Journal of Geriatric Cardiology | JGC
RESEARCH ARTICLE
J Geriatr Cardiol 2024; 21(9): 865–873

Causal effect of psoriasis on aortic valve stenosis: a two-sample Mendelian randomization study

Ke-Xin JIANG[1,2], Yan WANG[1,2], Yu-Tong LIU[3], Yanjiani XU[3], Fang-Yang HUANG[1,2,✉], Mao CHEN[1,2,✉]

1. Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China; 2. Laboratory of Cardiac Structure and Function, Institute of Cardiovascular Diseases, West China Hospital, Sichuan University, Chengdu, China; 3. West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

✉ Correspondence to: fyhuang1989@126.com (HUANG FY); hmaochen@vip.sina.com (CHEN M)

https://doi.org/10.26599/1671-5411.2024.09.002

ABSTRACT

Background Epidemiological studies have suggested a potential connection between psoriasis and an increased risk of aortic valve stenosis (AS), though the impact of psoriasis on AS progression remains uncertain. The study aims to investigate the causal relationship between psoriasis and AS using Mendelian randomization (MR) analysis, as well as to uncover potential mechanisms underlying this association.

Methods A two-sample MR analysis was conducted using publicly available summary statistics from genome-wide association studies (GWAS) of psoriasis and AS. Cis-eQTL and significant genes were identified for each causal single-nucleotide polymorphisms (SNPs), followed by pathway enrichment and protein-protein interaction (PPI) analysis for functional evaluation. Hub genes were pinpointed by Cytospace. The transcriptional profile of AS population was acquired, and interconnected genes networks were clustered using Molecular Complex Detection (MCODE).

Results Our results demonstrate a significant causal relationship between psoriasis and AS, with a genetic predisposition to psoriasis associated with a higher AS risk (odds ratio: 1.46). Pathway and PPI analyses unveiled 15 hub genes, including HLA-C, HLA-B, ISG15, IFIT3, and MX2, along with immune-related pathways linking psoriasis and AS. Moreover, the transcriptional profiling of the AS database highlighted the significant involvement of adaptive immune cells in AS development. Notably, among the 15 hub genes, ISG15, MX2, OAS3, OASL, IFI6, and EPSTI1 exhibited higher expression in the AS population.

Conclusion Our study provides compelling evidence supporting a causal relationship between psoriasis and AS. Furthermore, the identified hub genes and immune-related pathways may play an important role in the development of both diseases.

Psoriasis, a chronic and multifaceted skin condition affecting individuals across all age groups, poses a significant global health burden. This autoimmune disorder, characterized by chronic plaque formation, not only induces considerable morbidity but is also associated with various severe medical complications. Despite its prevalence, psoriasis lacks a definitive cure, and its etiology involves a complex interplay of genetic predisposition and environmental triggers, resulting in comorbidities such as arthritis, cardiovascular diseases (CVD), metabolic syndromes, inflammatory bowel disease, and depression.[1]

Genetic studies have shed light on key immune pathways implicated in psoriasis, involving IL-17, IL-23, TNF alpha, and interferons. Recent research has focused on unraveling the intricate crosstalk between innate and adaptive immune responses, amplifying the inflammatory process.[2] The unresolved nature of psoriasis, coupled with its systemic impact, underscores the urgency of understanding its associations with other diseases.

Aortic valve stenosis (AS), a prevalent heart valvular disease with significant global incidence, presents a formidable challenge in terms of treatment options and disease progression. Despite recent advancements, severe AS still carries a high 2-year mortality rate of around 50%.[3] The development of

© 2024 JGC All rights reserved; www.jgc301.com

AS involves endothelial cell dysfunction, immunological responses, and fibroblastic differentiation, with key cellular players such as macrophages, T cells, leukocytes, and dendritic cells participating in inflammation process, tissue regeneration, and mineralization.[4]

A case report highlighted a young patient with a prolonged history of psoriasis exhibiting symptomatic severe aortic stenosis, drawing attention to a potential link between the two conditions.[5] National cohort studies have further established an association between psoriasis and AS severity, suggesting psoriasis as an independent risk factor for heart disease.[6] However, the direct evidence linking psoriasis and AS is scarce,[7,8] and the observed correlations between an increased aortic root diameter, psoriasis severity, and platelet activation suggest an early reflection of the systemic nature of aortic stenosis, impacting both the left ventricle and downstream systemic vasculature.[9] All evidence suggests a link between psoriasis and AS, but the causal effect between is unclear.

To address this knowledge gap, we propose utilizing Mendelian Randomization (MR), a powerful method that is less prone to confounding and reverse causality biases, by employing valid instrumental variables. Our two-sample MR analysis, using independent genome-wide association studies (GWAS) databases for psoriasis and AS, aims to elucidate the causal role of psoriasis in AS. Besides, we seek to identify genes and pathways contributing to this association, offering insights into the physiopathology of these conditions and, ultimately, enhancing our understanding for disease management strategies.

