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ASSOCIATION OF IFNL4, IL10, IL-6 GENE POLYMORPHISM AND COVID VIRAL DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Aishwarya T [1], Sabarinath Ravichandar[2], Waheeda S[3], Dapkupar Wankhar[4], Gowtham Kumar Subbaraj[5]

[1]Dept of Anatomy, Karpaga Vinayaga institute of Medical Sciences and Research Centre, GST Road, Maduranthakam-603308, Tamil Nadu, India.
[2]Department of Respiratory Medicine, SRM Medical College Hospital and Research Center, Kattankulathur- 603203, Chennai, Tamilnadu, India.
[3]Department of Physiology, Vinayaka Missions Kirupananda Variyar Medical College and Hospital, Vinayaka Mission Research Foundation (Deemed to be University), Salem, Tamil Nadu, 636308, India
[4] Faculty of Paramedical Sciences, Assam down town University, Guwahati, Assam, 781026, India.
[5]Saveetha Institute of Basic Medical Sciences (SIBMS), Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Thandalam, Chennai - 602105, Tamil Nadu, India.
*Corresponding Author: Dr.S.Gowtham Kumar, Orcid ID: 0000-0002-0531-424X Email: gowthamkumars.sibms@saveetha.com

ABSTRACT:
The SARS-CoV-2 virus caused the respiratory illness known as coronavirus disease 2019 (COVID-19) in 2019 (Lai et al., 2020).The global outbreak of COVID-19, starting in Wuhan, China, affected countries worldwide. The condition might cause mild sickness or even death in certain people (Mohan & Nambiar, 2020; Manzoor et al,2026).Blood clotting abnormalities, linked to elevated D-dimer and fibrinogen, play a significant role in COVID-19 severity (Eljilany & Elzouki, 2020).Despite over 275 million confirmed cases worldwide, the actual number of infections is estimated to be much higher. Many individuals may have contracted COVID-19 without symptoms or hospitalization. It is possible that many genes and genetic variations enhance the risk of severe COVID-19 (Choudhary et al., 2021; Moneshwaran et al,2024).

INTRODUCTION

Tung hoang (2021) described that the individuals discharged after recovering from COVID-19, a subsequent positive COVID-19 test was observed in an estimated 15% (95% CI, 12%-19%) during the follow-up period. Notably, this re-positivity rate differed between China and Korea. In cases of recurrence, roughly 39% of patients had at least one underlying health issue. COPD is the fourth leading cause of mortality worldwide, posing a big threat to public health. This is a progressive disease characterized by persistent airflow limitation, as a consequence of chronic inflammation and structural changes in mediators and enzymes. COPD patients suffer from progressive reduction of lung function, loss of exercise capacity, frequent disease exacerbations, and advancement of non-pulmonary complications including infections, cardiovascular illness, and osteoporosis. Interferons are essential signalling molecules that play a crucial role in the immune response (Walter, 2020). They are classified into three groups such as: type I, II, III. Type I interferons, including the IFNL family, are primarily involved in antiviral responses (Hoagland et al., 2021).These four genes, IFNL1, IFNL2, IFNL3, and IFNL4 form a close-knit family (Woods et al., 2024). The JAK-STAT signalling pathway is activated when the proteins encoded by these genes engage with a shared co-receptor complex. This activation triggers a cascade of events that ultimately lead to the expression of genes involved in immune responses, such as antiviral and anti-inflammatory pathways (Zhou et al., 2020). IFNL4 has been implicated in several diseases, particularly viral infections. One notable association is with hepatitis C virus (HCV) clearance (Sung & Shin, 2020). Interleukin-10 (IL-10) is a crucial anti-inflammatory molecule that regulates immune responses (Islam et al., 2021). While it helps prevent inflammation and autoimmune disorders, an IL-10 deficiency can lead to increased susceptibility to infections (Martinez-Espinosa et al., 2021). The rs1800896 gene polymorphism in the IL10 gene is associated with higher IL-10 levels and a greater risk of severe pneumonia (Alagarasu et al., 2021). IL-10 can also suppress immune responses, potentially compromising the body's ability to fight infections (Jamilloux et al., 2020). The balance between IL-10 anti-inflammatory and immune-suppressive effects plays a critical role in overall health (Carlini et al., 2023).The IL-6 gene is located on chromosome 7 and contains several single-nucleotide polymorphisms (SNPs). IL-6 binds to its receptor, triggering a cascade of pro-inflammatory responses that can culminate in a cytokine storm (Akhtar et al., 2022). Interleukin-6 (IL-6), a prominent inflammatory cytokine, serves as a crucial biomarker for identifying patients at risk of
severe COVID-19 (Ulhaq & Soraya, 2020). Pro-inflammatory cytokines and IL6 are released when SARS-CoV-2 infects pathogenic T cells. This cytokine stimulates the production of more IL-6, TNF-α and other inflammatory molecules (Kany et al., 2019). Previous research has shown that tocilizumab, an IL-6 receptor antagonist, can reduce the likelihood of severe COVID-19 outcomes (Zhang et al., 2020). Improving the accuracy of findings may be achieved by boosting statistical power and refining estimates of genetic effects using meta-analysis, which combines the results of numerous COVID-19 GWAS investigations (Tan & Timpson, 2022; Biju and Patel,2025).

The diverse clinical manifestations of COVID-19, spanning from asymptomatic infection to severe and fatal illness, are influenced by various elements, including age, comorbidities, and environmental factors. A significant role is also attributed to the host's genetic characteristics. It is hypothesized that particular gene polymorphisms can alter immune responses and inflammatory pathways, consequently affecting an individual's likelihood of infection, the course of the disease, and the resulting clinical picture. Comprehending the relationship between genetic variants and COVID-19 severity is crucial for identifying individuals at higher risk and designing precise therapeutic interventions. Therefore, we examined the association of genetic variations in IFNL4 (rs12979860), and IL10 (rs1800896) with COVID-19, as well as the association of IL6 (rs1800795) gene polymorphism with COVID-19 and COPD in both Asian and Caucasian populations.

2. METHODS

2.1. Search strategy

We conducted database searches using PubMed, Elsevier, ScienceDirect, and Embase to identify case-control studies published before July 1, 2026. Our search terms included "Gene polymorphism, IFNL4 (rs12979860), IL10 (rs1800896), IL 6 (rs1800795), COVID-19.

2.2. Inclusion criteria

This present study eligibility requirements were: 1) perspective, articles as original, retrospective, cohort; 2) published articles pertaining to the impact of the rs12979860, rs1800896, and rs1800795 polymorphisms on COVID-19 vulnerability and COPD; 3) publications discussing the role of the rs12979860, rs1800896, and rs1800795 polymorphisms in the progression of COVID-19 infections from mild to severe; 4) gene polymorphism studies on human; 5) full-text available articles were considered.

