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Anemia is not a Risk Factor for Developing Pulmonary Embolism

John B. Harringa, BS¹, Rebecca L. Bracken, BA¹, Scott K. Nagle, MD, PhD², Mark L. Schiebler, MD², Brian W. Patterson, MD, MPH¹, James E. Svenson, MD, MS¹, and Michael D. Repplinger, MD, PhD^{1,2}

¹University of Wisconsin-Madison, BerbeeWalsh Department of Emergency Medicine

²University of Wisconsin-Madison, Department of Radiology

Abstract

Objective—Our aim was to validate the previously published claim of a positive relationship between low blood hemoglobin level (anemia) and pulmonary embolism (PE).

Methods—This was a retrospective study of patients undergoing cross-sectional imaging to evaluate for PE at an academic medical center. Patients were identified using billing records for charges attributed to either magnetic resonance angiography or computed tomography angiography of the chest from 2008 to 2013. The main outcome measure was mean hemoglobin levels among those with and without PE. Our reference standard for PE status included index imaging results and a six-month clinical follow-up for the presence of interval venous thromboembolism, conducted via review of the electronic medical record. Secondly, we performed a subgroup analysis of only those patients who were seen in the emergency department. Finally, we again compared mean hemoglobin levels when limiting our control population to an age and gender-matched cohort of the included cases.

Results—There were 1,294 potentially eligible patients identified, of whom 121 were excluded. Of the remaining 1,173 patients, 921 had hemoglobin levels analyzed within 24 hours of their index scan, and thus were included in the main analysis. Of those 921 patients, 107 (11.6%; 107/921) were positive for PE. We found no significant difference in mean hemoglobin level between those with and without PE, regardless of the control group used (12.4 ± 2.1 g/dL and 12.3 ± 2.0 g/dL [$p = 0.85$], respectively).

Conclusions—Our data demonstrated no relationship between anemia and pulmonary embolism.

Keywords

anemia; hemoglobin; pulmonary embolism; venous thromboembolism

Corresponding Author: Michael D. Repplinger, MD, PhD, 800 University Bay Drive, Suite 310, Mail Code 9123, Madison, WI 53705, rbracken@medicine.wisc.edu; (W) 608-890-5963, (F) 608-265-8241.

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1. Introduction

Pulmonary embolism (PE) is a relatively common pathology; in conjunction with deep vein thrombosis, venous thromboembolism affects between 1–2 per 1,000 people each year in the United States [1,2]. Estimates suggest that about 1% of all patients admitted to hospitals die of acute PE and 10% of all in-hospital deaths are PE-related [3]. In a multi-decade community-based report of the epidemiology of PE, 30-day mortality from acute PE was 13.3% [4]. Since the diagnosis of PE is challenging due to its non-specific symptoms and signs (i.e. shortness of breath, chest pain, coughing, tachycardia, etc. [5]), many researchers have attempted to develop rational approaches to the evaluation of patients with possible PE. Clinical decision instruments, like the Wells' [6] and Revised Geneva Scores [7], allow physicians to stratify patients with suspected PE into decision-making algorithms. Pretest probability and clinical algorithms guide the patient's subsequent workup, generally involving D-dimer testing and computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the chest [5,6].

Recently, an association between anemia and PE has been reported. In their retrospective study, Can et al. found that patients with PE had significantly lower mean hemoglobin levels than gender and age-matched controls. They proposed that this was due to decreased secretion of anti-thrombotic mediators, initiated by low blood viscosity in anemic states, resulting in increased clotting [10]. If validated, this finding could be of significant importance since the identification of a new risk factor for PE has the potential to direct further research and improve upon the performance of existing clinical decision instruments. Furthermore, previous literature has identified a trend of increased mortality in patients who are anemic [11].

Though hemoglobin level testing is not currently a component of any validated clinical decision instrument for PE, a complete blood count is often drawn in the workup of suspected PE due to the potential for other alternative 52 diagnoses, like pneumonia [12]. Indeed, 35% of all patients in United States emergency departments, regardless of chief complaint, have complete blood counts analyzed [13]. The integration of this test into updated clinical decision instruments for PE, therefore, would be relatively simple. The intent of this study is to validate the findings of Can et al. – that anemia has a positive association with the diagnosis of PE – using a control population of those evaluated for PE, but with a negative diagnostic workup. Although Can and colleagues supplied a plausible argument for why anemia would contribute to developing PE, we hypothesized that there would be no difference in hemoglobin levels between those with and without PE.

