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A Comprehensive Investigation of the Association between IL-6 rs1800795 (-147G/C) and Severity of COVID-19: A meta-analysis of Case-control Studies

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ABSTRACT

Background: To evaluate the relationship between COVID-19 and IL-6 polymorphism, a meta- analysis was conducted on seven studies, comprising 2265 controls and 1686 cases.

Materials & Methods: The literature on IL-6 polymorphism and its correlation with COVID-19 severity was extensively reviewed, covering research up to August 2023. Various databases including Google Scholar, PubMed, and Embase were utilized for literature search. Data analysis was performed using Cochrane Rob Tool 2 and Review Manager 5 software.

Findings: In this meta-analysis, none of the models showed a correlation between IL-6 polymorphism and COVID-19, including the allelic (G vs C, OR: 1.01, 95% CI: 0.63–1.64, p= .22, I^2=91%), homozygote (GG vs. CC, OR: 1.08, 95% CI: 0.41–2.83, p= .87, I^2=79%),heterozygote (GC vs. CC, OR: 0.78, 95% CI: 0.34–1.78, p= .55, I^2=73%), dominant (GG + GC vs CC, OR: 0.79, 95% CI: 0.32–1.95, p= .61, I^2=81%), and recessive (OR: 1.26, 95% CI:0.51–3.10, p= .61, I^2=81%) models. Notably, funnel plot analysis revealed no indication of publication bias.

Conclusion: The findings of this meta-analysis indicated no significant correlation between IL-6 polymorphism and COVID-19 severity, suggesting insufficient data to establish a link between IL-6 (rs1800795) and more severe COVID-19 cases.

Keywords: Interleukin-6, Severity, COVID-19, Gene polymorphism

CITATION LINKS

[1] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus... [2] Hussain M, et al. Acute respiratory distress ... [3] Gong B, et al. A genetic variant in ... [4] Costela-Ruiz VJ,SARS-CoV-2 infection: The role of cytokines in ... [5] Vatansever HS, Becer E. Relationship between IL-6... [6] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome... [7] Silva MJ, Ribeiro LR, Lima KV, Lima LN. Adaptive immunity to... [8] Haukim N, et al. Cytokine gene polymorphism in human disease... [9] Rehman K, et al. Role of interleukin-6 in development of insulin... [10] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity... [11] Rashid P, Salih GF. Genetic polymorphism between... [12] Villar-Fincheira P, et al. Role of interleukin-6 in vascular... [13] Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and... [14] Mauer J, Denson JL, Brüning JC. Versatile functions for... [15] Barrett D. IL-6 blockade in cytokine storm syndromes. In... [16] Bardhan K, Anagnostou T, Boussiotis VA. The PD1: PD-L1/2 pathway... [17] Channappanavar R, Perlman S. Pathogenic human... [18] Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of... [19] Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum... [20] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation... [21] Falahi S, et al. Evaluation of the relationship... [22] Rashid PM, Salih GF. Genetic polymorphism of... [23] Yektay S, et al. Association between the interleukin–6... [24] Altamemi IA, Khlebos AH. IL-6 predict disease severity... [25] Ghazy AA. Influence of IL-6 rs1800795 and IL-8... [26] Khafaei M, Asghari R, Zafari F, Sadeghi M. Impact of IL-6... [27] Rodrigues FB, et al. Association of polymorphisms...

Introduction

The SARS-CoV-2 virus, initially detected in Wuhan, China in late 2019, has emerged as the main driver of the ongoing COVID-19 pandemic, posing a serious global public health challenge [1]. While many individuals infected with COVID-19 exhibit no or only mild to moderate symptoms, more than 20% of cases could progress to acute lung injury (ALI), causing damage to the alveoli. Pneumonia and ARDS (acute respiratory distress syndrome) are potential complications, and death could occur in most severe cases [2]. Typical symptoms of COVID-19 encompass fever, sputum production, difficulty breathing, fatigue, dry cough, headache, sore throat, muscle pain, coughing up blood, and diarrhea [3]. COVID-19 infection is linked to excessive release of pro-inflammatory cytokines, including interleukins IL-6, IL-18, IL-10, IFN-γ, and TNFα [4]. Among these cytokines, IL-6 is crucially involved in diverse functions, including metabolic regulation, inflammation, autoimmunity, and acute-phase responses [5].

