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Ассоциация полиморфизма rs1800795 гена IL 6 с восприимчивостью и тяжестью COVID-19: метаанализ

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Коронавирусная инфекция 2019 года (COVID-19) является высококонтагиозным инфекционным заболеванием, вызвавшим глобальную пандемию. Различия в симптомах у пациентов с COVID-19 сделали важным поиск факторов, которые могут играть значительную роль в ее патогенезе. Целью настоящего исследования было изучение связи генетической вариации интерлейкина 6 (IL-6) rs1800795 как с восприимчивостью, так и с тяжестью заболевания COVID-19 путем проведения метаанализа имеющихся в литературе данных. Был проведен поиск по нескольким базам данных с использованием определенных ключевых слов, и в общей сложности в анализ были включены 12 полнотекстовых статей. Не было обнаружено никакой связи rs1800795 в гене *IL 6* с восприимчивостью к COVID-19. Однако была обнаружена значимая связь между изучаемым полиморфизмом и тяжестью COVID-19 при рецессивной модели наследования (OR =2,11, 95% CI [1,12; 3,98], p=0,02). Насколько нам известно, этот мета-анализ является первым, в котором изучается связь *IL6* rs1800795 как с восприимчивостью, так и с тяжестью заболевания.

Ключевые слова: IL-6, COVID-19, восприимчивость, тяжесть, ассоциация, метаанализ.

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Association of IL 6 rs1800795 genetic variation with the susceptibility and severity of COVID-19: A meta-analysis

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Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease, which caused a global pandemic. The differences of symptoms among COVID-19 patients made it important to search for the factors that may play a significant role in its pathogenesis. The aim of the current study was to investigate the association of interleukin 6 (IL-6) genetic variation rs1800795 with both susceptibility and severity of COVID-19, by performing a meta-analysis of the available data in the literature. Several databases were searched using specific keywords, and a total of 12 full-text articles were included in the analysis. No association was found with the COVID-19 susceptibility. However, a significant association was found between the studied polymorphism and the COVID-19 severity in the recessive model of inheritance (OR =2.11, 95% CI [1.12, 3.98], p=0.02). To our knowledge, this meta-analysis is the first to study the association of *IL6* rs1800795 with both susceptibility and severity of COVID-19, and its results reflect the current published data, and may serve as a guide for further research.

Keywords: IL-6, COVID-19, susceptibility, severity, association, meta-analysis.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world and led to the development of a pandemic. As of November 30th, 2023, there have been over 772 million confirmed cases and more than 6.9 million deaths worldwide according to the World Health Organization statistics (https://covid19.who.int, 30 Nov 2023). The pandemic has caused a severe blow to health care systems, economic progress and social cohesion around the world [1]. Patients with COVID-19 have shown a wide range of symptoms, from asymptomatic cases to severe infection with serious complications and even death [2].

COVID-19 is a systemic infectious disease, characterized by destabilization of the immune system, the release of a large number of pro-inflammatory cytokines, which is commonly referred to as a «cytokine storm» [3]. Cytokine storm – is a state of hyper activated immune response that disrupts normal physiological homeostasis and results in abnormal activation of various immune cells [4]. High levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1β, IL-10, IL-18, IL-4, IL-33, interferon (IFN)-γ, and tumor necrosis factor alpha (TNF-α) [5] are noticed in more severely ill patients and have been associated with inflammation and damage to the lungs, as well as multiple organ failure such as kidneys, heart, and lungs [6].

Interleukin-6, a protein encoded by the *IL6* gene, plays a role in the immune response in many diseases and is a cytokine with both pro- and anti-inflammatory properties [6]. IL-6 is released by macrophages and T cells and plays an important role in the induction of fever and in the response to acute inflammation, by stimulating the production of other cytokines and development of B cells [7]. Previous studies have shown that serum levels of IL-6 are elevated in patients with severe COVID-19, which correlates with adverse clinical outcomes, including intensive care unit (ICU) hospitalization, acute respiratory distress syndrome (ARDS), and death [5]. Throughout the pandemic, numerous attempts have been made to identify the causes of the severe course of COVID-19 infection and its adverse outcomes. One of the best achievements in this direction has been the identification of the important role of single nucleotide polymorphisms (SNPs) of several genes, involved in the mechanism of immune regulation. In fact, disease severity has been proved to be associated with various genes carrying specific SNPs [8]. Differences in cytokine production between individuals may be due to the presence of SNPs occurring in critical regulatory regions such as promoters, introns, 5'-UTR and 3'-UTR regulatory regions, which may influence the levels of cytokine expression, while genetic polymorphisms in the coding regions of a gene can result in the loss or alteration of the function of expressed proteins [5]. The aim of the current study was to perform a meta-analysis on the available studies in the literature to assess the association of *IL6* rs1800795 genetic variation with both COVID-19 susceptibility and severity.

