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Potential drug targets for peripheral artery disease identified through Mendelian randomization analysis

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Abstract

Introduction Peripheral Artery Disease (PAD) is a common cardiovascular condition marked by peripheral artery stenosis or occlusion. Despite treatment advancements, patients will still face vascular complications, highlighting the need for innovative therapies. Human proteins play crucial roles in biology and drug research. Mendelian randomization (MR) analysis, a gene-based method, is increasingly used in drug target identification. This study aims to identify PAD-associated plasma proteins through MR analysis for potential therapies.

Methods We first used GWAS data and seven pQTL datasets to identify plasma proteins causally linked to PAD through MR analysis. Then, we performed KEGG pathway enrichment analysis, Bayesian colocalization analysis, and MR-BMA analysis were carried out to investigate mechanisms and prioritize these proteins. Finally, we assessed the druggability of the target proteins using the DrugBank database.

Results MR analysis found four plasma proteins causally linked to PAD: MMP3 positively correlated with PAD, while CASS4, ISG15, and MMP1 exhibited negative associations. Bayesian colocalization analysis confirmed these relationships, and the MR-BMA analysis prioritized MMP1 as the main target. KEGG pathway enrichment analysis highlighted lipid metabolism and atherosclerosis pathways as central to these drug targets. The druggability evaluation indicated that drugs targeting these proteins are either in development or already in clinical use.

Conclusion This study integrates genetic and proteomic data to identify therapeutic targets for PAD and evaluate their potential for drug development. The prioritization of MMP1 and ISG15 as key targets shows promise for PAD treatment, but further validation and clinical exploration of these findings are needed.

Keywords Peripheral artery disease, Mendelian randomization, GWAS, pQTL, Protein targets, Drug development

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Introduction

Peripheral artery disease (PAD) ranks as the third-most-common cardiovascular disorder, marked by high incidence [1]. Yet, the majority of patients either show no symptoms or present atypical ones, with only around 10% experiencing classic claudication, which poses a great challenge to early diagnosis [2]. Notably, PAD patients, regardless of symptom presence, face a marked increase in cardiovascular adverse event rate and mortality. Their risk of cardiovascular-related death triples, and the more severe the disease, the higher the likelihood of fatal myocardial infarction or stroke [3, 4]. Estimates from the 2019 Global Burden of Disease study indicate approximately 113 million PAD patients globally [5]. Alarmingly, over a fifth will die from coronary or cerebrovascular diseases within a decade, underscoring a grave public-health concern [6]. Despite advances in surgical interventions, antithrombotic therapies, and treatments targeting conventional risk factors (such as lipid, blood pressure, and blood glucose reduction), the vascular complication risk for PAD patients remains unacceptably high [7]. Anti - thrombotic drugs like aspirin and clopidogrel effectively lower thrombosis risk, but can cause bleeding complications such as gastrointestinal bleeding and bruising. They may also interact with other medications, reducing effectiveness or increasing side effects. For example, aspirin, which can damage the stomach lining, poses a higher risk of gastrointestinal bleeding than other anti - thrombotic agents [8]. Some patients develop drug resistance or low responsiveness to these medications, weakening their effectiveness over time. Statins, while significantly lowering lipid levels, cannot adequately control lipids in all patients, especially those with complex lipid profiles. Blood pressure and glucose control measures may also fall short, particularly when patients have comorbidities or poor treatment adherence [9]. Follow-up studies indicate that even with current treatments, patients with PAD still face a significant residual risk of vascular complications. For instance, a clinical trial involving 6,564 PAD patients from 34 countries, with a median follow-up of 28 months, found they had a high risk of cardiovascular events despite standard therapy [10]. This study highlights the ongoing risk of cardiovascular death in PAD patients and underscores the need for improved treatment strategies. Therefore, alternative strategies are needed to mitigate this residual risk.

