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Exploration of the causal relationship and mechanisms between serum albumin and venous thrombosis: a bidirectional mendelian randomization analysis and bioinformatics study

Xuemei Xia[1], Xin Tie[1], Maolin Hong[1] and Wanhong Yin[1*]

Abstract

Background To explore the causal relationship between serum albumin and venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and its consequential condition, pulmonary embolism (PE), through Mendelian randomization (MR) design, seeking to clarify the protective roles of albumin in the development of venous thrombosis.

Methods We performed a bidirectional two-sample Mendelian randomization analysis utilizing albumin genome-wide association study (GWAS) data alongside VTE datasets from various sources. Additionally, to minimize heterogeneity across different datasets, a meta-analysis of the Mendelian randomization results was conducted. Furthermore, genes associated with such exposures were identified to unravel how exposure impacts outcomes. This was followed by applying bioinformatics techniques for gene enrichment analysis and employing the Cytoscape software to pinpoint the hub genes.

Results The findings from the meta-analysis of the Mendelian randomization indicate that reduced levels of albumin are associated with an elevated risk of VTE (OR = 0.739, 95% CI: 0.695 to 0.787, *P* = 1.82e-9), DVT (OR = 0.700, 95% CI: 0.646 to 0.772, *P* = 2.96e-15), and PE (OR = 0.717, 95% CI: 0.647 to 0.793, *P* = 1.74e-10). Bioinformatics analysis revealed that serum albumin primarily protects against VTE by influencing inflammation and cytokines.

Conclusions Our bidirectional MR analysis confirmed a substantial causal association linking serum albumin to VTE. Bioinformatics analysis revealed that this causal link is mediated by the immune response through inflammation and cytokines.

Keywords Venous thromboembolism, Serum albumin, Mendelian randomization, Bioinformatics analysis

*Correspondence:
Wanhong Yin
yinwanhong@wchscu.cn
[1]Department of Critical Care Medicine, West China Hospital, Sichuan University, No.37, Guoxue Alley, Wuhou District, Chengdu, Sichuan Province, China

Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and its consequential condition, pulmonary embolism (PE), is a prevalent and potentially lethal disorder encountered in medical settings [1]. In 2010, thromboembolic conditions were estimated to be responsible for a quarter of all global deaths, making them the primary cause of mortality [2]. Therefore, identifying the risk factors for VTE and early prevention are crucial for the patient's prognosis. Common risk factors for venous thrombosis consist of immobility, obesity, and older age [3]. Research has also shown that genetic factors significantly contribute to developing VTE [4], such as antithrombin (AT), protein C (PC), and protein S (PS) gene mutations, leading to loss of protein anticoagulant function [5].

Serum albumin is essential for the maintenance of plasma colloid osmotic pressure and exhibits a range of physiological properties, notably its antioxidant, anti-inflammatory, anticoagulant, and antiplatelet aggregation functions [6]. Numerous observational studies indicate that decreased albumin levels are associated with an elevated risk of VTE [7–10]. However, existing evidence from observational studies may be influenced by biases, including confounding or reverse causation. Serum albumin concentrations can be affected by various underlying factors, including infections, malnutrition, and renal disease, making it challenging to explain their direct causal relationship with VTE.

Based on Mendel's inheritance laws, the Mendelian randomization (MR) study design closely parallels that of randomized controlled trials (RCTs), allowing for the control of unmeasured confounders and distinguishing between causation and correlation [11]. Because genotypes are early biological markers, they are less vulnerable to the effects of environmental factors and disease status, thereby ruling out unmeasured confounders and the possibility of reverse causation [12]. This methodology offers a stronger foundation for assessing the causal associations between serum albumin and VTE occurrences. In this study, we employed bidirectional MR to probe the causal connections between serum albumin and the vulnerability to VTE, including its DVT and PE subtypes, using openly accessible genome-wide association study (GWAS) data retrieved from a European cohort. The objective of our research was to investigate, using MR design, the causal link between serum albumin and VTE, and to elucidate the protective mechanisms of albumin in the pathogenesis of VTE.

Methods

Study design

Genetic variants are instrumental variables in MR in determining causality. The MR approach rests on three critical assumptions: (1) The instruments must demonstrate a robust association with the exposure variable; (2) The instruments should not be influenced by any potential confounding variables; and (3) The instruments should affect the outcome solely through their relationship with the exposure variable [13]. Based on the three major assumptions above, we conducted a two-sample bidirectional MR analysis of serum albumin with VTE. To elucidate the mechanisms through which these exposures affect outcomes, we identified associated genes and applied bioinformatics techniques for gene enrichment analysis. CytoHubba, a plugin within Cytoscape, was utilized to pinpoint the key genes integral to this protective mechanism. The specific research methodology is depicted in Fig. 1. Given that this study relies on pre-existing publications and publicly available databases, there is no requirement for additional ethical approval or consent.

Data source

Table 1 provides a summary of the GWAS utilized for both exposures and outcomes in this study. The GWAS datas for serum albumin were sourced from three distinct datasets. GCST90025992 was obtained from the UK Biobank (UKB), where analysis encompassed 54 heritable traits, such as anthropometric measurements, blood pressure, pulmonary function, hematological indices, and serum biomarker levels [14]. GCST90092807 was derived from research conducted by Richardson TG et al., which focused on assessing the genetic predictive impact of therapeutic targets on the human metabolome [15]. This analysis was performed through large-scale phenotypic evaluation, integrating targeted metabolomics with GWAS genotyping within the UKB. GCST90018945 originated from the investigation by Sakaue S et al., carried out an extensive genome-wide association study with as many as 315,268 individuals from European cohorts [16].

The FinnGen consortium, focusing on leveraging genetic data from the Finnish population to comprehend the genetic foundation of diseases and characteristics, provided summary statistics on VTE, DVT, and PE in European populations. The study followed the principles set forth in the Declaration of Helsinki, and informed consent was secured from all participants before the commencement of the research. The institutional review boards approved the study protocol of the original research studies. Cases were identified using the codes from the International Classification of Diseases.

