Thrombophilia work-up and clinical outcomes in Indian patients with unprovoked venous and arterial thrombosis aged 18-50 years

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ABSTRACT

Background: The prevalence of thrombophilia in patients with unprovoked thrombotic events varies across populations, justifying the need for region-specific data to guide appropriate testing strategies.

Methods: This study included patients aged 18-50 years presenting with unprovoked venous thrombosis (VT), arterial thrombosis (AT), or combined thrombotic events at an Indian tertiary care center between January 2018 and January 2022. Clinical characteristics and results of the thrombophilia evaluation were analyzed.

Results: A total of 226 patients were analyzed, of whom 160 (70.7%) had VT, 53 (23.4%) had AT, and 13 (5.7%) experienced combined thrombotic events. A positive thrombophilia work-up was observed in 33.2% of VT cases and 20.1% of AT cases. Antiphospholipid antibody syndrome (APS) was the most frequent abnormality detected, whereas inherited thrombophilia was less common. In VT patients, pulmonary involvement was significantly associated with positive thrombophilia results (p=0.04).

Conclusions: These findings support a selective approach to thrombophilia testing in patients with unprovoked VT, in line with current guideline recommendations, and highlight APS as the predominant thrombophilic abnormality in this population.

Key words: antiphospholipid antibody; inherited thrombophilia; thrombosis.

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Introduction

Thrombophilia refers to a specific spectrum of disorders of the hemostatic system that predispose individuals to thrombosis, which is broadly categorized as either inherited or acquired.[1,2] The inherited thrombophilia may primarily arise from genomic defects that impede the natural anticoagulant pathways or augment the procoagulant activity.[3] The most predominant inherited defect is the factor V Leiden (FVL) mutation followed by the prothrombin G20210A mutation and deficiencies of protein C, protein S and antithrombin.[4]

Acquired thrombophilia encompasses a heterogenous group of conditions including antiphospholipid antibody syndrome (APS), malignancy, pregnancy, obesity, chronic inflammatory disorders and medication induced prothrombotic states. Among the aforesaid conditions, APS is recognized to be the most clinically significant , showing a well-established link to both venous and arterial thrombotic events.[5]

The international guidelines, especially those of the American Society of Haematology (ASH) advocate a selective strategy for thrombophilia testing. Routine testing is not advised for all patients having venous thromboembolism (VTE).[6] Instead, it is generally considered in particular situations including unprovoked VTE in patients younger than 50 years, thrombosis occurring in uncommon sites like the cerebral or splanchnic veins or in patients with frequent thrombotic events.[7] This circumstance justifies the limited clinical utility of thrombophilia testing in arterial thrombosis where the management is usually guided by cardiovascular risk factors.

The distribution followed by the prevalence of thrombophilia

markers differ significantly across the populations,[1] and the majority of the epidemiological data are primarily derived from Western Cohorts, while the evidence from South Asian countries remains limited. In Indian scenario, where specialized coagulation assays are constrained and the cost for the testing remaining high, investigating the pattern of local prevalence pattern is critical and vital to guide a high yield, cost effective and evidence-based approach. Such data can inform the prioritization of the specific assays and improves the secondary prevention strategies, thereby clearing the way towards genetic counselling for high-risk families.

The present study examined the prevalence of common inherited thrombophilia markers deliberately excluding methylenetetrahydrofolate reductase (MTHFR) polymorphisms, which are not recommended for routine testing given their controversial and limited clinical relevance.

While recognizing that thrombophilia screening has restricted clinical utility for arterial disease, the inclusion of such cases in this analysis offers an extensive epidemiological perspective of local thrombotic disease patterns across India. By positioning these regional findings towards the international data, the present study does not seek to modify the existing international guidelines but rather to complement them by supporting the development of locally adapted, resource sensitive strategies for thrombophilia testing.

Methods

Data of patients aged 18 to 50 years, who had previously undergone a thrombophilia work-up at our center since January 2018, for unprovoked venous or arterial thrombosis or both were extracted from the hospital medical records. Clinical outcomes of these patients during the first six months following the thrombotic event were assessed through telephonic interviews. New patients attending the Outpatient Department or admitted at the center from November 2020 till January 2022 were enrolled prospectively, after obtaining an informed consent. The clinical details along with the demographic information and relevant risk factors were systematically recorded with the standardized form to ensure uniform data collection.