Methods

Study strategies

Meta-analysis was carried out by following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Several databases (Pubmed, Science direct, Springer Link, Cyberleninka, and Google Scholar) were searched for studies by using the keywords («IL-6 or interleukin-6», «Polymorphism or genetic variation», «rs1800795 or G174C», «COVID-19», and «severity or susceptibility»). The search was in both English and Russian languages.

Inclusion and exclusion criteria

To include a study, it had to meet the following criteria: 1). Full-text published studies 2). Availability of data, needed to calculate Odds Ratio (OR) with confidence interval (CI) 3). The aim of the article is to study the association between *IL6* (rs1800795) polymorphism and COVID-19 susceptibility and/or severity.

Exclusion criteria: 1). review articles, meta-analyses, cohort studies, animal studies, duplications 2). irrelevant studies (other diseases or other polymorphisms) 3). studies without sufficient information, such as sample size, and genotype frequencies of cases and controls.

Data extraction

The following data were extracted from the eligible studies: 1). First author's surname; 2).Year of publication; 3). country of origin; 4s). ample size (case – control); 5). genotype distribution in cases and controls.

Statistical and sensitivity analysis

To perform the meta-analysis, Revman 5.4 software was used (Cochrane Collaboration, London, UK). The association between the *IL6* (rs1800795) polymorphism and the risk of COVID-19 infection was evaluated by OR with 95% CI in accordance with dominant, recessive, and allelic inheritance models. Significant difference was considered

when P value is less than 0.05. Heterogeneity between studies was evaluated by a χ2-based Cochran Q test and quantified with the I^2 statistic (heterogeneity was considered significant when $P<0.05$ or $I^2>50\%$). Fixed-effect model was used to calculate ORs and 95% CIs for lower heterogeneity values, while random-effect was used for higher values. Sensitivity analysis was performed to eliminate the possible impact of a single study on the overall risk by sequentially excluding one study at a time. Begg's funnel plots were used to investigate publication bias.

Results

Characteristics of Included Studies

198 articles were identified through database searching based on the selected keywords, of which 175 were excluded for the following reasons: 68 irrelevant articles, 27 duplicates, 37 reviews, 14 meta-analyses, and 29 cohort studies. The 23 remaining full-text articles were assessed for eligibility, of these, 11 articles were excluded for being without sufficient information. Hence, a total of 12 eligible articles were included in the meta-analysis. Some studies [6, 9, and 10] had studied the association of *IL6* rs1800795 genetic variation with both susceptibility, and severity of COVID-19. The flow chart of studies' identification, screening, and inclusion is presented in **Fig. 1**.

The included studies were carried out in Iraq [6, 11], Iran [5, 12], Italy [8,13], Turkey [14], Egypt [15], Russian Federation [9], India [16], Brazil [17], and Saudi Arabia [10]. 10 articles were included to assess the association between *IL6* rs1800795 and COVID-19 severity, with a total of 904 severe and 925 mild cases. While 5 articles were selected to study the association with COVID-19 susceptibility, including 531 patients and 352 healthy participants. The main characteristics of all studies of COVID-19 susceptibility and severity are shown in **Tables 1, 2** respectively.

Meta-analysis

The results of the meta-analysis, performed in dominant, recessive, and allelic models of inheritance, in addition to the results of heterogeneity test, were presented in **Table 3** for susceptibility and **Table 4** for severity.

