Exploring Causal Relationships between Circulating Inflammatory Proteins and Thromboangiitis Obliterans: A Mendelian Randomization Study

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Abstract

Background Thromboangiitis obliterans (TAO) is a vascular condition characterized by poor prognosis and an unclear etiology. This study employs Mendelian randomization (MR) to investigate the causal impact of circulating inflammatory proteins on TAO.

Methods In this MR analysis, summary statistics from a genome-wide association study meta-analysis of 91 inflammation-related proteins were integrated with independently sourced TAO data from the FinnGen consortium's R10 release. Methods such as inverse variance weighting, MR–Egger regression, weighted median approaches, MR-PRESSO, and multivariable MR (MVMR) analysis were utilized.

Results The analysis indicated an association between higher levels of C–C motif chemokine 4 and a reduced risk of TAO, with an odds ratio (OR) of 0.44 (95% confidence interval [CI]: 0.29–0.67; $p = 1.4 \times 10^{-4}$; adjusted $p = 0.013$). Similarly, glial cell line-derived neurotrophic factor exhibited a suggestively protective effect against TAO (OR: 0.43, 95% CI: 0.22–0.81; $p = 0.010$; adjusted $p = 0.218$). Conversely, higher levels of C–C motif chemokine 23 were suggestively linked to an increased risk of TAO (OR: 1.88, 95% CI: 1.21–2.93; $p = 0.005$; adjusted $p = 0.218$). The sensitivity analysis and MVMR revealed no evidence of heterogeneity or pleiotropy.

Conclusion This study identifies C–C motif chemokine 4 and glial cell line-derived neurotrophic factor as potential protective biomarkers for TAO, whereas C–C motif chemokine 23 emerges as a suggestive risk marker. These findings elucidate potential causal relationships and highlight the significance of these proteins in the pathogenesis and prospective therapeutic strategies for TAO.

Keywords
► thromboangiitis obliterans
► Mendelian randomization
► inflammatory proteins
► biomarkers
► therapeutic target

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* *These authors equally contributed to this paper and thus shared the co-first authorship.*

Visual summary. The Mendelian randomization analysis unveils the relationships between circulating inflammatory proteins and thromboangiitis obliterans.
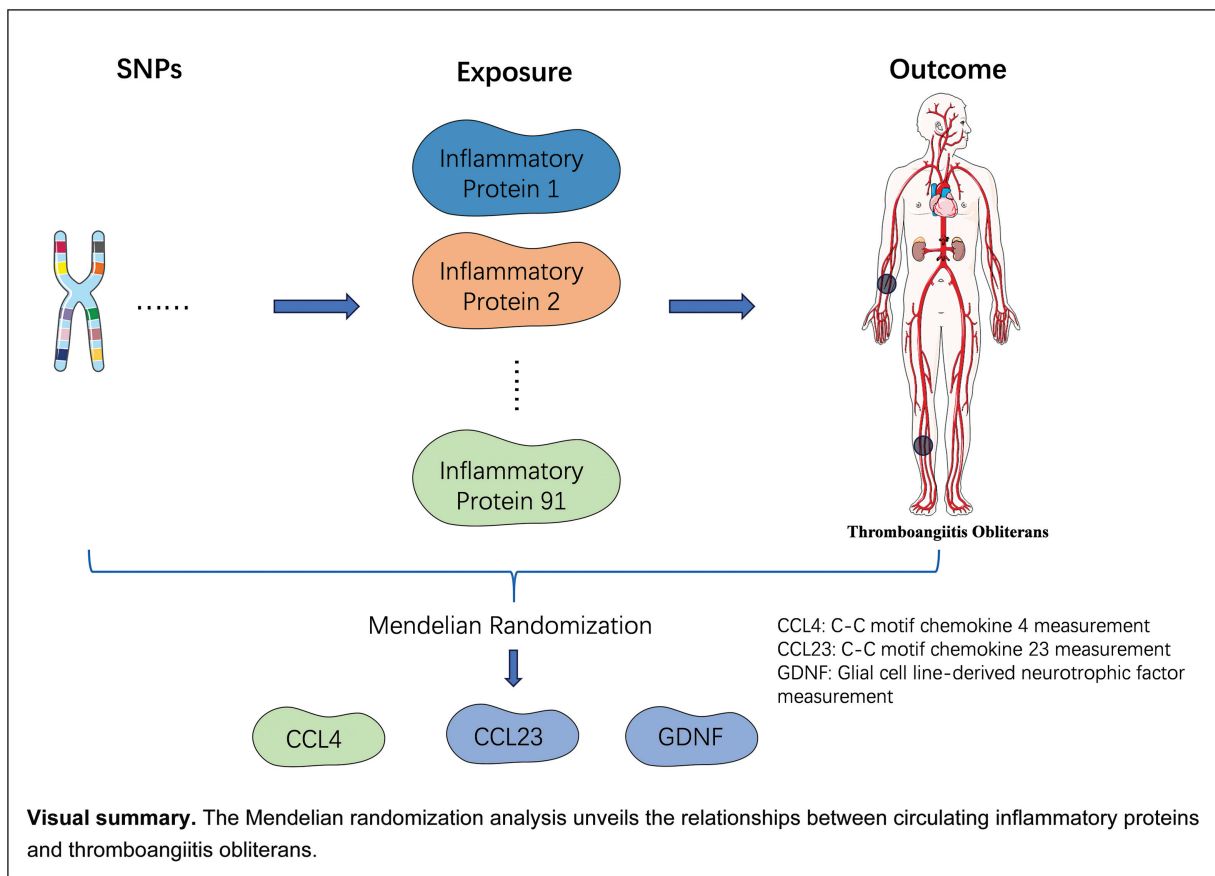
Introduction

