Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Immunology 238 (2022) 108990

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Protective HLA alleles against severe COVID-19: HLA-A*68 as an ancestral protection allele in Tapachula-Chiapas, Mexico

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ARTICLE INFO

Keywords:
HLA
MHC
SARS-CoV-2
COVID-19
México

ABSTRACT

HLA is a polymorphic antigen presenter which has provided valuable information on the susceptibility of populations to viruses. Therefore, the study of HLA can reveal specific susceptibility or resistance alleles to severe COVID-19 in an ethnically dependent manner. This pilot study investigated HLA alleles associated with COVID-19 severity in Tapachula, Chiapas, Mexico. A total of 146 Mexican Mestizos were typed for HLA class I and II using PCR-SSP. The patients were classified according to the outcome (death or improvement) and the infection's severity (mild or severe). In addition, a group of exposed uninfected individuals was included. HLA-A*68 was found to be a protective allele against the severe infection and fatal outcome; pC = 0.03, OR = 0.4, 95% CI =0.20–0.86, and pC =0.009, OR = 0.3, 95% CI =0.13–0.71 respectively. HLA-DRB1*03 also appears to be a protective factor against fatal outcome pC = 0.009, OR = 0.1, 95%IC = 0.01–0.66; however, the low frequency of this allele in the studied population limits the statistical power. The severity and fatal outcome of COVID-19 patients in Tapachula, Chiapas depend more on the lack of resistance than susceptibility HLA alleles.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute syndrome coronavirus 2 (SARS-CoV-2), has been the most challenging outbreak in recent history globally. It has had more impact than the outbreak produced by the severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) [1]. COVID-19 has a lethality rate, severity, and clinical behavior varying due to various factors that continue to be studied, such as age, comorbidities, geographical situation, and genetic predisposition.

GWAS studies have insight into genetic variants linked to susceptibility and severity in COVID-19, most of them implicated in immunological processes [2]. The immune response's effectiveness lies in the antigen presentation through Human Leukocyte Antigen (HLA), which varies among individuals. So, the HLA study could give an insight into the genetics affected in severe patients. HLA has been studied in the diversity of viral infections related to an adequate response to viruses and vaccines [3–5]. Relevantly, the study of Class II alleles allows

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https://doi.org/10.1016/j.clim.2022.108990
Received 22 October 2021; Received in revised form 13 February 2022; Accepted 25 March 2022
Available online 5 April 2022

capturing the susceptibility and resistance conferred by MHC genetic blocks [6]. Class II alleles are in linkage disequilibrium with Class I and other immune-related genes in the MHC area. The HLA genetic background is ethnically dependent, so the susceptibility and resistance HLA alleles for viruses vary across populations [7–9], and SARS-CoV-2 is not an exception, as demonstrated in recent studies [10]. Therefore, the HLA molecules that make up a haplotype determine survival during evolution. As a result, it seems advantageous to have HLA molecules with more significant binding specificities to SARS-CoV-2 virus peptides on the cell surface of antigen-presenting cells [11].

The infection statistics in countries and Mexico States are likely to be unfeasible to health measures' success and are likely to be determined by ethnicity and genetics [12]. The ethnicity patterns are of biomedical and anthropological importance due to the richness of admixture in Mexicans and SARS-CoV-2 HLA protection and resistance alleles and haplotypes, which have not been determined yet as a genetic factor of susceptibility or protection in Mexicans from Tapachula. Therefore, this research aims to study the HLA differences depending on the outcome (deceased vs. recovered), severity, and progression of COVID-19 in Mexican patients.

2. Materials and methods

2.1. Study population and COVID-19 Tapachula study design

Between March–December 2020, a prospective study was performed in Chiapas, southern México, to investigate the clinical, biochemical, and genetic factors associated with the progression of COVID-19 patients.

The study was developed in Tapachula, the second most populated municipality of Chiapas, located 23 km near the border with Guatemala, Central América, that provided attention to COVID-19 patients through two second-care hospitals.

The COVID-19 Tapachula study was conducted in the *"Clínica de enfermedades Respiratorias COVID-19"*, a care facility that provided attention to COVID-19 non-insured patients (unemployed population).

We enrolled any subject needing care attention for respiratory symptoms in the last seven days, independently of their requirement of hospitalization, that fulfilled the following eligibility criteria: 1) Met the operational definition of a suspected case of COVID-19 disease following WHO/PAHO, for the presence of sudden onset of fever and cough or sudden onset of three or more of the following symptoms: fever, cough, weakness or fatigue, headache, myalgia, sore throat, nasal cold, dyspnea, anorexia, nausea, vomiting, diarrhea or altered mental state; 2) has an available nasopharyngeal and/or pharyngeal swab for confirmation of SARS-CoV-2 infection; and 3) agreement of participation through an informed consent form. We excluded subjects with more than seven days of onset of symptoms at the moment of pharyngeal or nasopharyngeal swab collection. We prospectively collected all enrolled subjects' clinical and biochemical data through case report form (CRF).

