INFECTIOUS DISEASES

THE rs11385942 AND rs657152 VARIANTS ARE NOT ASSOCIATED WITH COVID-19 SEVERITY AND OUTCOMES IN PATIENTS TREATED WITH FAVIPIRAVIR AND REMDESIVIR

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ABSTRACT

Background. *There is a mounting evidence in the scientific literature that susceptibility to SARS-CoV-2 infection could vary. The severity of COVID-19 symptoms can range from asymptomatic to severe respiratory failure, requiring prolonged artificial ventilation. The underlying causes of this range of clinical manifestations remain unclear. Identification of the risk factors that may cause this variation in clinical symptoms is important for identifying the most susceptible populations at highest risk. This should help improve prevention measures, reduce hospitalizations, and decrease the mortality rate of the disease. Previously, an association has been found between the severity of COVID-19 and the genetic markers rs11385942 G>GA and rs657152 A>C.*

The aim. *To assess the impact of carrying polymorphic markers rs11385942 G>GA and rs657152 A>C on the severity of COVID-19 in patients undergoing specific therapy.*

Materials and methods. *A total of 240 patients hospitalized with a coronavirus infection were included in the study. All patients received therapy with favipiravir or remdesivir. The presence of the rs11385942 G>GA and rs657152 A>C variants was determined in all patients. The study compared the length of hospital stays, frequency of patient transfers to the intensive care unit (ICU), and frequency of clinical outcomes (recovery or death) among carriers of allelic variants of the markers under investigation.*

Results. *There were no significant associations between the carriage of variants rs11385942 G>GA and rs657152 A>C and the duration of patients' hospitalization, frequency of patient transfers to the ICU, and patient outcomes.*

Conclusion. *The carriage of rs11385942 G>GA and rs657152 A>C variants did not affect the severity or type of clinical outcomes in patients with COVID-19.*

Key words: *susceptibility to COVID-19, COVID-19 severity, etiotropic therapy of COVID-19, favipiravir, remdesivir, rs11385942, rs657152, polymorphisms*

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ВАРИАНТЫ rs11385942 И rs657152 НЕ АССОЦИИРУЮТСЯ С ТЯЖЕСТЬЮ ТЕЧЕНИЯ И ИСХОДАМИ COVID-19 У ПАЦИЕНТОВ, ПОЛУЧАВШИХ ТЕРАПИЮ ФАВИПИРАВИРОМ И РЕМДЕСИВИРОМ

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РЕЗЮМЕ

Обоснование. *В научной литературе появляется всё больше данных о различиях в чувствительности и восприимчивости к инфекции SARS-CoV-2, которые проявляются у пациентов в диапазоне от бессимптомного течения заболевания до тяжёлой дыхательной недостаточности и необходимости длительной искусственной вентиляции лёгких. Основные причины этого спектра клинических проявлений остаются неясными. Определение факторов риска, способных вызвать такую вариацию клинических симптомов, важно для выявления наиболее восприимчивых групп населения с наибольшим риском. Это должно помочь улучшить меры профилактики, сократить количество госпитализаций и снизить смертность от заболевания. Ранее для генетических маркеров rs11385942 G>GA и rs657152 A>C была показана связь с тяжестью течения COVID-19.*

Цель работы. *Оценить вклад носительства полиморфных маркеров rs11385942 G>GA и rs657152 A>C на показатели тяжести течения COVID-19 у пациентов, получавших этиотропную терапию.*

Материалы и методы. *В исследование было включено 240 пациентов, госпитализированных в ГБУЗ г. Москвы «Городская клиническая больница № 15 им. О.М. Филатова ДЗМ» с диагнозом COVID-19, получавших этиотропную терапию фавипиравиром или ремдесивиром. У всех пациентов определялось носительство вариантов rs11385942 G>GA и rs657152 A>C. Сравнивались длительность стационарного лечения, частота перевода пациентов в отделение реанимации и интенсивной терапии (ОРИТ), частота наступления клинических исходов (выписан или смерть) между носителями аллельных вариантов изучаемых генетических маркеров.*