Several treatment options are available for this condition, including statin therapy, P2Y12 inhibitors, low-dose rivaroxaban, vorapaxar, cilostazol, supervised exercise therapy, and revascularization for patients with severe pain. Proteins that regulate key molecular pathways are considered important for drug development. High-throughput methods enable efficient and precise measurement of circulating proteins in large samples. Many studies have explored the link between blood proteins and coronary atherosclerosis risk [11–14]. Plasma proteins have long been key biomarkers for disease diagnosis and prediction, greatly affecting clinical practice and drug development. They are promising targets because they can be directly modulated using traditional small molecules or biologics like monoclonal antibodies [15]. However, drug development success hinges on the target's causal role in the disease. Mendelian Randomization (MR) can clarify causality and has accurately predicted randomized controlled trials (RCTs) outcomes for targets like PCSK9, LpPLA2, and NPC1L1, making it a standard tool for testing new drug targets [16]. Unlike observational studies, MR avoids confounding factors. Progress in high-throughput genomic and proteomic tech in plasma and cerebrospinal fluid has helped find potential targets for diseases like stroke and Alzheimer's disease using MR-based strategies [17, 18]. However, few MR studies combine GWAS and plasma protein quantitative trait loci (pQTL) data for PAD.

In this study, we aimed to identify plasma proteins as potential therapeutic targets for PAD. Figure 1 outlines the study design. Initially, we harnessed GWAS data and seven plasma pQTL datasets, employing MR to identify potential pathogenic plasma proteins for PAD. Subsequently, we explored the potential roles and ranking of these proteins through Bayesian colocalization analysis (Coloc), kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment, and MR Bayesian Model Averaging (MR-BMA) analysis. Finally, we assessed the druggability of these target proteins using the Drugbank database.

Methods

Study design and data sources

The research design flowchart is shown in Fig. 1. Initially, data integrated from seven pQTL datasets were used as the exposure (Table S1), with "Occlusion and Tenosis of Arteries" as the outcome for MR analysis (Table S2). This analysis explores the causal link between the proteome and lower limb arterial stenosis risk. The MR methods hinge on three assumptions: [1] The selected single nucleotide polymorphisms (SNPs) used as genetic instruments are strongly associated with the exposure ("relevance"); [2] SNPs are independent of confounding factors ("exchangeability"); [3] SNPs affect the outcome only through the exposure ("exclusion restriction") [19]. To address multiple testing, false discovery rate (FDR) correction was applied.

Subsequently, we delved into enrichment pathways, priority targets for lower limb arterial stenosis treatment, and drugability of these causal proteins. KEGG pathway analysis was performed to pinpoint significantly enriched pathways among the causal proteins. The MR-BMA

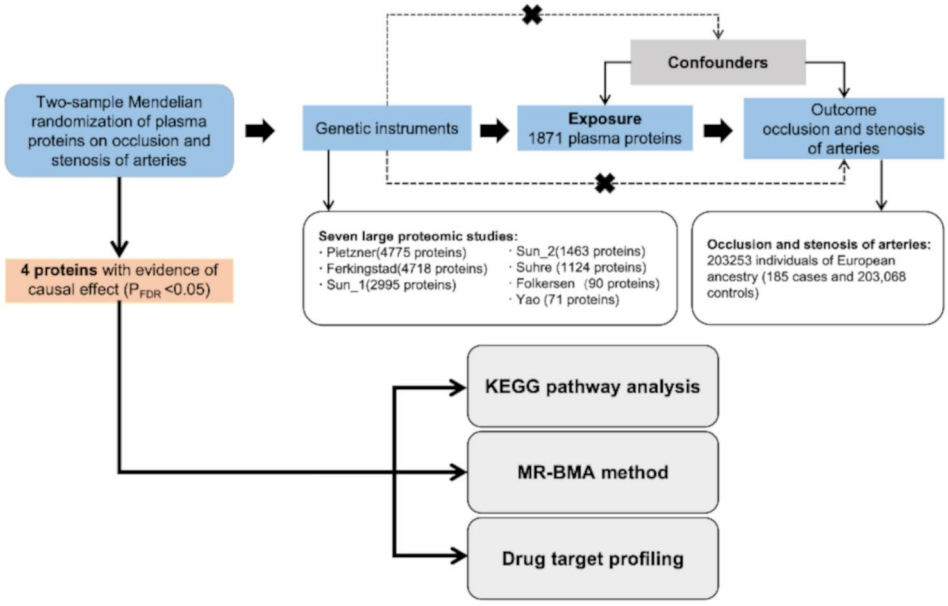

Fig. 1 Flowchart

method ranked these proteins based on their marginal scores. To evaluate the clinical potential of drugs targeting these proteins, we conducted a thorough search of the DrugBank database and clinical trial registries.