2.2. Confirmation of SARS-CoV-2 infection

The diagnosis of SARS-CoV-2 infection of the patients enrolled was made in pharyngeal and nasopharyngeal swabs collected at seven days since the onset of symptoms. We used CDC 2019-Novel Coronavirus (2019-nCoV) and proceeds as manufacturer indications [13].

2.3. Classification of severity of COVID-19

To classify the severity of the disease, we used as a reference the ordinal scale of clinical improvement of the World Health Organization (WHO), which classifies the severity of COVID-19 in eight categories, evaluating the need for oxygen and advanced support. The categories are as follows: 1) non-hospitalized without limitations of activities. 2) Non-hospitalized: activity limitation, home oxygen requirement, or both. 3) Hospitalized does not require supplemental oxygen and no longer requires ongoing medical attention (if hospitalization was extended for infection control reasons). 4) Hospitalized, not requiring supplemental oxygen but requiring continuous medical care (covid-19 related or other medical conditions). 5) Hospitalized, requiring supplemental oxygen. 6) Hospitalized, requiring non-invasive ventilation or the use of high flow oxygen devices. 7) Hospitalized, receiving invasive mechanical ventilation extracorporeal membrane oxygenation (ECMO), and 8) death. We calculated the score based on CRF records collected in each study visit.

The classification of individuals was performed with the guidance of the WHO system. Patients with classifications 1, 2, and 3 were regrouped as mild, while individuals with ratings from 5 to 8 were regrouped as severe. 1–3 were integrated as mild since they did not require mechanical ventilation or strict medical surveillance, while strata 5–8 required hospitalization or oxygen or mechanical respiratory assistance and/or strict medical surveillance. This simplification of the WHO classification was based on the medical experience at that time since the patients who required respiratory assistance or strict medical surveillance because of SARS-CoV-2 infection or other concomitant conditions progressed to the severe estate in most cases and many with fatal outcomes.

2.4. HLA study population

For this study, the groups to compare Class I and II HLA's allelic frequencies were classified by the primary outcome (deceased and recovered) of the COVID-19. The severity of the symptoms at the first 24 h after enrollment (mild and severe) was the other classification criterion. An additional group without infection was included as a reference group. This reference group included exposed individuals with negative qRT-PCR for SARS-CoV-2 infection.

2.5. Ethical considerations

The COVID-19 Tapachula Study fulfilled the principles of the Helsinki Declaration. The study protocol was evaluated and approved by the ethics and research committee of the Hospital Regional de Alta Especialidad Ciudad Salud (Id: 08/2020) and the research and ethics committee of the Ministry of Health of the state of Chiapas (Id: EADIS -010-2020). Participation was voluntary, and specific procedures were presented in writing in informed consent. All participants were over 18 years of age and gave their permission. If individuals had not been in eligible conditions, legal representatives authorized their participation. The data collected from each patient was captured in electronic databases and managed as confidential. Any informed consent form was obtained for the retrospective study, guaranteeing confidentiality and anonymization of data.

2.6. HLA typing

Genomic DNA was obtained from peripheral blood collected in EDTA tubes using the QIAamp DNA mini kit (Qiagen, Valencia, CA, USA). The DNA quality was assessed through spectrophotometry technique and agarose electrophoresis. HLA class I and II typing was performed using PCR-SSP Sequence-specific primers. The loci typed were HLA-A, —C, —B, -DRB1, -DQB1, and -DQA1. The data is shown in Supplementary material S1. The kit HLA-FluoGene DRDQDP plus (Inno-Train Diagnostic GmbH, Kronberg im Taunus, Alemania) was used. All the process was performed according to manufacturer instructions. Allele PCR products were analyzed in the FluoVista analyzer with a pre-PCR and post-PCR reading using Aspect F.A. V2.0 software. Subsequently, the raw data was imported into FluoGene V 1.5.5.x (Inno-Train Diagnosetik GmbH, Kronberg im Taunus, Germany) software. This software assigns the appropriate results.

2.7. Statistical analysis

Differences in HLA class I and II frequencies were analyzed using X^2, and *p*-values less than 0.05 were considered statistically significant. If appropriate, the p-values were also corrected using the Bonferroni method (for allele frequencies, multiplying the original p-value by the number of alleles); odds ratios and 95% confidence intervals (95%CI) were calculated to measure association strength with EPIINFO v7 software. Descriptive statistics were performed using the SPSS program.

