Article

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Exploring Correlation Between Alkaline Phosphatase and Venous Thromboembolism in East Asian Populations: A Cohort and Mendelian Randomization Study

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Background: Several studies have explored the association between alkaline phosphatase (ALP) and venous thromboembolism (VTE), yet the findings remain inconclusive and inconsistent. The correlation between them has yet to be definitively established. We conducted a multicenter cohort study and a two-sample Mendelian randomization (MR) analysis with the aim of investigating the association between serum ALP levels and acute VTE in East Asian populations.

Methods: We collected data on VTE patients from Taizhou Municipal Hospital and Taizhou Hospital of Zhejiang Province between January 2019 and October 2024, alongside data from routine health check-up participants as the control group. Employing propensity score matching (PSM) and cubic spline model analysis, we investigated the relationship between ALP levels and VTE. Additionally, we performed a bidirectional two-sample MR analysis using genome-wide association study (GWAS) data to assess the potential causal effect between them.

Results: The retrospective cohort study involving 720 VTE patients and 1000 healthy controls found significantly lower ALP levels in the VTE group, which remained consistent after propensity score matching, with a non-linear relationship between ALP levels and VTE risk. Two-sample MR analysis confirmed a negative causal effect of ALP on VTE, with no evidence of pleiotropy in the results.

Conclusions: Our study suggested a negative association between ALP levels and the risk of VTE in the East Asian population. This finding may provide valuable insights into the role of ALP as a potential biomarker for VTE risk assessment.

Keywords: alkaline phosphatase; venous thromboembolism; cohort study; Mendelian randomization

Introduction

Venous thromboembolism (VTE) is a vascular disorder characterized by abnormal clotting of blood in the veins, leading to obstruction of venous return. It is the third common vascular disease after myocardial infarction and stroke, which is clinically presented as deep-vein thrombosis (DVT) or pulmonary embolism (PE) [1,2]. Epidemiological study showed that the incidence of VTE has been reached to (1–2) ‰ worldwide [3]. In China, the incidence of VTE is also increasing steadily each year. According to the survey [4], the age- and sex-adjusted hospitalization rate of VTE increased significantly from 3.2 in 2007 to 17.5 in 2016 per 100,000 population. Other studies have also indicated a high mortality rate in patients with VTE. For example, a meta-analysis involving more than 70,000 people that reviewed 86 randomized controlled trials showed that even with treatment, VTE can still cause death in 9.8% of participants [5]. This imposes a heavy health and economic burden on both governments and individuals.

Alkaline phosphatase (ALP) is a phosphomonoesterase, situated on the external layer of the cell membrane, and is widely distributed in tissues such as the liver, bones, intestines, kidneys, and placenta [6]. Its main physiological function is to participate in bone formation, thereby promoting osteogenesis. Abnormal ALP levels are commonly observed in conditions like intrahepatic and extrahepatic bile duct obstruction, rickets,

severe chronic nephritis, anemia, and others [7]. Over the past decade, ALP has been recognized as a biomarker for cardiovascular disease (CVD) risk and has been identified as an independent risk factor for atherosclerosis, stroke, and coronary artery disease [8–11]. A retrospective study at Wuhan Union Hospital analyzed the association between serum ALP levels in late pregnancy and the incidence of postpartum VTE. The results indicated a negative correlation between ALP levels and the risk of VTE, lower ALP levels in late pregnancy were associated with increased risk of VTE occurrence postpartum [12]. This negative correlation between ALP levels and VTE risk may be related to ALP's role in regulating vascular homeostasis and inflammation—processes central to thrombogenesis. By neutralizing lipopolysaccharide and reducing the resulting inflammatory cytokine cascade (e.g., tumour necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1β), ALP may attenuate the inflammatory trigger for VTE [13,14]. Elevated inflammation is a well-established independent risk factor for VTE [15]. Furthermore, ALP inhibits vascular calcification and enhances endothelial elasticity by Regulating levels of Phosphate and nitric oxide [16], thereby reducing the risk of venous thrombosis. However, no relevant studies have been conducted within the general population to date.