Selection of instrumental variables

At first, genome-wide significant single nucleotide polymorphisms (SNPs) associated with the exposure were detected using a threshold of $p < 5.0 \times 10^{-8}$. Following this, a predetermined criterion ($r^2 < 0.001$ within a

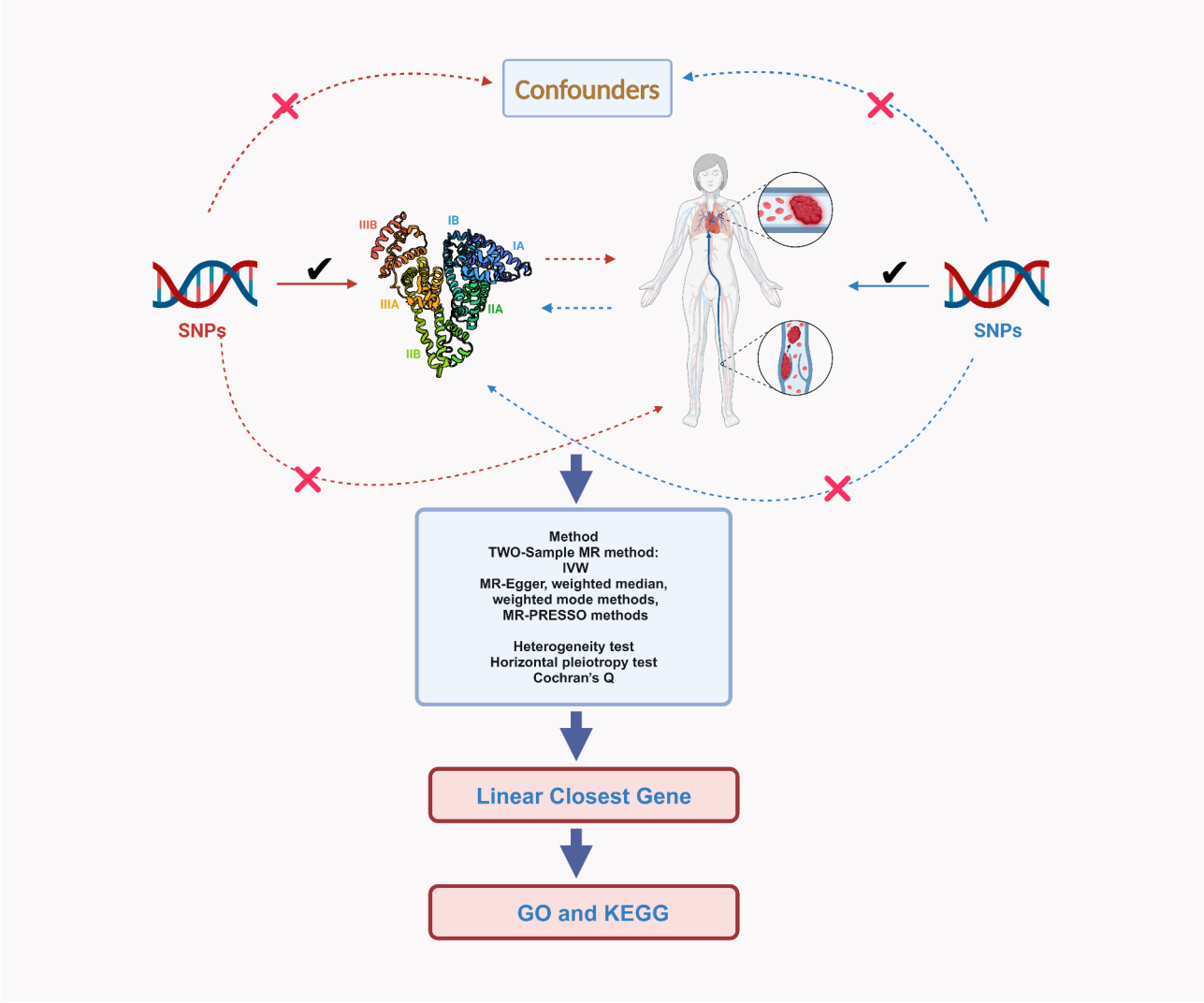

Fig. 1 A summary of the bidirectional Mendelian randomization study and bioinformatics study. Created in BioRender.com

Table 1 An overview of GWAS used for exposures and outcomes

Exposures/Outcomes	Source	PubMed ID	Author	participants	Year	Sample size
Venous thromboembolism	FinnGen	——	——	European	2021	21,021 cases and 391,160 controls
Deep vein thrombosis						6,501 cases and 357,111 controls
Pulmonary embolism						10,046 cases and 401,128 controls
Serum albumin levels	GCST90025992	34,226,706	Barton AR		2021	400,938 individuals
	GCST90092807	35,213,538	Richardson TG		2022	115,064 individuals
	GCST90018945	34,594,039	Sakaue S		2021	315,268 individuals

10,000 kb region) was applied to remove SNPs in linkage disequilibrium, thereby guaranteeing the independence of the selected instrumental variables [17]. The F-statistic was utilized to evaluate the strength of the instrumental variables (IVs), where values greater than 10 indicated a reduced likelihood of weak instrument bias greater than 10 [18]. The SNP F-statistics we selected were all greater than 10 (Supplementary File 1). Ultimately, aligning variants removed SNPs incompatible with the outcome datasets and those displaying a palindromic sequence.

Furthermore, the MR Steiger filtering technique was utilized to eliminate SNPs that had an incorrect causal orientation. We reviewed the human gene phenotypic association database (PhenoScanner V2) [19] to assess potential pleiotropic connections between instrumental variables and unrelated traits, excluding those linked to VTE, such as smoking and BMI. Subsequently, we

utilized the MR-PRESSO [20] and Radial MR techniques [21] to eliminate any potential pleiotropic SNPs.

Bioinformatics analysis

FUMA (Functional Mapping and Annotation, https://fuma.ctglab.nl/snp2gene) is a comprehensive online bioinformatics platform designed for the functional annotation, gene mapping, and downstream analysis of SNPs identified through GWAS or other genetic research. In this study, we employed its gene mapping functionality to assign SNPs to their nearest genes based on a linear closest-gene approach (within 100 kb), facilitating further analyses (Supplementary File 2).

