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HLA-DRB1 as a Predictor of Survival in Iraqi COVID-19 Patients

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ABSTRACT

Objective: *This study aimed to show some of the commensal species in the parts of the digestive system and their role in developing the immune system and other functions and their positive effect on the health of the host.* ***Method:*** *Molecular investigations have shown the presence of single, if not dozens of trillions of species, nutrients, and host cells.* ***Results:*** *The commensal bacteria in the digestive system play an important role in modifying and developing the immune system, as they provide environmental requirements of nutrients that protect the mucosal lining of the intestine, which in turn is affected by mutual interactions with the microbes of the digestive system.* ***Novelty:*** *Thus, the digestive system is considered one of the most complex systems due to the continuous interaction between the enormous number of microorganisms.*

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously provisionally named 2019 novel coronavirus or 2019-nCoV) disease (COVID-19) in China at the end of 2019 has caused a large global outbreak and is a major public health issue [1] , and with the spread of COVID-19, which was declared a pandemic in March 2020, more than 700 million confirmed cases and 6 million deaths have been recorded worldwide [2]. Although most patients are infected mildly or asymptomatically, a large percentage of the victims develop severe illnesses [3], such as pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure [4]. Due to the broad disparity in disease outcomes, the role of host factors in the manifestation of disease, as well as genetic differences in a person's vulnerability to COVID-19 and its severity, has been emphasized [5]. Of these genetic factors, the human leukocyte antigen (HLA) system, which is central to the immune system and its reaction to pathogens, has attracted interest due to its possible influence on the outcomes of COVID-19 [6]. *HLA-DRB1* gene is located in the Major Histocompatibility Complex (MHC) on the 6th chromosome [7], The DRB1 encodes the proteins required in presenting the peptide derived outside the cell towards the helper T lymphocytes (CD4+) thereby affecting response of the immune system to infection [8]. Based on several scientific studies, specific *HLA-DRB1* alleles depict favorable trends of immune response in HIV infection to influenza infection [9]. The article, [10] on disease severity of SARS-CoV-2 considered certain HLA alleles to reveal their influence on the outcome of the immune response, which would be protective against severe COVID-19 outcomes. Research on genetic background in the Iraqi population is scarce in spite of its unique heritage having evolved due to a number of historic movement of people and environmental factors and periods of conflict [11], [12], [13]. Iraq faced widespread challenges of the pandemic leading to the large upsurge in the number of infections combined with high mortality rates [14].

Research aims to establish the occurrence of *HLA-DRB1* alleles among Iraqi COVID-19 patients while studying if particular *HLA-DRB1* alleles are associated to disease development.

RESEARCH METHOD

Study Design and Participants

The current case-control study evaluated the frequency of alleles of the *HLA- DRB1* in Iraqi patients with COVID-19. This study includes 80 people 40 of them being positive with COVID-19 and the other healthy controls all of which adapted to the Iraqi ethnicity during the recruitment process between November 2020 and May 2022. The sample group of patients used in the study was individuals who had a positive result in RT-PCR of SARS-CoV-2 at least once during the period. The RT-PCR tests were conducted despite the situation (all participants of the control group tested negative) to confirm that the participants did not experience COVID-19 infections and related symptoms throughout the time of observations.

DNA extraction and *HLA* Typing

Genomic DNA extraction from peripheral blood was performed using the Promega Wizard Genomic DNA Purification Kit. *HLA-DRB1* genotyping was performed through the use of sequence-specific oligonucleotide PCR (SSO-PCR) since it is a high-throughput technique where probes are hybridized to obtain precise identification.

Statistical Analysis

The frequencies of alleles of *HLA-DRB1* in control and COVID-19 patients were calculated and compared with either the chi-square or fishers exact depending on the type of data being analyzed. To quantify the association between specific *HLA-DRB1* alleles and COVID-19 susceptibility, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analysis, including all procedures, was done in IBM SPSS Statistics version 20. The statistical outcomes, expressed both in ORs and as 95% CIs and p-values, are reported in Table 2.

RESULTS AND DISCUSSION

Table 1. Comparative gender among study groups.

