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ORIGINAL RESEARCH

No Genetically Predicted Association Between Human Papillomavirus and COVID-19: A Mendelian Randomization Analysis in European Ancestry Population

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Purpose: Previous studies reveal that coronavirus disease 2019 (COVID-19) infection accelerates the progression of Human papillomavirus (HPV)-related diseases, but the results remain controversial. We conducted a bidirectional two-sample Mendelian randomization (MR) study to evaluate the causal association between HPV infection and COVID-19 using genome-wide association study (GWAS) summary data from European ancestry populations.

Patients and Methods: Genetic summary data of HPV infection and COVID-19 were derived from the public GWAS meta-analysis and the COVID-19 host genetics initiative GWAS, respectively. The causal link between HPV infection and COVID-19 was evaluated by MR analysis with inverse variance weighting (IVW), MR-Egger, and weighted median methods. Additional MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR-Egger regression methods were used to identify the potential pleiotropy of the instrumental variables (IVs). Bonferroni correction was used to account for the issue of multiple comparisons, leading to a statistically significant *P*-value of less than 0.004 (0.05/2*3*2).

Results: There were no significantly causal links of HPV-16 or HPV-18 infection with COVID-19 infection, hospitalized COVID-19, or severe COVID-19 (all $P>0.05$). Furthermore, no significant causal effect of all three types of COVID-19 on HPV-16 and HPV-18 was observed in the reverse MR analyses (all $P>0.05$). MR-Egger regression and MR-PRESSO global test did not find the presence of horizontal pleiotropy between IVs of HPV infection and COVID-19.

Conclusion: This study shows that COVID-19 infection does not affect the risk of HPV-16/18 infection, nor does HPV-16/18 infection increase COVID-19 infection risk. It highlights the need to maintain routine health management and no change to HPV prevention strategies.

Keywords: HPV, COVID-19, mendelian randomization, causal relationship, genetic association

Introduction

Coronavirus disease 2019 (COVID-19) caused by coronavirus type 2 (SARS-CoV-2) is a severe acute respiratory syndrome, which has been declared a worldwide public health crisis.[1] Currently, the pandemic of COVID-19 is still developing and its morbidity and mortality continue to impose a significant social burden. More than 7.6 hundred million cases and 6.9 million deaths have been documented as of the writing of this article.[2] Patients with COVID-19 exhibit

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varying degrees of severity, from being asymptomatic to developing acute multiple-organ dysfunction.[3] Studies have indicated that COVID-19 can elicit symptoms in multiple physiological systems, including but not limited to the renal, cardiovascular, gastrointestinal, hematological, neurological, immunological, and reproductive systems.[4,5]

Human papillomavirus (HPV) is a non-enveloped, circular DNA virus with a double-stranded genome that can infect any area of the skin and mucous membranes.[6] Most infections of HPV are asymptomatic, but there exists a subset of women who experience persistent infections that may eventually turn into malignancies.[7] As of present, over 200 HPV genotypes have been identified with at least 15 types being capable of causing cervical and other site-specific cancers.[8] Notably, the two most prevalent oncogenic strains among them, HPV E7 type 16 (HPV-16) and HPV E7 type 18 (HPV-18) are responsible for almost 70% of all cervical malignancies globally. HPV-related cancers, especially cervical cancer, pose a significant public health challenge, disproportionately affecting women worldwide. Previous studies have suggested that factors such as sexual behavior, parity, genetic predisposition, and impaired immunity contribute to the risk of HPV infection.[9,10]

Numerous studies have established a correlation between COVID-19 and immune dysfunction and reproductive system malignancies.[11] Some studies also reported that COVID-19 infection accelerates the progression of HPV-related diseases, but the results remain controversial.[12,13] Vavoulidis et al's study provided evidence of its exacerbation of HPV-related disease progression, while the report of Demirbas et al suggested that SARS-CoV-2 may alleviate HPV symptoms.[12,13] Given the established role of immune response in controlling HPV persistence and progression, the potential relationship between HPV and COVID-19 warrants further investigation. However, research in this field is still relatively scarce, and there are also some limitations in previous related studies, including: 1) a scarcity of available evidence; 2) inconsistent findings across studies; 3) insufficient methodological strength to establish causality; 4) a lack of consideration regarding the relationship between specific HPV subtypes and COVID-19. Therefore, the causal relationship between specific HPV subtypes and COVID-19 remains unclear and warrants further investigation using methods with strong determination of causality.