Instrumental variable selection for two-sample Mendelian randomization (TSMR)

SNPs were selected as instrumental variables (IVs) for the TSMR analysis based on the following criteria: [1] The SNPs must be associated with the exposure at a genome-wide significance level ($P < 5 \times 10^{-8}$) in the GWAS or GWMA; [2] The SNPs must be independent of each other, with linkage disequilibrium (LD) characterized by $r^2 < 0.05$ within a 10 Mb window.

Statistical analysis

In our TSMR analysis, we used three methods: inverse-variance weighted (IVW) with random effects, weighted median, and MR-Egger. IVW was designated as the primary method, where we performed a weighted regression of the SNP-outcome effects on SNP-exposure effects, with the intercept set to zero. While IVW provides the highest statistical power, it assumes all instruments are valid and free from pleiotropy [20]. The weighted median and MR-Egger methods add robustness, offering estimates under diverse scenarios, albeit with reduced efficiency [21, 22].

We applied FDR correction for multiple independent tests. Results with FDR < 0.05 were considered significant, while thoes with $p < 0.05$ but FDR > 0.05 were deemed suggestive [23].

Finally, where applicable, we performed TSMR analyses using SNPs within protein-coding genes's cis-region (a ± 1 Mb window around the gene) to check if the significant associations we found were driven by cis-regulatory SNPs. For single-SNP analyses, the Wald ratio method was used, and for multiple SNPs, the IVW method was applied.

GO and KEGG pathway enrichment analysis

To explore the biological functions and molecular pathways of target genes, we performed Gene Ontology (GO) and KEGG pathway enrichment analyses on the target gene list (MMP3, CASS4, ISG15, MMP1). First, we converted gene symbols to standard Entrez IDs to ensure compatibility with annotation databases. Then, using the clusterProfiler package's enrichGO function, we conducted GO enrichment analysis, covering three main categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). We set the significance threshold at an adjusted p-value (padj) < 0.05, using the Benjamini-Hochberg method for multiple testing correction. For KEGG pathway enrichment analysis, we used the enrichKEGG function with the same significance threshold. All analyses were based on the human genome annotation database (org.Hs.eg.db) to ensure accuracy and reliability. By visualizing the enrichment results, we further clarified the potential roles of the target genes in biological processes and molecular pathways.

MR-BMA method

MR-BMA is an advanced form of multivariate MR paradigm. It ranks risk factors by their probability of being

causal determinants for an outcome. Within a Bayesian framwork, it selects causal risk factors from a set of correlated candidates, even when those candidates are highly correlated [24]. As previously mentioned, MR-BMA addresses "measurement pleiotropy" caused by high correlation between plasma proteins and other key proteins. This method helps identify dominant proteins and prioritize candidate causal proteins, particularly in thyroid cancer research [24, 25].

We integrated key protein-related SNPs (as per the aforementioned criteria) as instrumental variables for MR-BMA to clarify their causal effects. In MR-BMA, we conducted multivariate MR analyses using weighted regression across various protein combinations, including all individual proteins, all pairs, and all triplets. We assessed the goodness-of-fit of the regression models by the posterior probability that the combination represents true causal proteins. Each protein was assigned a marginal inclusion probability (MIP), which is the probability of that protein being a causal determinant for thyroid cancer based on the posterior probability of models including that protein. We also calculated the model-averaged causal effect (MACE) for each protein, which provides a conservative estimate of the direct causal effect of the protein on the disease within these models.

We computed empirical *p*-values for each protein's MIP using permutation methods and adjustments for multiple testing using FDR correction. In the MR-BMA models, we used Cochran's Q statistic to identify outlier SNPs and Cook's distance to identify influential SNPs (posterior probability > 0.02). Finally, we re-ran the MR-BMA analysis, omitting influential SNPs and outliers for our primary analysis [24, 26].

Colocalization analysis

To investigate the shared causal variation between proteins and PAD, we performed colocalization analysis using R Coloc [27]. We identified cis-pQTLs as the primary SNPs, and extracted all SNPs within a 1 MB window around them. We calculated the posterior probability of shared causal variation, H4 (PPH4), which represents the probability that the two traits share a common causal variant. A PPH4 value above 0.8 suggests colocalization. Shared variation between pQTLs and PAD can strengthen the causal effect of proteins on PAD [28–30].

Evaluation of druggability

We evaluated the druggability of the candidate target proteins by Drugbank database. Additionally, we searched https://www.ClinicalTrials.gov to obtain the name and clinical phase of protein-targeted drugs, if applicable.