According to the performed meta-analysis, there was no significant association of *IL6* rs1800795 with the susceptibility of COVID-19, as shown in **Fig. 2**. Furthermore, no association was found with the severity of COVID-19 in the dominant (**Fig. 3a**) nor the allelic (**Fig. 3c**) models of inheritance. However, there was a significant association between *IL6* rs1800795 and the COVID-19 severity in the recessive model (**Fig. 3b**) in both random-effect (OR=2.11, 95% CI [1.12, 3.98], p=0.02), and fixed-

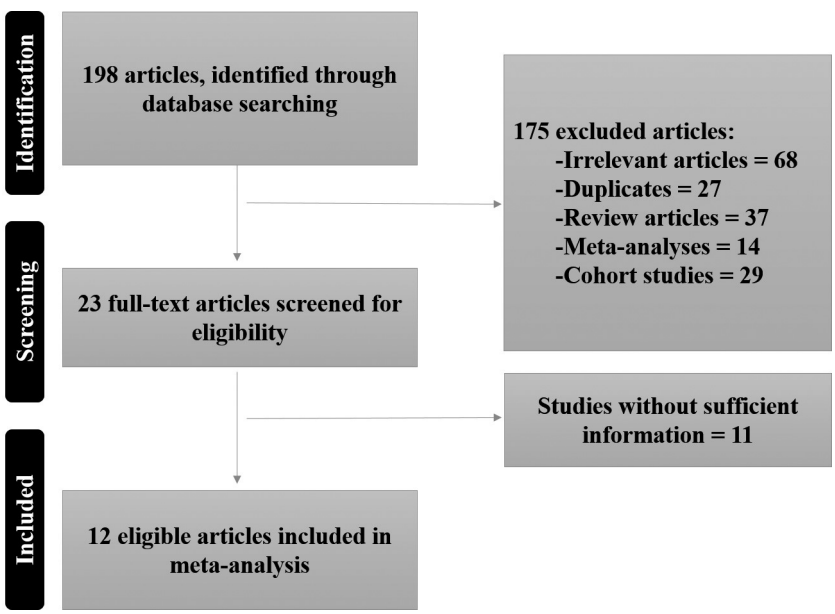


Рис. 1. Блок-схема отбора исследований PRISMA.

Fig. 1. PRISMA Flow chart of study selection.

Таблица 1. Характеристики исследований, включенных в метаанализ ассоциации SNP *IL6* rs1800795 с восприимчивостью к COVID-19.

Table 1. Characteristics of all studies included in the meta-analysis of *IL6* SNP rs1800795 association with COVID-19 susceptibility.

First author, year	Country	Cases	Control	Case			Control			HWE control (p value)
				GG	GC	CC	GG	GC	CC	
Aladawy, 2022	Egypt	50	20	38	11	1	16	4	0	0.6193
Balzanelli, 2022	Italy	41	43	29	11	1	14	23	6	0.4783
Belyaeva, 2022	Russia	60	89	18	28	14	21	45	23	0.9118
Dhabaan, 2022	Iraq	220	120	140	72	8	57	60	3	0.0054
Ghazy, 2023	Saudi Arabia	160	80	63	73	24	48	25	7	0.173

Таблица 2. Характеристики исследований, включенных в метаанализ ассоциации SNP *IL6* rs1800795 с тяжестью COVID-19

Table 2. Characteristics of all studies included in the meta-analysis of *IL6* SNP rs1800795 association with COVID-19 severity.

First author, year	Country	Severe cases	Mild cases	Severe			Mild			HWE control (p value)
				GG	GC	CC	GG	GC	CC	
Grifoni, 2020	Italy	33	103	20	10	3	69	33	1	0.168
Altamemi, 2021	Iraq	20	20	2	3	15	4	5	11	0.0544
Kerget, 2021	Turkey	40	30	18	22	0	3	27	0	0
Aladawy, 2022	Egypt	38	12	30	8	0	8	3	1	0.4017
Belyaeva, 2022	Russia	44	24	16	17	11	4	14	6	0.3917
Falahi, 2022	Iran	175	171	106	57	12	103	54	14	0.0802
Rahimlou, 2022	Iran	245	245	133	97	15	138	101	6	0.0114
Verma, 2022	India	97	145	66	31	0	120	25	0	0.256
Ghazy, 2023	Saudi Arabia	80	80	21	39	20	42	34	4	0.3824
Rodrigues, 2023	Brazil	132	95	71	51	10	56	35	4	0.6119

Таблица 3. Ассоциация между *IL6* rs1800795 и риском восприимчивости к COVID-19

Table 3. The association between *IL6* rs1800795 and COVID-19 susceptibility risk