Mendelian randomization (MR), which utilizes genetic variants as instrumental variables (IVs) to enhance the power of causal inference, is a robust method for investigating causal relationships between risk factors and diseases.[14] The assignment of single nucleotide polymorphism (SNP) sites is randomized at the outset, thereby avoiding potential bias stemming from reverse causation and residual confounding factors.[15] Furthermore, the potential negative impacts of COVID-19 make it infeasible to use randomized controlled trials (RCTs) as a causal relationship assessment tool for studying the association between COVID-19 and unfavorable outcomes. On the contrary, MR analyses can use existing open-access data from large-scale genome-wide association studies (GWAS), thus broadening its range of applications and enhancing its accuracy.

In this study, we conducted a bidirectional two-sample MR study to investigate the potential causal links between HPV and COVID-19, as well as to advance our comprehension of the feasibility and risks associated with administering HPV vaccination to COVID-19 patients. By clarifying whether there is a genetic causal link between HPV and COVID-19 (and vice versa), our study will inform the safe administration of HPV vaccines to COVID-19 patients and guide the clinical management of HPV-infected individuals during the pandemic. Furthermore, the findings will contribute to the development of evidence-based vaccination policies for women with COVID-19, ultimately improving women's health outcomes in the context of dual public health challenges.

Materials and Methods

Study Design

We used two-sample MR analyses to evaluate the association between HPV and COVID-19 in this study. Specifically, we focused on HPV-16 and HPV-18, which were the two most prevalent oncogenic strains among HPV. As for COVID-19, we selected three types of measures, including COVID-19 infection, hospitalized COVID-19, and severe COVID-19.

Data Sources and IVs Selection

GWAS of HPV

The genetic associations of HPV-16 and HPV-18 were extracted from a comprehensive and up-to-date public meta-analysis of GWAS, which was carried out by Suhre et al.[16] We reviewed and collected the genetic information

corresponding to SNPs in 3 different populations with COVID-19 infection from HPV GWAS data, respectively. The source of HPV GWAS data was listed in Table 1.

GWAS of COVID-19

The COVID-19-related data were obtained from the GWAS of the COVID-19 Host Genetics Initiative (Release 5).[17,18] We selected data that exclusively included participants of European descent. We assessed the causality between HPV and 3 distinct populations of COVID-19 infection, including COVID-19 infection, hospitalized COVID-19, and severe COVID-19. The origin of GWAS data for COVID-19 was listed in Table 1.

IVs Selection

The SNPs that exhibited significant association ($P < 5\times10^{-8}$) with exposure factors were selected from the GWAS of the exposure. We conducted a clustering process (R^2<0.001 and clumping distance=10,000 kb) to eliminate linkage disequilibrium (LD) between SNPs. Additionally, SNPs with a minor allele frequency (MAF < 0.01) were eliminated to ensure the validity and feasibility of our findings. As no genetic variants for HPV-16 and HPV-18 reached the genome-wide significant threshold, it was adjusted from $P < 5\times10^{-8}$ to $P < 5\times10^{-5}$ in the end. Consequently, we selected SNPs associated with HPV-16 and HPV-18 ($P < 5\times10^{-5}$) as IVs and matched them with the outcome GWAS. The proxy SNPs with high LD (R^2>0.8) were used as substitutes in case the correspondent SNPs were not found. Following the removal of palindromic SNPs, other selected SNPs were chosen as IVs. A total of 22 IVs for HPV-16 and 12 IVs for HPV-18 were included in the MR analyses, with 2 IVs for each COVID-19 phenotype (infection, hospitalized, and severe). Detailed SNP information for these IVs, including rsID, effect allele, beta coefficient, *P*-value, and F-statistic, can be found in Supplementary Table 1 for HPV and Supplementary Table 2 for COVID-19.

