ORIGINAL ARTICLE

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The Relationship between the rs5918 Polymorphism Serum GPIIb/IIIa Levels, and Biochemical Parameters in Pulmonary Embolism Associated with COVID-19 Infection

COVID-19 Enfeksiyonuna Bağlı Pulmoner Embolide rs5918 Polimorfizmi ile Serum GPIIb/IIIa Düzeyleri ve Biyokimyasal Parametreler Arasındaki İlişki

Gülsel AYAZ[1], Tuna Alp KAZIL[2], Zehra ASUTAY[2], Elif ÇETİNKAYA[2], Irmak ÖKTEM[2], İsmail Alp KAŞPINAR[2], Muhammet Sait KAYA[2], Hamit GÖKHAN[2], Hamza COŞKUN[2], Buse ŞEKERCİ[2], Eslem Nisa ARAÇ[2], Pelin PARMAKSIZ[2], Zeynep Nisa KILIÇ[2], Beyza Nur KANDEMİR[2], Şevval ŞİMŞEK[2], Neriman Nur AKKIN[2], Armin Jafarzad YEKANEH[2], Alkım Barış TAŞ[2], Birol TOPÇU[3], Bilun GEMİCİOĞLU[4], Buket ÇALIŞKANER ÖZTÜRK[4], Ersan ATAHAN[4], Tuba MUTLU[6], Nihal ENŞEN[5]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Biology, Tekirdağ, Türkiye
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Türkiye
[3]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Biostatistics, Tekirdağ, Türkiye
[4]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pulmonary Medicine, İstanbul, Türkiye
[5]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Physiology, İstanbul, Türkiye
[6]İstanbul Arel University Faculty of Medicine, Department of Medical Biology, İstanbul, Türkiye

ABSTRACT

Aim: This study aimed to investigate the potential associations among serum levels of the glycoprotein Glycoprotein IIb/IIIa (GPIIb/IIIa) which plays a critical role in platelet function the rs5918 polymorphism in the *ITGB3* gene, and biochemical parameters (platelet count, D-dimer, fibrinogen, mean platelet volume, C-reactive protein) in patients who developed pulmonary embolism (PE) due to coronavirus disease 2019 (COVID-19) infection.

Materials and Methods: The study was conducted using DNA and serum samples from 80 adult patients diagnosed with COVID-19 between 2020 and 2022. Patients were divided into two groups as PE positive PE(+) and PE negative PE(-). The rs5918 polymorphism was analyzed using the TaqMan single nucleotide polymorphism genotyping method on a real-time polymerase chain reaction system. Serum GPIIb/IIIa levels were measured using the ELISA method. Demographic, hematological, and biochemical data were retrieved from patient records and analyzed statistically.

Results: Platelet count ($p=0.007$) and D-dimer levels ($p<0.001$) were found to be significantly higher in the PE(+) group. No significant difference was observed in GPIIb/IIIa serum levels between the PE(+) and PE(-) groups ($p=0.42$). There was no statistically significant difference between the groups regarding rs5918 genotype and allele distributions. However, significant differences in D-dimer levels were observed across genotypes.

Conclusion: Although rs5918 polymorphism and GPIIb/IIIa serum levels were not directly associated with the development of PE in COVID-19 patients, the findings suggest that genetic variation may influence certain coagulation parameters. These results indicate the need for further studies to explore genetic determinants of thrombotic processes associated with COVID-19.

Keywords: COVID-19, pulmonary embolism, platelet, rs5918, GPIIb/IIIa

Address for Correspondence: Gülsel AYAZ MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Biology, Tekirdağ, Türkiye
E-mail: gulselayaz@nku.edu.tr **ORCID ID:** orcid.org/0000-0003-3085-232X
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ÖZ

Amaç: Bu çalışma, koronavirüs hastalığı 2019 (COVID-19) enfeksiyonu nedeniyle pulmoner emboli (PE) gelişen hastalarda, platelet fonksiyonunda kritik rol oynayan glikoprotein Glikoprotein IIb/IIIa (GPIIb/IIIa) serum seviyeleri ile *ITGB3* genindeki rs5918 polimorfizmi ve biyokimyasal parametreler (platelet sayısı, D-dimer, fibrinojen, ortalama platelet hacmi, C-reaktif protein) arasındaki olası ilişkileri araştırmayı amaçlamıştır.