			Groups		
			Control (n=40)	**Patients (n=40)**	**Total**
Gender	Men	n	28	26	54
		%	70	65	67.5%
	Women	n	12	14	26
		%	30	35	32.5%

Table 1 provides the comparative statistical analysis of gender distribution in both study groups indicating that males consisted of 70 percent in the case of control group and 65 percent in the case of patient group whereas only 30 percent of females in the case of the former and 35 percent in the case of the latter formed the study. In the study, there is an implication of predominance of the male participants in this population and also the support of global epidemiological trend of COVID-19 in cases where men are the subjects of undying complications. This difference is exhibited by various biology and immunologically through, behavior components [15].

Recent research has suggested that male patients are at a higher risk of severe COVID-19 as their immune reactions are not similar to those of female patients. The more intense innate and adaptive immune response that females tend to have is largely due to the effects of estrogen, in addition to immunologically skewed genetic factors carried on the X chromosome [16]. The improved immune response might explain why more males are enrolled in the patient group rather than the female group since they better protect against serious disease. The expression of angiotensin-converting enzyme 2 (ACE2) receptors represents a vital determinant of gender-related COVID-19 outcomes through its role in viral cell entry. several studies indicate men display elevated ACE2 expression levels which could explain why they face a higher risk of developing serious Infection [17]. Behavioral and lifestyle factors are the factors that predispose COVID-19 outcomes in males [18] and lower healthcare-seeking behaviour of males leads to a greater number of males as participants in both control and patient groups. The gender distribution presented during this study leads to significant clinical implications in addition to affecting public health outcomes. The higher proportion of males in patients indicates their susceptibility to severe illness which underscores the importance of specific defensive strategies including vaccination programs and early medical care. Research into women-specific risk factors for COVID-19 infection requires immediate attention because data shows the significant involvement of female patients The results of the current study are consistent with the findings of [19] regarding males being more infected with COVID-19 than females. Sex-based variations in individuals are a factor that needs to be comprehended since they act as a guide to creating a treatment as well as a prevention strategy, Witt et al.

Table 2. The association between *HLA-DRB1* alleles and the risk of Covid-19 among Iraqi population.

***HLA-B* alleles**	**Patients**		**Control**		**P value**	**OR**	**95% CI**
	2n	**F%**	**2n**	**F%**			
*DRB1*01:02*	3	0.03	7	0.08	0.33	1.90	0.51-7.11
*DRB1*04:01*	5	0.06	15	0.18	0.09	2.29	0.86-6.08
*DRB1*04:145*	0	0	8	0.1	0.02	9.75	1.15-82.10
*DRB1*07:01*	16	0.2	3	0.03	0.000008	0.60	0.46-0.77
*DRB1*08:04*	2	0.02	2	0.02	1.00	1.00	0.13-7.47
*DRB1*10:01*	1	0.01	7	0.08	0.15	4.03	0.78-20.76
*DRB1*10:02*	2	0.02	0	0	0.49	0.95	0.88-1.02
*DRB1*09:01*	1	0.01	0	0	1.00	0.97	0.92-1.02

*DRB1*11:01*	11	0.13	14	0.17	0.46	1.42	0.54-3.67
*DRB1*13:01*	5	0.06	7	0.08	0.53`	1.48	0.42-5.14
*DRB1*14:02*	1	0.01	0	0	1.00	0.97	0.92-1.02
*DRB1*15:01*	28	0.35	4	0.05	< 0.001	0.04	0.01-0.16
*DRB1*15:02*	5	0.06	13	0.16	0.03	3.37	1.07-10.61

n = number of alleles observed (each individual contributes two alleles 2
F% = allelic frequency percentage.
P-value < 0.05: Statistically significant.
P-value ≥ 0.05: Not statistically significant.

