Journal of Infection xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Infection

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

Letter to the Editor

Non-causal association of COVID-19 with systemic lupus erythematosus: Evidence from a bidirectional Mendelian randomization☆

Dear Editor,

The connection between autoimmune diseases and COVID-19 has garnered considerable attention. In this journal, Liu et al.[1] and Yang et al.[2] investigated this association in their publications; however, their findings had produced conflicting results. More recently, Peng et al.[3] reported a genetic causal association between gout, one of the most prevalent autoimmune diseases, and severe COVID-19. Their study provided valuable guidance on managing COVID-19 and gout. Nevertheless, the relationship between another common autoimmune disease, systemic lupus erythematosus (SLE), and COVID-19 is contentious. While some studies had confirmed the association between SLE and COVID-19, other epidemiological investigations found no association.[4–6] Interference from confounding factors and reverse causation may disturb traditional epidemiological findings. Mendelian randomization (MR) uses genetic instrumental variables to determine the genetic association between exposures and outcomes, thereby excluding potential confounders from interfering. In this study, we attempted to reveal the causal association between COVID-19 and SLE by using bidirectional MR, which assessed the effects of COVID-19 on SLE and SLE on COVID-19, respectively.

We conducted MR studies using summary statistics of genome-wide association studies (GWAS) in the European population and replicated the results in individuals of East Asian descent. The largest GWAS data of COVID-19 were obtained from the latest r7 version based on COVID-19 Host Genetics Initiative (https://www.covid19hg.org/results/r7/), including three sets of genetic instruments, SARS-CoV-2 infection, hospitalized COVID-19, and severe COVID-19 (n = 1,086,211 to 2,297,856 individuals). For the outcome of SLE, the meta-GWAS yielded the largest GWAS summary statistics to date, consisting of 14,267 individuals.[7] Detailed information for the data sources was presented in Supplementary Table 1. We summarized the confounders influencing the incidence of COVID-19 and SLE from previous meta-analysis studies (Supplementary Table 2). To avoid potential pleiotropic effects caused by confounders, we removed potential confounding SNPs associated with these confounders of COVID-19 and SLE through the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/), as presented in Supplementary Table 3. After removing potential confounders associated with outcomes, the used genetic instruments of exposures were shown in Supplementary Table 4**.** We chose inverse variance weighted (IVW) model as the main analysis method and applied additional sensitivity analysis methods, MR-Egger, weighted median, and weighted mode, to ensure the robustness of the results. The pleiotropy was estimated through the intercept from MR-Egger regression, and heterogeneity was assessed through Cochran's Q test in IVW approach. We also assessed whether bias existed due to individual SNP independently affecting the results by leave-one-out analysis.

The results suggested a non-causal association between of COVID-19 and risk of SLE. Neither the susceptibility, hospitalization, and severity of COVID-19 on SLE (IVW method: odds ratio (OR) = 0.89, 95% confidence interval (CI) 0.54–1.45, P = 0.63; OR = 0.94, 95% CI 0.75–1.18, P = 0.60; OR = 1.06, 95% CI 0.97–1.15, P = 0.18), nor SLE on susceptibility, hospitalization, and severity of COVID-19 (IVW method: OR = 0.99, 95% CI 0.99–1.00, P = 0.09; OR = 0.99, 95% CI 0.98–1.01, P = 0.49; OR = 0.99, 95% CI 0.96–1.02, P = 0.43) were genetically associated. The results from MR-Egger, weighted median, and weighted mode methods were consistent with IVW analysis (Fig. 1). Statistical power for MR analyses calculated based on sample size and explained variances was sufficient (90%) (Supplementary Table 5). No pleiotropy was identified in the sensitivity test, and no SNPs independently drove the results in the leave-one-out sensitivity, indicating the reliability of the causal effect estimates (Supplementary Tables 6 and 7). Replicated analyses in the East Asian population showed consistent results that genetically predicted susceptibility, hospitalization, and severity of COVID-19 were not associated with the risk of SLE (Fig. 2).