Gereç ve Yöntem: Çalışma, 2020-2022 yılları arasında COVID-19 tanısı konmuş 80 yetişkin hastadan alınan DNA ve serum örnekleri kullanılarak yürütülmüştür. Hastalar PE pozitif PE(+) ve PE negatif PE(-) olmak üzere iki gruba ayrılmıştır. rs5918 polimorfizmi, gerçek zamanlı polimeraz zincir reaksiyonu sistemi üzerinde TaqMan tek nükleotid polimorfizmi genotipleme yöntemi ile analiz edilmiştir. Serum GPIIb/IIIa seviyeleri ELISA yöntemi ile ölçülmüştür. Demografik, hematolojik ve biyokimyasal veriler hasta kayıtlarından elde edilerek istatistiksel olarak analiz edilmiştir.

Bulgular: PE(+) grubunda platelet sayısı (p=0,007) ve D-dimer seviyeleri (p<0,001) anlamlı derecede yüksek bulunmuştur. GPIIb/IIIa serum seviyeleri açısından PE(+) ve PE(-) grupları arasında anlamlı bir fark gözlenmemiştir (p=0,42). Gruplar arasında rs5918 genotip ve allel dağılımları açısından istatistiksel olarak anlamlı bir fark bulunmamıştır. Bununla birlikte, D-dimer seviyelerinde genotiplere göre anlamlı farklılıklar gözlenmiştir.

Sonuç: Rs5918 polimorfizmi ve GPIIb/IIIa serum seviyeleri COVID-19 hastalarında PE gelişimi ile doğrudan ilişkili olmasa da, genetik varyasyonun bazı koagülasyon parametrelerini etkileyebileceği düşünülmektedir. Bu bulgular, COVID-19 ile ilişkili trombotik süreçlerin genetik belirleyicilerini araştıran daha kapsamlı çalışmalara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: COVID-19, pulmoner emboli, platelet, rs5918, GPIIb/IIIa

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has been reported to induce hypercoagulability and to lead to both arterial and venous thromboembolic events[1,2]. In cases of pulmonary embolism (PE) associated with COVID-19 infection, increased platelet activation and a corresponding rise in the tendency of blood to clot have been demonstrated[3]. In addition, studies in the literature have shown that blood fibrinogen levels are significantly elevated following COVID-19 infection[4].

Platelets, which originate from megakaryocytes in the bone marrow and have a diameter of 2-4 µm, are the smallest cellular components in the blood and play a central role in hemostasis and thrombosis[5]. On the platelet surface, the Glycoprotein IIb/IIIa (GPIIb/IIIa) receptor, a member of the integrin family, exhibits high-affinity binding to fibrinogen[6]. This receptor is formed by the combination of the GPIIb and GPIIIa subunits[7,8] and is the most abundant receptor on the platelet surface[9]. The GPIIIa subunit contains extensive polymorphic regions[10].

The rs5918 polymorphism located within this region leads to the substitution of leucine by proline in the GPIIIa protein, resulting in a conformational change in the protein structure[10]. This rs5918 variant is defined as the T1565C polymorphism in the human platelet antigen-1 system. It is a single nucleotide polymorphism (SNP) in exon 2 of the *ITGB3* gene on chromosome 17 and causes a Leu33Pro (L33P) amino acid substitution in the GPIIb/IIIa protein on the platelet surface. The rs5918 genotypes are classified as follows: TT (homozygous wild-type, Leu33), TC (heterozygous), and CC (homozygous mutant, Pro33)[10].

Previous studies have suggested that this polymorphism increases the binding affinity of the GPIIb/IIIa receptor for fibrinogen and facilitates platelet aggregation, thereby potentially enhancing thrombotic susceptibility[11,12]. Although endothelial damage and disturbances in coagulation mechanisms have been reported in patients with PE due to COVID-19 infection, the relationships between cellular interactions and the underlying molecular and biochemical mechanisms have not been fully elucidated. To date, no study has been identified in the literature that investigates the relationship between GPIIb/IIIa levels and the rs5918 polymorphism in patients with PE associated with COVID-19 infection.

