosis of COVID-19 and predisposition to infection, flaws such as poor reproducibility, reporting quality, and assessment quality seem to be a major worry. Several analyses have underscored the importance of HLAs in both development and advancement of SARSCov2, whether integral to host's genetic responses or acting independently.

Due to the limited focus of these reviews, not all significant alleles could be thoroughly discussed, and there was a lack of cohesive discussion regarding various study methodologies and conflicting results across different alleles. Consequently, an effort was made to conduct a systematic comparative assessment of key HLAs and their implications in Covid19 predisposition, impact, and risks of death. This analysis utilized compiled data from 32 original research studies, following strict criteria for selecting studies and extracting data (Deb et al., 2022). This systematic review included experimental studies as well as population-based studies. Based on the research population, some contradicting results were discovered, and laboratory-based findings did not always match with bioinformatics analysis predictions. HLA-A produced the most contradictory results, but HLAs belong to class II produced more consistent results, regardless of study methodologies (Deb et al., 2022).

Because of the wide range of variation in research from diverse approaches, meta-analysis was not possible, implying that additional consistently designed investigations are needed. As a result, the findings should be interpreted with caution. Future research on underrepresented ancestries is also necessary since allelic frequency and linkage disequilibrium may differ between populations (Ferreira de Araújo et al., 2022). A review of several papers was conducted, revealing a range of findings and conclusions. According to one study, clinical outcomes following COVID exposure are predicted by HLA alleles in interaction with age, sex, and BMI (Langton et al., 2021). Another study found a link between HLA-A*02:01 and a higher susceptibility to COVID19 (Tomita et al., 2020). HLA -A01, -B07, -B08, -B44, & -C05 were found to be strongly linked with the chance of death in another investigation (Sakuraba et al., 2020). Other research suggests, the expanded haplotypes HLA -A02:05, -B58:01, -C07:01, & -DRB1*03:01 offer defense against infection with SARS coronavirus 2 in the Sardinian population. Lack of influenza vaccination may increase the chance of developing a more serious illness (Littera et al., 2020). One study found that HLA -DRB1*08 was linked to fatality in patients who are tested positive for COVID19 (Amoroso et al., 2021). Another study discovered that the prevalent HLA haplotypes

in the population of Italian individuals—HLA-A01:01g, -B08:01g, -C07:01g, -DRB103:01g and -A02.01g, -B18.01g, -C07.01g, -DRB111.04g—exhibited overlapping regional distributions. Furthermore, these haplotypes demonstrated significant associations, both positive and negative, with both the incidence and mortality rates of Covid19 (Pisanti et al., 2020). When compared to the moderate and severe groups, the findings indicate that individuals experiencing mild symptoms possess Class I HLA molecules potentially more adept at binding SARS coronavirus 2 peptides, alongside showing increased genetic diversity (Iturrieta-Zuazo et al., 2020; Shkurnikov et al., 2021). Researchers constructed basic HLA class I susceptibility index, finding a robust correlation with the severity rate through an exponential approximation (Ishii, 2020).

Table 2.

HLA loci	HLA allele/haplotype	Population	Sample size	Implication	Study	Year
A/B/C/DRB1/ DQA1/DQB1	A *01, 02, …, 68 B *07, 08, …, 58 C *01, 02, ..., 16 DRB1 *01, ..., 16 DQA1 *01, ..., 06 DQB1 *02, ..., 06	Asians (Bangladeshis, Indians, and Pakistanis)	95	The occurrence of HLA B *51 & DRB1 *13 was significantly elevated in individuals who died from the illness. Conversely, B*35 was observed with greater frequency in individuals with less severe infections compared to those who experienced fatal outcomes	Fatmah M. A. Naemi	2021
A/B/C/DRB1/ DRB3/DRB4/ DRB5/DQA/ DQB/DPA/DPB	B *53	African Americans	76	Black COVID-19 patients who were hospitalized and had the HLA B *53 had a 7.4-times greater chance of death compared to those who did not have the HLA B *53 allele.	Allen J. Norin	2021
A/B/C	B *15	Egyptians	69	Elevated levels of TLC, serum ferritin, and serum creatinine correlate with	Ahmed Samir Abdelhafiz	2021

				lower survival rates.		
A/B/C/DRB1/ DQB1	B *51:01, A*26:01, A *03:01, -DRB1 *15:01	UAE nationals	115	B *51:01 & A *26:01 are suggested to offer protection, Meanwhile, A *03:01, DRB1 *15:01, & B44 supertype have been linked to the severity of Covid19.	Habiba S. Alsafar	2021
DRB1/DQB1	DRB1 *04, DRB1 *11	Iranians	144	HLA class II played a pivotal role in the progression of disease and clinical features associated with coronavirus .	Ghasem Solgi	2021
A/B/C/DRB1/ DQB1	A *01,B *56, C*01,DRB1 *04	Saudi Arabians	135	HLA genotypes may influence both the predisposition to Covid19 infection and the outcomes following infection.	Fatmah M.A. Naemi	2021
A/B/C/DRB1/ DQB1	A *29:02,B *44:03, C *16:01,DRB1 *07:01,DQB1 *02:02	Spanish	450	HLA polymorphisms do not seem to affect predisposition to or resistance from Covid19.	Juan Francisco Gutie´rrez-Bautista	2021

