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ORIGINAL RESEARCH

Causal Impact of Immune Phenotypes on Herpes Zoster and Postherpetic Neuralgia: Insights from Mendelian Randomization Analysis

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Background: Previous research has investigated the contribution of immunological cells to both herpes zoster (HZ) and postherpetic neuralgia (PHN). This Mendelian randomization (MR) study seeks to further assess the cause-and-effect connection among 731 immune cell phenotypes and HZ and PHN providing partial causal evidence.

Methods: The data for HZ and PHN were sourced from the FinnGen database, and the 731 immune cell phenotypes were drawn from GWAS. Five analytical methods, primarily utilizing the inverse variance weighted (IVW) approach, were selected to assess the cause-and-effect connection in relation to exposure and outcomes. Finally, sensitivity analyses were undertaken to verify the robustness as well as validity of the data.

Results: The MR analysis utilizing the IVW method revealed that in the forward Mendelian randomization, two immune cell phenotypes of T cells were negatively connected with HZ($P < 0.05$, $OR < 1$). In comparison, two other immune cell phenotypes were advantageously linked with PHN($P < 0.05$, $OR > 1$). In the reverse Mendelian randomization, HZ was positively associated with five immune cell phenotypes from T cells and NK cells ($P < 0.05$, $OR > 1$). PHN demonstrated a positive association with nine immune cell phenotypes from T cells, myeloid cells, B cells, CDC, and monocytes ($P < 0.05$, $OR > 1$), while showing a negative association with the remaining 11 immune cells ($P < 0.05$, $OR < 1$). Likewise, No evidence of disparity, horizontal pleiotropy, or backward causality was found.

Conclusion: This study employs Mendelian randomization analysis to elucidate the complex causal relationships between various immune cell phenotypes and the development of HZ and PHN. The findings provide insights into the immune mechanisms underlying disease progression, advancing our understanding of immune-mediated pathways and their potential implications for future therapeutic strategies.

Keywords: causal effect, Mendelian randomization, immunophenotypes, herpes zoster, postherpetic neuralgia

Introduction

Herpes Zoster (HZ) is a viral infectious disease caused by the varicella-zoster virus (VZV), which is responsible for two types of human infections: chickenpox varicella) and herpes zoster.[1] Following chickenpox infection, VZV remains dormant in the dorsal root ganglia and can reactivate when immune function declines, leading to the development of herpes zoster.[2] HZ is characterized by erythema, clustered vesicles, and severe postherpetic neuralgia (PHN), with chronic pain from PHN lasting from one to three months or longer.[3] According to the 2019 Global Burden of Disease (GBD) study, there are approximately 84 million cases of HZ globally, with HZ-related disability-adjusted life years (DALYs) reaching 900,000. The incidence and disability rate significantly increase in individuals aged 50 years and older, with a rapid rise in DALYs among those aged 70 and above, indicating a growing global burden of HZ.[4] Current treatment approaches focus on antiviral medications, neuroprotective therapy, and anti-inflammatory analgesics. PHN severely impacts patients' work and quality of life, often requiring long-term or even lifelong treatment. Therefore,

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understanding the underlying etiology of HZ and PHN is essential for developing effective prevention and treatment strategies.[5]

Epidemiological data indicate that aging and immune deficiency are major risk factors for the development of HZ and PHN.[6] The occurrence of HZ is closely linked to the immune system's ability to control VZV, with T cells playing a central role in virus clearance and reactivation. CD8+ cytotoxic T cells (CTLs) secrete IFN-γ and TNF-α, which induce neuroinflammation and exacerbate pain,[7] whereas CD8+ regulatory T cells (CD8+ Tregs) secrete IL-10 and TGF-β, which suppress inflammation and reduce nerve damage.[8] Aging leads to a decline in CD8+ T cell function, weakening VZV control and increasing the risk of HZ and PHN. Vaccination, however, can enhance B cell production of anti-VZV IgG and reduce the risk of viral reactivation.[9] Additionally, dendritic cells (DCs) and monocytes/macrophages play a critical role in the immune response to HZ. DCs activate T cells via antigen presentation,[9] while the M1/M2 imbalance in macrophages during chronic inflammation may worsen nerve damage.[10] These findings suggest that immune-modulatory interventions, such as enhancing T cell function or regulating the inflammatory microenvironment, offer new avenues for the treatment of HZ and PHN.[11]

