Association of *MIR125A* and *H19* genetic variants with the severity of COVID-19

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Abstract:

Coronavirus disease 2019 (COVID-19) is an infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several risk factors of COVID-19 susceptibility and severity have been identified, including age, gender, comorbidities, and genetic predisposition of the host. The aim of the current study was to investigate the association of single nucleotide polymorphisms (SNPs) of microRNA125a and long non-coding RNA H19 genes with the severity of COVID-19. Study subjects were divided into two groups with mild and severe COVID-19 symptoms. Genotyping was performed using allele-specific real time polymerase chain reaction (RT-PCR), and multifactor dimensionality reduction (MDR) analysis was performed to evaluate the gene-gene interaction models of the studied SNPs. The results showed a significant association of *H19* rs217727 with the severity of COVID-19 (p=0.003). Carriers of *MIR125A* TC * *H19* CC were more likely to have mild symptoms, while *MIR125A* TC * *H19* CT carriers had a higher risk of severe COVID-19. The results of the current study may contribute to a better understanding of COVID-19 pathogenesis.

Keywords:

MicroRNA, long non-coding RNA, association, single nucleotide polymorphism, COVID-19.

1 Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak of COVID-19 was firstly reported in 2019 in Wuhan, China and then rapidly spread across the world, resulting in a global pandemic. According to the world health organization (WHO) COVID-19 dashboard, more than 775 million cases were confirmed globally, including over 7 million deaths (https://data.who.int/dashboards/covid19/cases?n=o). A total of 5.47 billion vaccine doses were administered worldwide since the introduction of the first COVID-19 vaccine in December 2020 (https://data.who.int/dashboards/covid19/vaccines?n=o). The pandemic has had a huge impact on the world in several ways, including health systems, economic progress, and even social life (Yuan et al., 2023). COVID-19 patients have exhibited a wide spectrum of symptoms, and therefore were grouped accordingly into different categories, such as asymptomatic, mild, moderate, and severe illness (Arjmand et al., 2023).

Non-coding RNAs (ncRNAs) are functional RNA molecule that are not translated into proteins. NcRNAs are considered important regulators of multiple biological functions across a wide range of cell types and tissues (Nemeth et al., 2024). NcRNA could be divided into two categories: Housekeeping ncRNAs, which are abundantly expressed in cells and regulate cellular functions (For example: ribosomal RNA and tansfer RNA), and regulatory ncRNAs, which are usually considered as key regulators of gene expression (For example: microRNA and long non-coding RNA) (Zhang et al., 2019). MicroRNAs (miRNAs) are the most abundant class of small ncRNAs. They regulate gene expression in both cytoplasm and nucleus through different mechanisms and mediate gene silencing at the post-transcriptional level (Lagos-Quintana et al., 2001). Long noncoding RNAs (LncRNAs) are defined as transcripts that longer than 200 nucleotides and do not code proteins (Zhang et al., 2019). LncRNAs are highly diverse and often show high tissue specificity (Cabili et al., 2011).

Since several ncRNAs play an important regulatory role for normal cell functions, their dysregulation has been implicated in multiple diseases, such as cancer, cardio vascular diseases (CVDs), neurological and infectious diseases

(Nemeth et al., 2024). Recently, the role of ncRNAs in the susceptibility and severity of COVID-19 has been of interest. Several studies have mentioned that the expression of specific lncRNAs was dysregulated in COVID-19 patients and correlated with the severity of its symptoms (Wu et al., 2021). In addition, miRNAs are suggested as promising biomarkers for COVID-19 susceptibility, severity and therapeutic possibilities (Jankovic et al., 2023).

Single nucleotide polymorphism (SNP), also known as single nucleotide variant (SNV) - a variation at a single nucleotide in DNA sequence among individuals. SNPs are the most common type of genetic variants, and they have been the subject of much research to understand their possible role in disease pathogenesis (Zou et al., 2020). Assessing the associations of SNPs with disease susceptibility and/or severity provides more information about the mechanisms of studied disease, and may also explain the variations of symptoms among individuals.

