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*HLA-DRB1** Alleles and Long COVID: A Mediation Analysis of Anti-RBD IgG, CRP, and Anti-β2GPI IgG

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ABSTRACT

Long COVID syndrome (LCS) is characterized by persistent multi-system manifestations with an unclear underlying pathophysiology. Identifying the genetic and immunological factors associated with LCS is essential for improved risk stratification and clinical management. This study investigated whether incorporating *HLA-DRB1** and *HLA-DQB1** genotyping data could enhance the predictive value of laboratory parameters for identifying individuals at higher risk of developing LCS.

Demographic characteristics and relevant clinical history data were extracted from the medical records of 88 individuals diagnosed with LCS (LCS+) and 96 individuals without LCS (LCS−). Serum levels of anti-receptor binding domain IgG (anti-RBD IgG), anti-β2-glycoprotein I IgG (anti-β2GPI IgG), and C-reactive protein (CRP) were measured. Low-resolution genotyping was performed to identify *HLA-DRB1** and *HLA-DQB1** alleles. Logistic regression analysis was employed to examine the associations between HLA alleles and LCS status. Subsequently, mediation analysis was conducted to explore the potential mechanistic roles of anti-RBD IgG, CRP, and anti-β2GPI IgG in these observed relationships.

The LCS+ group exhibited a significantly higher frequency of the *HLA-DRB1*01* allele and a lower frequency of the *HLA-DRB1*11* than the LCS− cohort. Serum levels of both CRP and anti-β2GPI IgG were substantially higher in the LCS+ cohort, whereas anti-RBD IgG levels were significantly lower. After adjusting for key variables, *HLA-DRB1*01* and *HLA-DRB1*11* remained significantly associated with LCS. Mediation analysis suggested that these HLA associations might be partially mediated by CRP, anti-RBD IgG, and anti-β2GPI IgG levels.

Our findings indicate that the combination of *HLA-DRB1*01* and *HLA-DRB1*11* allele screening with serological profiling (anti-RBD IgG, CRP, and anti-β2GPI IgG) may contribute to refining predictive models of LCS susceptibility, though clinical utility requires validation in larger, independent cohorts.

Keywords: Beta 2-glycoprotein I; C-reactive protein; Human leukocyte antigen; Post-acute COVID-19 syndrome; Receptor binding domain

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INTRODUCTION

Long COVID syndrome (LCS), also referred to as post-Acute COVID-19 syndrome or chronic COVID syndrome, is defined as the persistence or emergence of new symptoms extending beyond 12 weeks following acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection without an alternative diagnosis.[1] The prevalence, symptom severity, and patterns of relapse vary widely, manifesting as heterogeneous multisystem presentations across individuals.[2] A leading hypothesis implicates dysregulated and/or insufficient antiviral immune responses following acute SARS-CoV-2 infection as the primary drivers of these persistent symptoms.[3,4] The sequential consequences, including viral persistence, ongoing systemic inflammation, and the induction of autoimmune responses, likely contribute to the varied clinical manifestations observed in individuals with LCS.[5]

Human leukocyte antigen class II (HLA-II) molecules are critical modulators of adaptive immunity against SARS-CoV-2, presenting viral antigens to $CD4^+$ T cells, which ultimately influences COVID-19 outcomes.[6] Studies have shown that certain HLA alleles correlate with enhance viral clearance and reduced disease severity during the acute phase of SARS-CoV-2 infection.[7,8] In contrast, other alleles are associated with impaired viral or antigen clearance, potentially leading to persistent, dysregulated inflammation, and an increased risk of autoimmune reactivities.[9–11] These associations likely reflect differences in the efficiency of viral antigen presentation and subsequent T cell activation.[6] Although these HLA-II associations with the severity of acute COVID-19 are emerging, a critical knowledge gap remains regarding their impact on the long-term outcomes of SARS-CoV-2 infection.

Evidence indicates a significant association between specific HLA-II variants and levels of neutralizing antibodies against SARS-CoV-2.[12] Neutralizing antibodies targeting the SARS-CoV-2 spike protein's receptor-binding domain (RBD) are pivotal mediators of protective humoral immunity, facilitating viral neutralization and mitigating disease severity and mortality in the acute phase of COVID-19.[13,14] In the chronic phase, waning or dysfunctional anti-RBD antibody responses have been implicated in the development of persistent symptoms. Research has shown that individuals with persistent symptoms often exhibit lower levels of neutralizing antibodies and impaired immune memory, which may contribute to viral persistence and immune dysregulation.[15,16] However, the precise mechanisms linking anti-RBD antibodies to chronic COVID-19 complications remain poorly understood.

C-reactive protein (CRP) is a well-established systemic inflammatory marker frequently elevated in acute COVID-19, where its serum levels correlate with disease severity.[17,18] Persistent elevation of CRP has also been linked to the development of long-term symptoms in LCS.[19–21] One proposed mechanism is the association between persistent inflammation and autoantibodies targeting beta 2-glycoprotein I (β2GPI) and phospholipids. Chronic inflammation-induced oxidative stress may alter the conformation of β2GPI, exposing cryptic epitopes and triggering immune responses that result in the production of anti-β2GPI autoantibodies.[22–24] These autoantibodies are established mediators of prothrombotic pathways, potentially contributing to the thrombotic and inflammatory complications associated with prolonged disease manifestations.[23,25–27]

In addition to prothrombotic factors, other autoantibodies have been implicated in specific LCS symptoms. Previous studies have reported that persistent titers of antinuclear antibodies (ANA), as well as elevated levels of anti-U1-SnRNP and anti-SS-B/La autoantibodies, are associated with respiratory symptoms of LCS, such as dyspnea and cough severity.[28] Moreover, autoantibodies against G protein-coupled receptors (GPCRs), including anti-β_2-adrenoceptor, have been detected in individuals with LCS presenting primarily with neurological symptoms.[29] Supporting a potential pathogenic role, the passive transfer of IgG isolated from patients with long COVID into mice has successfully replicated certain neurological symptoms in the animal model.[30,31] Despite these accumulating findings linking inflammation and autoimmunity to LCS, research specifically investigating anti-β2GPI autoantibodies in this population remains scarce, underscoring a critical need for further investigation in this area.

