International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 17s, 2025
https://theaspd.com/index.php

# Genotyping Of COVID-19 Patients And Association Of Some HLA Alleles With The Infection And Cytokine Profile

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***Abstract***
*COVID-19 is a serious pandemic infection of the respiratory system that results in huge mortality; and affects the global economy and lifestyle. This study aimed to determine any role of genetic factors represented by the association of any HLA alleles with the susceptibility or resistance to the infection. Additionally, it aimed to study IL-6 levels in the cytokine storm and disease outcome.*
*:a whole blood samples from 30 patients with COVID-19 were used for HLA typing by (SSO PCR) with (Auto-Lipa) Automatic Line Probe Assay compared with another 20 healthy control samples. Serum samples from the same patients and control groups were used for estimation of the IL-6 levels by ELISA test. HLA-A *0201 P value 0.21 increased frequency in the healthy control group compared to the patient's group, HLA-B *0205 P value 0-020 increased frequency in the Covid-19 patients group compared to healthy control. Increased frequency of HLA-DR *0456 P value 0.02 in the patients group compared to the healthy group with no significant alleles in the HLA-DQ region. A significant difference between both patients and the control group was reported in IL -6 Levels. The high increase of allele frequency in the patients group compared to the healthy controls could be considered as a susceptibility factor for the infection. An increase in IL-6 levels in COVID-19 patients results in a cytokine storm which is linked with an increase of fatality.*
***Keywords***: *Covid-19, HLA, alleles, Cytokine, IL-6, auto-lipa*

## 1-INTRODUCTION

The World Health Organization declared COVID-19 a pandemic on March 11, 2020, with over 4 million deaths reported, particularly among the elderly, before vaccination campaigns began (4). Howard summarized COVID-19 deaths by various demographic factors (5). CoVs can induce acute respiratory distress syndrome (ARDS) and severe pneumonia, leading to life-threatening lung dysfunction characterized by widespread inflammation (6, 7).

Coronaviruses, known as CoVs are a group of enveloped viruses, with a stranded positive sense RNA that can cause diseases in both humans and animals. They are recognizable by their crown appearance when viewed under an electron microscope (1). The spike glycoproteins present on their surface. In 2019 the emergence of acute respiratory syndrome coronavirus 2 (SARS CoV 2) in China marked the beginning of the COVID 19 pandemic, which quickly spread worldwide (2,3). The World Health Organization officially declared COVID-19 as a pandemic on March 11 2020 after it caused over 4 million deaths, particularly affecting individuals before vaccination efforts commenced (4,5,6). Howard provided an overview of COVID-19-related deaths across groups (7). CoVs have the potential to trigger acute respiratory distress syndrome (ARDS) and severe pneumonia that can lead to life-threatening lung dysfunction characterized by inflammation. Interleukin 6 (IL 6) plays a role in the cytokine network (8,9). Acute inflammatory response by stimulating C reactive protein (CRP) production (10). The clinical trials exploring the use of tocilizumab an IL 6 receptor antibody for COVID-19 treatment have not shown consistent effectiveness, in alleviating symptoms or reducing mortality rates (11,12). However, more research is required to delve into its effectiveness, in cases (13).

Immune system can play a significant role in eliminating different kinds of infections either bacterial, viral or parasitic (14,15). Patients with cases of COVID-19 showed an IL 6/IFN ratio compared to those with milder

cases possibly due to a more pronounced cytokine storm (16). Common risk factors for COVID-19 include hypertension, diabetes, chronic obstructive pulmonary disease, difficulty breathing, history of substance use gender disparities, ARDS (acute respiratory distress syndrome) smoking habits, advanced age, levels of albumin, and D dimer (17, 18, 19, 20). Human Leukocyte Antigen (HLA) typing could assist in prioritizing vaccination efforts and estimating the seriousness of illnesses within communities (21). The presence of HLA alleles associated with defense against SARS-CoV 2 might contribute to variations in COVID-19 cases and severity across regions. This study seeks to explore the impact of factors especially HLA alleles on susceptibility or resilience to SARS CoV 2 infection. It also aims to investigate IL 6 levels, in relation to cytokine storms and disease outcomes.