3. Results

3.1. Clinical and sociodemographic characteristics of COVID-19 patients and exposed-non infected individuals

111 cases representing the whole spectrum of disease severity and the primary outcome were included. Those cases were considered in the present report. There were 51 mild and 60 severe cases; of the 111 patients studied, 69 patients recovered from COVID-19, while 42 died during follow-up. The exposed non-infected group consisted of 22 males (63%) and 13 females (37%) with a mean age of 46.3 ± 6.4 years.

The patients' main clinical and sociodemographic characteristics are shown for each group in Table 1.

Most of the symptoms showed an average distribution among the group; only dyspnoea showed statistical difference being evaluated by the outcome and the severity level at the first 24 h of hospital admission. The dyspnoea had a negative impact on the outcome. Deceased patients showed a higher frequency of dyspnoea than recovered patients, pC = 0.00004, OR = 8.07, 95%IC = 2.83–22.98. Similarly, the dyspnoea frequency was higher in severe than mild patients pC = 6.5E-7, OR = 8.9, 95%IC = 3.71–21.38. There was no statistical association among symptoms and specific HLA Class I or II alleles.

Table 1
(A, B y C). Clinical and sociodemographic characteristics in COVID-19 patients and exposed non-infected individuals, by outcome (A) and by severity (B).

Clinical variable	A. Outcome		B. Severity level		C.Controls
	Deceased *N* = 42	Recovered *N* = 69	Mild *N* = 51	Severe *N* = 60	Exposed non-infected *N* = 35
Mean age ± SD (years)	56.4 ± 11.7	42.30 ± 10.43	53.0 ± 12.5	56.4 ± 10.8	46.3 ± 6.4
Female, n (%)	12 (29)	28 (40)	22 (44)	17 (28)	13 (37)
Male, n (%)	30 (71)	43 (63)	29 (56)	43 (72)	22 (62)
Fever, n (%)	31 (74)	60 (86)	44 (86)	44 (73)	0 (0.0)
Cough, n (%)	30 (71)	52 (75)	37 (72)	42 (70)	0 (0.0)
Dyspnoea, n (%)●	37 (88)	33 (48)	17 (33)	49 (82)	0 (0.0)
Headache, n (%)	22 (52)	42 (61)	33 (64)	30 (50)	0 (0.0)
Others●, n (%)	34 (81)	61 (88)	42 (83)	49 (82)	0 (0.0)
Comorbidity●, n (%)	22 (52)	26 (38)	17 (33)	30 (50)	3 (9)
Deceased, n (%)	42 (100)	–	19 (19)	38 (63)	0 (0.0)
Health Improvement, n (%)	0 (0.0)	69 (100)	41 (81)	22 (37)	NA

●Others include diarrhea, conjunctivitis, rash, anosmia, dysgeusia, chest pain.
●Comorbidities include diabetes, heart disease, COPD, hypertension, kidney disease, obesity.
●The dyspnoea had a negative impact on the outcome. Deceased patients showed a higher frequency of dyspnoea than recovered patients, pC = 0.00004, OR = 8.07, 95%IC = 2.83–22.98.
Similarly, the dyspnoea frequency was higher in severe than mild patients pC = 6.5E-7, OR = 8.9, 95%IC = 3.71–21.38.

3.2. Hardy Weinberg equilibrium and diversity values

The Hardy Weinberg equilibrium (HWE) was calculated for the included Class I and II loci (Supplementary material S2). The estimation was performed using ARLEQUIN 3.5.2.2 human genetics program.

3.3. HLA-A*68 as a protection factor against severe COVID-19 disease and fatal outcome by SARS-CoV-2 infection

3.3.1. HLA-A*68

The comparison between COVID-19 patients and exposed non-infected individuals showed statistically significant differences, showing the HLA-A*68 as resistance factor pC = 0.003, OR = 0.4, 95% IC = 0.19–0.69 (Table 2). The comparison between severe COVID-19 patients and exposed non-infected individuals showed statistically significant differences pC = 0.03, OR = 0.4, 95% IC = 0.20–0.86 (Table 3). This data means the frequency of HLA-A*68 is diminished in Severe COVID-19 patients, and it confers 2.4 times the resistance against SARS-CoV-2 severe infection to carriers. In the same way, the comparison between diseased COVID-19 patients and exposed non-infected individuals showed statistically significant differences pC = 0.009, OR = 0.3, 95% IC = 0.13–0.71 (Table 4). This data means the frequency of HLA-A*68 is diminished in diseased COVID-19 patients, and it confers 3.3 times protection against a fatal outcome due to SARS-CoV-2 infection in Tapachula, Chiapas mestizo individuals. The complete resume of HLA-Class I allele frequencies is shown in the **Supplementary material S3.**

3.4. HLA-A*01 as a risk factor for fatal outcome

The comparison between patients who died and those who recovered showed statistically significant differences *Pc* = 0.03, OR = 4.73, 95%IC = 1.22–18.38.