Overall, the precise molecular and immunological pathways underlying LCS remain poorly characterized. A critical knowledge gap exists concerning the interaction between genetic variation in antigen presentation—particularly within HLA class II—and the dysregulated humoral and inflammatory responses characteristic of LCS. To address this, we hypothesized that susceptibility

to LCS is influenced by specific HLA-II alleles (*HLA-DRB1** and *HLA-DQB1**), and that any association with LCS could be mediated through alterations in key serological pathways: namely, the anti-SARS-CoV-2 humoral response (anti-RBD IgG), systemic inflammation (CRP), and autoimmunity (anti-β2GPI IgG). Consequently, this study aimed to determine whether incorporating *HLA-DRB1** and *HLA-DQB1** alleles with standard laboratory markers improves the predictive power of laboratory markers for LCS.

MATERIALS AND METHODS

Study Design and Populations

This case-control study enrolled a total of 184 participants. Participants were segregated into two cohorts: the long COVID syndrome group (LCS+), comprising 88 individuals diagnosed with persistent symptoms, and the control group (LCS−), consisting of 96 healthy individuals with a confirmed history of acute COVID-19 but no residual symptoms at the time of enrollment. Participant classification into LCS+ or LCS− was determined via a structured, multi-step protocol aligned with the most recent guidelines from the National Health Service (NHS) and the Centers for Disease Control and Prevention (CDC). Initial screening involved a standardized symptom checklist derived from these criteria. LCS+ participants were defined as those reporting one or more new-onset, persistent symptoms, such as cough, dizziness, fatigue, shortness of breath, or cognitive difficulties, lasting a minimum of three months following acute COVID-19 onset. Final case verification was conducted by a study physician blinded to laboratory results. Conversely, the LCS− group consisted of participants with confirmed SARS-CoV-2 infection who reported no persistent symptoms upon structured assessment post-acute phase recovery.

Eligibility was restricted to individuals who were referred to hospitals affiliated with Isfahan University of Medical Sciences between July and September 2021, a period corresponding to the peak circulation of the Delta variant, with documented SARS-CoV-2 infection confirmed via computed tomography (CT) scans and polymerase chain reaction (PCR). Medical records were required to detail the severity of the initial COVID-19 illness, classified according to the World Health Organization's (WHO) interim guidelines. Further strict inclusion criteria mandated that all participants be ethnically Persian (Fars) and fall within the age range of 30 to 65 years. Exclusion criteria encompassed a history of underlying chronic diseases, recent non-COVID-19 infectious diseases, or vaccination within the preceding three months. Individuals with a history of drug addiction or current smoking were also excluded. To minimize confounding from vaccine-related fluctuations in inflammatory markers, enrollment was further restricted to participants who had completed two doses of the Sinopharm vaccine post-recovery, with an interval of ≥3 months since the second dose.

Following the procurement of written informed consent from all participants, a 10 mL sample of peripheral whole blood was collected from each subject. This study was conducted in strict compliance with the ethical standards outlined in the Declaration of Helsinki for research involving human subjects. All procedures and protocols received prior approval from the Ethics Committee of Isfahan University of Medical Sciences (Ethics Code: IR.MUI.MED.REC.1400.796).

Sample Size Calculation

A priori sample size calculations were conducted for the primary comparison of allele frequencies between the study groups. Based on an estimated LCS prevalence of 38%,[32] and targeting the detection of a 24% absolute difference in frequency (ie, between 38% vs 62%) with 90% power and a two-sided alpha of 0.05, a minimum of 86 participants per group was required. This calculation utilized the standard formula for comparing two independent proportions: $n=(Z\alpha/2+Z\beta90\%)2\times(p1(1-p1)+p2(1-p2))/(p1-p2)2$. The final enrollment of 88 cases and 96 controls satisfied this calculated requirement.

Clinical Laboratory Tests

7 mL of whole blood were collected from each subject and immediately transported to a clinical laboratory for comprehensive analysis. This analysis included routine hematology (complete blood count [CBC]), clinical chemistry indicators (blood sugar [BS], lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine transaminase [ALT], and creatinine [Cr]), standard coagulation assays (partial thromboplastin time [PTT] and prothrombin time [PT]), and inflammatory indicators (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]).

HLA Typing

Genomic DNA was isolated from whole blood samples using a standard Proteinase K-based assay (AddBio, South Korea). Low-resolution HLA-DRB1* and HLA-DQB1* allele typing was performed via polymerase chain reaction with sequence-specific primers (SSP-PCR) using the Olerup SSP HLA-DR-DQ SSP Combi Tray kit (Olerup, Sweden), in accordance with the manufacturer's instructions. Following amplification, PCR products were separated by electrophoresis on a 2.5% agarose gel containing DNA-safe dye (SinaClon, Iran) and visualized under UV transillumination. *HLA-DRB1** and *HLA-DQB1** alleles were then ascertained using both worksheet and software methods, according to the manufacturer's guidelines.