METHODS

Database of Aortic Valve Stenosis

A GWAS of Icelandic AS including 4850 cases and 451,731 controls of European ancestry was reported.[10] Logistic or linear regression was used for association testing and inflation in tests caused by cryptic relatedness and stratification were corrected by LD score regression (LD score regression distinguishes confounding from polygenicity in genome-wide association studies). Threshold of genome-wide significance was tested using Bonferroni adjustment and family-wise error rates were rescaled.[11]

Database of Psoriasis

Summary statistics for psoriasis were extracted from a meta-analysis of three genome-wide association studies and two datasets on Immunochip, including 10588 cases and 22806 cases from European individuals.[12] In three GWAS databases, SNPs were pruned for redundancy by clumping and linkage disequilibrium (LD) $r^2 < 0.001$ were removed.[13-15]

Quality control of Immunochip datasets was performed and SNPs with call rate < 95% and Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$ were excluded; samples with extreme heterozygosity values or inbreeding coefficients were excluded by PLINK;[16] a linear mixed-model method was used for association analysis to avoid possible stratification between cases and controls.[17] Duplication among datasets was also removed from Immunochip. Detailed information and quality control of variants were described in Tsoi, *et al*.[12] *F*-statistic was to calculated to assess the strength of instruments and avoid weak instrumental bias. $F = R^2(N\text{-}K\text{-}1)/[K(1\text{-}R^2)]$. R^2 refers to variance of SNPs during exposure, K refers to the number of SNPs in MR analysis, and N refers to the number of samples in GWAS.[18]

Study Design and Statistical Analysis

We employed a two-sample MR model to assess the causal impact of psoriasis on AS. MR is a methodology used to examine whether an exposure has a causal influence on the development of a disease, employing genetic variations as instrumental variables. This approach helps overcome unmeasured confounding, leading to more robust causal inferences. The MR design relies on three key assumptions: (1) the genetic variants are strongly linked to the exposure; (2) the genetic variants do not correlate with other confounding factors; and (3) the genetic variants are associated with the outcome solely through the investigated exposure (Figure 1).

A two-sample MR analysis was performed utilizing TwoSampleMR R package (version 0.5.6) (https://mrcieu.github.io/TwoSampleMR/). The main analysis was inverse-variance weighted method which is the most accurate estimate. MR-Egger, weigh-

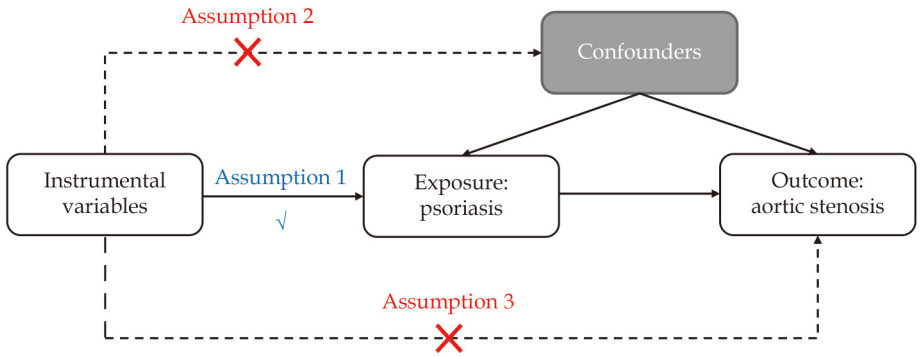

Figure 1 Assumptions of Mendelian randomization model of psoriasis and risk of aortic stenosis.

ted median, simple mode, and weight mode were also used for analysis and pleiotropy evaluation (Assumption 2 and 3). We utilized both fixed-effect and multiplicative random-effect in inverse-variance weighted method, however, the primary method would be adopted according to heterogeneity obtained by Cochrane's Q-statistics. The multiplicative random-effects approach would be applied when a $P < 0.05$ which indicated a high degree of heterogeneity. The multiplicative random-effects approach would be applied when a $P < 0.05$ which indicated a high degree of heterogeneity. A fixed-effect model would be applied otherwise. Potential pleiotropy and outlier instrument were detected by Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO), the interception of which provides *P*-value for horizontal pleiotropy (Assumption 3).[19] Heterogeneity among SNPs was estimated using Cochran's Q statistic. Also, leave-one-out method was applied for detection of single SNP whether elimination of each can cause bias in summary estimates. All *P*-values were two-sided and *P*-value < 0.05 signified suggestive relationship unless stated otherwise. All analyses were performed by R (version 4.2.2).