Statistical Analyses

The four methods, Inverse Variance Weighting (IVW), MR-Egger, Weighted, and Weighted Median, were incorporated to be complementary and mutually corroborative in evaluating the association between HPV and COVID-19. The IVW method was the predominant statistical approach among them. Simultaneously, we evaluated the potential level pleiotropy in IVs using two methods, including MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR-Egger regression techniques.[19] In the meantime, MR-PRESSO was also capable of detecting outliers in IVs. Following the removal of such abnormal values, we conducted multiple rounds of MR-PRESSO and MR-Egger testing until no horizontal pleiotropy in all IVs. A *P* value greater than 0.05 from both MR-PRESSO and MR-Egger tests indicated the absence of pleiotropy. Then, Cochran's Q statistic was conducted to detect and measure the level of heterogeneity in all IVs.[20] A *P* value greater than 0.05 for Cochran's Q statistic suggested that there was no significant heterogeneity. We performed a leave-one-out sensitivity analysis in this study to validate the reliability of estimating causal relationships by identifying and eliminating SNPs that exerted significant influence on the outcomes. In a sizable sample with a significant degree of overlap between exposure and outcome data, the strength of IVs was measured by calculating the F statistic.[21] To infer the causal relationship of HPV with COVID-19, a two-sample MR study was conducted to evaluate whether there were causal associations between two types of HPV and three distinct forms of COVID-19 to confirm their association. The Bonferroni correction technique was used to account for the issue of multiple comparisons, leading to

Table 1 Detailed Information on Studies and Datasets Used in the Present Study

Trait	GWAS ID	Year	Ancestry	Sample Size	Number of SNPs
HPV E7 Type 16	prot-c-2623_54_4	2019	European ancestry	997	501,428
HPV E7 Type18	prot-c-2624_31_2	2019	European ancestry	997	501,428
COVID-19 (RELEASE 5)	ebi-a-GCST011073	2020	European ancestry	1,683,768	8,660,177
COVID-19 (hospitalized vs population) RELEASE 5	ebi-a-GCST011081	2020	European ancestry	1,887,658	8,107,040
COVID-19 (very severe respiratory confirmed vs population) RELEASE 5	ebi-a-GCST011075	2020	European ancestry	1,388,342	9,739,225

Abbreviations: HPV-16, human papillomavirus type 16; HPV-18, human papillomavirus type 18; COVID-19, Coronavirus disease 2019.

a statistically significant *P*-value of less than 0.004 (0.05 was divided by 2*3*2).[22] All statistical analyses were conducted using R packages "TwoSampleMR" and "MRPRESSO" in version 4.1.1 of R software.

Results

IVs Selection

HPV IVs

After the clumping process to eliminate LD between SNPs, a collective of 23 SNPs exhibited significant association with HPV-16, whereas 13 SNPs associated with HPV-18 ($P < 5\times10^{-5}$) were selected. The MAF for all these SNPs were not less than 0.01, and the F values of all IVs were all above 10. As palindromic SNPs identified in MR analyses, rs2864426 of HPV-16 and rs249011 of HPV-18 were excluded. Ultimately 22 IVs of HPV-16 and 12 IVs of HPV-18 were included in the MR analyses. The SNP information selected as IV for HPV-16 and HPV-18, including rsID, effect allele, beta coefficient, *P*-value, and F-statistic, is provided in Supplementary Table 1.

