Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection 84 (2022) e19–e3

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Genetic variation of interleukin-1 receptor type 1 is associated with severity of COVID-19 disease

Dear Editor

In this journal, Rossotti and colleagues described the potential therapeutic benefit of the inhibition of interleukin (IL) pathways in COVID-19 disease.[1] Members of the IL-1 family are central mediators of the COVID-19 cytokine storm.[2] Thus, we aim to explore whether a genetic variation of the IL-1 family is associated with COVID-19.

The acronym IL-1 refers to two cytokines, IL-1α and IL-1β.[3] IL-1α and IL-1β bind to their common receptor, which is composed of an IL-1 receptor type 1 (IL-1R1) and the accessory protein (IL-1Racp); the IL-1 receptor antagonist (IL-1Ra) is an IL-1–specific receptor antagonist.[3, 4] We mainly explored the effect of the IL-1α, IL-1β, IL-1R1, IL-1Racp, and IL-1Ra genetic variation on the risk of COVID-19.

Many factors such as confounding and reverse causation that bias observational studies results in the absence of high-quality randomized controlled trials (RCTs) data, whereas Mendelian randomization (MR) is based on the principle that genetic variants are randomly allocated at meiosis, and consequently these genetic variants are independent of many factors that bias observational studies.[5] We used a two-sample MR study to explore the association of the IL-1α, IL-1β, IL-1R1, IL-1Racp, and IL-1Ra genetic variation with COVID-19 risk. The design for this MR study is shown in **Suppl. Fig. 1**. The MR study was performed using the following seven steps.

First, the IL-1α, IL-1β, IL-1R1, IL-1Racp, and IL-1Ra genetic instrumental variables (IVs) were chosen based on a recent MR report on the IL-1 family and lung cancer.[6] These genetic IVs were found in *cis*-protein quantitative trait loci (*cis*-pQTLs) in two recent proteomics Genome-wide Association Studies (GWASs) of 11,594 European participants.[7, 8] The proteomic GWAS was adjusted for age, sex, body mass index, and time between blood draw and processing.[7, 8] pQTLs strongly associated with IL-1 family members at a threshold of $p < 5 \times 10^{-6}$ were used as "suggestive" variants[9]. Based on the 1000-genome European reference panel, the *cis*-pQTLs ($r^2 > 0.05$) were removed by linkage disequilibrium (LD) analysis using LDlink (https://ldlink.nci.nih.gov/?tab=ldmatrix, CEU). To ensure that unconfounded instruments affected COVID-19 via the relevant exposure only, the *cis*-pQTLs associated with possible exposure-outcome confounders (e.g., age, smoking, socioeconomic position, and platelets) were removed. Single nucleotide polymorphisms (SNPs) associated with IL-1α, IL-1β, IL-1R1, IL-1Racp, and IL-1Ra- as potential IVs are shown in **Suppl. Table 1**.

Second, we used nine COVID-19 GWASs established by COVID-19 Host Genetics Initiative in 2020.[10] Summary information about nine COVID-19 GWASs of persons with European ancestry are shown in **Table 1**, and GWAS summary datasets are available in https://gwas.mrcieu.ac.uk/datasets/. Based on traits, nine COVID-19 GWAS datasets were divided into 3 groups: 1. COVID-19 (GWAS ID: ebi-a-GCST010776, ebi-a-GCST010777, ebi-a-GCST010778, ebi-a-GCST010779, ebi-a-GCST010780, ebi-a-GCST010781, and ebi-a-GCST010782); 2. COVID-19 (very severe respiratory confirmed vs population) (GWAS ID: ebi-a-GCST010783); 3. COVID-19 (very severe respiratory confirmed vs not hospitalized) (GWAS ID: ebi-a-GCST010775).

Third, we extracted the independent IL-1α, IL-1β, IL-1R1, IL-1Ra, and IL-1Racp genetic IVs from nine COVID-2019 GWAS datasets. When these IVs could not be found, potential proxy SNPs were identified by the LD proxy tool ($r^2 > 0.8$). The association of these IVs with the nine COVID-19 GWAS datasets is shown in **Suppl. Table 2**.