Function Evaluation of Causal SNPs

Information of each SNP (rsID, effect allele, and position etc.) was extracted using "singlesnp" function in TwoSampleMR. Locally expression quantitative trait loci (cis-eQTL) of each SNP were extracted using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/). Significantly related genes in whole blood (cis-eQTL genes with p value < 0.05/gene number and normalized effect size (NES) > 0) were identified by GTEx Portal (https://gtexportal.org/home/testyourown) and were enrolled in Gene Ontology (GO) enrichment analysis.

Protein-protein interaction (PPI) method utilizing STRING database (https://string-db.org) was used to cluster differential gene for their interaction.[20] Then Cytoscape (https://cytoscape.org/) was used for hub gene selection and final visualization.[21] Maximum cluster centrality (MCC) algorithm was used to find hub genes which might be important in disease phenotype, and top 15 genes with the highest connectivity and the most reciprocal linkage were defined and presented as hub genes.

Acquisition of Transcriptional Profile of Aortic Stenosis Progression

Transcriptional profile of human aortic valve was provided by Green, *et al*.[22] Significant genes among stenotic and normal valve population in this RNA sequencing data were identified using the OmicStudio tools at https://www.omicstudio.cn/tool. Significant genes and top modules were selected using Molecular Complex Detection (MCODE) plug-in in Cytoscape.

RESULTS

Causal Effect of Genetic Predisposition of Psoriasis to Aortic Valve Stenosis

Cochran's Q test showed heterogeneity ($P < 0.05$), in which case, random-effects IVW was performed. Two-sample analysis showed psoriatic genetic susceptibility was associated with higher AS risk (odds ratio: 1.46; 95% CI: 1.25-1.71; $P = 1.41e^{-06}$). MR-Egger, weighted median, simple mode, and weighted mode also provide evidence of significant association (Table 1). Characteristics of 65 SNPs in psori-

Table 1 Results of two-sample mendelian randomization analysis for psoriasis and AS.

Method	NSNP	b	se	OR (95% CI)	*P*
MR-Egger	65	0.19	0.09	1.21 (1.01-1.46)	0.047
Weighted median	65	0.28	0.02	1.33 (1.29-1.37)	$4.85e^{-61}$
Inverse variance weighted	65	0.38	0.08	1.46 (1.25-1.71)	$1.41e^{-06}$
Simple mode	65	0.45	0.03	1.56 (1.49-1.64)	$8.96e^{-25}$
Weighted mode	65	0.30	0.01	1.35 (1.31-1.39)	$2.14e^{-32}$

AS: aortic valve stenosis; NSNP: numbers of single-nucleotide polymorphisms.

asis GWAS database which were associated with AS are shown in Supplement Table 1. Forest plots and scatter plots of MR analysis are shown in Supplement Figure 1-2. No evidence of weak instrumental bias was identified (*F*-statistics = 23).

Sensitivity Analysis

No SNP outlier was detected according to MR-PRESSO, and MR-PRESSO Global Test indicated no evidence of pleiotropic effect ($P = 0.99$). In leave-one-out analysis, the results were strong since the odds ratio remained consistent after each elimination (Supplement Figure 3), suggesting robustness of the association.

Characteristics of Identified Genes in MR Analysis

We conducted a search for cis-eQTL in whole blood for functional significance of causal SNPs (Supplement Table 2). Genes with NES > 0 and *P*-value < 0.05 of gene number were selected. This screening yielded a total of 125 genes (Supplement Table 3).

Subsequently, pathway enrichment analysis revealed a total of 128 biological processes were associated with the identified genes (Figure 2A). GO enrichment analysis highlighted pathways involved in "regulation of natural killer cell-mediated cytotoxicity", "leukocyte-mediated cytotoxicity", and "T cell-mediated cytotoxicity", "antigen processing and presentation", "MCP-1 production", "chemokine production", and "T cell-mediated immunity". These pathways were found to be enriched in those genes connecting psoriasis and CAVD. PPI analysis of identified genes was conducted using STRING database and visualized by Cytoscape. Through the employment of the MCC algorithm and cytoHubba plug-in, we identified the top 15 hub genes: *HLA-C*, *HLA-B*, *ISG15*, *IFIT3*, *MX2*, *OASL*, *OAS3*, *OAS2*,