Lung fibroblasts, immune cells, and cells of non-immune origin provide a critical inflammatory signaling molecule known as IL-6 [6]. Elevated levels of IL-6 notably suppress the expression of human leukocyte D antigen (HLA-DR), leading to a marked reduction in lymphocyte function. This impact is accompanied by a decrease in CD19+ lymphocytes, natural killer (NK) cells, and CD4+ lymphocytes [7]. The human chromosome 7p21 region contains the IL-6 gene. Elements in the 5-prime region primarily control its transcription. There are several polymorphisms in the first 1.2 kb of the IL-6 promoter. An individual's cytokine output may be affected by this factor. However, genetic variations in the gene-coding areas result in loss or changes in the expressed proteins' function [8]. According to epidemiological studies, genetic polymorphisms at rs1800795, rs1800797, and rs1800796, located in the IL-6 gene promoter, are associated with the severity and susceptibility to various diseases, including diabetes mellitus and rheumatoid arthritis [9, 10]. The effect of rs1800795 (-147 G/C) single nucleotide polymorphism (SNP) on IL-6 gene expression levels has been the subject of much research. This SNP is considered as a potential candidate that could impact the severity of COVID-19 [11]. This study specifically focused on the IL-6 gene rs1800795 polymorphism due to extensive research on its association with COVID-19 severity. This variant has consistently shown associations with COVID-19 across various populations, making it a suitable gene for the present meta-analysis. The decision to study a single polymorphism was intentional, as the goal of this study was to provide a comprehensive analysis of the existing literature on this specific variant and its relationship with COVID-19. Focusing on a single polymorphism allows for a more in- depth investigation of its effects, potential interactions, and implications for COVID-19 severity.

Objectives: To explore the current knowledge regarding genetic factors impacting the progression and severity of COVID-19, published case-control studies on COVID-19 were collected following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta- Analyses) guidelines. Accordingly, a meta-analysis was performed for all genetic variants using specific genetic models.

Materials and Methods

Literature search strategy: A thorough literature search was conducted in PubMed, Google Scholar, and Embase databases to identify studies investigating the association between genetic variations and COVID-19 severity. To find relevant articles published up to July 2023, a variety of search terms, including "COVID-19," "polymorphism," "SARS- CoV-2", and "single nucleotide poly-

morphism (SNP)" along with terms like "case- control association", were employed in different combinations. As the study progressed, new reports beyond the initial search timeframe were identified. To ensure comprehensive coverage, the search period was extended until August 2023. This allowed us to incorporate the latest findings and previously overlooked studies into our analysis, enriching our dataset with the most up-to-date information.

In addition, the validity of the literature search was strengthened by carefully reviewing the references listed in all pertinent studies, including reviews, meta-analyses, and

original research articles. Relevant publications were identified, saved locally, and retrieved from the databases. After that, the required data were taken out, combined, and put in an analysis worksheet.

Ethical considerations: Because this study was based on published case-control studies, ethical approval was not necessary. Patient consent forms were not required since the current study was a meta-analysis.

Study identification and selection: A reviewer (PK) independently and iteratively screened abstracts and titles as part of the primary literature review. After a detailed review of the identified records, the same reviewer conducted a second review, and the findings were cross-checked and compared. After discussing the disagreements regarding the selection of studies and the review process, the reviewers reached a consensus, and the studies were finally chosen.

The following criteria were taken into consideration when determining whether a study could be included in this meta-analysis:

1. Subjects: Studies that exclusively involved human participants
2. Population: Studies on subjects whose positive SARS-CoV-2 infection test results were validated by RT-PCR
3. Article type: Research articles employing a case-control study design
4. Genetic data: Studies in which genotype information was analyzed in case and control groups
5. Language: Studies published only in English. The excluded studies met the following criteria:

1. Research with contradictory results
2. Studies lacking sufficient data
3. Animal research involving family cohorts or sibling pairs
4. Comments, reviews, and case reports

Data extraction: Data collection from each eligible study encompassed various statistics, including author and ethnicity information, details on alleles and genotypes, year of publication, IL-6 polymorphism frequency distribution, and SNP-related participant characteristics, such as total sample size, age, race, and gender.