Результаты. *Не было выявлено статистически значимых ассоциаций носительства различных вариантов rs11385942 G>GA и rs657152 A>C с длительностью госпитализации пациентов, частотой перевода пациентов в ОРИТ и наступлением того или иного исхода.*

Заключение. *Носительство вариантов rs11385942 G>GA и rs657152 A>C не определяло показатели тяжести течения и вид клинических исходов у пациентов с COVID-19.*

Ключевые слова: *восприимчивость к COVID-19, тяжесть течения COVID-19, этиотропная терапия COVID-19, фавипиравир, ремдесивир, rs11385942, rs657152, полиморфизмы*

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INTRODUCTION

The COVID-19 pandemic has had a significant impact on health systems in nearly every country in the world. The experience of coping with the COVID-19 crisis revealed many shortcomings in the organization of medical service and public drug supply. In the initial phase of the fight against the disease, the scientific community studied the possibilities of using already known drugs. Thus, in spring 2020, favipiravir and remdesivir were already proposed as treatment options for COVID-19 [1, 2]. According to the latest version of the Provisional Guidelines for the Prevention, Diagnosis and Treatment of COVID-19, both drugs are categorized as drugs for etiotropic therapy of COVID-19 and remain relevant [3].

There is increasing evidence in scientific literature of differences in sensitivity and susceptibility to SARS-CoV-2 infection, manifesting in a range from asymptomatic disease course to severe respiratory failure and the need for prolonged artificial lung ventilation (ALV) [4]. The underlying causes of this spectrum of clinical outcomes remain unclear. Identification of risk factors, such as genetic, clinical-demographic, environmental, and possible other factors that may cause this variation in clinical symptoms is important to identify the most susceptible populations at highest risk. This should protect them from infection, reduce hospitalizations and reduce mortality.

Previously, a group of scientists suggested that the severity of the course of COVID-19 may, among other things, be determined by the genetic profile of patients. D. Ellinghaus et al. (2020) in their work identified associations of carrying allelic variants of markers *rs11385942 G>GA* at locus 3p21.31 and *rs657152 C>A* at locus 9q34.2 with severe forms of respiratory failure in COVID-19 patients [5]: GWAS study showed that the signal at locus 3p21.31 covered the *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR* genes, while the association signal at locus 9q34.2 coincided with the ABO blood group locus. Based on these results, the authors concluded the possible role of the 3p21.31 gene clusters and ABO blood group as a predictor of COVID-19 susceptibility in patients with respiratory failure [5]. The impact of carrying these markers on the effectiveness of therapy in COVID-19 patients has not been previously studied.

Taking into account the abovementioned, the aim of the presented study was a comparative assessment of the distribution of carriage of allelic variants *rs11385942 G>GA* and *rs657152* in groups of patients with COVID-19, differing in the duration of hospitalization, frequency of transfer to the intensive care unit (ICU) and clinical outcomes of the disease treatment.

MATERIALS AND METHODS

The study was conducted at the Moscow City Clinical Hospital No. 15 named after O.M. Filatov Moscow Health Department and was approved by the local ethical committee of the Federal State Budgetary Educational Institution of Professional Education "Russian Medical Academy of Continuing Professional Education" of the Ministry of Health of Russia (Minutes No. 15 dated October 16, 2021). Voluntary informed consent was obtained from all patients for participation in this study.

Study sample characteristics

The authors performed a prospective observational unmasked study. The study was conducted from November 2021 through February 2022. The study included 240 patients, male and female, aged 18 years and older, hospitalised with confirmed new coronavirus infection (COVID-19) (U07.1, U07.2 according to ICD), complying with inclusion criteria and failing non-inclusion criteria. The age of all patients ranged from 44 to 96 years (mean age – 73.0 ± 12.5 years). Of these, 74 (31 %) were men (mean age – 72.91 ± 12.62 years) and 166 (69 %) were women (mean age – 73.0 ± 12.5 years).

Inclusion criteria were confirmed diagnosis of new COVID-19 coronavirus infection (U07.1, U07.2 according to ICD); duration of hospitalisation > 48 h; use of favipiravir and remdesivir as etiotropic therapy; and signed voluntary informed consent.

