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Family history of venous thromboembolism predicts the diagnosis of acute pulmonary embolism in the emergency department

Christopher Kelly, MD [a], Chad Agy, MD [b], Margaret Carlson, BS [a], Jacob Steenblik, MPH, MHA [a], Joseph Bledsoe, MD [b], Stephen Hartsell, MD [a], Troy Madsen, MD [a,*]

[a] Division of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, UT, United States
[b] Intermountain Medical Center, Murray, UT, United States

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ABSTRACT

Background: Pulmonary embolism (PE) clinical decision rules do not consider a patient's family history of venous thromboembolism (VTE). We evaluated whether a family history of VTE predicts acute PE in the emergency department (ED).

Methods: Over a 5.5-year study period, we enrolled a prospective convenience sample of patients presenting to an academic emergency department with chest pain and/or shortness of breath. We defined a family history of VTE as a first-degree relative with previous PE or deep vein thrombosis (DVT). We noted outcomes of testing during the patient's ED stay, including the diagnosis of acute PE by either computed tomography (CT) or ventilation/perfusion (VQ) scan.

Results: Of the 3024 study patients, 19.4% reported a family history of VTE and 1.9% were diagnosed with an acute PE during the ED visit. Patients with a family history of VTE were more likely to be diagnosed with a PE: 3.2% vs. 1.6% ($p = 0.009$). 82.3% of patients were Pulmonary Embolism Rule-out Criteria (PERC) positive, and among PERC-positive patients, those with a family history of VTE were more likely to be diagnosed with a PE: 3.6% vs. 1.9% ($p = 0.016$). Of patients who underwent testing for PE (33.7%), patients with a family history of VTE were more likely to be diagnosed with a PE: 9.4% vs. 4.9% ($p = 0.032$).

Conclusion: Patients with a self-reported family history of VTE in a first-degree relative are more likely to be diagnosed with an acute PE in the ED, even among those patients considered to have a higher likelihood of PE.

1. Background

Venous thromboembolism (VTE), and particularly pulmonary embolism (PE), remains a difficult entity to diagnose in the emergency department and much has been learned about the pathogenesis over the last several decades. As a disease entity, VTE has a multitude of associated risk factors including both acquired and genetic factors. It has been demonstrated that individuals with certain inheritable thrombophilias are at increased risk of VTE formation. Clinical decision rules have been developed to aid in the risk stratification of patients; however, current scoring systems do not utilize a patient's self-reported family history of VTE. It is unclear what impact such a family history of VTE may have on a patient's risk for the diagnosis of PE in the emergency department when presenting with chest pain or shortness of breath [1-5].

This study attempted to determine the prognostic and predictive value of a self-reported family history of VTE for the diagnosis of PE in the emergency department. The overall goal was to evaluate the role of a self-reported family history of VTE in ED patients presenting with chest pain and/or shortness of breath, and how this self-reported history may relate to the eventual diagnosis of PE during the ED visit. This study sought to determine both the prevalence of a self-reported family history of VTE and whether patients with this history are at an increased risk of diagnosis of acute PE. We hypothesized that a patient's self-reported family history of VTE would be a positive predictive factor for the diagnosis of acute PE.

2. Methods

We conducted a prospective, observational study over the 5.5-year period from July 2010 through December 2015 at the Univeristy of Utah Emergency Department (ED). The University of Utah ED is an urban, academic ED located in Salt Lake City, UT, with approximately 40,000 patient visits per year during the study period. The University of Utah Institutional Review Board (IRB) approved the study.

* Corresponding author at: University of Utah, Division of Emergency Medicine, 30 N. 1900 E. 1C26, Salt Lake City, UT 84132, United States.
E-mail address: troy.madsen@hsc.utah.edu (T. Madsen).

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Trained research assistants obtained informed consent from eligible patients and enrolled a convenience sample of patients who presented to the ED with chest pain and/or shortness of breath. Research associates staffed the ED from 0800 to 2400 seven days a week. We trained research associates in administering a standard survey to patients to obtain baseline characteristics, including information regarding the patient's demographic information, current symptoms, past medical history, family history, and additional relevant medical information. As part of the survey, research associates asked the question, "Do you have a first-degree relative (parent, sibling, or child) who has had a previous blood clot in their lungs or legs?" Research associates asked patients to identify their race/ethnicity utilizing United States Census classification categories. Those who self-identified as more than one race or who chose not to respond were classified as "other."

Research associates enrolled patients early in their stay in the emergency department, prior to the receipt of testing results in the ED. Research associates administered the survey separate from the clinical staff's visits with the patients, and physicians and staff in the emergency department did not have access to the patient responses to the survey. We described the study as creating a database of baseline characteristics and clinical outcomes for patients with the chest pain and/or shortness of breath, and research associates as well as clinical staff in the ED did not have knowledge of the specific study hypothesis or aims.