Quality assessment: Hardy-Weinberg equilibrium (HWE) probability value (*p*-value) was also calculated. Methodological biases in included studies were evaluated using NOS (Newcastle-Ottawa scale). A thorough assessment of methodology and possible biases in studied included in meta-analyses is crucial, with risk of bias assessment playing a pivotal role. Robvis visualization tool software was employed in this investigation to assess bias risk. Studies were categorized based on their risk level, including high risk, uncertain risk with some concerns, or low risk, indicating the degree of risk associated with each study.

Statistical analysis: Data analysis was performed through various statistical techniques, the study sought to determine whether the severity of COVID-19 and the IL-6 gene polymorphism are correlated. This involved the calculation of OR (odds ratio) and 95% CI (confidence interval), with a significance level set at $p < .05$. The inconsisten-

cy index (I^2) was utilized to assess the consistency across the results of included studies, where lower scores indicated complex consistency. Different models (fixed-effect or random-effect) were used based on heterogeneity levels, which were determined by the Q statistics via Chi-square test. Odds ratios were computed using Z test, with the combined OR representing the pooled effect estimate. Significance was determined using Egger's test and I^2 statistics, considering findings as significant if Egger's test yielded $p< .05$. Assessment of publication bias with potential bias was indicated by Egger's test if $p< .05$. Statistical analyses were performed using Review Manager software Version 5.4.

Findings

Search results: A comprehensive literature search in PubMed, Google Scholar, and Embase yielded 509 relevant records for this study, of which 191 studies were reviewed. Specifically, seven articles focusing on a variant of IL-6 gene polymorphism (rs1800795) were included. These seven articles collectively involved 1686 COVID-19 cases and 2265 healthy controls, forming the basis for the meta-analysis (Figure 1). Table 1 presents the primary genotype distribution and characteristics of the included studies.

Risk bias: The Cochrane Rob Tool 2 was utilized to thoroughly assess the methodological quality of the chosen studies as depicted in Figure 2. In this representation, each study is described in a row, and each column corresponds to a specific type of bias. The color assigned to each survey indicates the reviewer's evaluation of the bias risk associated with that particular type of analysis. Studies with a low bias risk are represented in green, while those with a high risk of bias are shown in red. Yellow indicates unclear risk of bias. Overall, the findings suggest a significantly low bias risk for the selected

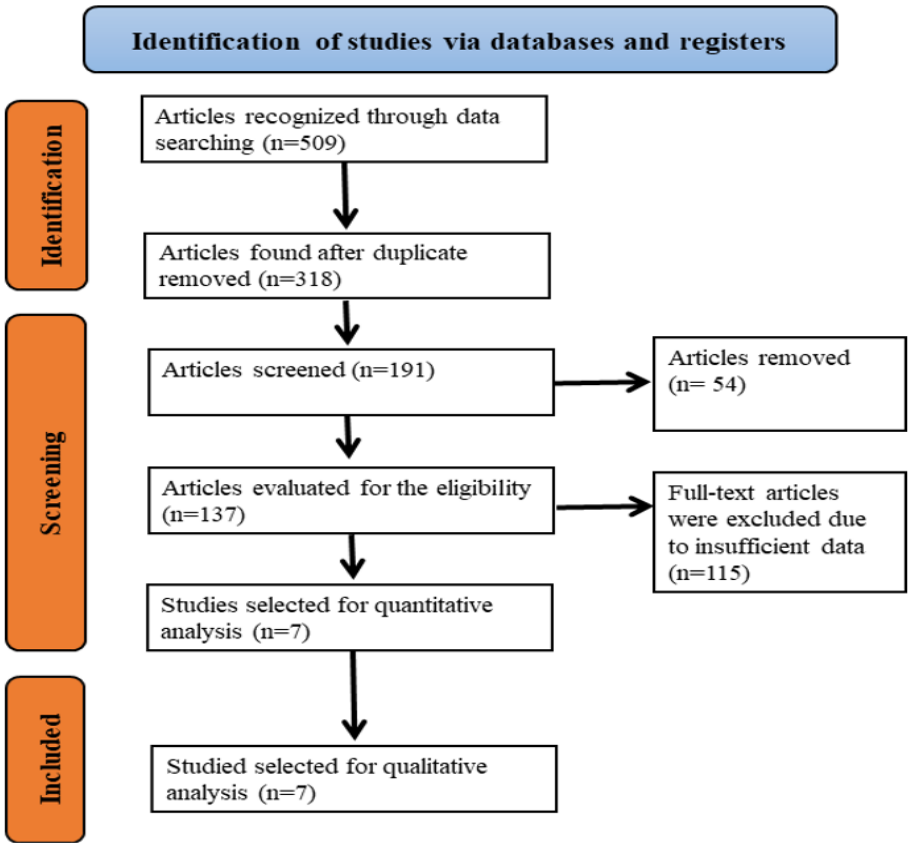

Figure 1) Flow chart of screening literature investigating IL6- (rs1800795) gene polymorphism

