Gene variants in pro-coagulant and anti-coagulant genes could be prognostic genetic markers of COVID-19 susceptibility

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ABSTRACT

Background: Present study aimed to identify DNA polymorphisms (variants) which can modulate the risk of COVID-19 infection progression to severe condition. TaqMan based SNP genotyping assay was performed for 11 single nucleotide polymorphisms (SNPs) in pro-coagulant and anti-coagulant genes.

Methodology: A total of 33 COVID-19 patients, including dead, severe and moderately infected individuals were compared to 35 healthy controls. Both alleles in the SNP were labelled with two different fluorescent dyes (FAM and VIC) during assay formulation. DNA of study subjects were mixed with SNP assay and TaqMan master mix on 96 well PCR plate according to manufacturer’s protocol and RT-PCR was performed. Allelic discrimination assay gave clear results for presence of specific allele in each sample. Three SNPs were located in the pro-coagulant genes, another three involved in blood clot dissolution while rest five were in the genes encoding natural anti-coagulants. COVID-19 infected patients were further sub-divided into three groups, deceased (n = 16), severe (n = 10) and moderately infected (n = 7).

Results: SNP genotyping showed significant differences between COVID-19 patients and controls in two SNPs, rs6133 in Selectin-P (SELP) and rs5361 in Selectin-E (SELE) gene. Also, rs2020921 and rs8176592, in clot dissolution genes, tissue Plasminogen activator (tPA) and tissue factor pathway inhibitor (TFPI) respectively showed significant genotypic and allelic difference in patients of COVID-19 compared to healthy controls. Further three SNPs rs2227589, rs757583846, and rs121918476 in natural anti-coagulant genes anti-thrombin III (ATIII), protein C (PROC), and protein S (PROS) respectively showed statistically significant difference between the study groups.

Conclusion: Our findings indicate that gene variants, those involved in coagulation and anti-coagulation may play a major role in determining individual susceptibility to COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious disease, first reported in December 2019 in Wuhan, Hubei Province, China (Zhu et al., 2020). Since then COVID-19 has spread rapidly across the world becoming a global pandemic. The outbreak of COVID-19 infection has completed more than two years, and even now effective measures for prevention and treatment of SARS-CoV-2 remains limited. The morbidity caused by COVID-19 infection varies significantly and is known to be associated with age, sex and specific pre-existing conditions (Zhou et al., 2020; Jin et al., 2020). Infection severity and mortality is significantly higher in people with advanced age and comorbid conditions like cancer, diabetes, hypertension, and other cardiovascular diseases (Garg et al., 2020). On the other hand, majority of COVID-19 infected individuals, especially younger population, recover within few days without any complications (Dong et al., 2020). Such variations in disease severity can be explained by

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genetic variability resulting in varying immune response amongst the affected individuals.

SARS-CoV-2 virus enters into the host cell via Angiotensin converting enzyme 2 (ACE2) and the transmembrane serine protease (TMPRSS2) of host for SARS-CoV-2 spike (S) protein priming (Hoffmann et al., 2020). So far, many independent research groups have demonstrated polymorphisms in ACE2 (p.Arg514Gly) and TMPRSS2 (p.Val160Met) genes to be associated with differential genetic susceptibility to COVID-19 (Hou et al., 2020). The other ACE2 variants (rs233575 and rs2074192) have also been associated with hypertension and more severe outcomes of COVID-19 infection (Hlamet et al., 2021). A recently conducted genome wide association (GWAS) study identified eight variants as susceptibility loci for COVID-19 mortality. These included genes related to cilia dysfunctions (DNAH7 and CLUAP1), cardiovascular diseases (DES and SPEG), thrombo-embolic disease (STXB5), mitochondrial dysfunction (TOMM7), and innate immune system (WSB1) (Yu et al., 2021).