Fourth, the MR-Egger_intercept, MR-PRESSO methods, MR-Egger, and Inverse variance weighted (IVW) in Cochran's Q statistic were used to test the pleiotropy or heterogeneity of the independent IL-1α, IL-1β, IL-1R1, IL-1Ra, and IL-1Racp genetic IVs in the nine COVID-19 GWASs. The results showed no obvious pleiotropy or heterogeneity of these IVs in the nine COVID-19 GWAS datasets (**Suppl. Table 3**). Therefore, all of the selected IL-1α, IL-1β, IL-1R1, IL-1Ra, and IL-1Racp genetic variants can be considered effective IVs in our MR study.

Fifth, we used MR to analyze the effect of the IL-1α, IL-1β, IL-1R1, IL-1Ra, and IL-1Racp genetic IVs on the risk of contracting COVID-19. We found that genetic variation of IL-1α, IL-1β, IL-1Ra, or IL-1Racp was not associated with an increased risk of COVID-19 **(Suppl. Table 4)**. Interestingly, we found that genetic variation of IL-1R1 was associated with very severe respiratory COVID-19 using MR Egger (Beta = 0.092, $p = 0.469$; OR = 1.097), simple mode (Beta = 0.241, $p = 0.109$; OR = 1.272), weighted mode (Beta = 0.235, $p = 0.089$; OR = 1.265), weighted median (Beta = 0.173, $p = 0.04$; OR = 1.189), and IVW (Beta = 0.143, $p = 0.014$; OR = 1.154) (**Table 2**).

Sixth, we tested the single SNP effect of the IL-1R1 genetic IVs on very severe respiratory COVID-19. The individual MR estimates demonstrated that as the effect of single SNP on IL-1R1 increased, the severity of COVID-19 also increased using MR Egger, weighted median, IVW, simple mode, and weighted mode **(Suppl. Fig. 2)**. Each effect size **(Suppl. Fig. 3)** and leave-one-out sensitivity **(Suppl. Fig. 4)** analysis of the IL-1R1 SNPs suggested that each effect of the IL-1R1 SNPs on very severe respiratory COVID-19 was robust and that no obvious bias was detected.

https://doi.org/10.1016/j.jinf.2021.12.010

Table 1
Corona Virus Disease 2019 (COVID-19) GWAS datasets.

GWAS ID	Year	Trait	ncase	ncontrol	nsnp	Population
ebi-a-GCST010775	2020	COVID-19 (very severe respiratory confirmed vs not hospitalized) RELEASE 4	269	688	9201,012	European
ebi-a-GCST010776	2020	COVID-19 (RELEASE 4)	14,134	1,284,876	11,435,708	European
ebi-a-GCST010777	2020	COVID-19 (hospitalized vs population) RELEASE 4	6406	902,088	12,832,272	European
ebi-a-GCST010778	2020	COVID-19 (covid vs lab/self reported negative) RELEASE 4	8818	101,806	12,832,272	European
ebi-a-GCST010779	2020	COVID-19 (hospitalized vs population) RELEASE 4	6406	902,088	11,272,365	European
ebi-a-GCST010780	2020	COVID-19 (RELEASE 4)	14,134	1,284,876	12,508,741	European
ebi-a-GCST010781	2020	COVID-19 (predicted covid from self-reported symptoms vs predicted or self-reported non-covid) RELEASE 4	3204	35,728	11,379,674	European
ebi-a-GCST010782	2020	COVID-19 (hospitalized covid vs not hospitalized covid) RELEASE 4	1776	6443	14,642,515	European
ebi-a-GCST010783	2020	COVID-19 (very severe respiratory confirmed vs population) RELEASE 4	3886	622,265	11,678,750	European

GWAS ID: Genome wide association study identity; ncase: the number of COVID-19 case; ncontrol: the number of the control; nsnp: the number of single-nucleotide polymorphism.

Table 2
The causal association of IL-1R1 with COVID-19.