All analyses were two-sided and conducted using TwoSampleMR (version 0.5.6), GSMR (version 1.0.9) and clusterProfiler (version 3.14.3) packages in R software (version 3.6.3). The R-code for MR-BMA was obtained from https://github.com/verena-zuber/demo_AMD.

Results

MR reveals 4 proteins causally associated with peripheral artery disease

In this study, after applying strict selection criteria for instrumental variables, 1,871 plasma proteins were included in the MR analysis. Details are in Tables S1-S4. Notably, using IVW or Wald ratio results(PFDR < 0.05), we found that among these 1,871 plasma proteins, MMP3, has a positive causal association with PAD with an odds ratio of 2.29 (95% CI: 1.48, 3.54). Conversely, CASS4, ISG15, and MMP1 were negatively correlated with PAD. Our preliminary analysis found no significant heterogeneity or pleiotropy among the analyzed proteins. Detailed results are presented in Figs. 2 and 3; Table 1.

Colocalization analysis

We conducted colocalization analysis within ±1 MB upstream and downstream of each gene to see if the causal relationships between the four plasma proteins and PAD were due to linkage disequilibrium. The results are shown in Fig. 4. Strong evidence for colocalization is indicated by PPH3 + PPH4 > 0.8.

For PAD, ISG15 and MMP3 has strong colocalization evidence. However, CASS4 and MMP1 did not show strong evidence of shared pathogenic variation with PAD in this region (PPH3 + PPH4 < 0.8).

MR-BMA method to identify leading targets for peripheral artery disease

We applied the MR-BMA method to rank the targets. In this method, we calculated the posterior probability (PP) for each model. The MIP, which is the sum of PPs across all possible models, was used to rank the targets from most to least important. A higher MIP indicates a stronger "true causal" association [23, 24].

Notably, MR-BMA results indicated that MMP1 expression was negatively associated with PAD risk. After correcting for outliers, we repeated the analysis and found that MMP1 plays a dominant role in PAD risk (Table 2, Table S5).

Exploring biological significance through enrichment analysis

GO and KEGG analyses help understand the functions, metabolic pathways, and interactions of similarly expressed proteins. For the top 10 proteins, GO annotation show that in Biological Processes (BP), terms like positive regulation of protein-containing complex assembly, cellular response to UV-A, and extracellular matrix disassembly were enriched. In Cellular Components (CC), terms such as cytosolic small ribosomal subunit,

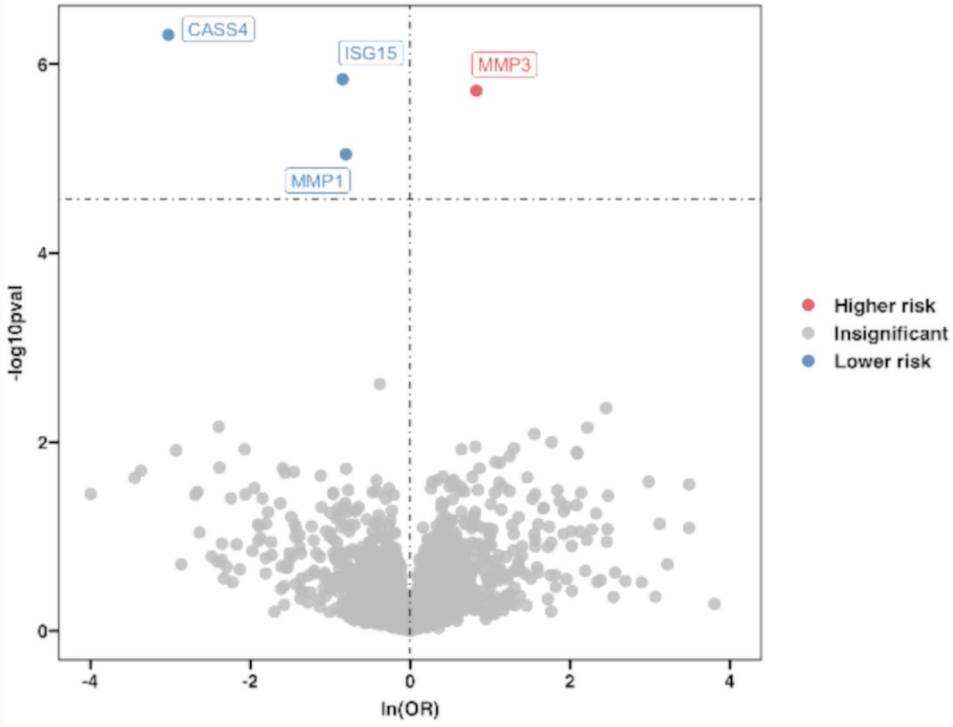

Fig. 2 The volcano plot of the results. MR analysis revealed 1871 proteins, and after *P*-value correction (Bonferroni correction), 4 proteins were significantly associated with the outcome