COVID-19 IVs

Following the clumping process to eliminate LD between SNPs, a total of 7 SNPs, 5 SNPs, and 8 SNPs were identified as strongly associated ($P < 5\times10^{-8}$) with COVID-19 infection, hospitalized COVID-19, and severe COVID-19 respectively. The F values of all IVs were all above 10. rs4971066, rs10936744, rs17078348, rs2271616, rs757405, rs12482060 of COVID-19 infection were not found in both HPV-16 and HPV-18 GWAS data, and only the proxy SNP rs34376498 was selected as the substitute of rs10936744, no proxy SNPs for other SNPs can be found in the outcome GWAS data. rs35081325, rs2109069, and rs13050728 of hospitalized COVID-19 were not found in both HPV-16 and HPV-18 GWAS data, and there were no proxy SNPs for them can be found in outcome GWAS data. rs35081325, rs2237698, rs10860891, rs77534576, rs2109069, rs13050728 of severe COVID-19 were not found in both HPV-16 and HPV-18 GWAS data, and no proxy SNPs for this variant were found in the outcome GWAS data. rs111837807 and rs2384074 of severe COVID-19 were not found in both HPV-16 and HPV-18 GWAS data, and their proxy SNPs rs17190776 and rs2285932 were selected as the substitutes, respectively. In total, 2 IVs for each COVID-19 phenotype (infection, hospitalized, and severe) were included in the MR analyses. Detailed SNP information for these IVs, including rsID, effect allele, beta coefficient, *P*-value, and F-statistic, can be found in Supplementary Table 2.

Causal Relationship Between HPV and COVID-19

HPV on COVID-19

The causal relationship between HPV-16 and HPV-18 and all three types of COVID-19 (COVID-19 infection, hospitalized COVID-19, and severe COVID-19) was not observed (all *P*>0.05) (Table 2 and Figure 1).

Table 2 Main Mendelian Randomization Estimates of the Causal Relationship Between HPV and COVID-19

Exposure	Outcome	Method	OR (95% CI)	*P* Value
HPV-16	COVID-19 infection	Weighted median	1.006 (0.979–1.033)	0.690
		MR Egger	1.034 (0.973–1.099)	0.294
		IVW	1.003 (0.983–1.024)	0.782
HPV-16	Hospitalized COVID-19	Weighted median	1.022 (0.969–1.077)	0.423
		MR Egger	0.987 (0.879–1.108)	0.822
		IVW	1.016 (0.976–1.058)	0.434
HPV-16	Severe COVID-19	Weighted median	1.029 (0.941–1.126)	0.534
		MR Egger	1.093 (0.915–1.305)	0.340
		IVW	1.023 (0.960–1.089)	0.490

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Method	OR (95% CI)	*P* Value
HPV-18	COVID-19 infection	Weighted median	0.973 (0.935–1.014)	0.192
		MR Egger	0.961 (0.850–1.085)	0.534
		IVW	0.978 (0.948–1.009)	0.164
HPV-18	Hospitalized COVID-19	Weighted median	0.945 (0.871–1.025)	0.174
		MR Egger	0.856 (0.687–1.067)	0.197
		IVW	0.966 (0.912–1.023)	0.237
HPV-18	Severe COVID-19	Weighted median	0.963 (0.862–1.077)	0.512
		MR Egger	0.885 (0.636–1.232)	0.486
		IVW	0.951 (0.873–1.036)	0.251
COVID-19 infection	HPV-16	IVW	1.368 (0.528–3.549)	0.519
Hospitalized COVID-19	HPV-16	IVW	1.284 (0.611–2.698)	0.510
Severe COVID-19	HPV-16	IVW	1.175 (0.838–1.647)	0.349
COVID-19 infection	HPV-18	IVW	0.854 (0.400–1.823)	0.683
Hospitalized COVID-19	HPV-18	IVW	0.577 (0.166–2.002)	0.386
Severe COVID-19	HPV-18	IVW	1.251 (0.810–1.931)	0.312

Abbreviations: HPV-16, human papillomavirus type 16; HPV-18, human papillomavirus type 18; COVID-19, Coronavirus disease 2019; IVW, inverse variance weighting.

COVID-19 on HPV

No significant causal effect of all three types of COVID-19 (COVID-19 infection, hospitalized COVID-19, and severe COVID-19) on both HPV-16 and HPV-18 was found (all $P>0.05$) (Table 2 and Figure 2).

