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Research article

Sickle cell disease and venous thromboembolism: A retrospective comparison of the rate of positive CT pulmonary angiography in the emergency department

D.D.B. Bates[a,*], Z. Liu[b], J. Gibbons[a], C.A. LeBedis[b], N.S. Holalkere[b]

[a] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY 10065,USA
[b] Department of Radiology, Boston University Medical Center, Boston University School of Medicine, 820 Harrison Ave, FGH Building, 3rd Floor, Boston, MA 02118, USA

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ABSTRACT

Background: Previous authors have reported an increased incidence of acute pulmonary embolism (PE) in patients with sickle cell disease (SCD) based on retrospective analysis of ICD codes. It is unknown whether patients with SCD have higher rates of positive CT pulmonary angiogram (CTPA) in the emergency department (ED).
Methods: The institutional review board (IRB) approved this retrospective study; informed consent was waived. Between January 1, 2005 and May 31, 2015, 28 patients with SCD underwent a total of 78 CTPA studies in the ED. A control group of 75 non-SCD patients matched for age, gender and race underwent 78 consecutive CTPA studies in the emergency department. Modified Wells' (mWells') scores were calculated for each CTPA study performed. The studies for both groups were blind read by two fellowship trained body radiologists. Descriptive statistics were performed, with significance considered if $p < 0.05$.
Results: The rate of positive CT pulmonary angiogram in patients with SCD was 6.4% (5/78), compared with 12.8% (10/78) in non-SCD matched controls. There was no significant difference in the rate of positive CTPA ($p = 0.277$). There was also no difference in the mean mWells' score between the two groups (2.44 for SCD vs. 1.95 for controls, $p = 0.120$).
Conclusion: SCD patients did not have a significantly different rate of acute PE when compared with matched controls undergoing CTPA in the ED.

1. Introduction

1.1. Venous thromboembolism

Venous thromboembolism (VTE), namely acute pulmonary embolus (PE), is a significant cause of morbidity and mortality in the United States. Domestically, VTE is responsible for 300,000 hospitalizations and 50,000 deaths annually [1].

Computed tomography pulmonary angiography (CTPA) is widely accepted as the modality of choice in the evaluation of patients with suspected PE. On modern CT scanners, the sensitivity and specificity of CTPA to diagnose acute PE are 90% and 95%, respectively [2–4]. The negative predictive value of a negative CTPA has been reported to be 99.05% [5].

The consequences of untreated acute PE are considerable, with reported mortality rates ranging from 18 to 35% [6]. In light of the high mortality of untreated acute PE, clinicians have a low tolerance for missing this crucial diagnosis and, as a result, CTPA has become widely used in the emergency department (ED).

In an effort to assist clinicians evaluating patients with suspected acute PE, several risk stratification models have been proposed and subsequently revised [7,8]. The two most widely accepted of these are the Modified Wells' Criteria (mWells') and Revised Geneva Score. More recently, evidence has suggested increased reliability of the mWells' criteria, making it the preferred method for risk-stratifying patients with suspected PE [9,10].

The mWells' criteria assign a weighted point value to both subjective and objective criteria to generate a cumulative mWells' score. Based on the cumulative score, patients are categorized as low, moderate, or high risk for acute PE. The subjective criteria account for 3 points apiece, and include clinical signs or symptoms of deep vein thrombosis (DVT) and whether or not acute PE is considered to be the

* Corresponding author.
E-mail addresses: batesd@mskcc.org (D.D.B. Bates), zliu00@gmail.com (Z. Liu), gibbonj2@mskcc.org (J. Gibbons), Christina.Lebedis@bmc.org (C.A. LeBedis), Nagaraj.Holalkere@bmc.org (N.S. Holalkere).

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Table 1
Modified Wells' Criteria components.

mWells' Criteria	Points
Clinical Signs DVT	3
PE most likely	3
Heart rate > 100	1.5
Immobilization/surgery past 4 weeks	1.5
Prior documented DVT or PE	1.5
Hemoptysis	1
Malignancy	1
* Risk by total score:	
< 2 = Low	
2-6 = Moderate	
> 6 = High	

most likely diagnosis by the ordering clinician. Objective criteria worth 1.5 points each include a heart rate greater than 100, recent immobilization or surgery within the past 4 weeks, and a prior documented DVT or PE. Objective criteria assigned 1 point each include hemoptysis or a history of malignancy [7]. [Table 1]

1.2. Sickle cell disease

Sickle cell disease (SCD) is an inherited hemoglobinopathy that affects between 72,000–98,000 persons in the United States [11]. In states of hypoxia or stress, the erythrocytes of SCD patients assume an abnormal sickled morphology as a result of the inherited abnormality. A coagulation cascade is activated and endothelial dysfunction ensues. The end result of this complex process is vaso-occlusion, which leads to end-organ ischemia in the form of acute chest syndrome (ACS), stroke, osseous avascular necrosis, and ischemic limb ulcers [12]. In recent years, authors have suggested increased rates of acute PE in patients with SCD [12–14]. The objective of our study is to determine whether there is a difference in the rate of positive CTPA studies positive in ED when comparing SCD patients and non-SCD matched controls.

