

Phenotype-based risk stratification for deep vein thrombosis in Behçet's disease: a global 10-year longitudinal study

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Abstract

Objectives

Vascular involvement, particularly deep vein thrombosis (DVT), is a major cause of morbidity and mortality in Behçet's disease (BD). This study aimed to identify independent risk factors for DVT and establish a robust framework for phenotype-based risk stratification.

Methods

We conducted a retrospective cohort study using the TriNetX global health research network and identified 19,739 patients with BD. Three independent propensity score-matched cohorts were established to evaluate the impact of intestinal involvement, thrombophlebitis, and antiphospholipid syndrome (APS). A multivariable Cox proportional hazards model was used to identify independent predictors of DVT over a 10-year follow-up. To ensure the robustness of our findings and minimise peri-diagnostic detection bias, a 90-day landmark analysis was performed as a sensitivity analysis.

Results

Multivariable analysis identified APS (adjusted hazard ratio [aHR] 6.28, 95% confidence interval [CI] 4.56–8.64) and a history of thrombophlebitis (aHR 5.92, 95% CI 4.72–7.41) as the strongest independent predictors of DVT. In the 90-day landmark analysis, these associations remained significant, with persistent risk observed for APS (aHR 5.10) and thrombophlebitis (aHR 2.50), confirming their long-term predictive value. Additional independent predictors included intestinal involvement (defined as non-infective inflammatory colitis; aHR 1.51), obesity (aHR 1.98), glucocorticoid use (aHR 1.78), and male sex (aHR 1.77).

Conclusion

APS and thrombophlebitis, markers of heightened inflammatory and thrombotic activity at diagnosis, also appear to be persistent indicators of elevated DVT risk in BD. These findings support phenotype-based risk stratification and highlight the need for intensive monitoring and individualised preventive strategies to improve long-term outcomes.

Key words

Behçet's disease, deep vein thrombosis, antiphospholipid syndrome, intestinal involvement, thrombophlebitis, real-world data

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Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder characterised by recurrent oral and genital ulcers, skin lesions, and uveitis (1-3). Among its various clinical manifestations, vascular involvement (vasculo-Behçet's) is one of the most severe complications, with venous thromboembolism (VTE), particularly deep vein thrombosis (DVT), being the most common vascular manifestation (4-6). In BD, DVT is not merely a mechanical obstruction but is primarily driven by inflammatory vasculitis of the vessel wall, contributing to substantial morbidity and a complex clinical course (5, 7).

The clinical management of BD-associated DVT remains challenging. Although traditional VTE management relies primarily on anticoagulation, the inflammatory pathophysiology of BD necessitates a dual approach that includes immunosuppressive therapy to stabilise the vascular wall and anticoagulation to prevent thrombus propagation (8-10). However, DVT risk is not uniform among patients with BD. Emerging evidence suggests that specific clinical phenotypes, including thrombophlebitis (11, 12), antiphospholipid syndrome (APS) (13), and intestinal involvement, may predispose patients with BD to an increased thrombotic risk (14, 15). In particular, intestinal involvement may promote systemic inflammation, endothelial activation, and a prothrombotic state, analogous to observations in inflammatory bowel disease (14). Seyahi *et al.* (15) highlighted similarities between intestinal BD and Crohn's disease with respect to mucosal inflammation and systemic inflammatory burden, supporting the hypothesis that intestinal involvement in BD may contribute to thrombotic complications. Although direct evidence linking intestinal involvement in BD to DVT is limited, converging clinical and mechanistic evidence supports evaluating intestinal disease as an independent risk factor in large-scale studies.

Despite these insights, several critical gaps remain in the literature (10). Most previous studies have been limited by small sample sizes, single-centre ret-

rospective designs, or short follow-up periods, precluding robust quantitative assessment of individual risk factors. Furthermore, although intestinal involvement is a well-recognised phenotype, its independent contribution to DVT risk, after adjustment for baseline confounders such as age, sex, and glucocorticoid use, remains controversial. To address these limitations, we conducted a large-scale, multinational real-world study using the TriNetX database, which encompasses a diverse global cohort of patients across various regions, including North America, Europe and Asia (16). The cohort included approximately 20,000 patients with BD with heterogeneous geographic and ethnic backgrounds and a follow-up period of up to 10 years. The primary objective of this study was to identify independent clinical predictors of DVT and quantify the impact of specific phenotypes, including APS, thrombophlebitis, and intestinal involvement. We used propensity score matching (PSM) and multivariable Cox regression to establish a comprehensive framework for phenotype-based risk stratification and optimise personalised management of patients with BD.

