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Determining the role of HLA-B27 on COVID-19

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Abstract

Aim: Human leukocyte antigen-B27 (HLA-B27) binds antigenic peptides in the structure of some viruses and presents them to cytotoxic T lymphocytes and plays a role in the immune response against these viruses. It has also been found to be associated with auto-immunity as an inverse relationship and is associated with a number of auto-immune inflammatory diseases, especially Ankylosing Spondylitis (AS). Our aim in this study is to determine the role of HLA-B27 in Severe Acute Respiratory Syndrome (SARS)-Cov-2 (Coronavirus Disease-COVID-19).

Materials and Methods: 90 HLA-B27 positive and 96 HLA-B27 negative cases were included in the study. COVID-19 Polymerase Chain Reaction (PCR) results and Thorax Computed Tomography (CT) results, hospitalization and death records of the cases were retrospectively analyzed from the system records. Results were compared between HLA-B27 positive and negative groups.

Results: Of the HLA-B27 positive cases, 32.2% had COVID-19 positivity, 5.6% had COVID-19 lung involvement. 44.8% of HLA-B27 negative cases had COVID-19 positivity and 11.5% had lung involvement. There was no significant difference between the HLA-B27 positive and negative groups in terms of having COVID-19 infection, lung involvement, hospitalization and death rates.

Conclusion: The results of our study show that HLA-B27 does not have a protective role in terms of having COVID-19 and lung involvement. Again, since no auto-immunity-related SARS was observed in any of the patients, it can be said that it did not increase the severity of the hyper-immunity-related disease and did not increase the risk of death in particular for COVID-19. These results need to be supported by more studies.

Introduction

Human leukocyte antigen (HLA)-B27 is a molecule encoded in the B locus of the major histocompatibility complex located on the short arm of chromosome 6 [1]. HLA class 1 molecules bind antigenic peptides for cell surface presentation to cytotoxic (CD8+) T lymphocytes. HLA-B27 binds and delivers peptides from Influenza, Human Immunodeficiency Virus (HIV), Epstein-Barr Virus, Hepatitis C Virus and other viruses. This leads to strong and specific cytotoxic T lymphocyte responses that play an important role in the body's immune response to these viruses [2].

While HLA-B27 plays a role in defense against viruses, it is adversely associated with auto-immunity and it has been found to be closely associated with some seronegative spondyloarthropathies, primarily ankylosing spondylitis (AS), inflammatory bowel diseases (IBD) and auto-immune uveitis [3]. There are also analyzes reporting the relationship of HLA-B27 with Behcet's Disease [4]. HLA-B27 is detected in approximately 90% of AS patients [1]. The prevalence of HLA-B27 in general populations has given different results according to regions and races around the world. The prevalence was found to be lowest in the equatorial region and highest in northern countries [3]. In a study conducted in Turkey, the frequency of HLA-B27 in the general population was reported to be less than 8% and AS was observed in 1-2% of positive individuals [5].

Coronaviruses are enveloped, positive, single-stranded RNA viruses with ~30 kb of genetic material. Severe Acute Respiratory Syndrome (SARS)-Cov-2 (SARS-CoV-2) is classified as a beta coronavirus subtype that was first detected in Wuhan, China in December 2019 [6]. The disease caused by SARS-CoV-2 was named Coronavirus disease (COVID-19) by World Health Organization (WHO). Symptoms of patients infected with SARS-CoV-2 range from minimal symptoms to severe respiratory failure that

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can progress to multi-organ failure [6]. Although lung involvement is prominent, many other organs can also be affected. In computed tomography (CT) scanning, a characteristic ground-glass appearance can be seen even in the lungs of asymptomatic patients [6]. It is stated that genetic variability causes different results in protection from COVID-19 infection or in the severe occurrence of infection [7]. Due to the important role played by HLA antigens in the defense against viruses, its response to COVID-19 infection deserves evaluation.

As a result of researches, 105 known subtypes of HLA-B27 have been identified and it is stated that these subtypes have different character traits [8]. Considering the role of HLA antigens in the regulation of immune response, it is stated that individual HLA subtypes give different responses in sensitivity and severity to SARS-CoV infections [9]. It has been reported that the alleles HLA-DR*0301, HLA-Cw*1502 and HLA-A*0201 are associated with protection from SARS infection [6]. On the other hand, HLA-B*07:03, B*46:01, DRB1*03:01, DRB1*12:02 alleles were associated with SARS susceptibility [9]. The role played by HLA-B27 in the susceptibility and severity of SARS-CoV-2 infections and in particular COVID-19 is not clear and studies on it are insufficient.