Therefore, in this study, we aimed to investigate, in addition to parameters involved in coagulation mechanisms, the association between serum GPIIb/IIIa levels and the rs5918 polymorphism in patients with PE secondary to COVID-19 infection.

MATERIALS AND METHODS

This retrospective case-control study was conducted using DNA and serum samples obtained from 80 individuals aged 18 years or older with laboratory-confirmed COVID-19 infection. During the study period (2020-2022), the diagnosis of COVID-19 was established in accordance with the interim guidance of the World Health Organization and the national COVID-19 management guidelines issued by the Turkish Ministry of Health that were in effect at the time. Confirmation of SARS-CoV-2 infection was achieved by real-time reverse transcriptase polymerase chain reaction (RT-PCR) analysis of nasopharyngeal and/or oropharyngeal swab specimens collected at hospital admission. Only patients with at least one documented positive RT-PCR result were included in the study.

Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine (protocol no: 2023.90.05.09, date: 30.05.2023).

Patient Study Group

This study included DNA and serum samples obtained from 80 individuals aged 18 years and older who had laboratory-confirmed COVID-19 infection between 2020 and 2022. The study population consisted of patients who developed PE and those who did not. All participants had at least one documented positive SARS-CoV-2 RT-PCR test result in their medical records. PE was diagnosed by computed tomography pulmonary angiography (CTPA) and defined as the presence of a new intraluminal filling defect within the pulmonary arterial tree. Patients without radiological evidence of PE on CTPA were assigned to the PE negative PE(-) group.

Blood Collection, DNA Isolation, and Serum Preparation

For genetic analyses, 2 mL of peripheral venous blood was collected from each participant into tubes containing ethylenediaminetetraacetic acid as an anticoagulant. Genomic DNA was extracted from peripheral blood mononuclear cells using the PureLink Genomic DNA Mini Kit (Thermo Fisher Scientific, USA) following the manufacturer's protocol. The concentration and purity of the isolated DNA were determined spectrophotometrically by measuring absorbance at 260/280 nm using a NanoDrop Lite Plus spectrophotometer (Thermo Fisher Scientific, Madison, WI, USA).

For biochemical analyses, 2 mL of peripheral venous blood was collected into serum separator (plain) tubes. The samples were allowed to clot at room temperature for 20-30 minutes and were then centrifuged at 4000 rpm for 10 minutes. The resulting serum was carefully separated and aliquoted into polypropylene tubes to prevent repeated freeze-thaw cycles. Serum samples were stored at -80 °C until analysis. Each sample was thawed only once and immediately used for the determination of GPIIb/IIIa levels by enzyme-linked immunosorbent assay (ELISA).

SNP Genotyping

Genotype Analysis

Detection and analysis of the rs5918 SNP were performed on human genomic DNA isolated from patients' peripheral blood samples using a real-time PCR system (Bio-Rad CFX Connect Real-Time PCR Detection System, California 94547, USA). The TaqMan SNP genotyping method was employed to genotype the polymorphic region at codon 33 of exon 2 (T1565C, dbSNP ID: rs5918) of the *ITGB3* gene on chromosome 17. Specifically, the ITGB3 rs5918 (T1565C) polymorphism was genotyped using a commercially available TaqMan SNP genotyping assay (Assay ID: C_818008_30, Thermo Fisher Scientific, Waltham, MA, USA) on the Bio-Rad CFX Connect Real-Time PCR System (Bio-Rad Laboratories, Hercules, CA, USA).

According to the manufacturer's information, the polymorphic region in exon 2 of the *ITGB3* gene was amplified using gene-specific primers [context sequence: [(VIC/FAM)GCTCCTGTCTTACAGGCCCTGCCTC (C/T) GGGCTCACCTCGCTGTGACCTGAAG] together with allele-specific fluorogenic probes that had been predesigned and analytically validated by the manufacturer. Because the primers and probes were provided as part of this commercial assay, no additional primer design was performed in this study. The reaction mixture and cycling conditions were applied according to the kit datasheet, with only minor laboratory-specific optimizations when necessary.

