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BRIEF REPORT

Clinical adherence to thrombophilia screening guidelines at a major tertiary care hospital

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Essentials

- Thrombophilia screening has significantly increased but has limited clinical utility.
- We evaluated the positive rate of thrombophilia screening and adherence to published guidelines.
- Both the positive rate for thrombophilia screening and the adherence to guidelines were low.
- Guidance implementation is essential to improve current thrombophilia screening practice.

Summary. *Background:* Thrombophilia screening is widely performed but provides limited clinical utility in managing patients predisposed to venous thromboembolism. Although guidelines to limit testing have been published, adherence to those guidelines in the outpatient clinical setting has not been assessed. *Objective:* To evaluate outpatient thrombophilia screening practices at a tertiary academic medical center. *Methods:* We performed a retrospective review of the electronic medical records and a computational analysis of thrombophilia tests collected during a 3-year period (August 2010 to June 2013) at a large teaching hospital. Our primary outcome measures were positive diagnostic yield for thrombophilia and clinician adherence to published thrombophilia screening guidelines in the outpatient setting. *Results and Conclusions:* We found a positive diagnostic yield of 13.8% (95% confidence interval 12.3% to 15.3%) for outpatient thrombophilia screening at our institution. Of the screening tests requiring a second confirmatory assay for definitive diagnosis, only 12% (95% confidence interval 10.3% to 13.7%) were appropriately obtained. We also observed that 73% of patients in our electronic medical record review were inappropriately tested based on existing screening guideline criteria. When parsed by specialty, we identified that hematologists had a higher adherence rate to guideline criteria than do physicians from other specialties. Our study confirms low adherence to thrombophilia screening guidelines across disciplines and indicates the need for continued clinician education.

Keywords: educational activities; guideline adherence; mass screening; practice guideline; thrombophilia.

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Introduction

Among patients presenting with venous thromboembolism (VTE), approximately half are found to have an underlying thrombophilia [1]. Although thrombophilias may be inherited, acquired, or mixed in nature, they all predispose patients to developing thrombotic events. Inherited thrombophilias include gain-of-function variants (e.g. factor V Leiden [FVL] or prothrombin G20210A) and deficiencies of the natural anticoagulants, namely antithrombin (AT), protein C (PC), and/or protein S (PS). The most common acquired thrombophilia is the antiphospholipid syndrome (APS), characterized by vascular thrombosis and/or pregnancy morbidity and laboratory evidence of antiphospholipid antibodies (aPLs) [2].

In recent years, the development of various tests has allowed clinicians to identify the specific causes of thrombophilia, leading to significant increases in screening for these conditions [3]. In general, the rationale for screening falls into one of three categories: predicting VTE recurrence and determining whether to maintain patients on long-term anticoagulation; managing asymptomatic family members of patients with confirmed thrombophilia; and satisfying patient curiosity as to an underlying explanation for a thrombotic event [4]. However, given the equivocal predictive value of thrombophilia for VTE recurrence, the clinical utility of widespread screening has not been substantiated [5]. A growing body of evidence suggests that overdetection may in fact cause unnecessary patient anxiety and overtreatment [6].

To address the problem of overdiagnosis, evidence-based guidelines for both inherited and acquired thrombophilia screening have been published. The British Society of Haematology [7], the American College of Pathologists [8], and the International Society on Thrombosis and Haemostasis [9] have officially issued guidelines on screening practices involving inherited or acquired thrombophilias. However, although the different guidelines share many similarities, no definitive consensus exists, largely due to the poor quality of supporting evidence. Unsurprisingly, the implementation of such screening guidelines has not been extensively described in the literature. Our study is the first to examine thrombophilia-screening practices in the outpatient setting, using a compilation of published guidelines to evaluate clinician adherence.

Methods

We performed a retrospective review of the outpatient electronic medical records (EMRs) and special coagulation laboratory data collected from patients at the New York-Presbyterian-Weill Cornell Medicine in New York City. Electronic medical records and laboratory data were examined for all patients who had thrombophilia testing performed between August 2010 and June 2013. Patients younger than 18 years at the time of screening and EMRs with incomplete documentation were excluded from analysis. The hospital's institutional review board approved the study.

