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Exploring the Potential Association between COVID-19 and Thyroid Cancer: A Mendelian Randomization Study

Dingtao Xu, Xinyu Wang, and Dehua Zhou*

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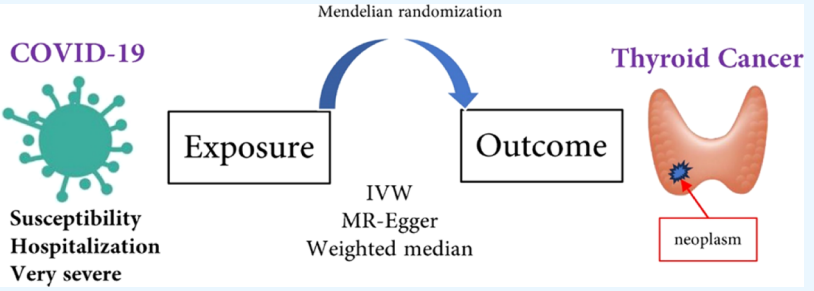

ABSTRACT: In order to address the ongoing debate surrounding the potential link between COVID-19 and thyroid cancer, our study was specifically designed to investigate the association between these two factors. We acquired summary data from a genome-wide association study (GWAS) concerning COVID-19 susceptibility and severity of COVID-19 in the European population, with a focus on their relationship with thyroid cancer. We applied three distinct methodologies to evaluate the causality between COVID-19 and thyroid cancer, employing Mendelian randomization (MR)−Egger, weighted median (WM), and inverse variance-weighted (IVW) approaches. Furthermore, we utilized a variety of techniques to assess pleiotropy and heterogeneity, including the MR−Egger intercept, MR−pleiotropy residual sum and outlier method (PRESSO), and Cochran's *Q* test. The MR analysis revealed associations between the susceptibility of COVID-19 and thyroid cancer (IVW odds ratio [OR]: 2.826, 95% confidence interval [CI]: [0.842, 9.483], $P = 0.093$) as well as between the risk of COVID-19 hospitalization and thyroid cancer (IVW OR: 1.630, 95% CI: [1.050, 2.529], $P = 0.029$). However, the relationship between COVID-19 and the occurrence of severe thyroid cancer cases was less evident (IVW OR: 1.061, 95% CI: [0.575, 1.956], $P = 0.850$). Our sensitivity analyses did not reveal any signs of horizontal pleiotropy or heterogeneity. Our MR study provided compelling evidence supporting a causal connection between the risk of COVID-19 hospitalization and thyroid cancer. Nevertheless, the MR results derived from genetic data do not support a causal link between susceptibility to COVID-19 and the risk of thyroid cancer or between very severe cases of COVID-19 and the risk of thyroid cancer. These findings have significant implications for further investigations into the impact of COVID-19 on health and the etiology of thyroid cancer.

1. INTRODUCTION

In the postpandemic era, the world has witnessed an unprecedented surge in scientific research on the various impacts of COVID-19 on human health.[1] Among these, the potential association between COVID-19 and various diseases, including thyroid cancer, has garnered significant attention.[2,3] Despite the widespread belief among the public that COVID-19 infection may increase the risk of health issues such as thyroid cancer, empirical evidence supporting such claims remains elusive.[4]

COVID-19, caused by the novel coronavirus SARS-CoV-2, presents a unique challenge to individuals with pre-existing health conditions, including cancer.[5] Cancer patients, already considered vulnerable due to compromised immune systems, face higher risks during the pandemic.[6] However, the extent of COVID-19's impact on this specific patient population has been a subject of debate and uncertainty.[7]

Many early observations regarding the potential association between COVID-19 and thyroid cancer were often based on individual reports and observational studies. While these preliminary findings have contributed to hypothesis generation, they are susceptible to bias and confounding factors that can distort the true causal relationship between COVID-19 and thyroid cancer.[8] Thus, establishing a definitive link

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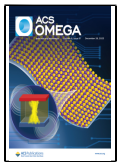

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Table 1. Mendelian Randomization Estimates of the Susceptibility of COVID-19 and Its Severity on Thyroid Cancer[a]

exposure	outcomes	methods	OR	95% CI	P	F
COVID-19 susceptibility	thyroid cancer	IVW	2.826	0.842−9.483	0.093	21
		MR−Egger	0.549	0.00006−4459.838	0.900	
		weighted median	2.520	0.598−10.616	0.208	
COVID-19 hospitalization		IVW	1.630	1.050−2.529	0.029	21
		MR−Egger	2.510	0.352−17.874	0.382	
		weighted median	1.772	0.975−3.222	0.061	
COVID-19 very severe		IVW	1.061	0.575−1.956	0.850	21
		MR−Egger	2.835	0.171−47.089	0.484	
		weighted median	1.328	0.874−2.018	0.183	

[a]COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; IVW, inverse variance-weighted; and MR, Mendelian randomization. All instrumental variables had *F*-statistics greater than 21.