2. Methods

2.1. Patient population

Our hospital's Institutional Review Board (IRB) approved this retrospective study; informed consent was waived. A query was performed in our institution's Clinical Data Warehouse to identify all CTPA studies performed in the ED between January 1, 2005 and May 31, 2015. From this group, 78 CTPA studies were identified that had been performed on patients with sickle cell disease (mean age 30.4 years, 25 males/53 females). From the same cohort of ED patients, 78 consecutive non-SCD control patients were selected (mean age 31.5 years, 25 males/53 females), matching for age, gender, and race as closely as possible to minimize any potential bias. Because the demographics of several SCD patient scans were listed as both "Black/Hispanic," a control was considered a race/ethnicity match if the demographics were listed as either "Black" or "Hispanic" when the age and gender were also a match.

2.2. Patient data collection

Medical records for patients in both the SCD and non-SCD control groups were reviewed. Data from the medical records at the time of the ED visit was used to calculate mWells' scores. D-dimer values were collected and compared between the two groups when available.

2.3. CT technique

All CT examinations were performed with a 64-detector CT scanner (LightSpeed VCT; GE Medical Systems, Milwaukee, WI) with the following acquisition parameters: reconstruction thickness, 1.25 and 3.75 mm; noise index, 24; pitch, 1:0.984; gantry rotation time, 0.5 s. All patients received a bolus of 80 mL of intravenous contrast (iopamidol, 370 mg iodine/mL, Isovue; Bracco Diagnostics, Monroe Township, NJ) at a rate of 3 to 5 mL/s with the use of a power injector through an 18- or 20-gauge cannula in an antecubital vein. CT examinations were acquired from the lung bases through the lung apices after a 25-s delay (pulmonary arterial phase). In all cases, reformations in coronal and sagittal planes were provided (2.5 mm thickness × 2.5 mm intervals).

2.4. Image interpretation

The CTPA studies were blind read by two attending radiologists fellowship trained in body imaging (7 and 10 years experience), indicating whether or not an acute PE was present. The mWells' criteria were calculated from the medical records for each CTPA in both the study and control groups. Both a total numeric mWells' score and mWells' categories were recorded.

2.5. Statistical analysis

Descriptive statistics were performed on the data, including the Student's two-sample *t*-test and Fisher's exact-test. Statistical significance considered as a p value < 0.05. Inter-observer agreement was assessed by kappa measurement using MedCalc software (MedCalc Software bvba, Version 16.2.1, Ostend, Belgium).

3. Results

There was no significant difference in the rate of positive CTPA studies when comparing patients with SCD to matched controls, 6.4% (5/78) versus 12.8% (10/78), $p = 0.277$. Almost perfect inter-observer agreement was noted between two readers for detection of acute PE, with a kappa value of 0.974.

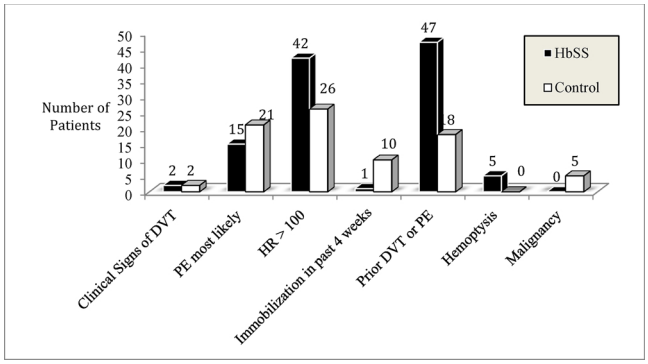
There was also no significant difference in the mean mWells' score of SCD patients and matched controls (2.44 versus 1.95, $p = 0.1204$) and no significant difference between the groups in the mWells' score grade of low risk, moderate risk, or high risk. (Table 2) Among the 5 patients with CTPA studies positive for acute PE in the SCD group, 3 were considered moderate risk and 2 were considered low risk by mWells' criteria. Among the 8 patients with CTPA studies positive for acute PE in the control group, 3 were considered high risk, 3 were considered moderate risk and 2 were considered low risk by mWells' criteria.