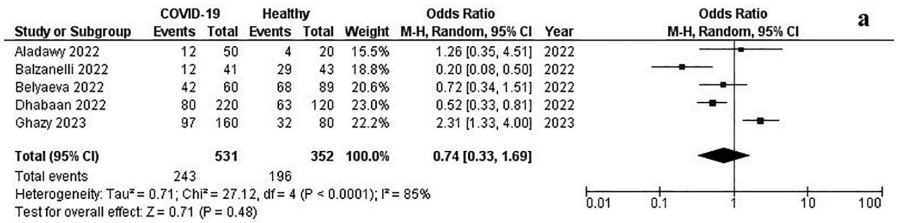
Genetic models	Number of studies	Test of association			Test of heterogeneity	
		OR	95% CI	*P*-value	*P*-value	I^2 (%)
Dominant (CC + CG vs. GG)	5	0.74	[0.33-1.69]	0.48	0.0001	85%
Recessive (CC vs. CG + GG)	4	1.06	[0.65-1.72]	0.82	0.17	40%
Allelic (C vs. G)	5	0.82	[0.45-1.51]	0.53	0.0001	84%

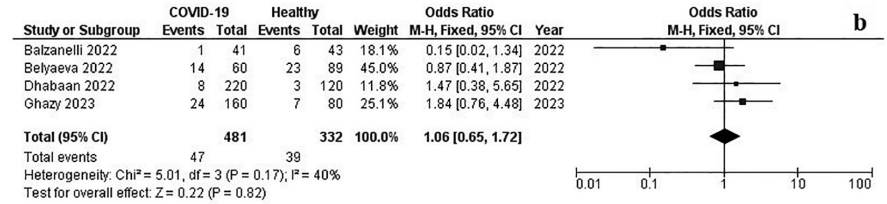
Таблица 4. Ассоциация между *IL6* rs1800795 и риском тяжелого течения COVID-19

Table 4. The association between *IL6* rs1800795 and COVID-19 severity risk

Genetic models	Number of studies	Test of association			Test of heterogeneity	
		OR	95% CI	*P*-value	*P*-value	I^2 (%)
Dominant (CC + CG vs. GG)	10	1.12	[0.74-1.68]	0.60	0.0007	69%
Recessive (CC vs. CG + GG)	7	2.11	[1.12-3.98]	**0.02***	0.05	52%
Allelic (C vs. G)	10	1.18	[0.86-1.62]	0.30	0.0004	70%

*p<0.05





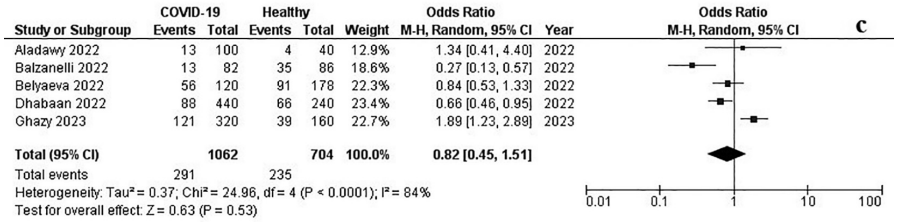
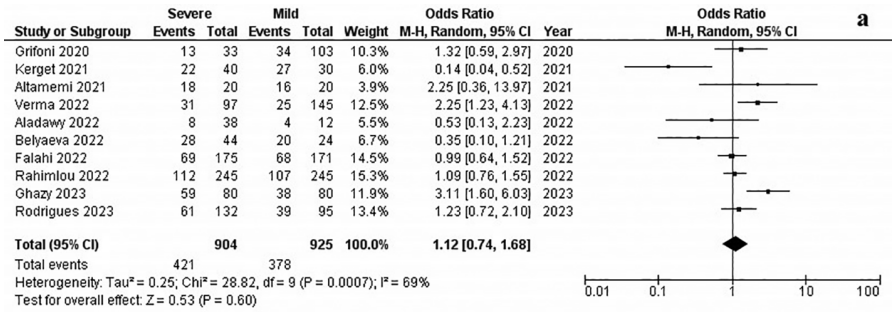
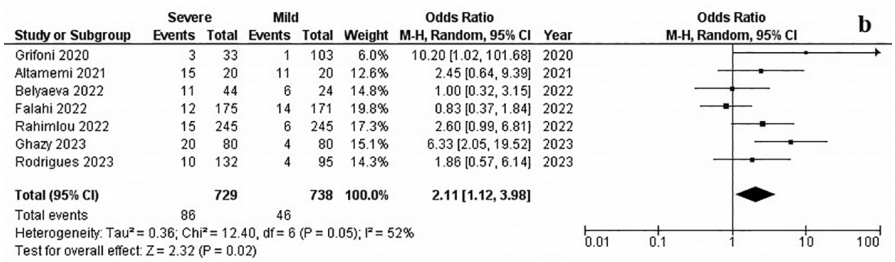