Thromboangiitis obliterans (TAO), commonly referred to as Buerger's disease, is a distinct nonatherosclerotic, segmental inflammatory disorder that predominantly affects small- and medium-sized arteries and veins in both the upper and lower extremities.[1] TAO, with an annual incidence of 12.6 per 100,000 in the United States, is observed worldwide but is more prevalent in the Middle East and Far East.[1] The disease typically presents in patients <45 years of age. Despite over a century of recognition, advancements in comprehending its etiology, pathophysiology, and optimal treatment strategies have been limited.[2,3] Vascular event-free survival and amputation-free survival rates at 5, 10, and 15 years are reported at 41 and 85%, 23 and 74%, and 19 and 66%, respectively.[4]

An immune-mediated response is implicated in TAO pathogenesis.[5] Recent studies have identified a balanced presence of CD4+ and CD8+ T cells near the internal lamina. Additionally, macrophages and S100+ dendritic cells are present in thrombi and intimal layers.[5,6] Elevated levels of diverse cytokines in TAO patients highlight the critical importance of inflammatory and autoimmune mechanisms.[2,7] Nonetheless, the clinical significance of these cytokines is yet to be fully understood, due to the scarcity of comprehensive experimental and clinical studies. Investigating circulating inflammatory proteins could shed light on the biological underpinnings of TAO, offering new diagnostic and therapeutic avenues.

Mendelian randomization (MR) is an approach that leverages genetic variants associated with specific exposures to infer causal relationships between risk factors and disease outcomes.[8] This method, which relies on the random distribution of genetic variants during meiosis, helps minimize confounding factors and biases inherent in environmental or behavioral influences.[9] It is particularly useful in addressing limitations of conventional observational studies and randomized controlled trials, especially for rare diseases like TAO.[10] For a robust MR analysis, three critical assumptions must be met: the genetic variants should be strongly associated with the risk factor, not linked to confounding variables, and affect the outcome solely through the risk factor, excluding any direct causal pathways.[10] In the present study, a MR was employed to evaluate the impact of genetically proxied inflammatory protein levels on the risk of developing TAO.

Materials and Methods

Study Design

The current research represents a MR analysis conducted in accordance with STROBE-MR guidelines.[11] Genetic variants associated with circulating inflammatory proteins were identified from a comprehensive genome-wide meta-analysis, which analyzed 91 plasma proteins in a sample of 14,824 individuals of European descent, spanning 11 distinct cohorts.[12] This study utilized the Olink Target-96

Inflammation immunoassay panel to focus on 92 inflammation-related proteins. However, due to assay issues, brain-derived neurotrophic factor was subsequently removed from the panel by Olink, resulting in the inclusion of 91 proteins in the analysis. Protein quantitative trait locus (pQTL) mapping was employed to determine genetic impacts on these inflammation-related proteins. The data on these 91 plasma inflammatory proteins, including the pQTL findings, are accessible in the EBI GWAS Catalog (accession numbers GCST90274758 to GCST90274848).

Flowchart of the study is shown in ►**Fig. 1**. Summary statistics for TAO in the genome-wide association study (GWAS) were derived from the FinnGen consortium R10 release (finngen_R10_I9_THROMBANG). Launched in 2017, the FinnGen study is a comprehensive nationwide effort combining genetic information from Finnish biobanks with digital health records from national registries.[13] The GWAS included a substantial cohort of 412,181 Finnish participants, analyzing 21,311,942 variants, with TAO cases (114) and controls (381,977) identified according to International Classification of Diseases (ICD)-8 (44310), ICD-9 (4431A), and ICD-10 (I73.1) classifications.

All included studies had received approval from their respective institutional review boards and ethical committees.
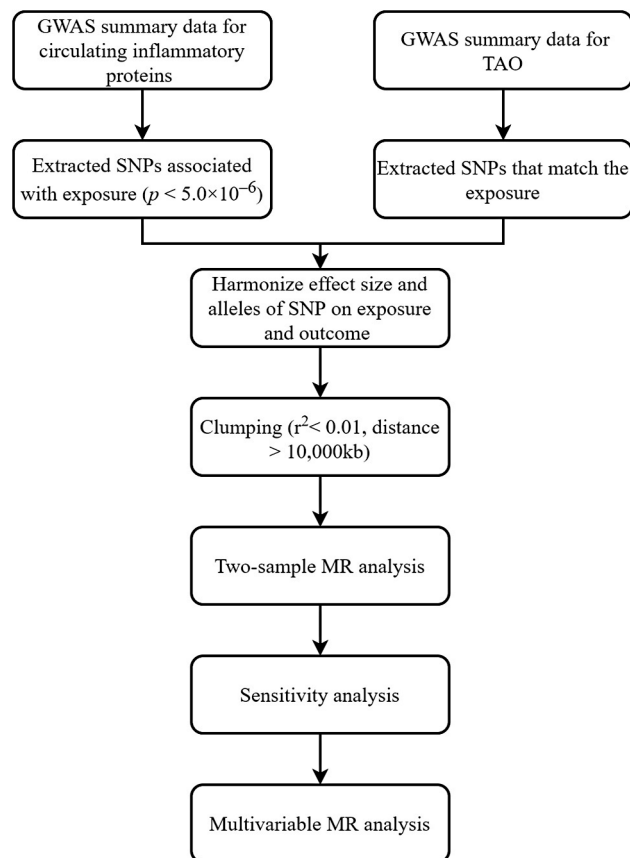

Fig. 1 The flowchart of the study. The whole workflow of MR analysis. GWAS, genome-wide association study; TAO, thromboangiitis obliterans; SNP, single nucleotide polymorphism; MR, Mendelian randomization.