There were, however, differences when comparing the breakdown of mWells' scores for patients with SCD to non-SCD controls. The following two scoring elements were found to be significantly more common in the SCD group: tachycardia ($p = 0.0152$) and a reported history of DVT or PE ($p = 0.0091$). Furthermore, non-SCD controls

Table 2
Summary of data comparing SCD patients with matched controls undergoing CTPA in the ED.

Parameter	Study Group	Control Group
Age	30.4 years	31.5 years
Sex	M = 25, F = 53	M = 25, F = 53
Race		
Black	38/78 (49%)	49/78 (63%)
Hispanic	15/78 (19%)	28/78 (35%)
Black/Hispanic	25/78 (32%)	1/78 (2%)
mWells' Grade		
Low	36/78 (46%)	51/78 (65%)
Moderate	40/78 (51%)	21/78 (27%)
High	2/78 (3%)	6/78 (8%)
Wells' Score	2.44	1.95
Positive PE	5/78 (6.4%)	10/78 (12.8%)

Table 3
Comparison of mWells' components between SCD patients and matched controls.



were more likely to have a recent history of immobilization or surgery in the past 4 weeks ($p = 0.001$). Lastly, based on the clinical notes from the emergency room physicians, acute PE was thought to be the most likely diagnosis in 19.23% (15/78) of SCD patients and 26.92% (21/78) of non-SCD controls, not significantly different between the two groups ($p = 0.3421$). [Table 3]

In the group with SCD, D-dimer values were obtained in only 3.8% (3/78) of patients. In contrast, D-dimer values were obtained in 42.3% (33/78) of patients in the non-SCD control group. In 11.5% of the control group (9/78), the D-dimer value was below the threshold for presumed VTE.

4. Discussion

Our study demonstrates no significant difference in the rate of acute PE for patients with SCD when compared with matched controls undergoing CTPA in the ED. These results are of interest because of the previous reports of increased rates of acute PE in patients with SCD [12–14].

Several previous studies have reported an increased incidence of acute PE in patients with SCD [12–15], with one study reporting a 55 to 100-fold increase in incidence of acute PE in SCD patients [13]. Previous studies were based on International Classification of Disease (ICD-9) codes from various databases of discharge data. Two of the studies used databases that contained data from the pre-CTPA era, covering the years 1978 through 1982 and 1979 through 2003(12, 14). In the pre-CTPA era, it is assumed that acute PE was diagnosed either with clinical judgment or by ventilation perfusion (V/Q) scan. However, it has been reported that the abnormalities of acute PE are the same as those seen in acute chest syndrome, the main differential consideration in SCD patients presenting with acute chest pain [16]. [Table 4]

A 2004 retrospective study by Kaur et al. [16] found that 100% of SCD patients diagnosed with ACS have perfusion abnormalities on V/Q scan, raising the possibility that SCD patients with ACS may be misdiagnosed as having acute PE. Although it was a small sample size (n = 10) and a single institution study, the implications of the findings have implications for the study of venous thromboembolic disease in patients with SCD.

It is known that overuse of CT pulmonary angiography is a problem in the ED, and efforts have been made to minimize the number of inappropriate CTPA studies [17]. Recommendations regarding the evaluation of patients with suspected acute pulmonary embolism have been put forth [18], and include the use of D-dimer values to stratify intermediate risk patients. Patients with SCD were significantly less likely to have D-dimer values obtained prior to CTPA (9.0% vs. 42.5%, p = 0.0001). The paucity of D-dimer testing in patients with SCD is likely attributable to the fact that elevated D-dimer values are also seen in SCD patients at baseline, with increased values during vaso-occlusive crises [19–21]. All 7 SCD patients with D-dimer values demonstrated elevated D-dimer levels, though only 1 out of 7 (14.3%) had an acute PE. This finding is consistent with the existing literature on D-dimer values in SCD patients, and suggests that D-dimer testing is not useful to distinguish between acute PE and an acute sickle crisis.

Recently, the RESPECT-ED study looked at the rate of positive CTPA studies across 15 emergency departments [22]. In that large cohort, 95% confidence interval for CTPA studies positive for acute PE was 13.8–15.4%, with a reported range of 9.3–25.3%. In our study, the rate of positive CTPA for the control group (10.3%) was within the range of reported values from RESPECT-ED though it was slightly below the 95% CI. The rate of positive CTPA in the SCD group, however, was below the positive CTPA rate from any of the 15 emergency departments in the RESPECT-ED study at just 6.4%.

