BJMG 26 (1), 2023 • 35-42
DOI: 10.2478/bjmg-2023-0005
sciendo
ORIGINAL ARTICLE

PROGNOSTIC VALUE OF *CYP1A2* (rs2069514 AND rs762551) POLYMORPHISMS IN COVID-19 PATIENTS

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ABSTRACT

The aim of the study was to examine the genotype-allele determination of *CYP1A2* rs2069514 and rs762551 polymorphisms in patients with mild and severe COVID-19 and to determine their effectiveness as prognostic criteria in COVID-19. The study consists of 60 patients who were hospitalized in intensive care or outpatient treatment due to COVID-19 in Istanbul NP Brain Hospital between 2020-2021. Genotyping was conducted by Real-Time PCR. Age ($p<0.001$); chronic disease ($p=0.002$); cardiovascular disease ($p=0.004$); respiratory distress ($p<0.001$); neurological disease ($p=0.004$); fatigue ($p=0.048$); loss of taste and smell ($p=0.003$); nausea/vomiting ($p=0.026$); intubated ($p<0.001$); ground glass image ($p<0.001$) and *CYP1A2* genotypes ($p<0.001$) showed a statistically significant difference between patients with and without intensive care admission. According to multivariate logistic regression analysis, *CYP1A2* *1A/*1C + *1C/*1C genotypes (OR:5.23 95% CI: 1.22-22.36; $p=0.025$), chronic disease (OR:4.68 95% CI:1.14- 19.15; $p=0.032$) or patients at 65 years or older (OR:5.17, 95%CI:1.26-21.14; $p=0.022$) increased the risk of admission to the intensive care unit. According to our results, we strongly suggest considering the *CYP1A2* rs2069514 and rs762551 polymorphisms as important predictors of Intensive Care Unit admission in patients with COVID-19, and we also suggest that genotype results will guide clinicians for the benefit and the efficiency of the treatment.

Keywords: *COVID-19, prognosis, hypoxia, CYP1A2, polymorphism*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was first reported as "pneumonia of uncertain etiology" in a group of patients in Wuhan, China, at the end of December 2019 [1]. Although the causative organism was initially identified as a new coronavirus (2019-nCoV), it was later changed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), as it was found to be genetically related to the coronavirus responsible for the 2003 SARS outbreak [2]. The infection spread from China to every continent of the world and was declared as an emerging pandemic by the WHO in March 2020 [3]. The COVID-19 epidemic is a pandemic caused by SARS-CoV-2, which becomes very difficult to manage after a certain stage and can often even result in death [4, 5]. Major clinical symptoms include gastrointestinal symptoms such as nausea, vomiting, and diarrhea, as well as upper respiratory symptoms such as sneezing, runny nose, and sore throat. In some patients, one week after the onset of the disease, respiratory symptoms mostly worsen, severe pneumonia was detected, acute respiratory distress syndrome (ARDS), respiratory failure, and multi-organ failure has also been detected [6].

It has been suggested that the factor leading to the death of the patient is an irregular inflammation that disrupts the exchange of oxygen (O_2) and carbon dioxide (CO_2) in general [7, 8]. Overwhelming proinflammatory cytokines damage alveolar epithelial and endothelial cells, leading to capillary permeability and pulmonary fibrinolysis, preventing O_2 and CO_2 exchange. Therefore, in the early stages of COVID-19,

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hypoxia occurs before the excessive inflammatory response occurs [9, 10]. However, the inflammatory response does not explain hypoxia in all COVID-19 patients. Some patients show minimal symptoms, referred to as "silent hypoxia," despite low blood O_2 levels [11]. Liu et al. (2020) reported that interferon (IFN) signaling triggered by SARS-CoV-2 induces excessive mucin production by lung epithelial cells, thickens the blood-air barrier, and inhibits O_2 diffusion, leading to hypoxia. They also stated that mucin expression is driven by the aryl hydrocarbon receptor (AHR), which is a potential target for the treatment of hypoxia in COVID-19 patients [12].

Cytochrome P450 (CYP) is a protein superfamily formed by enzymes that function as monooxygenases and contain hemes as cofactors and is found in all mammalian cell types and prokaryotes except mature erythrocyte and skeletal muscle cells [13]. CYPs are the best-known as drug-metabolizing enzymes and are mainly expressed in the liver [14]. Drug metabolism mediated by CYP enzymes is oxygen dependent. Therefore, hypoxia is one of the most important factors modulating hepatic CYP enzyme expression and may interrupt the biotransformation of drugs metabolized in the liver. Recent experimental findings are consistent with early reports that sustained hypoxia leads to the down-regulation of *CYP1A2* expression [15].