For the laboratory data set, a thrombophilia evaluation was defined as a group of two or more screening tests, including, but not limited to, at least one inherited thrombophilia test. Inherited thrombophilia tests were defined as functional assays for activated protein C resistance (APC-R), PC, PS, and AT and genetic tests for FVL or prothrombin G20210A variants. Acquired thrombophilia screening tests included the aPLs, namely the lupus anticoagulant (LA) and anticardiolipin and anti-B2 glycoprotein 1 antibodies IgG and IgM isotypes. Thrombophilias that required a confirmatory test for definitive diagnosis (i.e. PC, PS, AT, aPLs) were noted for adherence to reevaluation requirements. For instance, the confirmatory test for aPLs had to be performed at least 12 weeks after the date of the initial abnormal result to be considered valid [9]. Similarly, functional levels of PC, PS, and AT had to be confirmed after a 30-day period. Conversely, tests that did not require a confirmatory test (i.e. genetic assays for FVL, prothrombin G20210A) were checked for nonredundancy.

Positivity rate

We defined positivity rate as the number of positive thrombophilia diagnoses of the total number of thrombophilia evaluations performed. A positive thrombophilia diagnosis was defined as the presence of at least one abnormal test in the evaluation, with an additional appropriate confirmatory test if required for that particular assay. Using an original script in the statistical analysis software R, we calculated the positivity rate for our entire thrombophilia data set. In order to confirm our computational analysis, we randomly sampled 100 of the patients from the overall data set and individually examined whether the patients' test results met the criteria for thrombophilia diagnosis.

Clinical adherence

In the absence of definitive consensus guidelines for thrombophilia screening, we used a compilation of recommendations published by the British Society of Haematology, the American College of Pathologists, and the International Society for Thrombosis and Haemostasis [7–9] (Table 1) to develop our local screening guideline. We also ensured that our local guideline was in agreement with several other published documents, including the international consensus statement published in 2005 by the European Genetics Foundation, the Cardiovascular Disease Educational and Research Trust, the Mediterranean League on Thromboembolism, and the International Union of Angiology [10].

For the EMR review, medical records inadequately documenting the rationale for thrombophilia testing were excluded from further review. Eligible EMRs were then individually assessed for compliance to all guidelines as

Table 1 Recommendations for thrombophilia screening based on guidelines published by the British Journal of Hematology, American College of Pathologists, International Society for Thrombosis and Haemostasis, and the International Consensus Statement [7–10]

Inherited thrombophilia [7,8,10]	Acquired thrombophilia [8,9]
Unprovoked venous thromboembolism (VTE)	Unprovoked VTE
VTE in patients < 50 years old, including provoked	Unexplained arterial thrombosis in patients < 50 years old
VTE in patients with minor provoking risk factor (e.g. estrogen therapy only)	Thrombosis at unusual sites (e.g. splanchnic veins)
Recurrent VTE	Unexplained late spontaneous pregnancy loss
Skin necrosis associated with vitamin K antagonists	Thrombosis or pregnancy morbidity and autoimmune disease
Purpura fulminans in children or neonates	Recurrent early spontaneous pregnancy loss
Strong family history of unprovoked recurrent VTE	Incidentally prolonged activated partial thromboplastin time in asymptomatic individuals
Asymptomatic family member with known high-risk thrombophilia	Provoked VTE in young patients

determined in Table 1 [7–10]. Clinical 'no adherence' was determined when patients had a thrombotic event secondary to a major identifiable transient risk factor, such as surgery or prolonged immobilization. In addition, medications and comorbid conditions were evaluated for their potential effect on test results; for example, if a patient was taking a vitamin K antagonist or had liver dysfunction and had PC or PS levels checked [4], guideline 'no adherence' was also determined. Finally, the medical specialty of the attending physician approving the final order was noted during EMR review.

Confirmatory testing

We performed a separate computational analysis on all tests in our thrombophilia data set that required confirmatory testing, namely PC, PS, AT, and aPLs. Using another script in R*,* we classified all results as either normal or abnormal. We checked whether abnormal test results were appropriately followed by confirmatory tests in an acceptable period. Confirmatory results were classified as valid (test performed within the appropriate confirmatory period), invalid (test performed outside of the confirmatory period), or absent (test not performed despite presence of an initial abnormal result). The fraction of valid follow-ups of the total number of cases where follow-up should have been performed was then determined. Redundancy of tests that did not require confirmatory results (e.g. FVL, prothrombin G20210A) was also monitored.