3.5. HLA-DQB1*02 and HLA-DRB1*03 frequency is diminished in Severe COVID-19 patients & deceased individuals

3.5.1. HLA-DQB1*02

The analysis between severe COVID-19 patients and exposed non-infected individuals showed statistically significant differences pC = 0.05, OR = 0.2, 95% IC = 0.04–0.89 (Table 3). This data means the frequency of HLA-DQB1*02 is diminished in Severe COVID-19 patients, and it confers 5.5 times the resistance against SARS-CoV-2 severe infection to carriers. Likewise, the comparison between the deceased group and the exposed non-infected showed a diminished frequency of HLA-DQB1*02 without statistical significance showing a non-corrected $p = 0.05$ (Corrected $p = 0.104$), OR = 0.2, 95% IC = 0.05–1.12 (Table 4). On the other hand, this allele is enriched in patients with mild disease,

Table 2
HLA Class I and II alleles in COVID-19 patients.

HLA	Covid-19 *N* = 111 (222alleles)		Exposed non-infected N = 35 (70 alleles)		pC	OR	95%IC	
	n	AF	n	AF				
A*68	28	0.126	20	0.286	0.003	0.4	0.19	0.69
DRB1*15	16	0.072	3	0.043	0.558	1.7	0.49	6.14
DRB1*03	4	0.018	9	0.129	0.0003	0.1	0.04	0.42
DQB1*02	13	0.064	7	0.100	0.459	0.6	0.23	1.60

The HLA-DQB1*02 frequency for the COVID-19 group is based on a total of 204 alleles.

Table 3
HLA Class I and II alleles in Severe COVID-19 patients.

HLA	Severe N = 60 (120 alleles)		Exposed non-infected N = 35 (70 alleles)		pC	OR	95%IC	
	n	AF	n	AF				
A*68	17	0.142	20	0.286	0.03	0.4	0.20	0.86
DRB1*15	10	0.083	3	0.043	0.44	2.0	0.54	7.64
DRB1*03	3	0.025	9	0.129	0.01	0.2	0.05	0.67
DQB1*02	2	0.020	7	0.100	0.05	0.2	0.04	0.89

The HLA-DQB1*02 frequency for the Severe COVID-19 group is based on a total of 102 alleles.

Table 4
HLA Class I and II alleles and haplotypes in deceased COVID-19 individuals.

HLA	Deceased N = 42 (84 alleles)		Exposed non-infected N = 35 (70 alleles)		pC	OR	95%IC	
	n	AF	n	AF				
A*68	9	0.107	20	0.286	0.009	0.3	0.13	0.71
DRB1*15	10	0.119	3	0.043	0.161	3.0	0.80	11.43
DRB1*03	1	0.012	9	0.129	0.009	0.1	0.01	0.66
DQB1*02	2	0.024	7	0.100	0.104	0.2	0.05	1.12

The HLA-DQB1*02 frequency for the deceased COVID-19 group is based on a total of 82 alleles.

while patients with severe disease have low frequencies pC = 0.02, OR = 0.16, 95%IC = 0.03–0.74, so it is supported that it is a protective factor to develop severe disease. Supplementary material S6.

3.5.2. HLA-DRB1*03

The comparison between COVID-19 patients and exposed non-infected individuals showed statistically significant differences pC = 0.0003, OR = 0.1, 95% IC = 0.04–0.42 (Table 2). It shows 8.04 times protection for carriers. While the comparison between severe COVID-19 patients and exposed non-infected individuals showed statistically significant differences pC = 0.01, OR = 0.2, 95% IC = 0.05–0.67 (Table 3). It confers 5.7 times protection against developing the severe disease for carriers. Similarly, when compared deceased COVID-19 patients and exposed non-infected individuals was obtained pC = 0.009, OR = 0.1, 95% IC = 0.01–0.66. (Table 4). This represents a decrease in allele frequency of HLA-DQB1*03 in deceased COVID-19 individuals. It might confer 12.2 times the protection against a fatal outcome by SARS-CoV-2 infection. The complete HLA-Class II allele frequencies resume is shown in Supplementary material S3.