Hyper-immune response during COVID-19 infection leads to endothelial injury and activation of the coagulation cascade (Ahmed et al., 2020). This leads to increased risk of thrombo-embolic manifestations. Besides respiratory failure being the most common cause of death during COVID-19 infection, the progression of the disease is marked by disseminated intravascular coagulation (DIC) (Tang et al., 2020; Iba et al., 2020). As the infection progresses, it leads to coagulation abnormalities and significant elevation in the coagulatory parameters; such as increase in prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, and fibrin degradation products (FDP), along with consistent decline in anticoagulant levels during infection (Tang et al., 2020; Yu et al., 2020; Guan et al., 2020). Clinical relevance of coagulation system in COVID-19 is evident from higher incidences of venous thrombo-embolic events, stroke, and acute coronary syndrome in infected patients even after receiving prophylactic heparin (Tang et al., 2020; Lodigiani et al., 2020). Most of the guidelines for COVID-19 treatment published till date recommend therapeutic use of anticoagulants such as low-molecular-weight heparin (LMWH) or unfractionated heparin in patients who are suspected to develop macro-thrombi or pulmonary embolism (Cuker et al. ASH, 2021a). However, initially, these guidelines did not address the requirement of outpatient anti-coagulant prophylaxis (Moore et al., 2020; Chandra et al., 2022). Recent guidelines of American Society of Hematology (ASH) gave update on post-discharge thrombo-prophylaxis (Cuker et al. ASH, 2021b).

In view of above findings, the presence of natural anti-coagulants in blood might be playing a significant role against progression of COVID-19 infection. The present study hypothesizes that inherited deficiency of natural anti-coagulants and clot dissolution genes due to mutations, may be associated with increased risk of severe COVID-19 infection. Thus, we evaluated the possible association of eleven single nucleotide polymorphisms (SNPs) in nine genes including pro-coagulants and those reportedly involved in blood clot dissolution and synthesis of natural anti-coagulants in blood with COVID-19 susceptibility and severity.

2. Methodology

2.1. Study design

The study subjects were broadly classified into three study groups. Firstly, blood was collected from COVID-19 patients (diagnosis confirmed by RT-PCR) from Rajiv Gandhi Super Speciality hospital (RGSSH). Thirty three COVID-19 patients were further divided into three groups based on their infection severity, according to the guidelines laid by Ministry of health and family welfare, Government of India (https://www.mohfw.gov.in/pdf). These included 16 deceased, 10 severe and 7 moderately infected patients. Eleven common mutations in pro-coagulants, anti-coagulants and clot dissolution genes in these COVID-19 patients were compared with comparative number of healthy controls (n = 35). Amongst control group, subjects with any history of thrombotic risk factors were not included in the study. All control subjects were young healthy males with average age of 34. 5 years (IQR = 30.75–41.75).

The study parameters and design was approved by the Ethical Committee of Indian Council of Medical Research (ICMR), India. Written informed consent was obtained from all study participants before collection of their blood sample. All experimental protocols were conducted in accordance to the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Basic clinical characteristic was noted for each study participant, including, age, sex and presence of co-morbidity. The study comprises of 22 males and 11 female patients. The age of patients' ranges from 40 yrs to more than 60 yrs. Out of 33, twenty five patients were having co-morbid conditions.

2.2. DNA isolation and quantitation

For genotyping analysis, peripheral blood samples were collected in EDTA vacutainers. High molecular weight DNA was extracted using QIAampDNA isolation kit (Qiagen, Germany), using manufacturer’s protocol. Quantitative analysis of genomic DNA was done using Multiscan spectrophotometer (Thermo Fischer Scientific, USA). For qualitative analysis, 100ng DNA samples were loaded on 0.7% agarose gel containing Ethidium Bromide and run for 20 min and visualized under UV.

2.3. TaqMan based genotyping

A total of eleven SNPs in nine genes were selected for genotyping in the present study (Table 1). Profiling was done using RT-PCR based TaqMan SNP genotyping assay (Thermo Fischer Scientific, USA). Detailed steps for preparation of 96 well reaction plates and RT-PCR cycle is elucidated in Figure 1.

2.4. Statistical analysis

Statistical computations were performed using GraphPad Prism 5. Data sets were compared using the y2 test and Fisher’s exact test. p < 0.05 was considered statistically significant. Odds’ ratio (OR) with 95% confidence interval (CI) was calculated for all SNPs to compare COVID-19 patients with control groups. Forests plots depicting OR (with 95% CI) and heterogeneity were generated using online bioinformatics tool Genyo (Martorell-Marugan et al., 2017).

3. Results

3.1. Basic characteristics of COVID-19 patients

Twenty two out of thirty three COVID-19 infected patients were males. Twenty five amongst them were suffering from one or more co-morbidities, such as type 2 diabetes mellitus, hypertension, cardiovascular disorder, bronchial asthma, cystic bronchiectasis, nephrectomy etc. These patients were of varying age group, however, 20 out of 33 were above the age of 50 years. Also, 18 out of 25 co-morbid patients were above 50 years of age.

