Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2024; 41(3): 479-484
doi: 10.52142/omujecm.41.3.5

Investigation of HLA-DRB1*09:01 polymorphism and its association with COVID-19 severity in the Indonesian population

Reviono REVIONO, Hendrastutik APRININGSIH, Olivia Geraldine ROXANNE *

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia

Received: 06.11.2023 • **Accepted/Published Online:** 30.07.2024 • **Final Version:** 30.09.2024

Abstract

Coronavirus disease 2019 (COVID-19) manifests in a wide range of degrees of severity, ranging from asymptomatic to critical disease with high risk of mortality. Gene polymorphism has been found to be associated with severe COVID-19 in different populations around the world. Human Leukocyte Antigen (HLA)-DRB1*09:01, in particular, has appeared to be more significantly associated with severe COVID-19 compared to pre-existing comorbidities in a study involving an Asian population. This study investigated HLA-DRB1*09:01 polymorphism in Indonesian patients who were hospitalized in Sebelas Maret University Hospital with COVID-19 from October 2021 to October 2022 and analyzed whether there is an association with severe COVID-19. Of 154 subjects in total, 102 were non-severe and 52 were severe. We reviewed four single nucleotide polymorphisms (SNP) of HLA-DRB1*09:01, namely rs75314265, rs79572840, rs117501019, and rs11708573. The SNP rs 79572840 population was entirely heterozygote (100%) in both non-severe and severe groups. In both severity groups, SNP rs75314265 was dominated by heterozygote alleles, while rs117501019 and rs11708573 were dominated by homozygote alleles. None of the SNPs were significantly associated with severe COVID-19. Subject characteristics associated with severity were of older age, having comorbidities and higher neutrophil to lymphocyte ratio (p=0.010, 0.030, 0.001, respectively), which potentially confounded the effect of HLA polymorphisms on COVID-19 severity in this study. Gene polymorphism among different populations is a natural phenomenon, hence different studies may yield different conclusions about HLA's association with COVID-19 severity. Further studies involving more cases over various populations may allow better understanding of genetic markers linked to disease outcomes and prognosis.

Keywords: COVID-19, severity, risk factor, HLA-DRB, polymorphism

1. Introduction

Coronavirus disease 2019 (COVID-19), the viral disease caused by SARS-CoV-2 has recently become worldwide pandemic with a multitude of comorbidities and mortalities, generating a significant burden in health care and economics worldwide (1). In Indonesia, ever since first confirmed case being reported in March 2020, the number of cases rapidly rise and by August 2021 there had been 3,892,479 confirmed cases with 120,013 deaths (2). The disease manifests in a vast range of clinical appearance and degree of severity. While most individuals are asymptomatic or experiencing mild symptoms such as fever, cough, altered sense of smell and taste, gastrointestinal symptoms and cutaneous manifestations, some patients may have severe or critical illness, in which respiratory failure and/or hemodynamic instability can be found (3). As the pathogenesis of severe COVID-19 and the associated respiratory failure is yet to be comprehensively understood, potential risk factors associated with severity have been subject of multiple studies regarding COVID-19.

Among recorded factors with significant association to severe COVID-19 such as age, gender, race, comorbidities, smoking history and vaccination status (2), it is also found that genetic variations i.e. polymorphism may correlate with disease progression and manifestation (4). Variants of SARS-CoV-2 entry mechanism-related genes, immune response-related genes, and other potential genetic loci are found to be associated with degree of COVID-19 severity. Recent research recorded that individual with a varied expression of several genes and their alleles such as Human Leukocyte Antigen (HLA), Angiotensin-converting enzyme-2 (ACE-2), cellular proteases, and immune response proteins might be predisposed to severe COVID-19 (5).