In overweight males over 60 years of age, the presence of comorbid metabolic disorders such as hypertension and diabetes are included in the development and severity of COVID-19 [16, 17, 18]. However, there is evidence that genetic variants can influence the development and course of infectious diseases [19]. Multiple polymorphisms, mostly single nucleotide polymorphisms (SNPs) like the rs2070874 of IL-4, rs5743708 of TLR-2 and rs1024611 of CCL-2 had been associated with susceptibility to viral respiratory infections [20].

Studies including the *CYP1A2* gene and hypoxia-related diseases like COVID-19 are very limited. Also, studies that are trying to predict the prognosis, and manage the treatment of COVID-19 are inadequate to explain optimal care. The aim of this study was to examine the genotype-phenotype relationship of the hypoxia-related *CYP1A2* rs2069514 and rs762551 polymorphisms in patients with mild and severe COVID-19 infection and to determine their effectiveness as prognostic criteria in COVID-19.

MATERIALS AND METHODS

Patients and Study Design

60 patients (28 female and 32 male; aged 20-87) who were hospitalized in intensive care or outpatient treatment due to COVID-19 infection in the Istanbul NP brain hospital between 2020-2021 were enrolled for the study. The protocol of the study was approved by the Üsküdar University Non-Interventional Research Ethics Committee (No:61351342/2021-02) regarding to the Helsinki Declaration-II. Each participant signed an informed consent form before the study. All individuals provided written informed consent. Each of the patients was PCR-positive for the virus, and their symptoms started within five days before admission to the hospital, diagnosed by infectious diseases and clinical microbiology or pulmonary medicine doctors.

***CYP1A2* Genotyping**

DNA isolations were carried out from the peripheral blood samples and completed by a commercially available PureLink Genomic DNA isolation kit (Invitrogen, Van Allen Way Carlsbad, CA, USA), following the manufacturer protocols. Analysis of *CYP1A2* rs2069514 rs762551 polymorphisms was performed by Thermo Fisher Quanti Studio 5 Real-Time PCR (Thermo scıentefic, Waltham, Massachusetts, USA) system, using the TaqMan Genotyping Assays (Applied Biosystems Foster City, CA, USA) genotyping kit following the directions of the manufacturer protocols, as previously described [21].

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA) package program was used for the statistical analysis of the data obtained from the genotyping results. Sociodemographic, clinical, and *CYP1A2* (rs2069514 and rs762551) polymorphisms of the patients were given as categorical data (n and %) and numerical data as Mean±SD. The chi-square test or Fisher Exact Test were used to compare Intensive Care Unit (ICU) admission and sociodemographic, clinical, and *CYP1A2* (rs2069514 and rs762551) polymorphisms. Finally, Multivariate Logistic Regression analysis was used to evaluate the effects of various clinical factors on admission to the intensive care unit. $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 56.75±19.70 (age range: 20-87). Of the 60 patients, 53.3% (n=32) were male and 46.7% (n=28) were female. 33.3% (n=20) of the patients had a ground glass appearance; 36.7% (n=22) of the patients had a chronic disease and 25% (n=15) were intubated during their treatment. According to COVID-19 symptoms; 45% (n=27) of the patients were fatigued, 38.3% (n=23) had cough, 16.7% (n=10) had loss of taste-smell, 16.7% (n=10) had fever, 6.7% (n=4) had nausea/vomiting and 1.7% (n=1) had diarrhea. The patients in intensive care follow-up were 58.3% (n=35) and 41.7% (n=25) of the patients followed up in intensive care passed away (Table 1).

