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Original Article

Prospective Multicenter Evaluation of the Pulmonary Embolism Rule-Out Criteria

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Background: Over-investigation of low-risk patients with suspected pulmonary embolism (PE) represents a growing problem. The combination of gestalt estimate of low suspicion for PE, together with the PE rule-out criteria [PERC(-): age<50, pulse<100, SaO₂≥95%, no hemoptysis, no estrogen use, no surgery/trauma requiring hospitalization within four weeks, no prior venous thromboembolism (VTE), and no unilateral leg swelling], may reduce speculative testing for PE. We hypothesized that low suspicion and PERC(-) would predict a post-test probability of VTE(+) or death below 2.0%. **Methods:** We enrolled outpatients with suspected PE in 13 emergency departments (EDs). Clinicians completed a 72-field, web-based data form at the time of test order. Low suspicion required a gestalt pretest probability estimate <15%. The main outcome was the composite of image-proven VTE(+) or death from any cause within 45 days. **Results:** We enrolled 8,138 patients; 85% had a chief complaint of dyspnea or chest pain. Clinicians reported a low suspicion for PE, together with PERC(-) in 1,666 (20%). At initial testing and within 45 days, 561 patients (6.9%, 95% CI: 6.5-7.6) were VTE(+), and 56 others died. Among the low suspicion and PERC(-) patients, 15 were VTE(+) and 1 other patient died, yielding a false negative rate of 16/1666 (1.0%, 0.6-1.6%). As a diagnostic test, low suspicion and PERC(-) had a sensitivity of 97.4% (95.8-98.5%) a specificity of 21.9% (21.0-22.9%). **Conclusions:** The combination of gestalt estimate of low suspicion and PERC(-) reduces the probability of VTE below 2% in about 20% of outpatients with suspected PE.

INTRODUCTION

Studies that employed autopsy as a criterion standard have found that PE follows acute coronary syndrome as the second most common cause of sudden unexpected death in outpatients.(1-3) Pulmonary embolism manifests a broad clinical spectrum of severity, ranging from vague chest discomfort with normal vital signs to sudden death.(4-6) At least one-quarter of outpatients diagnosed with PE have no overt risk factors.(7;8) Experts often suggest that physicians continue to miss the diagnosis of PE at an unacceptably high rate, and patients with delayed diagnosis of PE have worsened outcomes.(9;10) Coincidentally, several reports have indicated that physicians hold an increasing perception of risk of medical malpractice secondary to failure to order a diagnostic test for PE.(11;12) These influences, together with the widened availability and acceptance of the D-dimer and CT angiography as diagnostic tests for PE, may have combined to cause an increase in frequency of testing for PE among very low-risk outpatients.(13) Speculative investigation for PE that leads to large numbers of negative CT angiograms in young patients may have negative consequences in the form of increase risk of malignancy secondary to radiation exposure.(14;15)

In 2004, we derived the pulmonary embolism rule-out criteria (PERC), an eight-factor decision rule, to support the decision not to order a diagnostic test for PE in in patients for whom the clinician already had a low clinical-suspicion for PE based on a gestalt impression.(16) The PERC criteria negative [PERC(-)], requires the clinician to answer no to the following eight questions:

1. Is the patient older than 50?
2. Is the pulse rate above 100 beats/min?
3. Is the pulse oximetry reading < 95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient taking exogenous estrogen?

6. Does the patient have a prior diagnosis of VTE?
7. Has the patient had recent surgery or trauma? (requiring endotracheal intubation or hospitalization in the previous 4 weeks)
8. Does the patient have unilateral leg swelling (visual observation of asymmetry of the calves)

We use the term *very low risk* to describe patients with the combination of both gestalt low suspicion and PERC(-). Each patient in the very low risk group should have a pretest probability less than the test threshold for PE. The test threshold represents a numeric estimate of the pretest probability which defines a point of equipoise; patients with a pretest probability lower than the test threshold should not benefit (and may even be harmed) from diagnostic testing. Using the method of Pauker and Kassirer, we have previously estimated the point of equipoise to be 2% (rounded to the nearest whole percent) (16;17) The ultimate goal is to produce an actual outcome frequency (i.e., a posterior probability) of VTE that is below 1%, as has been suggested to be the goal of a PE rule out protocol.(18) We hypothesized that patients undergoing evaluation for possible PE, but who satisfied our definition of very low risk would have a measured 45 day incidence of VTE(+) or death with an upper limit 95% confidence interval below 2.0%.

