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Association of Haptoglobin Heterozygosity (HP1-2) with the Risk of COVID-19 Infection in a Sample of the Iranian Population

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Abstract

Background: COVID-19 is a highly contagious viral disease that primarily affects the respiratory system and occasionally the gastrointestinal system, and it was declared a pandemic in 2020. Haptoglobin is an acute-phase protein and a potent antioxidant in the body, which exerts its antioxidant effect by binding to free hemoglobin. Haptoglobin has three main variants (Hp1-1, Hp1-2, Hp2-2), each with different antioxidant capacities. The purpose of this study is to investigate frequency of the haptoglobin variants in COVID-19 patients compared to a control group.

Methods: This study was conducted on 148 COVID-19 patients and 145 healthy individuals from the Sistan and Baluchestan province. DNA was isolated from whole blood using the salt precipitation method, and the determination of haptoglobin genotypes (Hp1-1, Hp1-2, and Hp2-2) was performed using Conventional PCR.

Results: This study analyzed haptoglobin (HP) genotypes in COVID-19 patients and controls, finding no significant difference in HP variant frequencies between groups (p= 0.529). However, the HP1-2 genotype was associated with a twofold increased COVID-19 risk in men (OR=2.069, p= 0.021), and the HP1 allele significantly raised infection risk (OR= 1.62, p= 0.039). Hospitalizations and respiratory symptoms were significantly higher in COVID-19 patients (p= 0.0001 and p= 0.0176, respectively).

Conclusions: These results suggest that haptoglobin variants are not risk factors for COVID-19 infection in the overall population (both males and females). However, men with the HP1-2 genotype are 1.9 times more likely to develop COVID-19 infection compared to men with HP1-1 and HP 2-2 genotypes.

Keywords: Acute phase proteins**,** SARS-CoV-2, Antioxidant activity**,** Haptoglobin protein.

Introduction

Coronavirus disease-19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first recognized in Wuhan, Hubei province, China, in December 2019 (1)**.** As the COVID-19 pandemic advanced, the SARS-CoV-2 virus infected greater number of persons aged 65 and older (2) while simultaneously elevating the rate of infections among children under 18 years of age (3, 4). Moreover, the virus was swiftly disseminated by respiratory droplets (from person to person), and insufficient preventive efforts during the early stages resulted in the disease's progression into a

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global pandemic, followed by a rise in fatality rates globally. As a result, on March 11, 2020, the World Health Organization (WHO) designated it as an pandemic (5). Earlier research established that oxidative damage and inflammation play critical roles in the progression of COVID-19, impacting the degree to which the illness progresses and the number of lives lost (6, 7).

Haptoglobin (HP), a positive acute-phase α2 glycoprotein and essential physiological antioxidant primarily synthesized in the liver, attaches to free hemoglobin, with the Hb-HP complex being cleared through the CD163 receptor, thus diminishing oxidative stress (8). It also helps regulate the immune system and manage inflammation by equilibrating helper T cells (T helper1 & 2) (9). The haptoglobin gene is located on the longer arm of chromosome 16 (16q22) and encodes alpha and beta chains. Two co-dominant alleles, Hp1 and Hp2 (the heavier allele), govern the haptoglobin chains, resulting in three principal haptoglobin phenotypes: HP1-1, 1-2, and 2-2 (10). According to studies, different genotypes have different antioxidant capacity levels; for example, the 1-1 phenotype has the highest quantities while the 2-2 phenotype has the lowest (11). The unique roles of haptoglobin phenotypes in reducing oxidative damage and their potential impact on how individuals respond to inflammation indicate that exploring the connection between these phenotypes and the severity of COVID-19 could help clarify their role in disease prevention. The association of different haptoglobin phenotypes with infectious diseases, including viral infections, has been identified (12, 13). In individuals with HIV, the H-P2-2 phenotype has shown a higher mortality rate than other phenotypes (14, 15).

To our knowledge, no study has been conducted in Iran on the association between the likelihood of contracting COVID-19 and haptoglobin variants, and the present study aimed to investigate the frequency of haptoglobin variants in individuals infected with COVID-19 compared to a control group without coronavirus infection.