Table 1: Distribution of age, gender, additional disease, and symptom information of patients with COVID-19 (n=60)

Variables		N (%)
Age	<65	29 (48.3)
	≥65	31 (51.7)
Gender	Male	32 (53.3)
	Female	28 (46.7)
Chronic Disease	No	38 (63.3)
	Yes	22 (36.7)
Cardiovascular Disease	No	47 (78.3)
	Yes	13 (21.7)
Respiratory Distress	No	39 (65.0)
	Yes	21 (35.0)
Neurological Disease	No	54 (90.0)
	Yes	6 (10.0)
Fever	No	50 (83.3)
	Yes	10 (16.7)
Fatigue	No	33 (55.0)
	Yes	27 (45.0)
Cough	No	37 (61.7)
	Yes	23 (38.3)
Loss of Taste and Smell	No	50 (83.3)
	Yes	10 (16.7)
Diarrhea	No	59 (98.3)
	Yes	1 (1.7)
Nausea Vomiting	No	56 (93.3)
	Yes	4 (6.7)
Intubated	No	45 (75.0)
	Yes	15 (25.0)
Expectoration	No	60 (100.0)
	Yes	0 (0,0)
Frosted Glass Image	No	40 (66.7)
	Yes	20 (33.3)
Mortality	Alive	47 (78.3)
	Ex	13 (21.7)
Intensive Care	Alive	35 (58.3)
	Passed away	25 (41.7)

For *CYP1A2* rs2069514 polymorphism of the patients hospitalized in intensive care; 44% (n=11) had AG, 40% (n=10) had GG and 16% (n=4) had AA genotypes. When we count the alleles, G was 62% (n=31) and A was 38% (n=19). For the rs762551 polymorphism, 60% (n=15) had CC, 20% (n=5) had AC and 20% (n=5) had AA genotypes. The C allele was counted as 70% (n=35) and the A as 30% (n=15).

For rs2069514 polymorphism of the passed-away patients; 53.8% (n=7) had AG, 23.1% (n=3) had GG and 23.1% (n=3) had AA genotypes. For the alleles, G was counted as 50% (n=13) and A was as 50% (n=13). For the rs762551 polymorphism, 53.8% (n=7) had CC, 23.1% (n=3) had AC and 23.1% (n=3) had AA genotypes. For the alleles, the C allele was counted as 65.4% (n=17) and the A as 34.6% (n=15) (Table 2).

In comparing the patients with and without intensive care; gender distributions of the two groups were detected as similar (p=0.382). Compared to the patients who were admitted to the intensive care unit, those aged 65 and over (64.5% vs 35.5%; p<0.001), chronic disease (68.2% vs 31.8%; p=0.002), cardiovascular disease (76.9% vs 23.1%; p=0.004), respiratory distress (95.2% vs 4.8%; p<0.001), neurological disease (100.0 vs. 0%) 0; p=0.004), fatigue (55.6% vs 44.4%; p=0.048), nausea/vomiting (100.0% vs. 0.0%; p=0.026), intubated (100% vs 0.0%; p<0.001), ground glass appearance (95.0% vs 5.0%; p<0.001), AA+AG genotype for the rs2069514 polymorphism (75.0 vs 25%, 0; p<0.001) and CC+CA genotype for the rs762551 polymorphism (51.3% vs 48.7%; p=0.040) were statistically significantly different. In addition, the number of patients with the *CYP1A2* *1A/*1C + *1C/*1C genotype (68.8% vs 31.3%; p<0.001) was found to be significantly higher in patients admitted to the intensive care unit compared to those without intensive care. The number of patients with the *CYP1A2* *1A/*1F + *1F/*1F genotype was also significantly different (16.1% vs 83.9%; p<0.001) (Table 3).

Table 2: Distributions of *CYP1A2* rs2069514 and rs762551 polymorphisms by ICU and Mortality Status

			Intensive Care		Mortality	
			No n = 35	**Yes n = 25**	**Alive n = 47**	**Ex n = 13**
CYP1A2 (rs2069514)	Genotype n (%)	AA	2 (5.7)	4 (16.0)	3 (6.4)	3 (23.1)
		AG	3 (8.6)	11 (44.0)	7 (14.9)	7 (53.8)
		GG	30 (85.7)	10 (40.0)	37 (78.7)	3 (23.1)
	Allele frequency, n (%)	A	11 (14.8)	19 (38.0)	13 (13.8)	13 (50.0)
		G	63 (85.2)	31 (62.0)	81 (86.2)	13 (50.0)
CYP1A2 (rs762551)	Genotype n (%)	AA	16 (45.7)	5 (20.0)	18 (38.3)	3 (23.1)
		AC	10 (28.6)	5 (20.0)	12 (25.5)	3 (23.1)
		CC	9 (25.7)	15 (60.0)	17 (36.2)	7 (53.8)
	Allele frequency, n (%)	A	42 (59.9)	15 (30,0)	48 (51.1)	9 (34.6)
		C	28 (40.1)	35 (70.0)	46 (48.9)	17 (65.4)