METHODS

This was a prospective, non-interventional, multicenter study of patients presenting to the ED in 12 hospitals in the United States and one in Christchurch, New Zealand. Prior to study initiation, a project manager traveled to each site (except New Zealand) to train site investigators and research associates on protocol methodology. This individual was then available full-time by telephone and email, and if needed with a face-to-face visit throughout the study duration as a resource to investigators. The study protocol was approved by the Institutional Review Boards

for the conduct of research on humans and the Privacy Boards of all 13 hospitals. Patients were enrolled from July 1, 2003 until November 30, 2006. The event that triggered eligibility for enrollment was an order for an objective diagnostic test for PE, written by or under the supervision of a board-certified emergency physician. The decision to order this test was based upon information obtained from the initial history and physical examination, and medical records immediately available in the ED. We defined objective diagnostic testing for PE as either a pulmonary vascular imaging study (CT angiography or scintillation ventilation-perfusion (V/Q) lung scanning) or a D-dimer assay ordered to evaluate for possible PE. Tests done only for suspected DVT only did not trigger enrollment. Pre-enrollment exclusions were: 1. Clinician knowledge of a diagnostic positive pulmonary vascular imaging study performed within the previous 7 days; 2. The patient indicated that the enrollment hospital was not his or her hospital system of choice for follow-up; 3. Any circumstance that suggested that patient would be lost to follow-up (e.g., homeless patients, patients with severe psychiatric disorders, patients who could not provide a reliable telephone number, international travelers, inmates in State or Federal penitentiaries, persons arrested for felonies). These exclusions were determined in the ED by qualified study personnel.

Sites had the option of enrolling patients in one of two ways; either using randomly selected 8 hour time blocks or all patients consecutively with a defined target rate of >85%. Adherence to the 85% threshold was estimated by retrospective review of computerized order entry databases (see Appendix) to locate and sum the number of D-dimer studies ordered for adults with one or more symptoms shown in Table 1 (or obvious documentation of PE suspicion), all VQ scans and all CT pulmonary angiography studies ordered and done during the active hours of enrollment. These reviews were done on a quarterly basis. A patient could be enrolled more than once if he or she had a test ordered for PE on separate days of presentation. Enrollment was completed after the first of 500 patients or 18 months of data collection. If a site could not

achieve greater than 85% capture with consecutive enrollment, this triggered a medical record review of patients who were eligible for enrollment, but who were missed (i.e., intent-to-study group). The purpose of this intent-to-study group was to allow statistical comparison of the key demographics and frequency of VTE between enrolled versus missed patients.(19) If the number of missed patients exceeded the number enrolled, then data were abstracted from a random sample of missed patients equal to the number enrolled. Data abstraction was performed using published methods.(20)

A key technical objective was to collect clinical data (including the gestalt estimate of clinical suspicion) that accurately represented the clinicians' beliefs at the time when he or she decided to order a diagnostic test for PE, but prior to knowing the results. To achieve this objective, clinicians collected and recorded study data coincident with clinical care, as illustrated in Figure 1. Data were entered into a web-based, secure, electronic data collection form. This protocol specified that the form be completed before the results of testing were known, and the form required the clinician to input if he or she had knowledge of any test results pertinent to diagnosis of VTE at the time it was populated. A full description of the content and methodology for this data collection system has been published.(21) Physicians clicked one of three radio buttons to encode gestalt pretest probability estimate for PE as less than 15%, 15-40% or greater than 40%. The form then asked for the data required for the PERC rule as well as 65 other data points. All fields had explicit definitions, available in a pop-up box at the click of a mouse. This form employed automated checks to prevent upload of missing or nonsensical data. Classification as very low risk required that the clinician encode a gestalt pretest probability less than 15%, as well as all 8 factors required for PERC(-) into the form. The protocol permitted use of a personal digital assistant loaded with the data form, or a paper template to facilitate data transfer to the web-based form. Once the data form was uploaded, the patient was enrolled, and no patients were excluded. To help ensure comprehensive follow-up,

we recorded if the patient stated that the enrollment hospital was his or her preferred hospital. Figure 2 shows the suggested diagnostic algorithm to allow exclusion of PE in the ED that was provided to all clinicians who participated. Imaging protocols were overseen by the Radiology Department at each institution and all image results were from the final interpretations signed by a board-certified radiologist.