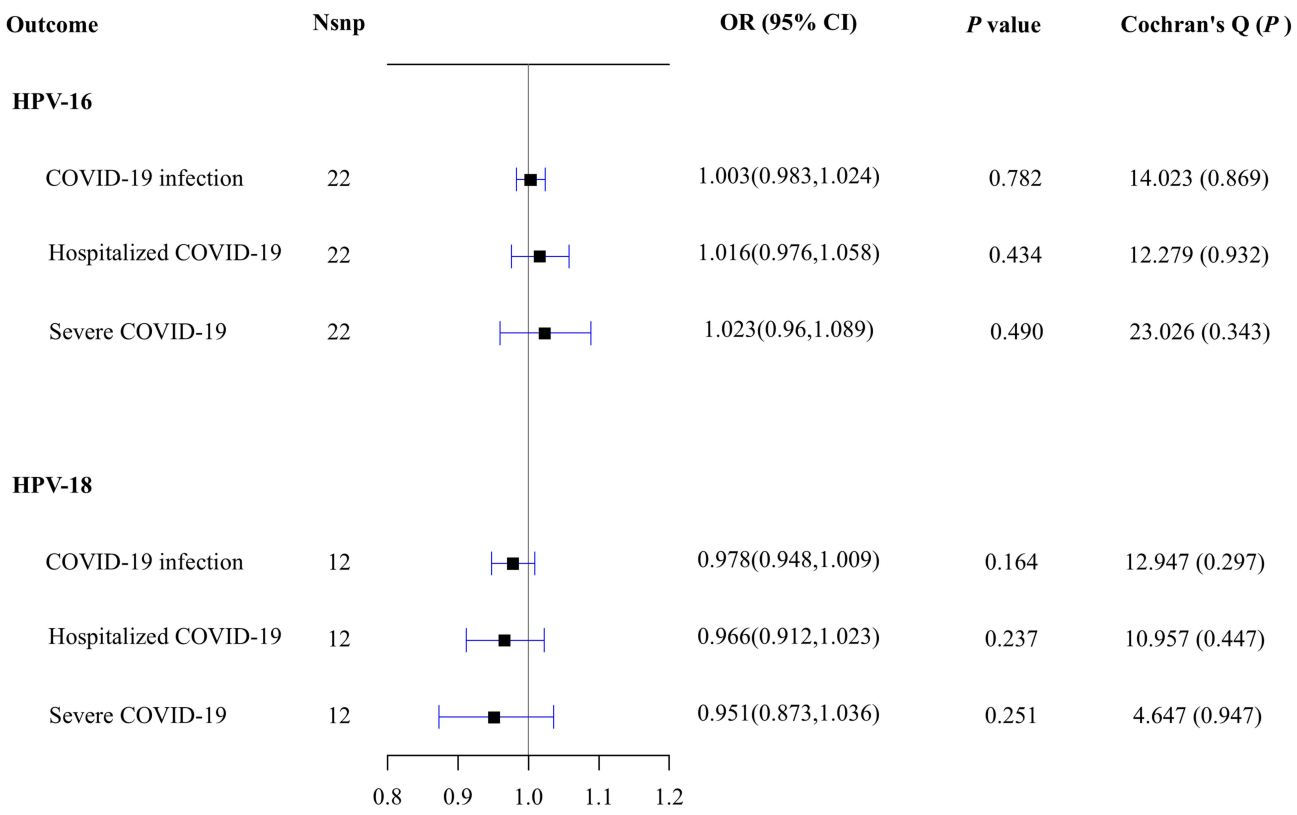

Figure 1 The IVW estimate results of HPV on COVID-19.
Abbreviations: HPV, human papillomavirus; COVID-19, coronavirus disease 2019; IVW, inverse variance weighting.