Mendelian Randomization (MR) is an epidemiological statistical technique that uses Mendelian genetic principles to infer causal relationships.[12] Genome-wide association Studies (GWAS) compare genetic variations in large populations to identify genetic markers associated with diseases. The GWAS data for HZ and PHN come from the 10th round of the FinnGen database, while the GWAS data for immune phenotypes are sourced from the GWAS catalog, covering 731 immune traits. In this study, we used GWAS data for MR analysis to investigate the causal relationships between immune cell phenotypes and HZ/PHN. The results provide new evidence of immune phenotypes associated with the progression of HZ and PHN.

Materials and Methods

Study Design

We reviewed the cause-and-effect relationships amid 731 immunophenotypes along with HZ as well as PHN using MR analysis. Initially, immunophenotypes were treated as exposure variables, while HZ and PHN were considered outcome variables, to assess whether these immune cell phenotypes promote or prevent the occurrence of HZ and PHN. Subsequently, a reverse MR analysis was carried out to probe the impact of HZ and PHN on immune cells. MR uses genetic variations as risk factor proxies, and causal inference is grounded in three important assumptions: 1) genetic variation, as well as exposure, are directly correlated; 2) confounding effects prevent a correlation linking genetic variation to outcome; and 3) genetic effect on the outcome happens only through the pathway of exposure (Figure 1).

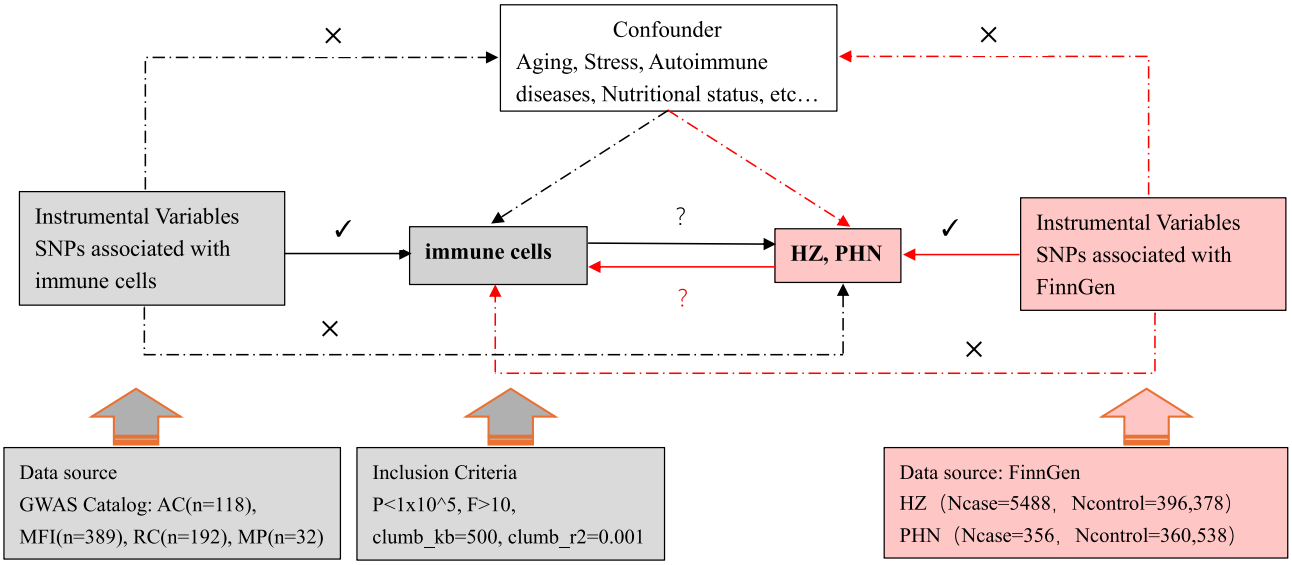

Figure 1 Plot of key assumptions for MR analysis.
Abbreviation: MR, Mendelian randomization.

Data Sources for GWAS of HZ and PHN

The consolidation of GWAS analytics for HZ and PHN was sourced from the 10th round of the FinnGen database. The HZ data summary was produced from a GWAS of 401,866 European people (Ncase = 5,488; Ncontrol = 396,378), which included 21,306,162 SNPs. The PHN data summary was generated from a GWAS including 360,894 European people (Ncase = 356; Ncontrol = 360,538), which included 21,305,231 SNPs.