In the prospective cohort, the patients underwent a thorough and comprehensive evaluation for thrombophilia. The work-up consisted of screening for anti-nuclear antibody (ANA) and antiphospholipid antibody (APLA) panel. The APLA panel,[8] comprised the anti-β2 glycoprotein antibodies (IgG and IgM), anti-cardiolipin antibodies (IgG and IgM) and testing for lupus anticoagulant, the latter only if the patient had not yet been initiated on anticoagulation therapy. ANA testing was removed from the revised analysis in accordance with the international recommendations. If the initial thrombophilia work-up was found to be negative, patients underwent further additional tests, which included factor V Leiden mutation and prothrombin gene mutation. The serum homocysteine levels were assessed in selected cases. Tests for protein C, protein S and antithrombin were performed only in patients evaluated outside the acute thrombotic phase after discontinuation of anticoagulant therapy.

In the retrospective cohort, thrombophilia work-up reports including APLA profile, protein C, protein S and antithrombin levels, mutational analysis for factor V Leiden and prothrombin gene were extracted from the hospital records when available. MTHFR mutation data together with homocysteine levels were excluded from the present analysis as per current guideline recommendation. Thrombophilia testing was performed for patients with arterial thrombosis who lacked traditional cardiovascular risk factors and in whom no clear etiology could be identified.

APS was defined according to the revised Sapporo criteria.[9] Positive anticardiolipin antibody test was defined as a IgG and/or IgM titer more than >/= 40 GPL or MPL/ml. A positive anti- β2 glycoprotein antibody test was defined IGG and /or IGM isotype at levels above 99th percentile. Lupus anticoagulant positivity was defined by the presence of a moderate to strong positive test in an activated partial thromboplastin assay (APTT) based assay. Protein C and antithrombin were assayed using functional chromogenic assays, while protein S was measured as free protein S level by an immune turbidimetric assay. Levels of protein S <60%, protein C <70% and antithrombin <80% were defined as deficiencies.[10]

Work-up for myeloproliferative neoplasm (MPN) using molecular studies and for paroxysmal nocturnal hemoglobinuria (PNH) using flow cytometry was performed in selected patients from the prospective cohort with thrombosis in splanchnic circulation and associated hematological abnormalities.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, IL, USA). The continuous variables are presented as mean±SD or in median (min-max) as appropriate. The categorical variables are expressed as frequencies and percentages. The associations between categorical variables were assessed using the Pearson Chi-Square test. The comparisons of continuous variables between two groups were performed using the Independent sample *t*-test. All statistical tests were two tailed and *p*-value <0.05 was considered as statistically significant.

Table 1. Baseline characteristics of patients with venous thrombosis (n=160).

Age in years, mean ±SD	36.6±8.5
Males:females	106:54
Site of thrombosis, n (%)	
Pulmonary embolism with deep vein thrombosis	43 (26.9%)
Isolated pulmonary embolism	41 (25.6%)
Cerebral venous thrombosis	31 (19.4%)
Multiple venous sites in combination	22 (13.7%)
Abdominal veins	13 (8.1%)
Deep vein thrombosis	10 (6.2%)
Positive family history	5 (3.1%)
Atypical venous sites	44 (27.5%)
Recurrent thrombosis	62 (38.7%)
Bleeding events	
Total	48 (31.6%)
3 months	12
6 months	8
Death	
Total	9 (5.9%)
3 months	1
6 months	2
Comorbidities	
Smoking	10 (6.3%)
Diabetes	6 (3.8%)
Hypertension	9 (5.6%)

Atypical venous sites include abdominal veins and other uncommon sites.

Table 2. Thrombophilia work-up details in venous thrombosis (n=160).

Thrombophilia testing	Positive, n (%)	Tested, n (%)	Not tested, n
Anti-cardiolipin antibodies (IGG or IGM)	22 (14%)	157 (98.1%)	3
Anti-β2 glycoprotein antibodies (IGG or IGM)	20 (13.2%)	131 (94.3%)	9
Lupus anticoagulant	23 (18.9%)	122 (76.2%)	38
APLA positive, total	33 (20.6%)	160 (100%)	0
Triple positive APLA	15 (9.4%)	113 (70.6%)	47
Protein C deficiency	1 (1.6%)	62 (39%)	98
Free Protein S deficiency	7 (10.9%)	64 (40%)	96
Antithrombin deficiency	3 (6%)	50 (31.2%)	110
Factor V Leiden mutation (heterozygous)	8 (9.1%)	88 (55%)	72
Prothrombin gene mutation (heterozygous)	1 (1.3%)	77 (48.1%)	83
Inherited thrombophilia, total	20 (12.5%)		

APLA, antiphospholipid antibody.