We followed all enrolled patients for outcome at 45 days. We have found that longer time interval reduces probability of successful contact.(20) No patients were excluded on the basis of follow-up, so the protocol required follow-up on every patient. The protocol required the one of the following: documented follow-up history and physical examination that contained sufficient information to allow the site investigator to determine the VTE status at 45 days, telephone or mail contact with the patient, family member or the patient's clinician Follow-up data were collected between 45 days after enrollment but before closure of the study. If we were unable to obtain a medical record, and could not contact the patient, we searched the social security death index to determine vital status (<http://ssdi.rootsweb.com>). We obtained the death certificate for all decedents. We documented results of tests, clinical diagnoses, treatments, death-related data, and findings from telephone interview on a more extensive, web-based follow-up form that encoded 143 data fields.(20) Consistent with contemporaneous research and expert opinion(22-25), we used either PE or deep venous thrombosis, DVT as evidence of VTE+ in the reference standard. The VTE status was established by adjudicated review of imaging results, medical records, and follow-up. Assignment of VTE present or absent within 45 days required agreement between two independent clinicians who used explicit criteria. Positive evidence of PE required either a high-probability VQ scan or CT angiogram or conventional pulmonary angiogram that demonstrated a pulmonary arterial filling defect interpreted as positive for acute PE, or autopsy positive for PE. Positive evidence of DVT required extremity

venous duplex Doppler-ultrasonography or CT venography interpreted positive for acute venous thrombosis in the popliteal, femoral, or axillary, (but not calf) veins. Diagnosis of VTE also required written documentation of a clinical plan to treat with anticoagulation using either a vitamin K antagonist, or parenteral low molecular weight heparin for ≥ 3 months, or insertion of a vena caval filtering device in a patient with a contraindication to anticoagulation. Exclusion of VTE required absence of positive imaging for VTE and no treatment for VTE within 45 days. For the intent-to-study group (eligible patients not enrolled during the time of active enrollment and not included in the main analysis), the diagnosis of VTE(+) required one or more VTE-related ICD-9 (or 10) codes (415.X, 451.X and 453.X) to be documented within 45 days after having a diagnostic test ordered to rule out PE in the ED while the study was actively enrolling.

Statistical analysis

The hypothesis stated that the upper limit of the 95% confidence interval for the proportion of very low risk patients who met the primary endpoints of VTE(+) or death from any cause within 45 days would not exceed 2.0%. For the sample size calculation, we estimated that approximately 20% of the cohort patients would fall into the very low risk category and that 1% of these patients would actually have the primary endpoint of VTE diagnosed within 45 days. Using the method described by Arkin, we computed a sample size of 7,000 patients would allow us reject the null hypothesis at $\alpha=0.05$ (i.e, <5% probability that the true incidence of VTE was >2.0% in very low risk patients) and to demonstrate an 80% power to narrow one side of the 95% CI to <1.0%.(26) We used the Clopper-Pearson exact method to compute confidence intervals for proportions (StatsDirect, v 2.4.4, Cheshire England).

RESULTS

The study enrolled 8,138 patients from 12,213 eligible patients. Figure 3 shows the outcomes of all patients. Table 1 describes the demographic data, age and clinical characteristics of the

cohort. The mean age was 49 years, and women comprised approximately two-thirds of the cohort. The first symptom that prompted the ED visit was chest pain (53%), dyspnea (33%), cough (3%), syncope (2%), respiratory distress (2%), seizure (0.1%), and other (7%). Fifty-five percent of patients indicated that their first symptom onset was “sudden” and 45% said the onset was “gradual.” Seventy-six percent of the cohort had one or more of the comorbid conditions listed in Table 1. Forty-two percent had either a respiratory rate greater than 22 breaths/min or a pulse rate greater than 100 beats/min at the time of enrollment.

Table 2 summarizes associated beliefs and actions of clinicians that are pertinent to assessing their clinical suspicion for PE. Clinicians documented a low clinical suspicion (i.e., gestalt impression <15%) in two-thirds of all patients, and 80% of clinicians recorded that they believed an alternative diagnosis was more likely than PE at the time they ordered a diagnostic test for PE.