Sources of GWAS Data for Immune Cell Phenotypes

Consolidated statistics for all immunophenotypes in the GWAS catalog (from accession numbers GCST0001391 to GCST0002121) are freely accessible.[13] The GWAS analyzed 3,757 non-overlapping European people, estimating approximately 22,000,000 SNPs utilizing a high-throughput array based on the Sardinian sequence reference pane[14] Correlation tests were performed while considering covariates, including sex, age, and age squared. In total, 731 immunophenotypes were studied, encompassing relative cell counts (RC) (n=192), median fluorescence intensity (MFI) (n=389), absolute cell counts (AC) (n=118), and morphological parameters (MP)(n=32), which represent levels of surface antigens. The AC, RC, and MFI qualities comprise B cells, phases of T lymphocyte maturation, CDC, monocytes, and myeloid cells together with TBNK, whereas the MP features encompass CDC as well as TBNK panels.

Selection of Instrumental Variables (IVs)

According to current findings, the significance criterion for instrumental variables for each immune feature was fixed at 1×10^{-5}[15,16] To refine these SNPs, we used instrumental variables (version v1.90) with an LD r^2 threshold of <0.1 and a distance of 500 kb. To reduce weak instrument-related bias as well as guarantee statistical significance, SNPs with F-values larger than 10 were also included.[17] In this research, the F-value is computed as follows: F is equal to $R^2 \times (N-2) / (1-R^2)$, where R^2 is a variation for each exposure-related IV that is explained. The formula for calculating R^2 is $2 \times EAF \times (1-EAF) \times Beta^2$, where Beta denotes the allele's effect size and EAF stands for the effect allele frequency. To guarantee uniformity in effect allele assignment, the exposure and result datasets were combined, and SNPs with intermediate allele frequencies were removed.

Statistical Analysis

The TwoSampleMR package and R 4.3.3 software were leveraged for statistical evaluation.[18] To assess the cause-and-effect relationships amid 731 immune phenotypes and HZ as well as PHN, we employed several methods: MR-Egger, IVW, weighted median, simple mode, and weighted mode method. In this study, the IVW method was designated as the chief analysis strategy.[19] Cochran's Q test and its associated P_{IVW} were utilized to appraise heterogeneity in the associations. Pleiotropy was evaluated utilizing the MR-PRESSO global test and the MR-Egger intercept tests.[20,21] MR-PRESSO was also employed to identify anomalies in the associations, along with to generate estimates after excluding these anomalies. Ultimately, sensitivity analyses were conducted using a leave-one-out test. Additionally, scatter plots and funnel plots were produced. The scatter plot showed that anomalies did not alter the findings, while the funnel plot showed how robust this connection was and revealed no heterogeneity.

Results

Examination of the Causal Impact of Immune Phenotypes on HZ

After fine-tuning for a false discovery rate (PFDR < 0.05), we recognized two immune phenotypes with protective effects against HZ: CD8 on CD8br and CD8 on CD28+ CD45RA- CD8br, both of which are T cell phenotypes. Specifically, the odds ratio (OR) for CD8 on CD8br cells reducing the risk of HZ, as estimated by the IVW method, was 0.883 (95% CI = 0.837–0.931, $P = 4.61 \times 10^{-6}$, PFDR = 0.003; Figure 2). Reproducible findings were obtained utilizing the other four tactics (Figure 2, Table S1).

The IVW method estimated OR for CD8 on CD28+ CD45RA- CD8br cells alleviating the likelihood of HZ to be 0.895 (95% CI = 0.848–0.945, $P = 5.33 \times 10^{-5}$, PFDR = 0.020, Figure 2, Table S1). Similar outcomes were observed utilizing the other four methods (Figure 2). Furthermore, horizontal pleiotropy in these correlations was ruled out by the

exposure	method	P	PFDR	OR(95%CI)
CD8 on CD8br	MR Egger	0.3773985550	0.003368984	0.934(0.805 to 1.085)
	Weighted median	0.0015876370		0.903(0.848 to 0.962)
	Inverse variance weighted (fixed effects)	0.0000046100		0.883(0.837 to 0.931)
	Weighted mode	0.1125596890		0.927(0.846 to 1.017)
	Simple mode	0.0762986620		0.879(0.765 to 1.011)
CD8 on CD28+ CD45RA− CD8br	MR Egger	0.0133278300	0.019470574	0.803(0.678 to 0.951)
	Weighted median	0.0003264640		0.890(0.835 to 0.948)
	Inverse variance weighted (fixed effects)	0.0000532711		0.895(0.848 to 0.945)
	Weighted mode	0.0445173030		0.883(0.784 to 0.995)
	Simple mode	0.1428816830		0.892(0.766 to 1.038)