The human leukocyte antigens (HLA) is the principal genetic region involved in human immunity against virus and has been shown to display a great degree of polymorphism. This variability is possibly maintained in human populations in order to successfully display a wide range of processed foreign peptides to T cell antigen receptor (6). HLA class I (HLA-A, -B, -C) proteins present viral peptides to CD8+, while HLA class II (HLA-DR, -DQ, -DP) to CD4+ T-cells to facilitate farther immunological cascade (7). Hence, polymorphism of HLA class II may modify host's adaptive immunity as well as humoral responses against virus, consequently determining the course of disease progression and outcome (8). Studies have shown that HLA genes polymorphism modulated the outcome

*Correspondence: oh.liviaroxanne@gmail.com

of infectious diseases caused by SARS-CoV-1, HIV, Influenza H1N1, and even bacterial infections (8, 9).

Earlier studies addressing HLA polymorphism and its association to severe COVID-19 have recorded various results, including contradictory ones. While some studies concluded that certain HLA polymorphism correlate to severe disease manifestation, some disprove the hypothesize. For example, Wang, et al. identified that the HLA-A*11:01, HLA-B*51:01, and HLA-C*14:02 alleles significantly predisposed patients to worse outcome (10). The HLA-A*11:01 was significantly associated with severe COVID-19 in Japanese and Chinese populations. Contradictory result was recorded in another publication by Toyoshima et al. (11), who investigated the relationship between HLA-A*11:01 allele frequency and SARS-CoV-2 infection or mortality rate and found that individuals with this allele could potentially be protected from SARS-CoV-2 infection. Other studies in Spanish, Israeli, and South Asians populations instead found no evidence of association between SARS-COV-2 susceptibility or severity and HLA alleles (12-14).

HLA-DRB1*09:01 has been specifically mentioned to show significant association with severe COVID-19 with odds ratio of 3.62 (95% CI, 1.57-8.35; p = 0.00251) (14). In Japanese population (14), the DRB1*09:01 allele interestingly showed stronger association with risk for severe COVID-19 compared to pre-existing medical conditions such as hypertension, diabetes, and cardiovascular diseases, indicating significant potential of HLA role in predisposition to severe COVID-19. As there are currently limited number of studies about genetic predisposition to severe COVID-19 in Indonesian population, this study aims to investigate polymorphisms in HLA-DRB1*09:01 and their association with severe COVID-19.

2. Materials and methods

2.1. Subjects

Subjects were patients hospitalized with COVID-19 within the said period that met these criterias: a) COVID-19 confirmed with two consecutive positive PCR, b) aged above 18 years old, c) willing to participate in study and give written consent.

2.2. Study Procedure

All subjects were taken record of their age, sex, comorbidities, COVID-19 symptoms, and leukocyte count at the point of admission. Subjects were then divided into 2 groups of COVID-19 severity: severe (patients admitted to intensive care unit or high care unit) and non-severe (admitted to ward). Criteria for intensive care admission were SpO2 <94% on room air, PaO2/FiO2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%. All eligible subjects got peripheral blood drawn for routine blood work and DNA polymorphism assessment. Correlation between patients' age, sex, presence of comorbidities, leukocyte count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), and HLA-DRB1*09:01 polymorphism with COVID-19 severity were then analyzed.

2.3. Single Nucleotide Polymorphism (SNPs) Genotyping Procedure

DNA samples taken from peripheral blood were genotyped for polymorphisms HLA-DRB1*09:01 gene rs75314265, rs2066992, rs79572840, rs117501019, rs11708573, rs75314265, rs79572840, rs75314265, rs117501019 using kiCqStart SYBR® Green ReadyMixTM (Sigma Aldrich, Germany) with primers as listed in Table 1. The procedure of the real-time PCR was as follows: 15 ng DNA, 15 µL of Taqman universal PCR master mix (Roche NJ, USA) and 6.5 µL of each probe. The conditions for amplification were the following: 94°C (3 min), 61°C (1 min), and 72°C (1 min); followed by 35 cycles of 94°C (1 min), 61°C (1 min), and 72°C (1 min); and a final cycle of 94°C (1 min), 61°C (1 min), and 72°C (5 min).