Instrumental Variable Selection

We employed comprehensive GWAS summary statistics for 91 inflammation-related proteins to select genetic instruments. The criteria for eligibility included: (1) single nucleotide polymorphisms (SNPs) must exhibit a genome-wide significant association with each protein ($p < 5.0 \times 10^{-6}$); (2) SNPs should be independently associated with the exposure, meaning they must not be in linkage disequilibrium (defined as $r^2 < 0.01$, distance $> 10,000$ kb) with other SNPs for the same exposure; (3) the chosen genetic instruments must account for at least 0.1% of the exposure variance, ensuring sufficient strength for the genetic instrumental variables (IVs) to assess a causal effect. For each exposure, we harmonized IVs to ensure compatibility and consistency between different data sources and variables. Since smoking is a well-accepted risk factor for TAO, SNPs that were associated with smoking or thrombo-associated events were deleted for MR due to the PhenoScanner V2 database (http://www.phenoscanner.medschl.cam.ac.uk/), details are shown in ►**Supplementary Table S1** (available in the online version).[14]

Statistical Analysis

The random-effects inverse variance weighted (IVW) method was used as the primary MR method to estimate the causal relationships between circulating inflammatory proteins and TAO. The IVW method offers a consistent estimate of the causal effect of exposure on the outcome, under the assumption that each genetic variant meets the IV criteria.[15,16] For sensitivity analysis, multiple methods, including MR–Egger regression, MR pleiotropy Residual Sum and Outlier (MR-PRESSO), and weighted median approaches, were employed in this study to examine the robustness of results. An adaptation of MR–Egger regression is capable of identifying certain violations of standard IV assumptions, providing an adjusted estimate that is unaffected by these issues. This method also measures the extent of directional pleiotropy and serves as a robustness check.[17] The weighted median is consistent even when up to 50% of the information comes from invalid IVs.[18] For SNPs numbering more than three, MRPRESSO was employed to identify and adjust for horizontal pleiotropy. This method can pinpoint horizontal pleiotropic outliers among SNPs and deliver results matching those from IVW when outliers are absent.[19] Leave-one-out analysis was conducted to determine if significant findings were driven by a single SNP. To mitigate potential pleiotropic effects attributable to smoking, a multi-variable MR (MVMR) analysis incorporating adjustments for genetically predicted smoking behaviors was conducted. The GWAS data pertaining to smoking were sourced from the EBI GWAS Catalog (GCST90029014), ensuring no sample overlap with the FinnGen database.[20]

