Letter to the Editor

Gout and susceptibility and severity of COVID-19: A bidirectional Mendelian randomization analysis

Dear Editor,

The pandemic of COVID-19, attributed to infection with SARS-CoV-2, has led to enormous health burdens globally. The relationships between autoimmune/rheumatic diseases and susceptibility and severity of COVID-19 have been broadly discussed in Journal of Infection, whereas the findings were inconsistent.[1,2] Most recently, Yang et al. reported that patients with autoimmune diseases have a 19% higher risk of severe COVID-19 using a meta-analysis including 58,183 COVID-19 patients. We extremely appreciate this discovery whereas some limitations should be noted. First, such association was likely to be potentially biased by confounders, such as disease-/treatment-related immune incompetence.[3] Moreover, it is unknown whether autoimmune/rheumatic diseases per se or patient-specific characteristics like genetic variation in immunity contribute to this association. In the present study, we attempted to determine the unconfounded associations between gout, one of the most common autoimmune/rheumatic diseases and susceptibility and severity of COVID-19, which may help inform clinical decision-making more efficiently.[4]

Mendelian randomization (MR) is a novel and promising approach utilizing genetic variants as instrumental variables (IVs) to evaluate the genetic associations between two phenotypes which are generally unconfounded, suggesting it can be employed as a useful tool to reveal the genetic susceptibility shared by gout and COVID-19.[5]
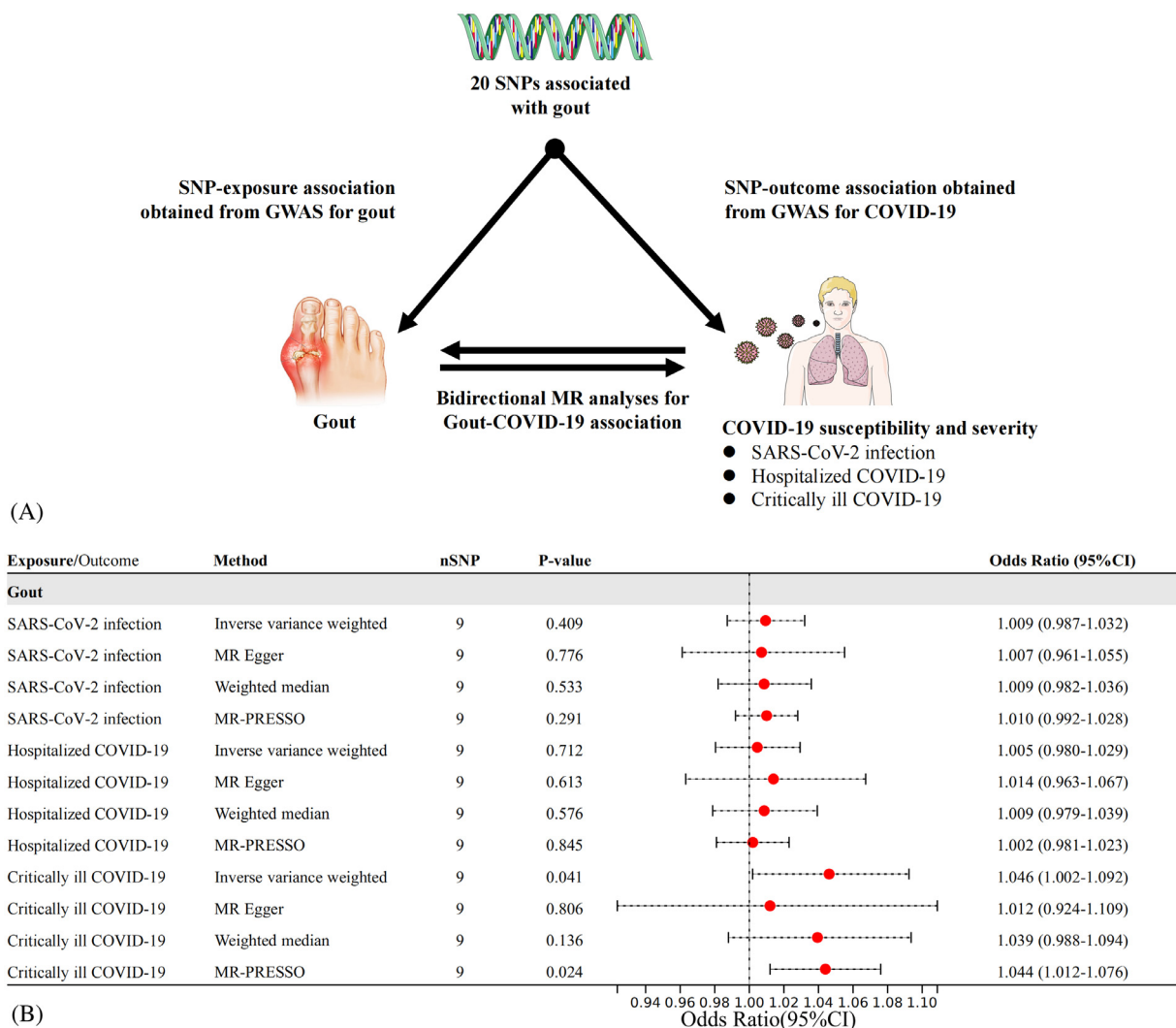
Twenty single-nucleotide polymorphisms (SNPs) robustly correlated with gout ($p < 5 \times 10^{-8}$) were extracted from the latest genome-wide association studies (GWASs), and the heritability of gout was around 30% (Supplementary Table 1). None of the SNPs were excluded for observation of linkage disequilibrium ($r^2 < 0.01$). Six SNPs with secondary phenotypes other than gout were identified using the PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and were subsequently removed to exclude the possible pleiotropic effects. Summary genetic data of susceptibility and severity of COVID-19 were extracted from the COVID-19 Host Genetics Initiative (14,134 cases and 1284,876 controls).[6] The main MR results were calculated by using the inverse variance weighted (IVW) method based on a random-effects model (Fig. 1). MR pleiotropy residual sum and outlier (MR-PRESSO), weighted median, and MR-Egger methods were applied for sensitivity analyses, and we further examined whether some SNPs could