2. Methods

2.1 Study design

This is a retrospective case-control study of patients who underwent cross-sectional imaging for the evaluation of PE between April 1, 2008 and March 21, 2013 at our academic medical center in the Midwestern United States. This cohort of patients represents a subset of a parent study that compared patient outcomes for those undergoing pulmonary CTA versus MRA for the evaluation of PE. In the parent study, the general prevalence of VTE for

patients evaluated in the emergency department was 8.9% (41/459). The study was HIPAA-compliant and approved by our university's institutional review board.

2.2 Patient Selection

All patients who underwent pulmonary MRA for the diagnosis of PE during the study period were identified using billing information. Next, we selected another group comprised of a random sample of patients who were age and gender-matched to the MRA group, but had undergone pulmonary CTA instead of MRA during the study period, using the same billing database. The combination of these two groups established our research cohort. Patients were only included in the study once; if a patient had multiple imaging tests performed during the study period to evaluate for PE, only the first encounter was used. Patients were excluded for pregnancy, concomitant acute atrial fibrillation, indwelling IVC filter, anticoagulant use for >30 days prior to index scan, or absence of a hemoglobin level analyzed in the 24 hours prior to the index scan.

2.3 Data collection

We used REDCap (Research Electronic Data Capture [14]) to develop a data abstraction instrument, which our abstractors used in conjunction with a standardized data abstraction protocol. This protocol made use of a search function embedded within our electronic health record, which returned notes that included specific search terms (e.g. – PE, venous thromboembolism, bleeding, etc.) as well as synonyms as defined by a robust medical dictionary provided by the electronic health record vendor (Epic Systems, Verona, WI). Using the original data abstraction protocol, the primary data abstractor (a full-time research specialist) trained on the first 80 cases, after which point the protocol was refined to address data abstraction uncertainties. The training cases were then re-evaluated and the primary abstractor trained two additional data abstractors (both research nurses) to use the protocol and REDCap. For subsequent uncertain outcomes, cases were flagged for review by an expert panel of three investigators including two radiologists and an emergency physician. The final results were adjudicated according to consensus opinion.

2.4 Outcomes and analysis

Our primary outcome was mean hemoglobin level among patients with versus those without pulmonary embolism. Negative and non-diagnostic imaging tests, which we defined as those marked “equivocal,” were considered negative for PE, unless a PE or deep vein thrombosis was diagnosed within 6 months of the index visit on chart review. This caveat was included to account for falsely negative index imaging test results. Conversely, all positive imaging test results at the index visit were considered positive for PE. Secondary analyses included a comparison of hemoglobin levels when the study population was limited to only those patients evaluated in the emergency department as well as a comparison of hemoglobin levels between those with PE and a randomly selected subset of controls that were matched to cases by age (± 2 years) and gender. Results are presented as mean values with standard deviations. Statistical significance was evaluated using a student's t-test, using a threshold of $p < 0.05$ for statistical significance. All calculations were performed using GraphPad Quick Calcs (GraphPad Software, La Jolla, California) [15].

3. Results

3.1 Patient Characteristics

Overall, 1,294 potentially eligible patients were identified during the study period. Of those, 121 were excluded; 87 were anticoagulated, 27 were in atrial fibrillation, 18 had an inferior vena cava filter, and 8 were pregnant (some patients met multiple exclusionary criteria). An additional 252 did not have a hemoglobin result documented in their chart in the 24 hours prior to their index imaging test. The remaining 921 constituted the research cohort. Among these, 107 patients had PE (11.6%) and served as cases while the remaining 814 patients served as controls. In the control group, 652 patients were female (80.1%) and the average age was 38.9 ± 16.5 years. In the case group (PE positive), 73 patients were female (68.2%) and the average age was 43.8 ± 19.0 years. Baseline characteristics of the case and control populations are displayed in table 1. Patient flow through the study and results are presented in figure 1.

3.2 Main Results

Mean hemoglobin levels were not different between those with versus those without PE. Hemoglobin levels were 12.4 ± 2.1 g/dL and 12.3 ± 2.0 g/dL ($p = 0.85$), respectively.

3.3 Secondary Results

When limited to the 607 patients who were evaluated in the emergency department, there was no significant difference in mean hemoglobin levels among those with PE compared to those without PE; hemoglobin levels remained comparable at 12.8 ± 2.0 g/dL and 12.9 ± 1.7 g/dL ($p = 0.66$). When our control group was limited to a randomly generated cohort of patients who were age and gender-matched to cases, hemoglobin levels were 12.4 ± 2.1 g/dL and 12.4 ± 1.8 g/dL ($p = 1.0$), respectively.