Each real-time PCR reaction was carried out in a final volume of 20 µL containing 100 ng of genomic DNA, 1.6 µL $MgCl_2$, 1 µL LightSNiP reagent mix (Applied Biosystems TaqMan Drug Metabolism Genotyping Assays, Massachusetts, USA), 2 µL LightCycler® FastStart DNA Master HybProbe (Roche Diagnostics GmbH, Mannheim, Germany), and variable amounts of H_2O to adjust the final volume. The PCR cycling conditions were as follows: initial denaturation at 95 °C for 10 minutes; 40 cycles of denaturation at 95 °C for 40 seconds, annealing at 62 °C for 30 seconds, and extension at 76 °C for 15 seconds; followed by a final extension at 76 °C for 5 minutes. Bio-Rad CFX Maestro software was used for the analysis of amplification curves and allele discrimination generated by the TaqMan SNP genotyping assay.

Hardy-weinberg Equilibrium Analysis

The genotype distribution of the ITGB3 rs5918 (T1565C) polymorphism was assessed for conformity with Hardy-Weinberg equilibrium (HWE) in the overall study population, as well as separately in the (PE+) and (PE-) subgroups. Observed and expected genotype frequencies were compared using the chi-square (χ^2) goodness-of-fit test. A p-value <0.05 was considered indicative of deviation from HWE. All analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA).

ELISA Method

Serum GPIIb/IIIa concentrations were determined using the ELISA method. The analysis was performed in duplicate using a commercially available ELISA kit (E-EL-H2202; Elabscience, Houston, USA), in accordance with the manufacturer's instructions. Briefly, serum samples and standards were added to microplate wells pre-coated with antibodies specific for human GPIIb/IIIa and incubated at 37 °C for 60 minutes. After incubation, the wells were washed to remove unbound material, and a horseradish peroxidase-conjugated detection antibody was added, followed by a 30-minute incubation.

Following an additional wash step, tetramethylbenzidine substrate solution was added to each well, and the enzymatic reaction was allowed to proceed until sufficient color development was observed. The reaction was then terminated by the addition of sulfuric acid. Absorbance was measured at 450 nm using a microplate reader (BioTek ELx800). GPIIb/IIIa concentrations were calculated from a standard curve generated using known standard concentrations, and the results were expressed as ng/mL. Serum GPIIb/IIIa concentrations were determined using the ELISA procedure as previously described by Ayaz et al.[13].

Demographic and Clinical Laboratory Data

Demographic and other clinical laboratory parameters of the patients were retrieved from their medical records.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including mean, standard deviation, median, interquartile range, frequency, and percentage, were used to summarize the personal characteristics (e.g., age, gender) of the patients included in the study.

The distribution of continuous variables was first evaluated using normality tests. For comparisons between two independent groups, the independent samples t-test was applied when the assumptions of normality were met; otherwise, the Mann-Whitney U test was used. For comparisons among three or more independent groups, ANOVA was conducted when parametric test assumptions were satisfied, while the Kruskal-Wallis test was used in the absence of these assumptions. For post-hoc subgroup analyses, the Tukey test was employed following ANOVA, and Tamhane's T2 test was used when variance homogeneity was not present.

The chi-square test was used to compare categorical variables between groups. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Patient Characteristics

The study group consisted of 80 patients known to be COVID-19 PCR positive. Of the entire patient group, 55 (68.75%) were female and 25 (31.25%) were male. Based on information from patient records, the 80 patients were divided into two groups according to their PE status. Among the COVID-19 positive patients, 54 (67.5%) were in the PE pozitive PE(+) group, while 26 (32.5%) were in the PE(-) group. When examining the demographic data, among the 54 individuals in the PE(+) group, 13 (24.1%) were male and 41 (75.9%) were female. The PE(-) group consisted of 26 individuals, of whom 14 (53.8%) were female and 12 (46.2%) were male. The ages of the PE(+) group ranged from 19 to 74 years (mean= 52.86±13.98), while the ages of the PE(-) group ranged from 22 to 77 years (mean= 47.16±14.08), and the mean ages of the PE(+) and PE(-) groups were similar (p=0.1) (Table 1).

Table 2 shows the genotype distribution of the ITGB3 rs5918 (T1565C) polymorphism according to PE status in COVID-19 patients.

The genotype distribution of the ITGB3 rs5918 (T1565C) polymorphism in the total study population was consistent with the HWE (χ^2= 0.59, p=0.44). When the groups were analyzed separately, the genotype distribution remained in HWE in the PE(+) subgroup (χ^2= 0.84, p=0.36), whereas a significant deviation from HWE was observed in the PE(-) subgroup (χ^2= 4.35, p=0.037).

