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Clinical and demographic predictors of thrombophilia among patients with venous thromboembolism: Data from a large referral center

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Abstract

Clinical and demographic predictors of thrombophilia among patients with venous thromboembolism: Data from a large referral center

By Zoë Wickham

Purpose: To develop a predictive model to identify factors associated with a positive thrombophilia workup.

Background and Rationale: The term 'thrombophilia' describes a group of intrinsic conditions that increase likelihood of blood clot formation. Testing is expensive and subject to misinterpretation if reviewed by a physician unfamiliar with hypercoagulable states. There remains considerable uncertainty on who should be tested and how thrombophilia status should inform clinical management of VTE.

Methods: With a sample of 345 patients treated for their first documented VTE event between January 2011 and December 2015 at Emory University Hospital, a series of logistic regression models were constructed to examine factors associated with positive thrombophilia status. We used a hierarchical backwards elimination approach to reduce the model to variables independently associated with a positive outcome, one more stringent with a cut-off of p-value of ≤ 0.1 and then another less stringent with a p-value cutoff of ≤ 0.25. Both models were examined for the presence of two-way interactions and collinearity. The results of all final models were expressed as multivariable adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI). Predictive value of the models was assessed by calculation of a c-statistic.

Results: The following variables were the strongest predictors within both models: sex (OR=2.24), race (specifically African American vs. White, OR =0.46), family history of hypercoagulable state (OR=45.2), active malignancy (OR=0.11), and liver disease (OR=2.49). The calculated c-statistic was 0.758 for model 1 and 0.761 for model 2.

Discussion: In this study, the strongest predictors in both logistic models were sex, race, active malignancy, and liver disease. Current testing guidelines instruct physicians to test patients in situations of unprovoked VTE, VTE is in an unusual site, strong family history of thrombotic disease, or patients' preference. This study was limited by its small sample size but despite this, the results of this paper suggest that guidelines for testing can be enhanced by considering additional clinical factors.

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Clinical and demographic predictors of thrombophilia among patients with venous thromboembolism: Data from a large referral center

A thesis by Zoë Wickham

Chapter I: *Introduction and Rationale:*

Venous thromboembolism (VTE), is a condition caused by a blood clot that has formed in a vein; it must be treated quickly with anticoagulant treatment after clinical diagnosis. VTE affects 300,000 to 600,000 Americans each year and each time a patient develops a VTE, whether it be a deep vein thrombosis (DVT) or pulmonary embolism (PE), they must be evaluated by a physician in order to determine anticoagulation treatment and duration of treatment (Beckman, Hooper, Critchley, & Ortel, 2010). Thrombosis, venous or arterial, can occur from many factors and potentiate each other, creating an additive effect (Stephan, 2015).

Factors influencing risk of VTE can be categorized as environmental or intrinsic (Bauer, 2003). Environmental factors include diseases such as cancer or nephrotic syndrome, as well as surgery, prolonged immobilization, hormonal therapy, and pregnancy (Bauer, 2003). The term 'thrombophilia' describes an intrinsic condition that confers high risk of VTE due to an inherited or acquired disorder of hemostasis, and it is now possible to identify inherited and acquired thrombophilia traits by a comprehensive laboratory panel. (Meyer et al., 2016).

At this time, treatment for thrombosis is based on clinical presentation, provoking factors, and risk of bleeding, and not on thrombophilia status (Meyer et al., 2016). Although current guidelines do not take into consideration the presence or absence of a thrombophilia, physicians often test for these to determine an underlying cause of clot formation (Meyer et al., 2016). Currently, there is a lack of data on the characteristics of patients with thrombophilia and there is considerable uncertainty on how thrombophilia status should inform clinical management of VTE (Bauer, 2003).

Thrombophilia screening, generally performed after a thromboembolic event, is a comprehensive evaluation that is based on personal and family history, clinical presentation, and laboratory diagnostics (Colucci & Tsakiris, 2020). Since most thrombophilia traits lead to a VTE in the presence of a provoking factor, such as smoking or hormonal use, it is important to understand the possible independent and joint effects of both intrinsic and environmental factors on the risk and clinical course of these conditions. Some associated risk factors of VTE include age, family history of VTE, active malignancy, hormonal therapy, surgery, trauma, obesity, pregnancy, congestive heart or respiratory failure, immobilization, and inherited or acquired thrombophilia conditions. Laboratory screening is not appropriate in every case of VTE and creating a clinical predictive model will make this process more cost-effective, without compromising the quality of clinical evaluation.