Table 2. Sensitivity Analysis of Mendelian Randomization[a]

	pleiotropy test						pleiotropy test			MR-PRESSO
	IVW			MR−Egger			MR−Egger intercept			global test
exposure	Q	Q_df	Q_pval	Q	Q_df	Q_pval	intercept	SE	P	P
COVID-19 susceptibility	11.418	8	0.179	11.209	7	0.130	0.103	0.285	0.729	0.202
COVID-19 hospitalization	6.906	10	0.734	6.710	9	0.667	−0.061	0.138	0.669	0.735
COVID-19 very severe	52.150	11	2.56×10^{-7}	49.691	10	3.04×10^{-7}	−0.200	0.284	0.498	0.646

[a]COVID-19, coronavirus disease 2019; IVW, inverse variance-weighted; SE, standard error; MR, Mendelian randomization; and MR-PRESSO, Mendelian randomization−pleiotropy residual sum and outlier.

between COVID-19 infection and the risk of thyroid cancer has remained a complex challenge.[9]

To overcome the limitations of observational studies and elucidate the causal relationship between COVID-19 infection and thyroid cancer, we conducted a Mendelian randomization (MR) study.[10] MR utilizes genetic variations as instrumental variables to assess causal relationships while minimizing the confounding biases that frequently affect observational studies. By applying MR, our aim is to provide a more rigorous and evidence-based assessment to determine whether COVID-19 susceptibility and severity of COVID-19 are associated with the risk of thyroid cancer.[11]

In this study, we employed the Mendelian randomization approach to explore the potential association between COVID-19 and thyroid cancer. By addressing the limitations of previous research and leveraging the advantages of genetic data, we endeavor to provide valuable insights into the intricate interactions between COVID-19 and thyroid cancer.[12] Our research findings have the potential to guide clinical practice, public health policies, and future studies aimed at mitigating the impact of COVID-19 and thyroid cancer on both individuals and populations.

2. RESULTS AND DISCUSSION

2.1. Results. *2.1.1. Causal Effects of COVID-19 Susceptibility on Thyroid Cancer.* After stringent criteria were applied to exclude single-nucleotide polymorphisms (SNPs), we utilized nine SNPs as instrumental variables (IVs) for thyroid cancer. All IVs had F-statistics greater than 10, indicating the absence of instrumental variable bias. The results of our various MR methods are summarized in Table 1.

Our analysis revealed a genetic correlation between COVID-19 susceptibility and thyroid cancer. We employed three methods [MR−Egger, weighted median (WM), and inverse variance-weighted (IVW)] to analyze the causal effect of the susceptibility of COVID-19 on thyroid cancer. Among the three MR methods, using the IVW method to estimate the susceptibility, there was no significant association found between the susceptibility of COVID-19 and thyroid cancer. The estimated odds ratio (OR) was 2.826, with a 95% confidence interval (CI) ranging from 0.842 to 9.483 and a *P*-value of 0.093. When using the MR−Egger method for estimation, the calculated OR was 0.549, and the 95% CI was remarkably wide, ranging from 0.00006 to 4459.838, with a high *P*-value of 0.900. These results indicate a substantial degree of uncertainty in the estimates obtained using the MR−Egger method with an extremely wide CI. In the case of the WM method, the estimated causal ratio was 2.520, with 95% CI ranging from 0.598 to 10.616 and a *P*-value of 0.208. Similarly, this method did not achieve conventional levels of statistical significance, indicating uncertainty in the estimates with a wide CI. In summary, these findings suggest that regardless of the statistical method used, no significant causal relationship was found between the susceptibility of COVID-19 and thyroid cancer, as the estimated results did not reach statistical significance. Additionally, the estimates obtained using the MR−Egger method exhibited substantial uncertainty, as evidenced by the wide CI. Therefore, further research is needed to determine whether a causal relationship exists between them.