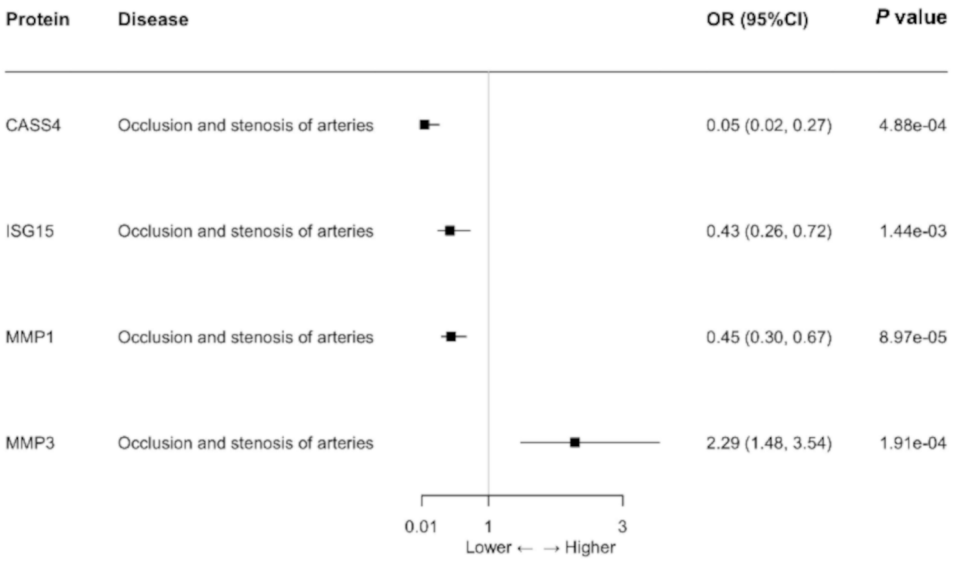

Fig. 3 Forest plot of MR results. The causal relationship between plasma proteins and lower limb arterial stenosis

Table 1 Results of MR analysis

Protein	SNP	Effect allele	OR (95% CI)	*P* value	F statistics	Author	Q_pval	egger_intercept_pval
CASS4	rs67041321	T	0.05 (0.01, 0.27)	4.88e-07	85.66	Pietzner	0.573608582	0.517998971
ISG15	rs4615788	C	0.43 (0.26, 0.72)	1.44e-06	1353.80	Pietzner	0.134536615	0.895412748
MMP3	rs632478	T	2.29 (1.48, 3.54)	1.91e-06	3903.94	Folkersen	0.562344613	0.714534235
MMP1	rs471994	A	0.45 (0.30, 0.67)	8.97e-06	1640.62	Pietzner	0.732274368	0.523514235