Serum Levels of Anti-RBD IgG and Anti-β2GPI IgG

Following serum isolation from 3 mL of non-anticoagulated blood, concentrations of anti-RBD IgG and anti-β2GPI IgG were quantified using commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (Pishtaz Teb, Iran, for anti-RBD IgG; ZellBio, Germany, for anti-β2GPI IgG) in accordance with the manufacturer's instructions. The kits had documented sensitivities of 1 RU/mL for anti-RBD IgG and 0.06 ng/mL for anti-β2GPI IgG.

Statistical Analyses

Categorical variables were compared between groups using the chi-square (χ^2) or Fisher's exact tests, as appropriate, and reported as counts (n) and percentages (%). Non-normally distributed continuous variables (as determined by Kolmogorov–Smirnov test where $p<0.05$) were analysed with Mann–Whitney U tests, with results presented as medians with interquartile ranges (IQR).

We modelled the relationship between *HLA-DRB1** and *HLA-DQB1** alleles and the odds of LCS using multiple logistic regression with the enter method. The model was adjusted for the available risk factors, including sex, body mass index (BMI), and acute phase COVID-19 severity. No collinearity was detected among the variables, and all were retained in the final analysis. Data on all variables were collected during the baseline assessment. The results are reported as odds ratios (OR) with 95% confidence intervals (CI).

To examine whether anti-RBD IgG, CRP, and anti-β2GPI IgG mediate the relationship between *HLA-DRB1**/*HLA-DQB1** alleles and LCS, we performed a mediation analysis following the Baron and Kenny's framework. The methodology incorporated acyclic diagrams to illustrate the hypothesized causal pathways.

All statistical analyses were conducted in SPSS (v26.0), with the level of significance set at $p<0.05$. Furthermore, all figures were generated using GraphPad Prism software (version 9.0.0).

RESULTS

Participant Demographics, Laboratory Indices and Clinical Background

The mean age (± standard deviation) of participants was 47.63 ± 11.52 years, with no significant age or sex differences between the LCS− and LCS+ cohorts (Table 1). However, the BMI was significantly higher in the LCS+ cohort than in the LCS− cohort ($p=0.002$). In comparison to the controls, the LCS+ cohort also demonstrated significantly higher blood sugar (BS), lymphocyte count, and white blood cell count (WBC) (all $p<0.05$). In addition, LCS+ participants experienced longer hospitalization, more frequent ICU admission, and a greater incidence of severe COVID-19 than LCS− participants (all $p<0.001$; Table 1).

Allele Frequencies of *HLA-DRB1* and *HLA-DQB1*

The *HLA-DRB1**01 allele frequency was significantly higher in the LCS+ cohort than in the LCS− ($p=0.026$). Conversely, the *HLA-DRB1**11 allele demonstrated lower prevalence within the LCS+ cohort ($p=0.016$; Table 2). These results aligned with the distribution of *HLA-DRB1** alleles according to acute-phase COVID-19 severity. Specifically, the frequencies of *HLA-DRB1**01 and *HLA-DRB1**03 alleles were higher in the severe cohort than in the non-severe cohort, whereas the frequency of *HLA-DRB1**11 was lower in the severe cohort than in the non-severe cohort (Supplementary Table S1).

Multiple Logistic Regression Modeling

As summarized in Table 3, even after adjusting for key LCS risk factors-including sex, BMI, acute-phase COVID-19 severity, and the presence of the *HLA-DRB1**03 alleles and *HLA-DRB1**13- both the *HLA-DRB1**01 and *HLA-DRB1**11 alleles remained statistically significant. Specifically, carriers of the

*HLA-DRB1**01 allele indicated higher odds of developing LCS (adjusted OR: 3.176, 95% CI: 1.073–9.398; *p*=0.036), whereas the *HLA-DRB1**11 allele was associated with a protective effect against LCS (OR: 0.379; 95% CI: 0.145–0.992; *p*=0.047).

Table 1. The demographic characteristics, laboratory parameters, and clinical history of the LCS+ and LCS− groups.

Variable		LCS+ (n=88) n (%) / Median (IQR1–IQR3)	LCS− (n=96) n (%) / Median (IQR1–IQR3)	*p*
Demographics	Sex			
	Male	43 (43.90)	55 (56.10)	0.252
	Female	45 (52.30)	41 (47.70)	
	Age, y	47.50 (39.00–55.25)	43.00 (37.25–58.00)	0.601
	BMI, kg/m^2	28.48 (26.49–30.81)	25.95 (24.14–28.29)	**0.002**
Laboratory parameter	WBC, ×10^3/µL	6.99 (5.95–7.97)	6.36 (5.80–7.36)	**0.016**
	Neu.C, ×10^3/µL	4.00 (3.27–4.75)	3.72 (3.25–4.38)	0.208
	Lym.C, ×10^3/µL	2.37 (1.95–3.02)	2.01 (1.79–2.48)	**<0.001**
	RBC, ×10^6/µL	5.15 (4.84–5.50)	5.18 (4.88–5.63)	0.568
	Plt, ×10^3/µL	319.00 (253.00–361.75)	290.50 (259.25–331.50)	0.129
	Hb, g/dL	14.25 (13.50–15.70)	14.65 (13.42–15.67)	0.837
	HCT, %	43.55 (40.22–47.07)	44.85 (41.42–47.37)	0.171
	BS, mg/dL	97.50 (89.00–111.75)	92.50 (85.00–102.00)	**0.025**
	Cr, mg/dL	1.06 (0.91–1.19)	1.04 (0.90–1.17)	0.775
	ALT, U/L	20.50 (16.00–26.75)	22.00 (16.25–29.00)	0.285
	AST, U/L	21.00 (19.00–24.00)	20.00 (18.00–24.00)	0.433
	LDH, U/L	332.00 (291.00–425.00)	327.00 (291.00–387.00)	0.487
	PT, sec	13.00 (13.00–13.00)	13.00 (13.00–13.00)	0.706
	PTT, sec	31.05 (29.22–33.00)	30.60 (29.37–32.77)	0.985
	ESR, mm/h	9.00 (4.00–13.00)	7.00 (4.00–11.00)	0.331
Clinical history	Duration of hospitalization in the acute phase	8.50 (6.00–13.00)	0.00 (0.00–6.00)	**<0.001**
	ICU admission in the acute phase			
	Yes	21 (23.90)	4 (4.20)	**<0.001**
	No	67 (76.10)	92 (95.80)	
	COVID-19 Severity in the acute phase			
	Severe	49 (55.70)	11 (11.50)	**<0.001**
	Non-Severe	39 (44.30)	85 (88.50)	