The aim of the current study was to investigate the association of *MIR125A* rs12976445 (T>C) and *H19* rs217727 (C>T), which are SNPs of two genes, that encode ncRNAs, with the severity of COVID-19 infection. In addition, a gene-gene interaction analysis was performed to evaluate the model of interaction between the two studied SNPs.

2 Materials and methods

2.1. Study subjects

A total of 351 COVID-19 patients were included in this study. They were divided into 2 groups, according to WHO guidelines (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2): 208 mild and 143 severe cases. Patients with comorbidities (such as diabetes and hypertension) were excluded. Age of participants was between 18 and 70 years old. Female/male ratio was around 2/1 in both mild and severe groups. Blood samples were collected in “Nauka” medical center (Rostov-on-Don, Russia) and analyzed in the post-COVID period, starting at least from 2 months after recovery. All performed procedures were in accordance with the Helsinki declaration (2013) and its later amendments or ethical standards. Informed consents were obtained from all study participants.

2.2. Genotyping

Total genomic DNA was extracted from venous blood samples using AmpliSens® RIBO-prep isolation kit (AmpliSens, FBSI "Central Research Institute of Epidemiology", Rospotrebnadzor, Russia). Quantitative assessment of the isolated DNA was by using NanoDrop (Thermo Fisher Scientific, USA). Candidate genes for the study were selected after studying the published literature, using several databases, such as NCBI-PubMed, Google Scholar, and CyberLeninka. The selection was based on their potential role in regulating the expression of antioxidant enzymes' genes. The functions of included genes were explored in the Genecards human gene database (https://www.genecards.org/). Next, genetic polymorphisms of the selected genes were chosen based on their functional properties. Databases, such as Ensembl and NCBI-SNP, were used to obtain mutant allele frequencies (MAF) of the studied SNPs *MIR125A* rs12976445 (T>C) and *H19* rs217727 (C>T). Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) was used to design allele-specific primers and probe-specific primers for the studied genetic variants. The sequences and characteristics of the primers and probes are presented in Table 1.

Table 1. Sequences and characteristics of primers and probes

SNP	Allele	Orientation	5′-3′ Sequence	Length (nucleotides)	GC, %
MIR125A rs12976445	-	Reverse	CAGGTTTCAGTTGGTG GTCA	20	50
	C (WT)	Forward	TCTCAGAATGTCTCTGT GCCC	21	52
	T (Mut)	Forward	CTCTCAGAATGTCTCTG TGCCT	22	50

H19 rs217727	-	Reverse	CAAAGAGACAGAAGG ATGAAAAAGAA	26	35
	-	Forward	CGGCGACTCCATCTTC ATG	19	58
	G (WT)	Probe	FAM-TCAACCGTCCGCCG-BHQ-1	14	71
	A (Mut)	Probe	ROX-TCAACCGTCCACCGC-BHQ-2	15	67

SNPs were investigated by real time polymerase chain reaction (RT-PCR) using PCR kits with the designed primers (“Syntol”, Moscow, Russia) with SYBR green for *MIR125A* rs12976445 and designed probes (FAM, ROX) for *H19* rs217727. The reaction was performed and visualized on QuantStudio™ 5 RT-PCR System (Applied Biosystems, Waltham, MA, USA).

2.3. Statistical analysis

Data analysis was performed using IBM SPSS Statistics 27.0 (IBM, Armonk, NY). Student’s t-test was used to compare variables between studied groups. Continuous variables were expressed as mean and standard deviation (M ± SD). Chi-square test was used to assess the differences in allelic variants distribution between the studied groups ($p \leq 0.05$ was considered statistically significant). Odds Ratios (OR), with 95% confidence intervals (CI), were calculated to evaluate the risk of COVID-19 severity. Hardy-Weinberg Equilibrium (HWE) was calculated using SNPStats web tool (https://www.snpstats.net/start.htm) (Solé et al., 2006). Multifactor Dimensionality Reduction (MDR) 3.0.2 software (Computational Genetics Laboratory, Institute for Quantitative Biomedical Sciences, Dartmouth,

NH, USA) was used to study the possible interactions between the studied genetic variants and evaluate their relation to the risk of severe COVID-19 outcome.