Lastly, the cumulative effects of ionizing radiation are worth considering in this unique subset of patients. Previous studies have identified specific patient populations that have high rates of repeat imaging, specifically patients with renal colic [23,24] and Crohn disease [25]. In our cohort, 28 SCD patients underwent a total of 78 CTPA studies (mean = 2.78 scans, range 1–26) during the study period. This suggests that SCD patients may be at risk exposure to ionizing radiation as well, a possibility that is particularly significant given the mean age (30.4 years) and female predominance (69.9% female, 53/78) of SCD patients in our study. It is well established that recurrent CT imaging may put patients at increased risk for radiation-induced cancers [26].

Our study has several inherent limitations, namely that it is a retrospective study performed at a single urban academic medical center. In addition, our sample size is relatively small with a total study population of 156 CTPA studies (78 SCD, 78 non-SCD). In the future, a larger sample size could potentially be obtained through multi-institutional efforts.

5. Conclusion

There was no difference in the rate of positive CT pulmonary angiogram comparing SCD patients with matched controls in the ED. The findings of this study may contribute to our further understanding of the relationship between SCD and acute PE.

Conflict of interest

We wish to confirm that there are no known conflicts of interest

Table 4
Summary of previous literature examining the relationship between SCD and pulmonary embolism.

Study	Description	Pertinent Results
Naik et al. (2014)	Observational Cohort of National Heart, Lung and Blood Institute database 1978-1982	1. SCD patients had higher incidence of VTE compared to other common thrombophilias 2. PE > > DVT in SCD
Stein et al. (2006)	National Hospital Discharge Survey Database 1979-2003	1. High apparent prevalence of PE in SCD 2. Same rate of DVT
Novelli et al. (2012)	Pennsylvania Health Care Cost Containment Council (PHC4) discharge data, 2001-2006	1. SCD have 50-100x increased incidence of PE than general population 2. Hospitalized PE rates are similar for SCD and non-SCD.

associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Disclosure

The authors have no relevant financial disclosures.

IRB statement

This study was approved by the institutional review board (IRB); informed consent was waived.

References

[1] C. Giuntini, G. Di Ricco, C. Marini, E. Melillo, A. Palla, Pulmonary embolism: epidemiology, Chest 107 (1995) 3S–9S.

[2] A. van Belle, H.R. Buller, M.V. Huisman, P.M. Huisman, K. Kaasjager, P.W. Kamphuisen, M.H. Kramer, M.J. Kruip, J.M. Kwakkel-van Erp, F.W. Leebeek, M. Nijkeuter, M.H. Prins, M. Sohne, L.W. Tick, Christopher Study I. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography, JAMA 295 (2006) 172–179.

[3] P.D. Stein, S.E. Fowler, L.R. Goodman, A. Gottschalk, C.A. Hales, R.D. Hull, K.V. Leeper Jr., J. Popovich Jr., D.A. Quinn, T.A. Sos, H.D. Sostman, V.F. Tapson, T.W. Wakefield, J.G. Weg, P.K. Woodard, P.I. Investigators, Multidetector computed tomography for acute pulmonary embolism, N. Engl. J. Med. 354 (2006) 2317–2327.

[4] A. Perrier, P.M. Roy, O. Sanchez, G. Le Gal, G. Meyer, A.L. Gourdier, A. Furber, M.P. Revel, N. Howarth, A. Davido, H. Bounameaux, Multidetector-row computed tomography in suspected pulmonary embolism, N. Engl. J. Med. 352 (2005) 1760–1768.

[5] M.D. Mamlouk, E. vanSonnenberg, R. Gosalia, D. Drachman, D. Gridley, J.G. Zamora, G. Casola, S. Ornstein, Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients, Radiology 256 (2010) 625–632.

[6] K.K. Calder, M. Herbert, S.O. Henderson, The mortality of untreated pulmonary embolism in emergency department patients, Ann. Emerg. Med. 45 (2005) 302–310.

[7] P.S. Wells, D.R. Anderson, M. Rodger, J.S. Ginsberg, C. Kearon, M. Gent, A.G. Turpie, J. Bormanis, J. Weitz, M. Chamberlain, D. Bowie, D. Barnes, J. Hirsh, Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer, Thromb. Haemost. 83 (2000) 416–420.

[8] G. Le Gal, M. Righini, P.M. Roy, O. Sanchez, D. Aujesky, H. Bounameaux, A. Perrier, Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann. Intern. Med. 144 (2006) 165–171.

[9] D.D. Wong, G. Ramaseshan, R.M. Mendelson, Comparison of the Wells and revised Geneva Scores for the diagnosis of pulmonary embolism: an Australian experience, Intern. Med. J. 41 (2011) 258–263.