Materials and Methods

Study Population

In this study, between February and August 2020, 293 participants with flu-like symptoms were enrolled after being referred to 16-hour centers and hospitals affiliated with Zahedan University of Medical Sciences. According to World Health Organization (WHO) case definition (1), after a clinical examination by an infectious diseases physician, and a real-time PCR testing for COVID-19, 148 patients with a positive test result were included in the case group, and 145 individuals with a negative result were included in the control group. Exclusion criteria included chronic respiratory diseases, concurrent infection with other infectious agents (virus, bacteria, etc.), and malignancy. This study was approved by Research Ethics Committees of Zahedan University of Medical Sciences with approval ID: IR.ZAUMS.REC.1402.180. After obtaining informed consent, a volume 2 to 5 ml of peripheral blood was collected from patients and stored at – 20 °C.

DNA Extraction and Genotyping

Genomic DNA was extracted using the salting-out method (16, 17). The DNA samples were evaluated qualitatively using agarose gel electrophoresis, and quantitatively using a NanoDrop spectrophotometer (Boeco, Germany). High-quality DNA was indicated by the absorbance ratio of 260/280 close to 1.8 in the majority of the extracted samples. Polymerase chain reaction (PCR) was used to determine haptoglobin genotypes. Taq DNA Polymerase Master Mix RED (20 mM $MgCl_2$) from AMPLIQON (Denmark) was used for PCR. The primers (Metabion, Germany) used were previously described by Koch et al (18) with minor modifications, and are listed in Table 1. Primers A and B generate a 1757-bp fragment for HP1 and one 3481bp fragment for HP2. Primers C and D amplify a 398 bp fragment for HP2 only. The haptoglobin gene sequence is available from the National Center for Biotechnology Information (NCBI) with the reference sequence: NG_012651.1 (Fig. 1).

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Table 1. Thermal cycling conditions of PCR tests for different primer pairs and product sizes according to genotype.

Primers	Primer Sequences (5'to3')	Annealing °C (time, S)	Cycle No	Size of Product (bp)	Genotype
A (forward)	GAGGGGAGCTTGCCTTTCCATTG	65 (40)	35	1757	HP1
B (reverse)	GAGATTTTTGAGCCCTGGCTGGT			3481	HP2
C (forward)	GACCCAGCCTCTTCTGCTCTT	65.5 (30)	30	-	HP1
D (reverse)	CCGAGTGCTCCACATAGCCAT			398	HP2
A (forward) **B (reverse)** **D (reverse)**	as above	68 (40)	30	196 and 1757	HP1
				196, 1920 and 3481	HP2

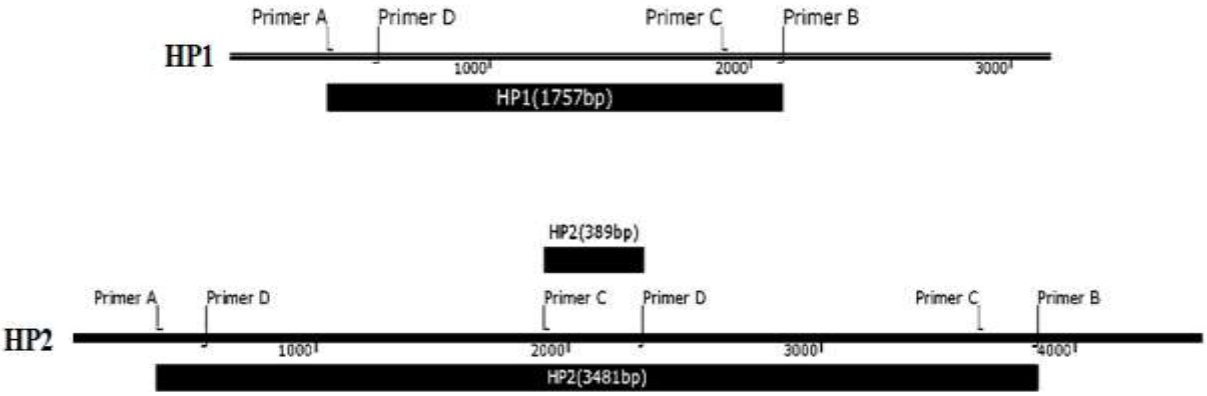

Fig. 1. Schematic representation of primers A, B, C and D on HP1 and HP2 alleles, and length of PCR products.