3 Results

3.1. Study subjects' clinical characteristics

There was no significant difference in the age and male/female ratio between mild and severe groups. Several biochemical indicators, such as glucose, ferritin, albumin, total protein, urea, uric acid, creatinine, and total bilirubin, were measured and compared between the studied groups with no significant differences. In addition, Lung computed tomography (CT) scan showed that all patients in the mild group were in the CT-1 category (pulmonary parenchymal involvement ≤ 25%), while severe group patients were in CT-3 and CT-4 categories (50-75% and ≥ 75%; respectively). Clinical characteristics of patients are presented in Table 2.

Table 2. Clinical characteristics of patients with mild and severe COVID-19 symptoms.

Characteristics	**Mild (n=208)**	**Severe (n=143)**	**P value**
Age (years)	44.85 ± 12.72	46.34 ± 12.51	0.28
Males (n)	82	52	0.57
Females (n)	126	91	
Glucose (mmol/l)	5.60 ± 0.31	5.62 ± 0.27	0.41
Ferritin (ng/ml)	72.87 ± 29.98	78.91 ± 33.95	0.08
Albumin (g/l)	42.53 ± 0.56	42.50 ± 0.62	0.60
Total protein (g/l)	73.29 ± 2.33	73.46 ± 1.87	0.46
Urea (mmol/l)	5.45 ± 0.77	5.54 ± 0.63	0.22
Uric acid (µmol/l)	263.74 ± 36.55	266.14 ± 26.16	0.49
Creatinine (µmol/l)	94.26 ± 6.95	94.02 ± 5.86	0.73
Total bilirubin (µmol/l)	12.47 ± 1.89	12.08 ± 1.98	0.06

Lung CT scan (CT category)	CT-1	CT-3, CT-4	

3.2. Association of *MIR125A* and *H19* genetic variants with COVID-19 severity

The distribution of *MIR125A* rs12976445 (T>C) genotypes and alleles were consistent with the Hardy-Weinberg equilibrium (HWE) in both study groups (p=0.46 for the mild COVID-19 group and 0.99 for the severe COVID-19 group). The same was for *H19* rs217727 (p=0.14 for mild, and 0.22 for severe group). The most common genotype in each of the studied genetic variants was considered the reference group for the association study.

Genotype frequencies of *MIR125A* rs12976445 did not differ significantly between the two study groups (p=0.76). The same applies to their allele frequencies (p=0.79). However, genotype frequencies of *H19* rs217727 showed significant associations with COVID-19 severity (p=0.003). The CT genotype was significantly less frequent in the mild group (21.6%) than in the severe group (35%), suggesting that it is associated with severe COVID-19 infection (OR=2.10; 95% CI [1.29–3.41]). Furthermore, the TT genotype frequency was higher in the severe group (7.7%) than in the mild group (3.8%) (OR=2.60; 95% CI [1.01–6.72]), and the CC frequency was higher in the mild group (74.5%) than in the severe group (57.3%). In addition, there was a significant difference in allele frequencies between the study groups (p=0.001). The minor allele T is associated with an increased risk of severe COVID-19 (OR=1.84; 95% CI [1.27–2.66]). The frequencies of genotypes and alleles of *MIR125A* rs12976445 and *H19* rs217727 polymorphism in both mild and severe groups of COVID-19 patients are presented in Table 3. The histograms of the distribution of genotypes in both groups of COVID-19 patients are shown in Figure 1.