Methods

Study design and data source

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement and the Declaration of Helsinki (17). We conducted a retrospective cohort study using TriNetX (Cambridge, MA, USA), a global federated health research network that provides access to de-identified electronic health records (EHRs) from large healthcare organisations worldwide, representing diverse geographic regions including North America, Europe and Asia (such as Turkey). The TriNetX dataset used for this study was finalised on 17 January 2026, to ensure consistency across all longitudinal analyses. Additional sex-stratified subgroup analyses requested during peer review were executed on 1 October 2026, on the TriNetX platform, which comprised 205,033,003 patients across 188 healthcare organizations (HCOs)

during execution. As TriNetX is a continuously updated dynamic global network, baseline patient counts for the additional subgroup analyses account for this updated network size. Because the TriNetX database is compliant with the Health Insurance Portability and Accountability Act, and provides fully de-identified, aggregated data, the institutional review board of St. Marianna University School of Medicine exempted this study from approval and waived the requirement for informed consent.

We identified patients with BD using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code M35.2. The detailed process of patient selection and PSM for each sub-cohort is illustrated in Supplementary Figure 1. We excluded patients with Crohn's disease or ulcerative colitis to ensure diagnostic specificity. Detailed definitions of all study variables, including ICD-10-CM and RxNorm codes, are provided in Supplementary Table S1.

Definition of sex and race/ethnicity

Sex and race/ethnicity were defined using information recorded in the EHRs of participating healthcare organisations. Sex was categorised as male or female and represented biological sex. Race and ethnicity were classified using standardised TriNetX categories, primarily based on patient self-report. These variables were used as covariates in PSM to ensure balanced cohorts. Although not included in the subsequent Cox proportional hazards models because of adequate post-matching balance, they were reported to describe population diversity in accordance with SAGER guidelines.

Clinical phenotypes and covariates

Patients were categorised into clinical phenotypes, including intestinal involvement, thrombophlebitis, and APS. Baseline covariates included demographics (age, sex, and ethnicity), comorbidities (obesity, diabetes, hypertension, and nicotine dependence), and glucocorticoid use. Medication exposure, specifically glucocorticoid use, was assessed as a baseline characteris-

tic based on prescription records documented on or before the index date, in accordance with the standard TriNetX analytic platform configuration. This approach ensured that covariates reflected pre-existing clinical status and minimised time-dependent confounding and overadjustment bias. To evaluate the phenotypic contribution to DVT risk, treatment modalities initiated after the diagnosis of specific manifestations (such as anticoagulation or biologics) were excluded from the multivariable model. Including these post-index treatments as covariates could introduce overadjustment bias or mediator-driven confounding, thereby masking the true independent prognostic value of the clinical phenotypes. Of note, minor or transient cardinal manifestations of BD, such as oral or genital ulcers, were not included as covariates. This is because such individual symptoms are widely known to be significantly under-coded (under-reported) in EHR databases once a definitive diagnosis of BD is established, and including these potentially misclassified codes would introduce classification bias.

Outcome and follow-up

The primary outcome was the incident development of DVT. In the Kaplan-Meier analysis of DVT-free survival, the study population included both treatment-naïve patients and those with a prior history of DVT. This analytic approach was adopted to capture the longitudinal burden of thrombotic events in BD, reflecting real-world clinical practice where management of both primary and recurrent thrombosis is critical. The cumulative incidence of DVT was evaluated over a 10-year follow-up period beginning at the index date.

Statistical analysis

A two-step statistical approach was employed to minimise confounding:

1. PSM: Three independent matched cohorts were established to isolate the impact of intestinal involvement, thrombophlebitis, and APS. Matching was performed at a 1:1 ratio using a greedy nearest-neighbour algorithm. Covariate balance was confirmed by a

standardised mean difference (SMD) of <0.1 for all variables.