Table 3 shows the results of diagnostic testing for PE. Seventy-four percent had a D-dimer ordered; 55% had CT angiography, VQ scanning, or both performed. In 5999 (74%) patients, the results of PE-related diagnostic tests were completely normal.

Table 4 shows the outcomes that occurred within 45 days of enrollment. Of 8,138 patients tested for possible PE in the ED, a total of 513 were diagnosed with VTE. Follow-up found that 47 patients (0.5% of the cohort) were diagnosed with VTE after discharge from the enrollment visit but were not diagnosed at the time of the index ED visit or hospitalization. One patient died of undiagnosed PE discovered at autopsy. Thus, 561 patients (6.9%) met a criterion standard for the diagnosis of VTE(+) within 45 days. The median incidence of VTE(+) among the 13 sites was 6.9% (interquartile range, 5.8 to 8.6%). The measured 45 day incidence of VTE(+)

stratified by the gestalt pretest probability estimates of <15%, 15 to 40% and >40% were 3.0%, 10.4% and 31.1%, respectively.

Additionally, 1,745 patients were classified by clinicians as having both an alternative diagnosis more likely than PE, and PERC(-), and 16 of these were VTE+ within 45 days, yielding a posterior probability of 0.9% (95% CI: 0.5 to 1.5%).

Four sites (Northwestern Memorial, Pitt County Memorial, St. Vincent Mercy Medical and William Beaumont) enrolled consecutively but did not meet the prespecified 85% goal, and were thus considered convenience samples. We therefore performed a medical record review of a random sample of missed patients, equal to the number enrolled at each of these four sites (n=2,040), and compared the demographics of these patients with the 8,138 patients that we enrolled. The mean age of these 2,040 patients was 52 ±18.7 years, 64% were female, 55% were Caucasian, and 130 (6.4%) were diagnosed with VTE(+), including 3.9% with PE only, 1.1% with DVT only, and 1.3% with both PE and DVT. The 95% CI for the 0.5% difference between this 6.4% versus the 6.9% in the study cohort was -1.7 to 0.7%, suggesting no significant difference in the VTE(+) rate between the study cohort and the intent-to-study group.

Table 5 shows the outcomes of patients based upon results of the PERC rule. Clinicians recorded all eight variables of the PERC rule as negative in 1952 (24%) of patients. The false negative rate in this subgroup was 1.2% (95% CI: 0.8%-1.8%) for VTE(+) and the false negative rate was 1.3% (95% CI: 0.8%-1.9%) for the combined endpoints of either VTE(+) or death from any cause within 45 days. If we were to treat PERC(-) as an independent diagnostic test, its sensitivity would have been 95.7% (95% CI: 93.6 to 97.2%), the specificity would equal 25.4% (24.4 to 26.4%) and the negative likelihood ratio would have been 0.17 (95% CI: 0.11 to 0.25).

Sixteen hundred and sixty-six patients (20% of the cohort) were classified as very low risk. On a per-site basis, the proportion of patients in this very low risk group ranged from 10 to 36%, with a median value of 19% for all 13 sites. The false negative rate in this very low risk subgroup was 0.9% (95% CI: 0.5 to 1.5%) for VTE(+) and 1.0% (0.6 to 1.6%) for VTE(+) or death from any cause within 45 days. If it were treated as a diagnostic test, the very low risk classification would have yielded a diagnostic sensitivity equal to 97.4% (95.8 to 98.5%), a specificity equal to 21.9% (21.0% to 22.9%), and a negative likelihood ratio equal to 0.12 (95% CI: 0.07 to 0.19).

DISCUSSION

In this large, multicenter study, we found that clinicians employ a very low threshold to test for PE, resulting in a very high rate of negative testing and a low rate of PE diagnosis. We used rigorous methodology to ensure a patient sample and a dataset that would allow broad inferences about the perceptions of clinicians when they tested for PE. To our knowledge, this is the largest prospective study of patients tested for PE. We enrolled patients from urban and rural settings, from teaching and community hospitals and at high altitudes. We recognized the potential roles of convenience sampling or the informed consent process as sources of bias, and we attempted to control for these by our sampling methods and cross-checking patients who were eligible but were missed for enrollment.(27) The population was diverse in racial and ethnic composition and the patients were drawn from a wide geographic range.