2.4. Statistical Analysis

Independent variables were age, sex, presence of comorbidities, leukocyte count, lymphocyte count, NLR, and HLA-DRB1*09:01 polymorphism. Dependent variable was severe COVID-19. Variables other than DNA polymorphism were tested for correlation with severe COVID-19 in bivariate manner with Chi-square, except for age which was regarded as numeric variable and was tested with Mann-Whitney. As for HLA-DRB1*09:01 polymorphism, each studied gene was divided according to its allelic variants as heterozygote and/or homozygote, and each variant was tested for correlation with severe COVID-19 in bivariate manner with Chi-square.

3. Results

The total number of recruited subjects were 154, subjects' characteristics were as described in Table 1. Subjects were divided into 2 groups based on severity of COVID-19 clinical manifestation: non-severe and severe. Most subjects were in non-severe group (102 vs 52). There were more male than female subjects in both severity groups, although the difference was slight (52.9% and 55.76%, respectively, p=0.739). The mean age of subjects in non-severe group was 45.30 $\pm$ 13.55 years old, whereas the mean age in severe group was significantly older at 55.23 $\pm$ 14.31 years old (p=0.011). In both severe and non-severe group, hypertension was the most commonly found comorbidity, followed by type II diabetes and chronic kidney disease. Having comorbidities was significantly associated with severe COVID-19 (p=0.030).

Table 1. Subject characteristics based on COVID-19 severity

Characteristics	Non severe (n=102) mean ± SD/(%)	Severe (n=52) mean ± SD/(%)	*p*
Sex			
Male	54 (52.9%)	29 (55.76%)	0.739
Female	48 (47.1%)	23 (44.24%)	
Age (years)	45.30 ±13.55	55.23 ±14.31	0.011
Comorbidities			
Type II diabetes	15 (20 .0%)	14 (18.66%)	
Hypertension	22 (29.33%)	33 (44.00%)	
Chronic kidney disease	1 (1.33%)	2 (2.66%)	
Chronic heart failure	0 (0%)	3 (0.0%)	0.030
HIV/AIDS	0 (0%)	1 (1.33%)	
Stroke	1 (1.33%)	0 (0%)	
Others	4 (5.33%)	1 (1.33%)	
None	59 (74.69%)	20 (25.31%)	
Laboratory results			
Leukocyte count	9.00 (1.88-29.39)	9.63 (3.64-24.43)	0.788
Lymphocyte count	23.26 (4.28-43.10)	14.84 (2.00-41.00)	0.457
NLR	4.19 (0.46-21.01)	9.45 (1.29-49.32)	**0.001**

The only laboratory parameter showing association to severe COVID-19 was NLR (p=0.001). The mean NLR in non-severe group was 4.19 (0.46-21.01), while in the severe group 9.45 (1.29-49.32). When tested in a regression analyses along with another subject characteristics hypothetically affecting COVID-19 severity, only age and NLR remained consistently having significant associated with severe COVID-19 (p=0.006 and p=0.007, respectively). Regression analyses of subjects' demographical, clinical, and genetic characteristics for their association to COVID-19 severity is shown in Table 2.

We used Taqman commercial probes for DNA genotyping as shown in Table 3. Upon reviewing four single nucleotide polymorphisms of HLA-DRB1*09:01 allele namely rs75314265, rs79572840, rs117501019, and rs11708573, we found no significant difference between non-severe and severe group (p>0.05) (Table 4). Appealingly, it was found in this study that SNP rs 79572840 population was entirely heterozygote (100%) regardless of disease severity. SNP rs75314265 was also dominated by heterozygote allele in both non-severe (86.66%) and severe groups (87.5%). In contrast, rs117501019 and rs11708573 were dominated by homozygote alleles. The SNP rs117501019 were dominantly homozygote in both non-severe (98.03%) and severe group (96.07%). Likewise, rs11708573 were dominantly homozygote in non-severe and severe group (67.27% and 57.14%, respectively).