Table 1) Characteristics of the reviewed studies on the association of IL6- (rs1800795) gene polymorphism with COVID19-

Author &Year	Genotypic Frequency						Allele Frequency				Sample Size		Ethnicity	HWE
	Case			Control			Case		Control					
	GG	GC	CC	GG	GC	CC	G	C	G	C	Case	Control		
Altameni & Khlebos (2021)	3	2	15	3	7	5	8	32	13	17	227	300	Asian	0.037
Falahi et al. (2022)	106	57	12	103	54	14	269	81	260	82	100	100	Asian	3.059
Rodrigues et al. (2023)	66	31	0	120	25	0	163	31	265	25	48	48	Caucasian	1.29
Khafaei et al. (2024)	127	86	14	207	85	8	340	114	499	101	80	80	Asian	0.042
Ghazy (2023)	78	49	13	51	67	22	205	75	169	111	140	140	Asian	3.978
Rashid & Salih (2023)	20	39	21	7	25	48	79	81	39	121	175	171	Asia	1.857
Yektay et al. (2023)	17	29	3	24	24	1	63	35	72	26	15	20	Asian	3.221

Figure 2) Risk of Bias summary and graph for investigating IL-6 (rs1800795) gene polymorphism

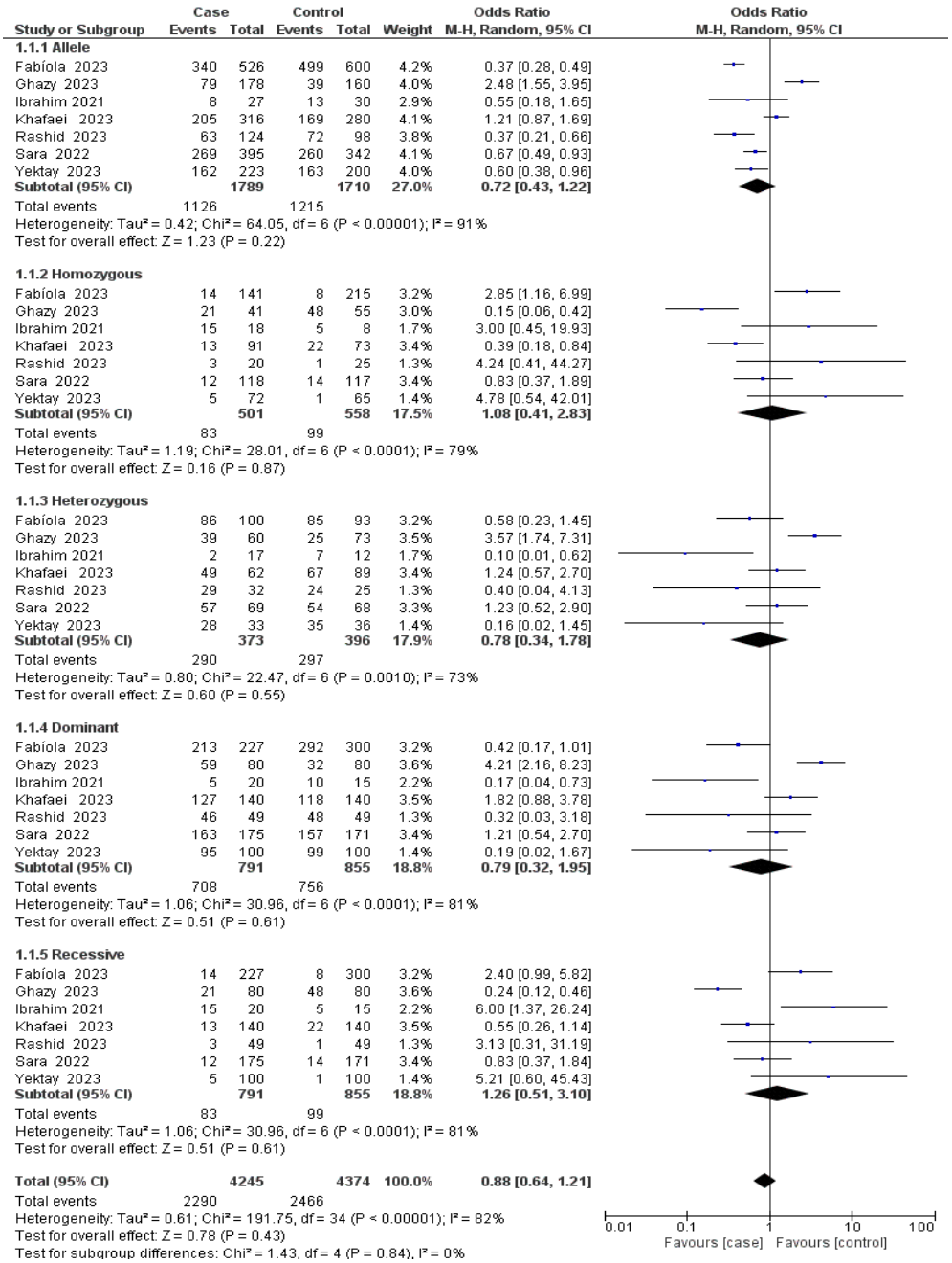

Figure 3) Forest plot showing no association between IL6- (rs1800795) gene polymorphism and COVID19-severity in genetic models

studies, indicating that the research was conducted, executed, and documented to substantially minimize or eliminate potential bias or error.

Data analysis of IL-6 and COVID-19: In the current meta-analysis, the genetic variants of IL-6, specifically rs1800795, were selected for examination based on the analyzed genotypes. Their association with COVID-19 was explored using multiple comparison models while considering Hardy-Weinberg equilibrium (HWE). Significant heterogeneity was noted among the studies (I^2 > 50%, p > .05). Based on the random- effects model, the analysis revealed no significant relationship between COVID-19 severity and IL-6 in any of the genetic models, including the homozygote (GG vs. CC , OR: 1.08, 95% CI: 0.41–2.83, p= .87, I^2=79%), allelic (G vs C, OR: 1.01, 95% CI: 0.63–1.64, p=.22, I^2=