3.2. SNP genotyping

Genotyping was performed for common polymorphisms in nine genes using TaqMan technology. Three SNPs were studied in the glycoproteins involved in adhesion of platelets and leukocytes during the process of coagulation and inflammation – selectin-P (SELP) and selectin-E (SELE). Six SNPs were studied in five genes, Protein C (PROC), Protein S (PROS), Anti-thrombin III (ATIII), Thrombomodulin (THBD) and Tissue factor pathway inhibitor (TFPI), involved in synthesis and activation of natural anti-coagulants in the body; while other two genes, tissue Plasminogen...
activator (tPA) and Urokinase plasminogen activator (uPA) are involved in the process of blood clot dissolution (Table 1).

To examine the potential impact of SNPs in these genes and their association with susceptibility and severity of COVID-19 infection, the genotypic and allelic frequency distribution of 11 SNPs were compared across the two study groups, COVID-19 patients and healthy controls. The distribution of three genotypes, allele 1, allele 2 and heterozygous as well as two allele types were compared using statistical tests (Chi Square and Fisher’s exact test respectively), using Graph Pad (Prism 5.0) and the significance value was noted (as listed in Table 2).

### 3.3. COVID-19 vs healthy controls

Significant difference was observed amongst patients of COVID-19 and healthy controls in seven out of eleven SNPs under study including, SELP (rs6136) A/C, SELE (rs5361) G/T, tPA (rs2020921) A/G, and Urokinase Plasminogen activator (uPA) rs2227564 C/T, rs2020921 A/G, and rs2227589 C/T.

### Table 1. Details of polymorphisms studied in clot dissolution and anti-coagulant genes.

| S. No. | Gene               | SNP             | Polymorphism                  | SNP Type            | SNP location and observed codons | Observed Amino acid | Function                                                                 |
|--------|--------------------|-----------------|-------------------------------|---------------------|---------------------------------|---------------------|--------------------------------------------------------------------------|
| 1.     | Selectin-P (SELP)  | rs6136          | G/T, Transversion Substitution | Intragenic          | 2328 ACT, CCT                    | T,P 756             | Mediates platelet activation and de-granulation                          |
| 2.     | Selectin-P (SELP)  | rs6133          | A/C, Transversion Substitution | Intragenic          | 1980                            | -                   | -                                                                         |
| 3.     | Selectin-E (SELE)  | rs5361          | G/T, Transversion Substitution | Missense Mutation   | 602 AGT, CGT                     | S,R 149             | Cell adhesion, leukocyte accumulation at the site of inflammation       |
| 4.     | Tissue Plasminogen activator (tPA) | rs2020921 | A/G, Transition Substitution | Silent Mutation     | 609 -                            | -                   | Catalyzes the conversion of the zymogen plasminogen to the active enzyme plasmin |
| 5.     | Urokinase Plasminogen activator (uPA) | rs2227564 | C/T, Transition Substitution | Missense Mutation   | 566 CGG, CTG                     | P,L 124             | Activates plasminogen and facilitates fibrinolysis                      |
| 6.     | Tissue factor pathway inhibitor (TFPI) | rs8176592 | A/G, Transition Substitution | Intron              | -                                | -                   | Inhibits coagulation factor Xa and Vlla                                  |
| 7.     | Anti-thrombin III (ATIII) | rs2227589 | C/T, Transition Substitution | Intron              | -                                | -                   | Inhibits coagulation by neutralizing the enzymatic activity of thrombin  |
| 8.     | Anti-thrombin III (ATIII) | rs121909569 | G/A, Transition Substitution | Missense Mutation   | 561 CCG, GTG                     | P,S 148             | Blocks activity of factor Va and factor Vila, thus inhibits coagulation |
| 9.     | Protein C (PROC)   | rs757583846     | C/T, Transition Substitution | Missense Mutation   | 186 CGG, TGG                     | R,W 57              | Protein S acts as a cofactor to activated protein C (APC) in the degradation of FVa and FVIII |
| 10.    | Protein S (PROS)   | rs121918476     | G/A, Transition Substitution | Missense Mutation   | 2109 -                           | -                   | -                                                                         |
| 11.    | Thrombomodulin (THBD) | rs16984852 | C/A, Transversion Substitution | UTR 5               | 10 -                             | -                   | Acts as co-factor, Enhances thrombin-induced activation of protein C     |

![Figure 1. Workflow of TaqMan SNP genotyping assay.](image-url)
Table 2. Statistical analysis depicting genotypic and allelic distribution significance amongst the two study groups across 11 SNPs.