Mendelian randomization (MR) takes genetic variation as an instrumental variable (IV) to examine the relationship between exposure and outcome, thereby inferring the causal relationship [17]. Due to the fortuitous distribution of alleles of genetic variation, MR is less vulnerable to be affected by confounding factors and reverse causality [18]. At present, genome-wide association study (GWAS) is constantly improving and developing, which provides a data source for MR analysis. However, no MR studies have hitherto explored the causal relationship of ALP and VTE.

Given the limited number of studies examining the relationship between ALP and VTE, most of which focus on European populations, we conducted a multicenter cohort study and a two-sample MR analysis to investigate the association between serum ALP levels and acute VTE in East Asian populations (Fig. 1).

Methods

Study Population and Data Collection

We conducted a retrospective cohort study by collecting data on 720 patients diagnosed with VTE from Taizhou Municipal Hospital and Taizhou Hospital of Zhejiang Province between January 2019 and October 2024. The diagnosis of VTE was confirmed based on clinical, laboratory, and imaging data. Patients were included if they met all the following criteria: (1) age $\geq$18 years with a first-time diagnosis of VTE (either DVT or PE) between January 2019 and October 2024 at Taizhou Municipal Hospital or Taizhou Hospital of Zhejiang Province; (2) confirmed incident VTE (DVT or PE), with: DVT: Presence of standard clinical symptoms and confirmation via venography or ultrasound; PE: Presence of clinical symptoms and confirmation via pulmonary angiography or ventilation-perfusion lung scans [19]; (3) complete ALP data and baseline covariates (age, height, weight, diabetes history, triglycerides, total cholesterol) available at admission. Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10) [19]. Patients were excluded from the study if they met any of the following criteria: (1) a prior history of VTE, thromboprophylaxis, intrahepatic cholestasis, chronic hepatitis, severe acute infection, or cancer; (2) absence of ALP data. The data collected included patients' age, height, weight, history of diabetes, and laboratory test results at admission, such as triglycerides, total cholesterol, and ALP levels.

The control group of 1000 healthy individuals was selected from outpatients receiving routine laboratory tests as part of their periodic health examinations. All participants were medically screened to ensure they had no diagnosed malignancies, liver dysfunction (including hepatitis, cirrhosis, or fatty liver disease), or other major systemic disorders (such as severe cardiovascular, renal, or autoimmune diseases) that could potentially interfere with the study outcomes. This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Taizhou Municipal Hospital (Approval No. LWYJ2025242). Informed consent requirement was waived by the ethics committee.

Initial Statistical Analyses

Continuous variables (age, body mass index (BMI), total cholesterol, and ALP) were compared using independent two-sample *t*-tests, with results presented as mean $\pm$ standard deviation. As triglycerides did not conform to a normal distribution, they were presented as median (interquartile range) and analyzed using the Mann-Whitney U test, with standardized test statistics reported as z-scores. Categorical variables (sex and diabetes) were analyzed using Pearson's chi-square test and reported as n (%). Logistic regression models were employed to compare differences in ALP levels between patients with acute VTE and healthy controls.

Propensity Score Matching and Restricted Cubic-spline Regression

To assess the robustness of the results and account for potential confounders, we used propensity score matching (PSM) [20], with VTE as the dependent variable and ALP as the main exposure factor of concern. The covariates taken into account in the matching process encompassed age, BMI, diabetes, triglycerides, and total cholesterol, with a 1:1 matching ratio. This methodology was intended to balance the baseline characteristics between the VTE and control groups, minimizing the impact of confounding fac-