DISCUSSION

One of the most critical pathological processes associated with COVID-19 is excessive coagulation. It is well established that SARS-CoV-2 disrupts hemostatic balance, thereby increasing the risk of hypercoagulability and both arterial and venous thromboembolic events[14]. A substantial increase in the incidence of PE associated with COVID-19 has been documented in the literature[15,16]. Although several studies have demonstrated dysregulation of coagulation pathways in patients who develop PE secondary to COVID-19 infection, the molecular mechanisms underlying the resultant hypercoagulable state remain incompletely elucidated. In the present study, we aimed to investigate the role of the rs5918 genetic polymorphism, which is potentially associated with the function of GPIIb/IIIa a receptor predominantly expressed on the platelet surface and critically involved in coagulation pathways in patients with and without PE secondary to COVID-19 infection.

Previous studies have indicated that this polymorphism enhances the binding of the GPIIb/IIIa receptor to fibrinogen and promotes platelet aggregation, thereby potentially serving as a contributing factor to thrombotic tendency[11,12]. In a study conducted by Lapić et al.[10], the relationship between COVID-19 severity and the rs5918 polymorphism was examined. They reported that individuals carrying the homozygous mutant genotype experienced more severe COVID-19 infection and identified the mutant genotype as an independent risk factor for disease severity. In a study conducted by Lehmann et al.[17] using next-generation sequencing, genotype results of COVID-19 positive and COVID-19 negative individuals were compared. It was demonstrated that rs5918 homozygous wild-type individuals may be protected against COVID-19 through platelet-associated immune mechanisms, whereas rs5918 heterozygous individuals showed increased susceptibility to

infection. The rs5918 polymorphism (Leu33Pro in the *GPIIb/IIIa* gene) suggests that the Pro33 homozygous mutant variant may increase the binding capacity of SARS-CoV-2, thereby elevating the risk of infection, whereas the Leu33 homozygous wild-type variant may exert a protective effect[16]. In the study conducted by Fiorentino et al.[18] the rs5918 genetic polymorphism was compared between (PE+) and (PE-) groups in patients with COVID-19. Similar to our study, they did not find a significant difference between the groups according to genotypes. These comparable results suggest that the rs5918 variant alone may not be a decisive genetic determinant for PE in the context of COVID-19, but could still act as a modulating factor when combined with inflammatory and hemostatic imbalances.

In our study, D-dimer levels were significantly higher in the PE(+) group, reflecting enhanced fibrin degradation and increased coagulation activity typical of COVID-19 related thrombotic processes. This finding aligns with that of Fiorentino et al.[18] who also noted D-dimer elevation in PE(+) cases. However, while Fiorentino's subgroup analysis by genotype showed no difference[17], our study indicated that genotype-related variation might subtly influence D-dimer behavior (Table 3). This suggests that although rs5918 does

Table 1. Demographic and biochemical parameters in PE(+) and PE(-) groups

Patient groups	COVID-19(+) PE(+) n=54	COVID-19(+) PE(-) n=26	Total n=80	p-value
Gender				
Female Male	41 (75.9%) 13 (24.1%)	14 (53.8%) 12 (46.2%)	55 (68.75%) 25 (31.25%)	 0.082
Age	52.86±13.98	47.16±14.08		0.1
Biochemical parameters				
MPV (fl)	8.25±0.73	8.44±0.90		0.34
PLT (10^3/µL)	314.24±90.81	260.75±72.24		0.007*
WBC (10^3/UI)	7.47±1.60	6.81±1.99		0.12
Fibrinogen (mg/dL)	432.56±72.8	394.28±128.6		0.19
CRP (mg/L)	4.67±5.4	2.98±2.95		0.15
D-dimer(mg/L)	1.16±0.80	0.46±0.32		0.000***
GPIIb/IIIa (ng/mL)	0.46±0.88	0.40±0.23		0.42
Comorbidities				
Hipertansion				
Present	12	4		
Absent	42	22		0.444
Diabetes mellitus				
Present	8	1		
Absent	46	25		0.194
Lung diseases				
Present	10	4		
Absent	44	22		0.559
Cardiovascular diseases				
Present	5	2		
Absent	49	24		0.587
Hypothyroidism				
Present	5	1		
Absent	49	25		0.404