The purpose of the current research was to assess the relationship between *HLA-DRB1* alleles and vulnerability to COVID-19 in the Iraqi people. Some interesting results were identified, which displayed the risk and protective relationships. One of the most statistically significant results was for the *HLA-DRB1**07:01 allele, which showed a protective effect against COVID-19 with an odds ratio (OR) of 0.60, 95% CI: 0.46–0.77, and a p-value of 0.000008, indicating a strong and statistically significant inverse association. This suggests that individuals carrying the DRB107:01 allele may have a lower risk of developing COVID-19. Protective roles of DRB107:01 have been suggested in other viral infections as well, possibly due to its efficient presentation of viral peptides to T-helper cells, thereby enhancing the immune response [20].

Another association with *HLA-DRB1**15:01 was observed, which was seen to be more common among COVID-19 patients as compared to controls, with an OR of 0.04 and p-value < 0.001, suggesting a strong association and potential risk factor. This allele may play a role in altered antigen presentation, which could impair immune recognition of SARS-CoV-2 antigens. Similar findings have been reported in prior studies linking DRB1*15:01 with increased severity or susceptibility in other viral diseases [21].

A less common allele, *HLA-DRB1**04:145, was also observed exclusively among the patient group and absent in controls, with an OR of 9.75 and a p-value of 0.02, suggesting a potential risk factor for COVID-19 infection, though the wide confidence interval (1.15–82.10) indicates uncertainty due to low allele frequency and sample size. Further studies with larger cohorts are needed to validate this finding.

Conversely, *HLA-DRB1**15:02 also showed a statistically significant association with COVID-19 risk, with an OR of 3.37, p-value of 0.03, and presence in 16% of patients compared to 6% in controls. This supports a possible risk-enhancing role for this allele as well, potentially reflecting population-specific effects.

Other alleles such as DRB1*01:02 (OR=1.90, p=0.33), DRB1*04:01 (OR=2.29, p=0.09), and DRB1*10:01 (OR=4.03, p=0.15) showed increased odds ratios, suggesting potential risk associations, but did not reach statistical significance. These results may still warrant attention in future studies with larger sample sizes.

In contrast, alleles such as DRB1*08:04, DRB1*09:01, DRB1*10:02, and DRB1*14:02 showed no significant associations, with odds ratios near 1 and high p-values, suggesting no meaningful contribution to COVID-19 susceptibility in the studied population.

The lack of significant association for several alleles, despite biologically plausible mechanisms, emphasizes the complexity of HLA-related immune responses and the importance of genetic-environmental interplay in determining disease susceptibility [22]. The variability in findings across different populations highlights the need for population-specific HLA studies, as genetic diversity can lead to differing impacts of the same allele.

Our findings contribute valuable insights into host genetic factors that may influence COVID-19 susceptibility and offer potential markers for risk stratification in the Iraqi population. However, this study is limited by a modest sample size, which may affect the power to detect weaker associations or rare allele effects. Future research with larger cohorts and functional assays is essential to validate these associations and unravel the immunological mechanisms through which specific *HLA-DRB1* alleles modulate responses to SARS-CoV-2.

CONCLUSION

Fundamental Finding : This study sheds light on the association between specific *HLA-DRB1* alleles and susceptibility to COVID-19 among the Iraqi population. The findings demonstrate that certain alleles, such as *HLA-DRB1*07:01, may confer a protective effect, while others, particularly *HLA-DRB1*15:01, DRB115:02, and the rare allele DRB104:145, appear to increase the risk of developing the disease. These associations underline the critical role of the HLA system in mediating host immune responses to SARS-CoV-2 infection. **Implication :** Given the limited representation of Middle Eastern populations in global genomic studies, this research offers important insights into the genetic landscape of COVID-19 in Iraq. The significant variability in *HLA-DRB1* allele distribution between cases and controls highlights the potential of HLA typing as a tool for identifying individuals at higher risk for severe disease. **Limitation :** However, the study is limited by its relatively small sample size, which may have constrained the ability to detect associations with rare alleles or moderate effect sizes. **Future Research :** Therefore, future investigations with larger, ethnically diverse cohorts and functional immunological assays are essential to validate these findings and further explore the mechanisms through which *HLA-DRB1* alleles influence COVID-19 outcomes. Understanding these immunogenetic associations could contribute to the development of more personalized approaches in public health, including risk prediction models, vaccine responsiveness assessment, and targeted interventions for vulnerable populations.

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