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; BS: blood sugar; Cr: creatinine; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; HCT: hematocrit; ICU: intensive care unit; IQR: interquartile range; LCS: long COVID syndrome; LDH: lactate dehydrogenase; Lym.C: lymphocyte count; Neu.C: neutrophil count; Plt: platelet; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cells; WBC: white blood cells.

Table 2. The frequencies of the *HLA-DRB1 and *HLA-DQB1** alleles in the LCS+ and LCS− groups.**

HLA alleles	LCS+, n (%)	LCS−, n (%)	*p*	OR	95% CI for OR Lower–Upper
*DRB1*01*	15 (8.50)	6 (3.10)	**0.026**	2.89	1.01–7.62
*DRB1*03*	19 (10.80)	11 (5.70)	0.076	1.99	0.92–4.31
*DRB1*04*	27 (15.30)	23 (12.00)	0.347	1.33	0.73–2.42
*DRB1*07*	14 (8.00)	18 (9.40)	0.629	0.84	0.40–1.73
*DRB1*08*	3 (1.70)	2 (1.00)	0.673	1.65	0.27–9.98
*DRB1*09*	NS	2 (1.00)	0.500	NA	NA
*DRB1*10*	4 (2.30)	10 (5.20)	0.141	0.42	0.13–1.37
*DRB1*11*	34 (19.30)	58 (30.20)	**0.016**	0.55	0.34–0.81
*DRB1*12*	5 (2.80)	1 (0.50)	0.108	5.59	0.65–48.28
*DRB1*13*	31 (17.60)	22 (11.50)	0.093	1.65	0.92–2.98
*DRB1*14*	6 (3.40)	12 (6.30)	0.207	0.53	0.19–1.44
*DRB1*15*	12 (6.80)	20 (10.40)	0.221	0.63	0.21–1.33
*DRB1*16*	6 (3.40)	7 (3.60)	0.902	0.93	0.31–2.83
*DQB1*02*	30 (17.00)	31 (16.10)	0.817	1.07	0.62–1.85
*DQB1*03*	64 (36.40)	72 (37.50)	0.822	0.95	0.62–1.46
*DQB1*04*	2 (1.10)	4 (2.10)	0.687	0.54	0.10–2.99
*DQB1*05*	42 (23.90)	44 (22.90)	0.830	1.05	0.65–1.71
*DQB1*06*	38 (21.60)	41 (21.40)	0.956	1.01	0.62–1.67

CI: confidence interval; HLA: human leukocyte antigen; LCS: long COVID syndrome; NA: not applicable; NS: not seen; OR: odds ratio.

Table 3. The multiple logistic regression model for the associations between the variables and the odds of LCS.

Variables	B	SE	Wald	df	*p*	OR	95% CI for OR Lower–Upper
Gender	0.436	0.455	0.918	1	0.338	1.546	0.634–3.768
BMI	0.120	0.062	3.797	1	**0.050**	1.128	1.000–1.273
Severe COVID-19	1.062	0.534	3.957	1	**0.047**	2.892	1.016–8.234
*HLA-DRB1*01*	1.156	0.554	4.358	1	**0.036**	3.176	1.073–9.398
*HLA-DRB1*03*	0.771	0.411	3.516	1	0.063	2.161	0.966–4.836
*HLA-DRB1*11*	−0.969	0.490	3.908	1	**0.047**	0.379	0.145–0.992
*HLA-DRB1*13*	0.361	0.544	0.440	1	0.507	1.434	0.494–4.165

B: regression; BMI: body mass index; CI: confidence interval; df: degree of freedom; HLA: human leukocyte antigen; LCS: long COVID syndrome; OR: odds ratio; SE: standard error.

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Serum Concentration of Anti-β2GPI IgG, Anti-RBD IgG, and CRP

We also evaluated the serum levels of CRP, anti-β2GPI IgG, and anti-RBD IgG in both cohorts. The serum concentration of anti-RBD IgG was significantly lower in the LCS+ cohort (10.75 [5.90–18.08]) than in the LCS− group (50.30 [31.90–77.00], $p<0.001$; Figure 1A). In contrast, the LCS+ cohort exhibited higher serum levels of both CRP and anti-β2GPI IgG than the LCS− group (2.40 [1.33–5.25] vs 1.80 [1.10–3.18], $p=0.005$ for CRP; and (1.68 [1.37–1.98] vs 1.46 [1.03–1.87], $p=0.004$ for anti-β2GPI IgG; Figure 1B–C).