Results and discussion

A total of 2081 patients had outpatient thrombophilia evaluations performed during the study period. The overall positive diagnostic yield for thrombophilia screening was 13.8% (95% confidence interval [CI] 12.3% to 15.3%). The accuracy of this positivity rate, which was obtained for the entire population through computational analysis, was confirmed by a manually analyzed random sample of 100 patient records (point estimate 18%, 95% CI 10.5% to 25.5%). Our positivity rate of 13.8% is significantly lower than even conservative estimates of diagnostic yield for high-risk populations; for instance, Roldan *et al.* (2008) [11] showed that in patients meeting international consensus criteria for thrombophilia testing (i.e. spontaneous VTE, VTE in patients < 50 years old, VTE in setting of minor risk factors such as hormonal contraceptives, or recurrent VTE), thrombophilia testing yielded positive diagnoses in 34% of cases. Such discrepancy suggests that thrombophilia screening at our institution is overperformed, likely due to unnecessary screening of low-risk populations.

Of the 400 charts reviewed for further evaluation of guideline adherence, 205 (51%) were excluded due to inadequate documentation of rationale for thrombophilia testing. The majority of excluded charts were of healthy female patients undergoing evaluation for *in vitro* fertilization. Although thrombophilia testing is frequently requested among patients being evaluated for infertility, this is not routine clinical practice at our institution. Given the relatively low risk of thrombophilia in this patient population, the guideline adherence rates noted from our chart review would have been even lower if we had included the infertility population screened for thrombophilia.

Among the 195 charts included in our review, only 59 (30.2%) had adequate indications for thrombophilia screening, in contrast to 60% from the Registro Informatizado de Enfermedad Tromboembolica (RIETE) registry [11]. Inherited thrombophilia screening was appropriate in 37.9% of cases, while acquired thrombophilia screening was appropriate in 58.1% of cases. In 14 patients (7.2%), we identified pharmacologic (e.g. warfarin) or pathologic interactions (e.g. liver disease) at the time of screening. Seven of the complete thrombophilia panels (3.6%) were ordered due to patient request, despite documentation that the patient was informed of the limited utility of testing (Fig. 1).

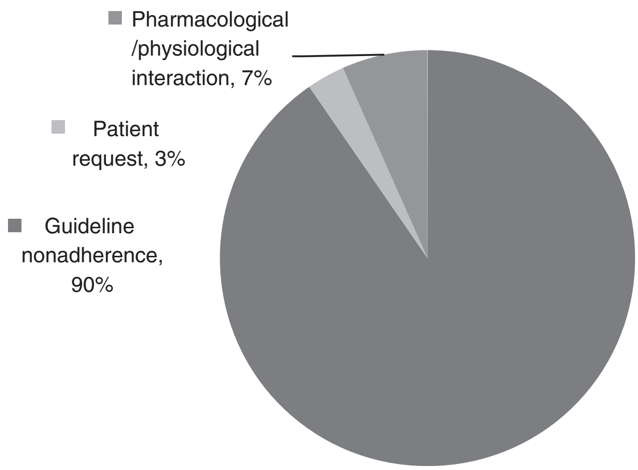

Fig 1. Reasons for incorrect thrombophilia screening (n = 136).

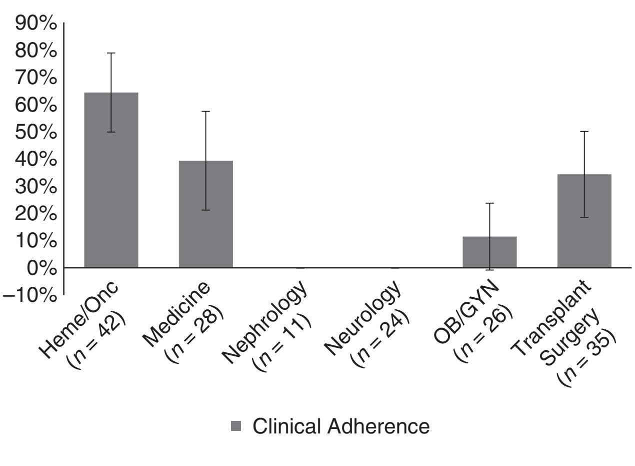

Fig 2. Rates of thrombophilia screening guideline adherence by department.