P<0.05 was considered statistically significant

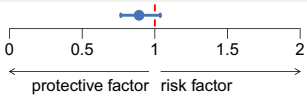

Figure 2 Forest plots showed the causal associations between immune cell phenotypes and HZ by using different methods.
Abbreviation: HZ, herpes zoster.

MR-Egger intercept and MR-PRESSO global test. Sensitivity analyses confirmed the validity of this observed cause-and-effect connection (Table S1). Additionally, scatter plots and funnel plots demonstrated this data's stability (Figure S1).

Examination of the Causal Impact of Immune Phenotypes on PHN

After fine-tuning for multiple tests using the FDR perspective, no immune traits were recognized at a significance criterion of 0.05. However, at a significance criterion of 0.20, we detected two immune phenotypes connected with an elevated risk of PHN: TD CD8br AC and CD45RA+ CD8br %T cell, both belonging to the T cell group. Specifically, the odds ratio (OR) for TD CD8br AC cells increasing the risk of PHN, as estimated by the IVW method, was 1.661 (95% CI = 1.279–2.157, P = 1.43×10^{-4}, PFDR = 0.058; Figure 3). Reproducible findings were obtained utilizing the other four tactics (Figure 3, Table S2).

The IVW method estimated the OR for the CD45RA+ CD8br %T cell increasing the risk of PHN to be 1.623 (95% CI = 1.262–2.087, P = 1.58×10^{-4}, PFDR = 0.058; Figure 3). Similar results were obtained using the other four methods (Figure 3, Table S2). In addition, horizontal pleiotropy in these correlations was ruled out by the MR-Egger intercept as well as the MR-PRESSO global test. Sensitivity analyses confirmed this validity of the evidenced causal links (Table S2). Scatter plots and funnel plots proved the data's stability (Figure S2).

Examination of the Causal Impact of HZ on Immune Phenotypes

After adjusting for the false discovery rate (PFDR < 0.2), five suggestive immune phenotypes were identified: four in T cell panel and one in NK cell panel.

exposure	method	P	PFDR	OR(95%CI)
TD CD8br AC	MR Egger	0.847835389	0.057783948	1.080(0.497 to 2.347)
	Weighted median	0.021330837		1.551(1.067 to 2.254)
	Inverse variance weighted (fixed effects)	0.000142548		1.661(1.279 to 2.157)
	Weighted mode	0.131934092		1.549(0.893 to 2.686)
	Simple mode	0.105955888		1.732(0.912 to 3.293)
CD45RA+ CD8br %T cell	MR Egger	0.061957481	0.057783948	1.785(0.996 to 3.197)
	Weighted median	0.007216811		1.636(1.142 to 2.343)
	Inverse variance weighted (fixed effects)	0.000157880		1.623(1.262 to 2.087)
	Weighted mode	0.379350294		1.356(0.695 to 2.644)
	Simple mode	0.054643176		2.067(1.017 to 4.203)

P<0.05 was considered statistically significant

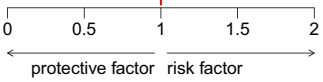

Figure 3 Forest plots showed the causal associations between immune cell phenotypes and PHN by using different methods.
Abbreviation: PHN, postherpetic neuralgia.