In this study, we investigate the clinical characteristics of patients with VTE to identify clinical factors associated with a positive diagnostic work-up for thrombophilia. The long-term goal of this work is to develop a predictive clinical model that will aid in determining the need for a thrombophilia work-up in patients who present with VTE. Identifying characteristics of individuals who have historically tested positive for a thrombophilia trait testing will help physicians better identify those patients that are likely to benefit from such a work-up and hopefully restrict the current practice of universal screening and reduce cost associated with care of patients with clots.

Definition of terms:

Antithrombin deficiency (AT) – An inherited thrombophilia trait. Antithrombin is a substance in the blood that plays a role in limiting blood clots and is a primary inhibitor of clotting factors, factor Xa and factor IIa.

Antiphospholipid syndrome (APLAS) – An autoimmune disorder as well as a major acquired thrombophilia in which vascular thrombosis and/or pregnancy losses occur in the presence of anti-phospholipid antibodies.

Deep Vein Thrombosis (DVT) – a condition when a blood clot forms in a deep vein, usually within an extremity.

Factor V Leiden mutation (FV) – An inherited thrombophilia trait caused by a mutation in the F5 gene (an important clotting factor).

Hypercoagulable state – synonym for thrombophilia, a medical term for a condition in which there is an abnormally increased tendency toward clotting.

Inpatient – Care given within a hospital admission normally lasting over 24 hours.

Outpatient – Care given at a medical facility or clinic without hospital admission.

Protein C deficiency (PC) - An inherited and acquired thrombophilia trait caused by mutations in the PROC gene or decreased synthesis/ increased loss due to an acquired condition such as liver disease/ kidney disease.

Protein S deficiency (PS) - An inherited and acquired thrombophilia trait caused by mutations in the PROS1 gene or decreased synthesis/ increased loss due to an acquired condition such as liver disease/ kidney disease.

Prothrombin mutation (PT) - An inherited thrombophilia trait caused by a mutation in the prothrombin (Factor II) gene. People with this mutation produce more prothrombin protein than is normal and increases their tendency for clotting.

Provoking factors – Known environmental risk factors that are associated with VTE.

Pulmonary embolism (PE) – a condition when a clot has traveled through the blood stream into the lungs.

Race – Subjects were characterized by the race they identified as in their electronic medical record. These are discussed in the following terms: African American, Asian, Hispanic, White, and "Race not specified".

Smoker Status – Subjects were characterized by a social history of smoking as either a "current smoker", a "former smoker", or as a "never smoker".

Unprovoked – When characterizing a clot, an unprovoked or idiopathic clot is one that has arisen spontaneously or for which the cause is unknown.

Venous Thromboembolism (VTE) - a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

Chapter II: ***Background & Review of the Literature***

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are subsets of venous thromboembolism (VTE). They are common and potentially lethal conditions that affect a wide portion of the population, inpatient and outpatient (Wells, Forgie, & Rodger, 2014). VTE recur frequently and can result in long-term issues. PE was found to the be the third most common cause of hospital-related death but it is also one of the most preventable conditions (Gjonbrataj et al., 2017). Some of the associated risk factors for VTE are: age, family history of VTE, active malignancy, hormonal therapy (such as hormone replacement therapy and oral contraception), immobilization (such as long travel or hospitalization), surgery, trauma, obesity, pregnancy, congestive heart or respiratory failure, and inherited or acquired coagulation conditions (Gjonbrataj et al., 2017). VTE among patients who do not possess any of these risk factors are regarded as "unprovoked" incidents (Wells et al., 2014).

Thrombophilia occurs from an imbalance of natural coagulants and anti-coagulants in the blood. Some result from deficiencies in natural anticoagulants such as antithrombin, protein C and protein S (Stephan, 2015). This leads to enhanced thrombin formation or hypercoagulability. Other types of thrombophilia result from increased level of clotting factors, polymorphism, or an autoimmune disorder (Khan & Dickerman, 2006). And as you can see from looking at this table 1, these traits are relatively rare. Recent studies have made it possible to identify acquired and hereditary risks factors in some patients that present with VTE (Bauer, 2003). A panel of tests is used to identify thrombophilia traits among thrombosis patients and includes tests for: Factor V Leiden mutation (FV), Protein C deficiency (PC), Protein S deficiency (PS), Anti-thrombin deficiency (AT), Prothrombin mutation (PT), and Antiphospholipid syndrome (APLAS). As mentioned before, even in those with thrombophilia, clots can be instigated by "provoking factors" like surgery, pregnancy, cancer therapy, or immobilization but occasionally, these factors expose a previously undetected or unknown hypercoagulable state (Bauer, 2003).