Table 2 Confirmatory testing rates

Test/Follow-up	Valid	Invalid	Absent	Total abnormal	Appropriate rate (%)	95% CI
Protein C (activity, antigen)	14	35	183	232	6.0	(0.03–0.09)
Protein S (activity, free, total)	71	71	402	544	13.1	(0.10–0.16)
Antithrombin (activity, antigen)	9	19	169	197	4.6	(0.02–0.08)
Antiphospholipid antibodies	78	–	–	459	17.0	(0.14–0.20)

We further evaluated adherence to thrombophilia screening guidelines according to hospital department. We identified that adherence rates were highest among hematologists/oncologists (64.3%), followed by general internists (39.3%), transplant surgeons (34.3%), obstetricians/gynecologists (11.5%), neurologists (0%), and nephrologists (0%) (Fig. 2). There were statistically significant differences in adherence rates between hematologists/oncologists and other specialists ($P < 0.01$), excluding general internists ($P = 0.013$). These results suggest that there is a need for continued education regarding proper utilization of thrombophilia testing.

Confirmatory results of abnormal thrombophilia tests were low. Only 6% of patients with decreased PC had the test repeated within the appropriate confirmatory period. Similarly low confirmatory rates were found for PS (13%), AT (4.6%), and LA/antiphospholipid antibodies (17%) (Table 2). These low rates indicate that even in patients with initially abnormal results, definitive diagnoses were not established, thereby contributing to unnecessary referrals to hematology, wasted health care costs, and adverse psychological burden for affected patients.

Our study has several strengths, including the large number of thrombophilia panels evaluated, the identification of reasons for incorrect screening, and the analysis of adherence patterns by department. Limitations of our study, however, are also significant. Some key issues include that our design was limited to a single center, thereby limiting the extent to which our results can be generalized; the necessary exclusion of EMRs during review may have introduced selection bias; and the variability of the R script may have influenced the accuracy of the positivity rate. Although our study may be limited in its generalizability, we believe that it serves as an important foundation for further investigation into thrombophilia screening practices. At the very least, it provides a structural basis on which other medical centers can design studies and compare rates of diagnostic yield of thrombophilia screening. With regards to selection bias, we believe that the indiscriminate test ordering in the excluded charts indicates that the overall positivity would have been lower had the charts been included, thus further emphasizing the need for better adherence to screening guidelines. Finally, although it is possible that scripting errors affected the computational analysis of the overall positivity rate, the fact that the calculated rate was manually confirmed by the random sample computation is reassuring.

In summary, our study shows that thrombophilia screening is often inappropriately performed. The positive diagnostic yield of testing is much lower than what would be expected if guidelines were appropriately followed. Limited clinician adherence to screening guidelines was identified as the major contributory factor for low positivity rate. Low rates of confirmatory testing also contributed to the low yield of definitive diagnoses. Departmental adherence to guidelines was found to be highest among hematologists, in contrast to physicians from other specialties.

Our study highlights the need for medical education regarding guidelines and practices for thrombophilia screening. Although the guidelines used for adherence analysis in this study were relatively liberal, the finding that the rate of thrombophilia diagnosis remained low is quite concerning. Other academic medical centers have found some success in reducing unnecessary testing by establishing clinical decision-making tools in the inpatient setting [6]. We believe that a similar tool may also help educate clinicians in their outpatient practices. We are committed to investigate changes in hospital culture that will encourage proper utilization of special coagulation laboratory resources. With proper education and frequent reevaluation of adherence practices for thrombophilia screening, we hope to achieve higher diagnostic yield and more effectively treat our patients.

Addendum

A. J. Kwon was responsible for computational design, chart review, data analysis and interpretation and is the primary author. M. Roshal was responsible for concept and design of project, was the primary data collector and gave final approval of submission. M. DeSancho was responsible for concept and design of project, revision of manuscript content and gave final approval of submission.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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