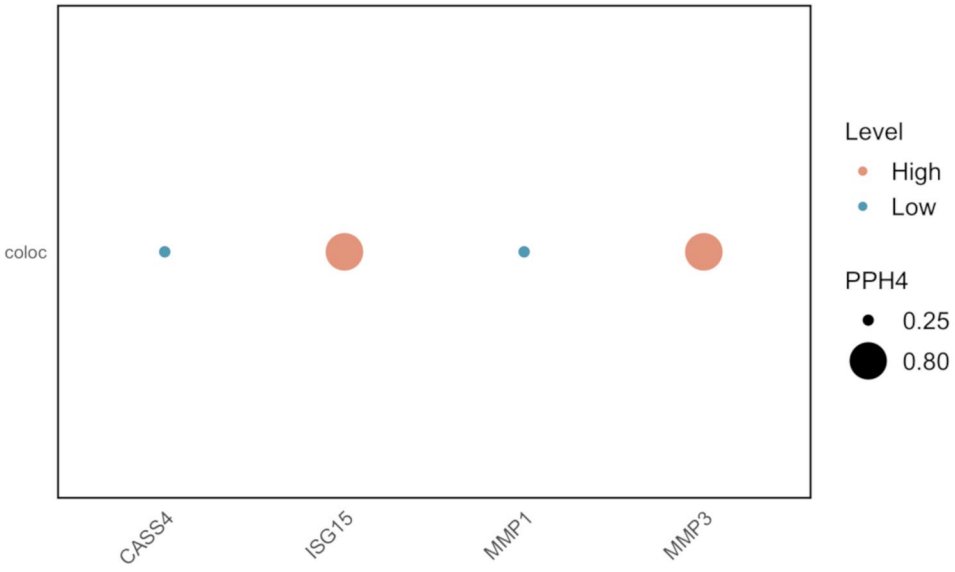

Fig. 4 Scatter plot of MR and co localization analysis results

Table 2 Analysis results of MR-BMA (Main results)

Trait	Ranking by MIP	MIP	MACE
MMP1	1	0.568	-0.074
ISG15	2	0.506	0.005
CASS4	3	0.49	-0.009
MMP3	4	0.428	-0.026

cytosolic ribosome, and focal adhesion are observed. Additionally, in Molecular Functions (MF), the top 10 proteins are mainly associated with metalloendopeptidase activity, serine-type endopeptidase activity, and serine hydrolase activity (Fig. 5A).

KEGG enrichment analysis identified that these proteins are primarily involved in pathways related to coronavirus disease-COVID-19, rheumatoid arthritis, IL-17 signaling pathway, and lipid and atherosclerosis (Fig. 5B, Tables S6-S7).

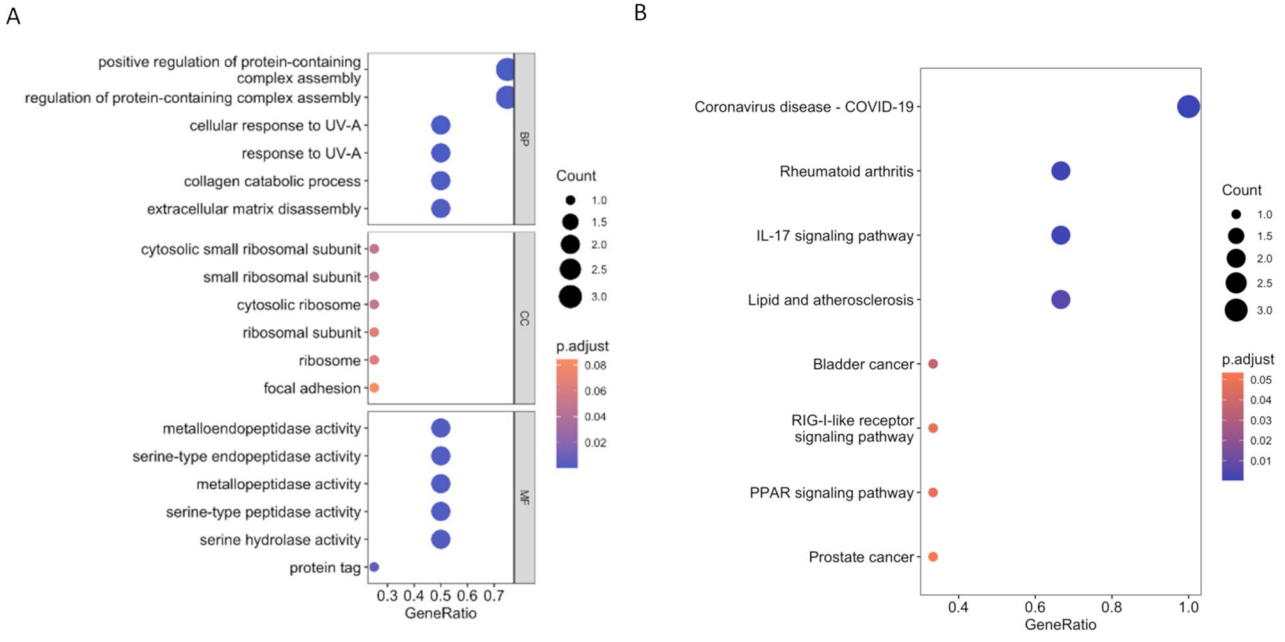

Fig. 5 (**A-B**) GO and KEGG enrichment analysis of identified lower limb arterial stenosis treatment proteins