The first hypercoagulable disorders to be fully characterized in the clinic were AT, PC and PS (White, 2009). The proteins affected by these condition are known to play an important role in blood coagulation and can be measured in patients with VTE (White, 2009). Hematologists have found that genetic variants resulted in type I deficiencies (decreased production) and type II deficiencies (abnormal function). Discovery of the factor V Leiden and prothrombin G20210A mutations resulted in many more patients being identified as having a VTE that could be attributed to a hereditary thrombophilia (Bauer, 2003). Currently, thrombophilia traits that are associated with a higher risk of thrombosis are Antiphospholipid syndrome, Anti-thrombin deficiency, Protein S deficiency, and Protein C deficiency (Hirmerova, Seidlerova, Subrt, & Slechtova, 2014). Hereditary thrombophilia does not pose the same risk of VTE. Those associated with only a mild risk of VTE are Factor V Leiden and Prothrombin mutations (Bertolettiakl et al., 2018; Hirmerova et al., 2014). Table 1 describes the global incidence of thrombophilia (White, 2009).

Summary of Current Problem and Study Relevance

When a patient is admitted with a documented VTE the following question is raised: *should* the patient be tested for a potential hypercoagulable inherited or acquired state? There are arguments in favor of testing all patients with unprovoked thromboses, arguments in favor of not testing at all, and arguments that advocate for select testing (Meyer et al., 2016). There is little consensus on who should be tested for thrombophilia but there are legitimate reasons for thrombophilia testing in patients that have presented with a thrombotic event (Stephan, 2015). Some reasons to test a patient are: 1) a patient's wish to understand why they have had a thrombotic event, 2) predicting the likelihood of a recurrent thrombosis and thus understanding how long to prescribe an anticoagulant, and 3) to understand any family implications and be able to detect any asymptomatic carriers of a thrombophilia trait (Stephan, 2015). Current guidelines for testing have significant limitations as they tend to be vague or overly general, and often not helpful in specific clinical situations. This is a highly contentious issue because identification of a thrombophilia trait or traits may not affect the patient's anticoagulation treatment plan. Testing is

expensive and subject to misinterpretation if reviewed by a physician unfamiliar with hypercoagulable states. Even with the current state of knowledge, there is still uncertainty and disagreements amongst hematologists about how information regarding presence or absence of thrombophilia in a patient should be used in treatment of VTE.

Chapter III: *Methodology*

Research Design

This is a single center retrospective study designed to identify which demographic and clinical factors may predict a positive thrombophilia testing result. The study represents an analysis of a clinical database maintained by the Emory University, Department of Hematology.

Study Sample

The analysis dataset includes patients over 18 diagnosed with and/or treated for their first documented VTE event between January 2011 and December 2015 at hematology clinic or inpatient hematology consult service of Emory University Hospital. The electronic data were supplemented by a detailed chart review to collect information on patients' demographic and clinical characteristics including age, gender, body mass index, race, habits and pertinent co-morbidities amongst others. Detailed information regarding VTE history, treatment, potential provoking factors and results of thrombophilia evaluation, was also collected, if available. All data were extracted from electronic medical records and recorded in a pre-designed study-specific case report form. Identifying information was removed and each subject was assigned a unique project identifier. The Emory IRB has approved this study and all study staff involved.

Statistical Analysis

Excel was used for database management and for statistical analysis, data were exported into SAS software 9.3. Using this clinical database, we compared two groups: patients who were diagnosed with their first VTE that tested positive for a thrombophilia trait and those with VTE that were found negative. Our goal was to create predictive models and identify one or two models with the best fit.

Chapter IV: ***Data analysis***

The data analysis involved a comparison of two groups of patients diagnosed with their first VTE: those with evidence of thrombophilia and those with a negative thrombophilia workup. The two groups under investigation were described with respect to the distributions of the demographic and clinical factors of interest using means and standard deviations (SD) for normally distributed continuous variables, medians and interquartile ranges (IQR) for skewed variables and counts and percentages for categories variables. Initial analyses involved a crude comparison of these distributions among thrombophilia positive patients and the thrombophilia negative group (reference) using t-tests, Mann-Whitney tests, chi-square tests, and Fisher's exact test as appropriate.