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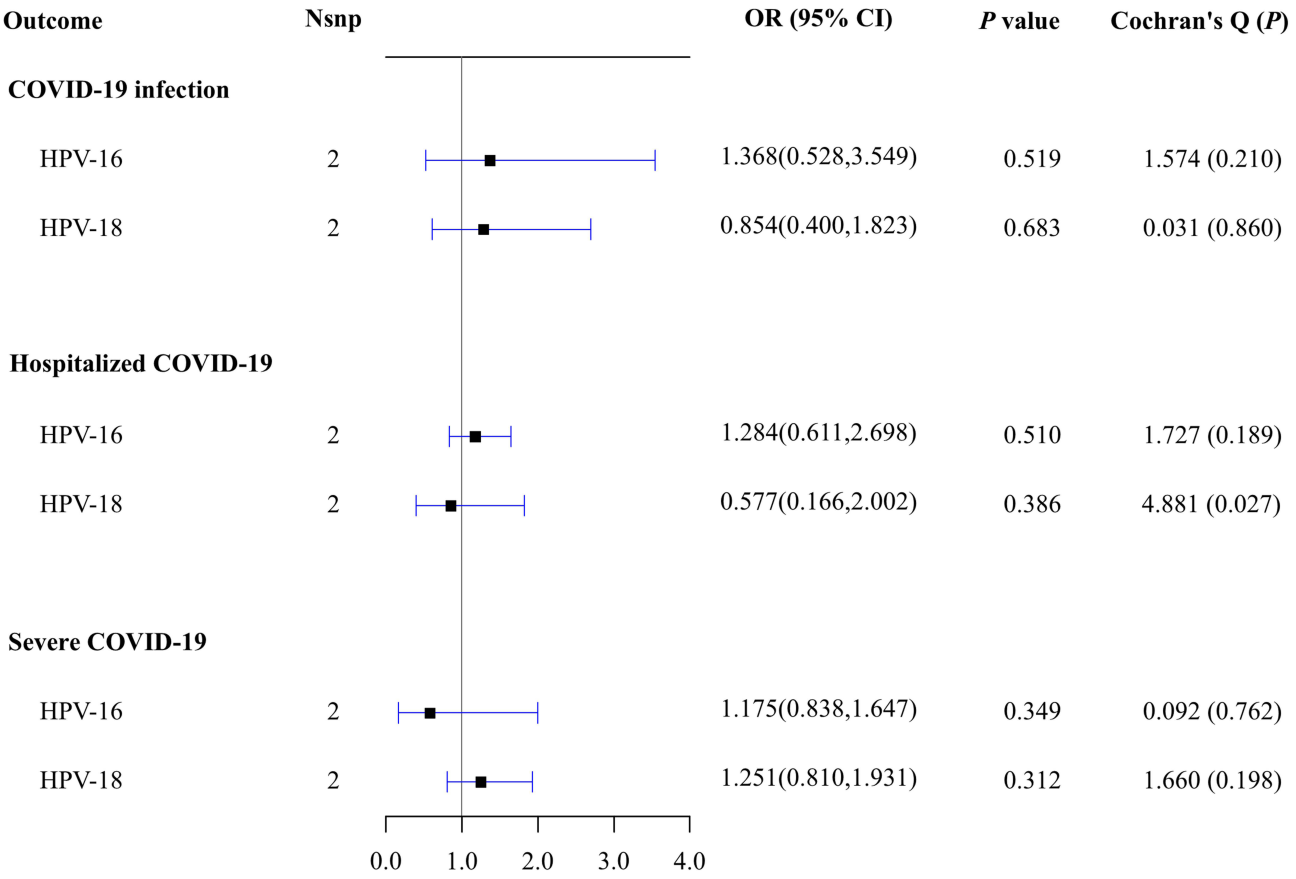

Figure 2 The IVW results of COVID-19 on HPV.
Abbreviations: HPV, human papillomavirus; COVID-19, coronavirus disease 2019; IVW, inverse variance weighting.