Association of *HLA-DRB1 Allele, Mediators, and the Odds of LCS**

The results of the sequential mediation analysis (Baron and Kenny's framework) are summarized in Table 4 and visually represented by the acyclic diagrams in Figure 2. Initial linear regression analysis revealed significant associations between the *HLA-DRB1**11 and *HLA-DRB1**01 alleles and the serum levels of anti-β2GPI IgG, CRP, and anti-RBD IgG. Subsequent multivariate models, which controlled for CRP and/or anti-RBD IgG, indicated that the initial associations with anti-β2GPI IgG were no longer significant, suggesting that these relationships may be depend on CRP and anti-RBD IgG. Specifically, in a model incorporating both CRP and anti-RBD IgG, *HLA-DRB1**01 demonstrated no significant relationship with CRP, implying that its association with CRP may be mediated by anti-RBD IgG. Conversely, *HLA-DRB1**11 maintained a significant correlation with both CRP ($p=0.024$) and anti-RBD IgG ($p<0.001$), suggesting an independent effect on both markers. In the second step of the analysis, both alleles were significantly associated with the odds of developing LCS ($p=0.032$ and $p=0.004$, respectively). However, in the final model, which included the HLA alleles, anti-β2GPI IgG, CRP, and anti-RBD IgG simultaneously, neither allele was a significant independent predictor of LCS. These comprehensive findings suggest that the association between HLA alleles and LCS may be partially mediated by anti-β2GPI IgG, CRP, and anti-RBD IgG. Furthermore, additional models demonstrated that anti-RBD IgG correlated with anti-β2GPI IgG via CRP, and both anti-β2GPI IgG and CRP were independently associated with the odds of LCS.

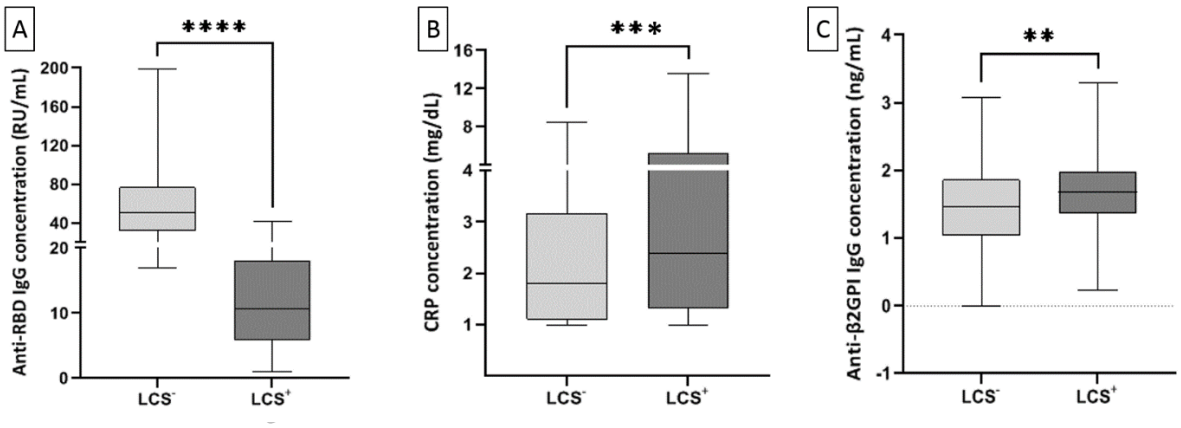

Figure 1. Serum levels of anti-RBD IgG, CRP, and anti-β2GPI IgG in the LCS+ and LCS− groups. β2GPI indicates beta 2-glycoprotein I; CRP, C-reactive protein; IgG, Immunoglobulin G; LCS, long COVID syndrome; RBD, receptor-binding domain; RU, relative units. **indicates $p=0.005$, ***indicates $p=0.004$, ****indicates $p<0.001$.

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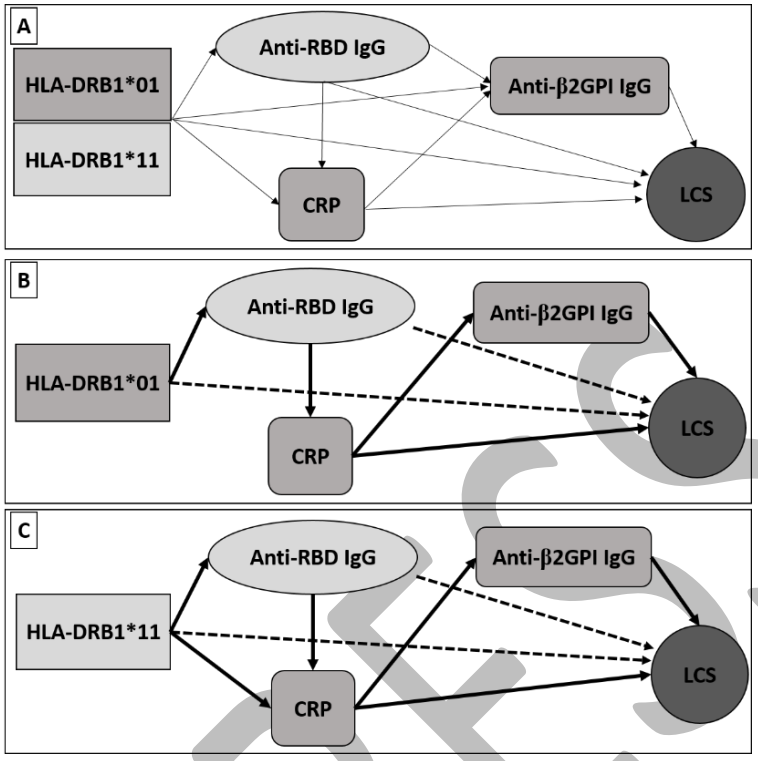