Non-inclusion criteria were contraindications to aetiotropic therapy: severe hepatic insufficiency (Child – Pugh class C); glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2; pregnancy and breastfeeding.

Patients received favipiravir and remdesivir as etiotropic therapy. Remdesivir was used in the standard dosage – 200 mg intravenously on the first day, then 100 mg once daily for 5–10 days. The dosing regimen of favipiravir was selected cause-specific to the patient's weight according to the instructions for medical use: for patients with body weight less than 75 kg – 1600 mg 2 times a day on the first day, further – 600 mg 2 times a day; for patients with body weight more than 75 kg – 1800 mg 2 times a day on the first day, further – 800 mg 2 times a day. The surveyor could not influence the choice of antiviral drug and the duration of therapy, which were determined by the treating physician.

Genotyping

After obtaining written informed consent and inclusion in the study, 10 ml of venous blood was sampled from each patient for subsequent genetic testing. Genomic DNA was isolated from whole blood using S-Sorb reagent kits (OOO "Syntol", Russia). The concentration of extracted DNA was determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). The carriage of allelic variants *rs11385942 G>GA* and *rs657152 A>C* was determined by the allele-specific polymerase chain reaction (PCR) in real time on the CFX96 Touch Real Time System (BioRad, USA) using commercial kits TaqMan®SNP Genotyping Assays and TaqMan Universal MasterMix II, no UNG (Applied Biosystems, USA) according to the manufacturer's instructions (Table 1). The amplification mode was: 95 °C for 5 min; 40 cycles, 95 °C for 10 s, 55 °C for 10 s; 72 °C for 10 s.

Statistical processing

Consistency of genotype frequencies with the Hardy – Weinberg equilibrium was assessed using Pearson's χ^2 (chi-square) criterion (equilibrium is satisfied at $p > 0.05$). Fisher's exact test was used to assess differences in the frequencies of occurrence of different alleles between groups.

The normality of the obtained results distribution was assessed using the Shapiro – Wilk W-test and the Kolmogorov – Smirnov criterion. Categorical variables were compared using Pearson's χ^2 test or Fisher's two-sided exact test (depending on the nature of the distribution of indicators). Multiple samples of continuous data were compared using one- or multivariate analysis of variance ANOVA or Kraskell – Wallis H-test (depending on the nature of data distribution).

IBM SPSS Statistics 22 software package (IBM Corp., USA) was used as a means of statistical processing. For all results, a value of $p < 0.05$ was considered statistically significant.

RESULTS

The severity of the course and outcome of the disease were assessed in groups with respect to the carriage of alleles of the studied polymorphic markers *rs11385942 G>GA* and *rs657152 A>C*. The following indices were used for analysis: 1) duration of COVID-19 patients' hospital stay; 2) frequency of patients' transfer to ICU; 3) outcome of the disease treatment in the form of discharge, transfer of the patient from the infectious diseases department to other departments and patient's death.

Correlations between the frequency of transfer to ICU, frequency of deaths, severity of course, sex and age of patients, level of comorbidity and concomitant therapy in the treatment groups were not analysed, which is a limitation of the conducted analysis.

Among all patients, the genotype distribution of markers *rs11385942 G>GA* and *rs657152 A>C* agreed with the Hardy – Weinberg law ($p > 0.05$) (Table 2).

Analysis of the correlation between the carriage of *rs11385942 G>GA* variants and the number of days the patient spent in hospital (bed-days) revealed no differences ($p = 0.8335$). Similar conclusions can be drawn for *rs657152 A>C*: there were no statistically significant differences between carriers of different genotypes ($p = 0.9693$) (Table 3). Carriage of *rs11385942 G>GA* and *rs657152 A>C* variants did not determine the length of hospitalization of COVID-19 patients.

In 75 patients included in the study, the disease was severe, which required transfer of these patients to ICU. Fisher's test showed that death was statistically significantly more frequent among patients who were admitted to ICU than among patients who were not admitted to ICU ($p < 0.0001$). When comparing the frequency of patients admitted to ICU cause-specific to *rs11385942 G>GA* and *rs657152 A>C* carrier variants, no statistically significant differences were also revealed (Table 4).