3.6. HLA-DRB1*15 ~ DQA1*01 ~ DQB1*06 haplotype and their individual alleles' frequency increased as the severity of the disease and the worsening of the outcome did it

Supplementary material S4 shows the frequency of Class II HLA haplotypes. There is shown how the frequency of HLA-DRB1*15 ~ DQA1*01 ~ DQB1*06 is increased as the severity of the disease, and the worsening of the outcome does it: exposed non-infected (2.5%), improvement (3.2%), mild (4.8%), severe (9,8%) and diseased group (12.2%). The frequency of individual alleles showed the same tendency. HLA-DRB1*15 is increased in diseased group (11.9%), Severe (8.3%), Mild (7.8%), improvement (5.8%) and exposed non-infected (4.3%). The HLA-DQA1*01 in diseased group (31.7%), Severe (27.5%), Mild (26.2%), improvement (21%) and exposed non-infected (17.5%) and finally the HLA-DQB1*06 in diseased group (19.5%), Severe (17.6%), Mild (15%), improvement (19.2%) and exposed non-infected (14.3%). (Fig. 1).

4. Discussion

In this pilot study in Tapachula, Chiapas México, the frequency of the allele HLA-A*68 is diminished in patients with severe disease and who had a fatal outcome. HLA-A*68 is an ancestral allele present in high frequencies in indigenous ancestral populations in Mexico, and the highest frequency is presented by the Teenek population [14], Yucatan Merida, and Yucatan rural inhabitants [15]. Around the World, the highest frequencies are presented in South American indigenous populations in Argentina, Paraguay, and Chile [16–18]. So far, there are no established studies of HLA in the population of Tapachula, Chiapas. Still, it has been estimated that the mestizo population of Chiapas has an indigenous component of 71.61% [19], partly explaining the high frequency of HLA-A*68 in mestizo individuals in Tapachula, Chiapas. The presence of protective alleles like HLA-A*68 could explain a little bit why this locality has been one of the least affected throughout Mexico, presenting low incidence rates of COVID-19.

Class I HLA proteins have been associated with SARS-CoV-2 effective or deficient presentation of peptides to T-Cells. In-Silico models of HLA I-viral peptide binding affinity have given a role to HLA Class-I genotype in SARS-CoV-2 infection and progression. HLA-A*68:01 and HLA-A*68:02 can bind a high number of SARS-CoV-2 peptides either loosely or tightly. The studies suggest that patients with mild disease present Class I HLA molecules with a higher theoretical capacity for binding SARS-CoV-2 peptides and showed greater heterozygosity than moderate and severe groups [20], congruent with this study findings.

In addition, recent in silico studies have demonstrated the ability of HLA-A*68 to bind peptides from the SARS-CoV-2 envelope, which have a homologous sequence to the neuronal cell adhesion molecule (NCAM) [21]. HLA-A*68 may be responsible for developing Guillain Barre Syndrome (GBS) after SARS-CoV-2 infection or SARS-CoV-2 vaccines application due to epitope mimicry phenomena. The envelope proteins are 85% identical to NCAM. Analysis of binding patterns between HLA-A*68, NCAM epitopes, and envelope epitopes revealed that both epitopes share binding sites in the groove of HLA-A*68. They share hydrogen bonds with tyrosine 99, Asparagine 66, and Asparagine 63 [21]. However, in the infected population in Tapachula, Chiapas, there have been no known cases of GBS due to SARS-CoV-2 infection or vaccination. Some variants of HLA-A*68 may be resistance factors against SARS-CoV-2 for their effective binding to envelope proteins. At the same time, A*68 variants could be susceptibility factors for GBS because of the epitopes similarity of NCAM and envelope proteins of SARS-CoV-2. However, amino acid changes among HLA-A*68 variants can determine both activities or one or the another.

The more frequent variants in nearby Chiapas indigenous populations are HLA-A*68:03 and -A*68:01. HLA-A*68:03 differs from variant HLA-A*68:01 and -A*68:02 at amino acid positions 70 and 97, respectively (Supplemental material S5 shows the protein alignments of different HLA-A*68 variants). These amino acid changes do not exactly match the share hydrogen bonds mentioned above. Still, they are close enough to change the binding dynamics, either by adding or removing a steric impediment or inducing a significant three-dimensional structure change and arrangement of the HLA-A*68 binding groove. Thus HLA-A*68 variants could show selectivity with the envelope proteins of SARS-CoV-2 and NCAM. It seems that the Chiapas individuals carry a variant with an affinity for the SARS-CoV-2 envelope proteins and not for NCAM. A high-resolution HLA study to define the HLA-A*68 variants present in this group would be helpful to support the assumptions around HLA-A*68 protection and susceptibility to GBS.