Heterogeneity among individual SNP-based estimates was assessed using Cochran's Q value. In instances with only one SNP for the exposure, the Wald ratio method was applied, dividing the SNP–outcome association estimate by the SNP–exposure association estimate to determine the causal link. The F-statistic was estimated to evaluate the strength of each instrument, with an F-statistic greater than
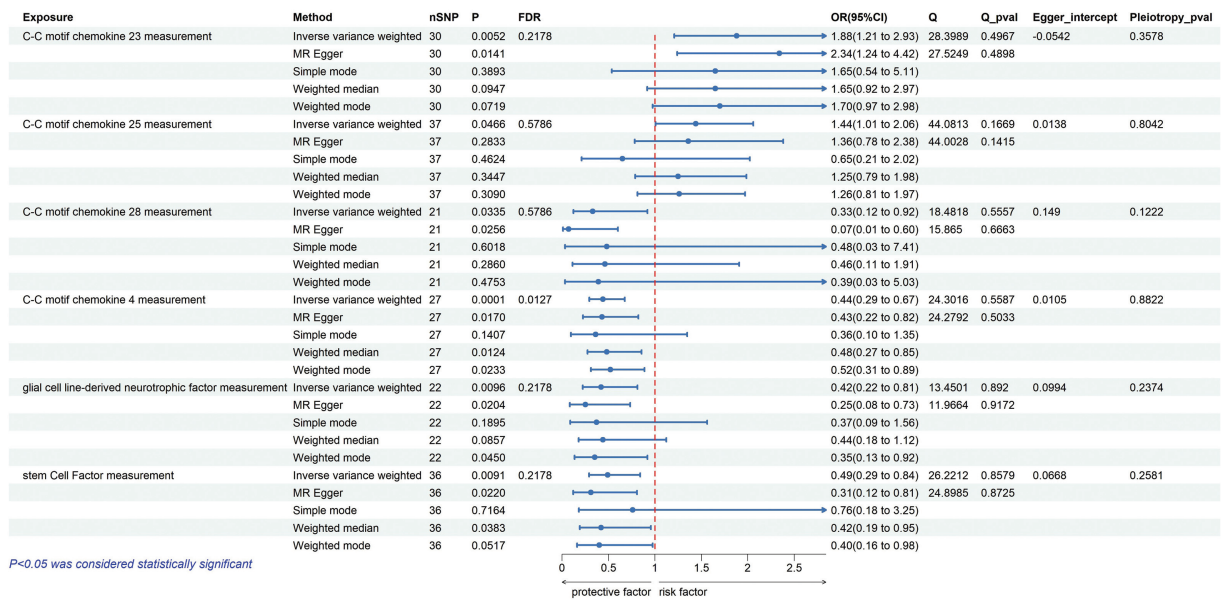
Exposure	Method	nSNP	P	FDR		OR(95%CI)	Q	Q_pval	Egger_intercept	Pleiotropy_pval
C-C motif chemokine 23 measurement	Inverse variance weighted	30	0.0052	0.2178		1.88(1.21 to 2.93)	28.3989	0.4967	-0.0542	0.3578
	MR Egger	30	0.0141			2.34(1.24 to 4.42)	27.5249	0.4898		
	Simple mode	30	0.3893			1.65(0.54 to 5.11)				
	Weighted median	30	0.0947			1.65(0.92 to 2.97)				
	Weighted mode	30	0.0719			1.70(0.97 to 2.98)				
C-C motif chemokine 25 measurement	Inverse variance weighted	37	0.0466	0.5786		1.44(1.01 to 2.06)	44.0813	0.1669	0.0138	0.8042
	MR Egger	37	0.2833			1.36(0.78 to 2.38)	44.0028	0.1415		
	Simple mode	37	0.4624			0.65(0.21 to 2.02)				
	Weighted median	37	0.3447			1.25(0.79 to 1.98)				
	Weighted mode	37	0.3090			1.26(0.81 to 1.97)				
C-C motif chemokine 28 measurement	Inverse variance weighted	21	0.0335	0.5786		0.33(0.12 to 0.92)	18.4818	0.5557	0.149	0.1222
	MR Egger	21	0.0256			0.07(0.01 to 0.60)	15.865	0.6663		
	Simple mode	21	0.6018			0.48(0.03 to 7.41)				
	Weighted median	21	0.2860			0.46(0.11 to 1.91)				
	Weighted mode	21	0.4753			0.39(0.03 to 5.03)				
C-C motif chemokine 4 measurement	Inverse variance weighted	27	0.0001	0.0127		0.44(0.29 to 0.67)	24.3016	0.5587	0.0105	0.8822
	MR Egger	27	0.0170			0.43(0.22 to 0.82)	24.2792	0.5033		
	Simple mode	27	0.1407			0.36(0.10 to 1.35)				
	Weighted median	27	0.0124			0.48(0.27 to 0.85)				
	Weighted mode	27	0.0233			0.52(0.31 to 0.89)				
glial cell line-derived neurotrophic factor measurement	Inverse variance weighted	22	0.0096	0.2178		0.42(0.22 to 0.81)	13.4501	0.892	0.0994	0.2374
	MR Egger	22	0.0204			0.25(0.08 to 0.73)	11.9664	0.9172		
	Simple mode	22	0.1895			0.37(0.09 to 1.56)				
	Weighted median	22	0.0857			0.44(0.18 to 1.12)				
	Weighted mode	22	0.0450			0.35(0.13 to 0.92)				
stem Cell Factor measurement	Inverse variance weighted	36	0.0091	0.2178		0.49(0.29 to 0.84)	26.2212	0.8579	0.0668	0.2581
	MR Egger	36	0.0220			0.31(0.12 to 0.81)	24.8985	0.8725		
	Simple mode	36	0.7164			0.76(0.18 to 3.25)				
	Weighted median	36	0.0383			0.42(0.19 to 0.95)				
	Weighted mode	36	0.0517			0.40(0.16 to 0.98)				

P<0.05 was considered statistically significant

protective factor   risk factor

Fig. 2 Causal relationship between circulating inflammatory proteins and TAO. TAO, thromboangiitis obliterans.