We ascertained that HZ might increase the criterion of Central Memory CD4+ T cells (β = 0.127, 95% CI = 1.055–1.222, P = 0.001, PFDR = 0.12; Figure 4). In addition, the proportion of CD28- CD8dim cells in T cells increased among HZ patients (β = 0.121, 95% CI = 1.049–1.215, P = 0.001, PFDR = 0.177; Figure 4). We also observed inflation in HVEM on CD4+ T cells (β = 0.203, 95% CI = 1.097–1.367, P < 0.001, PFDR = 0.115; Figure 4), as well as in HVEM on CD45RA- CD4+ T cells (β = 0.207, 95% CI = 1.100–1.374, P < 0.001, PFDR = 0.115; Figure 4). In the NK cell panel, a positive correlation was observed with SSC-A on HLA-DR+ cells (β = 0.132, 95% CI = 1.059–1.230, P = 0.001, PFDR = 0.124; Figure 4). Similar results were obtained using the other four methods (Table S3). Specifically, the likelihood of horizontal pleiotropy was eliminated by the MR-Egger intercept as well as MR-PRESSO global test (Table S3). The durability of these results was clarified further by scatter plots and funnel plots (Figure S3).

Examination of the Causal Impact of PHN on Immune Phenotypes

After adjusting for the FDR with a significance criterion of 0.20, no immune phenotypes were identified as significant. However, using the IVW method (P < 0.05), 20 suggestive immune phenotypes were detected. Among these, nine immune cell phenotypes were positively correlated with the occurrence of PHN(OR > 1, P_{IVW} < 0.05; Figure 5). B cell Panel: IgD+ CD38- B cell %lymphocyte; T cell maturation stage Panel: CD8 on Central Memory CD8+, CD8 on Terminally Differentiated CD8+, CD8 on naive CD8+, CD8 on CD28+ CD45RA+ CD8+; Monocyte Panel: CD11c+ CD62L- monocyte %, CX3CR1 on CD14- CD16-, CX3CR1 on CD14+ CD16- monocyte; TBNK Panel: SSC-A on HLA DR+. In contrast, the remaining 11 immune phenotypes were linked to a reduced incidence of PHN (OR < 1, P_{IVW} < 0.05). B cell Panel: CD20 on IgD+ CD24+, CD20 on IgD+ CD38+, CD20 on unswitched memory, CD20 on transitional; CDC Panel: FSC-A on myeloid Dendritic Cell; Myeloid cell Panel: CD11b on CD33dim HLA DR-, CD11b on basophil, CD45 on granulocyte, SSC-A on granulocyte; Monocyte Panel: CD14+ CD16- monocyte Absolute Count, Monocyte Absolute Count. The results of the five MR analysis techniques, together with sensitivity analyses, demonstrated the robustness of these recognized causal links (Figure S4). These discoveries point to that certain immunophenotypes may

outcome	method	P	PFDR	OR(95%CI)
Central Memory CD4+ T cell	MR Egger	0.008559071	0.123984553	1.231(1.064 to 1.424)
	Weighted median	0.038469275		1.123(1.006 to 1.254)
	Inverse variance weighted (fixed effects)	0.000678438		1.136(1.055 to 1.222)
	Weighted mode	0.101185048		1.141(0.979 to 1.329)
	Simple mode	0.158414197		1.151(0.951 to 1.394)
CD28− CD8dim T cell	MR Egger	0.030395254	0.177370402	1.207(1.025 to 1.420)
	Weighted median	0.019921739		1.143(1.021 to 1.278)
	Inverse variance weighted (fixed effects)	0.001213204		1.129(1.049 to 1.215)
	Weighted mode	0.040982546		1.185(1.013 to 1.387)
	Simple mode	0.218584323		1.135(0.931 to 1.383)
HVEM on CD4+ T cell	MR Egger	0.003651377	0.114878238	1.432(1.144 to 1.793)
	Weighted median	0.012357815		1.251(1.050 to 1.491)
	Inverse variance weighted (fixed effects)	0.000314304		1.225(1.097 to 1.367)
	Weighted mode	0.019233588		1.348(1.062 to 1.711)
	Simple mode	0.132815438		1.289(0.933 to 1.781)
HVEM on CD45RA− CD4+ T cell	MR Egger	0.022233928	0.114878238	1.329(1.053 to 1.676)
	Weighted median	0.009472767		1.254(1.057 to 1.488)
	Inverse variance weighted (fixed effects)	0.000277840		1.229(1.100 to 1.374)
	Weighted mode	0.021290538		1.318(1.053 to 1.649)
	Simple mode	0.047491029		1.347(1.014 to 1.788)
SSC−A on HLA DR+ Natural Killer	MR Egger	0.107443104	0.123984553	1.135(0.977 to 1.319)
	Weighted median	0.009928409		1.167(1.038 to 1.312)
	Inverse variance weighted (fixed effects)	0.000555600		1.141(1.059 to 1.230)
	Weighted mode	0.130035559		1.139(0.966 to 1.343)
	Simple mode	0.131054714		1.180(0.957 to 1.456)

P<0.05 was considered statistically significant

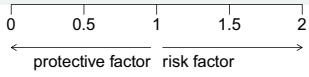

Figure 4 Forest plots showed the causal relations between HZ and immune cell phenotypes.