## 2-MATERIALS AND METHODS

### Blood Samples

We gathered blood samples from each participant taking 5 ml of blood, per person. Out of this amount 2 ml was preserved in EDTA tubes for DNA extraction while the remaining 3 ml was stored in tubes. The serum extracted from these tubes was frozen at 20°C for use. The research involved 30 patients who had tested positive for Covid 19 and were all linked to the center in Baghdad. These patients were examined between February and August 2021. Furthermore, the study included a comparison group comprised of 20 individuals.

### DNA Extraction and Genotyping

The extraction of DNA was carried out on blood samples using a QIAGEN kit according to the manufacturer's instructions. HLA A, B, DR, and DQ genes were amplified using the PCR SSO method with a Lipa HLA kit, from Innogenetics, Murex Biotech Limited. To determine HLA alleles molecularly an approach called Auto Lipa hybridization was applied with the kit. This technique is based on dot blot hybridization. The outcomes were analyzed using a typing chart provided with the kit to identify probes on each test strip.

The levels of IL 6, in the serum were measured using ELISA kits obtained from Demeditec Diagnostic in Germany. The assays were carried out with an automated ELISA system made by Diagnostic Automation Inc in the USA following the instructions provided in the kit manual.

### Statistical analysis

For the analysis SPSS version 14 software, commonly used in social sciences research was utilized as seen in studies. To examine the relationship between alleles and the development of the disease adjusted odds ratios and 95% confidence intervals were calculated using the Chi test. While serum cytokine levels were considered variables, they did not exhibit a distribution based on the Shapiro-Wilk test. Therefore, nonparametric methods were employed for their analysis with median values presented of means. The Mann-Whitney test was used to assess differences in medians, between study groups. Statistical significance was defined at a P value of 0.05 or lower.

## 3- RESULTS AND DISCUSSION

COVID-19 patients showed an IL 6 level of 98 pg./ml whereas the healthy control group exhibited an IL 6 level of 25 pg./ml. The comparison p-value was found to be, 0.001 as indicated in Table 1. The significant contrast highlighted in Table 1 points towards a difference between the two sets. This implies that the disparity in IL 6 levels is highly unlikely to be chance. The IL 6 level among COVID-19 patients (98 pg./ml) is four times higher than that of healthy controls (25 pg./ml). This considerable rise indicates a reaction in COVID-19 patients. The notable surge of IL6 in COVID-19 patients could potentially act as a biomarker for the disease or its severity aiding in diagnosis, prognosis, and monitoring of affected individuals. IL 6 serves as an inflammatory cytokine and its escalation aligns with the recognized inflammatory characteristics of severe COVID-19 cases supporting the notion that COVID-19 can instigate a pronounced inflammatory response possibly leading to complications like cytokine storms in critical scenarios. Elevated IL 6 levels may imply targets for interventions; certain treatments for severe cases of COVID-19 target the IL 6 pathway specifically

to alleviate inflammation, like tocilizumab. The information provided is interesting. It would be helpful to have specifics like the number of samples the seriousness of COVID-19, among the patients, and if there is a connection, between IL 6 levels and disease severity or results. This study investigated the association of different HLA class I and II alleles with the incidence of COVID-19 infection. The epidemiological studies could provide a great source of information for further studies. Recently, researchers tried using herbs or natural products to deal with infectious pathogens. The scientific community is intensely concentrating on figuring out the characteristics of the immune response to the COVID-19 virus and how heredity affects illness susceptibility and severity. An international partnership of European centers was set up to examine the issue of whether there were any possible genetic host variables related to the severe clinical development of the SARS-CoV-2 infection during the outset of the COVID-19 pandemic in Europe in the spring of 2020 (22).