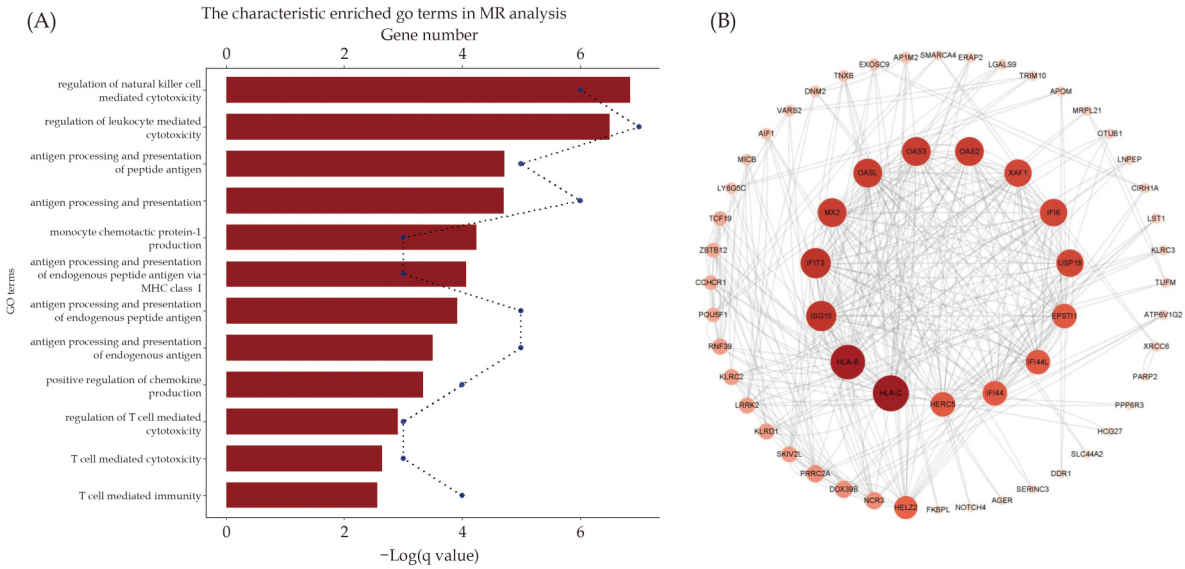

Figure 2 Enriched pathways and PPI network from MR analysis. (A): Enriched pathways of genes from SNPs identified by MR analysis; (B) PPI network and top 15 hub genes. Bar indicate -Log(q value), blue dot indicates gene number in each pathway. MR: Mendelian Randomization; PPI: protein-protein interaction.

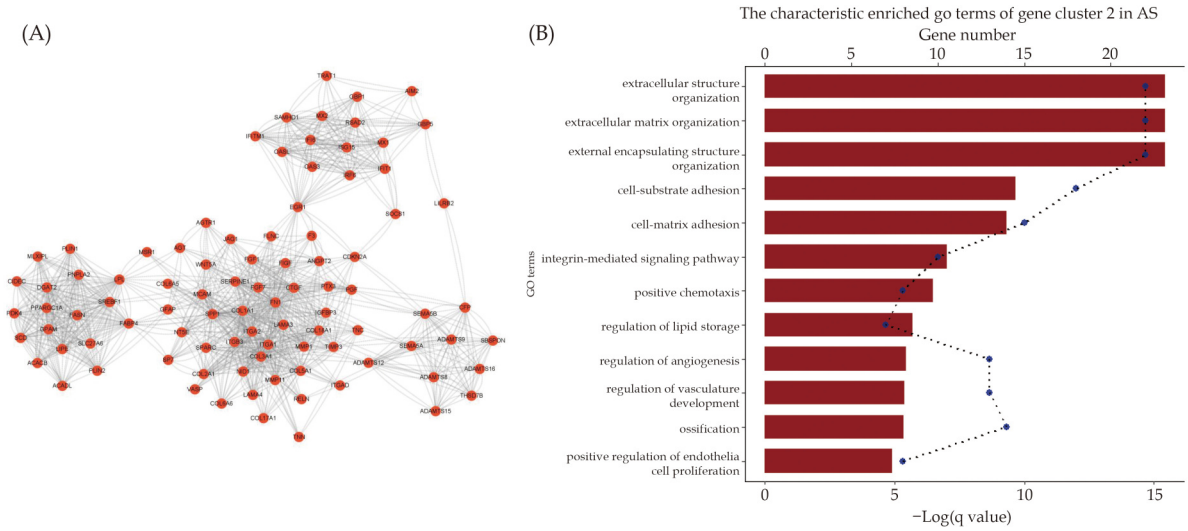

Figure 3 Module 1 and its enriched pathways. (A): Module 1 and the (B) enriched pathways of module 1. Bar indicate -Log(q value), blue dot indicates gene number in each pathway.

XAF1, *IFI6*, *USP18*, *EPSTI1*, *IFI44L*, *IFI44*, *HERC5* (Figure 2B). These hub genes represent key players in the molecular network linking psoriasis and CAVD, providing insights into potential mechanisms underlying their association.