2.3. Exclusion criteria

To ensure the analysis focused on high-quality, original research, this present investigation the following categories (a) abstracts, editorial letters, meta-analyses, systematic reviews, and research papers not written in English were excluded. This restriction aimed to limit the analysis to peer-reviewed articles in a language accessible to the research team, thereby enhancing the quality and comprehensibility of the data sources. (b) To maintain the rigor of the genetic association study, research conducted on animal models, case reports, and cell lines was excluded. Furthermore, case reports often lack the statistical power and control necessary for robust genetic analysis. Studies with insufficient genotypic data were also excluded, as inadequate genotypic evidence can compromise the quality and reliability of genetic association studies. (c) The relevance and integrity of the study, studies unrelated to COVID-19 or the selected gene, as well as those with missing genotype frequency data, were excluded. Including irrelevant studies can introduce noise and confounding factors into the analysis. Moreover, missing genotype data can compromise the completeness and accuracy of the genetic association analysis.

2.4. Data collection

Each study title, abstract, and entire text separately to determine its quality was examined. Standardized criteria were used for the assessment. The meta-analysis considered the following informations: the year of publication, initial author, nation of origin, and, the distribution of three unique genetic variations: rs12979860, rs1800896, and rs1800795 in COVID -19.

2.5. Statistical analysis

This study evaluated the association between IFNL4 (rs12979860), IL10 (rs1800896), and IL6 (rs1800795) gene polymorphisms and severe COVID-19 susceptibility using various statistical methods. Odds ratios (ORs) and 95% CIs were calculated to evaluate the strength of the connection between variables. The p-value threshold of 0.05 was used to evaluate statistical significance. A low index of inconsistency (I^2) implies strong consistency and a high I^2 suggests variability; this was used to assess the consistency of the findings across investigations. A fixed-effect model was used to evaluate the data since the studies indicated minimal heterogeneity (less than 50%). A random effect model was used when the heterogeneity was more than 50%. For the purpose of quantifying this variance, chi-square tests (Q statistics) were used. A p-value less than 0.05 was used to determine a statistically significant threshold for the calculation of odds ratios. Furthermore, the consistency of results across research was evaluated using the I^2 statistic; a lower number indicates better consistency. Using a sensitivity analysis, we looked at how research that may not have followed the Hardy-Weinberg Equilibrium might have affected the results. Using Egger's regression test and funnel plots, we investigated publication bias, which happens when research with non-significant findings is less likely to be published. To make the statistical analysis easier, MetaGenyo softwere (https://metagenyo.genyo.es/) was used.

2.6. Quality of study using risk bias

A thorough evaluation of the potential for bias in the included studies was carried out to guarantee the accuracy and credibility of the meta-analysis. To check for possible biases, every research was run using the Cochrane Risk of Bias Tool 2 (ROB2) program. Research was classified as either "high risk," "low risk," or "some concern" based on the potential for bias. By categorizing the studies, we can gain a better understanding of how bias may have influenced the overall meta-analysis.

2.7. Power analysis

The statistical power of the gathered metadata was evaluated by a power analysis with a 95% confidence interval (alpha error of 0.05). The power for each gene was calculated by combining the sample sizes of the case and control groups in each research. These power calculations were conducted using the G*Power 3.1 program.

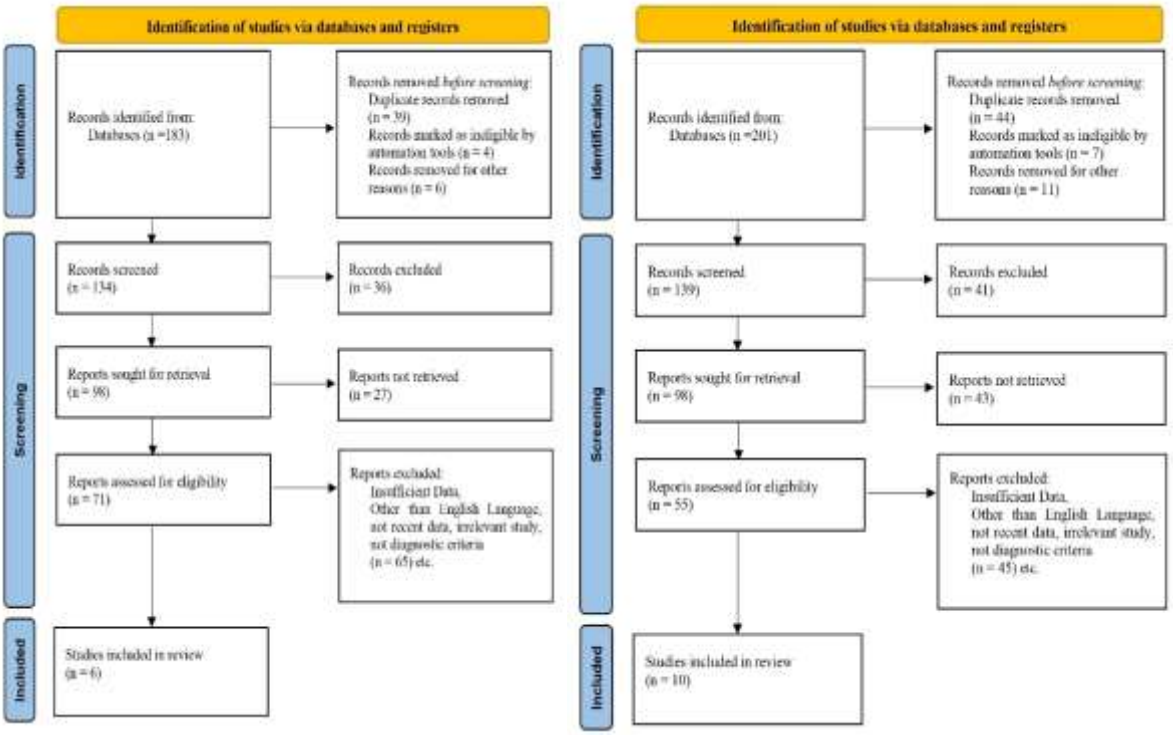
2.8. Protein-protein interactions

Protein-protein interaction (PPI) scores in the STRING database range from 0 to 1, with higher scores indicating a greater likelihood of an interaction between two proteins. A score of 0.4 generally signifies a moderate to strong level of confidence in the predicted interaction. The selection of a suitable threshold for PPI scores involves a balance between sensitivity and specificity. Higher thresholds increase specificity (reducing the number of false positive interactions) but may also miss genuine interactions. Lower thresholds enhance sensitivity (identifying more potential interactions) but increase the risk of including false positive interactions. The threshold of 0.4 is frequently used in research as it provides a reasonable balance between these two factors.

3. RESULTS

3.1. Characteristics of included studies

At first, 454 articles were collected from our literature search. Figure 1,2,3,4 shows the results of the statistical analysis for the 25 papers that were included after a comprehensive evaluation of the titles, abstracts, and full texts.



Other papers were not included for four main reasons: 1) they did not concentrate on rs12979860, rs1800896, and rs1800795 genetic variants 2) they did not have the same study aims 3) they did not have enough data or 4) they were the inappropriate article type. To investigate the rs12979860, rs1800795, and rs12979860 gene polymorphisms in COVID-19 patients and healthy controls, we meticulously reviewed twenty-one articles. In contrast, for the IL6 (rs1800795) gene polymorphism in COPD patients and healthy controls, we reviewed six articles.