In our study, we aimed to evaluate the HLA-B27- COVID-19 relationship and to determine the role of HLA-B27 on the risk of developing the disease and the severity of the disease. We think that studies on the protective or susceptibility-related role of HLA-B27 on COVID-19, as well as its potential effect in terms of auto-immunity, will provide important information for better recognition of COVID-19 and other Coronavirus infections.

Materials and Methods

This study was carried out by retrospectively evaluating the results of the patients, who applied to Turgut Özal University Faculty of Medicine Training and Research Hospital between 2020 and 2022 with the suspicion of COVID-19. Ethics committee approval of the study was obtained from the Turgut Özal University Local Ethics Committee with the number 2022/13. As a result of the power analysis performed by accepting an effect size of 0.5, a power of 95%, and a margin error of 5%, the required sample size for the study was determined as 176 individuals. One hundred eighty-six cases were included in the study. Ninety HLA-B27 positive and 96 HLA-B27 negative control subjects were included in the study. Informed consent forms for the cases were obtained.

Genetic Test	Chronic Rheumatological Diseases	Drugs Used
HLA-B27 (+)	1. Ankylosing spondylitis 2. Uveitis 3. Behcet's Disease 4. Inflammatory bowel disease (Crohn, Ulcerative colitis)	1. Drug-Free 2. Non-steroidal anti-inflammatory drug 3. Sulfasalazine 4. Mesalazine 5. Azathioprine 6. Biologic agents
HLA-B27 (-)	1. Ankylosing spondylitis 2. Uveitis 3. FMF (Familial Mediterranean Fever) 4. Inflammatory bowel disease (Crohn, Ulcerative colitis) 5. Rheumatoid Arthritis 6. Reactive arthritis and Spondyloarthropathies 7. Arthritis and myalgia	1. Drug-Free 2. Non-steroidal anti-inflammatory drug 3. Leflunomide 4. Sulfasalazine 5. Mesalazine 6. Azathioprine 7. Methotrexate 8. Biologic agents
	*Cases using steroids and colchicine were excluded from the study.	

Figure 1. Demographic characteristics of the cases in the HLA-B27 positive and negative groups.

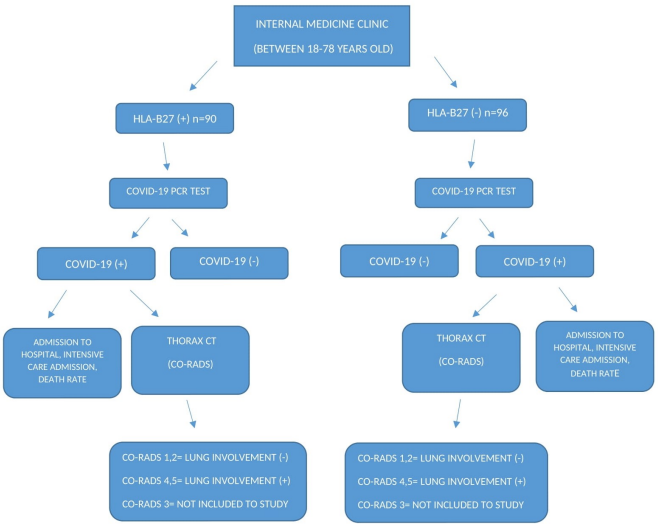

Figure 2. Case selection and flowchart in study design.

The results of the cases whose HLA-B27 test was studied in our clinic between 2018 and 2022 were accessed through the hospital's central computer system. Ninety cases over 18 years of age with positive HLA-B27 test results have been identified. Of these patients, 85 were being followed up with AS, 1 with IBD, 1 with Behcet's Disease and 3 with uveitis. The control group was selected from cases in a similar age group, whose results of the HLA-B27 genetic test were negative. The underlying rheumatic diseases of the cases and the drugs they used are indicated in Figure 1. HLA-B27 genetic evaluation was performed on a LightCycler 480 device (Roche Diagnostics GmbH, Germany) with a real-time polymerase chain reaction (PCR) method.