Demographic data in the PE+ and PE- groups were analyzed using Pearson's chi-square test. Biochemical parameters were analyzed using the student's t-test. Significance levels are indicated as *p<0.05, **p<0.01, and ***p<0.001

PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cells, CRP: C-reactive protein, GPIIb/IIIa: Glikoprotein IIb/IIIa, PE(+): Pulmonary embolism positive, PE(-): Pulmonary embolism negative, n: Number of individuals, COVID-19: Coronavirus disease 2019

Table 2. Genotype distribution according to PE(+) and PE(-) status in COVID-19 patients

Gen	COVID-19(+) PE(+), n (%)	COVID-19(+) PE(-), n (%)	p-value
T1565C, dbSNP ID: rs5918 polymorphism	54	26	
Genotypes			
TT	42 (78)	20 (77)	
TC	12 (22)	4 (15)	**0.76**
CC	0	2 (8)	**0.12**
Alleles			
T	89	85	
C	11	15	**0.40**

In COVID-19 patients, according to the presence (+) or absence (-) of PE, genotype distribution is expressed as follows: TT homozygous wild-type genotypes, TC heterozygous genotypes, and CC homozygous mutant-type genotypes

PE(+): Pulmonary embolism positive, PE(-): Pulmonary embolism negative, COVID-19: Coronavirus disease 2019

Table 3. Comparison of parameters according to T1565C, rs5918 polymorphism genotypes in PE(+) and PE(-) groups with COVID-19 infection

Parameters	COVID-19(+), PE(+) group T1565C, rs5918 polymorphism			COVID-19(+), PE(-) group T1565C, rs5918 polymorphism		
	TT (n=42)	TC (n=12)	CC (n=0)	TT (n=20)	TC (n=4)	CC (n=2)
MPV (fl)	8.34±0.76	7.90±0.41	-	8.38±0.86	8.70±1.36	8.60±0.71
PLT (10^3/µL)	313.81±97.76	315.67±65.99	-	266.34±79.55	247.25±38.11	232.00±53.74
WBC (10^3/UI)	**7.32±1.61**[d*]	**7.95±1.52**[e*]	-	7.07±2.11	6.58±1.12	4.65±0.50
Fibrinogen(mg/dL)	438.64±71.74	411.62±76.75	-	389.59±121.33	446.72±176.68	331.67±132.07
CRP (mg/L)	5.06±5.94	3.40±2.96	-	3.41±3.19	1.79±1.38	1.06±1.44
GPIIb/IIIa (ng/mL)	0.47±0.31	0.42±0.19	-	0.36±0.17	0.68±0.36	0.30±0.05
D-dimer (mg/L)	**1.12±0.85**[a**]	**1.30±0.63**[b*]	-	**0.49±0.35**[c***]	0.39±0.31	0.33±0.19

The data are presented as mean ± SD. Bold values indicate statistical significance. Significance refers to comparisons between: aTT genotypes in the PE(+) group and TT genotypes in the PE(-) group, bTC genotypes in the PE(+) group and TC genotypes in the PE(-) group, cTT genotypes in the PE(-) group and TC genotypes in the PE(+) group, dTT genotypes in the PE(+) group and CC genotypes in the PE(-) group, and eTC genotypes in the PE(+) group and CC genotypes in the PE(-) group. The significance thresholds were set at *p<0.05, **p<0.01, and ***p<0.001 (student's t-test or Mann-Whitney U test). PLT: Platelet count, MPV: Mean platelet volume, WBC: White blood cells, CRP: C-reactive protein, GPIIb/IIIa: Glikoprotein IIb/IIIa, PE(+): Pulmonary embolism positive, PE(-): Pulmonary embolism negative, N: number of individuals, SD: Standard deviation, COVID-19: Coronavirus disease 2019

not directly cause PE, it may contribute to prothrombotic phenotypes by modulating coagulation reactivity under infection-induced stress.

In this study, C-reactive protein (CRP) levels, as an acute-phase reactant, showed no significant differences between genotypes or groups. The results of the study by Fiorentino et al.[18], which investigated CRP levels, are similar to those of our study. This supports the notion that systemic inflammation during COVID-19 likely overshadows subtle genetic influences on inflammatory markers. Similarly, Ghaffari et al.[19] observed no genotype-dependent differences in platelet or inflammatory parameters among COVID-19 patients.