Table 3 Analysis of druggability of drug targets

Target	Status	Compound name	Role	Mechanism of Action
CASS4	-	-	-	-
ISG15	Approved	Irinotecan	Inhibitor	Topoisomerase I inhibitor, Small Molecule, Antineoplastic Agents
	Approved	Progesterone	-	Contraceptives, Small Molecule, Endogenous progesterone receptor agonist
	Experimental	Camptothecin	-	Topoisomerase I inhibitor, prototypic, Small Molecule
MMP3	Experimental	Ilomastat	Inhibition	Broad spectrum MMP inhibitor
	Approved	Pravastatin	Inhibition	Anticholesteremic Agents, Small Molecule
	Approved	Chlorthalidone	Inhibition	Diuretics, Antihypertensive Agents, Small Molecule
MMP1	Approved	Leflunomide	-	AHR agonist, immunosuppressive agent, Small Molecule, Antirheumatic Agents
	Approved	Sirolimus	-	Original antifungal antibiotic, Immunosuppressive Agents, Small Molecule

Drug applicability of proteins and their association with current PAD medications

Finally, to explore the repurposing potential of known drug compounds for the phenotype, we linked our findings with the DrugBank database using cis-pQTL. DrugBank [31] was used to assign drug compounds to protein targets curated by the ChEMBL database. For the identified plasma protein targets, two drugs were predicted as activators and two as inhibitors. For example, ISG15 was predicted to be targeted by Irinotecan, a small-molecule drug with antitumor activity. MMP1 was predicted to be targeted by Leflunomide, which is used for treating rheumatoid arthritis. Progesterone was also predicted to target ISG15, where it activates endogenous progesterone receptors and contributes to contraceptive effects. These findings suggest potential new uses for existing drugs in the context of PAD treatment. The details of these drug associations and their potential implications for PAD therapy canbe found in Table 3.

Discussion

In this study, we analyzed 1,871 plasma proteins associated with lower limb arterial stenosis. The primary TSMR analysis found causal relationships between four proteins and the risk of lower limb arterial stenosis. Among these, MMP3 was positively associated with the risk, while CASS4, ISG15, and MMP1 were negatively associated. KEGG pathway enrichment analysis then indicated that these four causal proteins were enriched in the atherosclerosis pathway. MR-BMA analysis ranked MMP1 as the top protein related to lower limb arterial stenosis. Finally, the identification of two developing protein-targeted drugs and six approved drugs supports the application of genomics and proteomics in drug development. Collectively, these findings highlight the utility of genetic analysis in identifying both known and novel causal loci and pathways related to lower limb arterial stenosis.

The etiology of lower limb arterial stenosis is complex, involving multiple genes, signaling pathways, and abnormal atherosclerosis regulation. Lipid metabolism abnormalities significantly contribute to atherosclerosis, the primary pathological basis for lower limb arterial stenosis. These factors interact through a complex mechanism, leading to endothelial damage, plaque formation, and ultimately arterial stenosis and blockage, which can result in severe the lower limbs ischemic diseases. Therefore, many studies are exploring signaling molecules in atherosclerosis as potential therapeutic targets for lower limb arterial stenosis. For example, pravastatin, a statin drug, is notable for its ability to inhibit HMG-CoA reductase, significantly reduce LDL cholesterol levels, and decrease the formation and progression of atherosclerotic plaques [32]. Our study consistently shows the aggregation of proteins related to lipid and cholesterol pathways in lower limb arterial stenosis, particularly MMP1, MMP3, CASS4, and ISG15. MMPs play a crucial role in plaque instability and rupture in atherosclerosis, and inhibiting MMP activity may reduce plaque rupture and related acute events [33]. Studies have shown that Illomastat, by inhibiting MMP activity, can slow the progression of atherosclerosis, particularly regarding plaque instability [34, 35]. Similarly, ISG15, a small molecular protein, may slow the progression of atherosclerosis by regulating endothelial cell oxidative stress responses [36, 37]. Lastly, CASS4, a cytoskeletal scaffolding protein, primarily participates in cell adhesion, migration, and signaling processes [38]. Members of the CAS family, such as p130Cas and BCAR1, have been shown to play significant roles in cardiovascular diseases, particularly in atherosclerosis [38, 39]. Overall, our results support the causal role of these proteins and confirm the importance of atherosclerosis in the etiology of lower limb arterial stenosis.