For the diagnosis of COVID-19, samples taken from the nose and throat of the cases were studied with the SARS-CoV-2 PCR test. SARS-CoV-2 PCR tests were performed on Rotor-Gene Q Real Time PCR (QIAGEN, Hilden Germany) brand device. SARS-CoV-2 PCR results of the cases were evaluated and grouped according to positive negativity (COVID-19 positive and negative groups). Again, the thorax CT results of the patients were examined. Thorax computed tomographies were taken with Siemens brand 128 section device. Thorax CT results were evaluated according to the presence of COVID-19 involvement and the severity of the involvement. Two groups were formed as those without COVID-19 lung involvement and those with lung involvement. Lung tomography of the patients was taken 3-10 days after the diagnosis of

COVID-19. The COVID -19 reporting and Data System (CO-RADS) was used when evaluating the diagnosis of COVID-19 lung involvement [10]. Those evaluated as CO-RADS 4-5 according to this classification were accepted as COVID-19 lung involvement. Those classified as CO-RADS 1 and 2 were considered negative for COVID-19 lung involvement. In addition, the CO-RADS classification system was used to distinguish and exclude possible lung involvement of auto-immune diseases. Those with CO-RADS 3 were not included in the study.

The severity score method, which is applied by scoring the percentages of each of the five lobes involved, was used to evaluate the severity of COVID-19 involvement in lung tomographies [11]. According to this classification involvement of lobes are classified as:

1. < 5% involvement
2. 5%-25% involvement
3. 26%-49% involvement
4. 50%-75% involvement
5. > 75% involvement.

The total CT score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all the five lobes show more than 75% involvement [11].

Again, hospitalization rates, intensive care unit admission rates, hospitalization days and death rates were evaluated. Results were compared between HLA-B27 positive and negative groups. The case selection and evaluation scheme is given in Figure 2.

Suspicion of auto-immune disease lung involvement, pulmonary findings compatible with CO-RADS 3, using steroids and colchicine for underlying rheumatic disease, and being under the age of 18 were considered as exclusion criteria.

Statistical analysis

The analysis of the data included in the research was carried out with the SPSS (Statistical Program in Social Sciences) 25 program. The significance level for comparison tests was taken as $p<0.05$. Values of the variables are given as numbers and percentages, mean and standard deviation. In categorical data analysis, the chi-square (χ^2) test was performed by creating cross tables. Logistic regression analysis for HLA-B27 dependent variable was performed with the Binary Logistic Regression model. The Hosmer-Lemeshow statistics were used to test the model's goodness of fit.

A Binary Logistic Regression model was established in which the HLA-B27 dependent variable, being COVID-19, thorax CT COVID-19 involvement, gender and age were independent variables.

In the binary logistic regression analysis, the "Enter" method, which is one of the model selection methods, in which the importance of the coefficients of all variables is evaluated in one step, was used. Hosmer-Lemeshow statistics were used to test the model's goodness of fit and it was found that the model was statistically sufficient in estimating the HLA-B27 of the established model correctly (χ^2= 6.420, sd= 8 p=0.600>0.05).

Results

Of the cases included in the study, 93 (50%) were female and 93 (50%) were male. The mean age of total cases was calculated as 39.86±13.27 (18-75 years), the mean age of HLA-B27 positive cases as 37.54±12.69 (18-78 years), and the mean age of HLA-B27 negative cases as 42.03±13.507 (19-76 years) (Table 1). Of the total 186 cases, 72 (38.7%) had COVID-19 infection. COVID-19 involvement was detected in the lungs of 8.6% (n=16) of total cases. 32.2% (n=29) of HLA-B27 positive cases had COVID-19 positivity, 5.6% (n=5) had COVID-19 lung involvement. There were 44.8% (n=43) COVID-19 positivity and 11.5% (n=11) lung involvement of HLA-B27 negative cases (Table 2). In statistical evaluations, no statistically significant correlation was found between the presence of HLA-B27 and COVID-19 in the participants included in the study (p>0.05) (Table 3). No statistically significant correlation was found between HLA-B27 positivity and COVID-19 lung involvement in thorax CT in the participants included in the study (p>0.05) (Table 3).

Again, when the cases infected with COVID-19 were evaluated in terms of lung involvement, it was calculated that 17.2% of 29 cases in the HLA-B27 positive group and 25.6% of 43 cases in the HLA-B27 negative group were affected (Table 4). No statistically significant correlation was found between the presence of HLA-B27 and lung involvement in COVID-19-positive cases included in the study (p>0.05). (Table 4). In terms of gender, there was no significant difference between HLA-B27 positive and negative cases about COVID-19 and lung involvement. Being COVID-19, COVID-19 lung involvement in Thorax CT, gender and age values were not statistically effective in the HLA-B27 basic variable (p>0.05) (Table 5).