Next, we annotated the mapped genes using the R package org.Hs.eg.db, which provides updated and comprehensive human genome annotations. Subsequently, we performed functional enrichment analysis using the clusterProfiler package in R to identify overrepresented pathways and biological processes. The analysis focused on Gene Ontology (GO) terms in three categories: biological processes (BP), molecular functions (MF), and cellular components (CC), as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Enrichment significance was evaluated using hypergeometric testing and adjusted for false discovery rate (FDR < 0.05) using the Benjamini-Hochberg method. For clarity, the enrichment results were visualized using the Sangerbox 3.0 platform, an open-access tool that provides interactive, publication-ready figures.

To explore protein-protein interactions, we queried the STRING database (https://string-db.org/), a curated platform that integrates experimentally validated and predicted protein-protein interaction data. Leveraging this interaction data, we constructed a preliminary interaction network and imported it into Cytoscape, an open-source platform designed for visualizing and analyzing complex molecular networks. Cytoscape employs computational metrics to prioritize nodes based on their network topology. We used degree centrality as the primary ranking criterion to identify the top 10 highly connected ("hub") genes within the network. This detailed network provides critical insights into the molecular interactions underlying VTE-related phenotypes and forms the foundation for further experimental validation and hypothesis development.

Statistical analysis

The inverse variance weighting (IVW) technique derived the primary causal estimates. In the random-effects IVW method, regression analysis is carried out by regressing genetic associations with the outcome against associations with the exposure, with the intercept set to zero. This method offers a reliable causation prediction when heterogeneity exists and no horizontal pleiotropy exists [22]. Additionally, we applied various other MR methodologies, such as the MR Egger approach [23], weighted median technique [24], weighted mode approach [25] and MR-PRESSO methodology [20], to assess the robustness of the IVW test outcomes. Subsequently, a meta-analysis was conducted to synthesize the aggregated estimates of albumin's association with the risk of VTE. The I^2 statistic was employed to quantify heterogeneity across the three studies, and P values were derived using the Cochran Q test. In the absence of heterogeneity, a fixed-effect model was applied to integrate the causal estimates. Conversely, a random-effects model was utilized when heterogeneity was present.

Pleiotropy was assessed using MR-Egger regression, revealing that the intercept was not significantly different from zero ($p > 0.05$), suggesting the absence of horizontal pleiotropy [20]. Heterogeneities were measured using the Cochran Q statistic within the IVW method, yielding a P value of < 0.05, signifying substantial heterogeneity [26]. Additionally, a leave-one-out sensitivity analysis was conducted to identify potentially impactful SNPs.

The study displays odds ratios (ORs) and 95% confidence intervals (CIs) to illustrate the causal effects. An adjusted p-value of 0.05/9 (combining three exposures and three outcomes) after the Bonferroni correction was considered statistically significant [27]. Results within the p-value range of 0.0056 to 0.05 were interpreted as providing suggestive indications of association. All statistical computations were performed using R software (version 4.2.0), utilizing the "TwoSampleMR" and "MR-PRESSO" packages for executing MR.

Results

Selection of instrumental variables

Comprehensive details regarding each independent SNPs linked to the exposure are provided in Supplementary File 1. Within our assessment, the F-statistics of the IVs associated with the exposure consistently surpassed the threshold of 10, indicating a low risk of bias due to weak instrumental variables.

Bidirectional MR analysis

The causal effect of serum albumin on VTE

Our research demonstrates a causal relationship between decreased albumin levels and the incidence of VTE. In the GCST90025992 study, MR analysis using the IVW method yielded an OR of 0.785 for VTE (95% CI: 0.709 to 0.870, $P = 7.87e\text{-}6$). In the GCST90092807 study, using the IVW method resulted in an OR of 0.796 for VTE (95% CI: 0.675 to 0.939, $P = 0.009$). In the GCST90018945 study, applying the IVW method in MR analysis produced an OR of 0.693 for VTE (95% CI: 0.635 to 0.756, $P = 9.78e\text{-}16$). A subsequent meta-analysis of the three

GWAS data yielded a combined OR of 0.739 (95% CI: 0.695 to 0.787, $P = 1.82e-9$) (Figs. 2A and 3A).

The causal effect of serum albumin on DVT

Using the IVW method, the primary analyses unveiled a substantial causal influence of albumin. In the GCST90025992 study, the IVW method in MR analysis produced an odds ratio of 0.741 for DVT(95% CI: 0.651 to 0.844, $P = 9.18e-6$). The GCST90092807 study similarly found an OR of 0.741 (95% CI: 0.577 to 0.952, $P = 0.019$). The GCST90018945 study reported an OR of 0.643 (95% CI: 0.559 to 0.739, $P = 1.49e-9$) with the IVW method. A meta-analysis combining these three GWAS results produced an overall OR of 0.700 (95% CI: 0.646 to 0.772, $P = 2.96e-15$) (Figs. 2B and 3B).

The causal effect of serum albumin on PE

The initial IVW analysis identified a significant causal effect of albumin. In the GCST90025992 study, MR analysis with the IVW method resulted in an OR of 0.717 for PE (95% CI: 0.647 to 0.793, $P = 1.74e-10$). Similarly, the GCST90092807 study reported an OR of 0.702 (95% CI: 0.569 to 0.866, $P = 0.001$). The GCST90018945 study also applied the IVW method, reported an OR of 0.669 (95% CI: 0.595 to 0.740, $P = 5.99e-13$). A meta-analysis of these three GWAS revealed an overall OR of 0.693 (95% CI: 0.646 to 0.743, $P = 9.64e-25$) (Figs. 2C and 3C).