GWAS ID	Method	nsnp	Beta	SE	*p* val	OR	OR_lci95	OR_uci95
ebi-a-GCST010775	MR Egger	18	−0.194	0.674	0.777	0.823	0.220	3.086
	Weighted median	18	0.112	0.416	0.787	1.119	0.495	2.529
	IVW	18	0.061	0.302	0.841	1.062	0.588	1.919
	Simple mode	18	0.256	0.767	0.743	1.292	0.287	5.806
	Weighted mode	18	0.221	0.728	0.765	1.247	0.299	5.196
ebi-a-GCST010776	MR Egger	20	−0.134	0.061	0.041	0.875	0.777	0.985
	Weighted median	20	−0.027	0.040	0.501	0.974	0.900	1.053
	IVW	20	−0.041	0.028	0.148	0.960	0.908	1.015
	Simple mode	20	−0.015	0.079	0.854	0.985	0.843	1.151
	Weighted mode	20	−0.016	0.076	0.832	0.984	0.848	1.141
ebi-a-GCST010777	MR Egger	20	−0.112	0.068	0.116	0.894	0.783	1.021
	Weighted median	20	−0.039	0.045	0.390	0.962	0.881	1.051
	IVW	20	−0.045	0.031	0.143	0.956	0.899	1.015
	Simple mode	20	−0.135	0.082	0.114	0.873	0.744	1.025
	Weighted mode	20	−0.024	0.081	0.770	0.976	0.834	1.143
ebi-a-GCST010778	MR Egger	20	−0.112	0.068	0.116	0.894	0.783	1.021
	Weighted median	20	−0.039	0.041	0.347	0.962	0.888	1.043
	IVW	20	−0.045	0.031	0.143	0.956	0.899	1.015
	Simple mode	20	−0.135	0.085	0.128	0.873	0.739	1.032
	Weighted mode	20	−0.024	0.081	0.771	0.976	0.834	1.144
ebi-a-GCST010779	MR Egger	20	0.041	0.097	0.678	1.042	0.862	1.260
	Weighted median	20	0.028	0.059	0.641	1.028	0.915	1.155
	IVW	20	0.027	0.044	0.531	1.028	0.944	1.119
	Simple mode	20	0.029	0.114	0.801	1.030	0.823	1.288
	Weighted mode	20	0.029	0.105	0.785	1.030	0.838	1.266
ebi-a-GCST010780	MR Egger	20	−0.112	0.057	0.065	0.894	0.800	1.000
	Weighted median	20	0.001	0.037	0.980	1.001	0.931	1.076
	IVW	20	−0.024	0.026	0.352	0.976	0.928	1.027
	Simple mode	20	−0.004	0.071	0.955	0.996	0.867	1.144
	Weighted mode	20	−0.002	0.060	0.968	0.998	0.887	1.122
ebi-a-GCST010781	MR Egger	20	0.039	0.113	0.735	1.040	0.833	1.297
	Weighted median	20	0.026	0.075	0.726	1.026	0.887	1.188
	IVW	20	0.002	0.053	0.968	1.002	0.903	1.112
	Simple mode	20	−0.006	0.146	0.970	0.995	0.747	1.325
	Weighted mode	20	0.028	0.127	0.826	1.029	0.801	1.321
ebi-a-GCST010782	MR Egger	20	0.096	0.188	0.615	1.101	0.761	1.593
	Weighted median	20	0.080	0.107	0.456	1.083	0.878	1.336
	IVW	20	0.010	0.083	0.906	1.010	0.858	1.189
	Simple mode	20	0.108	0.183	0.563	1.114	0.778	1.595
	Weighted mode	20	0.136	0.187	0.477	1.145	0.794	1.653
ebi-a-GCST010783	MR Egger	20	0.092	0.125	0.469	1.097	0.859	1.401
	Weighted median	20	0.173	0.085	**0.040**	1.189	1.008	1.404
	IVW	20	0.143	0.058	**0.014**	1.154	1.030	1.293
	Simple mode	20	0.241	0.143	0.109	1.272	0.961	1.683
	Weighted mode	20	0.235	0.131	0.089	1.265	0.978	1.635

COVID-19: Corona Virus Disease 2019; GWAS ID: Genome wide association study identity. IVW: Inverse variance weighted. Beta: the regression coefficient based on the vitamin C raising effect allele. nsnp: the number of single-nucleotide polymorphism. SE: standard error. $p < 0.05$ represents the causal association of IL-1R1 levels with COVID-19. OR: Odds ratio. OR_lci95: Lower limit of 95% confidence interval for OR. OR_uci95: Upper limit of 95% confidence interval for OR.

Finally, COVID-19 (very severe respiratory confirmed vs not hospitalized) GWAS was used to rule out the effect of other confounders, such as a hospitalized condition. We found that as the levels of genetic IL-1R1 increased, the risk of COVID-19 (very severe respiratory confirmed vs not hospitalized) did not obviously change **(Suppl. Table 4)**. Collectively, these results suggest no other confounders such as hospitalized condition involved in the effect of IL-1R1 on very severe respiratory COVID-19.