Table 3: Comparison of patients with and without intensive care

Intensive Care Hospitalization			
Parameters, n (%)	**Yes n = 25**	**No n = 35**	**p**
Age			
<65	5 (17.2)	24 (82.8)	**<0.001[a]**
≥65	20 (64.5)	11 (35.5)	
Gender			
Male	15 (60.0)	17 (48.6)	0.382[a]
Woman	10 (40.0)	18 (51.4)	
Chronic Disease			
No	10 (26.3)	28 (73.7)	**0.002[a]**
Yes	15 (68.2)	7 (31.8)	
Cardiovascular Disease			
No	15 (31.9)	32 (68.1)	**0.004[a]**
Yes	10 (76.9)	3 (23.1)	
Respiratory Distress			
No	5 (12.8)	34 (87.2)	**<0.001[a]**
Yes	20 (95.2)	1 (4.8)	
Neurological Disease			
No	19 (35.2)	35 (64.8)	**0.004[b]**
Yes	6 (100.0)	0 (0,0)	
Fever			
No	20 (40.0)	30 (60.0)	0.558[b]
Yes	5 (50.0)	5 (50.0)	
Cough			
No	13 (35.1)	24 (64.9)	0.193[a]
Yes	12 (52.2)	11 (47.8)	
Weakness			
No	10 (30.3)	23 (69.7)	**0.048[a]**
Yes	15 (55.6)	12 (44.4)	
Loss of Taste and Smell			
No	25 (50.0)	25 (50.0)	**0.003[b]**
Yes	0 (0,0)	10 (100.0)	
Diarrhea			
No	24 (40.7)	35 (59.3)	0.417[b]
Yes	1 (100.0)	0 (0,0)	
Nausea Vomiting			
No	21 (37.5)	35 (62.5)	**0.026[b]**
Yes	4 (100.0)	0 (0,0)	
Intubated			
No	10 (22.2)	35 (77.8)	**<0.001[a]**
Yes	15 (100.0)	0 (0,0)	
Frosted Glass Image			
No	6 (15.0)	34 (85.0)	**<0.001[a]**
Yes	19 (95.0)	1 (5.0)	
CYP1A2 rs2069514			
GG	10 (25.0)	30 (75.0)	**<0.001[a]**
AA+AG	15 (75.0)	5 (25.0)	
CYP1A2 rs762551			
AA	5 (23.8)	16 (76.2)	**0.040[a]**
CC+CA	20 (51.3)	19 (48.7)	
CYP1A2 Genotype			
*1A/*1A	5 (55.6)	4 (44.4)	**<0.001[a]**
*1A/*1F+*1F/*1F	5 (16.1)	26 (83.9)	
*1C/*1F	4 (100.0)	0 (0,0)	
*1A/*1C+*1C/*1C	11 (68.8)	5 (31.3)	

a = Chi-Square test; b= Fisher's Exact test, p<0.05 statistically significant

As a result of univariate analysis, age, *CYP1A2* polymorphisms, chronic disease, fatigue, and age values showed statistically significant upon admission to the intensive care unit ($p<0.05$, Table 3). These variables were included in the Multivariate logistic regression model and determined that the risk of admission to the intensive care unit increased in CYP1A2 *1A/*1C + *1C/*1C genotypes 5.23 times more than *1A/*1A + *1F/*1F (OR: 5.23 95% CI: 1.22-22.36; p=0.025) genotypes; and with chronic disease were 4.68 times more likely than those without (OR: 4.68, 95% CI: 1.14-19.15; p=0.032). Also, those ≥65 years old were 5.17 times more likely than those under 65 years of age (OR:5.17, 95%CI:1.26-21.14; p=0.022). It was determined that the variables in the model explained 48% of the factors determining intensive care admission (Table 4).

Table 4: Multivariate Logistic Regression Results on ICU Admission for Various Variables.