**Table 1: Differences in IL-6 levels between COVID-19 patients and Healthy control groups**

| IL-6 Average levels | Covid-19 patients Average | Healthy control Average | p.value |
|---|---|---|---|
| | 98 pg./ml | 25pg/ml | Less than 0.001 |

COVID 19 patients and individuals, in health were compared in terms of the frequency of alleles found in the HLA A region (as shown in Table 2). This table provides a comparison of how various HLA A alleles occur among COVID-19 patients versus those who are healthy. The HLA (Human Leukocyte Antigen) genes are essential for the system's ability to identify and respond to invaders.

The analysis compared the occurrence of HLA A alleles between COVID-19 patients and individuals who were healthy (see Table 2). The HLA genes, crucial for response play a role in this process. Sample size; It seems that the sample size is relatively small with 30 COVID 19 patients and 20 healthy individuals (based on the provided percentages). Allele distribution; Some alleles display variances between the two groups. For instance, while HLA A*0201 is found in 20% of individuals it is absent in Covid 19 patients. On the other hand, HLA A*0106 is present in 13.33% of Covid 19 patients. Not detected in healthy controls. The odds ratio values presented in Table 2 indicate the link between these alleles and Covid 19. An odds ratio more than 1 implies an increased risk while a value, less than 1 suggests a decreased risk.

For example, HLA A*0106 shows an odds ratio of 6.962 indicating a susceptibility, to Covid 19 while HLA A*0201 displays an odds ratio of 0.060 hinting at a possible protective impact against the virus. Most comparisons in the P value column are labeled as "NS" (Not Significant) except for HLA A*0201 (P = 0.21) suggesting that the observed disparities may not be statistically meaningful due to the sample size. The Fraction (EF) and Preventive Fraction (PF) offer insights, into the risk or protective effects associated with each allele. However, it is worth noting that HLA A*0607 appears in the table with varying values, which could be indicative of an error.

HLA genes are significant factors in an individual's response to a foreign pathogen. Therefore, in this investigation, we were interested in finding HLA-A and B alleles that are vulnerable and those that may be employed in risk prediction models for the early detection of severe COVID-19 in COVID-19 cases of Iraqi covid-19 patients who are hospitalized. in Medical City in Baghdad, when investigating the connection between COVID-19 susceptibility and HLA genotypes, it seems that while genetic and other environmental factors may have an effect, the presence of HLA and other polymorphisms increased the patient's vulnerability (21) and Tavasolian et al. also reported a similar outcome.

**Table 2: Comparison between Covid -19 patients and Healthy control allele frequency in the HLA-A region**

| HLA-A allele | Covid-19 patients | % | Healthy Control | % | OR | IOR | EF | PF | P value |
|---|---|---|---|---|---|---|---|---|---|
| *0201 | 0 | 0.00% | 4 | 20.00% | 0.060 | 16.636 | 0.00 | 0.00 | 0.21 |
| *0106 | 4 | 13.33% | 0 | 0.00% | 6.962 | 0.144 | 3.43 | 1.41 | NS |
| *0607 | 0 | 0.00% | 1 | 5.00% | 0.213 | 4.692 | 0.00 | 0.00 | NS |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *1106 | 5 | 16.67% | 2 | 10.00% | 1.596 | 0.627 | 1.87 | 2.15 | NS |
| *2408 | 2 | 6.67% | 0 | 0.00% | 3.596 | 0.278 | 1.44 | 3.25 | NS |
| *0607 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *3002 | 0 | 0.00% | 2 | 10.00% | 0.121 | 8.243 | 0.00 | 0.00 | NS |

HLA-B allele frequencies between COVID-19 patients and healthy controls were also compared. The "Healthy Control" column is missing a value for the *1561 allele Table 3). Some percentages are given, while others are not, which makes direct comparison difficult. *0205 is the most common allele in both groups, with a notably higher frequency in healthy controls (35%) compared to COVID-19 patients (6.67%). *1561, *5201, *5501, *4001, and *4006 is present in COVID-19 patients but not in healthy controls (or data is missing). *2718 is present in healthy controls but not in COVID-19 patients.