The sensitivity analysis for the causal effect of serum albumin on VTE, DVT, and PE

Funnel plots and Cochran's Q test indicated a lack of heterogeneity. Additionally, the MR-Egger intercept and MR-PRESSO analyses confirmed the lack of horizontal pleiotropy, as shown in Table 2 and Supplementary Figs. 1–9. Furthermore, a leave-one-out sensitivity analysis did not identify any single SNP as a significant driver behind the causal association between albumin and VTE, as illustrated in Supplementary Figs. 1–9.

Reverse MR analyses

In reverse analyses, all employed methods uniformly indicated a lack of significant causal association between genetically predicted VTE and serum albumin, as depicted in Supplementary Fig. 10.

Biological functional analysis

We used FUMA for gene mapping and identified genes situated 100 kb upstream and downstream of the SNPs associated with albumin. After removing duplicates, we identified 1,128 genes associated with albumin and VTE, 1,085 genes associated with DVT, and 1,231 genes associated with PE (Fig. 4A-C and Supplementary File 2). We conducted GO and KEGG functional enrichment analysis on these genes to further confirm the mechanism by which albumin leads to VTE, DVT, and PE. To obtain a more precise insight into the biological functions of these genes, we conducted a comprehensive enrichment analysis in three key categories: BP, MF, and CC. KEGG primarily focuses on the roles of these genes in metabolic and signal transduction pathways. Our analysis found no significant enrichment of genes in CC or KEGG pathways (Supplementary File 3–4).

For genes related to albumin and VTE, those involved in the BP are primarily enriched in inflammatory response to antigenic stimulus, collagen metabolic process and regulation of collagen biosynthetic process (Fig. 4D). The molecular functions of the gene products are mainly concentrated in interleukin-1 receptor binding, alcohol dehydrogenase [NAD(P)+] activity, and receptor tyrosine kinase binding (Fig. 4G).

Regarding the genes linked to albumin and DVT, those involved in BP show significant enrichment in inflammatory response to antigenic stimulus, negative regulation of catalytic activity, and regulation of peptidase activity (Fig. 4E). In the domain of MF, these gene products predominantly exhibit on IgG binding, interleukin-1 receptor binding, and alcohol dehydrogenase [NAD(P)+] activity (Fig. 4H).

For genes related to albumin and PE, those involved in BP are predominantly enriched in receptor-mediated endocytosis, regulation of sodium ion transmembrane transport, and regulation of sodium ion transport (Fig. 4F). The MF focuses on regulating receptor tyrosine kinase binding, alcohol dehydrogenase [NAD(P)+] activity, and sodium channel regulator activity (Fig. 4I).

Utilizing the Hub plugin within Cytoscape, we identified the top 10 hub genes. The hub genes associated with albumin in the contexts of VTE, DVT and PE exhibit remarkable similarity. The top 10 genes in VTE are TP53, TNF, IL6, ALB, BCL2, PPARG, ESR1, CD44, MTOR and CREBBP (Fig. 4J). For DVT, the top 10 genes are TP53, TNF, IL6, ALB, UBA52, BCL2, PPARG, CD44, ESR1 and MTOR (Fig. 4K). For PE, the top 10 genes are TP53, TNF, IL6, UBA52, ALB, UBB, ESR1, GRB2, BCL2 and PPARG (Fig. 4L).

Discussion

To investigate the possible causal link between serum albumin parameters and VTE events, we employed MR analysis with a substantial sample of GWAS data. The results of the MR suggest that low albumin levels lead to an increase in VTE, DVT, and PE. Furthermore, through bioinformatics analysis, we investigated the potential mechanism by which serum albumin exerts a protective effect against VTE.

Previous studies have also found that low serum albumin is a moderate indicator of increased risk of VTE. However, the association observed in observational

A

Exposure	No.of SNP	Method	OR(95% CI)	P
GCST90025992	210	Inverse variance weighted	0.785 (0.709 to 0.870)	7.87e−6
	210	MR Egger	0.831 (0.660 to 1.047)	0.237
	210	Weighted median	0.802 (0.703 to 0.915)	0.002
	210	Weighted mode	0.742 (0.592 to 0.930)	0.026
	210	MR Presso	0.785 (0.709 to 0.870)	6.86e−6
GCST90092807	20	Inverse variance weighted	0.796 (0.675 to 0.939)	0.009
	20	MR Egger	0.968 (0.606 to 1.546)	0.896
	20	Weighted median	0.861 (0.685 to 1.081)	0.262
	20	Weighted mode	0.892 (0.632 to 1.257)	0.695
	20	MR Presso	0.796 (0.686 to 0.922)	0.007
GCST90018945	157	Inverse variance weighted	0.693 (0.635 to 0.756)	9.78e−16
	157	MR Egger	0.724 (0.601 to 0.872)	0.003
	157	Weighted median	0.707 (0.615 to 0.814)	5.11e−6
	157	Weighted mode	0.746 (0.594 to 0.938)	0.026
	157	MR Presso	0.693 (0.637 to 0.754)	9.08e−15

B

Exposure	No.of SNP	Method	OR(95% CI)	P
GCST90025992	193	Inverse variance weighted	0.741 (0.651 to 0.844)	9.18e-6
	193	MR Egger	0.718 (0.554 to 0.930)	0.046
	193	Weighted median	0.703 (0.565 to 0.876)	0.003
	193	Weighted mode	0.658 (0.486 to 0.892)	0.023
	193	MR Presso	0.741 (0.660 to 0.831)	7.64e−7
GCST90092807	24	Inverse variance weighted	0.741 (0.577 to 0.952)	0.019
	24	MR Egger	0.993 (0.513 to 1.920)	0.983
	24	Weighted median	0.741 (0.520 to 1.057)	0.131
	24	Weighted mode	0.697 (0.395 to 1.228)	0.299
	24	MR Presso	0.741 (0.590 to 0.930)	0.017
GCST90018945	168	Inverse variance weighted	0.643 (0.559 to 0.739)	1.49e−9
	168	MR Egger	0.730 (0.557 to 0.955)	0.046
	168	Weighted median	0.667 (0.538 to 0.826)	8.27e−4
	168	Weighted mode	0.661 (0.482 to 0.908)	0.023
	168	MR Presso	0.643 (0.570 to 0.725)	2.23e−11