10 indicating a sufficiently strong instrument.[21] False discovery rate (FDR) correction was conducted by the Benjamini–Hochberg method, with a FDR of adjusted $p < 0.1$. A suggestive association was considered when $p < 0.05$ but adjusted $p \geq 0.1$. All analyses were two-sided and performed using the TwoSampleMR (version 0.5.8), MendelianRandomization (version 0.9.0), and MRPRESSO (version 1.0) packages in R software version 4.3.2.
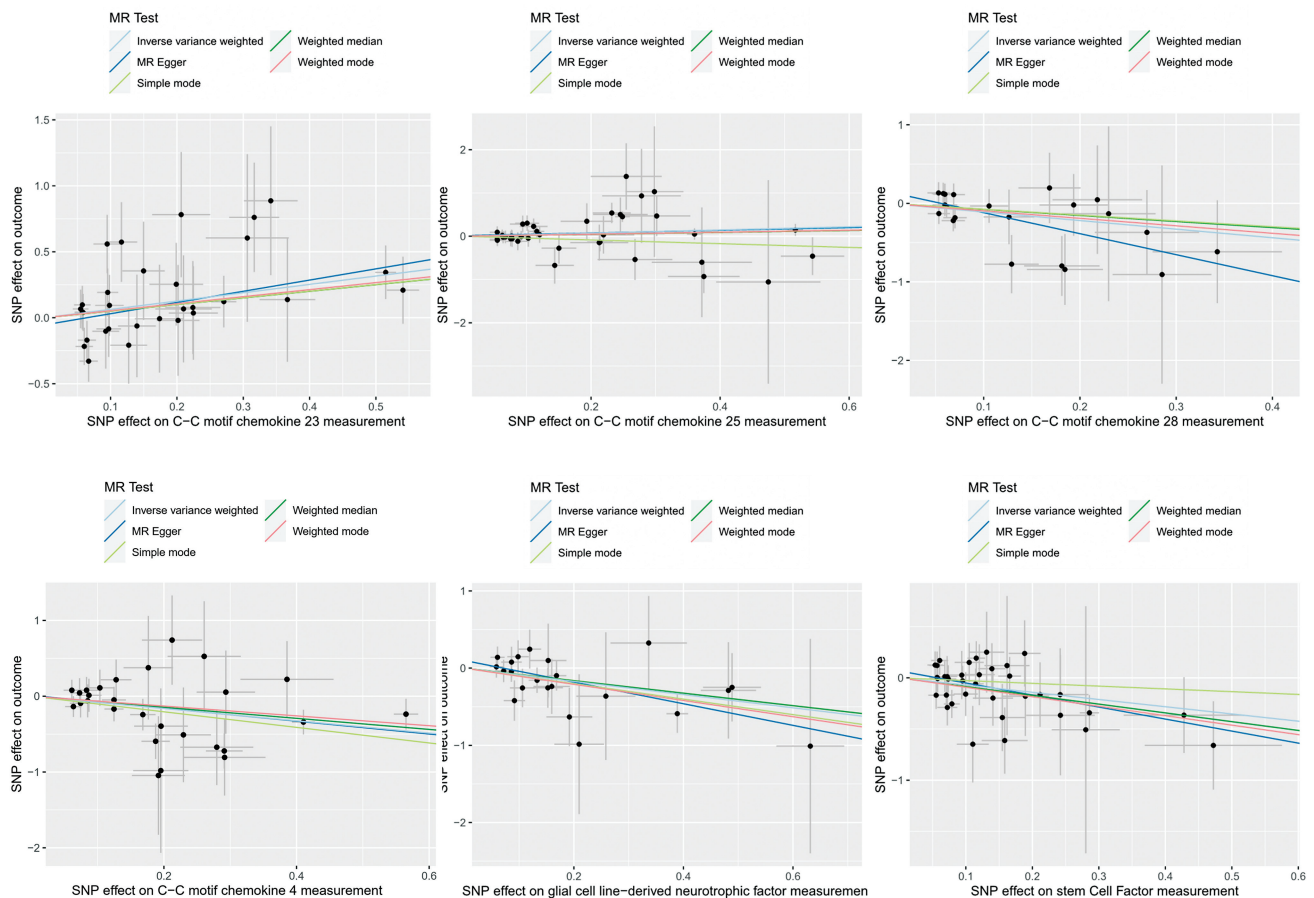
Fig. 3 Scatter plots for the causal association between circulating inflammatory proteins and TAO. TAO, thromboangiitis obliterans.

Results

Selection of Instrumental Variables

The association between 91 circulating inflammatory proteins and TAO through the IVW method is detailed in ►**Supplementary Table S2** (available in the online version). After an extensive quality control review, 173 SNPs associated with six circulating inflammation-related proteins were identified as IVs for TAO. Notably, C–C motif chemokine 23 (CCL23) levels were linked to 30 SNPs, C–C motif chemokine 25 to 37 SNPs, C–C motif chemokine 28 to 21 SNPs, C–C motif chemokine 4 (CCL4) to 27 SNPs, glial cell line-derived neurotrophic factor (GDNF) to 22 SNPs, and stem cell factor to 36 SNPs.

The Causal Role of Inflammation-Related Proteins in TAO

Elevated genetically predicted CCL4 levels were linked to a decreased TAO risk, as shown in ►**Fig. 2**. Specifically, each unit increase in the genetically predicted level of CCL4 was associated with an odds ratio (OR) of 0.44 (95% confidence interval [CI]: 0.29–0.67; $p = 1.4 \times 10^{-4}$; adjusted $p = 0.013$) for TAO. Similarly, levels of C–C motif chemokine 28 (OR: 0.33; 95% CI: 0.12–0.91; $p = 0.034$; adjusted $p = 0.579$), GDNF (OR: 0.43, 95% CI: 0.22–0.81; $p = 0.010$; adjusted $p = 0.218$), and stem cell factor (OR: 0.49, 95% CI: 0.29–0.84; $p = 0.009$;

adjusted $p = 0.218$) also showed a suggestive inverse association with TAO, as depicted in ►**Fig. 2**. Conversely, higher levels of genetically predicted CCL23 (OR: 1.88, 95% CI: 1.21–2.93; $p = 0.005$; adjusted $p = 0.218$) and C–C motif chemokine 25 (OR: 1.44, 95% CI: 1.01–2.06; $p = 0.046$; adjusted $p = 0.579$) suggested an increased risk of TAO.