**Table 3: HLA-B allele frequency of both COVID-19 patients and Healthy control**

| HLA-B allele | Covid-19 patients | % | Healthy Control | % | OR | IOR | EF | PF | P value |
|---|---|---|---|---|---|---|---|---|---|
| *1561 | 1 | 3.33% | | 5.00% | 0.661 | 1.513 | -0.51 | 0.34 | NS |
| *2718 | 0 | 0.00% | 1 | 5.00% | 0.213 | 4.692 | 0.00 | 0.00 | NS |
| *0205 | 2 | 6.67% | 7 | 35.00% | 0.158 | 6.333 | -10.67 | 0.91 | 0-020 |
| *5201 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *5501 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *4001 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *4006 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |

Odds Ratio (OR) in Table 3 is less than 1 which suggests the allele might be protective against COVID-19. While OR > 1 suggests the allele might increase susceptibility to COVID-19. *0205 has the lowest OR (0.158), suggesting a potential protective effect. *5201, *5501, *4001, and *4006 has ORs of 2.085, potentially indicating increased susceptibility. Only *0205 shows statistical significance (p = 0.020). *0205 has the highest PF (0.91), suggesting a strong preventive effect while other alleles have relatively small EF or PF values.

Table 4 shows the frequency of various HLA-DR alleles in COVID-19 patients compared to healthy controls. The data includes that COVID-19 patients: 9 (30.00%). HLA-DR*1109 shows a significant association with COVID-19. It appears in 30% of COVID-19 patients but is absent in healthy controls. The high odds ratio (OR) of 18.166 and low p-value (0.007) suggest this allele may increase susceptibility to COVID-19. However, HLA-DR*0456 also shows a significant difference between groups (p-value 0.02), but it's more common in COVID-19 patients (21.21%) than in healthy controls (5%). The low OR (0.156) suggests it might have a protective effect against COVID-19. While the other alleles (HLA-DR*0701, *1302, *1360, *1122, and *1101) do not show statistically significant differences between COVID-19 patients and healthy controls (p-values are listed as NS, presumably meaning "not significant"). The Etiological Fraction (EF) and Preventive Fraction (PF) provide additional information about the potential impact of each allele on disease risk, but their interpretation should be cautious given the small sample size.

**Table 4: Covid-19 and Healthy Control HLA-DR allele frequency**

| HLA-DR allele | Covid - 19 patients | % | Healthy Control | % | OR | IOR | EF | PF | P value |
|---|---|---|---|---|---|---|---|---|---|
| *1109 | 9 | 30.00% | 0 | 0.00% | 18.166 | 0.055 | 8.50 | 1.13 | .007 |
| *0456 | 7 | 21.21% | 1 | 5.00% | 0.156 | 5.333 | -9.67 | 0.89 | 0.02 |
| *0701 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *1302 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *1360 | 0 | 0.00% | 1 | 5.00% | 0.213 | 4.692 | 0.00 | 0.00 | NS |
| *1122 | 4 | 13.33% | 3 | 15.00% | 0.849 | 1.178 | 0.71 | 0.42 | NS |
| *1101 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |

Table 5 shows a comparison of HLA DQ allele frequencies, in COVID-19 patients and individuals in health. The analysis revealed no variations in allele frequencies among COVID-19 patients. The table illustrates how the occurrence of HLA DQ alleles differs between COVID-19 patients and healthy individuals. HLA (Human Leukocyte Antigen) genes are vital for the system's ability to detect and respond to pathogens. None of the differences in allele frequencies were statistically significant (all p values are indicated as NS meaning not significant).