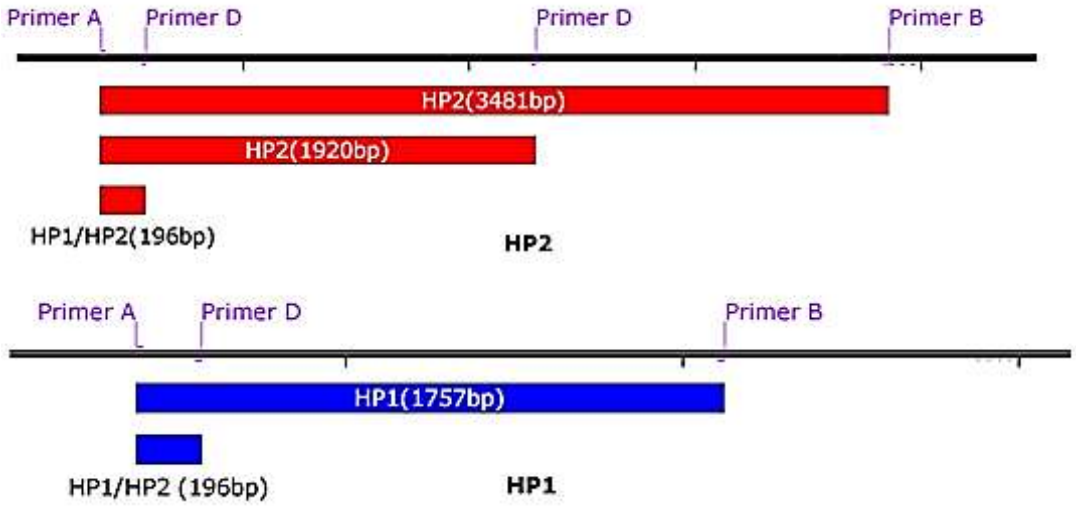

Fig. 2. Schematic representation of three primers A, B and D on haptoglobin alleles HP1 and HP2. Colored bars indicate amplified fragments.

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In a third PCR, we used a combination of three primers: A, B and D in one reaction mixture. The use of three primers (one forward and two reverse primers) resulted in amplification of multiple fragments for each of the HP1 and HP2 alleles (Fig. 2). In practice, we prepared a primer mixture consisting of 10 µl primer A (100 pM), 5 µl of primer B (100 pM), and 5 µl of primer D (100 pM), in a total volume 50 µl using double-distilled water (DDW) and applied 1 µl of this primer mixture for a 25 µl total PCR reaction volume. The thermal cycling conditions of the PCRs and the expected PCR product sizes for each primer pair is shown in Table 1. Three haptoglobin genotypes (HP1-1, HP1-2 and HP2-2) were identified by agarose gel electrophoresis of PCR products and visualized under ultraviolet light.

Data analysis

The frequency of haptoglobin genotypes in COVID-19 positive and control groups were compared using the chi-square test. The association between HP variants and the risk of COVID-19 infection was determined using odds ratio estimates with 95% confidence intervals, calculated by binary logistic regression. Statistical analyses were performed using IBM SPSS Statistics 26. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic findings

The study population included a COVID-19 positive group with an average age of 50±16.9 years and a COVID-19 negative group with an average age of 43.7±15.2 years, with no statistically significant differences (p= 0.342). The frequencies of haptoglobin variants and several characteristics studied are shown in Table 2.

Table 2. The characteristics of the covid-19 positive and control groups. P≤0.05 was considered as the level of statistical significance.