3.2. Quality assessment

The included studies were evaluated using a three-category measurement that focused on selection, comparison, and exposure. There were twelve high-quality studies and seven moderate-quality studies which were looked at both Asian and Caucasian populations. Analysing the information from 4,662 healthy people and 3,994 COVID-19 patients (Table 1, 2 and 3).

Study	CC Cases	CT Cases	TT Cases	CC Control	CT Control	TT Control	HW P.value	HW-adjusted. P.value
Elgedawy et al., 2024	39	27	8	54	62	34	0.0524	0.1572
Matic et al., 2023	19	18	2	61	63	15	0.8323	0.8445
Matic et al., 2023_1	27	28	5	40	40	11	0.8375	0.8445
Saponi-Cortes	67	92	18	247	161	37	0.145	0.29

et al., 2021								
Agwa et al., 2021	63	59	19	44	44	12	0.8445	0.8445
Amodio et al., 2020	158	182	41	31	31	29	0.0024	0.0144

Table 1: The distribution of the *IFNL 4 rs12979860* allele and genotype among COVID 19 cases and control in Caucasian population, Hardy–Weinberg equilibrium score.

Study	GG Cases	GC Cases	CC Cases	GG Control	GC Control	CC Control	HW P.value	HW-adjusted. P.value
Khafaei et al., 2024	78	49	13	51	67	22	0.9995	0.9995
Noureddine et al., 2024	103	23	6	101	35	2	0.5961	0.7451
Verma et al., 2023	66	31	0	120	25	0	0.256	0.4267
Ghazy., 2023	20	39	21	7	25	48	0.173	0.364
Falahi et al., 2022	106	57	12	103	54	14	0.0802	0.2673
Rodrigues et al., 2023	127	86	14	207	85	8	0.8364	0.9293
Sezer et al., 2024	47	50	12	26	10	3	0.182	0.364
Braga et al., 2024	41	30	5	38	34	2	0.0795	0.2673
El-Bendary et al., 2024	11	12	10	156	34	8	0.0018	0.018
Cekin et al., 2025	47	79	42	50	28	6	0.4565	0.6521

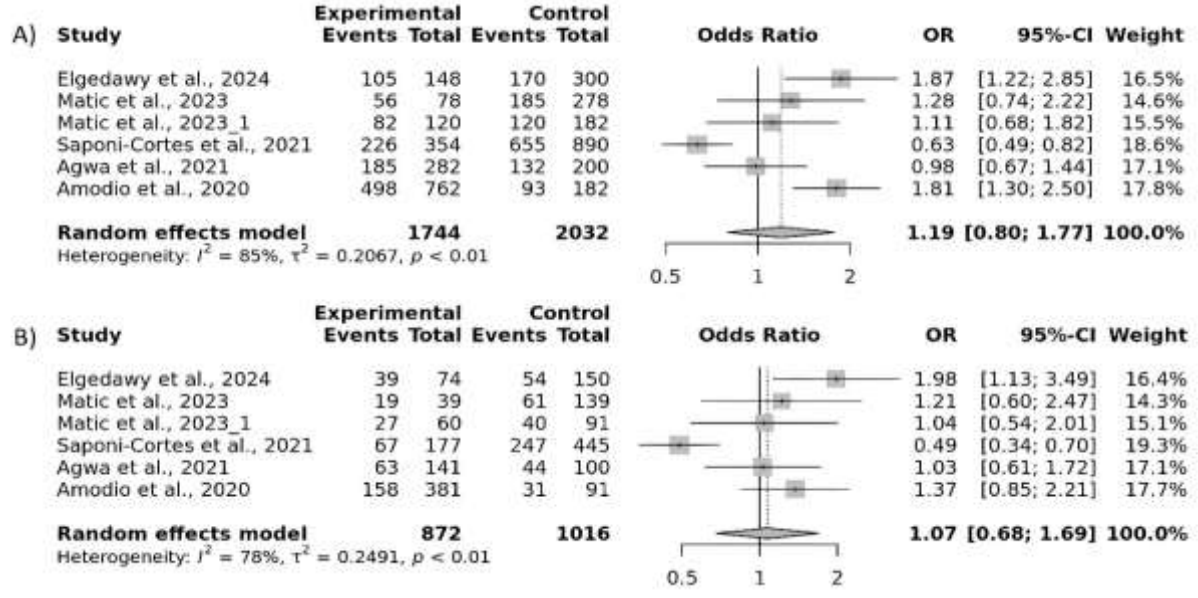
Table 2: The distribution of the *IL-6* rs1800795 allele and genotype among COVID 19 cases and control in Caucasian Population, Hardy–Weinberg equilibrium score.

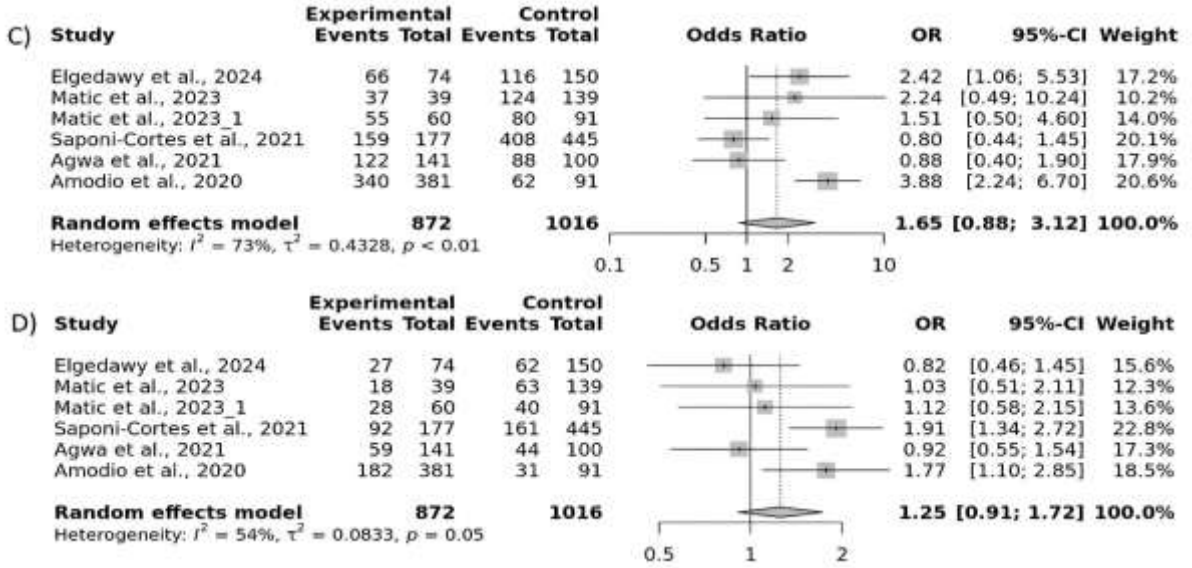
Study	AA Cases	AG Cases	GG Cases	AA Control	AG Control	GG Control	HW P.value	HW-adjusted. P.value
Eldesouki et al., 2024#	68	16	24	37	62	11	0.0419	0.0698
Abbood et al., 2023#	531	693	226	912	706	116	0.1866	0.1866
Rizvi et al., 2022@	49	23	3	45	38	2	0.063	0.0788
El-Bendary et al., 2024#	10	14	9	142	40	16	0	0
Azadinejad et al., 2024#	61	76	6	66	79	5	0.0013	0.0032

Table 3: The distribution of the *IL-10* rs1800896 allele and genotype among COVID 19 cases and controls, Hardy–Weinberg equilibrium score.