Moreover, given the associations of protein characteristics, we performed MR-BMA analysis to identify priority pathogenic proteins. It should be noted that this method primarily aims to detect causal risk factors among high-dimensional candidate populations, rather than unbiasedly estimating the extent of their pathogenic impact [24]. Our findings emphasize the necessity of prioritizing MMP1, as it may be more closely related to the occurrence of lower limb arterial stenosis. Specifically, MMP1 influences vascular smooth muscle cell migration and ECM degradation, affecting the remodeling

process of the vascular wall and potentially exacerbating vascular stenosis [34, 40]. Consistent with our findings, recent research has discovered that MMP inhibitors have strong effects on lower limb arterial stenosis, attributed to their inhibition of MMP1-induced vascular smooth muscle cell migration and ECM degradation [41]. Recent evidence also suggests that high expression of MMP1 is associated with poor prognosis in atherosclerosis patients [42]. Despite being considered a potential target in some cardiovascular diseases, the practical application of targeting MMP1 has not yet been realized. Nevertheless, the involvement of these proteins in lower limb arterial stenosis may be substantial and warrants further investigation.

The strength of this study lies in its comprehensive proteome-wide MR design, which systematically investigates the association between plasma protein biomarkers and PAD risk. This design has a large sample size, broad protein coverage, and minimal confounding biases. The consistent results across multiple rigorous analyses confirm the findings'robustness. Additional evidence from KEGG and drug availability assessments provides insights into the potential pathogenic roles of candidate proteins in PAD and further prioritizes druggable targets. Despite the lack of drug information for CASS4, these proteins remain promising new therapeutic targets for PAD. MMP1 has been found to strongly inhibit atherosclerosis [41]. However, several limitations should be considered in this study. First, the current analysis is limited to European populations. Extending these findings to other ancestries requires further validation. However, previous reports have indicated that some candidate biomarkers related to PAD are common across different ancestries, suggesting some degree of universality. Second, while we assessed the role of plasma proteins in PAD, we could not estimate the levels of relevant proteins in other tissues. Evaluating protein levels in other tissues may provide further insights into the pathogenesis of PAD. Third, current statistical analyses and stringent significance thresholds may filter out downstream effects of the driver proteins. Further mechanistic studies are needed to reveal the downstream effects involved in PAD development. Although this study identified several potential protein targets associated with PAD and assessed their drug development potential, these findings have not been clinically validated. Future research should further validate the therapeutic efficacy of these targets through clinical trials and explore the application of drugs targeting these proteins in PAD patients. Lastly, while KEGG enrichment analysis and MR-BMA methods revealed multiple biological pathways and potential mechanisms related to PAD, the complexity of these mechanisms implies that our understanding of the effects of some proteins remains limited. Future studies should further explore the specific functions of these proteins in the pathology of PAD to provide a more detailed biological foundation for developing more effective treatment strategies.

Conclusions

This study has identified several plasma proteins associated with an increased risk of PAD risk, providing new insights into the etiology of PAD and promising targets for developing PAD treatment drugs. Among these proteins, MMP3 shows a positive correlation with PAD risk, while ISG15 exhibits a negative correlation. Both proteins play significant roles in the process of atherosclerosis and thus represent crucial therapeutic targets for PAD. Although the study employs multiple methods to support these targets, further experiments and clinical research are necessary to confirm their treatment effects.

Abbreviations

BP	Biological Processes
CC	Cellular Components
Coloc	Bayesian Colocalization Analysis
FDR	False Discovery Rate
GWAS	Genome-Wide Association Study
IVs	Instrumental Variables
IVW	Inverse-variance Weighted
KEGG	Kyoto Encyclopedia of Genes and Genomes
MACE	Model-averaged Causal Effect
MF	Molecular Functions
MIP	Marginal Inclusion Probability
MR	Mendelian Randomization
MR-BMA	MR Bayesian Model Averaging
PAD	Peripheral Artery Disease
PPH4	Posterior Probability of Shared Causal Variation, H4
pQTL	Plasma Protein Quantitative Trait Loci
RCTs	Randomized Controlled Trials
SNPs	Single Nucleotide Polymorphisms
TSMR	Two-sample Mendelian Randomization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

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Author contributions

X.D. and Z.C. contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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Data availability
The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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