	Multivariate	
Variables	**OR (95%CI)**	**p**
CYP1A2 Genotype (ref: *1A/*1A+*1F/*1F)	5.23 (1.22-22.36)	**0.025**
Chronic disease (ref: none)	4.68 (1.14-19.15)	**0.032**
Fatigue (ref: none)	0.92 (0.21-3.94)	0.920
Age (ref: <65)	5.17 (1.26-21.14)	**0.022**
	R^2=0.48 -2 Log likelihood =55.201	

DISCUSSION

In this study, we examined 60 patients with a diagnosis of COVID-19; the predictability of *CYP1A2* polymorphisms with comorbidities and symptoms on the risk of ICU (intensive care unit) admission was examined. The mean age of 60 patients evaluated in the study was 56.75±19.70 years. 53.3% of the patients were male and 46.7% were female. Although the rates of male patients were higher in our study, there was no statistically significant difference between genders and admission to the intensive care unit. In a meta-analysis study, a total of 48 studies related to intensive care unit admission among COVID-19 cases were reported. In these studies, the rate of intensive care admission in hospitalized patients due to COVID-19 was higher in men than in women [22]. In our study, 64.5% of the patients admitted to the intensive care unit were 65 years or older; this rate was also statistically significant. In a meta-analysis study involving 8,088 patients diagnosed with COVID-19, it was reported that patients aged 65 and over had higher rates of intensive care admission [23]. Teker et al. (2021) stated that the course of COVID-19 disease gets worse with age and deaths increase [24].

Wang et al. (2020) reported that the elderly are at higher risk for chronic diseases and infections and that mortality due to COVID-19 increases in those with hypertension and coronary heart disease [15]. In our study, 68.2% of the patients hospitalized in the intensive care unit had a chronic disease and it was also statistically significant. This may be due to how chronic diseases weaken the immune system, or it may be related to the higher prevalence of other diseases in the elderly with COVID-19.

In a meta-analysis study by Jain and Yuan (2020), including 1813 people, the most common symptoms in patients in the intensive care group were cough (67.2%), fever (62.9%), and shortness of breath (61.2%). Similarly, the most common symptoms in our cohort who were hospitalized in the intensive care unit were respiratory distress (95.2%), cough (52.2%), and fatigue (55.6%) [25].

There are many studies in the literature on the relationship between *ACE* genotypes with COVID-19. Like *CYP1A2*, *ACE* I/D polymorphism is also related with adaptation to O_2 pressure conditions in blood and tissues. Yamamoto et al. (2020) showed that the *ACE* II genotype was negatively associated with the number of SARS-CoV-2 cases and deaths in East Asia [26]. In a case-control study involving 204 patients who were SARS-CoV positive, the *ACE* DD genotype was associated with a higher risk for COVID-19 [27]. In another study on the relationship between *ACE* I/D and *ACE-2* gene polymorphism with COVID-19, the *ACE-2* G allele and DD / GG+GA haplogroup together with the *ACE* D allele were reported as a risky genotype. The II / AA genotype has been reported to be protective [28]. However, the impact of *CYP1A2* genotypes on the poor prognosis of COVID-19 has not been focused on. When the studies in the literature about the *CYP1A2* gene are examined; it seems that the focus is on the effects of *CYP1A2* activity on drug efficacy and side effects in the treatment of COVID-19, as well as on the course and treatment response of COVID-19.

Lenoir et al. (2021) conducted a study evaluating the effects of SARS-CoV-2 infection on the activity of 6 different forms of the cytochrome P450 enzyme (*CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6,* and *CYP3A*) in 28 moderate to severe COVID-19 patients [29]. The study showed that *CYP1A2*, *CYP2C19,* and *CYP3A* activities were decreased and *CYP2B6* and *CYP2C9* activities were increased in COVID-19 patients. As a result of the

study, the activity of *CYP2D6* did not show any significant change. The study also found that inflammatory marker levels such as C-reactive protein, interleukin 6, and tumor necrosis factor-α were higher in COVID-19 patients. This suggests that SARS-CoV-2 infection may specifically alter the activity of these cytochrome P450 enzymes.

Clozapine is an effective antipsychotic drug approved for use in schizophrenia but is not used frequently due to its side effects and risk of agranulocytosis (reduction in blood cells). However, clozapine levels may need to be measured from time to time because many factors can affect the level of the drug. For example, the simultaneous use of certain medications, smoking cessation, and diseases such as COVID-19 can cause clozapine levels to increase and an increased risk of being toxic. Clozapine is metabolized by the cytochrome P450 system, primarily *CYP1A2*. During COVID-19, cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), and IFN-γ can slow down this metabolism. This may cause an increase in clozapine levels [30,31,32]. In a case study presented by DiAngelo et al. (2022), it was stated that frequent monitoring of clozapine levels and appropriate adjustment of clozapine doses would be of great importance in the setting of COVID-19 infection to avoid potential clozapine toxicity [33].