Pleiotropy and Sensitivity Analyses

The heterogeneity analyses revealed no significant differences among the selected IVs. Furthermore, MR-Egger regression indicated no evidence of horizontal pleiotropy between HPV-related IVs and outcomes, which was also supported by the MR-PRESSO global test. However, neither the MR-Egger regression nor MR-PRESSO global test could be conducted, due to insufficient IVs of three types of COVID-19 on HPV-16 and HPV-18 (Supplementary Tables 3 and 4). The results were determined to be unaffected by any SNPs based on the leave-one-out analyses. The results of the pleiotropic and sensitivity analyses were presented in Supplementary Figures 1–4.

Discussion

Our study found no evidence to support a causal relationship between HPV-16 or HPV-18 and the three COVID-19 groups. To avoid the potential bidirectional links between HPV infection and COVID-19, the reverse MR analysis was conducted, and we did not observe the presence of a causal association between COVID-19 and HPV infection.

Previous studies indicated that COVID-19 may potentially affect the immune and reproductive system.[23,24] COVID-19 infection may decrease male fertility by lowering the semen quality.[23] Additionally, pregnant women infected with COVID-19 may be at an increased risk of complications such as premature delivery and miscarriage.[11] Due to the impact of COVID-19 on both immunity and reproduction, there has been increased interest in exploring the relationship between HPV and COVID-19. HPV is closely linked to both these systems, making it a relevant factor for investigation.[25,26]

However, the conclusion about the relationship between HPV and COVID-19 is still inconclusive. According to Vavoulidis et al, a 32-year-old patient with HPV infection developed cervical epithelial lesions which were ultimately confirmed by histopathology as CIN1 after COVID-19 infection, suggesting that COVID-19 may improve progression in cervical pathology.[13] On the contrary, the report of Demirbas et al' supported the possibility of a negative correlation between HPV infection and

SARS-CoV-2.[12] Despite undergoing various treatment regimens for a decade without any response, a female patient aged 26 years with multiple HPV-induced warts on both hands experienced the autonomous disappearance of viral warts four weeks after the onset of COVID-19 symptoms.[12] Furthermore, a prospective cohort study including 310 Turkish women conducted by Purut et al found that the risk of HPV-16 infection was significantly increased in women with COVID-19 compared to those without COVID-19, while the prevalence of HPV was not different between these two groups.[27] The results of our bidirectional MR analyses, however, fail to support a causal association between HPV and three distinct forms of COVID-19 infection.

The inconsistent conclusions regarding the association between HPV and COVID-19 may be attributed to the bidirectional regulation of COVID-19's impact on immune function, which can lead to both immunosuppression and cytokine storm. Despite exhibiting little genetic similarity, papillomaviruses and coronaviruses may share commonalities in terms of aberrant immune responses or life cycles.[13] On the one hand, individuals diagnosed with COVID-19 may face an elevated susceptibility to HPV infection and poorer outcomes due to dysregulated inflammatory responses elicited by SARS-CoV-2.[28] Meanwhile, dysregulation of the immune system can be attributed to the persistence of HPV, which is a predominant factor in cell transformation and tumor progression resulting from HPV infection.[29] On the other hand, extensive lung inflammation resulting from SARS-CoV-2 infection could lead to the dysfunction of the immune system, which in turn may trigger related responses such as cytokine storm and delayed hypersensitivity.[30] These responses may suppress COVID-19 and HPV virus activity, resulting in the clearance of HPV infection and alleviation of associated symptoms.[28]

This study shows that the severity of previous SARS-CoV-2 infection does not increase the risk of HPV-16 or HPV-18 infection. Therefore, there is no evidence to support shortening cervical cancer screening intervals or accelerating HPV vaccination due to prior COVID-19 infection. Moreover, the study indicates that women diagnosed with HPV-16/18 infection do not have an increased genetic risk of severe COVID-19. As a result, women can continue routine prenatal care, cancer follow-up, and gynecological health management during the pandemic without additional adjustments. This provides clinical physicians with important scientific evidence when developing individualized health management plans. The study also supports that current HPV vaccination and cervical cancer screening strategies do not need to be modified due to COVID-19. Future research should further explore the interactions between HPV infection and other viral diseases, as well as optimize vaccination and health management processes to address similar public health crises.