Figure 2. Mediation analysis. Acyclic diagrams illustrate the hypothesized pathways, derived from the results presented in Table 4, through which specific *HLA-DRB1 alleles may influence the probability of developing LCS via alterations in key serological markers, including anti-RBD IgG, CRP, and anti-β2GPI IgG. A) Primary hypothetical model positing that *HLA-DRB1** alleles may indirectly affect susceptibility to LCS by modulating the levels of the three serological mediators. B) Pathway for *HLA-DRB1**01. The relationship between *HLA-DRB1**01 and LCS appears to follow a sequential mediation pattern: *HLA-DRB1**01 is associated with reduced anti-RBD IgG, which correlates with elevated CRP, subsequently linked to increased anti-β2GPI IgG. Elevated anti-β2GPI IgG, alongside other mediators, is associated with higher odds of LCS. Thus, the risk conferred by *HLA-DRB1**01 may depend on a weakened humoral response, subsequent systemic inflammation, and heightened autoimmune activity. C) Pathway for *HLA-DRB1**11. This protective allele influences LCS risk through two independent, parallel mechanisms: *HLA-DRB1**11 is associated with higher anti-RBD IgG and lower CRP. Both increased anti-RBD IgG and reduced CRP correspond with lower anti-β2GPI IgG levels and decreased LCS odds. Hence, the protective effect of *HLA-DRB1**11 may reflect a strong antiviral antibody response combined with attenuated systemic inflammation. β2GPI indicates beta 2-glycoprotein I; CRP, C-reactive protein; HLA, human leukocyte antigen; IgG, Immunoglobulin G; LCS, long COVID syndrome; RBD, receptor-binding domain.**

Table 4. Mediation analysis.

Step / Model	Variable(s)	*HLA-DRB1*01* B or OR	*p*	*HLA-DRB1*11* B or OR	*p*	Interpretation
Step 1: Association of *HLA-DRB1 alleles with mediators**						
Linear regression	Anti-β2GPI IgG	0.699	0.041	−0.161	0.039	- The associations between *HLA-DRB1*01* and *HLA-DRB1*11* alleles and serum levels of anti-β2GPI IgG may be mediated by anti-RBD IgG and CRP levels. - The association between *HLA-DRB1*01* and serum levels of CRP may be mediated by anti-RBD IgG levels. - The association between *HLA-DRB1*11* with serum levels of CRP and anti-RBD IgG may be mutually independent.
	CRP	0.166	0.022	−0.214	0.024	
	Anti-RBD IgG	−20.814	0.007	32.018	<0.001	
Multivariate regression	Anti-β2GPI IgG CRP	0.276 0.165	0.664 0.023	−0.241 −0.214	0.539 0.024	
	Anti-β2GPI IgG Anti-RBD IgG	0.441 −20.814	0.450 0.007	−0.170 32.018	0.633 <0.001	
	Anti-β2GPI IgG CRP Anti-RBD IgG	0.276 0.106 −18.266	0.664 0.492 0.027	−0.241 −0.214 32.022	0.539 0.024 <0.001	
	CRP Anti-RBD IgG	0.107 −18.266	0.491 0.027	−0.214 32.022	0.024 <0.001	
Step 2: Association of *HLA-DRB1 alleles with LCS**						
Odds of LCS with *HLA-DRB1**	*HLA-DRB1**	2.888	0.032	0.402	0.004	- Suggests the association between the *HLA-DRB1*01 / HLA-DRB1*11* alleles and LCS.
Step 3: Association of LCS with *HLA-DRB1 alleles and mediators**						
Odds of LCS with *HLA-DRB1** & anti-β2GPI IgG	Anti-β2GPI IgG *HLA-DRB1**	1.214 2.491	0.005 0.084	1.216 0.400	0.005 0.003	- The association between the *HLA-DRB1*01/HLA-DRB1*11* allele and the odds of LCS may be dependent upon serum levels of anti-β2GPI IgG, CRP, and anti-RBD IgG.
Odds of LCS with *HLA-DRB1** & CRP	CRP *HLA-DRB1**	2.360 1.863	0.003 0.258	2.183 0.402	0.010 0.007	
Odds of LCS with *HLA-DRB1** & anti-RBD IgG	Anti-RBD IgG *HLA-DRB1**	0.854 1.186	<0.001 0.839	0.836 0.186	<0.001 0.008	
Odds of LCS with *HLA-DRB1**, anti-β2GPI IgG & CRP	Anti-β2GPI IgG CRP *HLA-DRB1**	1.176 2.270 1.813	0.023 0.006 0.287	1.180 2.137 0.397	0.021 0.015 0.007	
Odds of LCS with *HLA-DRB1**, anti-β2GPI IgG & anti-RBD IgG	Anti-β2GPI IgG Anti-RBD IgG *HLA-DRB1**	1.261 0.855 1.165	0.089 <0.001 0.862	1.399 0.830 0.141	0.029 <0.001 0.004	
Odds of LCS with *HLA-DRB1**, CRP & anti-RBD IgG	CRP Anti-RBD IgG *HLA-DRB1**	2.090 0.855 1.596	0.013 <0.001 0.601	2.043 0.842 0.252	0.027 <0.001 0.033	
Odds of LCS with *HLA-DRB1**, anti-β2GPI IgG, CRP & anti-RBD IgG	Anti-β2GPI IgG CRP Anti-RBD IgG *HLA-DRB1**	1.207 1.336 0.856 0.641	0.010 0.032 <0.001 0.630	1.322 1.860 0.836 0.194	0.034 0.046 <0.001 0.601	

Table 4. Continued.