Variables	COVID19 test	Count (%)		Total	p value
		Negative (control)	Positive (case)		
HP variants	HP1-1	10 (6.9)	12 (8.1)	22 (7.5)	0.529
	HP2-1	52 (35.9)	61 (41.2)	113 (38.6)	
	HP2-2	83 (57.2)	75 (50.7)	158 (53.9)	
gender	male	94 (64.8)	86 (58.1)	180 (61.4)	0.237
	female	51 (35.2)	62 (41.9)	113 (38.6)	
status	No-hospitalization	98 (67.6)	54 (36.5)	152 (51.9)	0.0001
	hospitalization	47 (32.4)	94 (63.5)	141 (48.1)	
respiratory symptoms	without	114 (78.6)	98 (66.2)	212 (72.4)	0.0176
	with	31 (21.4)	50 (33.8)	81 (27.6)	
Age	-	50±16.9	43.7±15.2	46.85±16.05	0.324

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Haptoglobin genotypes

As mentioned before, we used two primer pairs to determine the haptoglobin genotype. The primer pairs of A and B amplify products with 1757bp and 3481bp length for HP1 and HP2 genes, respectively (Fig. 3). Homozygotes of HP1 had one band of 1757bp; HP2 homozygous generated one band 3481bp and heterozygotes (HP1-2) had both bonds 1757 and 3481 bp.

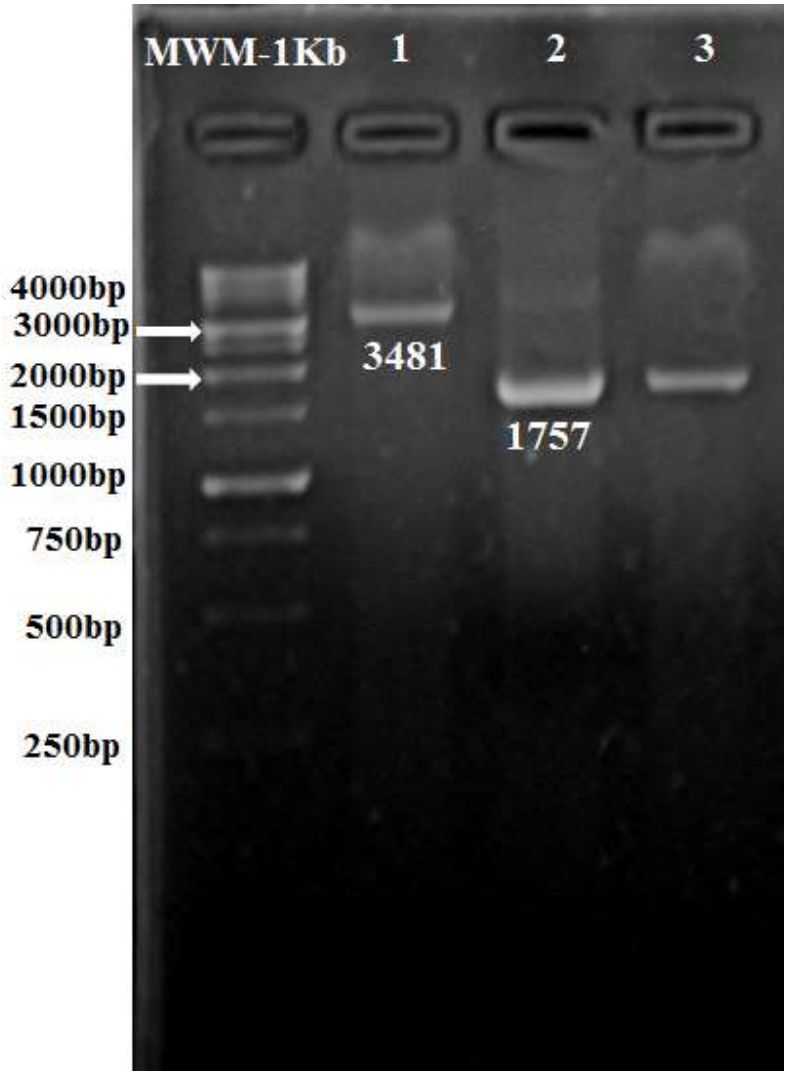

Fig. 3. Electrophoresis of PCR products on %1 agarose gel using A & B primers. Lane1; band of 3481bp for HP2-2 (HP2 homozygous), Lane2; the 3481bp and 1757bp bands for HP1-2 (heterozygous) and lane3 band 1757bp for HP1-1 (HP1 homozygous).