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outcome	method	P	PFDR	OR(95%CI)
IgD+ CD38− B cell %lymphocyte	Inverse variance weighted (fixed effects)	0.048491022	0.9946192	1.046(1.000 to 1.093)
CD11c+ CD62L− monocyte %monocyte	Inverse variance weighted (fixed effects)	0.049205742	0.9946192	1.049(1.000 to 1.101)
CD14+ CD16− monocyte Absolute Count	Inverse variance weighted (fixed effects)	0.044928767	0.9946192	0.957(0.917 to 0.999)
Monocyte Absolute Count	Inverse variance weighted (fixed effects)	0.027708112	0.9946192	0.953(0.913 to 0.995)
CD20 on IgD+ CD24+ B cell	Inverse variance weighted (fixed effects)	0.011256049	0.9946192	0.945(0.904 to 0.987)
CD20 on IgD+ CD38+ B cell	Inverse variance weighted (fixed effects)	0.017564182	0.9946192	0.948(0.908 to 0.991)
CD20 on unswitched memory B cell	Inverse variance weighted (fixed effects)	0.034969211	0.9946192	0.954(0.913 to 0.997)
CD20 on transitional B cell	Inverse variance weighted (fixed effects)	0.012145370	0.9946192	0.945(0.904 to 0.988)
CD45 on granulocyte	Inverse variance weighted (fixed effects)	0.007756961	0.9946192	0.931(0.883 to 0.981)
FSC−A on myeloid Dendritic Cell	Inverse variance weighted (fixed effects)	0.041896311	0.9946192	0.950(0.905 to 0.998)
CX3CR1 on CD14− CD16−	Inverse variance weighted (fixed effects)	0.008979045	0.9946192	1.061(1.015 to 1.109)
CX3CR1 on CD14+ CD16− monocyte	Inverse variance weighted (fixed effects)	0.046804034	0.9946192	1.047(1.001 to 1.095)
CD8 on Central Memory CD8+ T cell	Inverse variance weighted (fixed effects)	0.040574563	0.9946192	1.052(1.002 to 1.105)
CD8 on naive CD8+ T cell	Inverse variance weighted (fixed effects)	0.003676339	0.9946192	1.074(1.024 to 1.128)
CD8 on Terminally Differentiated CD8+ T cell	Inverse variance weighted (fixed effects)	0.047937349	0.9946192	1.050(1.000 to 1.103)
SSC−A on granulocyte	Inverse variance weighted (fixed effects)	0.043336213	0.9946192	0.947(0.898 to 0.998)
SSC−A on HLA DR+ T cell	Inverse variance weighted (fixed effects)	0.049404846	0.9946192	1.049(1.000 to 1.100)
CD11b on CD33dim HLA DR−	Inverse variance weighted (fixed effects)	0.011047180	0.9946192	0.918(0.859 to 0.981)
CD11b on basophil	Inverse variance weighted (fixed effects)	0.019128076	0.9946192	0.925(0.866 to 0.987)
CD8 on CD28+ CD45RA+ CD8+ T cell	Inverse variance weighted (fixed effects)	0.006597899	0.9946192	1.068(1.019 to 1.120)

P<0.05 was considered statistically significant

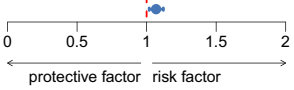

Figure 5 Forest plots showed the causal relations between PHN and immune cell phenotypes.

impact the risk of developing PHN, highlighting potential targets for further investigation into the immunological aspects of PHN (Table S4).