Table 3. Genotype and allele frequencies of *MIR125A* rs12976445 and *H19* rs217727 in mild and severe groups of COVID-19 patients

Genotypes/alleles	**Mild COVID-19 (н=208)**	**Severe COVID-19 (n=143)**	**P value**	**OR (95% CI)**
***MIR125a* rs12976445 (T>C)**				
Genotypes				

TT	103 (49.5%)	71 (49.6%)	0.76	1
TC	93 (44.7%)	61 (42.7%)		0.95 (0.61-1.48)
CC	12 (5.8%)	11 (7.7%)		1.33 (0.56-3.18)
TC+CC	105 (50.5%)	72 (50.4%)	0.98	0.99 (0.65-1.52)
Alleles				
T	299 (71.87%)	203 (70.98%)	0.79	1.05 (0.74-1.48)
C	117 (28.13%)	83 (29.02%)		
***H19* rs217727 (C>T)**				
Genotypes				
CC	155 (74.5%)	82 (57.3%)	**0.003***	1
CT	45 (21.6%)	50 (35%)		**2.10 (1.29-3.41)**
TT	8 (3.8%)	11 (7.7%)		**2.60 (1.01-6.72)**
CT+TT	53 (25.5%)	61 (42.7%)	**<0.0001***	**2.18 (1.38-3.43)**
Alleles				
C	355 (85.34%)	214 (74.83%)	**0.001***	
T	61 (14.66%)	72 (25.17%)		**1.84 (1.27-2.66)**

OR= Odds Ratio, CI= Confidence Interval, *p<0.05

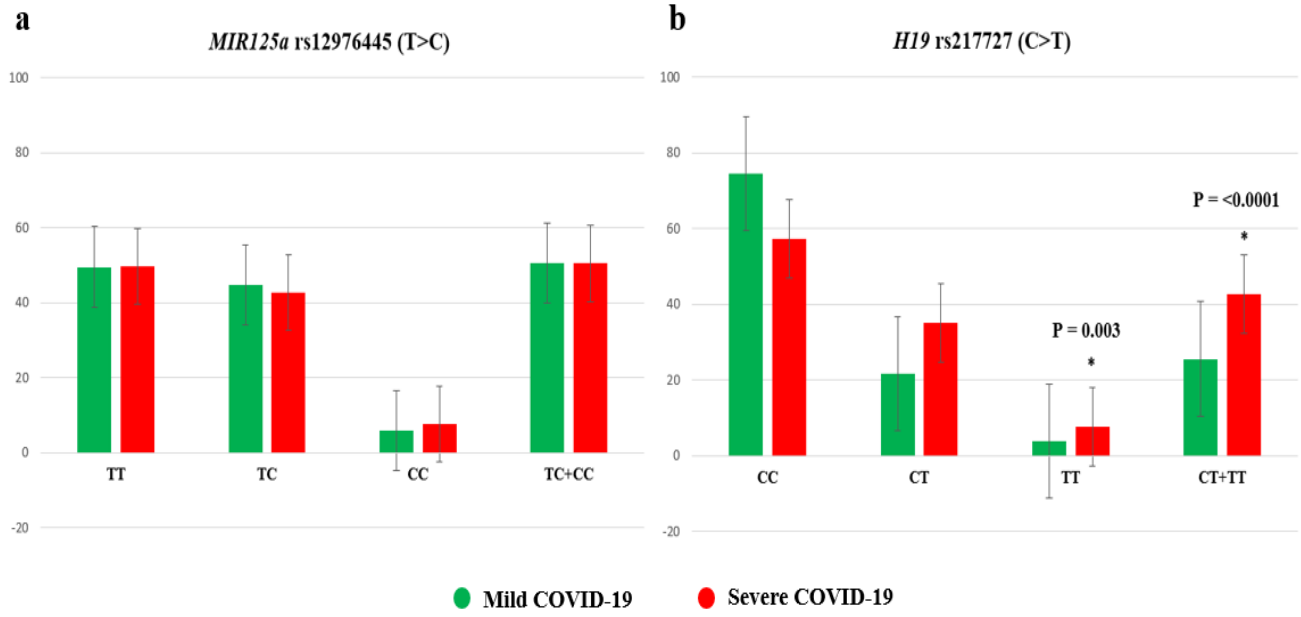

Figure1. Distribution of *MIR125a* rs12976445 and *H19* rs217727 genotypes in patients with mild and severe COVID-19.