3.3. The IFNL4 (rs12979860) polymorphism and susceptibility to SARS-CoV-2 infection

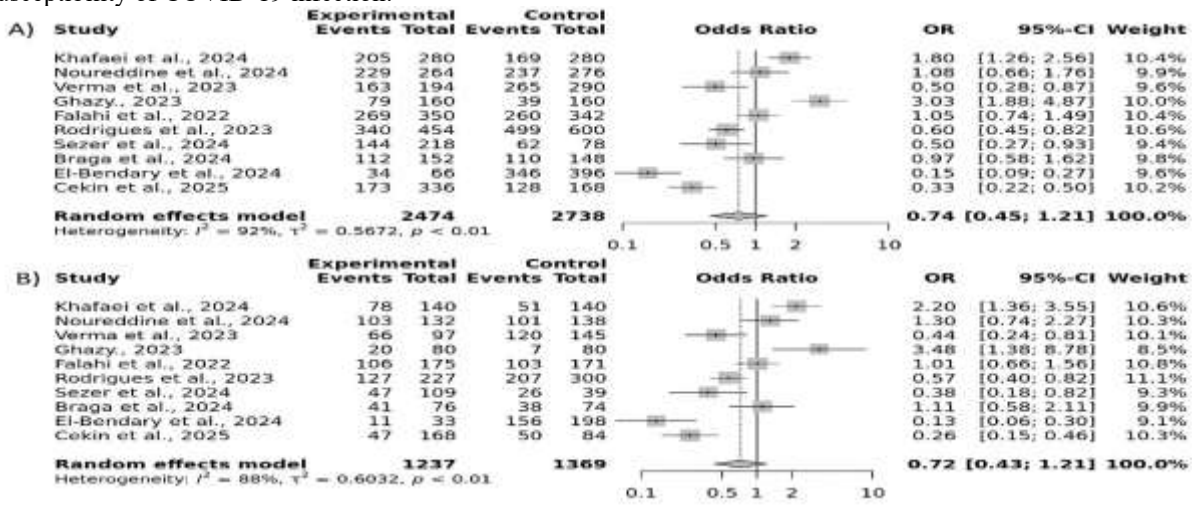
Relationship between IFNL4 (rs12979860) polymorphism and COVID-19 susceptibility in Caucasian analysis was assessed by OR and 95% CI under p-value < 0.1 for allelic (G vs. T), p-value < 0.1 for over dominant (GT vs. GG + TT), p-value = 0.5 for recessive (GG vs. GT + TT), and p-value < 0.1 for dominant (GG + GT vs. TT) genotype models. All genotypes of IFNL4 were statistically significant with COVID-19 infection risk (fig. 5 A-D).



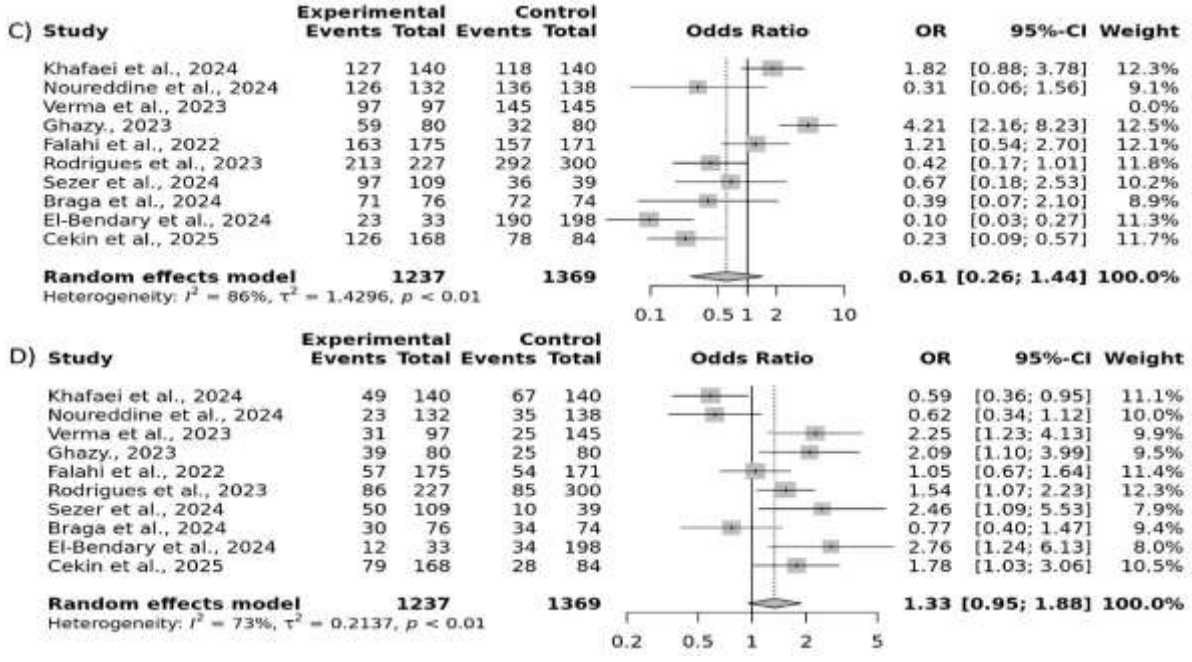


3.4. The IL-6 (rs1800795) polymorphism and susceptibility to SARS-CoV-2 infection

In both Asian and Caucasian populations, we assessed the correlation between the IL-6 (rs1800795) polymorphism with the susceptibility of COVID-19 infection.