On the other hand, the HLA-A*01 allele was associated with a fatal outcome. This allele has been described in the in-silico analysis with the ability to join SARS-CoV-2 epitopes [22]. Probably the binding effectiveness could be related to an excessive immune response that can lead to a serious inflammatory response predisposing to the fatal outcome. More research is necessary around this allele with a high number of participants.

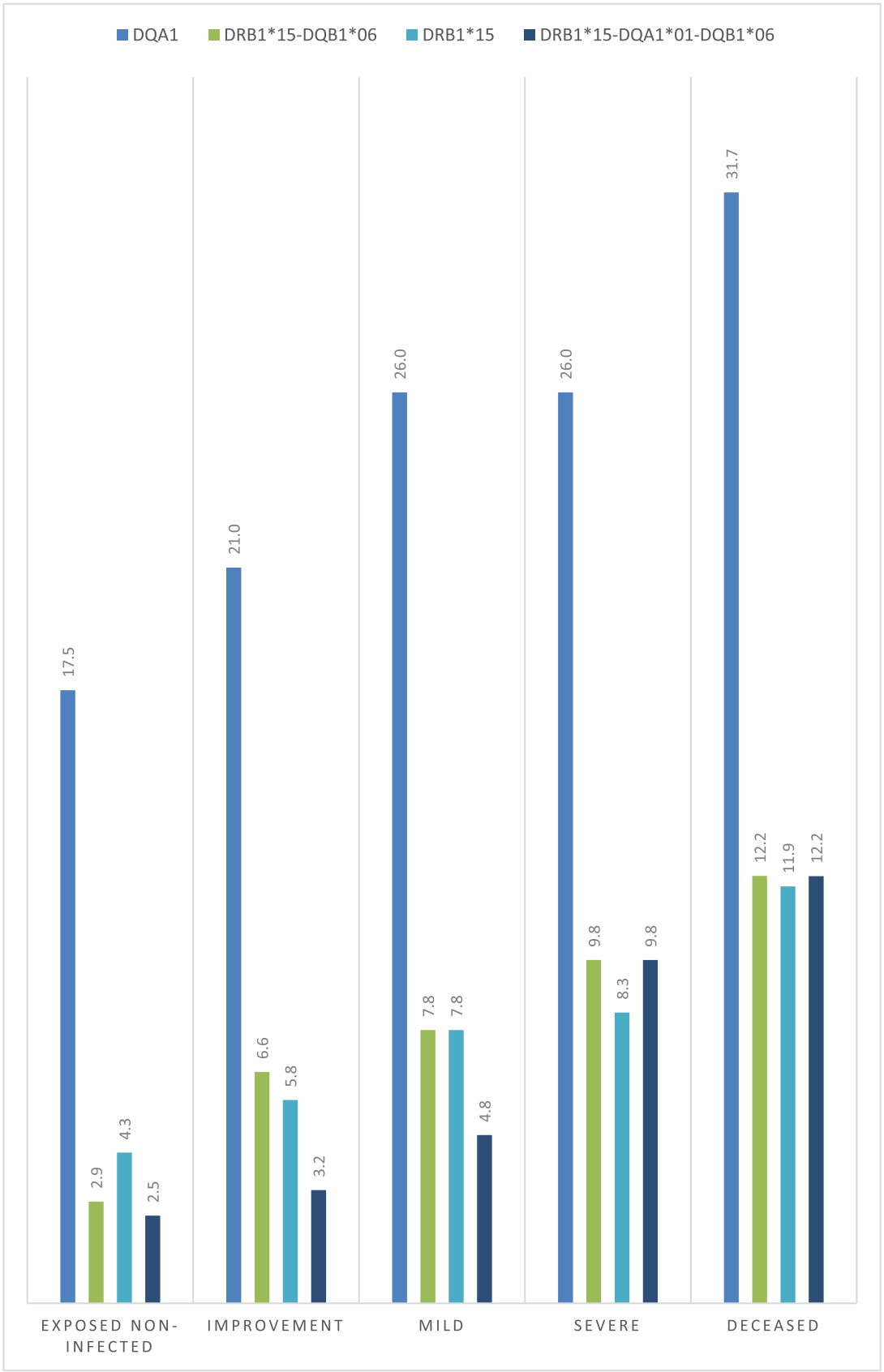

Fig. 1. HLA-Class II alleles and haplotypes with increased frequencies in COVID-19 patients. The graphic shows how the allele and haplotype frequencies increased as the severity of the disease and the worsening of the outcome did it.