HLA DQ*0321 displayed the odds ratio (2.804) hinting at a higher occurrence in COVID-19 patients but this was not statistically significant. The prevalent allele among both groups was HLA DQ0321 for COVID-19 patients (16.67%) and HLA DQ0201/*0603 for controls (15% each). The absence of significance for any allele implies that larger studies are required to confirm or disprove any connections. Factors like ethnicity, age and existing medical conditions, which are not detailed in this table could influence the distribution of HLA alleles and susceptibility, to COVID-19.

An increase in IL-6 levels in COVID-19 patients results in a cytokine storm which is linked with increase of fatality. It is better to increase the epidemiological studies which as previously proved, could provide a great source of information for further studies in addition, the authors suggest trying to use herbs or natural products in dealing with infectious pathogens as these natural products showed highly positive results in dealing with viral infections.

**Table 5: Comparison between Covid -19 and Healthy control groups in the HLA-DQ region**

| HLA-DQ allele | Covid -19 patients | % | Healthy Control | % | OR | IOR | EF | PF | P value |
|---|---|---|---|---|---|---|---|---|---|
| *0201 | 3 | 10% | 3 | 15.0% | 0.636 | 1.571 | 1.71 | 0.63 | NS |
| *0321 | 5 | 16.67% | 1 | 5.00% | 2.804 | 0.357 | 3.22 | 1.45 | NS |
| *0202 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *0204 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |
| *0502 | 0 | 0.00% | 1 | 5.00% | 0.213 | 4.692 | 0.00 | 0.00 | NS |
| *0603 | 4 | 13.33% | 3 | 15.00% | 0.849 | 1.178 | 0.71 | 0.42 | NS |
| *0402 | 1 | 3.33% | 0 | 0.00% | 2.085 | 0.480 | 0.52 | -1.08 | NS |

## 4-CONCLUSION

The information presented in Table 1 indicates a link, between elevated IL 6 levels in COVID-19 patients when compared to individuals underscoring the significance of the inflammatory response in this illness and hinting at potential avenues for diagnosis and treatment. On the other hand, the data provided in Table 2 hints at connections between specific HLA A alleles and susceptibility or protection against COVID-19. However, due to the sample size and lack of significance, the strength of these findings is constrained. To solidify these associations and their implications for COVID-19 risk or protection extensive research involving sample sizes would be required. Notably, the *0205 allele seems to be linked to reduced COVID-19 risk while other alleles do not exhibit significant associations. Nevertheless, with sample sizes (as indicated by frequencies) these conclusions lack robustness and demand further investigation on a larger scale for validation. Some HLA DR alleles like *1109 and *0456 might influence susceptibility or protection against COVID-19; however comprehensive studies are necessary to corroborate these findings and delve into their relevance. The limitations posed by sample sizes and the absence of significance restrain the extent of conclusions that can be drawn from this data set. To establish any connections between HLA DQ alleles and

susceptibility or severity related to COVID 19 it would be imperative to conduct research, with larger sample sizes while factoring in other relevant variables.

**Financial fund;** we declare no financial fund or grant the whole work was achieved with self-funding

**REFERENCES**

1. Cui, J.; Li, F.; Shi, Z.L. Origin and evolution of pathogenic corona viruses. Nat. Rev. Microbiol. 2019, 17, 181–192. [CrossRef] [PubMed]

2-. Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; et al. A pneumonia outbreak associated with a new corona virus of probable bat origin. Nature 2020, 579, 270–273. [CrossRef]

3- Wang, Y.T.; Landeras-Bueno, S.; Hsieh, L.E.; Terada, Y.; Kim, K.; Ley, K.; Shresta, S.; Saphire, E.O.; Regla-Nava, J.A. Spiking Pandemic Potential: Structural and Immunological Aspects of SARS-CoV-2. Trends Microbiol. 2020, 28, 605–618. [CrossRef]

4- WHO. Available online: https://covid19.who.int (accessed on 27 July 2021).