This MR study revealed a non-genetic association between COVID-19 and SLE using the largest GWAS data to date; however, the onset and development of COVID-19 and SLE shared similar underlying mechanisms. Our previous study indicated the key roles of interferon-related genes involving in the crosstalk of SLE and severe COVID-19.[8] Patients with COVID-19 and SLE also shared the identical macrophage activation pathway[9] and similar gut microbial dysregulation features.[10] Immunity dysregulation and gut microbes are related to the pathogenesis of both COVID-19 and SLE. Consequently, the connection between SLE and COVID-19 may function through other shared pathways, as opposed to the diseases themselves.

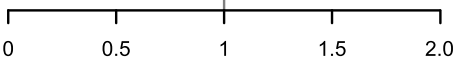
In conclusion, our MR analysis results do not support the relationship between COVID-19 and SLE from a genetic perspective. Large-scale randomized controlled trials are needed to gain a deeper understanding of this association in the future.

☆Feixiang Yang and Ning Zhang contributed equally to this work.

https://doi.org/10.1016/j.jinf.2023.02.028

A

Exposures & Outcome	Used SNPs	OR(95% CI)	*P*–value
SARS−CoV−2 infection on SLE			
Inverse variance weighted	12	0.89 (0.54 to 1.45)	0.63
MR Egger	12	0.67 (0.28 to 1.61)	0.39
Weighted median	12	1.09 (0.65 to 1.85)	0.74
Weighted mode	12	1.02 (0.60 to 1.75)	0.94
Hospitalized COVID−19 on SLE			
Inverse variance weighted	23	0.94 (0.75 to 1.18)	0.60
MR Egger	23	1.05 (0.70 to 1.57)	0.83
Weighted median	23	1.06 (0.88 to 1.29)	0.52
Weighted mode	23	1.06 (0.90 to 1.25)	0.51
Severe COVID−19 on SLE			
Inverse variance weighted	21	1.06 (0.97 to 1.15)	0.18
MR Egger	21	1.01 (0.88 to 1.16)	0.89
Weighted median	21	1.04 (0.93 to 1.17)	0.47
Weighted mode	21	1.04 (0.92 to 1.17)	0.56



B

Exposures & Outcome	Used SNPs	OR(95% CI)	*P*–value
SLE on SARS−CoV−2 infection			
Inverse variance weighted	39	0.99 (0.99 to 1.00)	0.09
MR Egger	39	0.99 (0.97 to 1.01)	0.32
Weighted median	39	0.99 (0.99 to 1.00)	0.20
Weighted mode	39	0.99 (0.98 to 1.00)	0.31
SLE on Hospitalized COVID−19			
Inverse variance weighted	37	0.99 (0.98 to 1.01)	0.49
MR Egger	37	0.98 (0.94 to 1.02)	0.37
Weighted median	37	0.99 (0.98 to 1.01)	0.56
Weighted mode	37	0.99 (0.97 to 1.02)	0.56
SLE on Severe COVID−19			
Inverse variance weighted	36	0.99 (0.96 to 1.02)	0.43
MR Egger	36	0.95 (0.89 to 1.03)	0.21
Weighted median	36	0.99 (0.96 to 1.02)	0.48
Weighted mode	36	0.99 (0.95 to 1.02)	0.43

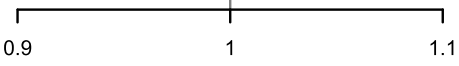


Fig. 1. Genetic causal associations between COVID-19 and risk of SLE in European population. (A) MR estimates of genetically predicted susceptibility, hospitalization, and severity of COVID-19 on the risk of SLE. (B) MR estimates of genetically predicted risk of SLE on susceptibility, hospitalization, and severity of COVID-19. The inverse variance weighted method is considered the main method.

