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Is the IL6-174 G/C (rs1800795) Single Nucleotide Polymorphism a Susceptibility Genetic Marker for COVID-19?

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ABSTRACT

Background and Aim: SARS-CoV-2 infection triggers immune response which can induce pro-inflammatory cytokines including IL6 expression. We attempted to assess this genetic factor among patients suffering from SARS-CoV-2 infection in Tehran during pandemic since we assumed that it can be introduced as a biomarker for this virus.

Methods: In this case- control study we collected blood samples from 71 individuals infected with Covid-19 and 86 healthy controls, respectively in Imam Hossein hospital. DNA was extracted using phenol- chloroform, and we evaluated IL6 G/C polymorphism by PCR-RFLP.

Results: Our data revealed that the GG genotype was less frequent in COVID-19 patients (59.2%) than in healthy controls (64.0%). In contrast, the GC (26.8%) and CC (14.1%) genotypes were more frequent in patients than in controls (23.3% and 12.8%, respectively).

Conclusion: IL-6 seems to be different in numerous areas which can be utilized as a biomarker; nevertheless, further studies are required to confirm it.

INTRODUCTION

Numerous infectious agents have been detected causing community- acquired pneumonia. Coronavirus disease 2019 (Covid-19) is one of them, which cast a shadow all around the world during the pandemic (1). This virus has a RNA genome encapsulated with glycoprotein (M), nucleocapsid protein (N), envelope protein (E), and the spike protein (2). Human angiotensin, which can convert enzyme 2 receptor (ACE2), and viral spikes are likely to help this virus to enter the cells, and the immune system can recognize them (3). This response can induce pro-inflammatory cytokines including interleukin-8 (IL-8), interleukin-1 beta (IL-1β), tumor necrosis factor- alpha (TNF-α), and interleukin-6 (IL-6) (4-6). This is the reason why some people infected with Covid-19 suffer from cytokine storm and acute respiratory distress syndrome (ARDS) which can claim their lives (4-6). Some risk factors, such as epigenetic ones can detrimentally progress these symptoms. Take, for example, lack of sufficient immune system putting the patients at the risk of death (7). Moreover, genetic items, ranging from ACE2, TMPRSS2, TLR-7 to androgen receptors, and protease genes expression can have an effect on this health problem (8).

Researchers have reported numerous genetic items which can have a significant role to play in monitoring Covid-19. IL-6 is likely to be one of them encoded by a variety of cell types due to a wide range of pathological stages (9). Activating nuclear factors, such as nuclear factor (NF)-IL-6, hypoxia inducible factor (HIF)-1α are usually responsible for controlling IL-6 expression (10, 11). IL-6 only has 20-60 min half-life causing to be regulated at the level of expression. Furthermore, scientists have found that IL6-174 G/C biallelic polymorphism is likely to regulate IL-6 expression (12).

Few studies in the Middle East countries have evaluated the IL6 G/C biallelic polymorphism in patients suffering from SARS-CoV-2 infection. In this study, we attempted to assess these genetic factors among these patients in Tehran during pandemic Covid-19 we hypothesized that this polymorphism

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may serve as a potential genetic risk factor for Coronavirus infection. However, to establish it as a diagnostic biomarker, further studies with appropriate sample sizes and diagnostic performance metrics (e.g., sensitivity, specificity, predictive values, and ROC curve analysis) are required.

MATERIALS and METHODS

Samples

Approval to conduct this study was obtained from the Shahid Beheshti University of Medical Sciences" IR.SBMU.MSP.REC.1399.200 (Grant No 23445). 71 and 86 whole blood samples from individuals infected with COVID-19 and healthy controls, respectively, were collected in tubes containing EDTA as an anticoagulant. The samples were centrifuged at 3000 rpm for 10 minutes, and the plasma fraction was separated and stored at -20°C until DNA extraction. The buffy coat layer, which contains white blood cells and is the primary source of genomic DNA, was also collected and stored under the same conditions for potential additional analyses.

DNA extraction

Phenol- chloroform protocol was used to extract DNA from each sample. To remove proteins, 200 µl of phenol was added to 200 µl of serum samples. After centrifuging, the combination of 200 µl Phenol- chloroform was added to the supernatant. To have a pure DNA samples, we centrifuged the samples, and 200 µl chloroform was employed to add to the supernatant. Finally, one more time centrifuging was used, and we dissolved the DNA to 50ul sterile water.

PCR for β-globin gene

12.5 µl master mix, 1 µl forward and reverse primer (10 pmol), 1 µl DNA and 8.5 µl sterile water in a 25ul PCR reaction was put into Bio Intellectica PCR. 5 min in 95 ºC as first denaturation, 30 cycles of 95 ºC for 30s, 55 ºC for 30s, 72 ºC for 30 s and 72 ºC for 7 min was the PCR schedule. β-globin gene product was about 100bp, and we evaluated the IL-6 in every positive β-globin gene in 2% agarose gel electrophoresis.

Amplification of IL6 G/C polymorphism

All samples were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to detect IL6-174 G/C (rs1800795) polymorphism as described by Duch et al. (15). We utilized primers 50-TGTCAAGACATGCCAAAGTG-3 (IL6-sense) and "5"-TCAGACATCTCCAGTCCTATA-30 (IL6-antisense). The initial denaturation for RFLP schedule at 95 °C for5 min was followed by 40 cycles of 94 °C for 30 s, 56 °C annealing for 40 s, and extension at 72 °C for 30 s. After running the products in gel electrophoresis, we analyzed them as 135 + 111 + 45 bp correspond to allele C while the fragments of 245 + 45 bp to allele G.