Step / Model	Variable(s)	*HLA-DRB1*01* B or OR	*p*	*HLA-DRB1*11* B or OR	*p*	Interpretation
Other relevant models						
Association of anti-RBD IgG with mediators	Anti-β2GPI IgG (Linear)	B = −0.011, *p*=0.049				- The association between serum levels of anti-RBD IgG and anti-β2GPI IgG may be mediated by CRP levels.
	CRP (Linear)	B = −0.004, *p*=0.006				
	Anti-β2GPI IgG CRP (multivariate)	B = −0.011, *p*=0.063 B = −0.004, *p*=0.006				
Odds of LCS with mediators	Anti-β2GPI IgG	OR = 1.218, *p*=0.004				- The association between LCS with serum levels of CRP and anti-β2GPI IgG may be mutually independent.
	CRP	OR = 2.390, *p*=0.003				
	Anti-β2GPI IgG & CRP	Anti-β2GPI IgG: OR = 1.178, *p*= 0.022 CRP: OR = 2.305, *p*=0.005				

B: regression; β2GPI: beta 2-glycoprotein I; CRP: C-reactive protein; HLA: human leukocyte antigen; IgG: Immunoglobulin G; LCS: long COVID syndrome; OR: odds ratio; RBD: receptor-binding domain.

DISCUSSION

Previous research has indicated that the occurrence of chronic inflammatory complications following viral infections can be partially attributed to underlying genetic factors, which may exert effects independently or synergistically with other determinants.[33–35] This body of work underscores the critical role of HLA molecules as central components of the adaptive immune system in response to viral pathogens, significantly influencing viral clearance or persistence and the subsequent clinical manifestations. Specifically, HLA-II molecules are crucial for presenting a broad spectrum of exogenous viral antigen peptides to $CD4^+$ T cells, thereby initiating their proliferation and differentiation. This activation cascade subsequently promotes B cell engagement and the resultant production of specific antibodies.[36,37] This mechanism is indispensable for mounting a robust humoral immune response against viral challenges and mitigating potential long-term sequelae.

In the context of SARS-CoV-2 infection, established evidence suggests that specific HLA-II alleles correlate with variations in acute COVID-19 severity and clinical outcomes. Notably, the *HLA-DRB1**01 allele has been associated with increased susceptibility to COVID-19.[38,39] Furthermore, carriers of the *HLA-DQB1**04 ,[11] -*DRB1**15, -*DQB1**06,[10] and -*DRB1**13[9] alleles have demonstrated a predisposition toward more severe COVID-19 and adverse outcomes. Conversely, the presence of *HLA-DRB1**11 and *HLA-DRB1**04 alleles has been linked to milder or asymptomatic disease courses.[40,41] However, the influence of HLA-II alleles on LCS has remained unexplored. Addressing this knowledge gap, our current investigation revealed that the *HLA-DRB1**01 allele correlates with an increased likelihood of developing LCS, while the *HLA-DRB1**11 allele conferred a protective effect against LCS.

A possible explanation for the observed allelic influence on LCS susceptibility lies in the binding affinity of these HLA molecules for SARS-CoV-2 peptides, which may impact the subsequent antibody response. HLA-II alleles capable of binding SARS-CoV-2 peptides with high affinity and presenting diverse epitopes typically elicit a more efficient humoral response, leading to higher circulating antibody titers. Conversely, some HLA-II alleles characterized by weaker binding kinetics and the capacity to present a restricted repertoire of SARS-CoV-2 antigens, result in an inefficient humoral immune response and lower antibody levels.[42] Previous studies have demonstrated that alleles such as *HLA-DRB1**08:01, *HLA-DRB1**01:01, and *HLA-DQB1**03:02, which exhibit low affinity for SARS-CoV-2 peptide binding,[8,43,44] are associated with reduced or absent antibody responses.[12,45] Specifically, at a median interval of 250 days post-infection, COVID-19 convalescents harboring the *HLA-DRB1**01:01 allele displayed attenuated anti-RBD IgG and total anti-NP IgG titres.[12] In the current study, individuals with the *HLA-DRB1**01 allele

exhibited significantly lower anti-RBD IgG levels, whereas those with the *HLA-DRB1**11 allele demonstrated elevated levels. Furthermore, our data established a correlation between high anti-RBD IgG levels and a reduced risk of developing LCS. Previous investigations have similarly reported lower anti-RBD IgG levels in individuals experiencing persistent neurological symptoms compared to those without such symptom.[15] Furthermore, Zhan et al demonstrated a negative correlation between long-term symptoms one year post-SARS-CoV-2 infection and higher anti-RBD IgG concentrations.[16] Anti-RBD antibodies are fundamental for viral neutralization and protection against SARS-CoV-2, primarily by impeding RBD binding to its cellular receptor and blocking viral entry.[13] Therefore, it is reasonable to assume that an efficacious immune response targeting the RBD during the acute phase may facilitate superior disease control and help in preventing protracted inflammatory sequelae. Inadequate immune responses lead to diminished antibody production and incomplete viral clearance, thus contributing to the perpetuation of inflammation.[46–48]

Consistent with the immunological findings, our data revealed that higher CRP levels were associated with LCS. Gameil et al previously reported increased CRP levels in COVID-19 survivors three months post-discharge, suggesting a potential link to long-term symptom development.[19] Similarly, Durstenfeld et al found that higher CRP levels correlated with the emergence of LCS-related cardiopulmonary symptoms seven months' post-infection.[20] Interestingly, ESR displayed only a statistically non-significant increasing trend in the LCS group. This divergence likely arises because CRP is rapidly induced via hepatic synthesis in response to pro-inflammatory cytokines, whereas ESR kinetics are slower and influenced by various variables, including immunoglobulin concentrations and erythrocyte properties.[49]