HLA responses can be altered by viral variations, therefore disregarding this variable could result in erroneous negative/positive outcomes. Because of the extensive diversity of HLA alleles, studies have not been able to encompass all Class I & II HLAs simultaneously. Consequently, specific alleles' co-occurrence could not be ruled out. Moreover, with the exception of one study, non-classical HLAs were disregarded in all research efforts. Given the impact of single nucleotide variations on HLA responses in human genomes, incomplete (GWAS) genome-wide association studies may raise doubt on the findings. These limitations were balanced against the value of a comprehensive review that provides a current scientific perspective. Initially, numerous studies used international data sources to depict a global perspective, essential for shaping any universal COVID-19 control strategy. Secondly, various analytical methods have been explored, spanning from laboratory-based to

computational approaches, all underscoring the link between HLA and COVID19. This underscores the need for further rigorous studies on this topic. Lastly, in the rapidly evolving landscape of the epidemic, which significantly impacts community well-being, staying informed about current findings is essential. Despite rigorous methodologies and comprehensive data analysis, this systematic review has several potential limitations. The exclusion of non-English articles might have led to the omission of relevant studies, potentially biasing the results. The reliance on published studies means that unpublished data, which might contain critical insights, were not considered. The evolving nature of the COVID-19 pandemic and advancements in our understanding of the virus and its interaction with HLA genotypes mean that newer studies might provide different insights. Furthermore, the exclusion of case reports, opinion papers, and non-peer-reviewed preprints, while ensuring data quality, might have excluded emerging data and perspectives relevant to this rapidly evolving field. These limitations highlight the need for ongoing research to continuously update and refine the understanding of the relationship between HLA genotypes and COVID-19 outcomes.

Despite certain limitations, it is evident that our understanding of the worldwide prevalence of HLA alleles and their relationship with Covid19 is no doubt inadequate but vital. Standardizing methods for investigating this relationship is considered essential. Establishing an international collaboration to work on a worldwide level, ensuring comprehensive HLA frequency data from diverse populations through a well-organized biobank, is imperative for implementing effective prevention strategies. This could involve public health interventions and ensuring global vaccine efficacy. HLA typing can significantly affect COVID-19 risk assessment and treatment strategies by identifying individuals at varying degrees of vulnerability and the potential severity of the disease. Moreover, HLA type can also be used to customize treatment regimens, such as selecting antiviral drugs based on the immunological profile of a patient. HLA typing has also been correlate to convalescent plasma therapy, where ensuring compatibility between donor and recipient HLA types can reduce the risk of transfusion-related complications (Chavda et al., 2023). Additionally, HLA alleles have been shown to correlate with vaccine responses, indicating that individuals with certain HLA types may benefit from tailored vaccination strategies to enhance immune protection against SARS-CoV-2 (Mentzer et al., 2024; Lin et al., 2023).Overall, integrating HLA typing into clinical practice can lead to more effective and individualized management of COVID-19, improving patient outcomes.

CONCLUSION

The association between HLA and Covid-19 requires investigation in larger cohorts of individuals, as research so far has only covered a limited number of HLA alleles. A potential drawback of these studies is the current inability to assess the relative importance of HLA types compared to other established factors that modify disease risk, such as elderliness and existing medical conditions. Nevertheless, these discoveries could provide fresh perspectives on the mechanisms of SARSCoV2, inform the creation of vaccination initiatives, and lead to improved infection control measures, ultimately enhancing treatment, patient management, risk identification, and reducing illness and death rates. Pinpointing individuals at elevated risk for SARSCoV2 infection could aid in curbing virus transmission, easing the public health burden, and focusing preventive efforts. Present scientific data indicates that incorporating HLA testing into clinical trials alongside Covid19 testing could swiftly identify predictors of disease severity in the community. This approach could also help in customizing immunization programs for genetically vulnerable groups.

The findings of this research can inform clinical decision-making and public health policies, ultimately leading to improved health outcomes for COVID-19 patients and alleviating the burden on healthcare systems. This study enhances the understanding of COVID-19 pathogenesis and aids in the development of effective vaccines and therapeutics. It identifies genetic factors contributing to the severity or mildness of COVID-19, facilitating personalized treatment plans based on genetic makeup. Additionally, the research highlights specific HLA alleles associated with a higher risk of severe infection, which can inform targeted vaccination campaigns and increased monitoring of high-risk individuals.

FUTURE DIRECTIONS

Future research should encompass a broader spectrum of variables, extending beyond HLA alleles, to comprehensively explore their potential influence on COVID-19 severity. Variables such as advanced age, sex, pre-existing medical issues, and lifestyle choices should be considered in these investigations. Expanding the scope of the study to incorporate a larger and more diverse sample size would be valuable. A longitudinal analysis could be employed to explore the temporal connection between HLA alleles and Covid19 severity. Longitudinal studies offer the potential to shed light on how HLA alleles influence the establishment of Covid19 immunity and its progression. To enhance the applicability of future research findings, it is advisable to include a more extensive representation of ethnicities within the study population. This would help to provide a more thorough understanding of how different ethnic groups' COVID-19 severity and HLA alleles relate to one another. Future studies should also explore the linkage between Covid19 severity & HLA haplotypes. Investigating the combined effects of multiple HLA alleles within haplotypes may prove to be more relevant in understanding the complex dynamics underlying COVID-19 outcomes than examining individual alleles in isolation.

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