Table 2. Regression analyses of subject characteristics and their association with COVID-19 severity

Subject Characteristics	Non-Severe COVID-19 (n = 102)	Severe COVID-19 (n = 52)	Odd Ratio (95% CI)	*p*
rs75314265				
Homozygote TT	6	4	0.905 (0.437–1.876)	0.789
Heterozygote CT	39	25		
Undetermined	57	23		
rs79572840				
Heterozygote CG	97	52	0.00 (0.00–0.00)	0.999
Undetermined	5	0		
rs117501019				
Homozygote GT	100	49	3.975 (0.578–27.341)	0.161
Heterozygote GG	2	2		
Undetermined	0	1		
rs11708573				
Homozygote CC	37	20	0.714 (0.425-1.199)	1.199
Heterozygote CT	18	15		
Undetermined	47	17		
Sex				
Male	54	29	0.981 (0.454–2.120)	0.981
Female	48	23		
Comorbidities				
Present	59 (0.38)	20	1.336 (0.596–2.993)	0.481
Absent	43	32		
Age	45.30±13.55	55.23±14.31	1.043 (1.012–1.075)	**0.006**
NLR	0 (0)	6 (1.89)	4.426 (1.501–13.052)	**0.007**

Table 3. Taqman commercial probes used for DNA genotyping

Gene	Probe
rs75314265	/rhAmp-F/AGT GTC TCG TTT ACT TTG GAA AAA TAT rATT TC/GT1/ /rhAmp-Y/GTG TCT CGT TTA CTT TGG AAA AAT ACrA TTT C/GT1/ GCA ATA GTG ACT TCT AAC CAA CCT CTrC CAA G/GT4/
rs79572840	/rhAmp-F/ACT GTA TTT TAG TAC ATT CTT GAT GTA GrAA TTA /GT3/ /rhAmp-Y/ACT GTA TTT TAG TAC ATT CTT GAT GTA CrAA TTA /GT3/ GCA GTA TTA CAG GAT AAA AGT GGA GGrC AAA A/GT4/
rs117501019	/rhAmp-F/ATG CTC ACC TCG CCG rCTG CA/GT3/ /rhAmp-Y/CAT GCT CAC CTC GCC TrCT GCA /GT3/ GCA CAC CTA CTG CAG ACA CAA CrUA CGG /GT2/
rs11708573	/rhAmp-F/CCC CCC ACC ATG CTC rACC TC/GT2/ /rhAmp-Y/CCC CCC ACC ATG CTT rACC TC/GT2/ GCC ACC TAC TGC AGA CAC AAC TrAC GGG /GT2/

Table 4. Allelic polymorphism and genotypic distribution of HLA-DRB1*09:01

SNP	Non severe n (%)	Severe n (%)	*p*
rs75314265			
Heterozygote T/C	39 (86.66%)	25 (87.5%)	0.955
Homozygote T/T	6 (13.33%)	4 (6.3%)	
rs79572840			
Heterozygote C/G	97 (100.0%)	52 (100.0%)	-
rs117501019			
Heterozygote G/T	2 (1.96%)	2 (3.92%)	0.474
Homozygote G/G	100 (98.03%)	49 (96.07%)	
rs11708573			
Heterozygote C/T	18 (32.72%)	15 (42.85%)	0.331
Homozygote C/C	37 (67.27%)	20 (57.14%)	

The four SNPs being investigated all showed insignificant correlation to severe COVID-19 with low correlation coefficient. Highest correlation coefficient was showed by rs117501019 (r=0.102) while the lowest was rs75314265. Difference was invalid to evaluate within rs79572840 population as 100% of the population in both non-severe and severe groups were homozygote (Table 5).

Table 5. HLA polymorphisms in study and the correlation to severe COVID-19

SNP	r (correlation coefficient)	*p*
rs75314265	0.007	0.956
rs79572840	-	-
rs75314265	0.058	0.477
rs117501019	0.102	0.336

4. Discussion

Despite multiple studies having been conducted and several risk factors associated with severe COVID-19 are figured, data on genetic involvement as host risk factor is limited (15). HLA region is the most variable in the human genome and the influence of these alleles on COVID-19 disease progression may differ among populations with different genetic profiles (16). The human leukocyte antigen (HLA) gene complex encodes major histocompatibility complexes (MHC), which is crucial for exposing and presenting antigens derived from pathogens to the appropriate T lymphocytes, triggering the immune response (17).