On the other hand, other non-autochthonous alleles HLA-DQB1*02 and HLA-DRB1*03 (identified previously as Caucasian alleles) frequencies were found diminished in Severe COVID-19 patients and patients who had a fatal outcome compared with exposed non-infected individuals. The results obtained with these alleles are less representative and have less statistical power due to the low frequency of these alleles in the Tapachula, Chiapas population. However, they are discussed because the results are congruent with some previously reported European populations.

It was observed that the frequency of HLA-DQB1*02 decreased as the severity of the disease and the worsening of the outcome increased. However, only the comparison between Severe Covid-19 patients and Exposed non-infected individuals reached a statistical difference. Both HLA-DQB1*02 and -DRB1*03 have probably shown differences because of the linkage disequilibrium between them and between other HLA-Class I alleles.

The HLA-DRB1*03 variants have been previously reported as protective factors for SARS-CoV-2 and other Coronaviruses as SARS-CoV and MERS-CoV. The epitopes presented by this allele could be in conserved regions of SARS and recognized coronaviruses, being similar to the viruses mentioned above. So far, Nucleocapsid epitope highly conserved in SARS-CoV, MERS-CoV, and even related bat CoV is presented by human leukocyte antigen (HLA) DR2 and DR3 molecules and mediated cross-protection between SARS-CoV and MERS-CoV [23]. Therefore, the epitope recognized in SARS-CoV-2 by HLA-DRB1*03:01 could be a region in the Nucleocapsid of the virus, which is highly conserved, immunogenic, and abundantly expressed during infection. The nucleocapsid region is also targeted by CD4+ T cells from SARS convalescent patients [24]. Congruently, HLA-DRB1*03:01 has been reported to provide protective antiviral effects in enhancing the function of CD4+ T-helper cells [25].

Additionally, the HLA-DRB1*03 resistance to SARS infection has been previously demonstrated. A case-control study revealed that the HLA-DR*03:01 alleles conferred resistance against SARS infection ($p < 0.05$) [26]. Another study corroborated the resistance role of HLA-DRB1*03 in the development of severe acute respiratory syndrome; pC = 0.004; OR = 0.06; 95%IC = 0.01–0.47 [25].

Recently, the extended haplotypes HLA-A*02:05 ~ B*58:01 ~ C*07:01 ~ DRB1*03:01 and HLA-A*01:01 ~ B*08:01 ~ C*07:01 ~ DRB1*03:01 have been cataloged with a protective effect against SARS-CoV-2 infection in an ethnically dependent manner [27,28]. However, we emphasize that the low frequency of HLA-DRB1*03 has limited a categoric conclusion of the resistance role of HLA-DRB1*03 in the Tapachula, Chiapas populace. On the other hand, the HLA-DRB1*08, an autochthonous and high-frequency allele in this populace, is a risk factor in two studies. Peptide binding prediction analyses showed that these HLA-DRB1*08 alleles could not bind any viral peptides with high affinity [27,29]. However, this fact has not been evident in this study.

Likewise, it was observed that the frequency of HLA-DQB1*02 decreased as the severity of the disease and the worsening of the outcome increased. The potential reasons could be related to the fact that HLA-DQ2 (DQA1*05:01 ~ DQB1*02:01 known as DQ2.5) has been associated with poor responses to several vaccines [30–32]; and failure to control hepatitis virus C [33]; and hepatitis virus B [34]. Moreover, this allele confers genetic risk to several autoimmune diseases such as type 1 diabetes, celiac disease, and systemic lupus erythematosus [35,36]. The importance of the HLA-DQB1*02 in virus response is related to the previous peptide presentation management by cofactors as the invariant chain (Ii) and HLA-DM. The peptide presentation by MHC Class II, including DQ2, is influenced by interaction with these antigen presentation cofactors. HLA-DM constrains epitope selection in the human CD4 T cell response to the vaccinia virus, which favors the presentation of peptides with longer HLA-DM-mediated half-lives [37]. HLA-DM protects peptide-receptive MHC II from degradation by peptide exchange when peptides are available. It edits bound peptides favoring the high-affinity ones for cell surface presentation [38]. Notably, HLA-DQ2 has reduced DM interaction compared with most other alleles [38–40]. In this context, the apparent protective role of HLA-DRB1*02 could be related to a less dynamic process of viral peptide presentation and the retarding or abolishment of the onset of the immune and inflammatory response. Which, on the contrary, is disadvantageous in inducing immunity with certain vaccines.