A potential mechanistic link between persistent inflammation and LCS involves the induction of autoimmunity.[50] Chronic inflammation and associated oxidative stress are known modifiers of endogenous antigens, such as β2GPI, capable of generating novel epitopes.[22,23] If these neo-epitopes are presented to $CD4^+$ T cells, they could theoretically disrupt immune tolerance and precipitate the generation of autoantibodies.[51] The binding of β2GPI by anti-β2GPI antibodies may subsequently activate pro-inflammatory and pro-coagulant pathways, contributing to chronic inflammatory complications, including LCS.[23,25,27] While this study does not provide direct molecular evidence for this specific cascade (e.g., via measurements of oxidative stress, β2GPI conformation, or antigen-specific T-cell responses), the elevated levels of anti-β2GPI IgG observed within our LCS cohort lend credence to this hypothesis. Nevertheless, experimental data addressing this mechanism remain scarce; only one previous study has reported increased anti-β2GPI IgM levels without a corresponding difference in anti-β2GPI IgG levels between patients with LCS and healthy controls.[52] These finding highlight a critical area for future translational research.

In further support of the proposed pathway, our mediation analysis suggested that the association between *HLA-DRB1**01 and *HLA-DRB1**11 and LCS was mediated by anti-RBD IgG, CRP, and anti-β2GPI IgG status. Thus, variations in the antigen-presenting capacity of specific HLA alleles may underlie the observed individual differences in anti-SARS-CoV-2 antibody profiles, the persistence of inflammation, autoantibody generation, and the subsequent long-term clinical sequelae following infection.

Limitations and Future Directions

Our study had several important limitations. First, we focused exclusively on *HLA-DRB1** and *HLA-DQB1** alleles based on our hypothesis that $CD4^+$ T cell–mediated mechanisms, particularly those regulating humoral responses and autoimmune reactivity, are central to the pathogenesis of LCS. We acknowledge, however, that other HLA loci, including class I genes (*HLA-A*, *-B*, *-C*), *HLA-DP*, and extended haplotypes, also play major roles in antiviral immunity and acute COVID-19 outcomes. Although our previous studies[53] have explored associations between HLA-I alleles and LCS, a comprehensive evaluation of the entire HLA region, encompassing full genotyping and haplotype-based analyses, remains necessary to fully define the genetic architecture underlying susceptibility to post–COVID sequelae. Second, the case-control design and cross-sectional assessment constrained our ability to determine temporal relationships. Longitudinal investigations tracking symptom progression and inflammatory marker dynamics among COVID-19 survivors are required to elucidate the mechanisms driving LCS pathogenesis. Third, our mediation analysis should be interpreted cautiously given the cross-sectional nature of the data. While the Baron and

Kenny's framework suggest potential mediating pathways, the absence of longitudinal measurement for anti-RBD IgG, CRP, and anti-β2GPI IgG relative to LCS onset limits causal inference. These biomarkers may represent either drivers or consequences of sustained inflammation in LCS. Prospective studies with serial sampling are needed to clarify temporal and causal relationships. Fourth, although we adjusted for the severity of acute COVID-19 in regression analyses, the marked differences between the LCS+ and LCS− groups (Table 1) may still have influenced inflammatory and antibody marker levels. Such residual confounding could affect the observed associations among HLA alleles, biomarkers, and LCS. Future studies employing disease severity-matched cohorts or longitudinal designs will be essential to isolate the specific contributions of genetic and immunological factors to LCS development. Fifth, the absence of standardized diagnostic criteria for LCS may have affected our case classification and findings, underscoring the urgent need for consensus guidelines to harmonize LCS research. Sixth, our study population was restricted to Persian adults aged 30 to 65 years, all of whom received the Sinopharm vaccine and were infected during the Delta variant wave. While this homogeneity helped control for key confounders such as vaccine type and viral variant, it inevitably limits the generalizability of our results to other ethnicities, age groups, variants, and vaccine platforms. In particular, absolute anti-RBD IgG levels and their associations may differ in populations exposed to other vaccine types. Future multicenter investigations involving diverse populations and vaccination regimens are needed to validate these findings. Seventh, we measured only total IgG against β2GPI. Subsequent studies should evaluate a broader antiphospholipid antibody panel, including anti-cardiolipin IgG/IgM and lupus anticoagulant, as well as perform IgG subclass analyses to better delineate the autoimmune component in LCS. Finally, our cross-sectional measurement of anti-RBD IgG precludes determination of whether reduced levels precede or result from LCS. Longitudinal studies measuring antibody kinetics from the acute infection phase through long-term follow-up will be necessary to resolve this question. While our findings implicate HLA-II alleles and specific serological markers in susceptibility to LCS, their clinical utility for early diagnosis and risk prediction remains to be established. These factors are likely to form part of a broader predictive framework that integrates clinical, genetic, and molecular biomarkers, an area warranting comprehensive future investigation.

Our findings suggest that the *HLA-DRB1**01 allele is associated with an increased, whereas *HLA-DRB1**11 is associated with a decreased, odds of LCS. These associations appear to be partially explained by serum levels of anti-RBD IgG, CRP, and anti-β2GPI IgG. Consequently, incorporating allelic status together with these serological biomarkers may improve predictive models for estimating the likelihood of LCS development.

STATEMENT OF ETHICS

This study strictly complied with the Declaration of Helsinki for research involving humans. The Ethics Committee of Isfahan University of Medical Sciences approved all procedures (ethics code: IR.MUI.MED.REC.1400.796).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Upon reasonable request, please contact corresponding author (Dr. Hamed Fouladseresht) for any data request. Email: fouladseresht@med.mui.ac.ir.

AI ASSISTANCE DISCLOSURE

Not applicable.

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