Results

A total of 226 patients with venous, arterial thrombosis or combined thrombosis were included in the present study. Of these, 160 (70.7%) patients had isolated venous thrombosis, 53 (23.4%) patients had isolated arterial thrombosis and 13 (5.7%) patients experienced both arterial and venous events.

Venous thrombosis

Among the 160 patients with venous thrombosis, 106 (66.2%) were male and 54 (33.8%) were female. The mean age at onset was reported to be 36.6 years. The most frequent sites of involvement were the lower limb veins and pulmonary vasculature either alone or in combination observed in 94 patients (58.7%). Cerebral venous thrombosis was identified in 31 patients (19.4%), while abdominal venous involvement and multiple venous territories were less frequent (Table 1). The number of venous sites per each patient ranged from 1 to a maximum of 4.

A positive etiological work-up was obtained in 53 patients (33.2%). Positive APS work-up was identified in 33 patients (20.6%), with lupus anticoagulant positivity being the most common abnormality (18.9%). Non-criteria antibodies, such as IgA anti-β2 glycoprotein, were detected in 13 patients (8.9%), and 15 patients had triple APLA positivity. Two of these patients also fulfilled the American College of Rheumatology criteria for systemic lupus erythematosus (SLE). Inherited thrombophilia was identified in 20 patients (12.5%) (Table 2). Factor V Leiden mutation was found in 8 patients (9.1% of 88 tested), protein S deficiency in 7 patients (10.9% of 64 tested), and antithrombin deficiency in 3 patients (6% of 50 tested). One patient had protein C deficiency and one had prothrombin gene mutation.

The most common comorbidities in this group were diabetes mellitus (5.6%), hypertension (3.7%), family history of venous thrombosis (3.1%), and chronic liver disease (3.1%). Recurrent venous thrombotic events occurred in 62 patients (38.8%). Vitamin K antagonists remained the predominant choice for long-term anticoagulation in 110 patients (69%).

Arterial thrombosis

Among 66 patients with arterial thrombosis, 53 had isolated arterial events, and 13 had combined arterial and venous thromboses. Of these, 43 (65.1%) were men and 23 (34.8%) were women, with a mean age of 36.3 years. The majority of arterial events were ischemic strokes (53%). Other affected sites included intracardiac thrombi, coronary artery, aorta, subclavian, femoral, popliteal, radial, and ulnar arteries, as well as splenic and renal arteries (Table 3).

A positive etiological work-up was identified in 14 patients (20.1%) (Table 4). Positive APS work-up was found in 7 patients (10.6%), of whom three had triple positivity. Inherited thrombophilia was found in 6 patients (9.5%), including factor V Leiden mutation (n=2), protein S deficiency (n=2) and antithrombin deficiency (n=2).

Vascular risk factors included diabetes mellitus in 16 patients

Table 3. Baseline characteristics of patients with isolated arterial thrombosis (n=53) and combined with venous thrombosis (n=13).

Age, mean	36.3 years
Males:females	43:23
Site of arterial thrombosis, n (%)	
Central nervous system	35 (53%)
Peripheral arteries	8 (12.1%)
Coronary artery disease	5 (7.6%)
Arterial sites in combination	4 (6.1%)
Intracardiac	1 (1.5%)
Combined arterial with venous thrombosis	13 (19.7%)
Positive family history	5 (7.6%)
Recurrent thrombosis	21 (31.8%)
Bleeding events	
Total	9 (13.6%)
3 months	3
6 months	1
Death	
Total	4 (6%)
3 months	1
6 months	1
Comorbidities	
Smoking	3(4.5%)
Diabetes	8(12.1%)
Hypertension	16(24.2%)

(24.2%), hypertension in 8 (12.1%), smoking in 3 (4.5%), and family history of arterial thrombosis in 5 (7.6%). Recurrent arterial events were noted in 21 patients (31.8%).

Combined arterial and venous thrombosis

Of the 13 patients with combined arterial and venous thrombosis, 3 (23.1%) had a positive APS work-up. Additionally, one patient had protein S deficiency and factor V Leiden mutation.

Factors associated with thrombophilia

Clinical correlates of positive thrombophilia work-up were assessed using Pearson's chi-square test. In patients with venous thrombosis, the site of thrombosis was significant, with pulmonary circulation involvement showing significant association with a positive thrombophilia work-up with p-value of 0.04 (Table 5). No similar clinical correlates were identified in patients with AT.