TABLE 1
USED PRIMERS

SNP	RefSeq	Primer F 5'-3'	Primer R 5'-3'
LZTFL1 *rs11385942*	NM_020347.4	TGGGGCTAGTGTGTGAGGA	AGCACCACCTTCTCAGAGTT
ABO *rs657152*	NM_020469.3	TCCTACGGGAGGCAGCAGT	AATTTAGGACATGTAAAGTTCA

Note. According to the ThermoFisher manufacturer's instructions (https://www.thermofisher.com/taqman/results?keyword=).

TABLE 2
GENOTYPE AND ALLELE FREQUENCIES OF *rs11385942 G>GA* AND *rs657152 A>C* ALLELIC VARIANTS IN THE GROUP

Markers	N		Genotypes, *n* (%)			Alleles, *n* (%)		Conformity to the Hardy – Weinberg distribution*	
			GG	G/GA	GA	G	GA	χ^2	p
rs11385942 G>GA	240	observed	162	72	6	396 (82.50)	84 (17.50)	0.3643	0.8335
		expected	163.4	69.3	7.4				
		%	67.5	30.0	2.5				
			AA	AC	CC	A	C		
rs657152 A>C	240	observed	49	121	70	219 (45.63)	261 (54.38)	0.0623	0.9693
		expected	50.0	119.1	71.0				
		%	20.4	50.4	29.2				

Note. * – Pearson's χ^2 criterion.

As mentioned above, patient discharge from the hospital, patient transfer to another department of the hospital and recording of patient death in the department were used as parameters to assess patient outcome in the Infectious Diseases Department.

A total of 41 deaths were recorded in the study group, accounting for 17.1 %. 165 (68.7 %) patients were discharged from the hospital, and 34 (14.2 %) patients were transferred to other hospital departments. When a patient was transferred to another hospital department, no further follow-up by the surveyor was conducted; therefore, such patients were excluded from the analysis of treatment outcomes in relation to marker carriage. Comparison of the number of discharged and deceased patients caused-specific to carriage of *rs11385942 G>GA* and *rs657152 A>C* variants revealed no statistically significant association ($p > 0.05$) (Table 5).

In case of transfer to another department, clinical outcome was not recorded in these patients, which is also one of the limitations of the study.

DISCUSSION

COVID-19 is an acute viral disease, causing predominant involvement of the respiratory tract, the course of which can vary from asymptomatic and mild (in most cases) to life-threatening conditions with the development of severe respiratory failure and acute respiratory distress syndrome (up to 5 %) [6, 7]. COVID-19 mortality was relatively higher among patients with severe disease and those treated in the ICU [8, 9]. It appears that the high mortality rate is primarily related to the manifestations of severe respiratory failure requiring transfer of patients to the intensive care unit [10].

TABLE 3

ASSOCIATION BETWEEN THE DURATION OF PATIENTS' PERIOD OF HOSPITALIZATION AND CARRIAGE OF *rs11385942 G>GA* AND *rs657152 A>C* VARIANTS

Markers	*N*	Genotypes	Number of bed days		*p**
			Mean (± SD)	Median bed days [Q1–Q3]	
rs11385942 G>GA	240	GG	11.41 (± 8.79)	9.0 [6.0–14.0]	0.2835
		G|GA	13.08 (± 8.99)	10.0 [7.0–16.0]	
		GA|GA	9.83 (± 5.42)	9.5 [9.0–10.0]	
rs657152 A>C	240	AA	12.06 (± 7.85)	9.0 [7.0–15.0]	0.6831
		AC	11.39 (± 7.73)	9.0 [6.0–13.0]	
		CC	12.59 (± 10.96)	10.0 [7.0–14.0]	

Note. SD – standard deviation; * – Kraskell – Wallis H-test.

TABLE 4

ASSOCIATION BETWEEN THE FREQUENCY OF TRANSFER OF PATIENTS TO INTENSIVE CARE UNIT AND CARRIAGE OF *rs11385942 G>GA* AND *rs657152 A>C* VARIANTS

Markers	*N*	Genotypes	Number of patients outside ICU, *n* (%)	Number of patients transferred to ICU, *n* (%)	χ^2	*p**
rs11385942 G>GA	240	GG	115 (47.9)	47 (19.6)	1.18159	0.553886
		G|GA	46 (19.2)	26 (10.8)		
		GA|GA	4 (1.7)	2 (0.8)		
rs657152 A>C	240	AA	33 (13.8)	16 (6.7)	0.255425	0.880106
		AC	85 (35.4)	36 (15)		
		CC	47 (19.6)	23 (9.6)		

Note. * – Pearson's χ^2 criterion.