In COVID-19, HLA gene is involved in encoding MHC class II as a part of individual's antiviral humoral and cellular immunity. In the setting of severe disease, possible higher viral load would mean the need for more MHC class II to present viral peptide to CD4+ T lymphocytes, subsequently involving more CD4+ and CD8+ T cell (cytotoxic T cell), whose activation lead to tissue destruction along with pathogen elimination. Understanding the genetic variance of the gene and its association to disease progression may provide new perspective to identify patients at high risk of high disease burden and mortality, develop plans for vaccines and pharmaceutical treatments as well as evaluating their efficacies (15, 18).

A study about the genotypes of HLA-A, HLA-C, HLA-B, and -DRB1 in 178 Japanese COVID-19 subjects investigated the HLAs' association with severe COVID-19 and found that HLA-DRB1* 09:01 was associated with severe COVID-19 (15). The association between this allele and severe COVID-19 was more significant than pre-existing medical conditions. Alongside HLA-DRB1* 09:01, HLA-DRB1*08 and HLA-DRB1*04 were the other alleles being associated with disease severity and mortality. In another meta-analysis in 2022, Dieter et al. figured alleles HLA-A*33, ACE1 Ins, and TMPRSS2 rs12329760T to be associated with protection against severe COVID-19 manifestation, while HLA-B*38, HLA-C*6, and ApoE rs429358C alleles were associated with risk for severe COVID-19 (19). As HLA-DRB1*09:01 has been readily reported to be associated with severe COVID-19, this study investigated the hypothesis specifically in Indonesian population. However, it is found in this study that HLA-DRB1*09:01 polymorphism for rs75314265, rs79572840, rs75314265 and rs117501019 show no significant association to severe manifestation of COVID-19.

The results across different studies for HLA polymorphism's impact to disease severity have been inconsistent and sometimes conflicting (9). Hence, its clinical relation to COVID-19 remains controversial. In a recent meta-analysis studying how genetic background among different populations may influence COVID-19 susceptibility and severity, the impact of a certain allele towards the disease's clinical course were difficult to evaluate due to the reviewed studies having subjects of different ethnicities (18). HLA alleles vary greatly across different populations. Certain alleles that have been identified as risk alleles in one association study may have little to no significance in other population because the studied alleles are uncommon in the population. Different HLA alleles may have different peptide binding site while being able to bind to the same virus. Unfortunately, data on allele distribution in normal South Asian population is scarce (14).

Besides of the presence of a certain HLA type being uncommon outside a particular population, studies about HLA polymorphism often have limited number of subjects, making it difficult to figure significant association of tested variables and results among different studies become inconsistent (14, 20). Furthermore, the impact other factors such as gender and age which may influence disease predisposition could not be assessed due to limited number of studies for each SNP. According to a systematic review and meta-analysis by Dieter, et al. in 2022, different studies also had different definition of "severe" COVID-19, putting the comparison into more risk of bias (19).

Based on our finding that HLA-DRB1*09:01 gene polymorphism did not associate with COVID-19 severity, it is indicated that variance in the particular gene may not limit a subject's immunological response against SARS-CoV-2. However, it is to be noted that actual immunological response was not directly measured in this study (with serological or cellular study), but instead severe disease manifestation was addressed as a proxy of one's immune response quality. Incomplete understanding about peptide synthesis and presentation via HLA, as well as direct impairment of T cell epitope presentation by SARS-CoV-2 may alter outcomes of predicted immunogenic response (21).

This study found that all population for rs79572840 were heterozygote C/G. Rs79572840 is a single nucleotide variant (SNV) located in HLA-DRB5 in chromosome 6. Some of the subjects being excluded for showing "undetermined" result on genotyping study may be homozygote. Earlier study by Liu, et al. mentioned that heterozygote polymorphism serves as biological mechanism to balance natural selection and is advantageous in human evolution (21).