C

Exposure	No.of SNP	Method	OR(95% CI)	P
GCST90025992	193	Inverse variance weighted	0.717 (0.647 to 0.793)	1.74e−10
	193	MR Egger	0.667 (0.546 to 0.816)	4.44e−4
	193	Weighted median	0.758 (0.641 to 0.896)	0.002
	193	Weighted mode	0.766 (0.599 to 0.980)	0.071
	193	MR Presso	0.717 (0.650 to 0.789)	1.81e−10
GCST90092807	22	Inverse variance weighted	0.702 (0.569 to 0.866)	0.001
	22	MR Egger	0.753 (0.432 to 1.311)	0.327
	22	Weighted median	0.760 (0.571 to 1.012)	0.081
	22	Weighted mode	0.778 (0.538 to 1.124)	0.261
	22	MR Presso	0.702 (0.591 to 0.833)	5.92e−4
GCST90018945	177	Inverse variance weighted	0.664 (0.595 to 0.740)	5.99e−13
	177	MR Egger	0.709 (0.573 to 0.877)	0.004
	177	Weighted median	0.729 (0.609 to 0.872)	0.002
	177	Weighted mode	0.745 (0.584 to 0.949)	0.071
	177	MR Presso	0.664 (0.598 to 0.737)	1.14e−12

Fig. 2 (**A**) The results of the MR analysis between albumin and VTE. The GCST90025992 study showed an OR of 0.785 (95% CI: 0.709–0.870, *P* = 7.87e-6). The GCST90092807 study reported an OR of 0.796 (95% CI: 0.675–0.939, *P* = 0.009). The GCST90018945 study yielded an OR of 0.693 (95% CI: 0.635–0.756, *P* = 9.78e-16). (**B**) The results of the MR analysis between albumin and DVT. The GCST90025992 study reported an OR of 0.741 (95% CI: 0.651–0.844, *P* = 9.18e-6). The GCST90092807 study found an OR of 0.741 (95% CI: 0.577–0.952, *P* = 0.019). The GCST90018945 study yielded an OR of 0.643 (95% CI: 0.559–0.739, *P* = 1.49e-9). (**C**) The results of the MR analysis between albumin and PE. The GCST90025992 study reported an OR of 0.717 (95% CI: 0.647–0.793, *P* = 1.74e-10). The GCST90092807 study found an OR of 0.702 (95% CI: 0.569–0.866, *P* = 0.001). The GCST90018945 study yielded an OR of 0.669 (95% CI: 0.595–0.740, *P* = 5.99e-13)

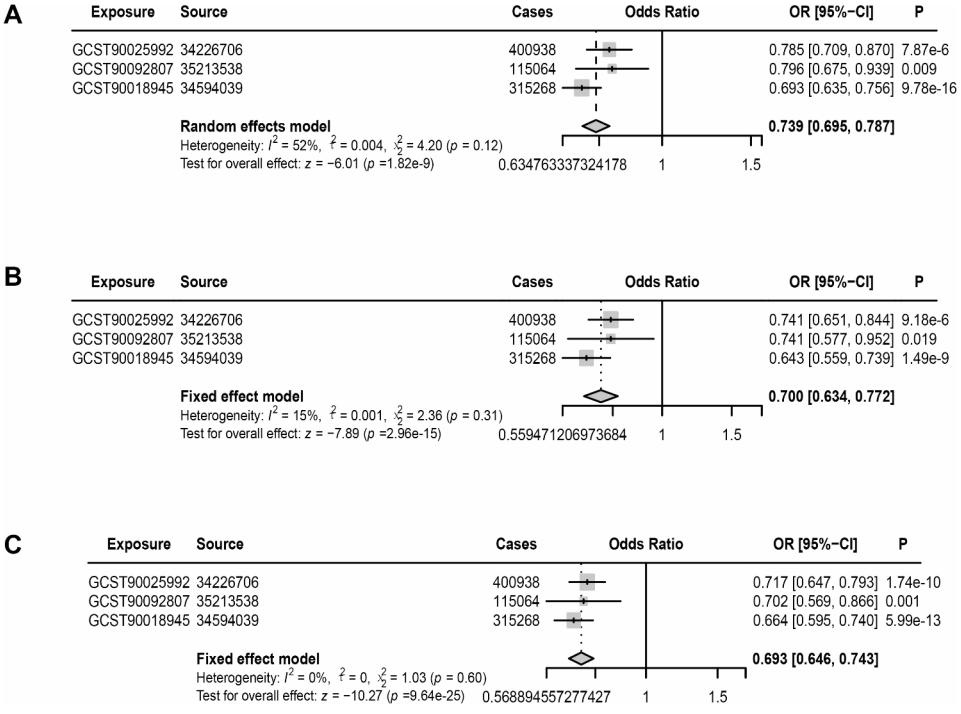

Fig. 3 (**A**) The results of the MR-meta between albumin and VTE. The meta-analysis combined three GWAS datasets, yielding a pooled odds ratio (OR) of 0.739 (95% CI: 0.695 to 0.787, *P* = 1.82e-9), indicating higher albumin levels may have a protective effect in reducing the risk of VTE. (**B**) The results of the MR-meta between albumin and DVT. The meta-analysis combining the three GWAS datasets generated a pooled odds ratio (OR) of 0.700 (95% CI: 0.646 to 0.772, *P* = 2.96e-15). The results suggest that higher albumin levels may have a protective effect in reducing the risk of DVT. (**C**) The results of the MR-meta between albumin and PE. The meta-analysis combining the three GWAS datasets generated a pooled odds ratio (OR) of 0.693 (95% CI: 0.646 to 0.743, *P* = 9.64e-25). The results suggest that higher albumin levels may have a protective effect in reducing the risk of PE