5-.Koh, H.K.; Geller, A.C.; VanderWeele, T.J. Deaths from COVID-19. JAMA 2021, 325, 133–134. [CrossRef]

6- Tay, M.Z.; Poh, C.M.; Renia, L.; MacAry, P.A.; Ng, L.F.P. The trinity of COVID-19: Immunity, inflammation and intervention. Nat. Rev. Immunol. 2020, 20, 363–374. [CrossRef]

7~ Liang, Y.; Wang, M.L.; Chien, C.S.; Yarmishyn, A.A.; Yang, Y.P.; Lai, W.Y.; Luo, Y.H.; Lin, Y.T.; Chen, Y.J.; Chang, P.C.; et al. Highlight of Immune Pathogenic Response and Hematopathologic Effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 Infection. Front. Immunol. 2020, 11, 1022. [CrossRef]

8-Lee, D. W., Gardner, R., Porter, D. L., Louis, C. U., Ahmed, N., Jensen, M., et al. (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood 124 (2), 188–195. doi:10.1182/blood-2014-05-552729

9-Stone, J. H., Frigault, M. J., Serling-Boyd, N. J., Fernandes, A. D., Harvey, L., Foulkes, A. S., et al. (2020). Efficacy of tocilizumab in patients hospitalized with covid-19. N. Engl. J. Med. 383 (24), 2333–2344. doi:10.1056/NEJMoa2028836

10-Declercq, J., Van Damme, K. F. A., De Leeuw, E., Maes, B., Bosteels, C., Tavernier, S. J., et al. (2021). Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-aid): A factorial, randomised, controlled trial. Lancet. Respir. Med. 9 (12), 1427–1438. Doi: 10.1016/S2213-2600(21)00377-5

11-Soin, A. S., Kumar, K., Choudhary, N. S., Sharma, P., Mehta, Y., Kataria, S., et al. (2021). Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): An open-label, multicentre, randomised, controlled, phase 3 trial. Lancet. Respir. Med. 9 (5), 511–521. doi:10.1016/S2213-2600(21)00081-3

12-Lagunas-Rangel, F. A., and Chavez-Valencia, V. (2020). High IL-6/IFN-gamma ratio could be associated with severe disease in COVID-19 patients. J. Med. Virol. 92 (10), 1789–1790. doi:10.1002/jmv.25900

13-Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, Quaderi S, Mandal S, Hurst JR. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS ONE. 2020;15(5):e0233147.

14-Chen M, Fan Y, Wu X, Zhang L, Guo T, Deng K, Cao J, Luo H, He T, Gong Y. Clinical characteristics and risk factors for fatal outcome in patients with 2019-coronavirus infected disease (COVID-19) in Wuhan, China. SSRN Electron J. 2020;. https://doi.org/10.2139/ssrn.3546069.

15-Liu W, Tao Z-W, Wang L, Yuan M-L, Liu K, Zhou L, Wei S, Deng Y, Liu J, Liu H-G. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel corona virus disease. Chin Med J. 2020; 133(9):1032–8.

16-Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1054–62.

17. Littera R, Campagna M, Deidda S et al. (2020): Human Leukocyte Antigen Complex and Other Immunogenetic and Clinical Factors Influence Susceptibility or Protection to SARS-CoV-2 Infection and Severity of the Disease Course. The Sardinian Experience. Front Immunol., 11: 605688. doi: 10.3389/fimmu.2020.605688.

18. Migliorini F, Torsiello E, Spiezia F et al. (2021): Association between HLA genotypes and COVID-19 susceptibility, severity, and progression: a comprehensive review of the literature. European Journal of Medical Research, 26(1): 1-9.

19. Douillard V, Castelli E, Mack S et al. (2021): Current HLA Investigations on SARS-CoV-2 and Perspectives. Frontiers in Genetics, 12: 774922. doi: 10.3389/ fgene.2021.774922.

20. Tavasolian F, Rashidi M, Hatam G et al. (2021): HLA, immune response, and susceptibility to COVID19. Frontiers in Immunology, 11: 3581. doi: 10.3389/fimmu.2020.601886

**21.** Cavalli G, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinfammation: a cohort study. Lancet Rheumatol. 2021;