Table 2) Subgroup analysis of IL6- (rs1800795) gene polymorphism with COVID19-

Model	Ethnicity	Test of Association			Test of Heterogeneity			I^2	Publication bias P (Egger's test)
		Number of Studies	OR	95 % CI	P	Model	P		
Allele contrast (G vs. c)	Overall	7	1.0138	0.6277-1.6376	.955215	Random	0	0.8745	.8786
	Amazanion (Caucasian)	1	0.6037	0.4467-0.8158	.001022	Fixed	NA	NA	NA
	Iran (Asia)	3	1.1167	0.6592 1.8916	.681529	Random	.0095	0.7854	.504
	Iraq (Asia)	2	0.6243	0.2199-1.7727	.376271	Random	.0696	0.6963	NA
	Saudi Arabia (Asia)	1	3.0260	1.8805-4.8692	5.07E-06	Fixed	NA	NA	NA
Recessive model (GG vs. GC+CC)	Overall	7	1.1119	0.6713-1.8419	.680289	Random	.0001	0.7938	.5578
	Amazanion (Caucasian)	1	0.5706	0.3987-0.8166	.002158	Fixed	NA	NA	NA
	Iran (Asia)	3	1.1319	0.5554-2.3067	.732986	Random	.0065	0.8014	.645
	Iraq (Asia)	2	1.0890	0.6259-1.8950	.762781	Fixed	.6115	0	NA
	Saudi Arabia (Asia)	1	3.4762	1.3770-8.7754	.008362	Fixed	NA	NA	NA
Dominant model (GG+GC vs.CC)	Overall	7	0.793	0.3234 1.9443	.612188	Random	0	0.8059	.0639
	Amazanion (Caucasian)	1	0.4168	0.1718 1.0114	.053008	Fixed	NA	NA	NA
	Iran (Asia)	3	1.3957	0.8253-2.3604	.213667	Fixed	.331	0.0955	.266
	Iraq (Asia)	2	0.1743	0.0515-0.5899	.00498	Fixed	.916	0	NA
	Saudi Arabia (Asia)	1	4.2143	2.1578-8.2309	2.53E-05	Fixed	NA	NA	NA
Overdominant (GC vs. GG + CC)	Overall	7	1.0131	0.6610-1.5527	.952526	Random	.0013	0.7255	.3812
	Amazanion (Caucasian)	1	1.5428	1.0684-2.2277	.020719	Fixed	NA	NA	NA
	Iran (Asia)	3	0.9187	0.5519-1.5293	.744463	Random	.0797	0.6048	.6258
	Iraq (Asia)	2	0.3736	0.0715-1.9511	.243031	Random	.0695	0.6965	NA
	Saudi Arabia (Asia)	1	2.0927	1.0982-3.9876	.02478	Fixed	NA	NA	NA