Table 2 The sensitivity analysis of serum albumin on VTE, DVT, and PE

		Pleiotropy			Heterogeneity	
		MR-Egger intercept test		MR-PRESSO global test	Cochran's Q test IVW	Cochran's Q test Egger
Exposure	**Outcome**	**intercept**	**Pval**	**Pval**	**Pval**	**Pval**
GCST90025992	VTE	-0.001	0.592	0.700	0.701	0.667
	DVT	0.001	0.781	0.991	0.989	0.987
	PE	0.002	0.422	0.798	0.796	0.791
GCST90092807	VTE	-0.008	0.393	0.707	0.709	0.699
	DVT	-0.012	0.358	0.703	0.702	0.699
	PE	-0.003	0.792	0.892	0.865	0.829
GCST90018945	VTE	-0.001	0.599	0.770	0.773	0.761
	DVT	-0.004	0.284	0.993	0.993	0.993
	PE	-0.002	0.483	0.792	0.774	0.765

studies may not necessarily reflect causality. Our MR study precisely addresses this limitation. However, the protective mechanism of albumin against VTE is not yet clear. By conducting functional enrichment analysis on genes related to albumin and VTE, we found that they are primarily enriched in pathways such as inflammatory response to antigenic stimulus, interleukin-1 receptor binding, and alcohol dehydrogenase activity. Key gene analysis further highlights a strong association with inflammation and cytokines. Research has now recognized a bidirectional relationship between inflammation and thrombosis [28].TP53 is the primary focus of this investigation. It is a critical tumor suppressor gene and plays a role in modulating immune responses and regulating inflammatory signaling [29]. Loss of TP53 function affects the expression, activity, and release of coagulation factors, including tissue factor [30]. Numerous studies highlight TP53 as a key biomarker for VTE [31–34]. Recent clinical studies in liver cancer have demonstrated a correlation between a high coagulation-related risk score and a higher TP53 mutation rate [35]. This may partially elucidate the elevated prevalence of VTE

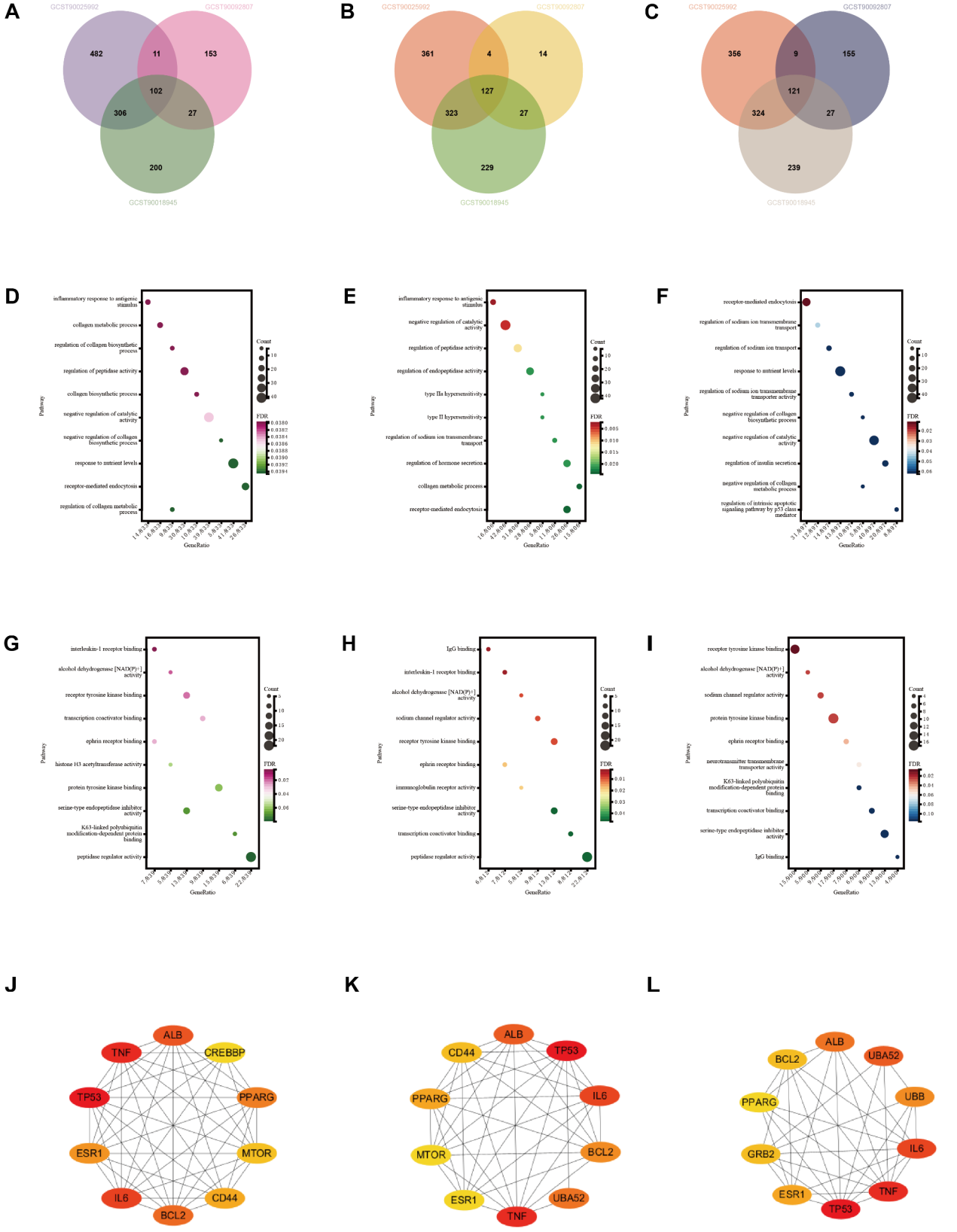

Fig. 4 Biological functional analysis. The Venn diagram displays genes closely associated with albumin and VTE (**A**), DVT (**B**) and PE (**C**). The GO enrichment analysis of VTE includes: (**D**) Biological Process, (**G**) Molecular Function. The GO enrichment analysis of DVT includes: (**E**) Biological Process, (**H**) Molecular Function. The GO enrichment analysis of PE includes: (**F**) Biological Process, (**I**) Molecular Function. A protein-protein interaction network to identify the top 10 hub genes associated with VTE (**J**), DVT (**K**) and PE (**L**)