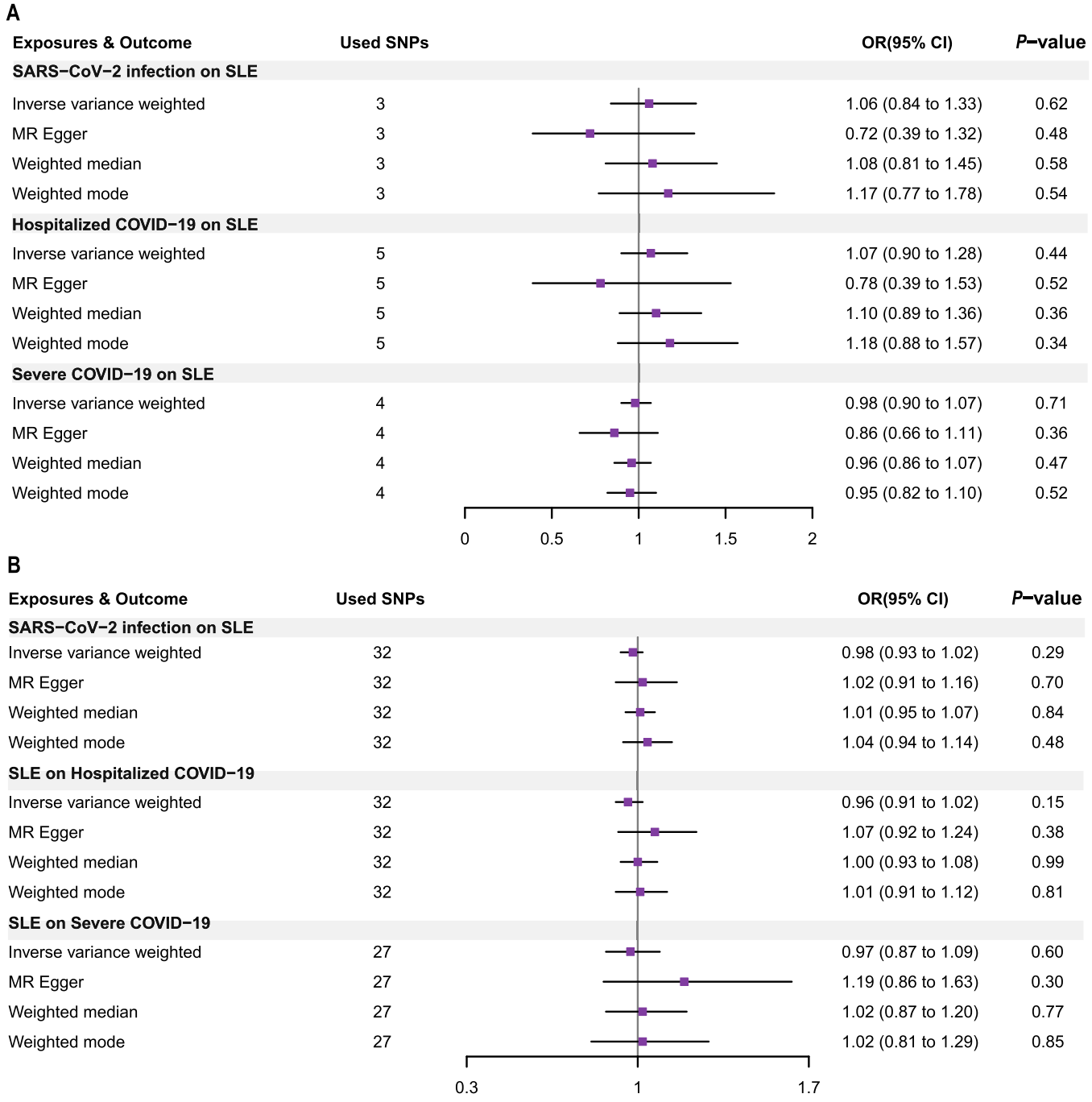


Fig. 2. Genetic causal associations between COVID-19 and risk of SLE in East Asian population. (A) MR estimates of genetically predicted susceptibility, hospitalization, and severity of COVID-19 on the risk of SLE. (B) MR estimates of genetically predicted risk of SLE on susceptibility, hospitalization, and severity of COVID-19. The inverse variance weighted method is considered the main method.