OR: Odds ratio; CI: Confidence interval

91%), heterozygote (GC vs. CC, OR: 0.78, 95% CI: 0.34–1.78, p= .55, I^2=73%), dominant (GG + GC vs CC, OR: 0.79, 95% CI: 0.32–1.95, p= .61, I^2=81%), and recessive (OR: 1.26, 95% CI: 0.51–3.10, p = .61, I^2=81%) models. The results presented in Figure 3 suggest no association between IL-6 rs1800795 polymorphisms and COVID-19 severity. The results of subgroup analysis revealed that individuals of Asian and Caucasian descent were more susceptible to developing severe COVID-19 symptoms. This finding further supports the notion that the severity of COVID-19 may vary significantly across different ethnic and racial groups (Table 2).

An examination of publication bias and sensitivity: To evaluate potential publication bias, the study looked at the distribution of plots showing the IL-6 gene polymorphisms (rs1800795) among COVID-19 cases and controls. This analysis, which employed the funnel plot and Egger's test, showed no evidence of statistical bias in the research (p= .43) (Figure 4). Additionally, sensitivity

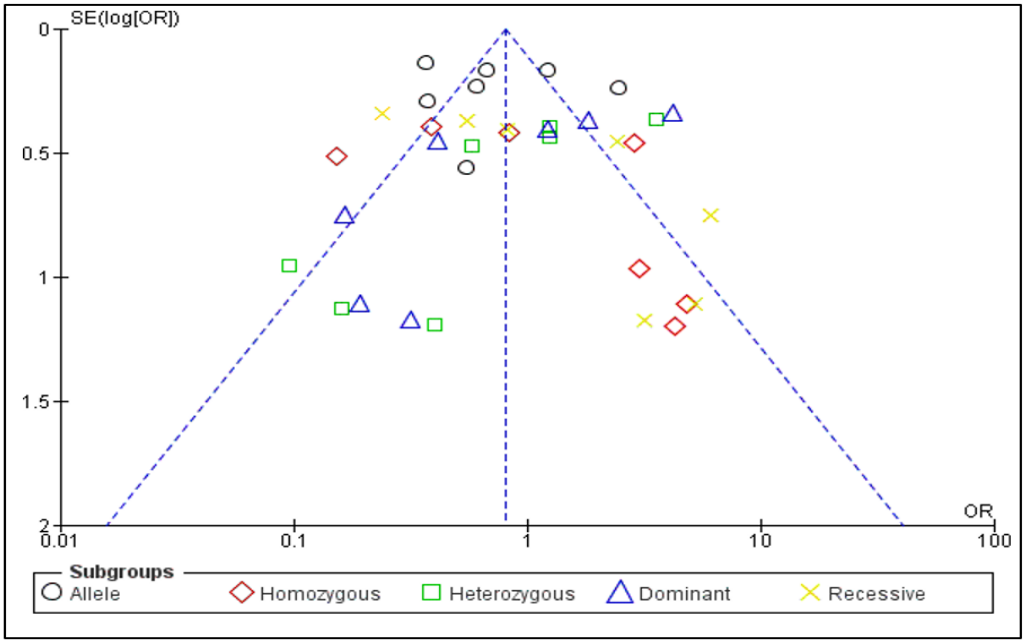

Figure 4) Distribution of the investigated IL6- rs1800795 among COVID19- cases and controls