RESULTS

In this study, 71 blood samples (including 39 male and 32 female) from individuals infected with Covid-19 and 86 healthy ones (including 49 male and 37 female) were collected. The mean age of patients suffering from Covid-19 and control group were 58.37 ± 17.08 years and 37.53 ± 14.18, respectively. Our data showed that the GG genotype was lower in COVID-19 patients (59.2%) than in healthy controls (64.0%). However, the GC (26.8%) and CC (14.1%) genotypes were higher in patients compared with controls (23.3% and 12.8%, respectively). Table 1 summarizes these results.

Table1. Single nucleotide polymorphisms in IL6 gene data

Genotype	Patient's number	Patient's percentage	Control (number)	Control (percentage)
GG	42	59.2 %	55	64%
GC	19	26.8%	20	23.3%
CC	10	14.1 %	11	12.8%

STUDY LIMITATIONS

This study has several limitations. First, the sample size was relatively small (71 patients and 86 controls), which limited the statistical power to detect small effect sizes and prevented subgroup analyses (e.g., disease severity, mortality, or treatment response). Second, the mean age of the patient group (58.37 ± 17.08 years) was significantly higher than that of the control group (37.53 ± 14.18 years), and age is a known confounder in COVID-19 susceptibility and severity. One limitation of this study is that DNA was extracted from the plasma fraction rather than whole blood or buffy coat. Although plasma contains cell-free DNA and is a valid source for genetic analysis, the DNA yield and quality may be lower compared to whole blood or buffy coat, which could potentially affect the reliability of genotyping results. Future studies should ideally use whole blood or buffy coat for DNA extraction to ensure optimal DNA quality. We did not perform matching for age and gender, which may have introduced bias. Third, DNA was extracted from serum samples rather than whole blood, which may yield lower

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DNA quality and quantity; however, this was necessary due to sample availability. Fourth, the study was cross- sectional in design and cannot establish causality. Finally, we did not assess other IL-6 polymorphisms (e.g., rs2069837 or rs1800797) or haplotypes, which may also contribute to COVID-19 susceptibility. Future studies with larger sample sizes, age- and gender- matched controls, and longitudinal designs are warranted to confirm these findings and to evaluate the association with disease severity and treatment outcomes.

DISCUSSION

4 years after Covid-19 pandemic, some points of this virus's function have not been clear. It seems that covid-19 is able to trigger immune system response, including inflammatory pathways (13, 14). Take, for example, IL-6 which is likely to be secreted by immune cells (macrophages, fibroblasts, keratinocytes, mast cells, DCs, monocytes, mesangial cells, vascular endothelial cells (ECs), T and B lymphocytes) to eliminate *Covid-19* (15). These cells can secrete IL-6 and other inflammatory cytokines which can perform as a double-edged sword. Indeed, it is true that IL-6 can involve in proliferation and differentiation of leukocytes (16); nevertheless, cytokine storms can disrupt the appropriate immune response (7). It has been reported that the promoter region of the IL-6 gene can effect on some inflammatory health problem, and *Covid-19* is not an exception.

In this study, we attempted to found about the relation between IL6 gene and CoV-2 Infection. Our data demonstrated that the GG genotype was less frequent in infected patients than in controls, while the GC and CC genotypes were more frequent in patients than in controls. Studies have been conducted in some countries about this issue reporting different results. To illustrate, Turkish patients suffering from Covid-19 had IL-6 polymorphism at position- 174 G/C (rs1800795). In this study, patients with macrophage activation syndrome (MAS) had higher GG genotype and G allele in comparison with non-MAS group (17). Fishchuk et al showed opposite results as they reported a surge in the CC genotype and C allele of the - 174 G/C (rs1800795) SNP (18). In a study conducted in Iran, authors did not find any differences in IL-6 promotor genotypes (rs1800795 (-174 G > C), rs1800796 (-572 G > C), and rs1800797 (-597 G > A) of Covid-19 positive patients (19). In 2020 it was found that the more 174c polymorphism in the IL-6 can be existed, the more chance of severe Covid-19 can be observed (OR = 3.14; 95% CI = 2.02-4.88 and OR = 2.75; 95% CI = 1.66-4.57) (P < 0.001) (20). When researchers compared 195 Covid-19 and 470 healthy people, there was a relation between rs2069837 of IL-6 and Covid-19 ($p = 8.89 \times 10\text{-}3$, OR = 0.67) (21). In another study, it seems that CC genotype can increase the severity of Covid-19 according to rs12252 (42 T/C) SNP of the IFITM3 gene distribution (22). However, TT genotype of IL-6 in patients who survived with mild symptoms was common, and the same situation was true for CC genotype among sever Covid-19 (23). In Iraq which is a country near Iran, authors did not observe any changes in IL-6 genotype or allele distribution among patients suffering from this virus (24).

CONCLUSION

IL-6 seems to be different in numerous areas which can be utilized as a biomarker; nevertheless, further studies are required to confirm it.

DECLARATION

Ethics Approval and Consent to Participate: This study has been conducted in Department of the School of Medicine Shahid Beheshti University of Medical.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from the participants or their guardians.

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Not declared.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS

Please contact author for data requests.

AUTHORS' CONTRIBUTIONS

E.F., SH.T designed the study and performed the molecular experiments. H.G performed the statistical Analyses. All authors read and approved the final version of the manuscript.

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Using Artificial Intelligence (AI)

No AI-assisted technologies were used in the creation of this manuscript.

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