We found that in two-thirds of cases, emergency clinicians harbor a low suspicion for PE when they order a diagnostic test to evaluate for PE. In 80% of cases, clinicians ordered a diagnostic test for PE with the belief that an alternative diagnosis was more likely than PE. 1843 patients underwent CT angiography that yielded images interpreted as completely normal by a board-certified radiologist. While we recorded the category of “other” interpretations in 36% of CT angiograms, the majority of these were of questionable significance (e.g., enlarged lymph nodes

or small pleural effusion). Taken together, the combination of low physician pretest suspicion and the preponderance of negative imaging results, infer the opportunity for the PERC rule to save resources and time, and to reduce patient exposure to potential negative impact of ionizing radiation and iodinated contrast.(14;15;28;29) Of relevance, the very low risk subgroup included 362 patients who had a completely normal CT angiography.

The clinician's clinical suspicion for PE was low and the PERC rule was negative in 1666, or 20% of the cohort. In this very low risk subgroup, 1.0% were VTE(+) or died within 45 days, and the top limit 95% confidence interval of this proportion was 1.6%. Similarly, the clinician indicated that an alternative diagnosis were more likely than PE and the PERC rule was negative in 1,745 patients, and only 16/1,745 (0.9%, 95% CI: 0.5 to 1.5%) had VTE within 45 days. Thus, the very low risk categorization produced a false negative rate similar to that observed after a negative quantitative D-dimer, a normal scintillation lung scan, negative multidetector CT chest angiography, or formal pulmonary angiography negative for PE.(30;31) Only one very low risk patient died (of end-stage cancer) within 45 days.

Three published studies have performed secondary analyses of existing databases to test the performance of the PERC rule, independent of gestalt reasoning.(32-34) In aggregate, these studies included 1542 patients, of whom 362 (24%) were PERC negative, and 9 (2.4%) had VTE. The present study found the PERC rule had a negative likelihood ratio equal to 0.17 within the entire cohort, suggesting that the PERC rule negative would afford a false negative rate below 1.0% only if the initial prevalence of VTE is less than 6% in the population under consideration. These data underscore the need for gestalt reasoning to precede the PERC rule. We submit that in real practice, clinicians will use a validated clinical decision rule to rule-out PE only when they believe that the clinical picture portrays a low-risk profile. Moreover, no sensible decision rule could exclude all possible high-risk PE cases. Runyon et al. previously found that

unstructured gestalt categorization of pretest probability into three categories (low, moderate and high) yields results that exactly mirrored those of a validated, structured scoring system, and that the sensitivity of gestalt did not decrease based upon year of experience.(35)

Moreover, two studies independently found the interobserver reliability for gestalt reasoning to be very good, based upon a Cohen's kappa value above 0.60. (35;36) Regardless of its level of validation, we submit that most clinicians currently employ gestalt reasoning as their primary method of formulating pretest probability.(37)

Limitations of our study could include the position that gestalt interpretation of low risk limits generalizability. Moreover, this was not a management study; clinicians did not use the PERC rule instead of diagnostic testing in any patient, therefore the true safety of the PERC rule cannot be fully inferred. Some may hesitate to use clinical criteria that are not 100% sensitive to exclude a potentially fatal disease. It could be speculated that patients in our cohort differ from ED patients in other countries. We found that only 5.9% of our cohort had PE within 45 days, and 6.9% had either PE or DVT within 45 days. The classification of VTE status by adjudicators also was dependent upon the judgment of their physicians. It should be emphasized that the underlying prevalence of VTE may be too high in other emergency department populations for this strategy to safely rule out PE. (23;38;39) Thus, we would suggest that prior to implementation at any hospital, the tandem strategy of using gestalt <15% and PERC(-) should be pilot-tested in an observational quality assurance study, to ensure an acceptably low posterior probability (e.g. <1%).(18)

In summary, we followed a cohort of 8,138 outpatients who were tested for PE in the ED, and found that 6.9% were VTE(+) within 45 days. One-fifth of the cohort could have been classified as very low risk, defined as a gestalt pretest probability less than 15% and PERC(-). In this very low risk subgroup, 1.0% (95% CI: 0.6 to 1.6%) had VTE within 45 days. The combination of a

clinician's gestalt estimate of a pretest probability less than 15% and PERC(-) selects a subgroup of patients with a very low probability of VTE.

Addendum

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Author contributions

JAK conceived and organized the study, obtained funding, collected and analyzed data and drafted the manuscript.