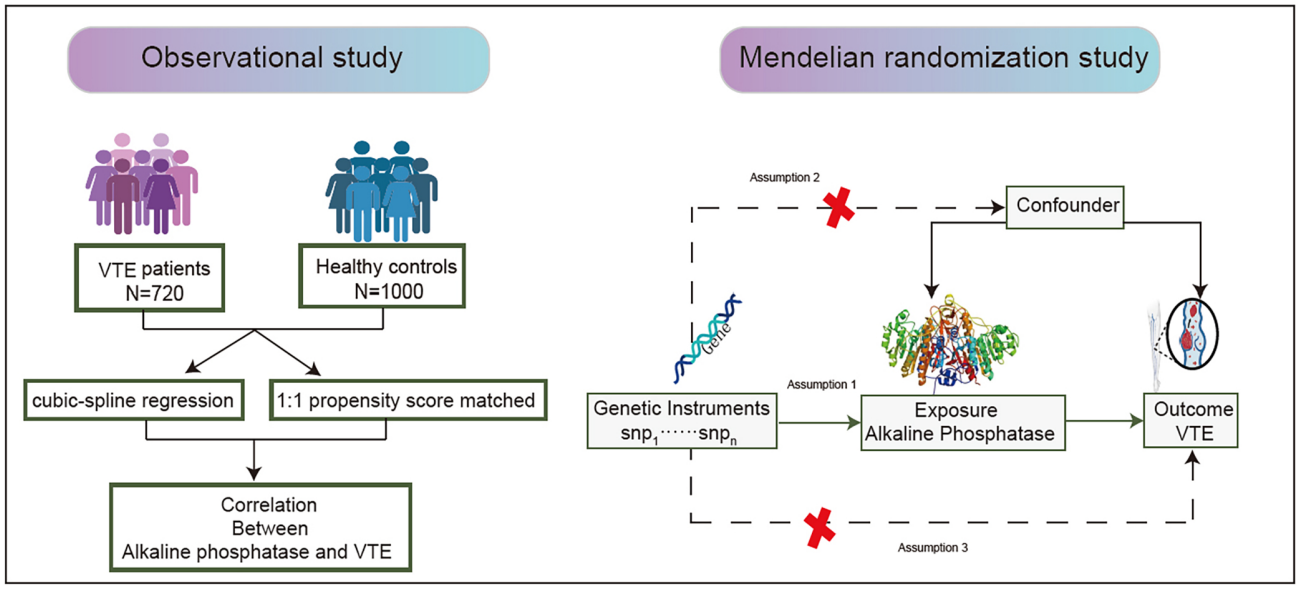

Fig. 1. The study flowchart of cohort and Mendelian randomization study. In the observational study, we performed a 1:1 propensity score match (PSM) between 720 included venous thromboembolism (VTE) patients and 1000 healthy controls, followed by cubic-spline regression to analyze the relationship between alkaline phosphatase levels and VTE risk. In the Mendelian randomization study, selected single nucleotide polymorphisms (SNPs) served as genetic instruments in a two-sample Mendelian randomization (MR) analysis evaluating the causal effect of alkaline phosphatase on VTE. This figure was created with Adobe Photoshop 2020 (Adobe Inc., San Jose, CA, USA).

tors. To further investigate the non-linear effects between ALP levels and VTE risk, restricted cubic spline (RCS) regression was employed [21], adjusting for age, BMI, diabetes, triglycerides, and total cholesterol. All *p*-values were two-tailed, with statistical significance defined as $p < 0.05$. Statistical analyses were performed using R software (version 4.4.2, R Core Team, Vienna, Austria), and the cubic spline model was implemented using the "Hmisc" and "rms" packages.

GWAS Summary of ALP and VTE

A bidirectional two-sample MR analysis was designed to evaluate the potentially causal effects of ALP and VTE. GWAS summary statistics for ALP were obtained from a GWAS study of the Biobank Japan Project (BBJ), which comprising 179,000 East Asian participants [22]. The pooled data for the study on VTE was derived from the China Pulmonary Thromboembolism Registry Study (CURES), a multicenter registry of PE cases in China, spanning from 2009 to 2015. The genetic data encompassed 1268 cases and 17,663 controls, as part of a comprehensive GWAS [23]. This study used previously published GWAS summary statistics and did not require Institutional Review Board approval.