Discussion

In this research, we examined the linkage among 731 immunocyte morphologies together with HZ and PHN, as well as their putative causes, using bidirectional two-sample MR analysis for the first time. In the forward Mendelian randomization analysis, we found partial evidence that two immune cell phenotypes in T cells exert a protective effect against HZ. Conversely, two other immune cell phenotypes in T cells (TD CD8br AC and CD45RA+ CD8br %T cell) were connected to an elevated risk for PHN. In the reverse Mendelian randomization analysis, several immune cell phenotypes in T cells and NK cells were positively associated with HZ, indicating a risk effect. Additionally, 20 immune cell phenotypes across T cells, myeloid cells, B cells, CDC as well as monocytes demonstrated a causal association with PHN in the reverse analysis. Among these, nine immune cell phenotypes were positively associated with PHN, suggesting a risk effect, while the remaining 11 phenotypes were associated with a decreased incidence of PHN. Furthermore, no bidirectional causal associations were found for the same immune cell phenotypes.

Our study revealed that, in the forward Mendelian randomization analysis, the likelihood of HZ diminished with an increase in the proportion of CD8+ T cells. Upon encountering antigenic stimulation, CD8+ T cells convert into various memory cells, effector cells, and regulatory T cells to combat viral infections and inflammatory responses. Cytotoxic T lymphocytes (CTLs), which typically express high levels of CD8, mediate cytotoxic activity by secreting cytokines including IL-2, TNF-α, and IFN-γ, effectively killing virus-infected cells and inhibiting viral spread.[22] Research indicates that CD28 is instrumental throughout the differentiation process of CD8+ T cells, enabling the proliferation in lymphoid tissues and facilitating a rapid response that aids in the recognition and elimination of virus-infected cells.[23]

However, this study discovered that the likelihood of PHN increases with the ratio of TD CD8br AC and CD45RA+ CD8br % T cells. TD CD8br AC represents terminally differentiated activated CD8+ T cells, which produce a robust immune response during viral infections. However, their secretion of cytokines such as IFN-γ may inadvertently attack self-tissues, increasing the risk of nerve damage.[24,25] The CD45RA+ CD8br % refers to a subset of naive or terminally differentiated CD8+ T cells that are ineffective at regulating immune responses, leading to persistent inflammation. Prior studies have proposed that CD8+ T cells can contribute to pain relief,[26,27] but their absolute numbers tend to decline with aging and in the progression of PHN.[28] Compared to younger individuals, older adults exhibit a slower and less effective CD8+ T cell response when exposed to varicella-zoster virus (VZV).[29] Dysregulation of CD8+ T cells, particularly when

their numbers decline due to aging or iatrogenic immunosuppression, is associated with increased susceptibility to VZV reactivation and subsequent HZ. This further impairs the immune control of the virus, leading to HZ and PHN.[30,31]

During the onset of HZ, the antiviral immune response predominantly relies on T cell-mediated cellular immunity. However, the development of PHN is influenced not only by direct viral reactivation but also by prolonged neuroinflammation, neuronal hypersensitivity, and the sustained activation of glial cells.[32] Studies have indicated that, following acute HZ infection, some patients may experience immune dysregulation, characterized by impaired regulatory T cell (Treg) function, elevated levels of pro-inflammatory cytokines (eg, IL-6, TNF-α), and insufficient regulation of anti-inflammatory cytokines (eg, IL-10, TGF-β).[24,25] This imbalance may create a chronic neuroinflammatory microenvironment, promoting the persistence of PHN-related pain.

It is worth noting that throughout the acute phase of the HZ infection, the activation of CD8+ T cells is crucial for controlling varicella-zoster virus (VZV) infection. While CD8+ T cells effectively eliminate invaded cells by secreting cytokines including IL-2 and IFN-γ,[32] excessive activation could lead to tissue damage and inflammatory responses, exacerbating neuropathological conditions and increasing the risk of PHN.[24,25] Therefore, regulating the differentiation of various immune cell phenotypes offers a valuable therapeutic strategy to optimize immune responses and minimize tissue damage.