Рис. 2. Лесовидный график связи между *IL6* (rs1800795) и риском восприимчивости к COVID-19 в различных моделях: а) доминантная б) рецессивная в) аллельная.

Fig. 2. Forest plot of the association between *IL6* genetic variation (rs1800795) and COVID-19 susceptibility risk in different models: a) Dominant b) Recessive c) Allelic.





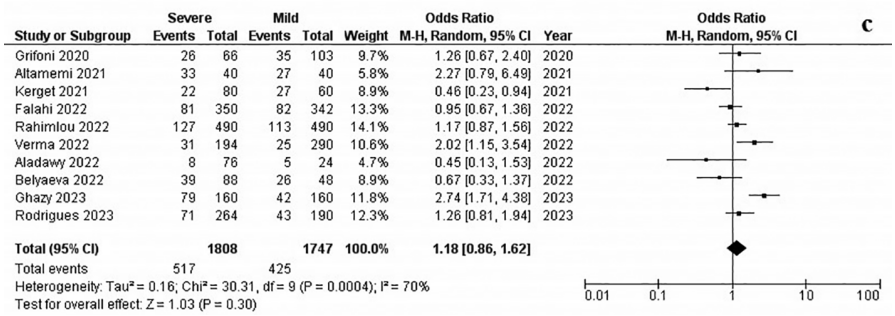


Рис. 3. Лесовидный график связи между *IL6* (rs1800795) и риском тяжелого течения COVID-19 в различных моделях: а) доминантная б) рецессивная в) аллельная.

Fig. 3. Forest plot of the association between *IL6* genetic variation (rs1800795) and COVID-19 severity risk in different models: a) Dominant b) Recessive c) Allelic.

effect (OR=1.98, 95% CI [1.32, 2.96], p=0.0009). The funnel plots of all the studied models showed no evidence of publication bias (**Fig. 4, Fig. 5**). The stability of the meta-analysis was confirmed by conducting sensitivity analysis, which showed that the pooled ORs was not altered qualitatively by the exclusion of any individual study.

Discussion

Numerous studies have already evaluated the association of angiotensin-converting enzymes (*ACE1*, *ACE2*), transmembrane serine protease 2 (*TMPRSS2)*, interferon induced transmembrane protein 3 (*IFITM3)* polymorphisms with an increased COVID-19 susceptibility. In addition, there was a significant association between the *ACE2* rs2285666, *ACE2* rs2106809, *TNFα* rs1800629, and *TMPRSS2* rs12329760 polymorphisms and the severity of COVID-19 [18-21]. There are also growing reports of the influence of genetic variants, related to the immune system genes, on the susceptibility and severity of COVID-19, including the 174G/C polymorphism in the *IL6* gene [22].

The *IL6* gene is located on chromosome 7 at 7p21, with 5 exons and 5 kb long. Numerous SNPs have been found in both the coding sequence and the promoter of *IL-6* gene [23, 24]. One of the most studied SNPs of the *IL6* gene is rs1800795 (174G/C) [25]. This polymorphism consists of a single nucleotide substitution of glycine (G) to cytosine (C) in the promoter region at position -174 and is associated with elevated serum levels of IL-6 protein [26].