| Study name | SNP                  | Chi-square | Genotypic association p-value | Allelic association p-value | Statistically significant association |
|------------|----------------------|------------|------------------------------|-----------------------------|--------------------------------------|
| COVID-19 vs Control |                      |            |                              |                             |                                      |
| SELE (rs5361) G/T     | 6.18                  | 0.04       | 0.28                         | Non significant             |                                      |
| SELE (rs5361) A/C     | 3.25                  | 0.19       | 0.0002                       | Significant                 |                                      |
| SELP (rs6133) A/C     | 1.46                  | 0.08       | 0.099                        | Non significant             |                                      |
| SELP (rs6136) G/T     | 7.59                  | 0.0058     | 0.0001                       | Significant                 |                                      |
| TFPI (rs8176592) A/G  | 15.34                 | 0.0005     | 0.688                        | Non significant             |                                      |
| ATIII (rs121990569) G/A | 29.97              | < 0.0001    | 0.01                         | Significant                 |                                      |
| ATIII (rs2227589) C/T | 0.029                | 0.8645     | 1                            | Non significant             |                                      |
| PROC (rs757583846) C/T | 15.34               | 0.0005     | 0.688                        | Non significant             |                                      |
| PROS (rs121918476) G/A | 9.008               | 0.0027     | 0.0001                       | Significant                 |                                      |
| THBD (rs16984852) C/A | 2.38                 | 0.304      | 0.09                         | Non significant             |                                      |

TFPI (rs8176592)A/G, ATIII (rs121990569) G/A, PROC (rs757583846) C/T and PROS (rs121918476) G/A. Statistical significance was both at genotypic and allelic level except for ATIII (rs121990569) which showed significant difference only at genotypic level, and SELP (rs6133) and SELE (rs5361) which showed significant allelic difference only, when the two groups were compared (Table 2).

OR was found to be significant for SELP (rs6136 and rs6133), SELE (rs5361), tPA (rs2020921), ATIII (rs121990569) and PROC (rs757583846) (Figure 2). This indicates that these SNPs are significantly associated with COVID-19 (Figure 2). In case of SELP rs6136 and ATIII rs 121990569, the value of OR is slightly greater that one, which is statistically significant, however the association with the disease does not appear to be strong as compared to other variants.

Sub-group analysis was also done for the 11 SNPs under study, including 3 SNPs in pro-coagulant genes, 2 in clot-dissolution genes and 6 in anti-coagulant genes. Overall OR was significant for both pro-coagulant and anti-coagulant SNPs (Table 3).

While the COVID-19 patients and control group showed significant change in genotypic and allelic distribution of seven SNPs, there was no specific pattern of allelic frequency distribution amongst the deceased, severe and moderately infected COVID-19 patients. This could be attributed to low and uneven sample size amongst the patients' subgroups in the present study. However, specific risk alleles could be recognized when the total COVID-19 patients were compared with the healthy controls (Table 4).

4. Discussion

COVID-19 infection is frequently associated with thrombo-embolic events especially venous thrombosis. All COVID-19 patients admitted to hospital are recommended to receive pharmacologic thromboprophylaxis unless they have risk of bleeding. Chandra and co-workers recently reviewed and listed all on-going randomized control trials (RCTs) in patients with COVID-19 regarding timing, dosage, choice and duration of anti-coagulation along with current guidelines and recommendations on use of anti-coagulation in COVID-19 (Chandra et al., 2021). Most of these RCTs are in phase 3 and phase 4 of clinical trials and results are very promising. VTE prophylaxis and treatment with anti-coagulants reduces mortality rate in patients hospitalized with COVID-19 (Vaughn et al., 2021).