The PCR with another pair of primers, C and D, generates a 398 bp fragment for the HP2 genotype only. Results of PCR using C and D primers confirmed HP2 genotype in individuals with HP2-2 and HP1-2 genotypes; it was also consistent with results using A and B primers (Fig. 4).

We performed a PCR using a mixture of three primers A, B and D As expected, applying this primer combination produced two fragments of 196 bp and 1757 bp in lengths for HP1-1 genotype (Fig. 5). Given the position of the primers, the HP2-2 genotype should have produced three bands 196, 1920, and 3489 bp, but only two bands 196 and 1920 bp, were amplified. Also, the fragment of 3489 bp was not generated in HP1-2 heterozygotes, but three bands were amplified (Fig. 5).

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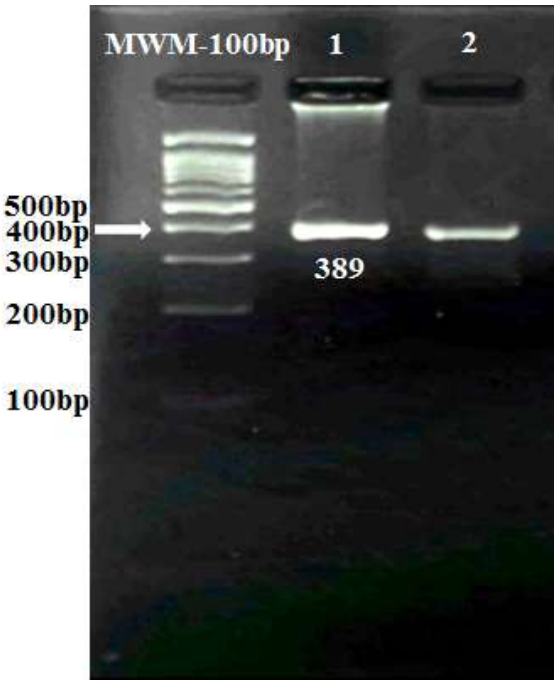

Fig. 4. Representative 2% agarose gel electrophoresis of PCR products with C&D primers. Lanes of 1 and 2; band 389 bp for HP2 allele.

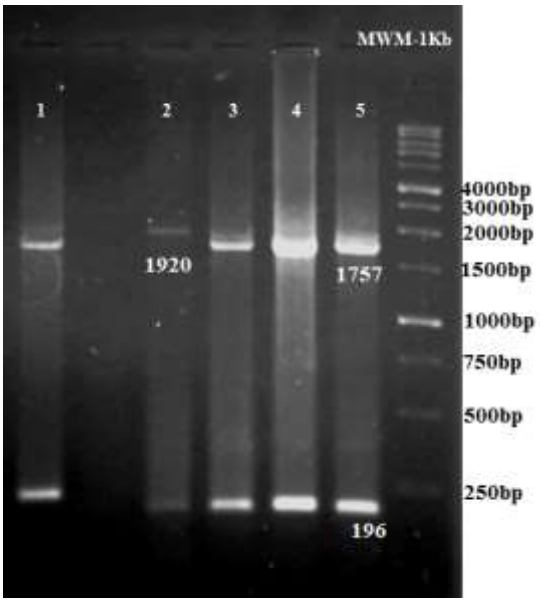

Fig. 5. Representative 1% agarose gel electrophoresis of PCR products using combination three primers A, B and D. lane1; HP1-2 heterozygous genotype, lane2; HP2-2 homozygous of HP2, lanes 3, 4 and 5 HP1-1 homozygous HP1. A non-specific band of 196 bp is present in all samples.

Distribution of haptoglobin frequency

The frequencies of haptoglobin variants and several characteristics studied are shown in Table 2. The frequency of haptoglobin genotypes in both COVID-19 positive and control groups was in Hardy-Winter equilibrium (HWE) with p values of 0.93 and 0.64, respectively.

The comparison of haptoglobin variants between two groups, COVID-positive and COVID-negative, did not show any statistically significant difference (p= 0.529).

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The incidence of COVID-19 infection was higher in men (58.1%) than in women (41.9%), but this increase was not statistically significant. There was a significant increase in hospitalizations due to COVID-19 infection (p= 0.0001) as well as respiratory symptoms such as sore throat, cough asthma, etc. (p= 0.0176).