Adaptive Immune Cells are Involved in the Onset of Psoriasis and AS

Transcriptional profile data of normal human aortic valves and valves of AS patients was acquired. Through differential gene expression analysis, we identified 1782 significant genes that differentiate between normal and AS valves (Supplement Table 4). These significant genes were further analyzed using MCODE plug-in in Cytoscape, resulting in the identification of the top 2 significant modules. 51 genes in Module 1 and 92 genes in Module 2 (Supplement Table 5 and 6) were enrolled for GO analysis separately (Figure 3A and 4A). Consistent with the GO enrichment analysis from MR analysis, adaptive immune cells are largely involved in development of AS (Figure 3B): "Regulation of lymphocyte proliferation", "regulation of monocular cell proliferation", "regulation of leukocyte activation", "regulation of T cell activation" were enriched in AS; Module 2 contains pathways such as "ECM organization", "cell-substrate adhesion", and "integrin-mediated signaling" (Figure 4B). We further

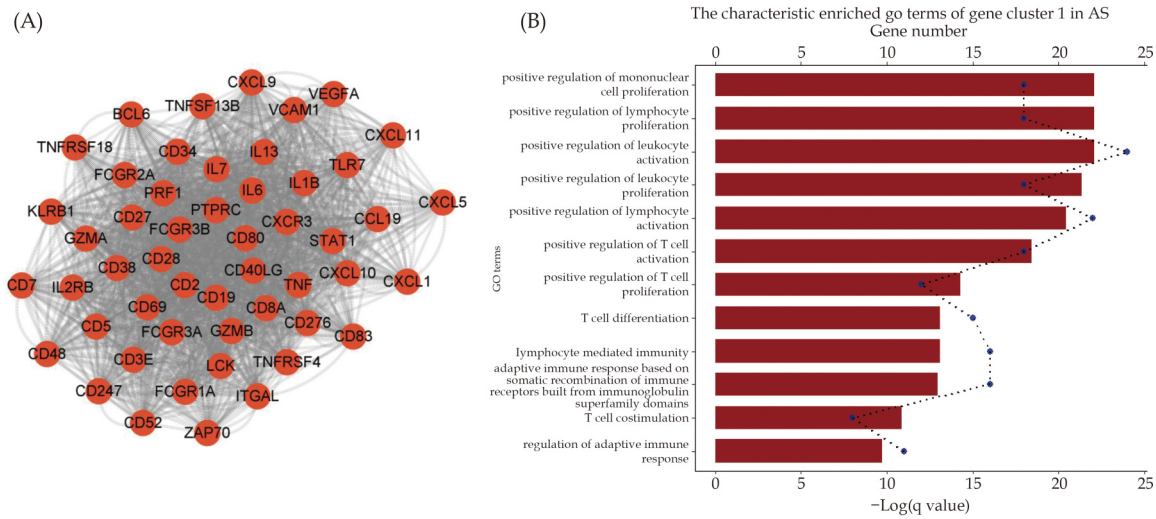

Figure 4 Module 2 and its enriched pathways. (A) Module 2 and the (B) enriched pathways of module 2. Bar indicate -Log(q value), blue dot indicates gene number in each pathway.

analyzed the expression of the 15 hub genes identified above in MR analysis and found the following 6 genes to be significantly over-expressed in stenotic valves: *ISG15*, *MX2*, *OAS3*, *OASL*, *IFI6*, and *EPSTI1*.

DISCUSSION

Previous epidemiological studies had attracted considerable interest in exploring the association between CVD and psoriasis.[23] Khalid and colleagues provided pioneering evidence in 2015, demonstrating a clear dose-response relationship, with the incident rate ratio of AS being 1.31 for individuals with mild or severe psoriasis.[6] The identification of shared risk factors and underlying pathophysiological mechanisms has prompted speculation regarding whether AS can be a cardiovascular comorbidity of psoriasis. In light of this context, we delve deeper into the causal relationship between psoriasis and aortic valve stenosis. Utilizing a two-sample MR analysis approach, we found compelling evidence suggesting that genetic susceptibility to psoriasis is indeed associated with a higher risk of AS. Importantly, our results remained robust even after conducting sensitivity analysis.

Our findings shed light on the intricate interplay between psoriasis and AS at the molecular level. Through the analysis of causal SNPs and GO enrichment analysis of transcriptional profiles obtained from independent databases of psoriasis and AS, we identified key pathways implicated in the pathogenesis of both conditions. Specifically, our results reveal the involvement of pathways related to "regulation of natural killer cell-mediated cytotoxicity", "leukocyte-mediated cytotoxicity", and "T cell-mediated cytotoxicity", "antigen processing and presentation", "MCP-1 production", "chemokine production", and "T cell-mediated immunity".