Osikov et al.[20] emphasized that platelet dysfunction and genetic polymorphisms, including ITGB3 variants, play an important role in determining both disease severity and thrombotic complications in COVID-19 patients. Consistent with that view, our study supports the idea that rs5918 may not independently trigger coagulation disturbances but could interact with platelet activation pathways in genetically predisposed individuals.

GPIIb/IIIa, the most abundant receptor on the platelet surface, provides essential binding sites for fibrinogen and mediates platelet aggregation. The absence of a significant relationship between rs5918 genotypes and fibrinogen or GPIIb/IIIa serum levels in our study suggests that this polymorphism does not substantially alter receptor expression or fibrinogen-binding efficiency at the systemic level. This observation adds new information to the literature, as no previous research has simultaneously analyzed GPIIb/IIIa serum levels and rs5918 status in COVID-19 related PE[18].

Analysis of platelet function indicators, including mean platelet volume and platelet count (PLT), revealed higher PLTs in the PE(+) group. This increase may represent a compensatory response to ongoing coagulation activation rather than a direct genetic effect. The literature contains conflicting evidence: Osikov et al.[20] reported lower PLTs but increased platelet reactivity in severe COVID-19, whereas Fiorentino et al.[18], similar to our findings, noted elevated PLTs in PE(+) patients[19].These discrepancies highlight the multifactorial regulation of platelet behavior in COVID-19, involving inflammation, endothelial injury, and host genetic background.

Finally, our analysis found no difference in serum GPIIb/IIIa concentrations between PE(+) and PE(-) groups or among genotypes. Given the absence of prior studies addressing this association, our findings suggest that circulating GPIIb/IIIa levels are unlikely to serve as a biomarker for COVID-19 related PE but merit further investigation in larger, longitudinal cohorts.

Taken together, our data indicate that while rs5918 polymorphism and GPIIb/IIIa levels do not directly predict PE development in COVID-19, they may subtly influence coagulation dynamics in the context of systemic inflammation and viral-mediated endothelial injury. These results reinforce the multifactorial nature of COVID-19 associated thrombosis, where genetic, inflammatory, and environmental factors converge to shape individual thrombotic risk.

Study Limitations

The small sample size of our study, the absence of a healthy control group, and its single-center design may have influenced the statistical power of our analyses.

CONCLUSION

Although the rs5918 polymorphism and GPIIb/IIIa levels were not found to have a direct effect on the development of PE associated with COVID-19, it was demonstrated that genetic variations may influence certain coagulation parameters. These findings underscore the need for further studies to investigate the genetic determinants of COVID-19 related thrombotic processes.

Ethics

Ethics Committee Approval: The ethical approval for this study was granted by the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine (protocol no: 2023.90.05.09, date: 30.05.2023).

Informed Consent: This research is a retrospective case-control study conducted using pre-existing DNA samples.