Follow-up outcomes

The median follow-up duration for the cohort was 30 months. During the aforesaid period, 58 patients (28.1%) experienced bleeding complications associated with the anticoagulation therapy. Of them, 15 patients (7.2%) and 9 patients (4.3%) were reported to develop bleeding manifestations within 3 months and 6 months of therapy initiation respectively. Among the 206 patients with complete follow up details, 13 patients (6.3%) had died.

Table 4. Thrombophilia workup details in arterial and combined arterial and venous thrombosis (n=66).

Thrombophilia testing	Positive, n (%)	Tested, n (%)	Not tested, n
Anti-cardiolipin antibodies (IGG or IGM)	3 (5%)	60 (90.9%)	6
Anti-β2 glycoprotein antibodies (IGG or IGM)	3 (5%)	60 (90.9%)	6
Lupus anticoagulant	5 (9.2%)	54 (81.8%)	12
APLA positive, total	7 (10.6%)	65 (98.5%)	1
Triple positive APLA	3 (5%)	44 (66.6%)	22
Protein C deficiency	—	30 (45.4%)	36
Free protein S deficiency	2 (6.7%)	30 (45.4%)	36
Antithrombin deficiency	2 (8.3%)	24 (36.3%)	42
Factor V Leiden mutation (heterozygous)	2 (5.1%)	39 (59%)	27
Inherited thrombophilia, total	6 (9.5%)		

APLA, antiphospholipid antibody.

Table 5. Factors associated with positive thrombophilia workup in venous thrombosis.

Venous thrombosis Patient characteristics		Thrombophilia work-up				*p*-value
		Positive		Negative		
		n	%	n	%	
Sex	Male	31	58.5	75	70.1	0.19
	Female	22	41.5	32	29.9	
Site of thrombosis	Isolated PE	10	18.9	31	28.9	0.04
	CVT	10	18.9	21	19.6	
	DVT	2	3.7	8	7.5	
	PE with DVT	21	39.6	22	20.5	
	Abdominal vein	1	1.9	12	11.2	
	Venous sites in combination	9	16.9	13	12.2	
Atypical venous sites	Yes	10	18.9	34	31.8	0.12
	No	43	81.1	73	68.2	
Family history	Yes	2	3.8	3	2.8	1.0
	No	51	96.2	104	97.2	
Recurrent thrombosis	Positive	26	49.1	36	33.6	0.08
	Negative	27	50.9	71	66.3	
Residual thrombosis	Positive	31	58.5	59	55.1	0.41
	Negative	22	41.5	58	44.9	
Arterial and combined thrombosis Patient characteristics						
Sex	Male	9	69.2	34	68	0.98
	Female	4	30.8	19	32	
Recurrent thrombosis	Yes	5	38.5	16	30.2	0.80
	No	8	61.5	37	69.8	

Thrombosis in the pulmonary circulation showed a statistically significant association with a positive thrombophilia workup in patients with venous thrombosis (p=0.04).
PE, pulmonary embolism; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis.

Discussion

The present study examined the prevalence of inherited and acquired thrombophilia in patients presenting with venous, arterial, or combined thrombotic events, and further explored clinical factors associated with a positive thrombophilia work-up. Understanding these associations is clinically important, as, although current guidelines emphasize that thrombophilia testing does not typically alter the initial choice or intensity of anticoagulation in VTE, results may guide decisions regarding extended therapy in selected high-risk groups, particularly those with severe inherited thrombophilia.[11]

Venous thrombosis

Deep venous thrombosis and pulmonary embolism were the most frequent presentations in our cohort. Similar observations were made in agreement with earlier reports.[12,13] Cerebral venous thrombosis (CVT) and splanchnic vein thrombosis were also encountered, highlighting the diverse spectrum of venous thrombosis in younger patients.[14]

About one- third of the patients in our cohort had a positive thrombophilia work-up which was comparable to the prevalence reported earlier by Mishra *et al*. (34%) in a North Indian cohort, after excluding increased fibrinogen levels which was considered a thrombophilia factor in their study.[15]

APS emerged as the most frequent acquired thrombophilia, detected in 20.6% of venous thrombosis cases. This prevalence is consistent with international studies,[13] and with the limited data available from Indian cohorts.[16] Notably, some patients with APS also demonstrated coexisting inherited thrombophilia, reinforcing prior evidence of an additive risk. The inherited thrombophilia was detected and reported in 12.5% of venous thrombosis with factor V Leiden, protein S deficiency, and antithrombin deficiency being the most common abnormalities. These findings were consistent with reports from other Asian cohorts,[17] and in some Caucasian populations.[18] Notably, some of the patients had multiple thrombophilic abnormalities and this underlines the importance of a thorough and targeted work-up under suitable clinical settings.