A series of logistic regression models were constructed to examine factors associated with positive thrombophilia status. The initial models included all variables of clinical interest: sex, race, BMI, age, family history of VTE, family history of hypercoagulable state, provoked VTE, smoker status, surgery, prolonged nonsurgical hospitalization/ immobilization, active malignancy in last 2 years, liver disease, indwelling venous catheter, and visceral clot. Using backwards elimination, we reduced the model to variables independently associated with the outcome. The backwards elimination was carried out using two cutoffs: the more stringent model that only retained variables associated with a p-value of ≤ 0.1, and an alternative model that used the p-value cutoff of ≤ 0.25. All models were examined for the presence of two-way interactions and collinearity. The results of all finals models were expressed as multivariable adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI). Predictive value of the models was assessed by calculating a c-statistic.

Chapter V: *Results*

From the pooled database of 345 patients with validated first VTE, 73 were positive for a thrombophilia. Factor V Leiden (36%) and antiphospholipid syndrome (28%) were the most commonly detected thrombophilia types. The characteristics of the study population are shown in Table 2.

A comparison of distributions across the two study groups demonstrated significant or borderline significant differences with respect to gender ($p = 0.034$), race ($p = 0.005$), hypercoagulable state in the family ($p < 0.001$), unprovoked VTE ($p = 0.057$), active malignancy within 2 years ($p = 0.058$), and liver disease ($p = 0.059$).

Table 3 reports the results for the two models, created using different cutoff criteria for backwards elimination; 0.25 for Model 1 and 0.1 for Model 2. After backwards elimination, sex, BMI, race, family history of hypercoagulable state, family history of VTE, smoking status, active malignancy in last 2 years, liver disease and indwelling venous catheter were retained in Model 1. Model 2 included the same variables, with the exception of BMI. The following variables were the strongest predictors within both models: sex (OR=2.24), race (specifically African American vs. White, OR =0.46), family history of hypercoagulable state (OR=45.2), active malignancy (OR=0.11), and liver disease (OR=2.49).

The calculated c-statistic was 0.758 for model 1 was c=0.758 and 0.761 for model 2, c=0.761. No significant interactions or collinearities were observed between any of the variables tested.

Chapter VI: *Discussion*

Current thrombophilia general testing guidelines dictate that it is appropriate to test patients with unprovoked VTE, a VTE in an unusual site (such as cerebral, abdominal or in cases where there is both an arterial and venous thrombosis), or strong family history of thrombotic disease (Henry-Bonniota, Côtéb, Yannoutsosc, & Emmerichc, 2020). Identifying additional predictive factors for a positive thrombophilia workup may help physicians more appropriately test VTE patients.

In this study, we aimed to identify clinical determinants of positive thrombophilia testing result. The overall goal was to construct predictive models that may be used to improve identification of VTE patients who require a workup for thrombophilia trait.

We observed that sex, race, active malignancy within 2 years of VTE and liver disease were the strongest predictors in both models. The c-statistic estimates were over 0.7, indicating a "good" predictive ability of the models, although a value of 0.8 or higher would have been preferred (Roy et al., 2017).

Our study has several limitations. First, the sample size of the study is relatively small because the condition of interest is relatively rare and the data were limited to a single clinical center. Two potentially important variables, hormonal therapy and pregnancy, both considered provoking factors of VTE, could not be included in the analysis because that would require restricting the sample to females; thereby further reducing the statistical power.

Second, due to the cross-sectional design of the study the exposures and the outcome of interest were measured simultaneously limiting the inferential value of the model. Additionally, as the sample consisted only of subjects who underwent thrombophilia testing, the models could not be applied to the general population of VTE patients.

Third, it is important to keep in mind the drawback of the backwards elimination approach. As the model eliminates variables one by one, once a variable is removed, it cannot reenter the model. Thus, the final model may not necessarily offer the best possible fit.

Lastly, it remains unclear if the results are expected to replicate in other samples. This is normally done by dividing the data into a testing and validation sets; however, the relatively small sample size prevented us from using this approach.