Instrumental Variable Selection

To satisfy three hypotheses of MR analysis, we selected genetic variants that passed GWAS threshold ($p < 5 \times 10^{-8}$) as instrumental variables (IVs). Moreover, to ensure independence between IVs, we set the linkage disequilibrium (LD) threshold for grouping to $r^2 < 0.001$ and a window size of 10,000 kb [24]. Harmonization of ALP and VTE summary statistics was performed via the TwoSampleMR package to align effect alleles, and exclude palindromic single nucleotide polymorphisms (SNPs) with ambiguous strand. Effect estimates were standardized to the same effect allele across datasets. All SNPs with missing summary statistics such as allele frequencies and effect sizes in either the exposure (ALP) or outcome (VTE) datasets were excluded. MR-PRESSO was executed to exclude any outliers with potential pleiotropy to ensure the reliability of our MR estimates [25,26]. The F-statistic for IV strength was calculated using the formula $F = (\beta\_exposure/SE\_exposure)^2$, where only variants with $F > 10$ were retained to mitigate weak instrument bias.

Two-sample MR Analysis

We used the inverse variance weighted (IVW) method as the primary method of analysis, which incorporated Wald ratios to obtain consistent estimates of the causal impact of exposure on outcomes [27]. In addition, other MR analysis methods, including MR-Egger regression [28], weighted median [29] and weighted mode [30], were used to verify the causal relationship between exposures (ALP) and outcomes (VTE). Additionally, we carried out reverse MR analysis to evaluate the evidence for reverse causal association.

Table 1. Baseline characteristics of participants of the control versus VTE groups before and after propensity score matching.

	Before matching				After matching			
	Control	VTE	$t/\chi^2/z$	p	Control	VTE	$t/\chi^2/z$	p
n	1000	720			564	564		
Age	58.93 ± 10.48	65.17 ± 13.46	–10.80	<0.001	61.83 ± 10.26	62.23 ± 12.16	–0.60	0.552
Male (%)	522 (52.20)	372 (51.70)	0.05	0.827	290 (51.40)	291 (51.60)	0.00	0.952
BMI (kg/m^2)	24.08 ± 3.85	24.21 ± 3.35	–0.74	0.459	24.14 ± 3.77	24.23 ± 3.42	–0.46	0.688
Diabetes (%)	125 (12.50)	138 (19.20)	14.36	<0.001	93 (16.50)	82 (14.50)	0.82	0.366
Total cholesterol (mmol/L)	5.15 ± 1.09	4.83 ± 1.13	5.92	<0.001	4.97 ± 1.09	5.00 ± 1.10	–0.46	0.643
Triglycerides (mmol/L)	1.21 [0.84, 1.75]	1.23 [0.90, 1.70]	–0.52	0.60	1.17 [0.84, 1.72]	1.25 [0.89, 1.70]	–1.28	0.20
Alkaline phosphatase (U/L)	87.22 ± 22.39	77.79 ± 36.87	6.58	<0.001	82.23 ± 22.05	76.34 ± 26.65	8.16	<0.001

VTE, venous thromboembolism; BMI, body mass index.

In this study, Cochran's Q test was employed to evaluate the heterogeneity of the IVW model. The presence of heterogeneity was determined by a significance level of $p < 0.05$, prompting the utilization of the random-effects model of IVW for causal inference. Conversely, a fixed-effects model was used. MR-Egger regression analysis and funnel plots were employed to assess the potential bias resulting from genetic pleiotropy. The regression intercept of the MR-Egger analysis was used to estimate the magnitude of horizontal pleiotropy, with a value closer to 0 indicating a lower likelihood of horizontal pleiotropy. Moreover, the SNPs were eliminated one by one by performing the leave-one-out sensitivity analysis. The TwoSampleMR and MR-PRESSO packages of R software (version 4.2.3) were used for statistical analysis.

Results

Population and Baseline Characteristics

The retrospective cohort study encompassed a total of 720 VTE patients and 1000 healthy controls. Table 1 delineated the baseline characteristics of both the VTE and control groups. Before matching, compared to the healthy control group, the VTE group was significantly older (65.17 ± 13.46 years vs. 58.93 ± 10.48 years, $p < 0.001$), had a higher prevalence of diabetes (19.20% vs. 12.50%, $p < 0.001$), and had lower total cholesterol levels (4.83 ± 1.13 vs. 5.15 ± 1.09, $p < 0.001$). However, these differences were no longer significant after matching (Age: 61.83 ± 10.26 years vs. 62.23 ± 12.16 years, $p = 0.552$; Diabetes: 16.50% vs. 14.50%, $p = 0.366$; Total Cholesterol: 4.97 ± 1.09 vs. 5.00 ± 1.10, $p = 0.643$). And no significant differences were observed in other factors such as sex, BMI and triglyceride levels, either before or after matching.