Among the cases in the HLA-B27 positive and negative groups, 1 patient in each group was hospitalized. The lung involvement of the patient requiring hospitalization in the HLA-B27 positive group was evaluated as moderate involvement (severity score: 11) with bilateral ground-glass consolidations in the middle and lower lobes that tend to merge in a crazy-paving pattern. In the HLA-B27 negative group, lung involvement of the patient requiring hospitalization was evaluated as diffuse involvement (severity score: 23) with bilateral ground-glass appearance in all lobes from basal to apex and a consolidation trend showing a crazy-paving pattern. In another patient in the HLA-B27 negative group, who was not hospitalized, lung involvement was evaluated as moderate involvement (severity score:12) with bilateral ground-glass consolidations in the middle and lower lobes that tend to merge in a crazy-paving pattern. Lung involvement of the other patients in

Table 1. Descriptive age statistics of the cases.

Values	Total Age	HLA-B27 (-) Age	HLA-B27 (+) Age
Mean	39.86	42.03	37.54
Std. Deviation	13.275	13.507	12.691
Minimum	18	19	18
Maximum	78	76	78

Table 2. Distribution of variables of HLA-B27, COVID-19 status and COVID-19 lung involvement.

Variable	Group	Total		HLA-B27 (-)		HLA-B27 (+)	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
COVID-19 STATUS	Negative	114	61.3%	53	55.2%	61	67.8%
	Positive	72	38.7%	43	44.8%	29	32.2%
THORAX CT COVID-19 Involvement	Negative	170	91.4%	85	88.5%	85	94.4%
	Positive	16	8.6%	11	11.5%	5	5.6%
Gender	Female	93	50.0%	51	53.1%	42	46.7%
	Male	93	50.0%	45	46.9%	48	53.3%
Total		186	100.0%	96	51.6%	90	48.4%

Table 3. Comparison of HLA-B27 status with COVID-19 status and lung involvement status.

Variable	Group	HLA-B27		Total	χ^2 Value	p value
		Negative (n / %)	Positive (n / %)			
COVID-19 STATUS	Negative	53 (55.2%)	61 (67.8%)	114 (61.3%)	2.586	0.108
	Positive	43 (44.8%)	29 (32.2%)	72 (38.7%)		
THORAX CT COVID-19 Involvement	Negative	85 (88.5%)	85 (94.4%)	170 (91.4%)	2.112	0.146
	Positive	11 (11.5%)	5 (5.6%)	16 (8.6%)		
Total		96 (100.0%)	90 (100.0%)	186 (100.0%)		

n; number of samples, %; percent, p value; statistical significance.

Table 4. Comparison of HLA-B27 status and lung involvement status in COVID-19 positive cases.

Variable	Group	HLA-B27		Total	χ^2 Value	p value
		Negative (n / %)	Positive (n / %)			
THORAX CT COVID-19 Involvement	Negative	32 (74.4%)	24 (82.8%)	56 (77.8%)	0.832	0.362
	Positive	11 (25.6%)	5 (17.2%)	16 (22.2%)		
Total		43 (100.0%)	29 (100.0%)	72 (100.0%)		

n; number of samples, %; percent, p value; statistical significance.

Table 5. Estimated values of the parameters in the model.

Values	β	S.E.	W	sd	p value (sig)	Exp(β)	95% C.I.for EXP(B)	
							Lower Limit	Upper Limit
Age	0.007	0.018	0.155	1	0.694	1.007	0.972	1.044
Gender	0.215	0.474	0.206	1	0.650	1.240	0.490	3.138
THORAX CT COVID-19 Involvement	-2.231	1.145	3.795	1	0.051	0.107	0.011	1.014
Constant	0.980	1.329	0.544	1	0.461	2.666		

β; parameter estimation, se; standard error; W; Wald statistic, sd; degrees of freedom, Exp (β); odds ratio, 95% CI; confidence interval.

both groups was evaluated as mild involvement (severity score: 0-5) with rare peripheral ground glass opacities in a single lobe. No cases of intensive care hospitalization or death were observed. There were no cases of SARS in either group.

Discussion

The number of studies on the relationship between COVID-19 and HLA-B27 is very limited in the literature. According to the analysis of Rosenbaum JT et al., it is stated that while HLA-B27 has protection against HIV and Hepatitis C Virus, it is not protective against COVID-19 [12]. The results of our study showed that there is no relationship between HLA-B27 and the risk of contracting COVID-19 and the severity of the disease. The results show that HLA-B27 positive people and negative people suffer from COVID-19 disease at a similar rate and have similar severity. The results of Rosenbaum JT et al. and the results of our study support each other. In fact, in the literature search, only one study was found directly related to COVID-19 and HLA-B27 outside of our study.