Some subject characteristics in this study showed significant association to severe COVID-19, serving as risk factors of severity. Those factors were age ($p = 0.011$), presence of comorbidity ($p = 0,030$) and NLR from peripheral blood examination ($p = 0,001$). This finding is consistent to many earlier studies, as it is mentioned by Mohan et al. that age and comorbidities successfully predict COVID-19 outcome regardless of innate immune response severity (22). Neutrophilia and NLR have also showed consistent association to disease severity throughout worldwide studies, making it a cheap, simple and readily available marker of severity and mortality of COVID-19 (23). Older age and higher NLR were consistently associated with severe COVID-19 after regression analysis with another independent variables in this study including sex, presence of comorbidities, and HLA-DRB1*09:01 polymorphism itself (Table 5).

COVID-19 severity may also be greatly affected by comorbidities. The conditions that most often lead to the mortality in patients with chronic diseases are arterial hypertension, diabetes mellitus, metabolic syndrome, coronary heart disease, chronic obstructive pulmonary disease (COPD), nicotine addiction, inflammatory bowel diseases, and cancers.[4] Presence of comorbidities potentially acted as a factor confounding HLA effect towards severity.[24]

In conclusion, this study found that HLA-DRB1*09:01 is not associated with severe COVID-19 in Indonesian population. The main limitations of this study are presence of factors other than genetic variance that potentially confounded subjects' clinical outcome such as age and comorbidities, as well as limited understanding on individual genetic information and actual immunological response. Gene polymorphism is naturally found between different populations, hence some HLA can both offer protection and cause harm for the same disease throughout different studies, depending on the population and research design. Further studies involving more cases over various populations may be beneficial to better understand genetic markers linked to clinical outcomes of COVID-19.

Ethical statement

This study has obtained ethical approval from Ethical Committee of Sebelas Maret University under the reference number 46/UN27.06.6.1/KEP/EC/2021.

Conflict of interest

The authors state that there are no conflicts of interest in this study.

Funding

This study was funded by research grant from Sebelas Maret University, Surakarta, Indonesia.

Acknowledgments

None to declare.

Authors' contributions

Concept: R.O., H.A., O.G.R., Design: R.O., H.A., O.G.R., Data Collection or Processing: R.O., H.A., Analysis or Interpretation: R.O., H.A., Literature Search: R.O., H.A., O.G.R., Writing: R.O., O.G.R.