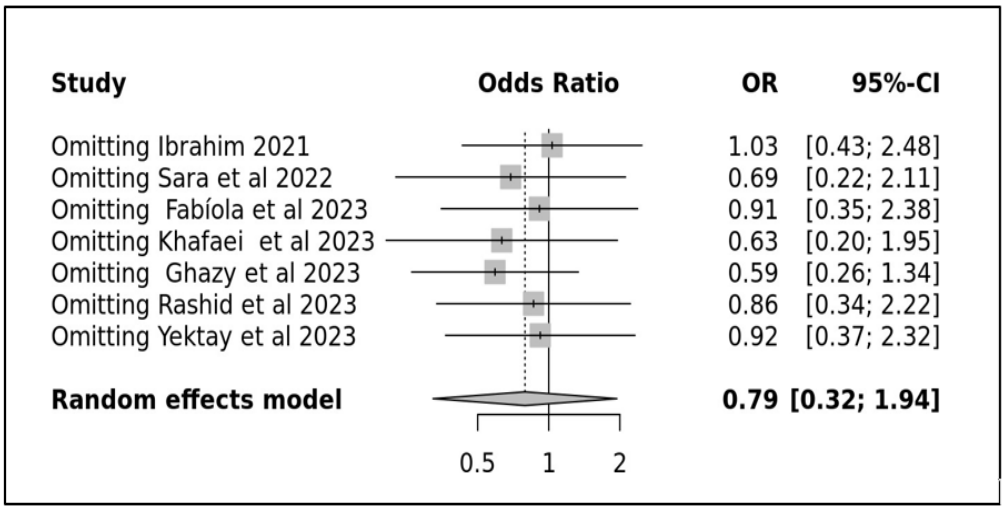

Figure 5) Sensitivity analysis of rs 1800795 gene polymorphism among COVID19- cases and controls

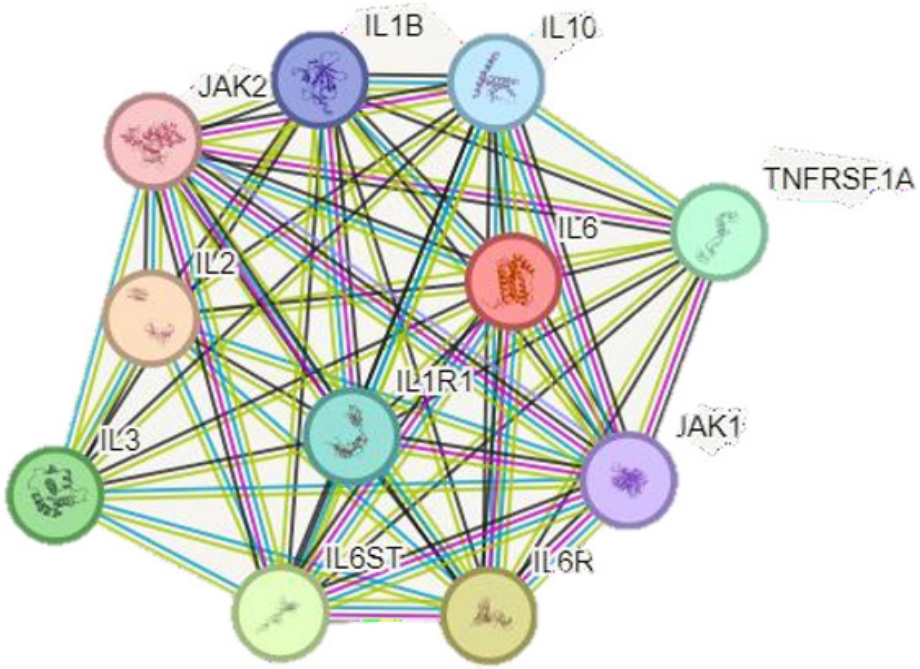

Figure 6) Protein-protein interaction associated with COVID19- and IL6- gene polymorphisms

analysis was performed for IL-6 genetic variants (rs1800795), and the results consistently remained unchanged (Figure 5). This suggests that the present study findings are statistically robust.

