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Letter to the Editor

Allopurinol increased the risk of COVID-19 hospitalization mediated by E-Selectin downregulation

Dear Editors,

Since early 2020, the SARS-CoV-2 virus (COVID-19) had led to a global pandemic. Exacerbated inflammation and oxidative stress are characteristics of COVID-19 infection.[1] We read with great interest the recent publication in the Journal of Infection written by Peng et. al. on the association between gout and COVID-19 susceptibility.[2] Their study found that gout was correlated with a higher risk of severe COVID-19 genetically. Allopurinol, a xanthine oxidase inhibitor, is a first-line drug for gout treatment by reducing urate formation.[3] A case-control study involving 3712 patients identified Allopurinol as a drug that increases COVID-19 mortality.[4] Meanwhile, a cohort study concluded that adding allopurinol to standard COVID-19 treatment may improve clinical outcomes.[5] The controversy in these results makes the use of allopurinol in COVID-19 treatment debatable. Also, the use of allopurinol for gout treatment in COVID-19 patients need reconsideration. Mendelian Randomization (MR) is an epidemiological method to analyze causal interference using a genetic variation. This study aims to use MS to explore the exact relationship between allopurinol and COVID-19.

The summary-level GWAS data of 32519 hospitalized COVID-19 cases and 2,062,805 controls were downloaded from COVID-19 Host Genetics Initiative (https://www.covid19hg.org/results/r7/) and only data with population labeled as EUR (European) were included in the current study. The data of allopurinol treatment and proteins were downloaded from IEU open GWAS project, also European data only. Inverse variance weighted (IVW) was used as the standard method for MR analysis and supplemented with MR Egger, Weighted Median, Simple mode, and Weight Mode. When allopurinol treatment was the exposure and COVID-19 hospitalization was the outcome, 16 single nucleotide polymorphisms (SNPs) were identified as instrumental variables following strict criteria ($r^2 < 0.001$, Kb > 10,000, $p < 5 \times 10^{-8}$). The pleiotropy and heterogeneity were analyzed using MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) and Cochran's Q test IVW approach, respectively. To further confirm the robustness of our result, we underwent a 'Leave-one-out' sensitivity analysis to ensure the result was not influenced by individual instrumental variables.

From our results, allopurinol treatment was significantly associated with an increased risk of COVID-19 hospitalization (β = 1.936; 95%CI: 0.039, 3.832; p = 0.045) (Table 1). When analyzing proteins as the outcome, the use of allopurinol led to a significant reduction in soluble E-Selectin (β = −9.003; 95%CI: −16.224, −1.783; p = 0.015). In addition, we set E-Selectin as the exposure and COVID-19 hospitalization as the outcome to ensure the robustness of the result. The threshold of p-value was altered this time to secure sufficient SNPs as instrumental variables ($p < 5 \times 10^{-6}$). With the rest of the methods remaining the same, we found a negative correlation between E-Selectin and COVID-19 hospitalization (β = −0.105; 95%CI: −0.152, −0.059; p < 0.001). All sensitivity analysis showed no significance, suggesting our result was not under the influence of individual SNPs. The mediating effect of E-Selectin on the relationship between allopurinol and COVID-19 hospitalization was analyzed by calculating the percentage of the intermediary effect. Equation β2 × β3/β1 was used with β1 being the causal effect of allopurinol on COVID-19 hospitalization, β2 being the causal effect of allopurinol on serum E-Selectin, and β3 being the causal effect of serum E-Selectin on COVID-19 hospitalization. The intermediary effect was calculated to be 0.945, accounting for 48.83% of the overall effect.

In the present study, we found that allopurinol treatment has an adverse effect on COVID-19 hospitalization. Taking allopurinol may increase the risk of COVID-19 hospitalization by downregulating the E-Selectin protein. This causal relationship was further confirmed as the expression of E-Selectin is associated with reduced risk of COVID-19 hospitalization.

As a first-line drug for gout, the use of allopurinol in COVID-19 patients had been looked at in previous studies. It was identified as a drug associated with increased COVID-19 mortality in a case-control study.[4] The present study used MR to back up this conclusion that allopurinol treatment is not only not helpful for COVID-19 but harmful.

E-Selectin is a protein expressed on the endothelial cell surface, involved in leukocyte adhesion during inflammation.[6] The importance of E-Selectin in COVID-19 has been reported by other MR studies[7,8] which all had a similar result to the current study. The inverse relationship between E-Selectin and COVID-19 severity and hospitalization seems to be robust. The underlying mechanism is likely due to the role of E-Selectin in the chemotaxis of leukocytes during inflammation. Increased E-Selectin expression on the endothelial cell surface could encourage leukocytes to enter the tissue and initiate inflammation to fight the infection. Although allopurinol is a drug with anti-inflammation properties,[5] reducing E-Selectin expression led to an unexpected increase in COVID-19 severity and hospitalization.

To our understanding, this is the first study proposing the causal relationship between allopurinol and COVID-19 hospitalization with E-Selectin being the mediating factor. This has important meaning to patients who are taking allopurinol for treating gout as they are predisposed to higher risks of severe COVID-19 and hospitalization. Currently, no established COVID-19 guideline has suggested pausing the use of allopurinol for COVID-19 patients. Further study with a large sample size is needed.

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Table 1
The association between each exposure and outcome from MR analysis.

Exposure	Outcome	SNPs	β (95% CI)	P
Allopurinol	**COVID-19 hospitalization**	16		
IVW			1.936(0.039, 3.832)	0.045
MR Egger			3.668(0.617, 6.719)	0.034
Weighted median			2.296(−0.168, 4.761)	0.068
Simple mode			2.754(−2.124, 7.633)	0.286
Weighted mode			2.832(0.485, 5.180)	0.032
Allopurinol	**SELE**	4		
IVW			-9.003(−16.224, −1.783)	0.015
MR Egger			-9.844(−20.603, 0.915)	0.215
Weighted median			-8.980(−16.040, −1.919)	0.013
Simple mode			-7.842(−21.671, 5.988)	0.347
Weighted mode			-9.034(−16.524, −1.544)	0.099
SELE	**COVID-19 hospitalization**	6		
IVW			-0.105(−0.152, −0.059)	< 0.001
MR Egger			-0.076(−0.170, 0.017)	0.186
Weighted median			-0.108(−0.136, −0.079)	< 0.001
Simple mode			-0.203(−0.180, 0.026)	0.203
Weighted mode			-0.108(−0.137, −0.079)	0.001

Author contribution

KZ completed all statistical analysis; RC wrote and revised the manuscript; QJ supervised this study.

Declarations of interest

All authors declare no conflict of interest.

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