References

1. Richards F, Kodjamanova P, Chen X, Li N, Atanasov P, Bennetts L, et al. Economic burden of COVID-19: a systematic review. Clinicoecon Outcomes Res. 2022 Apr 28;14:293-307.
2. Setiadi W, Rozi IE, Safari D, Daningrat WO, Johar E, Yohan B, et al. Prevalence and epidemiological characteristics of COVID-19 after one year of pandemic in Jakarta and neighbouring areas, Indonesia: A single center study. PLOS ONE [Internet]. 2022 May 12 [cited 2023 Oct 31];17(5):e0268241. Available from: https://doi.org/10.1371/journal.pone.0268241.
3. Martono, Fatmawati F, Mulyanti S. Risk factors associated with the severity of COVID-19. Malays J Med Sci. 2023 Jun;30(3):84-92.
4. Ishak A, Mehendale M, AlRawashdeh MM, Sestacovschi C, Sharath M, Pandav K, et al. The association of COVID-19 severity and susceptibility and genetic risk factors: A systematic review of the literature. Gene. 2022 Aug 20;836:146674.
5. Yıldırım M, Arslan G. A moderated mediation effect of stress-related growth and meaning in life in the association between Coronavirus suffering and satisfaction with life: Development of the stress-related growth measure. Front Psychol. 2021 Mar 16;12:648236.
6. Williams TM. Human leukocyte antigen gene polymorphism and the histocompatibility laboratory. J Mol Diagn. 2001 Aug;3(3):98-104.
7. Copley HC, Gragert L, Leach AR, Kosmoliaptsis V. Influence of HLA class II polymorphism on predicted cellular immunity against SARS-CoV-2 at the population and individual level. Front Immunol. 2021 Jul 19;12:669357.
8. Kakodkar P, Kaka N, Baig MN. A comprehensive literature review on the clinical presentation, and management of the pandemic Coronavirus Disease 2019 (COVID-19). Cureus. 2020 Apr 6;12(4):e7560.
9. Fakhkhari M, Caidi H, Sadki K. HLA alleles associated with COVID-19 susceptibility and severity in different populations: a systematic review. Egypt J Med Hum Genet. 2023;24(1):10.
10. Wang F, Huang S, Gao R, Zhou Y, Lai C, Li Z, et al. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. Cell Discov. 2020 Nov 10;6(1):83.
11. Toyoshima Y, Nemoto K, Matsumoto S, Nakamura Y, Kiyotani K. SARS-CoV-2 genomic variations associated with mortality rate of COVID-19. J Hum Genet. 2020 Dec;65(12):1075-82.
12. Gutiérrez-Bautista JF, Rodriguez-Nicolas A, Rosales-Castillo A, López-Ruz MÁ, Martín-Casares AM, Fernández-Rubiales A, et al. Study of HLA-A, -B, -C, -DRB1 and -DQB1 polymorphisms in COVID-19 patients. J Microbiol Immunol Infect. 2022 Jun;55(3):421-7.
13. Ben Shachar S, Barda N, Manor S, Israeli S, Dagan N, Carmi S, et al. MHC Haplotyping of SARS-CoV-2 Patients: HLA Subtypes Are Not Associated with the Presence and Severity of COVID-19 in the Israeli Population. J Clin Immunol. 2021 Aug;41(6):1154-61.
14. Naemi FMA, Al-Adwani S, Al-Khatabi H, Al-Nazawi A. Association between the HLA genotype and the severity of COVID-19 infection among South Asians. J Med Virol. 2021 Jul;93(7):4430-7.
15. Anzurez A, Naka I, Miki S, Nakayama-Hosoya K, Isshiki M, Watanabe Y, et al. Association of HLA-DRB1*09:01 with severe COVID-19. HLA. 2021 Jul;98(1):37-42.
16. Migliorini F, Torsiello E, Spiezia F, Oliva F, Tingart M, Maffulli N. Association between HLA genotypes and COVID-19 susceptibility, severity and progression: a comprehensive review of the literature. Eur J Med Res. 2021 Aug 3;26(1):84.
17. Kulski JK, Shiina T, Dijkstra JM. Genomic diversity of the major histocompatibility complex in health and disease. Cells. 2019 Oct 17;8(10):1270.
18. Fakhkhari M, Caidi H, Sadki K. HLA alleles associated with COVID-19 susceptibility and severity in different populations: a systematic review. Egypt J Med Hum Genet. 2023;24(1):10.
19. Dieter C, Brondani LA, Leitão CB, Gerchman F, Lemos NE, Crispim D. Genetic polymorphisms associated with susceptibility to COVID-19 disease and severity: A systematic review and meta-analysis. PLoS One. 2022 Jul 6;17(7):e0270627.
20. Liu Q, Wu S, Xue M, Sandford AJ, Wu J, Wang Y, et al. Heterozygote advantage of the rs3794624 polymorphism in CYBA for resistance to tuberculosis in two chinese populations. Sci Rep. 2016 Nov 30;6:38213
21. Taefehshokr N, Taefehshokr S, Hemmat N, Heit B. Covid-19: Perspectives on innate immune evasion. Front Immunol. 2020 Sep 30;11:580641.
22. Mohan AA, Olson LB, Naqvi IA, Morrison SA, Kraft BD, Chen L, et al. Age and comorbidities predict COVID-19 outcome, regardless of innate immune response severity: A single institutional cohort atudy. Crit Care Explor. 2022 Dec 5;4(12):e0799.
23. Toori KU, Qureshi MA, Chaudhry A, Safdar MF. Neutrophil to lymphocyte ratio (NLR) in COVID-19: A cheap prognostic marker in a resource constraint setting. Pak J Med Sci. 2021 Sep-Oct;37(5):1435-9.
24. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. Nat Med. 2023 Feb;29(2):334-43.