4. Discussion

The goal of this study was to assess a previously reported positive correlation between anemia and the diagnosis of pulmonary embolism. We found no evidence to support this reported relationship. Mean hemoglobin levels were comparable among patients with and without PE throughout the main analysis and the two sub-analyses we conducted.

Very limited research exists investigating the association of anemia and pulmonary embolism, save for a single case report regarding autoimmune hemolytic anemia and subsequent PE shortly after AIHA diagnosis [16]. A fundamental distinction between the Can et al. study and ours was the inclusion criteria. Since all patients in our study were of high enough risk to warrant cross-sectional imaging (CTA or MRA) to evaluate for PE, we enrolled a more uniform risk profile of patients. In the previous study, controls for PE cases were selected based on their proximity of arrival time to the emergency department, gender, and age. As such, 162,153 patients presented to their emergency department during the two study years and only 212 had PE (0.13%). Of the 402 patient case-control cohort, the average age was 63 ± 17 years and both case and control groups had an even gender divide.

This contrasts with our study cohort, which had an average age of 44 ± 19 years and high proportion of women, comprising 68% of our cases as well as 80% of controls.

While this difference in age and gender may partially explain the difference in study outcomes, it is important to note that the basis of selection for the Can et al. study neglected to account for suspicion of PE. Patients with PE present to the emergency department with varying symptoms like chest pain, exercise intolerance, and shortness of breath. Generally, these chief complaints are associated with more serious pathologies than those of the general emergency department population. Because of this, the control group in Can et al. may have been, on average, a healthier cohort than their case group. It is possible that patients who are suspected of PE are a population with higher mortality and morbidity than the general emergency department population, and by extension, a population with a higher frequency and/or greater degree of anemia. This critical difference likely contributed to our study findings: no correlation between anemia and PE.

Though we feel that our case-control study was generally well designed, it has limitations. First, not every patient suspected of PE had a hemoglobin level in our electronic health record, which could have led to information bias. Though we do not have data to explain why these patients did not have a level drawn, it seems plausible that these patients may have been referred from another hospital or clinic where the test was performed. Notably, our overall mean hemoglobin level for both cases and controls was the similar to the population reported by Can et al. A second limitation was the selection method for our research cohort. Since we first identified all patients who underwent pulmonary MRA for the diagnosis of PE, and our physicians preferentially order this test on young women to spare them the radiation exposure of pulmonary CTA, our overall cohort had significantly higher proportion of young women than the general population of patients undergoing evaluation of possible PE [17]. This selection difference could have masked a possible relationship between PE and anemia in older and male patients. Finally, the determination of PE status when imaging results were negative was reliant on electronic health record notes to verify the absence of PE. It is possible that patients had a falsely negative index imaging test, but no subsequent notes within the electronic health record that identified the missed PE.

In conclusion, we found no relationship between anemia and the presence of pulmonary embolism or the interval development of venous thromboembolism at 6 months after undergoing cross-sectional imaging for the diagnosis of PE. We respectfully suggest that the correlation reported by Can and colleagues was spurious.

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Figure 1. Patient Flow and Results

Schematic representation of patient movement through the study steps as well as primary and secondary results. Hemoglobin levels are reported in g/dL.

Table 1
Baseline characteristics of cases and controls

Data are reported as means or proportions with associated confidence intervals as well as associated p-values testing for differences between groups.

	Controls (95% CI)	Cases (95% CI)	P-Value
Age, mean	38.9 (37.8–40.0)	43.8 (40.1–47.6)	0.01
Percent women	80% (77.1–82.6)	68.3% (58.7–76.6)	0.01
Clinical signs and symptoms of DVT?	9.0% (7.3–11.2)	19.8% (13.2–28.6)	0.00
Heart Rate >100	40.4% (37.1 – 43.8)	40.6% (31.5–50.3)	1.00
Immobilization at least 3 days or surgery in the previous 4 weeks	20.6% (18.0–23.5)	22.8% (15.7–31.9)	0.61
Previous, objectively diagnosed PE or DVT	8.8% (7.0–10.9)	16.8% (10.8–25.3)	0.01
Hemoptysis	3.5% (2.5–5.0)	6.9% (3.4–13.6)	0.10
Malignancy with treatment within 6 months or palliative	10.9% (8.9–13.2)	16.8% (10.8–25.3)	0.08

DVT = deep vein thrombosis, PE = pulmonary embolism.