Association Between ALP Levels and VTE Risk

As illustrated in Table 1, prior to PSM, ALP levels were significantly lower in the VTE group compared to the healthy control group (77.79 ± 36.87 vs. 87.22 ± 22.39, $p < 0.001$). Following adjustment for potential confounders through PSM, a total of 564 VTE patients were matched with 564 controls, and the findings remained consistent, with ALP levels still significantly reduced in the VTE group relative to the control group (76.64 ± 26.38 vs. 87.84 ± 21.89, $p < 0.001$). These results are further corroborated by cubic-spline model analysis. As depicted in Fig. 2, using an ALP level of 80 U/L as a reference point (odds ratio (OR) = 1), VTE risk exhibited a significant decrease as ALP levels increased, reaching a nadir then plateauing ($p < 0.001$).

Selection of Instrumental Variables

According to the SNPs selection criteria ($p < 5 \times 10^{-8}$, $r^2 < 0.001$, kb = 10,000), 48 independent SNPs for ALP were filtered primordially (**Supplementary Table 1**). After excluding SNPs with potential pleiotropy and palindromic SNPs, 48 SNPs were selected as IVs for two-sample MR analysis ultimately. According to the MR-PRESSO global test, no potential pleiotropy was detected ($p > 0.05$) (Table 2). The F-statistics of IVs were all largely >10, indicating no evidence of weak instrument bias. The details of the IVs in MR analysis were represented in **Supplementary Table 1**.

Causal Effects of Alkaline Phosphatase on VTE

Fig. 3 and **Supplementary Table 2** presented the causal effects of ALP on VTE based on IVW, MR-Egger, and weighted median. We employed the fixed-effect model for analysis since no significant heterogeneity was observed. The MR analysis robustly demonstrated a significant protective causal effect of ALP on VTE risk, with consistent directionality and statistical significance across all primary MR methods. The IVW estimate (OR = 0.79, 95% CI: 0.64–0.97, $p = 0.028$) indicated a 21.3% reduction in VTE risk per standard deviation increase in ALP, corroborated by MR-Egger (OR = 0.58, 95% CI: 0.42–0.81, $p = 0.002$), weighted median (OR = 0.65, 95% CI: 0.47–0.90,