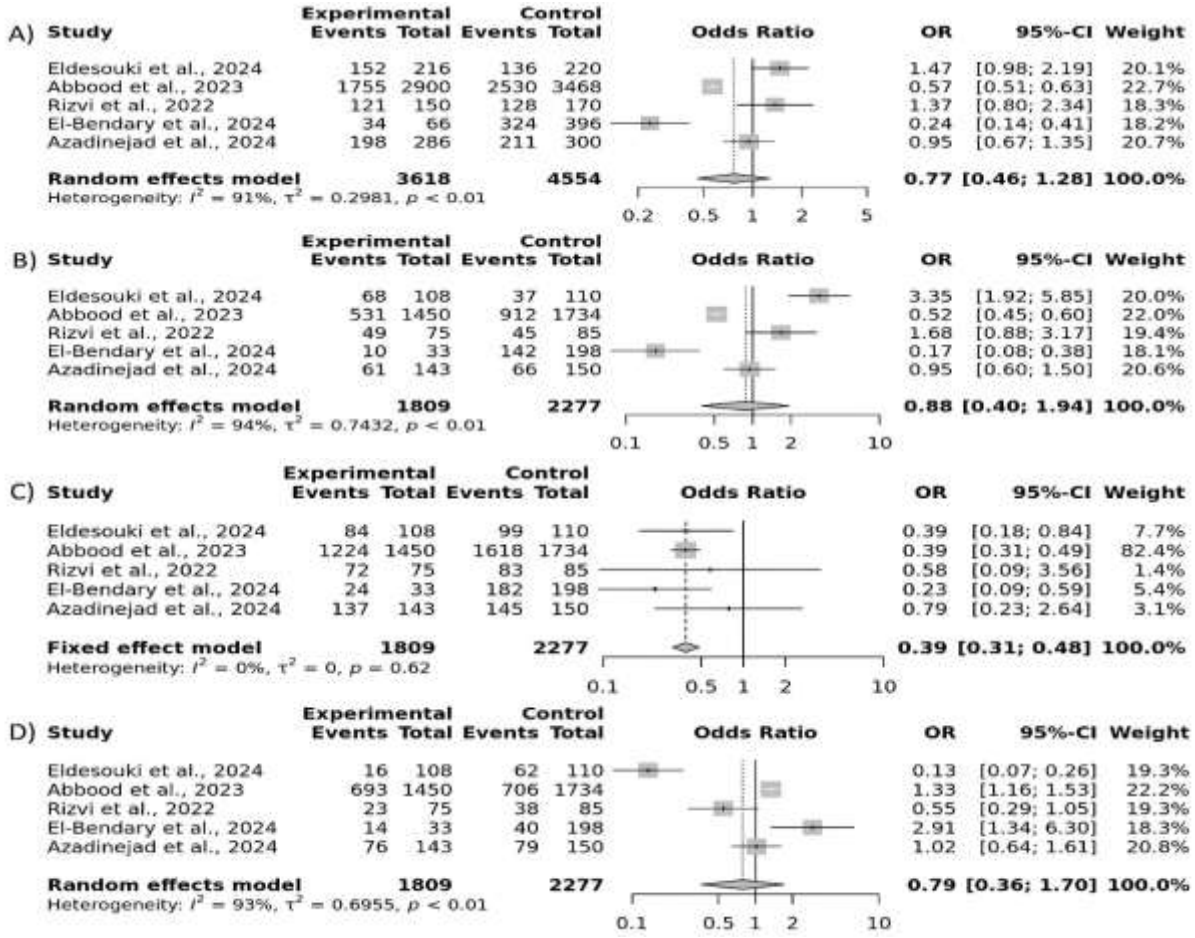


We compared distinct genetic models using odds ratios (ORs) and 95% confidence intervals (CIs): p-value 0.69 for dominant (CC + CT vs. TT), p-value 0.81 for recessive (CC vs. CT + TT), p-value 1.29 for over-dominant (CT vs. CC + TT), and p-value 0.81 for allelic (C vs. T). All genotypes of IL-6 were statistically insignificant with COVID-19 infection risk (I^2 vale fig. 6 A-D).



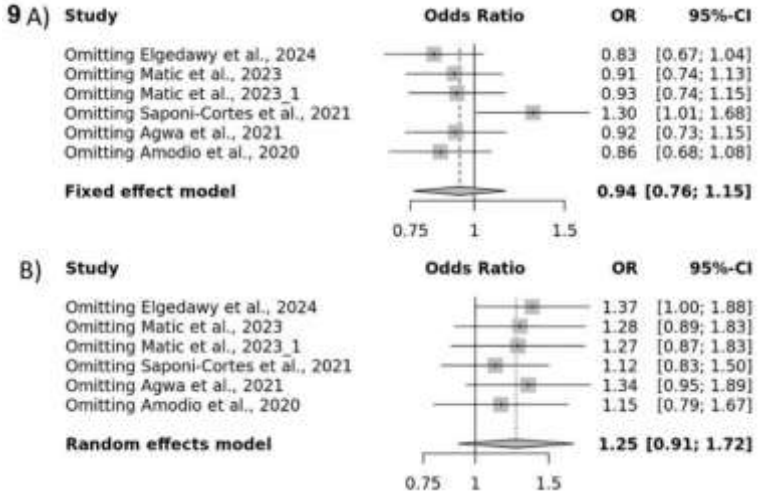
3.5. The IL-10 (rs1800896) polymorphism disease and severity of SARS-CoV-2 infection

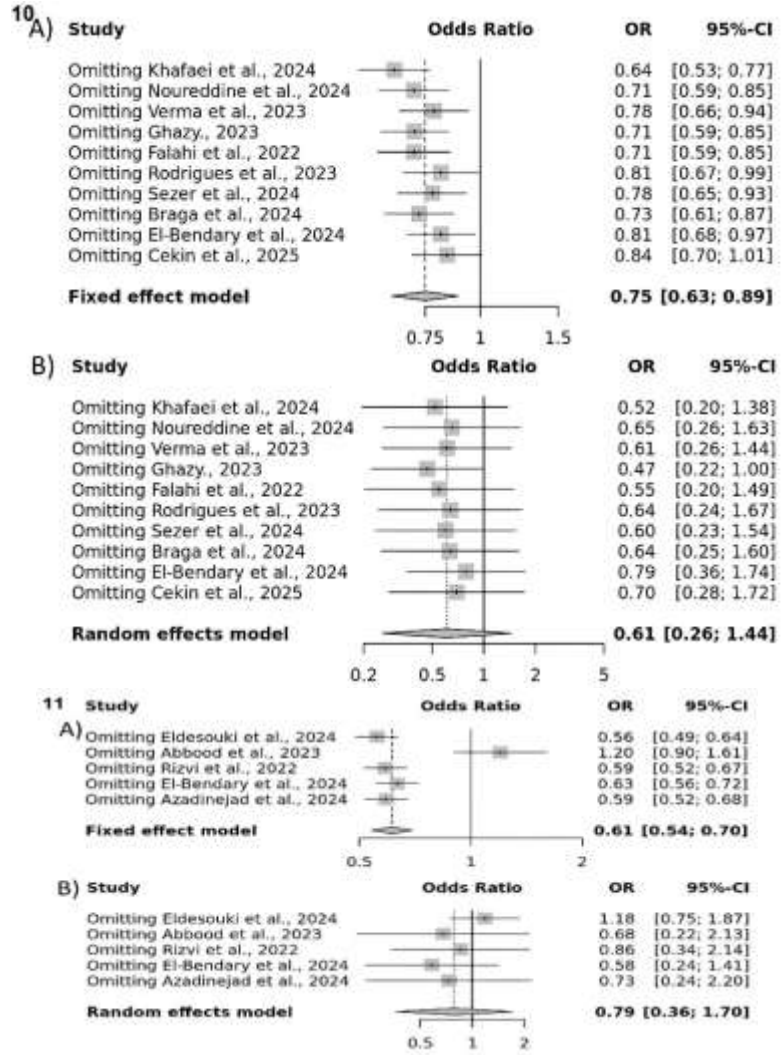
Caucasian and Asian risk with COVID-19 and the IL-10 (rs1800896) polymorphism were assessed by OR and 95% CI under p-value 0.72 for allelic (A vs. G), p-value 0.73 for over dominant (AG vs. AA+ G), p-value 0.85 for recessive (AA vs. AG+GG), and for dominant (AA+AG vs. GG) p-value 0.37. All genotypes of IL-10 were statistically insignificant with COVID-19 infection risk (I^2 vale fig. 7 A-D).