In contrast, it was observed an increased frequency of the haplotype DRB1*15 ~ DQA1*01 ~ DQB1*06 as the severity, and the worsening of COVID-19 increased. The HLA-DRB1*15:01 and -DQB1*06:02 have been found as risk alleles for COVID-19 in Italian patients [41]. Furthermore, this haplotype and the individual alleles have been associated with autoimmunity and cancer in specific seropositive individuals. For instance, the HLA-DR15-DQ6 and tumor necrosis factor a-11 haplotype increase the risk for cervical intraepithelial neoplasia in human papillomavirus 16 seropositive women [42]. Additionally, it has been determined that HLA-DRB1*15 restricts an epitope on dengue-4 recognized by human CD4+ CD8- cytotoxic T lymphocyte clones, showing a flavivirus-cross-reactive reaction [43]. Other studies have associated HLA-DRB1*15 with no Virus C hepatitis progression in an ethnically dependent manner [44]. In silico studies have predicted more than 628 epitopes in the S protein for HLA Class II, which underlines the importance of studying HLA in different populations, considering the admixture.

Further studies in the Mexican population are necessary to accomplish the differences in some of the wealthiest admixed populations and know the influence of the genetic background in responding to the disease that has been markedly differing around the country.

This study's slight association of some HLA-Class II alleles shows that the severity of COVID-19 is described partly as an autoimmune phenomenon. In contrast, disease onset and progression by viral infections are usually associated with Class I polymorphisms.

It is well known that genetic factors partially contribute to the clinical outcome. Nevertheless, other confusing factors might also be applied—comorbidities, such as hypertension, diabetes, male gender, and older age. Interestingly, none of them are statistically relevant in this study. The only clinical feature that reached statistical significance was the presence of dyspnoea in the more severe cases. This may be related to access to health care providers in specialized hospitals.

Finally, it was noteworthy that HLA-DR alleles were in Hardy Weinberg equilibrium in patients and controls except for the severe and deceased groups, which required further investigation. The slight deviation from HWE could tell us something about the dynamic of autoimmune response HLA-Class II-mediated in Severe SARS-CoV-2 infected individuals who are driven to a fatal outcome.

5. Conclusions

HLA-A*68 Class I, an ancestral allele present in high frequencies in indigenous populations of Mexico, contributes to the resistance to develop the severe disease by SARS-CoV-2 infection in Tapachula, Chiapas. HLA-DRB1*03 and -DQB1*02 showed diminished frequencies in severe patients and deceased individuals. It could be assigned a protective role with an effective peptide presentation, previously studied in mice models with other coronaviruses strains.

Acknowledgments

This work was funded by the National Council for Science and Technology (CONACyT) through the Support Program for scientific, technological and innovation activities (PAACTI) in its 2020-1 call with project number 312321. Additionally, a part of the collection and processing of samples was financed with research resources from budget item E022 "Research and Technological Development in Health" of the Regional Center for High Specialty of Chiapas in the years 2020 and 2021. The authors thank all individuals with COVID-19 and healthy controls who have participated in this genetic study.

The authors appreciate the support of the following people: Dr. Jose Manuel Cruz Castellanos, Ministry of Health of the State of Chiapas, for supporting the evaluation, planning, and correct execution of the project in the COVID-ISSSTECh Clinic; Dra. Leticia Jarquin Estrada, Director of Public Health of the State of Chiapas, supports the project's planning, Dra. Concepción Domínguez Gonzalez, Dr. Fernando Tapia Garduño, Lic. Guillermina Grajales and C.P. Elizabeth Abarca from Centro Regional de Alta Especialidad de Chiapas, for their support with the project's financial management; Dr. Angel Gabriel Ocampo, for his help in the District of Health No. 7 in Tapachula and access of data in Clínica COVID-ISSSTECh; QFB. Edna del Alba Garcia Gómez for her support in providing data and information regarding patients' molecular tests; Dr. Omar Gómez Cruz, for his help planning and executing the project inside Clínica Covid-ISSSTECh during the period of enrollment; Lic. Vania Mazariegos Cancino and C.P. Fabiola Martinez Alvarado, from Hospital Regional de Alta Especialidad Ciudad Salud for their administrative support procedures the project; Dr. Fernando Tapia Garduño, C.P. Crisoforo Ruperto Trejo, Lic. Daniela Cunjama, Lic. Gilberto Orozco and C. P. Elizabeth Abarca, from the Centro Regional de Alta Especialidad de Chiapas, for their invaluable administrative support with the correct management project budget; Dr. Julio Adrian Rosales Trujillo, Rosales, Dra. Fernanda Santiago Roman, Dr. Victor Hugo Figueroa Zariñana, and Dr. Manuel Rojas Maldonado, medical undergraduate students from de Tapachula Faculty of Medicine, Universidad Autónoma de Chiapas, for their important support with the management of datasets; and QFB Zyania Arroyo Chiu for her support with sample management across the project.

Appendix A. Supplementary HLA data tables

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2022.108990.

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