The distribution of HP variants in women did not show significant difference between the COVID-19 positive and control groups (p= 0.447). However, HP1-2 variant was increased in men with positive COVID-19 test compared to those with a negative COVID-19 test.

In binary logistic regression analysis, considering HP2 as the reference variant, odds Ratio (OR) values were estimated with 95% confidence intervals. The HP1-2 variant significantly (OR= 2.069, CI= 1.109-3.859, P= 0.021) increased the risk of Coronavirus infection in men by 2-fold compared to the HP2-2 variant (Table 3). Also, men who were homozygous for HP1-1 showed an increased risk of COVID-19 infection with an odds ratio of 1.8 (CI= 0.514-6.298, p= 0.357), however the increase was not statistically significant.

Table 3. Binary logistic regression analysis comparing haptoglobin genotypes in the COVID-19 positive group and control group and adjusted by gender.

Parameter / Risk Estimate	Count (%)		OR	95% Confidence Interval		
	positive	Negative		Lower	Upper	P value
HP2-2	75 (50.7)	83 (57.2)	1.000	-	-	-
HP1-2	61 (44.9)	52 (38.5)	1.298	0.800	2.107	0.290
HP1-1	12 (13.8)	10 (10.8)	1.328	0.542	3.251	0.534
Co-dominant	61 (41.2)	52 (35.9)	1.254	0.783	2.009	0.347
HP1 vs. HP2	85 (28.7)	72 (24.8)	1.220	0.845	1.760	0.288
Male						
HP2-2	40 (46.5)	60 (63.8)	1.000	-	-	-
HP1-2	40 (50)	29 (32.6)	2.069	1.109	3.859	0.021
HP1-1	6 (13)	5 (7.7)	1.800	0.514	6.298	0.357
Co-dominant	40 (46.5)	29 (30.9)	1.949	1.060	3.584	0.031
HP1 vs. HP2	52 (30.2)	39 (20.7)	1.656	1.025	2.675	0.039
Women						
HP2-2	35 (56.5)	23 (45.1)	1.000	-	-	-
HP1-2	21 (37.5)	23 (50)	0/600	0/272	1/324	0/205
HP1-1	6 (14.6)	5 (17.9)	0/789	0/215	2/888	0/720
Co-dominant	21 (33.9)	23 (45.1)	0.624	0.291	1.336	0.223
HP1 vs. HP2	33 (26.6)	33 (32.4)	0/758	0/427	1/348	0/345

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The frequency of haptoglobin genotypes was investigated using co-dominant model (Table 3). In the whole population, the frequency of HP1-2 was higher than that of HP1-1+HP2-2 (homozygotes) by 41% to 35% (OR=1.254, CI=0.783-2.009, p=0.347) but it was not statistically significant. The risk of infection with COVID-19 in heterozygous (HP1-2) men was increased by 1.9 times compared to those who were homozygous (HP1-1+HP2-2; OR=1.949, 1.060-3.584, p=0.031). The investigation of HP allele frequencies indicated an association of the HP1 allele with COVID-19 infection by an odds ratio of 1.62 (CI= 1.025-2.675, p= 0.039) which was statistically significant.

Discussion

Following the outbreak of COVID-19 in 2019 and the declaration of a pandemic by the WHO, extensive studies were conducted on the pathophysiology of COVID-19 (1). These studies have reported liver injury, hypoxia, thrombotic complications (19), and oxidative hemolysis in addition to acute respiratory distress syndrome (ARDS) and pneumonia (2, 20, 21). Haptoglobin, as an acute phase protein, plays an important role in reducing and preventing tissue damage caused by free hemoglobin through binding to hemoglobin (22). In the present study, we determined for the first time the distribution of haptoglobin variants in patients with COVID-19 infection and compared with those without COVID-19 infection, in a sample of the population of Sistan and Baluchestan Province from Iran who were exposed to the virus for the first time.