3.3. Gene-gene interactions

The gene-gene interactions between *MIR125A* rs12976445 and *H19* rs217727 were assessed and a two-locus model was created using MDR algorithm. *MIR125A* rs12976445 * *H19* rs217727 interaction model was significant (p = 0.006, OR = 4.18; 95% CI [1.46–11.99]). Characteristics of the resulting model were as follows: accuracy - 65.7%; sensitivity - 51.85%; specificity: 79.55%; consistency 10/10. A graphical representation of the resulting model (Figure 2, a) showed that *MIR125A* TC * *H19* CC carriers were more likely to have mild symptoms of COVID-19. On the other hand, *MIR125A* TC * *H19* CT carriers have a higher risk of severe COVID-19.

Fruchterman-Reingold plot (Figure 2, b) showed synergy (0.97%) between *MIR125A* rs12976445 and *H19* rs217727. The independent effect of *H19* rs217727 on the risk of developing a severe form of COVID-19 infection is significantly higher than the effect of *MIR125A* rs12976445 (2.25% and 0.07%, respectively).

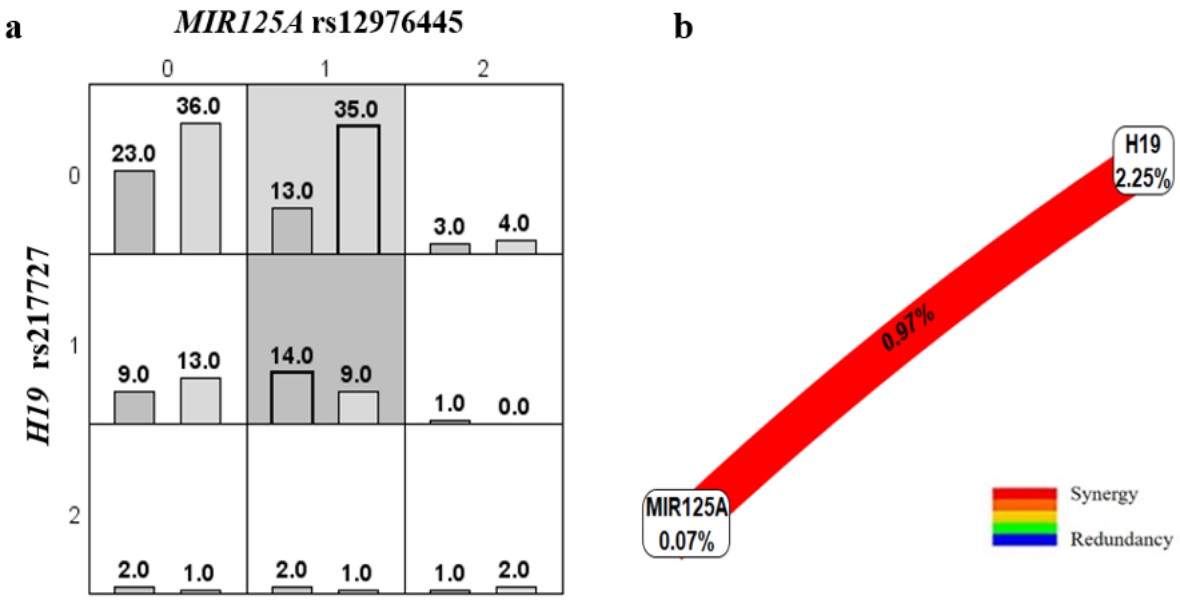

Figure 2. Multifactor dimensionality reduction (MDR) analysis of *MIR125A* and *H19* interactions in patients with mild and severe COVID-19. ***a*** Brief description of the two-factor model (*MIR125A* rs12976445 and *H19* rs217727). Dark and light backgrounds represent high-risk and low-risk combinations respectively. 0 – homozygous for wild-type allele, 1- heterozygous, and 2- homozygous for mutant allele. Right columns are for mild COVID-19 cases, whereas left columns are for severe cases. ***b*** Fruchterman-Reingold plot with the type of interaction between polymorphisms. Each polymorphism block (box) contains an entropy value (%), indicating its independent effect. The colors and values between the boxes indicate interaction effects. Positive values represent a synergistic effect, and negative values represent antagonism. The color of the line indicates the type of gene-gene interaction (For example: red line represents synergy, while blue line represents redundancy).