Several studies have suggested a correlation between psoriasis and natural killer (NK) cell receptors[24] and increase in infiltrated NK cells within psoriatic plaques.[25] Our findings contribute further evidence supporting the involvement of NK cells in the pathogenesis of psoriasis. However, the pathological role of NK cells in psoriasis has not been clarified, and further relevant research is still needed. There is substantial evidence connecting both conditions to T cell-mediated immune responses. Up-regulated T cells, macrophages, dendritic cells, neutrophils, and inflammatory cytokines in psoriasis promote keratinocyte hyperproliferation and angiogenesis.[2] Also, T-cell and elevated inflammatory mediators had been reported correlated with AS progression and severity.[26,27] There are evidences proposing antigen-specific immunological response and antigen-independent role of T lymphocytes in aortic valves;[28] T lymphocyte-specific signaling pathways are also upregulated in calcified aortic valves versus noncalcified ones.[29] Natural killer cell is also associated with increased pressure gradient.[30] While the involvement of other pathways in the progression of both diseases may require further investigation, our findings provide valuable insights into their potential participation and contribute to a better understanding of the molecular mechanisms underlying psoriasis and AS.

Through PPI analysis, we identified 15 hub genes, suggesting they could serve as candidate biomarkers which involved in the pathophysiological process of both AS and psoriasis. Among them, ISG15, a gene encoding a ubiquitin-like protein, exhibits broad expression across vertebrate cell types. This protein can exist freely or conjugate to lysine residues of target proteins via ISGylation, a post-translational process. ISG15 deconjugation, mediated by USP18, plays a role in various physiological process and has been extensively explored in the context of viral and bacterial infections, as well as in cancer research. Emerging evidence suggests the involvement of *ISG15* and its catalyze *USP18* in vascular fibrosis, stiffness, endothelial dysfunction, inflammation, aortic dilation, and aortic rupture both in mice and dilated human hearts.[31] While *USP18* expression is higher in dilated human hearts, its precise role in cardiac remodeling remains controversial.[32] Other hub genes, such as *IFIT3*, *IFI44L* and *XAF1*, has been identified as potential biomarkers in ischemic cardiomyopathy and heart failure databases.[33,34,35] In athero-prone condition, *OASL* has been demonstrated to regulate endothelial cells, with its absence preceding endothelial dysfunction and elevated vascular inflammation.[36] Notably, *ISG15* and *OASL* were also identified among differential genes in AS and normal patients, suggesting possible mechanism connecting AS and psoriasis.

While the functions of other hub genes with respect to CVD have been relatively less explored, our study highlights statistically significant hub genes, including *ISG15*, *MX2*, *OAS3*, *OASL*, *IFI6*, and *EPSTI1*, warranting further in-depth investigation. One strength of our study is the use of large sample size in the GWAS of Icelandic AS, which enhances the statistical power of the study. Additionally, employing various statistical methods increases the robustness of our results. The functional evaluation of causal SNPs and PPI analysis further underscore the significance of hub genes, emphasizing the importance of needing a more thorough comprehension of immune-related pathways and genes associated with AS and psoriasis. Such insights are crucial for the development of innovative diagnostic or prognostic biomarkers and the identification of therapeutic targets for both diseases.

However, our study has certain limitations. Firstly, despite employing multiple steps to examine pleiotropy, it was challenging to entirely eliminate the influence of potential pleiotropy. This led to an imprecise evaluation of the three key hypotheses. Fortunately, various methods consistently produced similar results, and sensitivity analyses revealed limited indications of horizontal pleiotropy. This helps mitigate the risk of pleiotropy bias. Another limitation of this study is that the analysis was based on summary-level data, which limits the interpretation of causality. Due to the observational nature of the original data, assessing or elucidating the impacts of psoriasis severity stratification was not feasible. Therefore, we could not evaluate the causal impact of AS in relation to the stratification of psoriasis severity. Moreover, the study was performed on individuals of European ancestry, which may limit the generalizability of the results to other populations. Also, there might be overlaps between GWAS samples (both AS and psoriasis datasets included participants from European ancestry), creating a weak instrumental bias. Nonetheless, high F-statistic of instruments undermined such bias. We look forward to further in-depth studies to confirm the causal relationship between psoriasis and aortic valve stenosis and to investigate the underlying mechanisms.