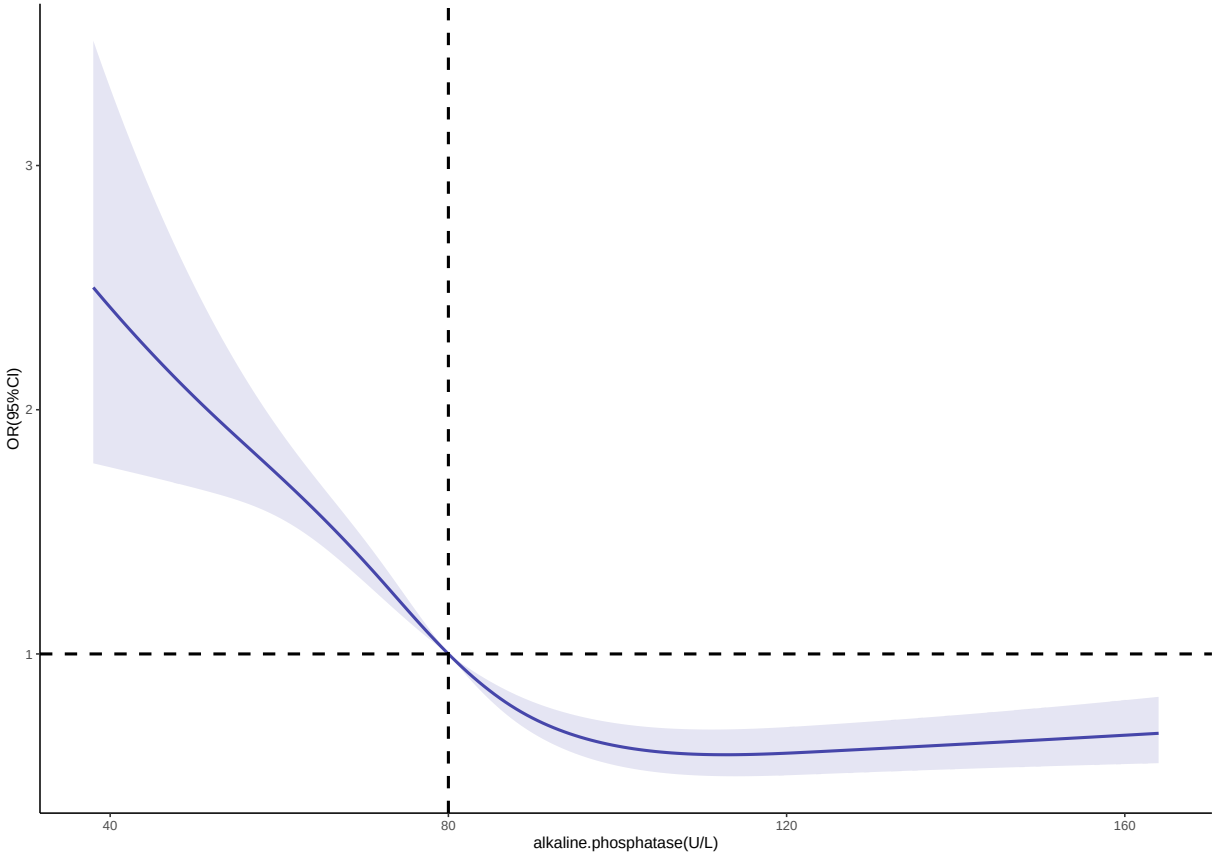

Fig. 2. Association between alkaline phosphatase and VTE risk, allowing for non-linear effects. OR, odds ratio; CI, confidence interval.

$p = 0.009$), and weighted mode (OR = 0.65, 95% CI: 0.49–0.86, $p = 0.005$) analyses, collectively indicating remarkable methodological concordance despite differing sensitivity assumptions. Crucially, reverse MR analysis definitively excluded reverse causation, yielding non-significant null associations across all complementary methods (IVW OR = 0.99, 95% CI: 0.98–1.00, $p = 0.161$; MR-Egger OR = 0.99, 95% CI: 0.96–1.03, $p = 0.885$; Weighted median OR = 0.99, 95% CI: 0.97–1.01, $p = 0.308$; Weighted mode OR = 0.99, 95% CI: 0.97–1.00, $p = 0.153$), with confidence intervals effectively excluding clinically meaningful effects of VTE on ALP levels (**Supplementary Table 3**).

As demonstrated in Table 2, the MR-Egger regression showed no evidence of significant horizontal pleiotropy intercept ($p > 0.05$), and Cochran's Q test indicated no substantial heterogeneity ($p > 0.05$). These findings were further supported by visual inspection of the scatter plot (**Supplementary Fig. 1**), which revealed a consistent directional effect across IVW, weighted median, and MR-Egger methods, and the funnel plot (**Supplementary Fig. 2**), which demonstrated symmetrical distribution of SNP effects. Additionally, the leave-one-out sensitivity analysis (**Supplementary Fig. 3**) confirmed that no single SNP disproportionately influenced the causal estimate of ALP on VTE risk.