To build on this research, a prospective longitudinal cohort study would be beneficial. Following VTE patients with and without thrombophilia would allow comparing health outcomes in the two groups. Especially informative would be to include patients whose thrombophilia status was never tested. Observing differences in recurrent VTEs or bleeding events between these two groups could show the benefits of testing over not testing and provide basis for testing guidelines. In general, studies of rare diseases will become easier to carry out with the expanding adoption of electronic health record systems. Access to large clinical datasets may make it possible to build strong clinical predictive models and algorithms to transform healthcare.

To summarize, the present study demonstrated several notable differences between VTE patients with and without evidence of thrombophilia. The models had good predictive strength and although more works needs to be done, our findings suggest that the guidelines for testing could be enhanced by considering additional factors. If these models are refined and extended using data from future prospective studies, the results may be used for updating the management guidelines for patients with VTE.

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Tables:

Table 1. Most Common Thrombophilic Disorders (White, 2009)

Thrombophilic Condition	**Prevalence in the Population**	**Inherited or Acquired**
Factor V Leiden (FV)	3% - 7%	Inherited
Prothrombin Mutation (PT)	1% - 2%	Inherited
Protein C Deficiency (PC)	0.3%	Inherited and acquired
Protein S Deficiency (PS)	0.1%	Inherited
Anti-thrombin deficiency (AT)	0.1%	Inherited and acquired
Antiphospholipid syndrome (APLAS)	1%	Acquired

Table 2. Baseline Characteristics by Thrombophilia Testing Status

	Total (N = 345)	**Positive (N = 73)**	**Negative (N = 272)**	***p*-value**
Age at Evaluation	48.2 (± 15.2)	45.4 (±17)	49 (±14.6)	0.104
Male	156 (45.2)	41 (56.2)	115 (42.3)	**0.034**
BMI	30.5 (±7.7)	29.2 (± 6.1)	30.7 (± 8.1)	0.209
Race				
White	185 (53.6)	49 (67.1)	136 (50)	**0.005**
African American	122 (35.4)	14 (19.2)	108 (39.7)	
Other	38 (11)	10 (13.7)	28 (10.3)	
Smoking status				
Current	30 (8.7)	9 (12.3)	21 (7.7)	0.161
Former	54 (15.7)	7 (9.6)	47 (17.3)	
Never	261 (75.7)	57 (78.1)	204 (75)	
Family History of MI, Stroke or VTE	62 (18)	11 (15.1)	51 (18.6)	0.467
Family History of a Hypercoagulable state	10 (2.9)	8 (11)	2 (0.7)	**<0.001**
Unprovoked VTE	193 (55.9)	48 (65.8)	145 (53.3)	0.057
Visceral Clot	88 (25.5)	19 (26)	69 (25.4)	0.909
Indwelling Venous Catheter	25 (7.3)	2 (2.7)	23 (8.5)	0.094
Prolonged nonsurgical hospitalization/ immobilization	30 (8.7)	5 (6.9)	25 (9.2)	0.528
Recent Surgery	54 (15.7)	8 (11)	46 (16.9)	0.214
Active Malignancy Within 2 years	28 (8.1)	2 (2.7)	26 (9.6)	0.058
Liver Disease	25 (7.3)	9 (12.3)	16 (5.9)	0.059

Table 3: Multivariate Logistic Regression Analysis and Prediction Models Using Backward Elimination

	Model 1 ($p \leq 0.25$)		**Model 2 ($p \leq 0.1$)**	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Male	2.24	1.24, 4.03	2.27	1.26, 4.09
BMI	0.98	0.94, 1.02	--	--
Race: African American (vs. white)	0.46	0.23, 0.92	0.43	0.22, 0.86
Race: Other/multiracial (vs. white)	1.24	0.50, 3.05	1.18	0.48, 2.89
Family history of Hypercoagulable state	45.2	6.61, 309.27	43.59	6.62, 287.21
Family history of VTE	0.37	0.14, 1.03	0.38	0.14, 1.03
Smoke: Current (vs. never)	1.47	0.59, 3.65	1.42	0.58, 3.49
Smoke: Former (vs. never)	0.38	0.14, 1.04	0.38	0.14, 1.03
Active Malignancy within 2 years of VTE	0.11	0.01, 0.90	0.12	0.02, 0.92
Liver Disease	2.49	0.95, 6.51	2.48	0.95, 6.45
Indwelling Venous Catheter	0.23	0.05, 1.17	0.25	0.05, 1.22
****C Statistic per model*	***c = 0.758***		***c = 0.761***	