Overall, our research offers proof of a causal connection between psoriasis and AS. It indicates that the hub genes (e.g., *HLA-C*, *HLA-B*, *ISG15*, *IFIT3*, and *MX2*) and immune-related pathways (e.g., adaptive immunity) identified in the study may play a significant role in the development of both diseases. The epidemiological association and the causal relationship between the two diseases underscore the importance of conducting regular examinations related to CVD. For patients diagnosed with psoriasis, it is advisable to consider the use of moderate-intensity statins as part of the recommended therapeutic approach.[37] Besides, given the immune-mediated inflammatory diseases are recognized risk factor for cardiovascular burden, CVD risk-stratification among patients with inflammatory diseases is considered essential for more precise guidance regarding the utilization of statins and other prognostic interventions.[38] Furthermore, Yang, *et al*.[39] indicates that IL-17A triggers inflammation in valvular endothelium, exacerbating calcific aortic valve disease. This finding offers theoretical backing for anti-IL-17 therapy as a potential treatment for patients with both psoriasis and AS.

ABBREVIATIONS

MCP-1: Monocyte chemotactic protein-1
HLA: Human leukocyte antigen
ISG15: Interferon-stimulated gene 15
IFIT3: Interferon Induced Protein with Tetratricopeptide Repeats 3
MX2: MX Dynamin Like GTPase 2
OAS3: 2'-5'-oligoadenylate synthetase 3
OASL: 2'-5'-Oligoadenylate Synthetase Like
XAF1: XIAP Associated Factor 1
IFI6: Interferon Alpha Inducible Protein 6
USP18: Ubiquitin specific peptidase 18
EPSTI1: Epithelial Stromal Interaction 1
IFI44: Interferon induced protein 44
IFI44L: Interferon induced protein 44 like
HERC5: HECT And RLD Domain Containing E3 Ubiquitin Protein Ligase 5
ECM: Extracellular matrix

DECLARATIONS

Fundings

This work was supported by the National Natur-

al Science Foundation of China (81970325, and 82170375); Sichuan Science and Technology Program (2023YFS0296); Key Research and Development Project of Science & Technology Department of Sichuan Province (2022ZDZX0020 and 2023YFS-0296); Key Research and Development Support Project of Science & Technology Department of Chengdu (2021-YF08-00121-GX); Chinese Medical Association Cardiovascular Branch (CSC) Clinical Research Special Fund Project (CSCF2020B04); West China Hospital "1·3·5" Discipline of Excellence Project–"Percutaneous transcatheter aortic valve implantation" and "Mechanisms of aortic stenosis and the clinical applications".

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any generative AI or AI-assisted technologies.

Data Availability Statement

The authors confirm that summary statistics of psoriasis could be downloaded from ieu open gwas project (https://gwas.mrcieu.ac.uk/, ID: ebi-aGCST005527). Summary statistics of AS can be found form an open-access Genome-wide analysis (https://www.nature.com/articles/s41467-018-03252-6#Sec2). Other data supporting the findings of this study are available within the article and its supplementary materials.

REFERENCES

[1] Parisi R, Iskandar IYK, Kontopantelis E, *et al*. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ* 2020; 369: m1590.
[2] Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J. Psoriasis. *Lancet* 2021; 397: 1301–1315.
[3] Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. *N Engl J Med* 2014; 371: 744-756.
[4] Moncla LM, Briend M, Bosse Y, Mathieu P. Calcific aortic valve disease: mechanisms, prevention and treatment. *Nat Rev Cardiol* 2023; 20: 546-559.
[5] Antuna P, Cuesta J, Rivero F, *et al*. Severe calcified aortic stenosis in a young patient with psoriasis. *Int J Cardiol* 2016; 222: 656–657.
[6] Khalid U, Ahlehoff O, Gislason GH, *et al*. Increased risk of aortic valve stenosis in patients with psoriasis: a nationwide cohort study. *Eur Heart J* 2015; 36: 2177–2183.
[7] Yeung H, Takeshita J, Mehta NN, *et al*. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol* 2013; 149: 1173–1179.
[8] Samarasekera EJ, Neilson JM, Warren RB, *et al*. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *J Invest Dermatol* 2013; 133: 2340–2346.
[9] Saleh HMA, Attia EAS, Onsy AM, *et al*. Platelet activation: a link between psoriasis per se and subclinical atherosclerosis--a case-control study. *Br J Dermatol* 2013; 169: 68-75.
[10] Helgadottir A, Thorleifsson G, Gretarsdottir S, *et al*. Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nat Commun* 2018; 9: 987.
[11] Sveinbjornsson G, Albrechtsen A, Zink F, *et al*. Weighting sequence variants based on their annotation increases power of whole-genome association studies. *Nat Genet* 2016; 48: 314–317.
[12] Tsoi LC, Spain SL, Knight J, *et al*. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet* 2012; 44: 1341–1348.
[13] Ellinghaus E, Ellinghaus D, Stuart PE, *et al*. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. *Nat Genet* 2010; 42: 991–995.
[14] Genetic Analysis of Psoriasis C, the Wellcome Trust Case Control C, Strange A, *et al*. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 2010; 42: 985–990.
[15] Nair RP, Duffin KC, Helms C, *et al*. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 2009; 41: 199–204.
[16] Purcell S, Neale B, Todd-Brown K, *et al*. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007; 81: 559–575.
[17] Kang HM, Sul JH, Service SK, *et al*. Variance component model to account for sample structure in genome-wide association studies. *Nature Genetics* 2010; 42: 348–354.
[18] Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol* 2011; 40: 755–764.
[19] Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics* 2018; 50: 693–698.
[20] Szklarczyk D, Kirsch R, Koutrouli M, *et al*. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any se-