Sensitivity Analyses

MR–Egger regression intercepts were not significantly different from zero, suggesting no horizontal pleiotropy (all intercept $p > 0.05$), as depicted in ►**Fig. 2**. The MR-PRESSO test also found no pleiotropic outliers among these SNPs ($p > 0.05$), further corroborating the absence of pleiotropy. Consistency with these findings was confirmed by the weighted median approach. Scatter plots illustrating the genetic associations with circulating inflammatory proteins and TAO are presented in ►**Fig. 3**. Cochran's Q test detected no heterogeneity among the genetic IVs for the measured levels (all $p > 0.1$). Additionally, funnel plots showed no significant asymmetry, suggesting negligible publication bias and directional horizontal pleiotropy (►**Fig. 4**). The robustness of these causal estimates was further validated by a leave-one-out analysis, demonstrating that no single IV disproportionately influenced the observed causal relationships, as shown in ►**Fig. 5**.
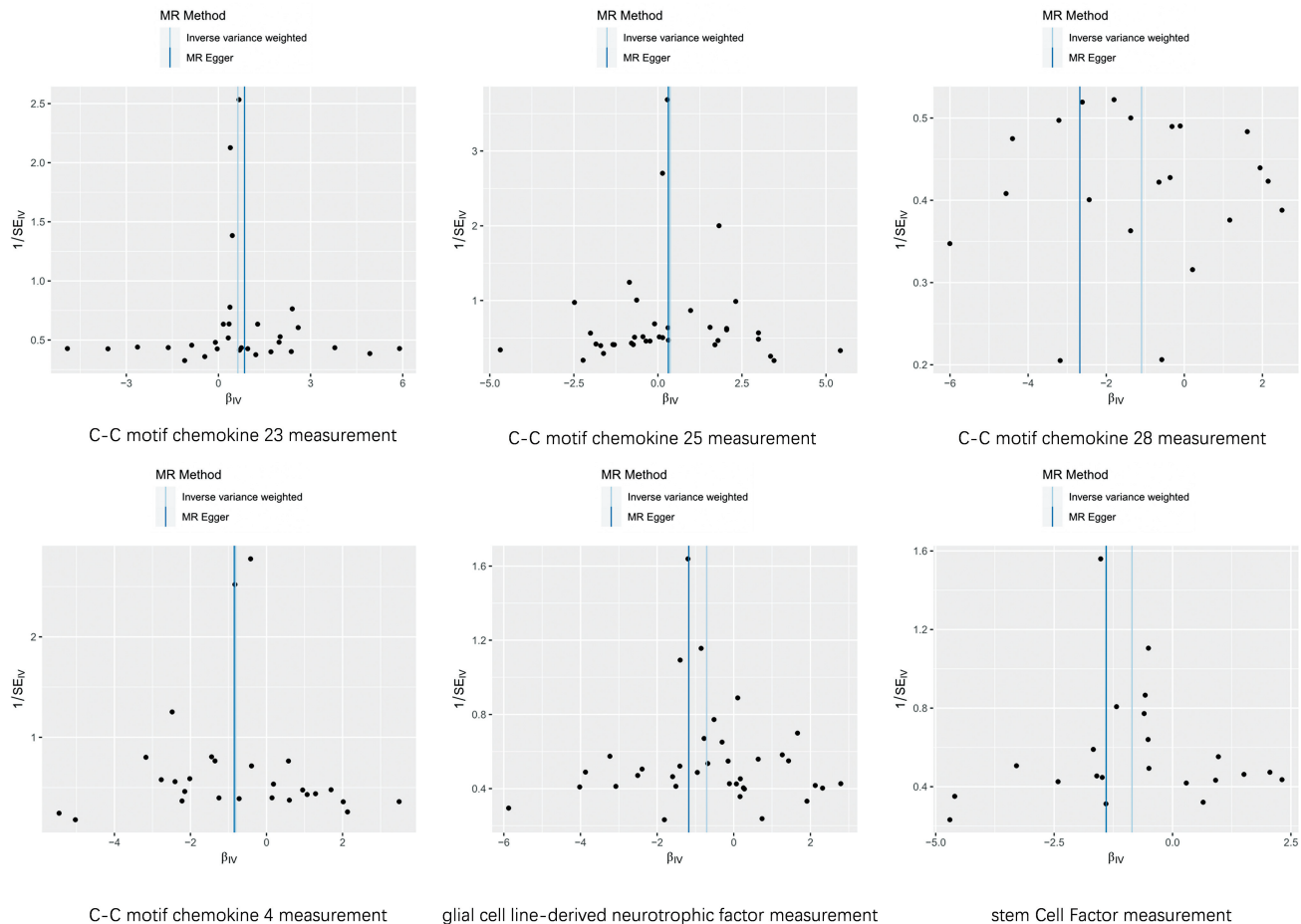

Fig. 4 Funnel plots of circulating inflammatory proteins.