2. Multivariable Cox Proportional Hazards Regression: To identify independent predictors of DVT development, multivariable Cox proportional hazards regression models were constructed separately for each of the three PSM cohorts. The models included age, sex, clinical phenotypes, obesity, and glucocorticoid use as covariates to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). In addition, to complement these relative risk estimates, absolute risks over the 10-year follow-up period were evaluated and compared using Kaplan-Meier cumulative incidence curves and the log-rank test.

The Kaplan-Meier method was used to estimate 10-year DVT-free survival, and groups were compared using the log-rank test. Sex-stratified subgroup analyses were also conducted for each clinical phenotype to evaluate potential sex-specific differences in DVT risk predictors. All statistical analyses, including 1:1 propensity score matching (PSM), multivariable Cox proportional hazards regression, log-rank tests, and Kaplan-Meier survival curves, were performed directly using the built-in analytic platform of TriNetX. Statistical significance was set at $p < 0.05$.

Due to the nature of the EHR database, missing data were not imputed, and complete-case analysis was applied during the PSM process.

Sensitivity analysis

We performed a 90-day landmark analysis to evaluate the robustness of the identified risk factors. Patients who developed DVT or were censored within the first 90 days after the index date were excluded to minimise potential protopathic bias.

Results

Baseline characteristics and PSM

A total of 19,739 patients with BD were identified, and three independent, baseline-balanced cohorts were successfully established through PSM to evaluate the impact of intestinal involvement, thrombophlebitis, and APS on DVT risk. Before matching, patients

Table I. Baseline characteristics of propensity score-matched cohorts of patients with Behçet's disease (exemplified by the intestinal involvement cohorts).

Variable class	Characteristic	Without intestinal involvement (n=1,332)	With intestinal involvement (n=1,332)	SMD
Demographics	Age: mean (SD), years	43.9 (18.3)	43.4 (18.0)	0.029
	Sex: male, n (%)	300 (22.5)	296 (22.2)	0.007
Ethnicity, n (%)	Not Hispanic or Latino	937 (70.3)	923 (69.3)	0.023
	Hispanic or Latino	62 (4.7)	74 (5.6)	0.041
	Unknown ethnicity	333 (25.0)	335 (25.2)	0.003
Comorbidities, n (%)	Overweight and obesity	245 (18.4)	233 (17.5)	0.023
	Type 2 diabetes mellitus	164 (12.3)	172 (12.9)	0.018
	Essential hypertension	422 (31.7)	398 (29.9)	0.039
	Nicotine dependence	117 (8.8)	146 (11.0)	0.073
Medication, n (%)	Glucocorticoids	918 (68.9)	916 (68.8)	0.003

Baseline clinical and demographic characteristics are compared between pairs of propensity score-matched cohorts based on clinical phenotypes: patients with *versus* without intestinal involvement. Data are presented as counts (percentages) or means (standard deviations). Detailed baseline characteristics for all three matched cohorts, including those based on history of thrombophlebitis and comorbid antiphospholipid syndrome (APS), both before and after propensity score matching, are available in Supplementary Table S2. All standardised mean differences were <0.1, indicating excellent covariate balance after matching.

SD: standard deviation; SMD: standardised mean difference.