2.1.2. Causal Effects of COVID-19 Hospitalization on Thyroid Cancer. Similarly, there is an association observed between COVID-19 hospitalization and thyroid cancer (IVW OR: 1.630, 95% CI: [1.050, 2.529], $P = 0.029$; MR−Egger OR: 2.510, 95% CI: [0.352, 17.874], $P = 0.382$; WM OR: 1.772, 95% CI: [0.975, 3.222], $P = 0.061$). While the MR−Egger genetic prediction model did not provide evidence that COVID-19 hospitalization causes thyroid cancer (MR−Egger OR: 2.510, 95% CI: [0.352, 17.874], $P = 0.382$), there is general consistency between the IVW and WM estimates. Given that tests for horizontal pleiotropy and heterogeneity did not reach statistical significance ($P > 0.05$), the use of IVW values rather than MR−Egger regression may offer a more accurate estimation of causal effects. In summary, these

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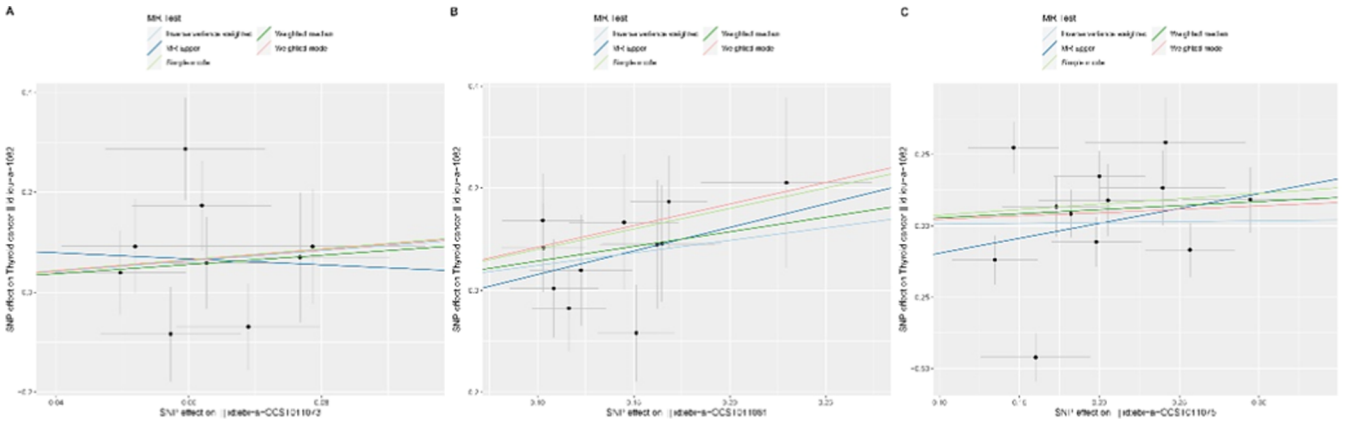

Figure 1. Scatter plot of the results of Mendelian randomization analysis. (A) COVID-19 susceptibility; (B) COVID-19 hospitalization; and (C) COVID-19 severity.