Discussion

This study was the first to provide significant insights into the correlation between ALP levels and the risk of VTE in East Asian population, addressing a gap in research predominantly focused on European cohorts. The results suggested that ALP levels were significantly lower in VTE patients compared to healthy controls, and this relationship persisted even after adjusting for potential confounders through PSM. Furthermore, the cubic-spline analysis revealed a non-linear relationship between ALP and VTE risk, which was further supported by causal inference from MR analysis. The MR analysis, including IVW, MR-Egger, weighted median and weighted mode approaches, consistently showed a negative association between ALP levels and VTE risk. The reverse MR analysis which yielded no statistically significant association was methodologically critical for causal inference, as it provided statistical evidence against reverse causality, effectively ruling out VTE occurrence as a meaningful driver of alterations in ALP levels within this East Asian population. Consequently, this result substantiated the hypothesized unidirectional causal pathway from ALP to VTE inferred from the primary MR analyses. Sensitivity analysis did not reveal any significant horizontal pleiotropy and heterogeneity, suggesting that the

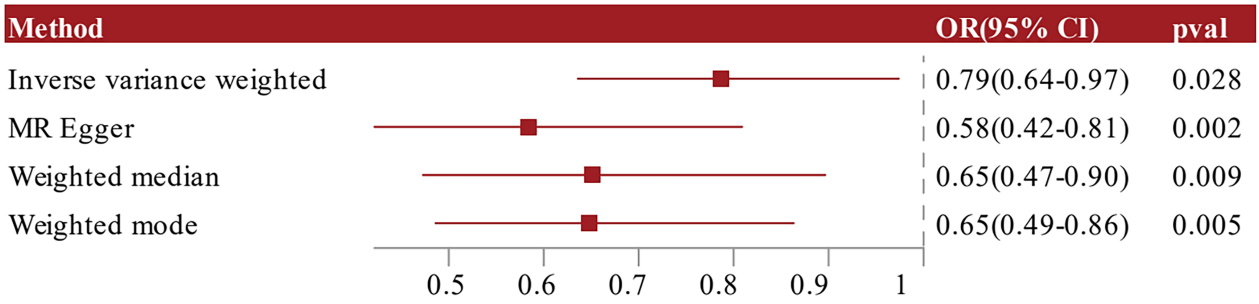

Fig. 3. MR analysis of causal association between alkaline phosphatase and VTE in East Asian populations. MR, Mendelian randomization; OR, odds ratio.

Table 2. Assessment of heterogeneity and directional pleiotropy.

Exposure	Heterogeneity		MR-Egger			MR-PRESSO
	Q	Q-*p*val	Intercept	SE	*p*	Global test-*p*val
ALP	51.64	0.30	0.02	0.01	0.08	0.27

Q, heterogeneity statistic Q; SE, standard error; ALP, alkaline phosphatase.

results are robust and consistent across different genetic instruments. The leave-one-out analysis indicated that no single SNP was disproportionately influencing the results, further confirming the reliability of the MR analysis.

A recent study corroborated our findings [12]. They included 10,044 pregnant women from three hospitals in Wuhan, after adjusting for covariates of demographic, lifestyle, birth outcomes, and other liver enzymes. They found that low ALP levels in late pregnancy were significantly associations with increased risk of VTE postpartum based on a cohort design. What's more, they further investigated the potential mechanism underlying and speculated that the ALP-associated VTE risk may be partially mediated by hemoglobin. However, this contrasts with some other studies. Motaganahalli *et al*. [31] analyzed 71 COVID-19 patients and found elevated alkaline phosphatase levels significantly associated with increased DVT risk. Similarly, two studies [32,33] on DVT following lower limb fractures identified elevated alkaline phosphatase as an independent risk factor. Nevertheless, their study in question possesses certain limitations. Prolonged immobility after fractures, a known VTE risk factor [34] reduces venous return and promotes thrombus formation. Additionally, trauma-induced inflammation [35], immune overactivation, and disrupted hemostasis [36] further contribute to coagulation and clot formation.