In agreement with previous studies (23), the present study confirms that the most frequent haptoglobin allele is HP2, and its associated variants, HP2-2 and HP1-2. Hosseinali Khazaei et al. reported a similar distribution in a study of allergic rhinitis patients (24). With the exception of Africa and Latin America, where the HP-1 genotype is very common, the HP-2 allele is the most common in most geographic regions, including Asia (25, 26). Our study showed an association between the HP1-2 genotype and the risk of COVID-19 in men. It was also found that the HP1 allele increases the risk of COVID-19 infection in men. However, a comparison of the haptoglobin genotypes in the entire population showed no association between haptoglobin genotypes and COVID-19 disease.

Studies have shown that gender-related differences contribute to susceptibility to infectious diseases and the prevalence of a number of diseases (27-29). Females generate a stronger innate and adaptive immune response to pathogens and antigenic challenges than males, which can help to eliminate the pathogen (29). Several mechanisms are known to cause sex differences in immune responses including; genetic, epigenetic, and hormonal determinants. Estrogen receptors (ERs), androgen receptors (ARs), and progesterone receptors (PRs) have been shown to be expressed on lymphocytes and myeloid cells. these receptors (ligand-bound or ligand-unbound) act as transcription factors and can modulate transcriptional responses in immune cells (27). It is also suggested that HP exerts immunomodulatory effects through suppression of lymphocyte function (30). Therefore, it can be expected that the final immune response to the presence of a pathogen or infectious agent will be a result of the combined effects of all factors.

In terms of the effect of HP1 on the occurrence or association with disease, our findings are comparable with Nils Frohlande's 1988 research in Sweden involving 189 ovarian cancer patients, which indicated an elevated risk of ovarian cancer associated with the Hp1-2 phenotype (31), and with Andrew P. Levy's 2004 study in the United States, which examined 3537 participants and revealed that non-diabetic individuals possessing the Hp1-2 phenotype exhibited a greater prevalence of coronary heart disease (32). Previous research indicated that the HP1 allele plays a protective role in the organism by modulating cytokine release and maintaining the balance between

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T-helper 1 and T-helper 2. However, this allele may function precariously under extreme hemolytic conditions caused by pathogen attacks. Under these circumstances, the HP1 allele, being smaller than the HP2 allele, is eliminated from the bloodstream more rapidly through glomerular filtration, resulting in cytokine storms, hypoxia, and diminished T-cell proliferation, which may negatively impact patient health (33-35). This also incites autoimmune attacks to preserve immune system homeostasis, leading to elevated hemoglobin-related indicators, such as bilirubin and ferritin, exacerbating the condition. These problems are clearly linked to clinical symptoms during the COVID-19 phase (36). Furthermore, certain studies indicate that individuals possessing the HP2 allele demonstrate an enhanced immune response; hence, these individuals may display superior responses and generate elevated quantities of protective antibodies, including IgM and IgG (37). There are also studies yielding divergent outcomes from our research. Kasvosve I et al. 2000 study in Zimbabwe with 98 tuberculosis patients and 98 controls identified a correlation between the HP2-2 phenotype and heightened tuberculosis mortality (38). The study by Speeckaert et al. (2009) on patients with EBV infection showed the protective effect of HP1-1 and HP1-2 phenotypes against EBV infection (30). In a comparable study, Andrew P. Levy (2002) examined 206 cardiovascular disease patients and 206 controls in the United States, revealing that diabetes patients with the HP2-2 phenotype exhibited a greater likelihood of cardiovascular disease than those with other phenotypes (39). Variations in results may be due to different research methods, distinct disease classifications, ethnic heterogeneity in study populations, survival biases, genetic associations between the HP gene and other related genes, or random variability.

In summary, this study reveals that HP2 allele and its variants (HP2-2, HP1-2) are most prevalent, consistent with global trends. The HP1-2 genotype and HP1 allele were associated with increased COVID-19 risk in men, though no overall link between HP genotypes and COVID-19 was found. Discrepancies in findings across studies may stem from methodological differences, disease variability, or population genetics. To achieve more conclusive and generalizable results, it is suggested to Increase the sample size and conduct research across multiple geographic regions to account for ethnic and environmental variability.

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Conflict of interest

There are no conflicts of interest to declare by the authors.

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