However, the immunophenotypes identified in this study were primarily associated with susceptibility to HZ, while their direct role in the development of PHN remains uncertain. This uncertainty may arise because the pathophysiological mechanisms of PHN are predominantly driven by neurological changes, including neuronal disinhibition, glial cell activation, and remodeling of pain signaling pathways, rather than solely by alterations in peripheral immunity.[33,34]

Additionally, we observed statistically significant odds ratios (ORs) indicating a reduced risk of HZ associated with certain immunophenotypes (eg, OR = 0.883). Given the relatively small effect sizes, it is unclear whether these immunophenotypes could serve as viable therapeutic targets or predictive biomarkers in clinical practice.[35] Future research should integrate longitudinal cohort studies and functional experiments to assess the real-world impact of these immune traits on patient prognosis.[7,36]

In the reverse Mendelian randomization analysis, we found that PHN exerts a risk effect on four CD8+ T cell phenotypes: Central Memory CD8+, naive CD8+, Terminally Differentiated CD8+, and CD28+ CD45RA+ CD8+. This finding indicates a close bidirectional relationship between CD8+ T cells and PHN. CD8+ T cells regulate both pro-inflammatory and anti-inflammatory signals via differentiation into diverse lineages, each exhibiting distinct cytokine profiles and functions.[10,11,37] However, no correlations of reverse causation between immune cell morphologies and PHN or HZ were found. In other words, immune cell phenotypes that contribute to or alleviate HZ and PHN do not influence the development of these conditions. These findings provide new evidence for considering CD8+ T cells as auxiliary biomarkers for the clinical evaluation and therapy of HZ and PHN.

In this study, we utilized data from large-scale cohort genomics studies, which provided extensive sample sizes and high statistical power, to perform a bidirectional two-sample Mendelian randomization (MR) analysis. We employed genetic instrumental variables to infer causal relationships and applied multiple MR techniques to ensure robustness against confounding factors, including horizontal pleiotropy.

However, this study has several limitations. First, while MR analysis theoretically mitigates confounding bias, it may still be influenced by uncontrolled environmental, lifestyle, and genetic factors that simultaneously affect immunophenotypes and the risk of HZ/PHN. Second, we applied a relatively lenient threshold (p-value < $1\times10^{-}$□) to include more single nucleotide polymorphisms (SNPs) as instrumental variables, allowing for a more comprehensive assessment of associations between immunological traits and HZ or PHN but potentially increasing the risk of false positives. Third, since this study is based on European ancestry datasets, the findings may not be generalizable to other ethnic populations, limiting their broader applicability. Fourth, despite performing multiple sensitivity analyses, fully assessing the impact of horizontal pleiotropy remained challenging. While MR-Egger regression can detect horizontal pleiotropy, its statistical power is limited, and MR-PRESSO relies on outlier detection, which may not comprehensively identify all pleiotropic instrumental variables. Future studies should consider incorporating more advanced methods, such as MR-Clust and LHC-MR, to enhance the robustness of causal inference and minimize the influence of horizontal pleiotropy on research conclusions. Fifth, the two-sample MR approach has inherent limitations in handling multiple exposures, as it does not

account for correlations between exposure variables that may influence outcomes. Thus, exploring more suitable analytical methods remains necessary. Finally, the pathogenesis of HZ and PHN is highly complex and influenced by multiple factors, with many genetic instrumental variables' functions still unclear. Therefore, larger genome-wide association studies (GWAS), in-depth analyses, animal model validations, and comprehensive clinical trials are needed to elucidate the immunological mechanisms underlying HZ and PHN and identify novel immunotherapeutic targets.

Conclusion

In conclusion, bidirectional Mendelian randomization analysis identified causal relationships between immunophenotypes and HZ as well as PHN, underscoring the immune system's complex role in these diseases. Moreover, shared immune pathways may contribute to these causal associations. The methodology employed in this study is applicable to other immune-mediated diseases, including autoimmune diseases and viral infections, enabling further exploration of immunophenotype-disease interactions. This study advances our understanding of the genetic and biological mechanisms underlying HZ and PHN and provides insights into common pathways to refine early intervention and treatment strategies.

Abbreviations

HZ, herpes zoster; PHN, postherpetic neuralgia; MR: Mendelian randomization; IVW, inverse variance weighted; GBD: Global Burden of Disease; GWAS, genome-wide association study; VZV, varicella-zoster virus.

Data Sharing Statement

This study examined publically available data. These datasets are available at the listed URLs: FinnGen (https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_MXX_CONDITION.gz) and GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads/summary-statistics). The datasets generated and analyzed during this study can be obtained from the corresponding authors upon reasonable request.

Ethics Declarations

According to items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, dated February 18, 2023, China, studies utilizing publicly available secondary data or data that have already undergone ethical review may be exempt from further ethical approval.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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