observed in oncology patients. A meta-analysis revealed a significant association between elevated IL-6 levels and the incidence of VTE in COVID-19 patients [36]. A case-control study also identified IL-6 as an independent risk factor for VTE [37]. This aligns with the established role of IL-6 in the coagulation cascade. Inflammation-induced IL-6 elevation stimulates the synthesis of acute-phase proteins such as C-reactive protein, thrombopoietin, and fibrinogen [38, 39]. IL-6 initiates the coagulation cascade through the upregulation of tissue factor expression on monocytes, promoting thrombin activation and accelerating fibrin clot formation [40]. Concurrently, IL-6 contributes to endothelial dysfunction via multiple mechanisms, including the disruption of vascular endothelial-cadherin (VE-cadherin) junctions and upregulation of C5a receptor expression on endothelial cells. Furthermore, IL-6, through its interaction with the soluble IL-6 receptor (sIL-6R) and subsequent activation of endothelial cells, stimulates the release of IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1). This, in turn, recruits immune cells and plasminogen activator inhibitor-1 (PAI-1), further amplifying the coagulation cascade [41]. Collectively, these mechanisms implicate IL-6 as a key contributor to the pathogenesis of venous thrombosis. The study conducted by McInnes et al. demonstrated that the interleukin-6 receptor (IL-6R) antagonist tocilizumab (TCZ) significantly reduces circulating D-dimer levels in patients with rheumatoid arthritis (RA) [42]. As one of the most widely utilized clinical biomarkers of blood coagulation activation, D-dimer is closely associated with an increased risk of vascular events when elevated. These findings underscore the pivotal role of the IL-6 signaling pathway in coagulation and suggest a promising therapeutic strategy for mitigating thrombotic risk in patients. In addition to IL-6, elevated TNF-α levels are linked to a heightened risk of VTE [43]. Studies have shown that infusion of TNF-α can rapidly generate thrombin, ultimately leading to the formation of deep vein thrombosis [44]. Tissue factor (TF) is the primary initiator of the extrinsic coagulation cascade. Inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), potently induce the expression of both full-length and alternatively spliced TF in endothelial cells and blood cells [45]. Beyond its influence on TF, TNF-α also downregulates thrombomodulin (TM), a key anticoagulant protein [46]. Furthermore, it promotes leukocyte recruitment and platelet activation by upregulating adhesion molecule expression [47]. In addition, TNF-α stimulates the release of other pro-inflammatory cytokines, establishing a positive feedback loop that amplifies the coagulation response [48]. Furthermore, the levels of IL-1 are significantly elevated in patients with VTE [43]. IL-1 is also an inflammatory cytokine that, when bound to IL-1R1, leads to the expression of many inflammation-related genes [49]. Tissue factor is central in initiating coagulation, and pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6 can upregulate tissue factor expression [50]. This indicates a close relationship between inflammation and a procoagulant state. BCL-2, known for its anti-apoptotic properties, is one such protein. In an animal model of chronic thrombotic pulmonary arterial hypertension caused by inflammation-triggered VTE, the mRNA and protein levels of BCL-2 rise with the frequency and duration of embolisms [51]. Moreover, the balance of pro- and anti-apoptotic BCL-2 family protein expression influences platelet apoptosis [52, 53]. In patients with acute PE, platelets exhibit increased mitochondrial reactive oxygen species (ROS) production and reduced mitochondrial BCL-2 protein levels, suggesting a state of concurrent platelet activation and apoptosis [54]. Reports on vascular diseases and thrombosis related to these mutations are limited. Evidence has demonstrated that thromboembolism constitutes a significant complication for women undergoing tamoxifen treatment for breast cancer. Genotypic analysis of estrogen receptors (ESR) can facilitate the identification of thromboembolism risk subsequent to tamoxifen exposure [55]. Furthermore, research indicates that kidney transplant recipients undergoing treatment with mTOR inhibitors are subject to an elevated risk of thrombotic events. This increased risk is correlated with mTOR inhibitor therapy, which induces endothelial activation, promotes thrombin generation, and impairs fibrinolytic activity in patients [56].

Gene enrichment analysis has revealed significant differences in the pathways enriched in PE compared to VTE and DVT. Notably, PE is predominantly associated with pathways involving receptor-mediated endocytosis and sodium ion transmembrane transport, whereas VTE/DVT is primarily enriched in pathways related to antigen-driven inflammatory responses. These disparities are likely attributable to the unique structural and functional characteristics of pulmonary vascular endothelial cells. Pulmonary endothelial cells internalize albumin via receptor-mediated endocytosis (e.g., gp60 and FcRn receptors) [57]. The internalized albumin plays a pivotal role in maintaining vascular integrity by regulating endothelial barrier function and exerting anti-inflammatory effects, which help modulate both inflammatory and coagulation pathways—functions that are crucial for the proper physiology of the pulmonary circulation. In the context of hypoalbuminemia, impaired albumin uptake and function can lead to endothelial dysfunction, characterized by barrier breakdown, increased inflammation, and fibrin deposition, thereby markedly elevating the risk of PE. Sodium ion transmembrane transport is critical for maintaining cellular ion homeostasis and vascular tone [58]. Compared to the systemic deep venous system, the

pulmonary circulation is characterized by low-pressure, high-flow hemodynamics [59]. These unique hemodynamic properties render pulmonary vascular endothelial cells particularly susceptible to disruptions in ion transport. Dysregulation of sodium ion transport may therefore exert a more pronounced effect on pulmonary vascular endothelial function, ultimately contributing to the development and progression of PE.