The majority of HLA-B27 positive cases in our study

were followed up with auto-immune diseases such as AS, uveitis, IBD, and Behcet's Disease. While some of these cases were receiving anti-inflammatory and immune-modulatory treatments related to their underlying diseases, some of them were in the follow-up without treatment. Again, among the HLA-B27 negative cases, there were rheumatological diagnoses and those who received anti-inflammatory treatments and immune-modulatory treatments, while there were also cases without treatment and without a rheumatological diagnosis. Studies on the effect of auto-immune diseases and anti-inflammatory and immune-modulating drugs used for these diseases on COVID-19 susceptibility give conflicting results. In the study conducted by Ferri C et al., it is stated that COVID-19 is more common in people with auto-immune rheumatic diseases. Again, the same study stated that patients who received anti-inflammatory and immune-modulatory treatment were less likely to get COVID-19 infection [13].

Another study states that the spondyloarthropathies themselves and the treatments applied for spondyloarthropathies are not associated with getting COVID-19 and the severity of the disease [14]. Murtas R et al. in their study performed in Italy stated that regardless of the drugs used, those with auto-immune rheumatic diseases were not at greater risk for COVID-19 and they did not have a worse prognosis even if they got the disease [15]. Eder L et al. in their study, in which they compared those with immune-related inflammatory diseases and normal subjects in terms of hospitalization due to COVID-19 infection, they stated that those with immune rheumatic diseases had a higher rate of hospitalization [16]. Our study may be more valuable in terms of determining the role of HLA-B27, since autoimmune disease diagnoses and drugs used are heterogeneous in both HLA-B27 positive and negative groups, and our study compared HLA-B27 positive and negative groups one-to-one. In our study, there was no difference in hospitalization rates, lung involvement rates and disease severity between HLA-B27 positive and negative patients.

The average age of our study group can be considered as relatively young. This is due to the population that applied to the clinic and underwent HLA-B27 genetic testing. Advanced age is stated as an important risk factor for the severity of COVID-19 infection and the risk of death [17]. In our relatively young study population, the rates of getting COVID-19, lung involvement and disease severity were lower in the HLA-B27 positive group than in the same age HLA-B27 negative control group, but there was no significant difference.

In our country, the incidence of COVID-19 positivity in the population was calculated as 17.13% according to the data of the Ministry of Health [18]. In our study, the rates of contracting COVID-19 in both groups were higher than in the general population. These rates may be associated with underlying auto-immune rheumatic diseases, as reported by Ferri C et al. [13]. However, there is no difference between HLA-B27 positivity and negativity. Based on these results, it can be stated that HLA-B27 positivity has no role in protection against COVID-19, does not prevent disease-related lung involvement and is not related to the severity of the disease.

SARS, which is associated with hyper-immune response, is stated as an important cause of morbidity and mortality in COVID-19 [19]. As none of the patients in our study developed SARS, it can be said that HLA-B27 did not trigger autoimmunity in COVID-19. In these results, the role of anti-inflammatory and immunomodulatory drugs used for the underlying rheumatic disease should also be considered. Since the effects of this group of drugs on the course of COVID-19 have not been clarified, more research is needed to determine their importance in this regard.

It is stated that there are 105 subtypes of HLA-B27, and these subtypes have different characteristics and different roles. [8]. Leite MM et al. in their analysis to determine the role of HLA subtypes on COVID-19, stated that HLA-B13:01 was a protective allele among the subtypes evaluated, while the HLA-B27:05 subtype did not have a protective role [20]. Novelli A et al. reported that HLA-B27:07 was associated with susceptibility in their evaluation of HLA subgroups in terms of COVID-19 susceptibility on 99 Italian patients [21]. In our study, no evaluation was made on the subtypes of HLA-B27. However, it does provide an assessment of the HLA-B27 general allele. More detailed studies covering the HLA-B27 gene sequence and its subtypes are necessary to better understand the relationship between the HLA-B27 gene family and COVID-19.

Our study has limitations such as the relatively small number of cases due to its single-center nature, the inability to study HLA subgroups, the fact that it is a retrospective study, and the drugs used by the cases were not homogenized.

Conclusion

In conclusion, the results of our study may suggest that HLA-B27 does not have a protective role against COVID-19 and does not prevent COVID-19 lung involvement. The results also suggest that, as an inverse effect, HLA-B27 does not increase the risk of hyper-immune response and SARS, which play a role in the severe course of the disease. Supporting our study with new studies will provide important results in better analysis of COVID-19 and other Coronavirus infections in terms of their association with HLA-B27 and related auto-immune diseases and immune-modulating drugs.

Ethical approval

Ethics committee approval of the study was obtained from the Turgut Özal University Local Ethics Committee with the number 2022/13.

Conflicts of interest

The authors declare that they have no conflict of interest.

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