Discussion

The pleiotropic cytokine IL-6 regulates anti-inflammatory and inflammatory responses, acting as a double-edged sword. The particular signaling pathway that is mainly activated determines how it works [12]. Leukocyte migration, proliferation, and survival are just a few biological processes that depend on this cytokine [13]. Various cell types, such as fibroblasts, monocytes, keratinocytes, mast cells, macrophages, T and B lymphocytes, and vascular endothelial cells, synthesize and release IL-6 in response to tissue injury or infection [14]. These cytokines, jointly with other pro-inflammatory cytokines like IL-8 and TNF-α, could set off cytokine storms that disrupt immune response regulation and cause tissue damage [15]. IL-6 also has other unfavorable effects, such as impeding effective immune responses against cancer and viral infections. Inhibitory molecules like PD-1 and PDL-1 are upregulated during this process [16]. It has been observed that cytokine storms and lymphopenia are two prominent immunopathological features in the context of viral infections like SARS-CoV-2 [17]. Furthermore, it has been observed that individuals with severe COVID-19 infection tend to have higher levels of IL-6. These elevated IL-6 levels are positively correlated with lung tissue damage and progression of infection [18–20].

Several studies have been conducted on the connection between SNPs in the IL-6 gene's promoter region and the risk of different inflammatory diseases. Data indicate that IL-6 polymorphism and COVID-19 severity are correlated.

Several studies with various ethnic backgrounds have been conducted to assess the connection between COVID-19 and IL-6. Studies by Falahi et al. (2022), Rashid and Salih (2023), and Yektay et al. (2023) have shown no correlation between COVID-19

and IL-6 polymorphism in Iranian and Kurdish populations [21-23]. Conversely, several studies have indicated a potential correlation between IL-6 polymorphism and the severity of COVID-19 in populations from Saudi Arabia, Iraq, Iran, and the Amazon region [24-27]. After a thorough literature search, a total of 191 studies were initially found. Of these, 184 studies were eliminated because they did not fit the inclusion criteria. To definitively determine whether the severity of COVID-19 is associated with IL-6, a meta-analysis was conducted on seven studies that met the research criteria. IL-6 and COVID-19 were not associated in any of the genetic models obtained. The meta-analysis findings are inconsistent with the findings of some previous case-control studies [24–27]. The underlying pathophysiology of different inflammatory diseases and the ethnic and racial diversity within the study populations account for the variation in the results reported in this meta-analysis.

Conclusion

In conclusion, this meta-analysis confirms that the presence of rs1800795 in the IL-6 gene is not associated with an increased likelihood of experiencing severe COVID-19. Additionally, this study found no correlation between rs1800795 and COVID-19 severity across multiple models. The severity of COVID-19 appears to be linked to various genes located at different locus regions, each serving a distinct purpose. Therefore, conducting repeated, large-scale, multicenter studies worldwide is crucial to validate the association between COVID-19 and other genetic variants.

Justification for the study: The SARS-CoV-2 virus is the causative agent of the COVID- 19 pandemic, which is a serious global health emergency with severe cases that may lead to ARDS and death. COVID-19 is believed to be influenced by genetic factors; distinct gene polymorphisms have been linked to the illness in various studies. The levels of IL-6 have been reported to be higher in those with severe COVID-19.

The possibility of an association between the IL-6 gene variant rs1800795 and the likelihood of developing severe COVID-19 has been extensively studied. Although the results of individual studies may differ, meta-analyses indicate no association between these SNPs and COVID-19.

Limitations of the study: The presence of variations in the IL-6 gene is not associated with increased susceptibility to COVID-19. It is critical to remember that a multifaceted interplay of environmental, genetic, and lifestyle factors leads to the development of the disease, and that the IL-6 gene is not the only determinant. Moreover, the exact processes by which variations in the IL-6 gene affect susceptibility to COVID-19 are not completely comprehended, and the practical importance of these genetic data in risk assessment and customized therapeutic approaches is continuously developing. It's also important to remember that not everyone may have access to or be able to undergo genetic testing for IL-6 variants. In light of the practical implications for clinical practice, the IL-6 gene's role should be evaluated in the larger framework of multifactorial disease causation, even though it provides insightful information about the genetic foundation of COVID-19.

Abbreviations

IL: Interleukin
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses NOS: Newcastle-Ottawa scale
HWE: Hardy-Weinberg equilibrium OR: Odds ratio
CI: Confidence interval
PDL-1: Programmed cell death ligand 1 PD-1: Programmed cell death protein 1

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