The results of a study by Reis et al. (2022) showed that the use of fluvoxamine (an antidepressant drug) can help to reduce the need for hospitalization in patients with COVID-19 [34]. However, it has also been stated that fluvoxamine has the potential to interact with many drugs and caution should be exercised during its use. Fluvoxamine is metabolized by CYP enzymes and therefore may interact with many other drugs. On the other hand, fluvoxamine is a potent inhibitor of *CYP1A2* and *CYP2C19* as well as a moderate inhibitor of *CYP2C9, CYP2D6,* and *CYP3A4*, and as a result, it may increase the exposure of drugs metabolized by these enzymes. Therefore, the dosage of the drug should be determined correctly and kept under control. The authors emphasized that COVID-19 patients are usually patients with more than one disease and use more than one drug, and therefore, caution should be exercised in terms of drug-drug interactions.

A case study presented by Tio et al. (2021) stated that COVID-19 is associated with hyperinflammation and extremely severe pneumonia [35]. Additionally, factors such as discontinuation of smoking and stimulant drugs, and co-administration of drugs that inhibit *CYP1A2*, such as caffeine, may cause a decrease in metabolic activity with this disease. Elfaki et al. (2022) emphasized that COVID-19 infection reduces liver functions, including clearance or detoxification of drugs administered by CYP450s [36]. Health care providers have stated that they should be aware of this disease-drug interaction when prescribing drugs for the treatment of COVID-19 and other comorbidities.

In our cohort, *CYP1A2* rs2069514 genotypes of the patients hospitalized in the intensive care unit were as 44% for AG, 40% for GG, and 16% for AA. For rs762551 polymorphism, 60% had CC, 20% had AC, and 20% had AA genotypes. The number of patients with *CYP1A2* *1A/*1C + *1C/*1C genotype (68.8% vs 31.3%) was found to be significantly higher in patients admitted to the intensive care unit compared to those without intensive care. However, the number of patients with CYP1A2 *1A/*1F + *1F/*1F genotype (16.1% vs 83.9%) was found to be significantly lower.

In addition, the risk of hospitalization in intensive care, was determined that those with *CYP1A2* *1A/*1C + *1C/*1C genotype increased 5.23 times compared to those with *1A/*1A + *1F/*1F, and those with chronic diseases increased 4.68 times compared to those without. Those at ≥65 years of age increased 5.17 times compared to those under 65 years of age. Compared with *CYP1A2* *1A, *CYP1A2* *1C and *CYP1A2* *1K are associated with decreased induction and *1F with increased induction [37]. In the early stages of COVID-19, hypoxia has been reported to occur before the excessive inflammatory response occurs [9, 10]. Recent experimental findings have shown that sustained hypoxia leads to the downregulation of *CYP1A2* expression [38,15]. Multiple genetic polymorphisms, mostly single nucleotide polymorphisms (SNPs), have been associated with susceptibility to viral respiratory infections [20].

Loss of taste and smell, which is widely used to predict infection and disease is an important marker for COVID-19. There are some controversial results about smell and taste loss in the terms of different populations and different virus variants. Our cohort showed the importance of loss of taste and smell in the severity of the disease. Like the loss of taste and smell, intubated conditions were statistically different between groups. But for intubation, it is impossible to discuss it with the data we have, there should be much more information about the patients' conditions. Therefore, for intubation, although we had a statistically significant difference, with the data we have, we can not speculate on the condition.

Our results show that the *CYP1A2* gene, whose association with hypoxia has been shown in studies, increases the risk of hospitalization in intensive care in patients with *1A/*1C + *1C/*1C genotype, and *CYP1A2* polymorphisms may be of great importance in predicting prognosis in patients with COVID-19. However, more research needs to be carried out to fulfill the role of *CYP1A2* polymorphisms, not only in the terms of COVID-19 but also in other hypoxia conditions.

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

Author Contributions

IB: Evaluation of the manuscript, study design, clinical data; IY: manuscript design; TY: Laboratuvary design, study protocol, manuscript design; KU: Evaluation of the genetic results, manuscript design; KNT: Study protocol, clinical evaluation, genetic results.

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