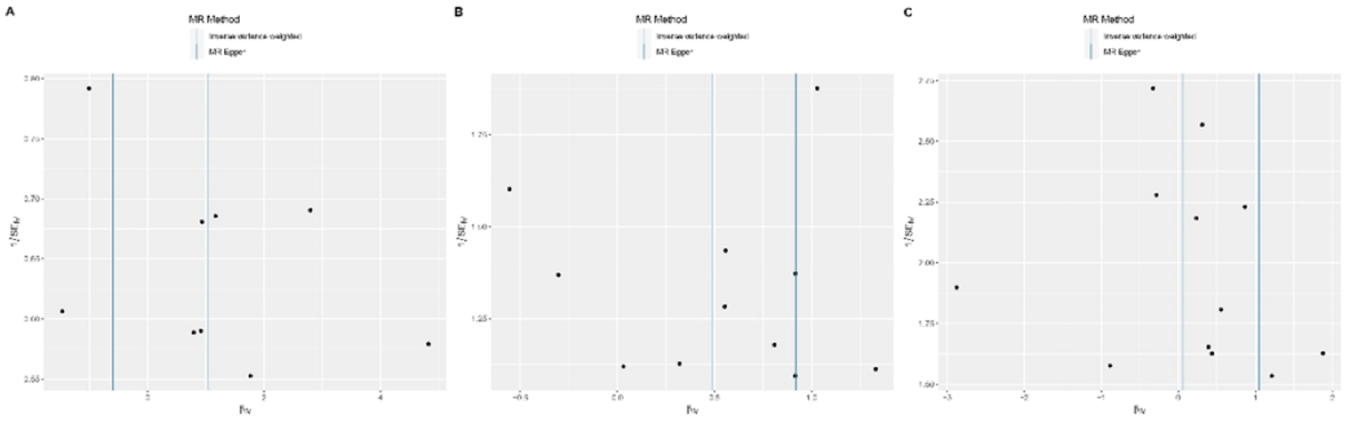

Figure 2. Funnel plot of the results of Mendelian randomization analysis. (A) COVID-19 susceptibility; (B) COVID-19 hospitalization; and (C) COVID-19 severity.

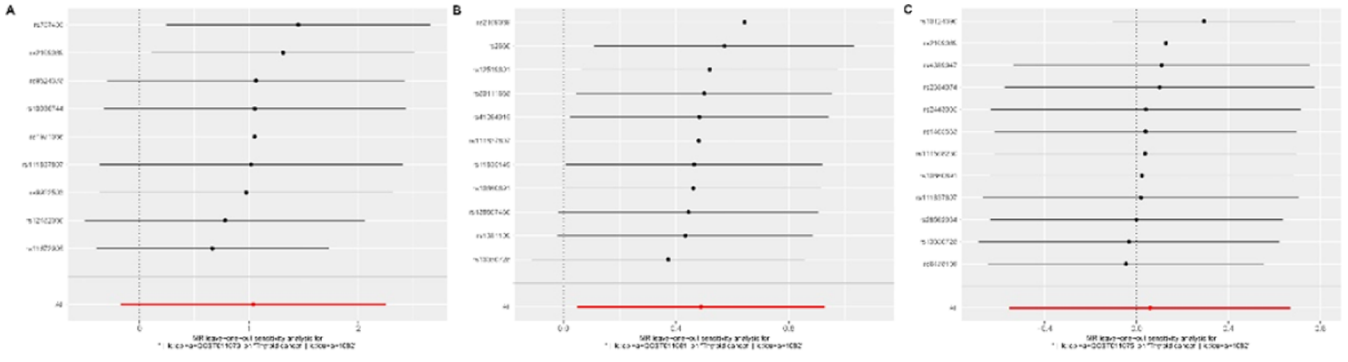

Figure 3. Leave-one-out analysis plots of the results of Mendelian randomization analysis: (A) COVID-19 susceptibility; (B) COVID-19 hospitalization; and (C) COVID-19 severity.

findings suggest a potential association between COVID-19 hospitalization and thyroid cancer, but different analytical methods yield varying degrees of uncertainty. Therefore, further research and validation are needed to confirm the robustness and specificity of this association.

2.1.3. Causal Effects of Very Severe COVID-19 on Thyroid Cancer. However, we found no genetic causal association between very severe COVID-19 and thyroid cancer (IVW OR: 1.061, 95% CI: [0.575, 1.956], P = 0.850; MR−Egger OR: 2.835, 95% CI: [0.171, 47.089], P = 0.484; WM OR: 1.328, 95% CI: [0.874, 2.018], P = 0.183). Therefore, different analytical methods yielded varying degrees of uncertainty, necessitating further research to confirm the causal relationship between very severe COVID-19 and thyroid cancer.

Table 2 provides additional details regarding heterogeneity and pleiotropy. For both the COVID-19 susceptibility and COVID-19 hospitalization factors, the Q values and degrees of freedom (Q_df) in the pleiotropy tests were not significant, with P values greater than 0.05, indicating no apparent pleiotropy. For these two factors, the MR−Egger intercept was close to zero with small standard errors (SE), suggesting that the MR−Egger method did not detect substantial horizontal pleiotropy. The Global test's P value was also >0 05, indicating the absence of overall pleiotropy in the MR analyses of these