Strengths and Limitations

This study has several advantages. The bidirectional two-sample method used in this study effectively mitigates potential confounding factors and reverse causation that are commonly encountered in case reports, making it a primary strength. Furthermore, we investigated the relationship between HPV-specific subtypes and three distinct populations of COVID-19 infection, thereby enabling a more precise assessment of the association between HPV and COVID-19.

Nevertheless, there are some constraints to be acknowledged. First, generalizability to non-European populations is severely limited: All GWAS data for HPV-16/18 and COVID-19 were derived exclusively from participants of European ancestry, and no public, high-quality GWAS meta-analyses for these phenotypes were available for non-European groups at the time of analysis. Population differences in HPV genotype distribution, COVID-19 severity drivers (genetic, socioeconomic, healthcare access), and genetic architecture mean our findings cannot be extrapolated to other ancestries, and we cannot quantify how these differences might alter causal inference.

Second, the strength of the IVs for HPV exposure is a matter of significant concern. In the source GWAS, no SNPs related to HPV-16 or HPV-18 were found to meet the traditional genome-wide significance threshold ($P < 5\times10^{-8}$). As a result, we relaxed the significance threshold to $P < 5\times10^{-5}$. However, this adjustment may introduce some SNPs that are either weakly associated with HPV or have low specificity, potentially leading to subtle bias in causal estimates. Although the F-statistics of all selected instrumental variables exceed 10, suggesting a lower likelihood of weak instrument bias, the use of a relaxed threshold could still incorporate SNPs with weaker effects or those with pleiotropic effects, thereby affecting causal estimates. Additionally, the lack of sufficient IVs for specific COVID-19 types related to HPV-16 and HPV-18 limits our ability to implement sensitivity analyses such as MR-Egger regression and MR-PRESSO in all analyses, which may undermine the credibility of null association results. Consequently, careful interpretation of causal inference results is essential to avoid potential weak instrument bias.

Third, due to limitations in the availability of publicly accessible GWAS data, we were unable to adjust for confounding factors such as gender and age, which are crucial for understanding gender differences in HPV-related diseases and COVID-19 outcomes. Gender-related mechanisms, such as immune responses, hormonal influences, and behavioral differences, may interact with genetic susceptibility to influence HPV persistence and the COVID-19 progression. However, a lack of GWAS summary data stratified by gender currently precludes gender-specific MR analyses. This gap is particularly pronounced given the well-established gender distribution disparities in HPV infection-related diseases and the increasingly recognized gender imbalance in COVID-19 severity and mortality. Future studies incorporating gender-stratified genetic analyses may yield deeper insights into these complex interactions.

Conclusions

The results of the two-sample MR study do not provide sufficient evidence to support a genetically predicted causal relationship between HPV and COVID-19, suggesting that the association observed in previous observational studies may be due to potential confounders. The impact of COVID-19 infection on clinical manifestations of patients infected with HPV-16/18 may be transient, temporary, and recoverable, which should be considered in disease management. The findings of this study necessitate further validation through additional GWAS summary data, more advanced MR analysis techniques, and robust genetic instrumentation. It is important to note that the conclusions of this study are limited by factors such as the racial diversity of the available GWAS data, limited statistical power, and the scarcity of strong instrument variables. Future research should consider using more diverse samples and advanced analytical methods to further validate our findings and explore potential genetic mechanisms.

Data Sharing Statement

The publicly available datasets used in the present study are included in the article/Supplementary material.

Ethics Approval and Consent to Participate

This study relied solely on anonymized, publicly available datasets that meet the exemption criteria outlined in Article 32 (1–2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of China, effective 18 February 2023). These datasets have been previously reviewed and approved by their respective ethics committees. Therefore, no additional ethical review or informed consent was required for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Sha-Sha Tao, Man Ge, and Yi-Fan Cai contributed equally to this work and should be considered co-first authors.

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Disclosure

All authors affirm that there are no potential conflicts of interest including any financial or commercial ties.

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