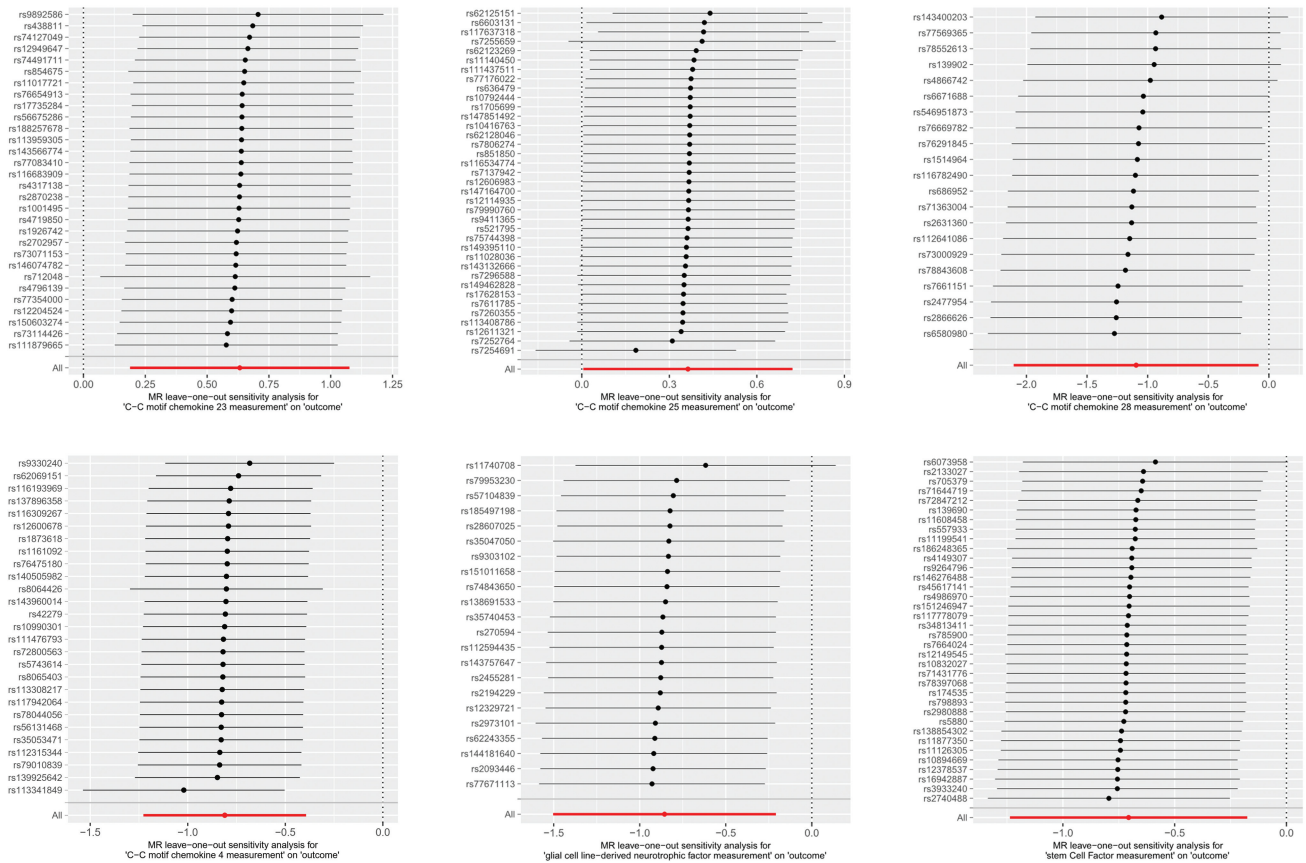**Fig. 5** Leave-one-out plots for the causal association between circulating inflammatory proteins and TAO. TAO, thromboangiitis obliterans.
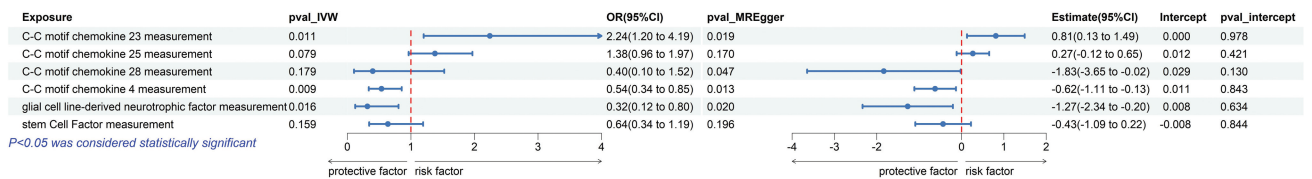

Fig. 6 Results from multivariable Mendelian randomization analysis on the impact of circulating inflammatory proteins on TAO, after adjusting for genetically predicted smoking. IVW, inverse variance weighting; TAO, thromboangiitis obliterans.

MVMR Analyses

►**Fig. 6** reveals that, even after adjusting for genetically predicted smoking, the level of CCL4 still exerts a direct protective influence against TAO (IVW: OR= 0.54, $p = 0.009$; MR–Egger: $p = 0.013$, intercept $p = 0.843$). The level of CCL23 is suggestively associated with an increased risk of TAO (IVW: OR = 2.24, $p = 0.011$; MR–Egger: $p = 0.019$, intercept $p = 0.978$). GDNF levels show a suggestively protective effect against TAO (IVW: OR = 0.315, $p = 0.016$; MR–Egger: $p = 0.020$, intercept $p = 0.634$). However, no significant direct impacts were observed for the levels of C–C motif chemokine 25 ($p = 0.079$), C–C motif chemokine 28 ($p = 0.179$), or stem cell factor ($p = 0.159$) on TAO.

Discussion

This study utilized a two-sample and MVMR approach to evaluate the causal relationships between specific circulating

inflammation-related proteins and TAO. Utilizing summary statistics from GWAS meta-analyses for these proteins, alongside TAO data from the FinnGen consortium R10 release and GWAS information on smoking, our findings underscore a protective influence of CCL4 and GDNF on TAO. In contrast, elevated levels of CCL23 emerge as potential risk indicators for TAO. These insights position these proteins as potential biomarkers for TAO, offering new avenues for understanding its pathogenesis.

C–C motif chemokines, a subfamily of small, secreted proteins, engage with G protein-coupled chemokine receptors on the cell surface, which are distinguished by directly juxtaposed cysteines.[22] Their renowned function is to orchestrate cell migration, particularly of leukocytes, playing crucial roles in both protective and destructive immune and inflammatory responses.[23] CCL4, also known as the macrophage inflammatory protein, is a significant member of the CC chemokine family. This protein, encoded by the CCL4 gene

in humans, interacts with CCR5 and is identified as a pivotal human immunodeficiency virus-suppressive factor secreted by CD8+ T-cells.[24] Additionally, its involvement has been increasingly recognized in cardiovascular diseases.[23] While CCL4 exhibits a protective effect in Type 1 diabetes mellitus patients, it is also found to be elevated in conditions such as atherosclerosis and myocardial infarction.[23] CCL4's ability to activate PI3K and MAPK signaling pathways and inhibit the NF-κB pathway contributes to the enhanced proliferation of porcine uterine luminal epithelial cells.[25] This mechanism may elucidate CCL4's protective role in TAO, as demonstrated in this study (OR: 0.44; 95% CI: 0.29–0.67; $p = 1.4 \times 10^{-4}$; adjusted $p = 0.013$), highlighting its potential as both a biomarker and a therapeutic target.