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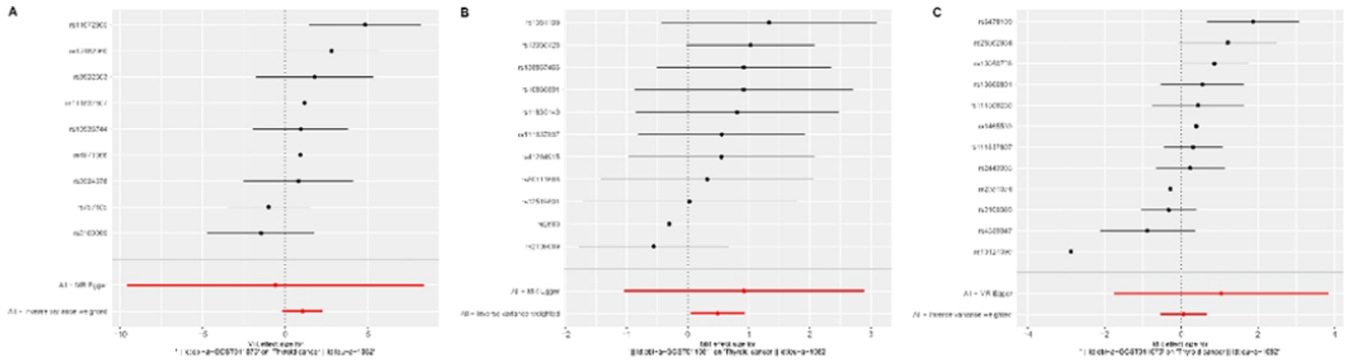

Figure 4. Forest plot of the results of Mendelian randomization analysis. (A) COVID-19 susceptibility; (B) COVID-19 hospitalization; and (C) COVID-19 severity.

two factors. In contrast, for the very severe factor of the COVID-19 syringe, the pleiotropy test results showed highly significant *Q* values and *Q*_df, with very low *P* values, indicating the presence of pleiotropy. The MR−Egger intercept was negative but close to zero, and the *P* value for the Global test remained greater than 0.05, suggesting that while pleiotropy exists, it does not significantly affect the overall causal estimation. Overall, these results indicate that there was no apparent horizontal pleiotropy or global pleiotropy in the MR analyses of COVID-19 susceptibility and COVID-19 hospitalization factors. However, there was some degree of pleiotropy in the very severe factor of COVID-19, but it did not substantially impact the overall causal estimation. To provide a more intuitive and visual representation of the study results, scatter plots (Figure 1), funnel plots (Figure 2), leave-one-out plots (Figure 3), and forest plots (Figure 4) were employed.

2.2. Discussion. The COVID-19 pandemic has emerged as a global health challenge, drawing widespread attention to its various health implications. This study aims to explore the potential association between COVID-19 and thyroid cancer using MR methodology to provide initial insights.

First, our research findings indicate a significant causal relationship between the risk of COVID-19 hospitalization and thyroid cancer. This observation aligns with some early epidemiological observations, suggesting a potential increase in thyroid cancer incidence among COVID-19 patients. However, it is crucial to emphasize that our study did not delve into the biological mechanisms underlying this association, which remains a focus for future research. Previous studies have suggested that COVID-19 infection may lead to abnormal activation of the immune system, triggering inflammatory responses that could be linked to the development of thyroid cancer.[6,13,14] The COVID-19 virus enters human cells by interacting with the ACE2 receptor, which is also expressed in the thyroid.[15] Hence, further investigation is warranted to explore the interaction between COVID-19 infection and thyroid ACE2 receptors and its impact on thyroid cancer risk.

However, surprisingly, our study did not find a causal relationship between the susceptibility of COVID-19 and thyroid cancer. Despite some studies suggesting the crucial role of the immune system in the COVID-19 infection, our MR analysis did not confirm this association. This may be partially due to the fact that COVID-19 susceptibility is influenced by various genetic and environmental factors, including genetic polymorphisms, age, gender, and lifestyle.[16] Therefore, at the genetic level, the contribution of the susceptibility of COVID-19 to thyroid cancer risk appears relatively small and was not significantly captured.

Furthermore, our study also found that the relationship between very severe cases of COVID-19 and thyroid cancer was not evident. Although our analysis did not rule out the possibility of some association, the results did not reach statistical significance. This may reflect the relatively low number of extremely severe cases of COVID-19 and its associated causes, making it challenging to draw effective causal inferences from a genetic perspective.