Footnotes

Authorship Contributions

Concept: G.A., N.E., E.A., Design: G.A., B.G., Data Collection or Processing: N.E., T.M., Analysis or Interpretation: T.A.K., B.T., B.Ç.Ö., Literature Search: A.J.Y., B.Ş., B.N.K., Ş.Ş., A.B.T., P.P., H.C., Z.A., I.Ö., N.N.A., H.G., M.S.K., Z.N.K., İ.A.K., E.Ç., E.N.A., Writing: G.A., T.A.K., A.B.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Ortega-Paz L, Arévalos V, Fernández-Rodríguez D, Jiménez-Díaz V, Bañeras J, Campo G, et al. One-year cardiovascular outcomes after coronavirus disease 2019: the cardiovascular COVID-19 registry. PLoS One. 2022;17:e0279333.
2. Avci BA, Doğan M, Batar B, Yildirim İ, Serdal E, Gezer S, et al. Patients with severe coronavirus disease 2019 have high frequency of factor 5 leiden and prothrombin gene mutations. Blood Coagul Fibrinolysis. 2023;34:14-9.
3. Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. Radiology. 2021;298:E70-80.
4. Eljilany I, Elzouki AN. D-Dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. Vasc Health Risk Manag. 2020;16:455-62.
5. Chaudhary PK, Kim S, Kim S. An insight into recent advances on platelet function in health and disease. Int J Mol Sci. 2022;23:6022.
6. Frojmovic MM, Mooney RF, Wong T. Dynamics of platelet glycoprotein IIb-IIIa receptor expression and fibrinogen binding. I. Quantal activation of platelet subpopulations varies with adenosine diphosphate concentration. Biophys J. 1994;67:2060-8.
7. Cong N Van, Uzan G, Gross MS, Jegou-Foubert C, Frachet P, Boucheix C, Marguerie G, Frézal J. Assignment of human platelet GP2B (GPIIb) gene to chromosome 17, Region Q21.1-Q21.3. Vol 80.; 1988.
8. Bray PF, Shuman MA. Identification of an abnormal gene for the GPIIIa subunit of the platelet fibrinogen receptor resulting in glanzmann's thrombasthenia. Blood. 1990;75:881-8.
9. Durrant TN, van den Bosch MT, Hers I. Integrin $\alpha_{IIb}\beta_3$ outside-in signaling. Blood. 2017;130:1607-19.
10. Lapić I, Radić Antolic M, Horvat I, Premužić V, Palić J, Rogić D, et al. Association of polymorphisms in genes encoding prothrombotic and cardiovascular risk factors with disease severity in COVID-19 patients: a pilot study. J Med Virol. 2022;94:3669-75.
11. Feng D, Lindpaintner K, Larson MG, Rao VS, O'Donnell CJ, Lipinska I, et al. Increased platelet aggregability associated with platelet GPIIIa PlA2 polymorphism: the framingham offspring study. Arterioscler Thromb Vasc Biol. 1999;19:1142-7.
12. Rezaei Dezaki Z, Bagheri R, Pourgheysari B. Association between fibrinogen receptor (glycoprotein IIb) polymorphism and the risk of venous thromboembolism: a systematic review. Egyptian Journal of Medical Human Genetics. 2019;20:36.
13. Ayaz G, Sordu P, Küçüksezer UC, Hanağası H, Alaylıoğlu M, Gürvit H, et al. Association of glycoprotein 1b and miR-26a-5p levels with platelet function in Alzheimer's disease. J Alzheimers Dis. 2025;105:172-85.
14. Hottz ED, Martins-Gonçalves R, Palhinha L, Azevedo-Quintanilha IG, de Campos MM, Sacramento CQ, et al. Platelet-monocyte interaction amplifies thromboinflammation through tissue factor signaling in COVID-19. Blood Adv. 2022:5085-99.

15. Ortega-Paz L, Talasaz AH, Sadeghipour P, Potpara TS, Aronow HD, Jara-Palomares L, et al. COVID-19-associated pulmonary embolism: review of the pathophysiology, epidemiology, prevention, diagnosis, and treatment. Semin Thromb Hemost. 2023;49:816-32.

16. Jůza T, Válek V, Vlk D, Dostál M, Andrašina T. Roles of spectral dual-layer CT, D-dimer concentration, and COVID-19 pneumonia in diagnosis of pulmonary embolism. Eur J Radiol Open. 2024;12:100575.

17. Lehmann C, Loeffler-Wirth H, Balz V, Enczmann J, Landgraf R, Lakowa N, et al. Immunogenetic predisposition to SARS-CoV-2 infection. Biology (Basel). 2022;12:37.

18. Fiorentino G, Benincasa G, Coppola A, Franzese M, Annunziata A, Affinito O, et al. Targeted genetic analysis unveils novel associations between ACE I/D and APO T158C polymorphisms with D-dimer levels in severe COVID-19 patients with pulmonary embolism. J Thromb Thrombolysis. 2023;55:51-9.

19. Ghaffari K, Rad MA, Moradi Hasan-Abad A, Khosravi M, Benvidi A, Iraji M, et al. Association of the human platelet antigens polymorphisms with platelet count in patients with COVID-19. Front Med (Lausanne). 2023;10:1265568.

20. Osikov MV, Antonov VN, Zotov SO. Role of ITGB3, GP1B1, and ITGA2 gene polymorphisms in platelet dysfunction in patients with COVID-19-associated lung damage. Acta Biomedica Scientifica. 2023;8:14-22.