Albumin is among the most prevalent proteins in the human body, serving a vital function in regulating blood osmotic pressure and facilitating the transport of nutrients. It also exhibits antioxidant and anti-inflammatory properties[60, 61]. Albumin reduces vascular permeability by protecting and restoring the glycocalyx of vascular endothelial cells [62]. This endothelial protection mechanism may also be associated with its protective effect against thrombus formation. Albumin can significantly reduce TNF-α, IL-6, and IL-1 levels in patients with liver cirrhosis [63, 64]. In vitro studies have found that albumin can inhibit the production of cytokines by blocking TLR9 activation and signaling in leukocytes [64]. It can also protect tissues from inflammatory damage by inhibiting the leakage of lysosomal proteinase B, releasing mitochondrial cytochrome c, and reducing caspase-3 activity [65]. Research on CD44 primarily focuses on tumor metastasis, with studies in vascular diseases suggesting that loss or inhibition of CD44 expression may hinder pathological angiogenesis [66]. Albumin can induce cell expression of CD44 by activating the ERK signaling pathway [67]. Hypoalbuminemia is a clinical feature of nephrotic syndrome and diabetic nephropathy, and studies have shown that urinary UBA52 levels in these patients are significantly elevated [68, 69]. To date, no empirical investigations have elucidated a correlation between PPARG, UBA52, CREBBP, GRB2, and UBB in relation to VTE and albumin. Additional research is required to elucidate the mechanisms of these genes in VTE and their therapeutic potential.

Serum albumin has been identified as a reasonable, cost-effective biomarker for assessing the risk of VTE [70]. Low serum albumin levels have been shown to be an independent risk factor for DVT, underscoring the importance of evaluating DVT risk in patients with hypoalbuminemia [71]. A recent meta-analysis further supports this association, demonstrating that hypoalbuminemia (defined as < 3.5 g/dL) is a significant risk factor for VTE in both medical and surgical patients [72]. Additionally, a large population-based cohort study revealed a linear inverse relationship between serum albumin levels and VTE risk, with a marked increase in risk observed when albumin levels fall below 45 g/L [73]. These findings propose the potential for albumin-based or albumin-enhancing therapeutic strategies in the prevention and management of VTE. Despite these promising insights, several challenges must be addressed before these findings can be effectively translated into clinical practice. Serum albumin levels are subject to fluctuation across various pathological conditions, highlighting the need for the establishment of standardized thresholds to quantify thrombosis risk. Rigorous clinical trials will be essential to validate the feasibility and efficacy of albumin-based therapeutic interventions, as well as to investigate potential synergistic effects with existing antithrombotic therapies. While serum albumin demonstrates substantial promise as both a biomarker and therapeutic target in VTE management, further research is imperative to fully realize its clinical potential.

From a biological perspective, VTE may influence serum albumin levels through various indirect mechanisms. For instance, systemic inflammation triggered by VTE can suppress hepatic albumin synthesis or promote albumin degradation, thereby leading to altered serum albumin levels [74]. However, in our MR analysis, the genetic instruments utilized are predominantly SNPs directly associated with VTE. While this approach is effective for evaluating whether VTE has a direct causal relationship with serum albumin levels, it may not fully account for other potential indirect pathways, such as chronic inflammation, hepatic metabolic dysfunction, or prolonged tissue injury. Given these limitations, future studies should integrate functional research approaches, including animal models and cell-based experiments, to further investigate these potential mechanisms. Such supplementary studies will provide a more comprehensive understanding of the possible reverse causal relationship between VTE and serum albumin levels and elucidate the underlying biological mechanisms.

A notable strength of this study is the use of extensive serum albumin GWAS datasets and MR to investigate the causal relationship between serum albumin levels and VTE. However, a significant limitation is the reliance on GWAS data exclusively from European-ancestry populations, which may limit the generalizability of the findings. To improve validity across diverse genetic and environmental contexts, future research should include underrepresented populations, such as those of Asian and African descent. Sensitivity analyses using MR-Egger and MR-PRESSO tests showed no evidence of horizontal pleiotropy, supporting the robustness of the results. Horizontal pleiotropy occurs when a genetic variant influences the outcome through pathways other than the exposure of interest, potentially biasing the results of MR analyses. This can be particularly problematic as it violates a key assumption of MR — that the instrumental variables only affect the outcome through the exposure. While the lack of evidence for horizontal pleiotropy is reassuring, it is important to note that the power of MR-Egger to detect balanced pleiotropy is inherently limited,

especially in cases where the sample size is restricted or the genetic variants used as instruments are relatively weak. Moreover, MR-PRESSO requires that the majority of instrumental variables are valid, an assumption that, if violated, can lead to inaccurate interpretations. Additionally, while genome-wide significance-based SNP selection ensures strong associations with the exposure, it may inadvertently include SNPs with downstream pleiotropic effects or exclude biologically relevant variants with moderate effects. Despite these limitations, the study provides valuable insights into the potential causal role of serum albumin in VTE, laying a solid foundation for future research to expand on these findings.

Conclusions

In summary, our bidirectional MR analysis confirmed a significant causal relationship between serum albumin and VTE, which includes DVT and PE. Bioinformatics analysis suggests that this causal relationship may be mediated by inflammation and cytokines.

Abbreviations

VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary embolism
MR	Mendelian randomization
RCT	Randomized controlled trial
AT	Antithrombin
PC	Protein C
PS	Protein S
GWAS	Genome-wide association study
SNPs	Single nucleotide polymorphisms
IVs	Instrumental variables
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
BP	Biochemical processes
MF	Molecular functions
CC	Cellular components
IVW	Inverse variance weighting
ORs	Odds ratios
CIs	Confidence intervals
FUMA	Functional Mapping and Annotation
FDR	False discovery rate
VE-cadherin	Vascular endothelial-cadherin
sIL-6R	Soluble IL-6 receptor
MCP-1	Monocyte chemoattractant protein-1
PAI-1	Plasminogen activator inhibitor-1
TCZ	Tocilizumab
RA	Rheumatoid arthritis
TF	Tissue factor
TM	Thrombomodulin
ROS	Reactive oxygen species

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

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

Supplementary Material 13

Supplementary Material 14

Supplementary Material 15

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Author contributions

WH wrote the manuscript and revised the manuscript. XM organized and analyzed data, wrote the manuscript. XT and ML revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. This study utilized publicly available data from previously published research, all of which had obtained the necessary ethics approvals and participant consent. No new data were collected, and no personally identifiable information was accessed or used in this analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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