It is essential to emphasize that our study has some limitations. First, our research was limited to the European population, and as such, the results may not be generalizable to other populations. Second, MR analysis relies on a set of assumptions, and although we employed various methods to test these assumptions, there may still be unaccounted potential confounding factors.[17] Lastly, due to the ongoing COVID-19 pandemic, long-term follow-up data for patients are still incomplete, and we are unable to assess the actual impact of COVID-19 on the survival and clinical outcomes of thyroid cancer patients.[18]

In conclusion, our study offers a new perspective through MR analysis and delves into the potential association between COVID-19 and thyroid cancer. Our findings underscore a causal relationship between the COVID-19 hospitalization risk and thyroid cancer but do not support a significant association between the susceptibility of COVID-19 and thyroid cancer. Future research should further elucidate the biological mechanisms underlying this relationship and consider more diverse populations and longer term follow-up data to comprehensively understand the impact of COVID-19 on thyroid cancer risk.

This study employed MR methodology, using genetic variations as IVs, to assess the causal relationship between COVID-19 and thyroid cancer. It offers strengths such as addressing confounding factors, utilizing extensive genome-wide association study (GWAS) data, and employing various MR methods for robustness. However, limitations include a lack of insights into biological mechanisms and potential population-specific effects. Future research should explore these mechanisms, expand sample diversity, and investigate clinical outcomes for a more comprehensive understanding of the COVID-19 and thyroid cancer association.

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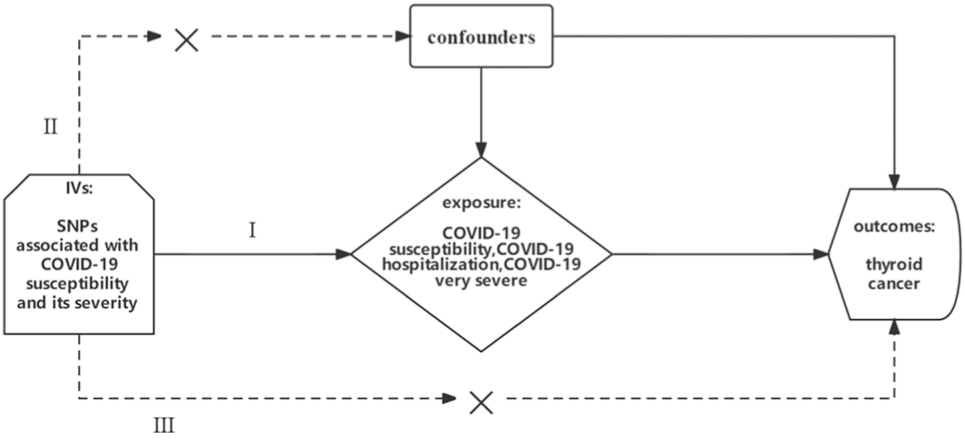

Figure 5. Research design concept. IVs, instrumental variables and SNPs, single-nucleotide polymorphisms.

Table 3. Exhaustive Description of the Studies and Datasets Employed in the Analyses[a]

phenotype	GWAS ID	source (PMID)	ancestry	number of SNPs	cases	controls
COVID-19 susceptibility	ebi-a-GCST011073	32,404,885	European	8,660,177	38,984	1,644,784
COVID-19 hospitalization	ebi-a-GCST011081	32,404,885	European	8,107,040	9986	1,877,672
COVID-19 very severe	ebi-a-GCST011075	32,404,885	European	9,739,225	5101	1,383,241
thyroid cancer	ieu-a-1082	23,894,154	European	572,028	649	431

[a]SNPs, single-nucleotide polymorphisms; COVID-19, coronavirus disease 2019; and GWAS, genome-wide association studies.

3. CONCLUSIONS

In summary, our study was designed to investigate the potential association between COVID-19 and thyroid cancer using the MR methodology. We analyzed summary data from a GWAS study concerning COVID-19 susceptibility and disease severity in the European population, exploring their relationship with thyroid cancer. Our MR analysis revealed a significant association between the risk of COVID-19 hospitalization and thyroid cancer, providing robust evidence of a causal relationship between these two factors. However, based on genetic data, our study did not support a causal link between COVID-19 susceptibility and the risk of thyroid cancer or support a causal relationship between severe cases of COVID-19 and the risk of thyroid cancer. These findings hold substantial implications for understanding the impact of COVID-19 on health and the etiology of thyroid cancer. This study contributes to a more in-depth exploration of the potential connections between COVID-19 and thyroid cancer, emphasizing the necessity for further research in this field to gain a better understanding of the complexity of these relationships and their implications for public health.