CCL23, also known as myeloid progenitor inhibitory factor-1, represents another key member of the CC chemokine subfamily. It plays a role in the inflammatory process, capable of inhibiting the release of polymorphonuclear leukocytes from the bone marrow.[26] As a relatively novel chemokine, CCL23's biological significance remains partially unexplored.[27] Circulating CCL23 exhibited a continuous increase from baseline to 24 hours in ischemic stroke patients and could predict the clinical outcome after 3 months.[28] Elevated blood levels of CCL23 have been linked with antineutrophil cytoplasmic antibody-associated vasculitis.[29] Although its mechanisms are largely uncharted, CCL23 is known to facilitate the chemotaxis of human THP-1 monocytes, increase adhesion molecule CD11c expression, and stimulate MMP-2 release from THP-1 monocytes.[30] Moreover, CCL23 can enhance leucocyte trafficking and direct the migration of monocytes, macrophages, dendritic cells, and T lymphocytes.[27] This study posits CCL23 as a suggestive risk factor for TAO (OR: 1.88, 95% CI: 1.21–2.93; $p = 0.005$; adjusted $p = 0.218$), warranting further investigation into its precise role.

GDNF was first discovered as a potent survival factor for midbrain dopaminergic neurons and has shown promise in preserving these neurons in animal models of Parkinson's disease.[31] Recent studies have further elucidated GDNF's significance in neuronal safeguarding and cerebral recuperation.[32] Additionally, GDNF has been implicated in inflammatory bowel disease (IBD), where it bolsters the integrity of the intestinal epithelial barrier and facilitates wound repair, while also exerting an immunomodulatory influence.[33,34] In our study, GDNF is identified as a potential protective agent against TAO, with an OR of 0.43 (95% CI: 0.22–0.81; $p = 0.010$; adjusted $p = 0.218$). It is postulated that GDNF's protective mechanism in TAO may involve the inhibition of apoptosis through the activation of MAPK and AKT pathways, akin to its action in IBD.[34]

This study utilized MR analysis to ascertain the causal relationship between circulating inflammation-related proteins and TAO. This approach was chosen to mitigate confounding factors and the potential reverse causation in causal inference. Genetic variations linked to these proteins were sourced from a recent GWAS meta-analysis, ensuring robust instrument strength in the MR analysis. MR-PRESSO and MR–Egger regression intercept tests were employed to assess the level of pleiotropy. A two-sample MR design was adopted, using nonoverlapping summary data for exposure and outcomes to minimize bias. An MVMR was finally performed to adjust the possible cofounding of smoking.

Nonetheless, this study is subject to several limitations. First, the absence of additional GWAS cohorts encompassing TAO precluded replication analysis, thereby constraining the validation of the causal relationship and impacting the study's credibility. Second, while the case count in our study is constrained, potentially increasing the likelihood of Type II errors, robust IVs were carefully chosen, and both sensitivity and MVMR analyses were conducted. These measures were taken to mitigate risks, and the outcomes affirm the study's resilience. Third, given that the FinnGen study exclusively comprised Finnish participants and considering the lower prevalence of TAO in Northeastern European countries compared with other regions globally, the findings' applicability may be somewhat restricted.

Conclusion

This two-sample and MVMR analysis reveals a protective effect of CCL4 and GDNF on TAO, and suggests a potential causal relationship between CCL23 and TAO. These findings offer new perspectives on potential biomarkers and therapeutic targets for TAO.

What is known about this topic?

- Thromboangiitis obliterans (TAO), or Buerger's disease, is a distinct, nonatherosclerotic inflammatory condition.
- It primarily impacts small- and medium-sized arteries and veins in the extremities, with uncertain etiology and prognosis.
- The disease is thought to involve an immune response, but evidence supporting this is limited.

What does this paper add?

- Utilizes a two-sample and multivariable Mendelian randomization approach, integrating GWAS data of 91 inflammation-related proteins with TAO data.
- Identifies C–C motif chemokine 4 and glial cell line-derived neurotrophic factor as potential protective biomarkers for TAO, offering new insights for diagnosis and treatment.
- Suggests that C–C motif chemokine 23 emerges as a suggestive risk marker in TAO, offering new insights for diagnosis and treatment.

Ethical Approval Statement

This research has been conducted using published studies and consortia providing publicly available summary statistics. All original studies have been approved by the corresponding ethical review board, and the participants have provided informed consent. In addition, no individual-level data were used in this study. Therefore, no new ethical review board approval was required.

Authors' Contribution

Conception and design: M.Y. and B.Z. Administrative support: X.T. and Y.Z. Provision of study materials or patients: Z.Y. and G.N. Collection and assembly of data: B.Z., Z.Y., and R.H. Data analysis and interpretation: B.Z., R.H., and Z.Y. Manuscript writing: All authors. Final approval of manuscript: All authors.

Conflict of Interest

None declared.

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