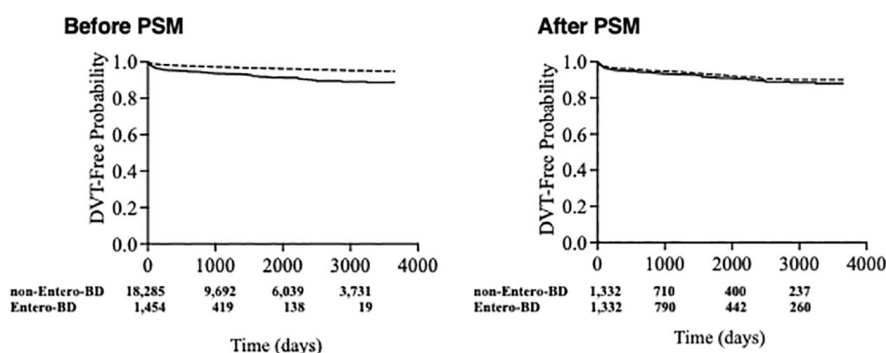


Fig. 1. Kaplan-Meier analysis of deep vein thrombosis-free survival according to intestinal involvement. **Before PSM:** cumulative incidence of DVT in the entire cohort (n=18,285 non-entero-BD vs. n=1,454 entero-BD). **After PSM:** cumulative incidence after 1:1 propensity score matching (n=1,332 in each group). Solid and dashed lines represent patients with and without intestinal involvement, respectively. Groups were compared using the log-rank test ($p=0.798$ after PSM). Numbers at risk are shown below the curves. Note that the study population included both treatment-naïve patients and those with a prior history of DVT. BD: Behçet's disease; DVT: deep vein thrombosis.

with these phenotypes were generally older and had a higher prevalence of comorbidities than those without these phenotypes. After 1:1 PSM, baseline characteristics, including age, sex, ethnicity, comorbidities (obesity, diabetes, and hypertension), and glucocorticoid use, were well balanced between groups across all three cohorts, with all SMDs <0.1 (Table I and Supplementary Table S2).

DVT-free 10-year survival according to clinical phenotypes

Kaplan-Meier analysis provided long-term estimates of DVT occurrence over

a 10-year follow-up period across different clinical phenotypes.

- **Intestinal Involvement (Fig. 1):** In the overall cohort analysis (unadjusted), patients with intestinal involvement (entero-BD) showed a significantly higher cumulative incidence of DVT, resulting in lower DVT-free survival than those without intestinal involvement (log-rank $p<0.0001$) (Fig. 1A). However, after PSM to adjust for age, sex, comorbidities, and glucocorticoid use, the difference in DVT-free survival between groups was no longer statistically significant (log-rank

$p=0.798$) (Fig. 1B). These findings suggest that the increased DVT risk observed in the unadjusted entero-BD cohort was largely attributable to baseline differences in clinical characteristics rather than intestinal involvement itself.

- **Thrombophlebitis (Fig. 2):** In contrast, the impact of thrombophlebitis remained robust after matching. Patients with a history of thrombophlebitis had significantly lower DVT-free survival than matched controls (log-rank $p<0.0001$), supporting thrombophlebitis as a persistent clinical risk marker.
- **APS (Fig. 3):** Similarly, APS was associated with a marked decline in DVT-free survival in the matched cohort analysis (log-rank $p<0.0001$). The APS group exhibited the highest cumulative incidence of DVT among all phenotypes.

Sex-stratified subgroup analyses

To evaluate whether the identified risk factors consistently predict DVT across the sexes, subgroup analyses were conducted separately for male and female patients (Supplementary Table S3). Owing to the limited sample size of patients with concomitant APS, PSM could not be reliably performed for this subgroup; thus, unadjusted incidence rates and hazard ratios are presented. Concomitant APS significantly increased DVT risk in females (17.8% vs. 2.5%, Log-rank $p<0.0001$; unadjusted HR= 7.81, 95% CI: 5.78–10.64) and males (39.6% vs. 3.5%, Log-rank $p<0.0001$; unadjusted HR= 14.08, 95% CI: 10.20–19.23). Thrombophlebitis remained a strong independent predictor after PSM in females (HR= 4.29, 95% CI: 2.40–7.69, $p<0.0001$) and males (HR= 2.80, 95% CI: 1.57–4.98, $p=0.0002$). Intestinal involvement significantly increased DVT risk in females (HR= 1.59, 95% CI: 1.13–2.25, $p=0.008$) and demonstrated a comparable hazard ratio in males (HR= 1.44, 95% CI: 0.78–2.67, $p=0.244$).