[10] A. Penaloza, C. Melot, S. Motte, Comparison of the Wells score with the simplified revised Geneva score for assessing pretest probability of pulmonary embolism, Thromb. Res. 127 (2011) 81–84.

[11] K.L. Hassell, Population estimates of sickle cell disease in the U.S, Am. J. Prev. Med. 38 (2010) S512–21.

[12] R.P. Naik, M.B. Streiff, C. Haywood Jr., J.B. Segal, S. Lanzkron, Venous thromboembolism incidence in the cooperative study of sickle cell disease, J. Thromb. Haemost. 12 (2014) 2010–2016.

[13] E.M. Novelli, C. Huynh, M.T. Gladwin, C.G. Moore, M.V. Ragni, Pulmonary embolism in sickle cell disease: a case-control study, J. Thromb. Haemost. 10 (2012) 760–766.

[14] P.D. Stein, A. Beemath, F.A. Meyers, E. Skaf, R.E. Olson, Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease, Am. J. Med. 119 (897) (2006) e7–e11.

[15] C.D. Seaman, J. Yabes, J. Li, C.G. Moore, M.V. Ragni, Venous thromboembolism in pregnant women with sickle cell disease: a retrospective database analysis, Thromb. Res. 134 (2014) 1249–1252.

[16] N. Kaur, B. Motwani, D. Sivasubramaniam, L. Feldman, S. Allen, R. Ferguson, G. Shiomoto, D. Ansell, M. Westerman, L. Feldman, Potential role of the ventilation and perfusion (V/Q) lung scan in the diagnosis of acute chest syndrome in adults with sickle cell disease, Am. J. Hematol. 77 (2004) 407–409.

[17] A. Crichlow, A. Cuker, A.M. Mills, Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department, Acad. Emerg. Med. 19 (2012) 1219–1226.

[18] A.S. Raja, J.O. Greenberg, A. Qaseem, T.D. Denberg, N. Fitterman, J.D. Schuur, Clinical Guidelines Committee of the American College of P, Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines Committee of the American College of Physicians, Ann. Intern. Med. 163 (2015) 701–711.

[19] J. Dar, I. Mughal, H. Hassan, T.E. Al Mekki, Z. Chapunduka, I.S. Hassan, Raised D-dimer levels in acute sickle cell crisis and their correlation with chest X-ray abnormalities, Ger. Med. Sci. 8 (2010) Doc25.

[20] T.A. Ekwere, U. Ebele, M. Ekanem, P.S. Ogunro, Relevance of fibrinolytic protein (D-dimer) and fibrinopeptide A as markers of sickle cell anaemia vaso-occlusive crisis, Niger. Postgrad. Med. J. 21 (2014) 225–230.

[21] R.B. Francis Jr., Elevated fibrin D-dimer fragment in sickle cell anemia: evidence for activation of coagulation during the steady state as well as in painful crisis, Haemostasis 19 (1989) 105–111.

[22] D. Mountain, G. Keijzers, K. Chu, A. Joseph, C. Read, G. Blecher, J. Furyk, C. Bharat, K. Velusamy, A. Munro, K. Baker, F. Kinnear, A. Mukherjee, G. Watkins, P. Buntine, G. Livesay, D. Fatovich, RESPECT-ED: rates of pulmonary emboli (PE) and subsegmental PE with modern computed tomographic pulmonary angiograms in emergency departments: a multi-center observational study finds significant yield variation, uncorrelated with use or small PE rates, PLoS One 11 (2016) e0166483.

[23] S.I. Katz, S. Saluja, J.A. Brink, H.P. Forman, Radiation dose associated with unenhanced CT for suspected renal colic: impact of repetitive studies, AJR Am. J. Roentgenol. 186 (2006) 1120–1124.

[24] J. Broder, J. Bowen, J. Lohr, A. Babcock, J. Yoon, Cumulative CT exposures in emergency department patients evaluated for suspected renal colic, J. Emerg. Med. 33 (2007) 161–168.

[25] T.A. Jaffe, A.M. Gaca, S. Delaney, T.T. Yoshizumi, G. Toncheva, G. Nguyen, D.P. Frush, Radiation doses from small-bowel follow-through and abdominopelvic MDCT in Crohn's disease, AJR Am. J. Roentgenol. 189 (2007) 1015–1022.

[26] A. Sodickson, P.F. Baeyens, K.P. Andriole, L.M. Prevedello, R.D. Nawfel, R. Hanson, R. Khorasani, Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults, Radiology 251 (2009) 175–184.