Previous studies have shown that the *IL6* promoter variant rs1800795 affects IL-6 transcription and secretion, and these changes are considered important risk factors for the occurrence and intensity of human inflammatory, autoimmune, and infectious diseases [24, 27]. For example, a previous study showed a significant association of the *IL6*-174G > C (rs1800795) with an increased risk of

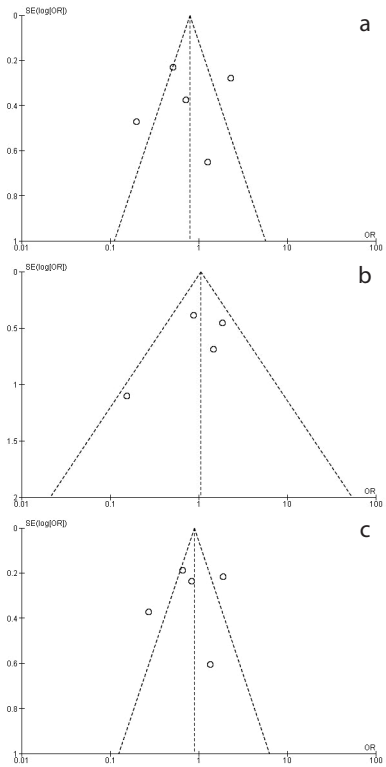


Рис. 4. Воронкообразный график связи между *IL6* (rs1800795) и риском восприимчивости к COVID-19 в различных моделях: а) доминантная б) рецессивная в) аллельная**.**

Fig. 4. Funnel plot of the association between *IL6* genetic variation (rs1800795) and COVID-19 susceptibility risk in different models: a) Dominant b) Recessive c) Allelic.

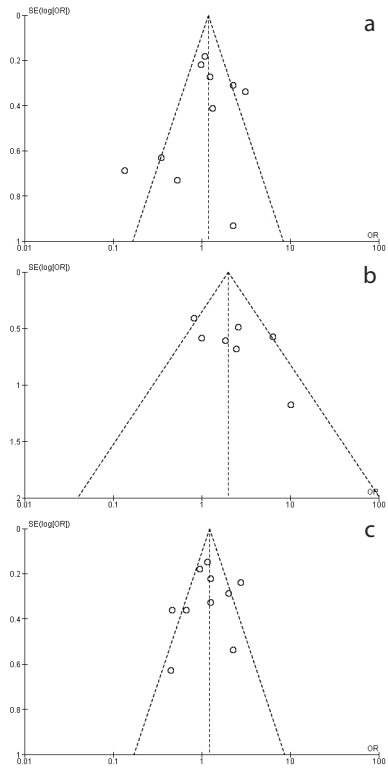


Рис. 5. Воронкообразный график связи между *IL6* (rs1800795) и риском тяжелого течения COVID-19 в различных моделях: а) доминантная б) рецессивная в) аллельная.

Fig. 5. Funnel plot of the association between *IL6* genetic variation (rs1800795) and COVID-19 severity risk in different models: a) Dominant b) Recessive c) Allelic.

rheumatoid arthritis [28]. Furthermore, *IL6* rs1800795-C allele was associated with septic shock and severe systemic inflammatory response in patients with community-acquired pneumonia (CAP) [29]. A high risk of death from septic shock in patients undergoing extensive cardiac or abdominal surgery was associated with *IL6* rs1800795 CC genotype [30]. In addition, numerous studies showed that the C allele of the *IL6* rs1800795 is associated with an increased risk of cardiovascular diseases and type 1 diabetes mellitus [27, 31-33], which are known to be among the comorbidities that strongly correlate with increased COVID-19 severity [34].

In our study, a meta-analysis was performed on *IL6* rs1800795 genotyping data, collected from 12 published articles. The results showed a significant association of the studied genetic variation with COVID-19 severity in the recessive model, with no association in dominant or allelic models. This suggests that only people with homozygote CC genotype are more likely to have a severe course of COVID-19. The obtained result is consistent with the findings of a previous study that has linked the increased levels of IL-6 with the severity of COVID-19 [35]. However, there was no significant association between *IL6* rs1800795 and the susceptibility of COVID-19 in any of the three inheritance models.

Limitations should be mentioned. First, the number of included studies was relatively small, which may reflect available published data, but is still not conclusive evidence for the results. Second, our results were based on unadjusted estimates. Therefore, for a more accurate analysis, additional individual data, including other variables such as age, lifestyle and environmental factors, should be taken into account, if this information was available. To our knowledge, this is the first meta-analysis to investigate the association of *IL6* rs1800795 with the susceptibility and severity of COVID-19. Further research will be conducted in our laboratory to assess this association in Rostov region patients' groups.

Conclusion

Our meta-analysis suggests that the CC genotype of *IL6* rs1800795 genetic variation might be a risk factor for a severe COVID-19 infection. However, this need to be confirmed by more case–control studies with larger sample size.

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