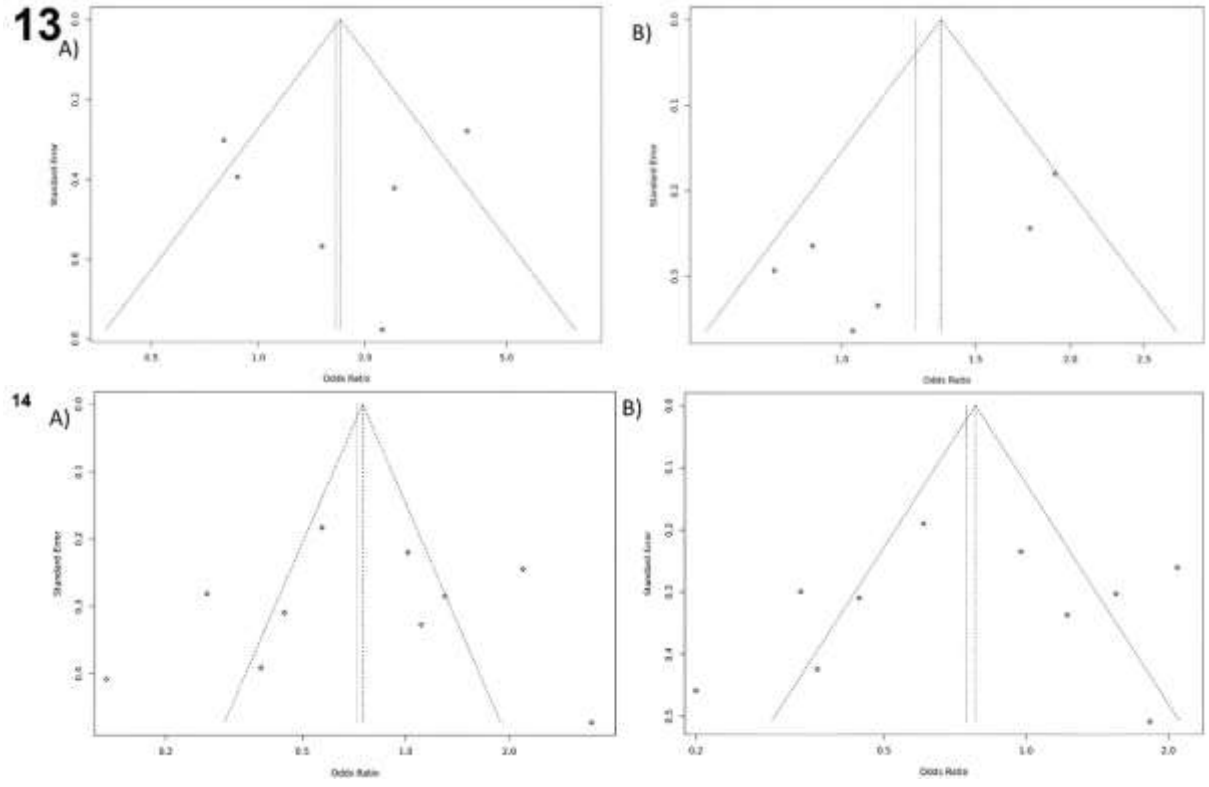
3.6. Sensitivity analysis and publication bias

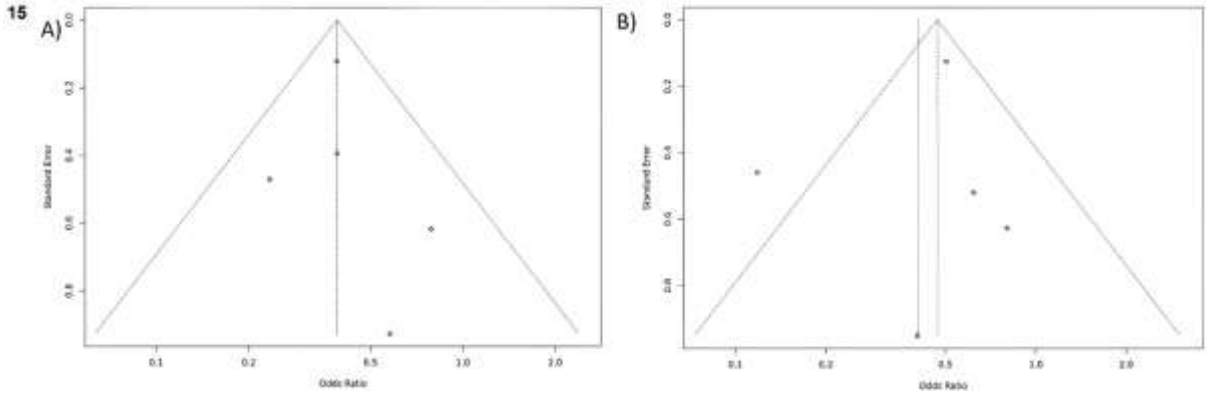
The analysis revealed inconsistencies between the study results and the Hardy-Weinberg Equilibrium (HWE). The Hardy-Weinberg principle is a fundamental concept in population genetics. It posits that, in the absence of evolutionary forces, the frequencies of alleles and genotypes within a population will remain stable across generations. To investigate whether inclusion criteria influenced these discrepancies, a sensitivity analysis was performed (Fig. 9, 10, 11, and 12). The key results indicated that no individual study had a significant impact on the overall results.