DMC, CK, CLM, HAS, TRM, MCP, PRB, BJO participated in writing the study protocol, obtaining funding, data collection and analysis, and drafting and revising the manuscript.

DMB, MT, AMM and KEN collected and analyzed data and helped write the manuscript

CAC helped write the protocol, analyze and interpret data, and draft and revise the manuscript

CLJ contributed to the overall study design based upon design and operation of the web-based data collection system, he helped to collect and analyze data and draft the manuscript.

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William B. Webb, BS was the research project manager.

Conflicts of interest and Financial disclosure

JAK owns stock in CP Diagnostics LLC and Studymaker LLC

CLJ owns stock in CP Diagnostics LLC and Studymaker LLC

All authors have access to all data using the rules of the data use agreement

Reference List

- (1) Courtney DM, Sasser H, Pincus B, Kline JA. Pulseless electrical activity with witnessed arrest as a predictor of sudden death from massive pulmonary embolism in outpatients. *Resuscitation* 2001;49:265-72.
- (2) Kurkciyan I, Meron G, Sterz F, Janata K, Domanovits H, Holzer M, Berzlanovich A, Bankl HC, Laggner AN. Pulmonary embolism as a cause of cardiac arrest. *Arch Intern Med* 2000;160:1529-35.
- (3) Manfredini R, Portaluppi F, Grandi E, Fersinsi C, Gallerani M. Out of hospital sudden death referring to an emergency department. *J Clin Epidemiol* 1996;49:865-8.
- (4) Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest* 1997;112:974-9.
- (5) Susec O, Boudrow D, Kline J. The clinical features of acute pulmonary embolism in ambulatory patients. *Acad Emerg Med* 1997;4:891-7.
- (6) Ryu JH, Olson EJ, Pellikka PA. Clinical recognition of pulmonary embolism: Problem of unrecognized and asymptomatic cases. *Mayo Clin Proc* 1998;73:873-9.
- (7) Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, Melton LJ, III. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Archives of Internal Medicine* 2002;162:1245-8.
- (8) Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *American Journal of Medicine* 2004;117:19-25.
- (9) Ota M, Nakamura M, Yamada N, Yazu T, Ishikura K, Hiraoka N, Tanaka H, Fujioka H, Isaka N, Nakano T. Prognostic significance of early diagnosis in acute pulmonary thromboembolism with circulatory failure. *Heart & Vessels* 2002;17:7-11.
- (10) Kline JA, Hernandez J, Jones AE, Rose GA, Norton HJ, Camargo CA, Jr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med* 2007;14:592-8.
- (11) Studdert DM, Mello MM, Sage WM, DesRoches CM, Peugh J, Zapert K, Brennan TA. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment *JAMA* 2005;293:2609-17.
- (12) Taylor H. Doctors and other health professionals report that fear of malpractice has a big and mostly negative effect on clinical practice, unnecessary defensive medicine and openness to discussing medical errors. Taylor H, Leitman R, editors. 2[3], 1-5. 2003. Harris Interactive. Health Care News.

- (13) Kabrhel C, Matts C, McNamara M, Katz J, Ptak T. A highly sensitive ELISA D-dimer increases testing but not diagnosis of pulmonary embolism. *Acad Emerg Med* 2006;13:519-24.
- (14) Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007;298:317-23.
- (15) Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277-84.
- (16) Kline JA, Mitchell AM, Kabrhel C., Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thrombosis Haemostasis* 2004;2:1247-55.
- (17) Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *New England Journal of Medicine* 1980;302:1109-17.
- (18) Kline JA, Wells PS. Methodology for a rapid protocol to rule out pulmonary embolism in the emergency department. *Ann Emerg Med* 2003;42:266-75.
- (19) Kline JA, Israel EG, Michelson EA, O'Neil BJ, Plewa MC, Portelli DC. Diagnostic accuracy of a bedside D-dimer assay and alveolar deadspace measurement as for rapid exclusion of pulmonary embolism. A multicenter study. *JAMA* 2001;285:761-8.
- (20) Kline JA, Mitchell AM, Runyon MS, Jones AE, Webb WB. Electronic medical record review as a surrogate to telephone follow-up to establish outcome for diagnostic research studies in the emergency department. *Acad Emerg Med* 2005;12:1127-232.
- (21) Kline JA, Johnson CL, Webb WB, Runyon MS. Prospective study of clinician-entered research data in the emergency department using an internet-based system after the HIPAA Privacy Rule. *BMC Medical Informatics and Decision Making* 2004 2005;4:17-25.
- (22) Wolde MT, Hagen PJ, MacGillavry MR, Pollen IJ, Mairuhu ATA, Koopman MMW, Prins MH, Hoekstra OS, Brandjes DPM, Postmus PE, Buller HR. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. *J Thrombosis Haemostasis* 2004;2:1110-7.
- (23) Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, Leftheriotis G, Barghouth G, Cornuz J, Hayoz D, Bounameaux H, Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, Leftheriotis G, Barghouth G, Cornuz J. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *American Journal of Medicine* 2004;116:291-9.
- (24) Wolfe TR, Hartsell SC. Pulmonary embolism: making sense of the diagnostic algorithm. *Ann Emerg Med* 2001;37:504-14.
- (25) Moores LK. Diagnosis and management of pulmonary embolism: are we moving toward an outcome standard? *Arch Intern Med* 2006;166:147-8.