Funding

This work was funded by the National College Students' Innovation and Entrepreneurship Training Program (No. 202210366002) and the College Students' Innovation and Entrepreneurship Training Program of Anhui Province (No. S202210366013, S202210366021, and S202210366017).

Author contributions

Feixiang Yang: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft. **Ning Zhang**: conceptualization, investigation, validation, writing – review & editing. **Ruogang Meng**: formal analysis, investigation, validation. **Kun Wang**: formal analysis, investigation, validation. **Tianrui Liu**: formal analysis, investigation, validation. **Jialin Meng**: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, writing – review & editing. **Yinan Du**: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, writing – review & editing.

Declaration of Competing Interest

The authors declared no competing interests.

Acknowledgments

We thank the Mathematical Medicine Integration Innovation Training Program for Undergraduate Students (MITUS) for providing valuable guidance, support, research opportunities, and resources.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.02.028.

References

1. Liu M, Gao Y, Zhang Y, Shi S, Chen Y, Tian J. *The association between severe or dead COVID-19 and autoimmune diseases: a systematic review and meta-analysis. J Infect* 2020;**81**(3):e93–5.
2. Yang H, Xu J, Liang X, Shi L, Wang Y. *Autoimmune diseases are independently associated with COVID-19 severity: evidence based on adjusted effect estimates. J Infect* 2021;**82**(4):e23–6.
3. Peng H, Wu X, Xiong S, Li C, Zhong R, He J, et al. *Gout and susceptibility and severity of COVID-19: a bidirectional Mendelian randomization analysis. J Infect* 2022;**85**(3):e59–61.
4. Chang R, Yen-Ting Chen T, Wang S-I, Hung Y-M, Chen H-Y, Wei C-CJ. *Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. EClinicalMedicine* 2023;**56**:101783.
5. Favalli EG, Gerosa M, Murgo A, Caporali R. *Are patients with systemic lupus erythematosus at increased risk for COVID-19? Ann Rheum Dis* 2021;**80**(2):e25.
6. Zen M, Fuzzi E, Astorri D, Saccon F, Padoan R, Ienna L, et al. *SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: a cross-sectional study on 916 patients. J Autoimmun* 2020;**112**:102502.
7. Bentham J, Morris DL, Graham DSC, Pinder CL, Tombleson P, Behrens TW, et al. *Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet* 2015;**47**(12):1457–64.
8. Meng R, Zhang N, Yang F, Xu Z, Wu Z, Du Y. *Blood transcriptome analysis revealed the crosstalk between severe COVID-19 and systemic lupus erythematosus. J Infect* 2023. In press.
9. Simmons DP, Nguyen HN, Gomez-Rivas E, Jeong Y, Jonsson AH, Chen AF, et al. *SLAMF7 engagement superactivates macrophages in acute and chronic inflammation. Sci Immunol* 2022;**7**(68):eabf2846.
10. Katz-Agranov N, Zandman-Goddard G. *Autoimmunity and COVID-19 – the microbiotal connection. Autoimmun Rev* 2021;**20**(8):102865.

Feixiang Yang
School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China
First School of Clinical Medicine, Anhui Medical University, Hefei 230032, China
Department of Urology, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

Ning Zhang
School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China
First School of Clinical Medicine, Anhui Medical University, Hefei 230032, China
Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

Ruogang Meng
School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China
First School of Clinical Medicine, Anhui Medical University, Hefei 230032, China

Kun Wang, Tianrui Liu
School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China
Second School of Clinical Medicine, Anhui Medical University, Hefei 230032, China

Jialin Meng *
Department of Urology, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China
E-mail address: mengjialin@ahmu.edu.cn

Yinan Du *
School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China

*Correspondence to: Department of Urology, First Affiliated Hospital of Anhui Medical University, 218th Jixi Road, Hefei 230022, China.
*Correspondence to: School of Basic Medical Sciences, Anhui Medical University, 81th Meishan Road, Hefei 230022, China.

E-mail address: duyinannan@126.com