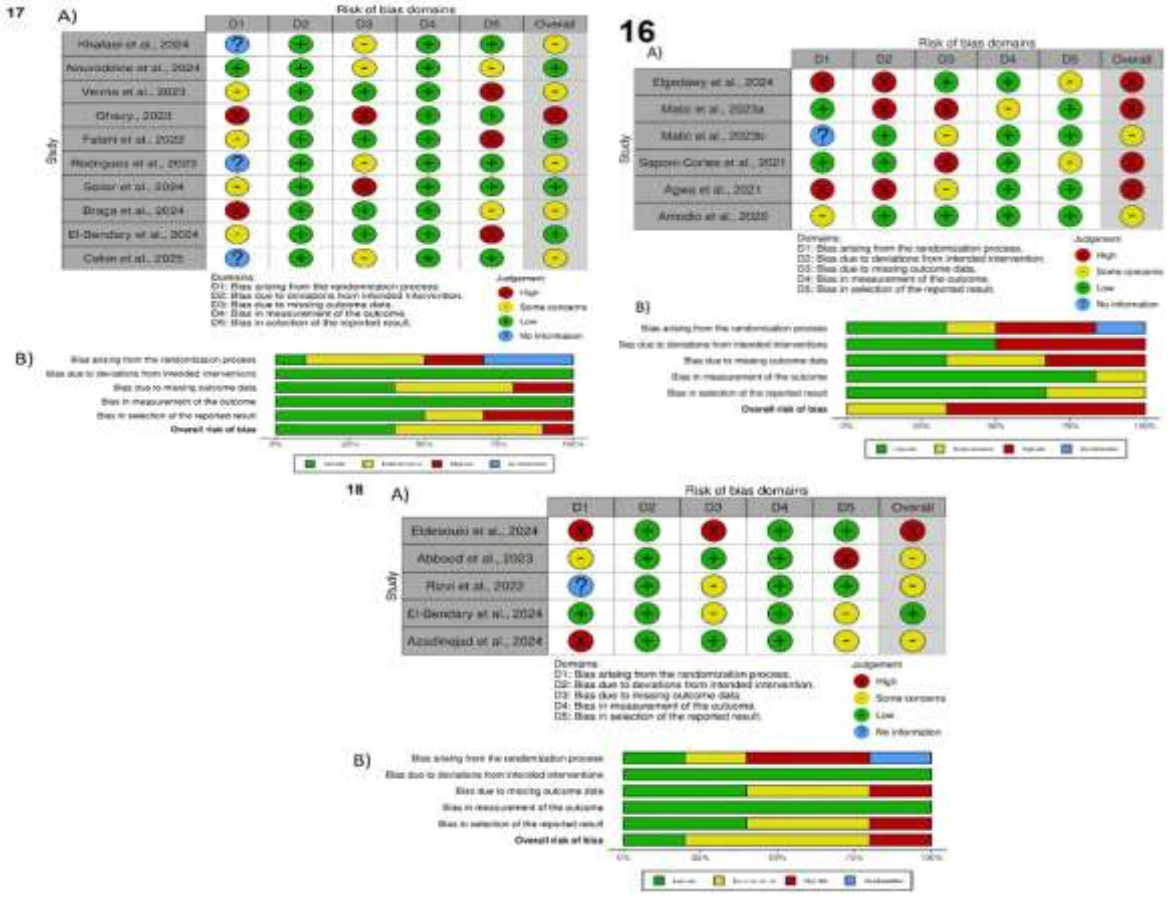
Using funnel plots and Egger's tests, we evaluated the data for publication bias. There was statistical robustness and validity shown by the meta-analysis findings (Fig. 13, 14, and 15).





3.7. Risk bias assessment

We systematically investigated the methodological quality of the selected studies using the Cochrane Risk of Bias Tool 2. The results are visualized in Figures 17, 18, 19 and 20. Studies are shown in each row of the chart, whereas biases are shown in each column. The reviewer's assessment of the risk of bias for each research is indicated by the colour coding: red for severe risk, yellow for moderate threat, and the colour green for minimal risk and beyond. The majority of studies demonstrated minimal risk of bias, suggesting that they were conducted and reported in a manner that effectively mitigated bias or systematic errors (Fig. 16, 17,and 18).



3.8. Power analysis, and Construction of PPI network

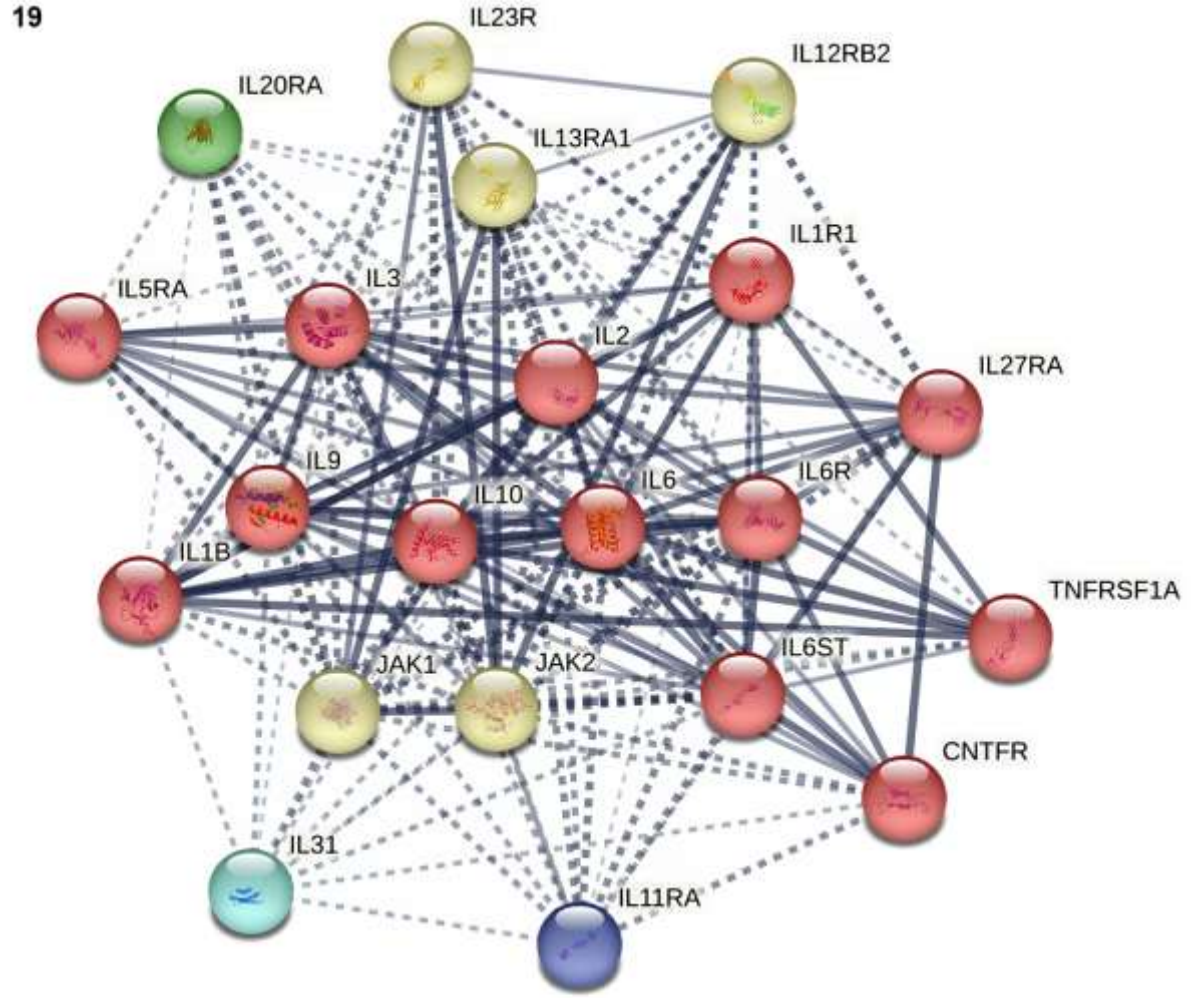
A power analysis was conducted to evaluate the statistical significance of the selected SNPs in each study. The results indicated that the sample sizes in the literature were sufficient to achieve a significant level with a Type I error probability of 0.05 α error. Power analysis conducted on three gene polymorphisms- IFNL4 (rs12979860), IL10 (rs1800896), and IL6 (rs1800795) - revealed a significant level of statistical power for all three. The analysis, based on sample sizes of 948 cases and 1016 controls for IFNL4, 1809 cases and 2277 controls for IL10, and 1237 cases and 1369 controls for IL6 in COVID-19, and 954 cases and 1449 controls for IL6 in COPD, yielded a power value (1-β error probability) less than 1 in each instance (Table 4).