4 Discussion

Since the onset of COVID-19 pandemic, scientists around the world have been focused on understanding the pathogenesis of the disease and explaining the wide range of observed symptoms among patients. The studies included SARS-CoV-2 structure, its interaction with the host, and the molecular mechanisms underlying the COVID-19 outcome. Regardless of the significant progress and the huge amount of collected data, the differences between patients in the term of

symptoms' severity are yet to be fully understood. Several published studies have took into account the genetic variations and assessed its possible effect on the severity of disease (Eid et al., 2023). The candidate genes are not necessarily protein-coding, they could be also the genes of regulatory ncRNA, such as miRNA and lncRNA, based on the well-known roles, played by those ncRNAs in cellular biological processes.

The *MIR125A* gene is located on chromosome 19 (19q13.41). Decreased levels of hsa-miR-125a have been detected in several diseases, including breast (Iorio et al., 2005) and gastric cancer (Nishida et al., 2011). Furthermore, miR-125a has been suggested to be involved in the regulation of cell responses against oxidative stress in endothelial cells (Chen et al., 2018). In this study, the association of a single nucleotide change from T to C (*MIR125A* rs12976445) with COVID-19 severity was evaluated. *MIR125A* rs12976445 T allele impairs processing and expression of mature miR-125a, which leads to increased expression of target genes (Jiao et al., 2014). This SNP contributes to the susceptibility to multiple diseases, such as autoimmune thyroid diseases (Inoue et al., 2014), recurrent pregnancy loss (Hu et al., 2011), and esophageal squamous cell carcinoma (Wu et al., 2014). However, the results of this study showed no significant differences in genotypes' distribution between the studied groups (p=0.76).

LncRNA H19 is known as the first discovered lncRNA with its gene, located on chromosome 11 (11p15.5) (Lu et al., 2016). H19 contributes to the controlling of genome expression at different levels, and SNPs of its gene has been reported to be associated with the development of tumors (Guo et al., 2017). For example, it was shown that *H19* rs217727 is associated with the risk of breast cancer (23). It also may affect oral squamous cell carcinoma (OSCC) susceptibility (Ghapanchi et al., 2020). In this study, an association of *H19* rs217727 with COVID-19 severity was noticed. The differences between the studied groups were significant in both genotype (p=0.003), and allelic (p=0.001) frequencies. Carriers of *H19* rs217727 minor allele (T) were more likely to have a severe COVID-19 outcome (OR=1.84; 95% CI [1.27–2.66]). This could be explained by the fact that *H19* rs217727 may influence the susceptibility and/or severity of disease by altering miRNA–lncRNA interactions, leading to changes in the binding sites of several miRNAs on H19 (Deng et al., 2020).

The performed gene-gene interaction analysis using MDR algorithm showed that the resulted two-locus model was significant (p=0.006), and the independent contribution of the studied SNPs to the risk of a severe COVID-19 outcome was notably higher in of *H19* rs217727 (2.25%) than in *MIR125A* rs12976445 (0.07%). This confirms the results of association analysis, presented in Table 3.

5 Conclusion

In this study, a significant association of *H19* rs217727 with COVID-19 severity was noticed. To our knowledge, this is the first study to investigate the association of *MIR125A* rs12976445 and *H19* rs217727 and their SNP-SNP interaction with the severity of COVID-19. The obtained results may contribute to a better understanding of COVID-19 pathogenesis.

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Declaration of competing interest

The authors declare no conflict of interests.

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