influence the results independently via leave-one-out analysis. Examination of pleiotropic effects was employed by MR-Egger regression analysis. Heterogeneity between estimates from contributing studies was tested using Cochran's Q test in the IVW approach. A bi-directional MR analysis was also exploited to explore the bidirectional effects between COVID-19 and gout.

Based on the sample size of study population in gout, results from power calculation suggested a sufficient power (90%) for MR analyses (Supplementary Table 1). The primary results of the MR analyses indicated that gout was correlated with a 4.6% higher risk of critically ill COVID-19 (odds ratio (OR) = 1.046, 95% confidence interval (CI) 1.002–1.092, $P = 0.041$), directionally consistent in MR-PRESSO (OR = 1.044, 95%CI 1.012–1.076, $P = 0.024$), weighted median (OR = 1.039, 95%CI 0.988–1.094, $P = 0.136$), and MR-Egger (OR = 1.012, 95%CI 0.924–1.109, $P = 0.806$) methods. A trend of higher risk of SARS-CoV-2 infection (OR = 1.009, 95%CI 0.987–1.032, $P = 0.409$) and hospitalized COVID-19 (OR = 1.005, 95%CI 0.980–1.029, $P = 0.712$) was also observed in gout patients whereas without statistical significance. Single MR analysis showed that rs141982039 ($\beta = 0.51$, $p = 0.026$) and rs75674432 ($\beta = 0.92$, $p = 0.034$) was independently associated with a higher risk of SARS-CoV-2 infection and critically ill COVID-19 in gout patients, respectively (Supplementary Table 2). The bidirectional effects between COVID-19 and gout were not supported (Supplementary Fig. 1). Pleiotropy and heterogeneity were not observed (Supplementary Tables 3, 4). Leave-one-out results indicated that no SNP could drive MR results independently (Supplementary Table 5).

To our knowledge, we first found that gout was genetically associated with an increased risk of critically ill COVID-19 using data from large-scale GWASs. Our findings might help inform clinical decision-making from two aspects. Firstly, early detecting patients susceptible to developing critical illness is vital and may help allocate proper care and optimize the usage of restricted medical resources under the pandemic of COVID-19 worldwide. Several metabolic complications, like obesity, hypertension, and type 2 diabetes mellitus, which were also comorbidities of gout, have been underscored to be high-risk factors of critically ill COVID-19.[7] Moreover, the prevalence of gout is as high as 14% in men older than 70 years, who are also the high-risk population predisposed to critically ill COVID-19.[4] Therefore, gout patients diagnosed with COVID-19 might need additional care and special attention to prevent developing the critical illness. Secondly, given that vaccination could prevent critically ill COVID-19 efficiently, our findings might help inform suggestions on vaccination decisions for gout patients. The reported positive association between gout and critically ill COVID-19 in present study should be verified in larger datasets, and future studies are warranted to investigate the underlying mechanisms. In conclusion, our study identified gout as a risk factor of critically ill COVID-19 genetically.

(A)

Exposure/Outcome	Method	nSNP	P-value		Odds Ratio (95%CI)
Gout					
SARS-CoV-2 infection	Inverse variance weighted	9	0.409		1.009 (0.987-1.032)
SARS-CoV-2 infection	MR Egger	9	0.776		1.007 (0.961-1.055)
SARS-CoV-2 infection	Weighted median	9	0.533		1.009 (0.982-1.036)
SARS-CoV-2 infection	MR-PRESSO	9	0.291		1.010 (0.992-1.028)
Hospitalized COVID-19	Inverse variance weighted	9	0.712		1.005 (0.980-1.029)
Hospitalized COVID-19	MR Egger	9	0.613		1.014 (0.963-1.067)
Hospitalized COVID-19	Weighted median	9	0.576		1.009 (0.979-1.039)
Hospitalized COVID-19	MR-PRESSO	9	0.845		1.002 (0.981-1.023)
Critically ill COVID-19	Inverse variance weighted	9	0.041		1.046 (1.002-1.092)
Critically ill COVID-19	MR Egger	9	0.806		1.012 (0.924-1.109)
Critically ill COVID-19	Weighted median	9	0.136		1.039 (0.988-1.094)
Critically ill COVID-19	MR-PRESSO	9	0.024		1.044 (1.012-1.076)

0.94 0.96 0.98 1.00 1.02 1.04 1.06 1.08 1.10
Odds Ratio(95%CI)

(B)

Fig. 1. Genetic associations between gout and susceptibility and severity of COVID-19. Schematic overview of the bidirectional Mendelian randomization (MR) design (A). Summary MR estimates of genetically predisposed gout and susceptibility and severity of COVID-19 (B).

Declaration of Competing Interest

All authors declare no conflicts of interest.

CRediT authorship contribution statement

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Data Availability Statement

The authors acknowledge the efforts of the COVID-19 Host Genetics Initiative (COVID-19 HGI) in providing high quality GWASs data in the MR-Base platform for researchers.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.05.042.

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