Gene	SNP	Number of studies	Control	Case	α err prob	Power (1-β err prob)
IFNL4	rs12979860	6	1016	948	1×10^{-7}	1

IL-6	rs1800795	10	1369	1237	1×10^{-7}	1
IL-10	rs1800896	5	2277	1809	1×10^{-7}	1

Table 4: Highlights the significance of sample size estimation in accurately assessing the statistical significance and ensuring the reliability of findings in genetic association studies for COVID 19 infection, particularly in the context of selected polymorphism investigations. Sample size estimation plays a critical role in determining the statistical power of these studies.

A protein-protein interaction (PPI) network analysis was performed on polymorphic proteins related to IFNL4, IL10, and IL6 using the STRING database. The network includes 21 nodes and 170 edges for these genes (Fig. 19). While there are no direct interactions, IFNL4, IL10, and IL6 genes are connected through intermediary genes.



Clusters

color	cluster Id	gene count	description
	Cluster 1	13	JAK-STAT signaling pathway
	Cluster 2	5	+ Interleukin-12 family signaling
	Cluster 3	1	IL20RA
	Cluster 4	1	IL31
	Cluster 5	1	IL11RA

DISCUSSION

It is of the utmost importance to comprehend how SARS-CoV-2 influence human (Trypsteen et al., 2020). Compared to viral receptor alterations and infection susceptibility, less is known about genetic factors that cause sickness (Kwok et al., 2021). In genome-wide association studies, COVID-19 has been associated to several protein-coding and non-coding genomic variants. Protein coding variants may disrupt protein function and harm health (Sun et al., 2024). The functions of most COVID-19-related polymorphisms in non-coding regions are unclear. Mutations in the non-coding sequences may indirectly affect gene expression by DNA replication timing or gene structural modifications (Bhatti et al., 2021).

The purpose of this study was to investigate the role of gene polymorphisms in the IL6 gene had an impact on the susceptibility of COVID-19 and chronic obstructive pulmonary disease (COPD).Host genetic variables, notably IFNL4 polymorphisms, have been linked to COVID-19 severity and outcome in several populations. In the host antiviral response, the IFNL4 gene is crucial. In a case–control study of Egyptian patients, FURIN, IFNL4, and TLR2 gene polymorphisms were associated with COVID-19 severity, indicating that they may affect viral entry and immunological regulation, affecting clinical outcomes (Elgedawy et al., 2024). Another study revealed that rs12979860 showed both protection and risk, suggesting a complicated role in illness development of COVID-19. Also, sex-specific effects have been linked, that IFNL4 polymorphisms may mitigate COVID-19-related pneumonia in females, suggesting a link between sex hormones and IFN-λ signalling pathways (Matic et al., 2023). However, a genetic variation of IFNL4 may predispose people to more severe COVID-19, emphasizing the need of allele-specific functional investigations in risk profiles (Saponi-Cortes et al., 2021). Additionally, an observational investigation identified relationships between SARS-CoV-2 viral burden, interferon polymorphisms, and illness severity, suggesting that certain polymorphisms may increase viral loads and worsen clinical outcomes (Amodio et al., 2020). These investigations demonstrate the importance of IFNL4 polymorphisms in SARS-CoV-2 host responses. Cytokine gene polymorphisms, notably IL-10 and IL-6, have been intensively studied in COVID-19 severity. Numerous studies across populations have shown SNPs that substantially correlate with illness risk COVID-19 and COPD outcomes (Azadinejad et al., 2024). IL-10 SNPs rs1800871, rs1800872, and rs1800896 were substantially related with increased COVID-19 severity, indicating they may impair IL-10's anti-inflammatory response. Other Iranian studies related rs1800896 and rs1800872 to poorer clinical outcomes in affected people (Eldesouki et al., 2024). Regardless of viral alterations, IL-10 rs1800871, rs1800872, and rs1800896 were consistently related with illness severity in a study of SARS-CoV-2 variations (Abbood et al., 2023). IL-10 (rs1800896) and IL-2R (rs1801274) and IL-6 (rs2069840) SNPs were also linked to immunothrombosis biomarkers and COVID-19 severity (Yessenbayeva et al., 2023). The IL-10 promoter polymorphisms -592 C>A (rs1800872) and -1082 A>G (rs1800896) and TNF-α -308 G>A were linked to COVID-19 susceptibility and poor clinical outcomes (Rizvi et al., 2022). In Amazonians, SNPs in the IL6, IL6R, and IL6ST genes were connected to severe illness, underlining the relevance of IL-6 pathway diversity across ancestries (Rodrigues et al., 2023). IL-8 gene rs2227306 and IL-6 gene rs1800795 also affected illness prognosis in Iranians (Ghazy, 2023). Polymorphisms in TLR3, TICAM1, and IFNA1 genes modulated immunological responses and COVID-19 severity in southern Brazil. These data show that cytokine gene polymorphisms, notably IL-10 rs1800871,rs1800872, rs1800896, and IL-6 rs1800795, are crucial in defining COVID-19 severity between worldwide populations. Global clinical outcomes vary according to ethnic group allele distribution, emphasizing the necessity for population-specific genetic risk profiling in pandemic preparation and treatment. Our meta-analysis revealed significant heterogeneity across all three gene models. However, subgroup analyses were not feasible due to the limited number of studies focused on Asian populations. Despite this, sensitivity analysis confirmed the robustness of our findings, and no publication bias was detected through statistical tests or funnel plot assessments. Nonetheless, several limitations should be noted. The limited sample size may affect the reliability of our results. Our restriction to English-language publications could have excluded relevant data, and we did not assess gene–environment interactions that might influence cancer risk. Although no publication bias was evident, the possibility of unpublished studies affecting our conclusions cannot be entirely ruled out. Despite these limitations, our study provides valuable insights. Host factors such as immune status, age, sex, ethnicity, and comorbidities (e.g., lung or heart disease, hypertension, diabetes, cancer) can affect disease outcomes, but such data were not detailed in the studies analysed. Our findings suggest that IFNL4 rs12979860, IL10 rs1800896, and IL6 rs1800795 polymorphisms are not significantly associated with susceptibility to COVID-19. To properly understand these correlations and provide individualized therapy options, large-scale, ethnically varied investigations are needed due to population inconsistencies and complex nature of COVID-19 variants.

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Ethical approval
This study does not involve experiments with animals or human subjects.

Consent for publication
Not applicable.

Availability of data and materials
Data and materials used/analysed during the current study are available from the corresponding author upon reasonable request.

Funding
Not Applicable.

Author's contributions
TA and SR conducted literature searches, collected data, developed the methodology, contributed to writing, and performed data analysis. SW performed data analysis and created tables and figures. DW has done validation and data curation; GK conducted investigations, provided editing assistance, supervised, and conceptualized. All authors have thoroughly reviewed and approved the manuscript.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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