This study has several limitations. First, IL-1α, IL-1β, IL-1R1, IL-1Ra, and IL-1Racp genetic IVs and nine COVID-19 GWAS are from European ancestry. Our conclusion need be proven in other ancestries. Second, it is necessary to clarify whether blockade of IL-1R1

could reduce the risk of very severe respiratory COVID-19 by randomized controlled trials.

In summary, our analysis suggests that genetic variation of IL-1R1 is associated with severity of respiratory COVID-19. Thus, inhibition of IL-1R1 may be value treatment of patients with severe respiratory COVID-19.

Funding

This study was supported by grants from National Natural Science Foundation of China (82071758 and 31770956). The funders had no role in the study design, collection, analysis and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication

Ethical approval

Our study was approved by the Ethics Committee of Beijing Institute of Brain Disorders in Capital Medical University. This article contains human participants collected by several studies performed by previous studies. All participants gave informed consent in all the corresponding original studies, as described in the Methods.

Authors' contributions

RW conceived and initiated the project, analyzed the data and wrote the manuscript, contributed to the interpretation of the results and critical revision of the manuscript, and approved the final version of the manuscript.

Availability of data and materials

The summary statistics for genetic associations of IL-1α, IL-1R1, and IL-1Racp in the INTERVAL study (http://www.phpc.cam.ac.uk/ceu/proteins/) and IL-1β and IL-1Ra in YFS and FINRISK survey (https://grasp.nhlbi.nih.gov/FullResults.aspx) are available. COVID-19 GWAS datasets (GWAS ID: ebi-a-GCST010775, ebi-a-GCST010776, ebi-a-GCST010777, ebi-a-GCST010778, ebi-a-GCST010779, ebi-a-GCST010780, ebi-a-GCST010781, ebi-a-GCST010782, and ebi-a-GCST010783) can be found on ieu open gwas project at https://gwas.mrcieu.ac.uk/datasets/. The MR analysis code can be found at https://mrcieu.github.io/TwoSampleMR/articles/index.html.

Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgement

We thank ieu open gwas project (https://gwas.mrcieu.ac.uk/datasets/) for providing summary results data for these analyses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.12.010.

References

1. Rossotti R, Travi G, Ughi N, Corradin M, Baiguera C, Fumagalli R, et al. Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: a comparative analysis. *J Infect* 2020;**81**(4):e11–ee7.
2. Conti P, Caraffa A, Gallenga CE, Ross R, Kritas SK, Frydas I, et al. Coronavirus-19 (SARS-CoV-2) induces acute severe lung inflammation via IL-1 causing cytokine storm in COVID-19: a promising inhibitory strategy. *J Biol Regul Homeost Agents* 2020;**34**(6):1971–5.
3. Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. *Nat Rev Rheumatol* 2010;**6**(4):232–41.
4. Dinarello CA. The IL-1 family of cytokines and receptors in rheumatic diseases. *Nat Rev Rheumatol* 2019;**15**(10):612–32.
5. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008;**27**(8):1133–63.
6. Yang Z, Schooling CM, Kwok MK. Mendelian randomization study of interleukin (IL)-1 family and lung cancer. *Sci Rep* 2021;**11**(1):17606.
7. Ahola-Olli AV, Wurtz P, Havulinna AS, Aalto K, Pitkanen N, Lehtimaki T, et al. Genome-wide association study identifies 27 Loci influencing concentrations of circulating cytokines and growth factors. *Am J Hum Genet* 2017;**100**(1):40–50.
8. Sun BB, Maranville JC, Peters JE, Stacey D, Staley JR, Blackshaw J, et al. Genomic atlas of the human plasma proteome. *Nature* 2018;**558**(7708):73–9.
9. Manolio TA. Genomewide association studies and assessment of the risk of disease. *N Engl J Med* 2010;**363**(2):166–76.
10. The COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur J Hum Genet* 2020;**28**(6):715–18.

Renxi Wang*
Beijing Institute of Brain Disorders, Laboratory of Brain Disorders, Ministry of Science and Technology, Collaborative Innovation Center for Brain Disorders, Capital Medical University, Beijing 100069, China
*Corresponding author at: Beijing Institute of Brain Disorders, Laboratory of Brain Disorders, Ministry of Science and Technology, Collaborative Innovation Center for Brain Disorders, Capital Medical University, No.10 Xitoutiao, You An Men, Beijing 100069, China.
E-mail address: renxi_wang@ccmu.edu.cn