Arterial thrombosis

Stroke was the most common arterial event in this study, followed by peripheral arterial and coronary thromboses. A positive thrombophilia work-up was documented in 20.1% of arterial cases. APS was detected in 10.6%, a proportion somewhat lower than in larger case-control studies of stroke and myocardial infarction.[19] The role of APS in arterial thrombosis remains a subject of debate, with evidence varying across cohorts.[20]

Inherited thrombophilia was identified in 9.5% of arterial events, most often factor V Leiden mutation, protein S and antithrombin deficiencies. While these abnormalities are classically associated with venous disease, our findings are in line with previous reports suggesting that inherited thrombophilia may confer a modest but measurable increase in the risk of arterial events.[21,22]

Hyperhomocysteinemia

A substantial number of patients demonstrated elevated homocysteine levels, frequently in association with vitamin B12 deficiency. Although earlier studies suggested a strong causal link between hyperhomocysteinemia and thrombosis,[23] more recent analyses argue that it may represent a confounding marker rather than an independent risk factor.[24] Consistent with these interpretations, we did not consider hyperhomocysteinemia as a primary risk factor in our analysis, however many patients exhibited vitamin B12 deficiency, which may contribute indirectly to the elevated homocysteine levels and warrants clinical attention, specifically in younger patients with unprovoked events. Although findings from studies,[25] have unveiled a prominent relationship between hyperhomocysteinemia and thrombotic risk, we propose that elevated homocysteine may serve as a marker of underlying nutritional deficiency rather than an independent risk factor for thrombosis. From Indian context, where dietary patterns and socioeconomic factors significantly contribute to a higher prevalence of vitamin B12 deficiency,[26] the reported findings justifies the importance of assessing and correcting nutritional deficiencies as part of a comprehensive thrombotic risk evaluation, specifically in younger patients with unprovoked events.

Factors associated with a positive thrombophilia work-up

Pulmonary embolism was significantly associated with a positive thrombophilia profile, consistent with the findings of Obaid *et al*.[27] Conversely, thrombosis at atypical sites such as CVT and splanchnic veins showed no association with a positive work-up, reflecting the multifactorial pathogenesis of thrombosis in these locations.[28] Current guidelines differ in their recommendations for thrombosis at atypical locations (cerebral and splanchnic vein thrombosis) with some advocating selective testing for specific conditions (myeloproliferative neoplasms or paroxysmal nocturnal hemoglobinuria in splanchnic vein thrombosis with hematological features), while others discourage routine thrombophilia evaluation.[6,29]

In our study, recurrent thrombosis was seen in 62% which is slightly higher than the rates reported in previous studies.[30] The median duration of recurrence was 24 months after discontinuation of medications. Nineteen of our patients (8.6%) had recurrent thrombotic events while on therapy. This is in agreement with the findings of Douketis *et al*.[31] who reported a 6% prevalence of recurrence VTE in patients receiving anticoagulation.

In arterial thrombosis, no clinical correlates were found to be significantly associated with a positive thrombophilia work-up.

Follow-up

During a median follow-up of 30 months, 28.1% of patients experienced bleeding complications while on anticoagulation, and 6.3% died. These figures are broadly comparable with outcomes from other prospective thrombosis cohorts, though direct comparisons are challenging given variations in patient populations and inclusion of both arterial and venous events in our study.[32]

Limitations

The present study poses certain limitations. This study was primarily based on retrospective hospital records, which may limit completeness. Thrombophilia testing was not fully standardized and hence it may result in some incomplete procoagu-

lant work-ups. The relatively small number of patients with arterial thrombosis limits statistical power; hence the related results can be considered only descriptive.

Conclusions

The results of the present study suggest that both the inherited and acquired thrombophilia may play a prominent role in unprovoked thrombotic events within Indian population. The elevated diagnostic yield in venous compared to arterial thrombosis, together with the predominance of APS and certain specific inherited defects including factor V Leiden and protein S deficiency align with the earlier patterns reported across other populations and offers significant regional inferences. The reported findings illustrate the significance of selective and context driven strategy to thrombophilia testing. Careful implementation of current guidelines in clinical practice can balance diagnostic value in a cost-effective manner, while further large-scale studies are required to refine the proposed testing strategies across the South Asian direction.

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