Several Genome wide association analysis have been conducted by independent research groups to identify potential genetic risk factors which may lead to susceptibility to COVID-19. In one such study involving 1980 patients of COVID-19 from Italy and Spain, researchers identified a 5p21.31 gene cluster (spanning genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1) as genetic susceptibility locus along with potential involvement of ABO blood group system (The Severe Covid-19 GWAS Group, 2020). Another genome wide association study (GWAS) from China, conducted on 885 severely infected COVID-19 patients and 546 mild or moderately infected patients highlighted two loci at 11q23.3 and 11q14.2, which confer susceptibility to COVID-19 severity (Li et al., 2021). Besides these, genetic association studies have been conducted so far to link SNPs with COVID-19 severity. GG genotype and G allele of ACE rs2285666 SNP has been significantly associated with 2 fold increase in SARS-CoV-2 infection risk (Mühlendick et al., 2021). A recent study on 750 SARS-CoV-2 patients also evaluated impact of polymorphisms in interferon lambda 3 and 4 (IFNL3/4) on resistance and susceptibility to COVID-19 and found that frequency of favourable genotypes was higher in survivors group compared to non-survivors. They also associated higher levels of low density
lipoprotein (LDL), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP); and lower levels of hydroxyvitamin D and unfavourable genotypes (IFNL3: rs12979860 TT, rs8099917 GG, rs12980275 GG, and IFNL4 rs368234815) with severity of COVID-19 infection (Rahimi et al., 2021).

Although the association of COVID-19 infection progression and coagulopathy is well established along with the significance of anti-coagulant therapy (Al-Samkari et al., 2020; Leentjens et al., 2021), no study has reported significance of SNPs in pro-coagulant and anti-coagulant genes with COVID-19 susceptibility and severity. Thus, the present study focuses on the variants in pro-coagulant genes, clot dissolution and anti-coagulant genes for their association with COVID-19 susceptibility. Diminished activity of anti-coagulants such as Protein S has been found in 65% of COVID-19 patients and was also associated with survival and disease severity (Stoichitoiu et al., 2020). Thus, we hypothesize that the common mutations in natural anti-coagulants may play a role in thrombotic manifestations during COVID-19 infection and thus might be related to its pathogenesis and severity.

SNPs in genes associated with coagulation such as Fibrinogen (FG) Gamma, FG-Alpha, and F5 which mediate increase in the D-dimer concentration and SNPs in ABO, CBS, CPS1, and MTHFR which mediate changes in the homocysteine levels, could confer to greater risk of thrombotic complications in COVID-19 patients (Abu-Farha et al., 2020). However, the common mutations present in the coagulation factors such as pro-thrombin (F2, rs1799963), factor V leiden (F2, rs6025); and thrombosis pre-disposing gene, plasminogen activator inhibitor (PAI-1, s1799768) did not show any relation with severe novel coronavirus pneumonia (NCP) (Kiraz et al., 2021). Interestingly, present study revealed seven common genetic variants located in pro-coagulant genes (SELP and SELE), clot dissolution gene (tPA) and natural anti-coagulant genes (ATIII, PROC, PROS) to be significantly associated with COVID-19 disease when the patients were compared with healthy controls. Combined effect of these mutations could produce a hyper-coagulable state during COVID-19 infection and might lead to severe infection. The results of the present study need to be validated in a larger cohort.

5. Conclusions

The development of preventive and therapeutic strategies to combat COVID-19 progression can only be developed by understanding the molecular and genetic basis of its prognosis. At present there are no definite guidelines for anti-coagulation therapy, its dosage and duration for the patients diagnosed with novel coronavirus. Although number of clinical trials and supportive studies are available which suggest thrombo-prophylaxis during COVID-19 infection, its post discharge need, duration and dose remains a matter of debate! To the best of our knowledge, this is the first study which highlights the significance of SNPs in pro-coagulant genes and anti-coagulant genes associated with susceptibility and severity of COVID-19 infection.
5.1. Limitation of study

Availability of samples was the limitation of the present study. Our preliminary results need to be validated in a larger cohort.

Declarations

Author contribution statement

Swati srivastava: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Babita Kumar: Performed the experiments; Analyzed and interpreted the data.

Iiti Garg: Conceived and designed the experiments; Analyzed and interpreted the data.

Vikas Dogra; Nilanjana Ghosh; Yamini Singh; Mona Bargotya; Sonali Bhatter; Utkarsh Gupta; Shruti Jair; Lavish Hussain: Contributed reagents, materials, analysis tools or data.

Rajeek Varshney; Lilly Ganju: Conceived and designed the experiments.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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Iti Garg: Conceived and designed the experiments; Analyzed and interpreted the data.

Babita Kumari: Performed the experiments; Analyzed and interpreted

Rajeev Varshney; Lilly Ganju: Conceived and designed the experiments; Analyzed and interpreted the data.

It is one of the limitations of this study that the results cannot be generalised to the entire population of COVID-19 patients due to the small sample size. However, the findings provide valuable insights into the pathophysiology of COVID-19 and its impact on coagulation.

Data availability statement

Data included in article/supp. material/referenced in article.

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