quenced genome of interest. *Nucleic Acids Res* 2023; 51: D638−D646.
[21] Shannon P, Markiel A, Ozier O, *et al*. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003; 13: 2498−2504.
[22] Greene CL, Jaatinen KJ, Wang H, *et al*. Transcriptional Profiling of Normal, Stenotic, and Regurgitant Human Aortic Valves. *Genes* (*Basel*) 2020;11: 789.
[23] Gelfand JM, Mehta NN. Aortic valve stenosis: a new cardiovascular comorbidity of psoriasis? *Eur Heart* J 2015; 36: 2134-2135.
[24] Zeng X, Chen H, Gupta R, *et al*. Deletion of the activating NKG2C receptor and a functional polymorphism in its ligand HLA-E in psoriasis susceptibility. *Exp Dermatol* 2013; 22: 679−681.
[25] Polese B, Zhang H, Thurairajah B, King IL. Innate Lymphocytes in Psoriasis. *Frontiers In Immunology* 2020; 11: 242.
[26] Kraler S, Blaser MC, Aikawa E, *et al*. Calcific aortic valve disease: from molecular and cellular mechanisms to medical therapy. *Eur Heart J* 2022; 43: 683−697.
[27] Dweck MR, Jones C, Joshi NV, *et al*. Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. *Circulation* 2012; 125: 76−86.
[28] Raddatz MA, Madhur MS, Merryman WD. Adaptive immune cells in calcific aortic valve disease. *Am J Physiol Heart Circ Physiol* 2019; 317: H141−H155.
[29] Guauque-Olarte S, Droit A, Tremblay-Marchand J, *et al*. RNA expression profile of calcified bicuspid, tricuspid, and normal human aortic valves by RNA sequencing. *Physiol Genomics* 2016; 48: 749−761.
[30] Mazur P, Mielimonka A, Natorska J, *et al*. Lymphocyte and monocyte subpopulations in severe aortic stenosis at the time of surgical intervention. *Cardiovasc Pathol* 2018; 35: 1−7.
[31] González-Amor M, García-Redondo AB, Jorge I, *et al*. Interferon-stimulated gene 15 pathway is a novel mediator of endothelial dysfunction and aneurysms development in angiotensin II infused mice through increased oxidative stress. *Cardiovasc Res* 2022; 118: 3250−3268.
[32] Ying X, Zhao Y, Yao T, *et al*. Novel protective role for ubiquitin-specific protease 18 in pathological cardiac remodeling. *Hypertension* 2016; 68: 1160−1170.
[33] Yang Y, Yang W, Huo W, *et al*. Identification of biomarkers for ischemic cardiomyopathy based on microarray data analysis. *Cardiol J* 2017; 24: 305−313.
[34] Chen C, Tian J, He Z, *et al*. Identified three interferon induced proteins as novel biomarkers of human ischemic cardiomyopathy. *Int J Mol Sci* 2021; 22: 13116.
[35] Yu H, Yu M, Li Z, Zhang E, Ma H. Identification and analysis of mitochondria-related key genes of heart failure. *J Transl Med* 2022; 20: 410.
[36] Kim TK, Jeon S, Park S, *et al*. 2'-5' oligoadenylate synthetase-like 1 (OASL1) protects against atherosclerosis by maintaining endothelial nitric oxide synthase mRNA stability. *Nat Commun* 2022; 13: 6647.
[37] Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 139: e1046−e1081.
[38] Peverelli M, Maughan RT, Gopalan D, *et al*. Use of coronarycomputed tomography for cardiovascular risk assessment in immune-mediated inflammatory diseases. *Heart* 2024; 110: 545-551.
[39] Yang Z, Zhang J, Zhu Y, *et al*. IL-17A induces valvular endothelial inflammation and aggravates calcific aortic valve disease. *Biochem Biophys Res Commun* 2023; 672: 145−153.

Please cite this article as: JIANG KX, WANG Y, LIU YT, XU Y J N, HUANG FY, CHEN M. Causal effect of psoriasis on aortic valve stenosis: a two-sample Mendelian randomization study. *J Geriatr Cardiol* 2024; 21(9): 865−873. DOI: 10.26599/1671-5411.2024.09.002