- (26) Arkin CF, Wachtel MS. How many patients are necessary to assess test performance? *JAMA* 1990;263:275-80.
- (27) Mitchell AM, Kline JA. Systematic bias introduced by the informed consent process in pulmonary embolism prevalence. *Ann Emerg Med*. In press 2008.
- (28) Coche E, Vynckier S, Octave-Prignot M, Coche E, Vynckier S, Octave-Prignot M. Pulmonary embolism: radiation dose with multi-detector row CT and digital angiography for diagnosis. *Radiology* 2006;240:690-7.
- (29) Mitchell AM, Kline J.A. Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. *J Thromb Haemost* 2007;5:50-4.
- (30) PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. *JAMA* 1990;263:2753-9.
- (31) Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, Leeper KV, Jr., Popovich J, Jr., Quinn DA, Sos TA, Sostman HD, Tapson VF, Wakefield TW, Weg JG, Woodard PK. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 2006;354:2317-27.
- (32) Righini M, Le Gal G, Perrier A, Bounameaux H. External evaluation of the performance of the pulmonary embolism research consortium rule (PERC rule). *J Thrombosis Haemostasis* 2004;3:188-9.
- (33) Hogg KE, DAWSON D, Kline JA. Application of pulmonary embolism rule-out criteria to the UK Manchester Investigation of Pulmonary Embolism Diagnosis (MIOPED) study cohort. *J Thromb Haemost* 2005;3:592-3.
- (34) Wolf SJ, McCubbin TR, Naviaux NW, Nordenholz KE, Haukoos JS. External Validation of the Pulmonary Embolism Rule-out Criteria Rule. *Academic Emergency Medicine* 2005;12:40.
- (35) Runyon MS, Webb WB, Jones AE, Kline J.A. Comparison of the unstructured clinician estimate of low clinical probability for pulmonary embolism to the Canadian score or the Charlotte rule. *Acad Emerg Med* 2005;12:587-93.
- (36) Nordenholz KE, Naviaux NW, Stegelmeier K, Haukoos JS, Wolf SJ, McCubbin T, Heard K. Pulmonary embolism risk assessment screening tools: the interrater reliability of their criteria. *Am J Emerg Med* 2007;25:285-90.
- (37) Runyon MS, Richman PB, Kline JA. Emergency medicine practitioner knowledge and use of decision rules for the evaluation of patients with suspected pulmonary embolism: variations by practice setting and training level. *Acad Emerg Med* 2007;14:53-7.
- (38) van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruij MJ, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Sohne M, Tick LW. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006;295:172-9.

- (39) Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, Revel MP, Carette MF, Laurent M, Charbonnier B, Laurent F, Mal H, Nonent M, Lancar R, Grenier P, Simonneau G, Evaluation du Scanner Spirale dans l'Embolie Pulmonaire study group. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. *Lancet* 2002;360:1914-20.