4. MATERIALS AND METHODS

4.1. Study Design. We employed a two-sample MR approach to investigate the causal relationship between the susceptibility of COVID-19 and its severity and thyroid cancer in the European population. The following are the three most crucial assumptions that must be maintained throughout the entire MR analysis process: (I) there is an extremely high degree of association between instrumental variables (IVs) and COVID-19 susceptibility and its severity (exposure); (II) the IVs are not related to any confounding factors that affect both exposure (COVID-19 susceptibility and its severity) and the outcome (thyroid cancer); and (III) the IVs are not directly linked to the outcome (thyroid cancer), and their impact on the outcome (thyroid cancer) can only be indicated through exposure (COVID-19 susceptibility and its severity).[19] The current research design is illustrated in Figure 5. This study adhered to the most recent STROBE-MR guidelines.

4.2. Data Sources. IVs were selected based on SNPs associated with COVID-19 susceptibility and its severity. For the exposure (COVID-19 susceptibility, COVID-19 hospitalization, and very severe COVID-19), we employed summary statistics from GWAS of the COVID-19 susceptibility and severity. These data encompassed 38,984 individuals of European ancestry with COVID-19 susceptibility and 1,644,784 controls, 9986 individuals of European ancestry with COVID-19 hospitalization and 1,877,672 controls, and 5101 individuals of European ancestry with very severe COVID-19 and 1,383,241 controls.[20,21] For the outcome dataset, we obtained genetic instruments for thyroid cancer (649 cases and 431 controls) from publicly available summary statistics.[22] All datasets are downloadable from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/datasets/). Additional information regarding GWAS can be found in Table 3.

The data used in our MR analysis are entirely from previously reported summary data. Therefore, neither patient consent nor ethical approval was necessary for the study.

4.3. Instrumental Variable Selection. As a first step to validate the first hypothesis, we conducted a search for SNPs across the entire genome that were associated with the exposure ($P < 5 \times 10^{-6}$) and exhibited a high degree of correlation. These SNPs were determined to be independent by excluding those with an r^2 value less than 0.001 within a 10,000 kb window.[23] Additionally, we adjusted for horizontal pleiotropy using the MR-PRESSO method to mitigate the weak instrument bias. To address weak instrument bias, we employed F-statistics and variance (R^2) to assess the strength of the selected SNPs.[24] The most recent and precise calculation method was used, where $F = R^2(N - K - 1)/K(1 - R^2)$. Here, R^2 represents the cumulative variance of the

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COVID-19 susceptibility and its severity; K corresponds to the total number of IVs; and N denotes the total number of samples included in the COVID-19 susceptibility and its severity GWAS. An F-statistic exceeding 10 was considered indicative of a sufficiently strong correlation to prevent weak instrument bias.

4.4. Mendelian Randomization Analysis. In our study, we established the causal relationship between the susceptibility of COVID-19 and its severity with thyroid cancer using the MR−Egger, WM, and IVW methods, with IVW being the primary statistical analysis technique. The IVW method is our primary statistical analysis technique, although it could be skewed if the IVs exhibit horizontal pleiotropy. To examine the reliability of our findings and potential pleiotropy, we conducted sensitivity analyses using the weighted median and MR−Egger regression approaches. The WM technique produces an unbiased causal estimation when 50% or more of the weights are based on valid SNPs. The MR−Egger regression method is capable of providing estimates with pleiotropy corrections applied to them. Additionally, we employed the MR−Egger intercept to determine whether pleiotropy was present. The heterogeneity of IVW estimates was quantified using Cochran's Q test. Furthermore, we conducted the MR-PRESSO test to check for outliers, and any SNPs found to be outliers were manually removed. To assess the robustness of the results, we applied the leave-one-out method to remove specific SNPs that had a negative impact on the research outcomes and then recalculated the results. These analyses were conducted using R software (R version 4.3.0) and utilized the "TwoSampleMR" (version 0.5.7) and "MRPRESSO" packages.

AUTHOR INFORMATION

Corresponding Author

Dehua Zhou − *Department of Gastrointestinal Surgery, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, Shanghai 200434, China;* orcid.org/0000-0003-2877-7746; Email: deachzdh@163.com

Authors

Dingtao Xu − *Department of Anesthesia and Perioperative Medicine, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, Shanghai 200434, China*

Xinyu Wang − *Department of Thyroid, Breast and Vascular Surgery, Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine, Shanghai 200434, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c07287

Notes

The authors declare no competing financial interest.

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