Sensitivity analysis (landmark analysis)

To ensure that the identified risk factors were not driven solely by events occur-

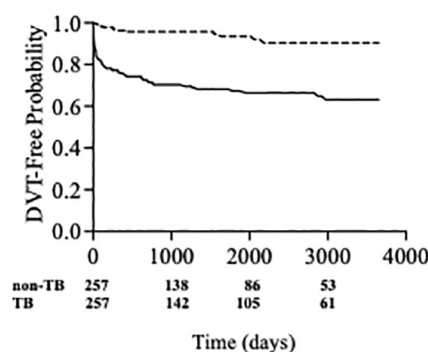


Fig. 2. Kaplan-Meier analysis of deep vein thrombosis-free survival according to thrombophlebitis status. Cumulative incidence of deep vein thrombosis is shown for propensity score-matched cohort of patients with BD with and without a history of thrombophlebitis (solid and dashed lines, respectively; $n=257$ in each group). Patients with thrombophlebitis showed a significantly higher risk of deep vein thrombosis (HR: 5.92; $p<0.001$).

BD: Behçet's disease; DVT: deep vein thrombosis; HR: hazard ratio.

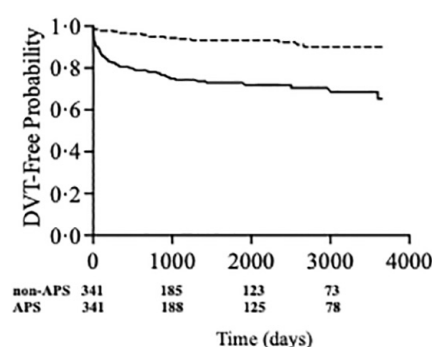


Fig. 3. Kaplan-Meier analysis of deep vein thrombosis-free survival according to antiphospholipid syndrome status. Cumulative incidence of deep vein thrombosis is shown for propensity score-matched cohort of patients with BD with and without comorbid antiphospholipid syndrome (solid and dashed lines, respectively; $n=341$ in each group). The presence of antiphospholipid syndrome was associated with a marked reduction in DVT-free survival (HR: 6.28), reaching approximately 65.3% at 10 years ($p<0.001$).

APS: antiphospholipid syndrome; BD: Behçet's disease; DVT: deep vein thrombosis; HR: hazard ratio.

ring around the time of diagnosis, we conducted a 90-day landmark analysis. Even after excluding patients who developed DVT or were censored within the first 90 days after the index date, both APS and a history of thrombophlebitis remained robust independent predictors of DVT. The aHR for APS remained markedly elevated at 5.10 (91 days to 10 years), and thrombophlebitis was also associated with a persistently

Table II. Risk factors for deep vein thrombosis in patients with Behçet's disease.

Covariate	Adjusted HR (95% CI)	p-value
History of thrombophlebitis	5.917 (4.717–7.407)	<0.001
Antiphospholipid syndrome	6.277 (4.560–8.642)	<0.001
Intestinal involvement (K52.9)	1.508 (1.123–2.024)	0.006
Overweight and obesity	1.983 (1.586–2.478)	<0.001
Glucocorticoid use	1.779 (1.509–2.096)	<0.001
Male sex	1.766 (1.510–2.066)	<0.001
Age at index date	1.009 (1.005–1.014)	<0.001

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) from multivariable Cox proportional hazards regression analysis identifying independent risk factors for deep vein thrombosis in patients with Behçet's disease.

CI: confidence interval; HR: hazard ratio.

increased risk (aHR 2.50). These findings confirm the long-term predictive value of these clinical phenotypes.

Independent risk factors for DVT development

A multivariable Cox proportional hazards regression model was used to identify independent predictors of DVT, including clinical phenotypes, demographics, comorbidities and medication use (Table II).

The analysis revealed that APS and a history of thrombophlebitis were the strongest independent risk factors for DVT in patients with BD. Specifically, APS was associated with a more than six-fold increase in DVT risk (aHR 6.277; 95% CI 4.560–8.642; $p<0.001$). Similarly, a history of thrombophlebitis was associated with an approximately six-fold higher risk of DVT (aHR 5.917; 95% CI 4.717–7.407; $p<0.001$). Among intestinal manifestations, unspecified noninfective gastroenteritis and colitis (K52.9) remained a significant independent predictor of DVT, although the effect size was modest (aHR 1.508; 95% CI 1.123–2.024; $p=0.006$). Other significant contributors to DVT risk included overweight/obesity (aHR 1.983; $p<0.001$), glucocorticoid use (aHR 1.779; $p<0.001$), and male sex (aHR 1.766; $p<0.001$). Age at index was also statistically significant, although the magnitude of the association was small (aHR 1.009 per year; $p<0.001$).