A trained subset of research associates reviewed the medical record and recorded triage vital signs as well as the results of testing performed during the ED visit. Patients were considered to have an acute PE if they had computed tomography (CT) or ventilation-perfusion (VQ) scan performed during the ED stay with the clinical diagnosis of acute PE assigned to the patient based on the results of this test. Two of the study's investigators (CA, TM) reviewed all cases of acute PE to confirm the diagnosis via CT or VQ scan during the ED stay as well as to confirm the diagnosis of acute (as opposed to chronic) PE.

Testing for PE in the ED was at the discretion of ED providers. Providers typically utilize d-dimer testing for patients who are low risk by Wells' Criteria and proceed to CT or VQ scan for patients with a positive d-dimer. For patients who are not low-risk by Wells' Criteria, providers typically perform CT or VQ scan without d-dimer testing [4]. We noted rates of testing among study patients, including d-dimer testing, the combination of d-dimer testing and CT or VQ scan, and those who underwent CT or VQ scan without d-dimer testing. We defined patients who had d-dimer testing and/or CT or VQ scan as having undergone testing for PE.

We utilized clinical variables to calculate the components of the PE Rule-out Criteria (PERC) [6]. Based on information gathered by research associates from the review of the ED record, we noted whether the patient was 50 years of age or older, whether they had a triage heart rate of 100 beats per minute or greater, and whether their triage room air oxygen saturation was 95% or less. We additionally utilized clinical variables obtained by research associates during their initial survey with patients, including a patient's prior history of VTE, trauma or surgery within the previous four weeks, hemoptysis, exogenous estrogen use, or unilateral leg swelling. Individuals who met any of these criteria were classified as "PERC positive" and considered to be higher risk for PE than those who were PERC negative.

We collected and managed study data using REDCap, an electronic data capture tool hosted at the University of Utah [7]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing:

1. An intuitive interface for validated data entry;
2. Audit trails for tracking data manipulation and export procedures
3. Automated export procedures for seamless data downloads to common statistical packages
4. Procedures for importing data from external sources.

Table 1
Study participants' self-reported race and ethnicity. "Other" includes those reporting more than one race/ethnicity or those who chose not to report their race or ethnicity. Race and ethnicity categories are listed according to United States Census classifications.

Self-reported race/ethnicity	Percent of total
White non-Hispanic	78.6%
Hispanic	7.6%
Black	3.7%
Native American	2.0%
Pacific Islander	1.3%
Asian	1.2%
Other	5.6%

The primary study outcome was acute PE diagnosed by CT scan or VQ scan during the ED stay in which the patient agreed to participate in the study and completed the baseline questionnaire. We classified those who answered "yes" to the question regarding family history of VTE as having a "positive family history of VTE." Our primary analysis compared baseline characteristics and rate of acute PE diagnosis between this group and those who answered "no" to this question. Additionally, we evaluated the rate of PE between these two groups among those who met at least one of the PERC and were classified as PERC positive, in order to determine the potential impact of a self-reported family history of VTE among patients considered higher risk for the diagnosis of PE.

We performed data analysis utilizing descriptive statistics with data presented as percentages for categorical variables and means for continuous variables. We evaluated differences between groups of categorical variables utilizing the Pearson's chi-square test and differences between continuous variables using Student's *t*-test. We present results using odds ratios (ORs) and 95% confidence intervals (CIs), with a p-value < 0.05 considered statistically significant. We performed analysis using STATA vs. 12.0 (StataCorp, College Station, TX) and VassarStats Statistical Computation Website.

3. Results

Over the 5.5-year study period, 3024 patients presented to the ED with chest pain and/or shortness of breath and agreed to participate in the study. Average patient age was 51.7 ($\pm$0.3) years and 54.8% of patients were female. Of the study population, 56.4% presented with chest pain and shortness of breath, 23.2% presented with shortness of breath without chest pain, and 20.4% with chest pain without shortness of breath. When asked to self-report their race and/or ethnicity, 78.6% self-identified as white non-Hispanic race. We present additional race/ethnicity information in Table 1.

We asked patients the question, "Do you have a first-degree relative (parent, sibling, or child) who has had a previous blood clot in their lungs or legs?" If the patient answered, "yes" to this question, they were considered to have a family history of venous thromboembolism (VTE). Based on this question, 19.4% of study patients reported a positive family history of VTE. Those who reported a family history of VTE were more likely to be female, white non-Hispanic, and to report a prior history of pulmonary embolism (PE) or deep vein thrombosis

Table 2
Comparison of baseline characteristics between participants with a self-reported family history of venous thromboembolism (VTE) and those who did not report a family history of VTE

Baseline characteristic	Family history of VTE	No family history of VTE	P-value
Female	61.5%	53.2%	<0.001
White non-Hispanic race	84.5%	77.2%	<0.001
Age	50.9 years	51.9 years	0.206
Previous PE or DVT	23.9%	12.6%	<0.001

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