TABLE 5

ASSOCIATION BETWEEN THE DEATH RATE AND PATIENT HOSPITAL DISCHARGE AND CARRIAGE OF *rs11385942 G>GA* AND *RS657152 A>C* VARIANTS

Markers	*N*	*n*	Genotypes	Treatment outcomes		χ^2	*p**
				Death, *n* (%)	Discharged, *n* (%)		
rs11385942 G>GA	206	138	GG	28	110	0.041900	0.979268
		63	G|GA	12	51		
		5	GA|GA	1	4		
rs657152 A>C	206	40	AA	7	33	1.21099	0.545803
		110	AC	25	85		
		56	CC	9	47		

Note. * – Pearson's χ^2 test.

Patient genetic characteristics may also contribute to the severity of the COVID-19 course. In the GWAS study by D. Ellinghaus et al. it was revealed that the frequency of carrying the risky GA allele of the *rs11385949 G>GA* marker was higher among patients who developed acute respiratory failure during COVID-19 and were placed on artificial ventilation compared to those who received only oxygen support [5]. The explanation for this association of the *rs11385949 G>GA* variant was that the region near *rs11385942* on chromosome 3p21.31 significantly affects the expression of the *LZTFL1* gene ($p < 0.05$), a regulator of the cilia of the respiratory tract [11]. The second identified risk marker for COVID-19 severity *rs657152 A>C* was more frequent in patients with COVID-19 and development of respiratory failure. This marker matched the locus coding for ABO system blood groups [5].

In the study of O. Balanovsky et al. (2021) the distribution frequencies of *rs11385942 G>GA* and *rs657152 A>C* among populations living in Russia and bordering countries were studied. Analysis of the correlation between the frequency of carriage of these markers and COVID-19 mortality rates revealed a positive association. The correlation was stronger for *rs657152 A>C* ($r = 0.59$; $p = 0.02$). The authors pointed out that such a correlation was revealed only for the Russian sample and was not relevant for data for global populations [12].

In this study, we attempted to assess the putative impact of carriage of COVID-19 severity markers over the length of hospital stay, the frequency of transfer of such patients to the ICU, and the final therapy outcomes. Carriage of the studied markers *rs11385942 G>GA* and *rs657152 A>C* was not associated with prolongation of the patient's length of hospital treatment, had no statistically significant effect on the proportion of patients transferred to ICU, and was not associated with a statistically significant difference in mortality between patients with different genotypes. Our data are consistent with the findings of other studies. For instance, E.A. Orlova et al. analysed the frequency of *rs657152 A>C* in cohorts of 129 COVID-19 patients and 466 healthy individuals and found no statistically significant differences between them. The distribution of *rs657152 A>C* frequencies between patients with high and low viral loads revealed no differences. The authors therefore concluded that carriage of *rs657152 A>C* alone cannot be considered a risk factor for a more severe course of COVID-19 [13]. Similar findings about the lack of association between the carriage of the markers in question and the severity of the disease course were obtained in a case-control study by R. Marçalo et al. When comparing patients with chronic obstructive pulmonary disease (COPD) ($n = 255$) and patients without COPD ($n = 243$) in terms of COVID-19 course severity and survival, no differences were found between groups: all *p* values > 0.01 when considering both risk alleles individually and combinations of alleles or polygenic risk assessment [14].

CONCLUSION

The multifaceted nature of the risk of COVID-19 course severity requires consideration of multiple factors: clinical and demographic parameters, comorbid background, concomitant therapy, patient genetics, etc. Within the current understanding of COVID-19's nature, assessing the contribution of a patient's genetic profile to the severity of the course and clinical outcomes of the disease remains challenging. The problem requires further study.

Conflict of interest

The authors declare the absence of a conflict of interest.

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