The exact mechanisms of ALP and risk of VTE have not been clarified. Several potential hypotheses have been posited to elucidate the impact of ALP on VTE. ALP is known to be involved in the regulation of vascular calcification, a process that can contribute to endothelial dysfunction, a key factor in thrombogenesis [14]. ALP regulates vascular calcification, where calcium phosphate deposits stiffen vessels and damage the endothelium, promoting thrombosis. While normal ALP activity may protect against thrombosis by maintaining phosphate balance, lower ALP might indicate impaired ability to inhibit vascular calcification, contributing to endothelial injury and higher VTE susceptibility [37–39]. ALP is also a key enzyme in the liver, reduced levels of ALP may indicate impaired liver function, which- disrupt the synthesis of proteins involved in coagulation, leading to an increased risk of thrombosis. The liver produces many of the proteins that regulate blood clotting, and a deficiency in ALP activity could alter this balance, contributing to a hypercoagulable state [40–42]. Chronic inflammation is a well-established risk factor for VTE. The anti-inflammatory properties of ALP are mediated through its ability to dephosphorylate pro-inflammatory mediators such as lipopolysaccharide (LPS) and extracellular ATP [43]. ALP exerts its effects by inhibiting LPS-TLR4 binding and subsequent TLR4-mediated NF-κB signaling, modulating purinergic signaling pathways, and promoting the autophagy and endocytosis of pro-inflammatory phosphoproteins and phospholipids. These actions collectively dampen pro-inflammatory signaling pathways, thereby reducing the occurrence of chronic inflammation [44].

Our study has furnished initial evidence for plausible causal connections between ALP and VTE. The current investigation holds several advantages. Firstly, the combination of PSM and MR analysis enables a more precise assessment of the relationship between ALP and VTE risk, minimizing confounding and reverse causality. Secondly, the application of cubic-spline modeling to evaluate the nonlinear relationship between ALP levels and VTE risk offers valuable insights into the threshold effects of ALP on thrombotic risk. Last, the findings of this study, derived from East Asian population, provide valuable insights into this specific demographic. This focus allows for a deeper

understanding of the relationship between ALP and VTE within this group, paving the way for future research to explore whether these associations hold true across diverse ethnic and geographic populations.

While the findings of this study are robust, several limitations should be acknowledged. Firstly, the cross-sectional and retrospective design of the study is more prone to various biases, emphasizing the need for prospective cohort studies to support and validate the findings. Secondly, ALP levels were measured at a single time point in our study. However, ALP levels can fluctuate over time in response to various factors, such as inflammation, liver function, and phosphate metabolism. Longitudinal studies are required to assess how changes in ALP levels over time affect VTE risk. Thirdly, although PSM was employed to adjust for confounding factors, there might still be residual confounding from variables not captured in the analysis. For instance, lifestyle factors like physical activity, diet, and smoking status could influence both ALP levels and VTE risk. Fourthly, the outcome sample size (N = 18,931) was substantially smaller than the exposure dataset (N = 118,886), which may limit power to detect modest causal effects and reduce precision of SNP-outcome associations. While instrument strength metrics (F-statistics) appear robust due to the large exposure sample, the smaller outcome sample increases susceptibility to Type II error. Fifthly, our study utilized data from two tertiary hospitals in Taizhou, China. While this facilitates internal consistency, it may introduce selection bias that limits generalizability to broader East Asian populations. Prospective studies are needed to validate the feasibility of ALP as a biomarker.

Conclusion

In conclusion, our study observed an inverse association between ALP levels and VTE risk in the East Asian population. These preliminary findings suggest that ALP might serve as a potential biomarker for VTE risk assessment in this population, though further validation is required. If corroborated by future studies, ALP measurement—a widely available and inexpensive test—could offer a pragmatic tool to aid in risk stratification, possibly supporting targeted prevention strategies.

Availability of Data and Materials

GWAS summary statistics of VTE used in this study were deposited in The National Genomics Data Center under the accession number: OMIX001381 (https://ngdc.cncb.ac.cn/omix/release/OMIX001381).

Author Contributions

LZ designed the study. HW and HL conducted most of the MR analysis and were contributors in writing the manuscript. TW, ZX and HC contributed to the clinical data collection, and TW was mainly responsible for the cohort analysis. QW, ZZ, ZGZ and SL performed the research. SL and ZGZ were responsible for revising the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Taizhou Municipal Hospital (Approval No. LWYJ2025242). Informed consent requirement was waived by the ethics committee.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537201.187.

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