Discussion

This study represents the largest real-world analysis to date investigating risk factors for DVT in patients with BD,

using a global database of more than 20,000 patients. Our longitudinal study using a 10-year follow-up identified APS and a history of thrombophlebitis as the strongest independent predictors of DVT, each associated with an approximately six-fold increase in risk. Notably, although the association between overall intestinal involvement and DVT was attenuated after PSM, specific non-infectious gastrointestinal manifestations remained significant independent risk factors in multivariable analysis.

The notable aHR for APS (6.28) and thrombophlebitis (5.92) highlight their critical role in the pathogenesis of BD-related venous thromboembolism. To ensure the robustness of these findings, we conducted a 90-day landmark analysis to minimise potential detection bias and the impact of peri-diagnostic clinical activity. Even after excluding the first 90 days of follow-up, the predictive value of these phenotypes remained highly significant. Most notably, the risk associated with APS remained elevated (aHR 5.10), whereas thrombophlebitis remained associated with a 2.5-fold increased risk of subsequent DVT. These results demonstrate that these clinical features were not only markers of inflammatory activity at the time of BD diagnosis but also enduring indicators of a long-term prothrombotic state. Although superficial thrombophlebitis has long been recognised as a clinical "red flag" [5], our data suggest that its impact is substantially greater than that of traditional risk factors such as obesity (aHR 1.98) or male sex (aHR 1.77). Furthermore, the combination of the vasculitic nature of BD and the hypercoagulable

state associated with APS may create a particularly high-risk environment for thrombus formation.

Beyond these strong predictors, our analysis of intestinal involvement yielded complex but clinically informative results. Although the apparent association between entero-BD and DVT in the unadjusted cohort diminished after PSM, suggesting that baseline confounders such as age, sex, and glucocorticoid exposure largely explained the observed risk, non-infectious inflammatory colitis (K52.9) remained a significant independent predictor in multivariable analysis. These findings are particularly relevant in the era of real-world data, in which disease phenotypes are often defined pragmatically through clinical coding rather than mechanistically by underlying pathology. Importantly, our results challenge the traditional view that intestinal involvement is relevant solely to gastrointestinal morbidity. The observed associations suggest that specific patterns of intestinal inflammation may reflect a heightened systemic inflammatory burden and thereby contribute indirectly to a prothrombotic milieu. From a clinical perspective, this distinction is critical because it cautions against overgeneralising risks based on broad phenotypic categories while identifying a subset of patients in whom intestinal disease activity may warrant intensified surveillance for thrombotic complications. To bridge this gap, the gut-microbiota-reactive oxygen species (ROS)-thrombosis axis may provide a plausible mechanistic framework linking intestinal inflammation to BD-related thromboembolism. Patients with BD exhibit a distinct gut microbial signature that has been associated with a reduced capacity for butyrate production (18). From an immunological perspective, butyrate is a critical metabolite involved in inducing regulatory T (Treg) cell differentiation and maintaining immune tolerance (19, 20). Clinically, intestinal inflammation is known to contribute to systemic venous thromboembolism through alterations in microbial homeostasis (14, 21).

In BD, this persistent inflammatory burden may promote oxidative stress, with

activated neutrophils releasing excessive ROS that oxidise fibrinogen and contribute to the formation of lysis-resistant clots (22). Therefore, our finding that specific intestinal manifestations independently predict DVT is biologically consistent with this proposed pathobiological sequence. Notably, emerging clinical evidence suggests that butyrate-rich diets or oral butyrate supplementation may reduce intracellular leukocyte ROS production and improve fibrin susceptibility to lysis in patients with BD (23). Although these findings require validation in larger cohorts, they support the possibility that identifying intestinal disease activity via clinical coding may help identify patients who could potentially benefit from microbiota-targeted or dietary interventions. Modulating the gut environment may therefore represent a promising non-pharmacological adjunctive strategy to attenuate the ROS-mediated thrombo-inflammatory cascade and mitigate thrombotic risk in BD. Clinical phenotypes of BD exhibit geographical variations, with intestinal involvement being more prevalent in East Asia and vascular involvement predominating in the Mediterranean and Middle Eastern regions (5, 24, 25), our study design directly addressed this confounding. Although race/ethnicity was balanced in our PSM models, geographic origin often served as a surrogate for unmeasured genetic factors (such as regional variations in HLA-B51 positivity rates) or diagnostic thresholds (24).

Notably, phenotype clustering studies in BD yielded conflicting results regarding gastrointestinal and vascular lesions. Nationwide registry and cohort studies in Japan demonstrated co-clustering of gastrointestinal and vascular manifestations (26, 27). Conversely, large cohort studies from China identified gastrointestinal and vascular manifestations as distinct, non-overlapping phenotype clusters (28, 29). These discrepancies across East Asian cohorts underscore subtle population-level genetic variations or sub-phenotypic heterogeneity. Our findings from a global cohort demonstrated that active intestinal mucosal inflammation and systemic hypercoagulability are clinically linked across diverse patient popula-

tions, emphasising the need to monitor DVT risk in patients with intestinal BD regardless of region.

The utilisation of the multicentre Tri-NetX database enhances the generalisability of our findings to a broad real-world population of patients with BD. By examining these relationships in a large longitudinal cohort, our study refines current risk stratification paradigms and underscores the importance of phenotypic granularity in the personalised management of BD. Managing DVT in BD remains uniquely challenging and requires a careful balance between controlling vascular wall inflammation and preventing clot propagation (5, 8, 9). Our study identifies specific phenotypes associated with markedly elevated risk and provides an evidence-based framework for risk stratification. Patients with APS, a history of thrombophlebitis, or specific patterns of intestinal involvement may warrant closer monitoring. Because our analysis accounted for both primary and recurrent events, these clinical markers may be relevant not only for primary prevention but also for long-term secondary prophylaxis of DVT in BD.

Study limitations

This study has some limitations. First, as with any database study relying on ICD-10 codes, there is a possibility of misclassification or underreporting of clinical manifestations. However, the use of a large-scale global network and PSM helped mitigate baseline imbalances. Second, the diagnosis of APS may be subject to detection bias, as antiphospholipid antibodies are more likely to be tested following a DVT event. To address this concern, we performed a 90-day landmark analysis that excluded events occurring during the initial diagnostic period. The fact that APS maintained a markedly elevated hazard ratio (aHR 5.10) even after this exclusion suggests that the association is robust and not merely a consequence of post-thrombotic testing. Similarly, although a history of thrombophlebitis showed a lower aHR in the landmark analysis, its persistent significance (aHR 2.50) underscores its value as a long-term predictor. Third,

although we adjusted for major confounders, including glucocorticoid use and obesity, the database did not allow for a precise calculation of cumulative glucocorticoid dosages or treatment durations. Additionally, data on other treatments, such as immunosuppressants and anticoagulants, were not fully integrated into the matching process, which may have influenced the absolute risk estimates. Forth, due to the inherent nature of the electronic health record database, some clinical manifestations of BD (such as oral or genital ulcers) may have been under-reported or under-coded, as clinicians often document only the primary diagnosis of BD (ICD-10: M35.2) for billing purposes rather than coding every individual symptom. Finally, although the TriNetX database provides a global perspective, the clinical granularity regarding the severity of organ involvement was limited by the nature of EHRs. Despite these limitations, the magnitude and consistency of the hazard ratios observed for specific phenotypes support their potential utility in DVT risk stratification in BD.

In conclusion, we identified specific clinical phenotypes, particularly APS and a history of thrombophlebitis, as the strongest predictors of DVT in patients with BD. The risk associated with these factors remained elevated even after the initial diagnostic period, suggesting an enduring prothrombotic state. These findings provide a robust evidentiary basis for phenotype-based risk stratification. Implementing intensive monitoring and personalised preventive strategies for patients exhibiting these high-risk phenotypes may help reduce the burden of venous thromboembolism in BD.

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