Table 1. Clinical features of 8,138 emergency department patients who were tested for pulmonary embolism

Demographic data		
	<i>mean or n</i>	<i>±SD or %</i>
Age (years)	49.1±17.8	
Black race	2669	32%
Caucasian race	4811	59%
Latino or Hispanic descent*	461	6%
Asian race	66	1%
Other race	131	2%
Female gender	5428	67%
Symptoms		
Pleuritic chest pain†	3598	44%
Substernal chest pain	2785	34%
Dyspnea	4129	51%
Syncope	478	6%
Cough	2381	29%
Hemoptysis	243	3%
Comorbid Conditions		
Current smoker	2850	35%
Active malignancy	1216	15%
Immobility‡	2067	25%
Recent surgery§	540	7%
Pregnant or post-partum <4 weeks	808	10%
Prior PE or DVT	860	11%
Congestive heart failure	804	10%
Chronic obstructive pulmonary disease	474	6%
Known coronary artery disease	1041	13%
Connective tissue disease	529	7%
Exogenous estrogen	870	11%
Taking warfarin	543	7%
Hematological thrombophilia¶	412	5%

(Table 1 continued from page 21)

Physical findings

Highest pulse rate (beats/min) ††	92±21	
Highest respiratory rate (breaths/min) ††	21±9	
Lowest systolic blood pressure (mm Hg) ††	131±28	
Lowest room air pulse oximetry (%)††	96±4	
Temperature (°C)	37±1	
Body Mass Index (kg/m ²)	29±8	
Wheezing	781	10%
Unilateral leg swelling	707	9%

*Recorded as a race. †Non-substernal and worse with breathing or cough; ‡generalized immobility >72 hours, therapeutic limb fixation causing immobility of >1 major joint, or continuous travel in seated position >6h; § surgery or trauma within four weeks and requiring endotracheal intubation; ¶patient report or medical record, including genetic variations, hemoglobinopathies, and antiphospholipid antibody syndromes; . ††Highest and lowest values prior to ordering the first test for PE.

Table 2. Perceptions of clinicians pertinent to pretest probability of pulmonary embolism

Clinicians' unstructured estimate of pretest probability of PE	n	%
less than 15%	5425	67%
15 to 40%	2182	27%
greater than 40%	531	7%
Other data documented at the time of testing		
Plan to administer heparin before imaging completed	351	4%
Alternative diagnosis more likely than PE	6514	80%
DVT imaging preplanned*	867	11%

* This field indicated explicit plan to perform lower extremity ultrasound if results of pulmonary vascular imaging were negative.

Table 3. Frequency of ordering and results of diagnostic testing for pulmonary embolism

Diagnostic Test	n	%
D-dimer	6019	74%
positive	2797	
negative	3222	
CT angiography	4127	51%
PE	365	
PE and DVT*	73	
DVT only†	24	
pulmonary infiltrate, no PE	230	
other non-PE finding	1506	
normal	1843	
indeterminate or inadequate imaging	86	
Scintillation lung scanning	486	6%
high probability	40	
intermediate probability	47	
low probability	273	
normal	126	
Venous ultrasound	962	12%
negative for DVT	808	
calf or saphenous thrombosis	86	
femoral or axillary vein thrombosis	68	

*Four of 13 sites used CT venography as part of the CT angiography protocol

†Includes 12 who had follow-up venous ultrasonography that was negative and who were not treated.

Table 4. Outcomes at 45 days for the cohort of 8,138 emergency department patients

Outcome*	n	%	95% CI
Any VTE	561	6.9%	6.3 to 7.5%
PE only	371	4.6%	4.1 to 5.0%
DVT only	80	1.0%	0.8 to 1.2%
PE and DVT	109	1.3%	1.1 to 1.6%
Death from PE	1	0.0%	0.0 to 0.1%
Death, no known VTE	56	0.7%	0.5 to 0.9%

*PE or DVT required imaging evidence and clinical plan to treat within 45 days of enrollment.

Table 5. Outcomes of low-risk patients

Outcome	PERC(-)* n=1,952			Very low risk n=1,666		
	n	%	95% CI	n	%	95% CI
PE	19	1.0%	0.6 to 1.5%	15	0.9%	0.5 to 1.5%
Any VTE	24	1.2%	0.8 to 1.8%	15	0.9%	0.5 to 1.5%
VTE or Death	25	1.3%	0.8 to 1.9%	16	1.0%	0.6 to 1.6%

*age<50, pulse<100, SaO₂≥95%, no hemoptysis, estrogen use, surgery/trauma requiring hospitalization within four weeks, prior VTE, and no unilateral leg swelling.

Abbreviations: very low risk-no test needed; PERC-pulmonary embolism rule-out criteria; PE-pulmonary embolism; VTE-venous thromboembolism.

Figure 1. Overview of research-related activities, relative to the main steps in clinical care.

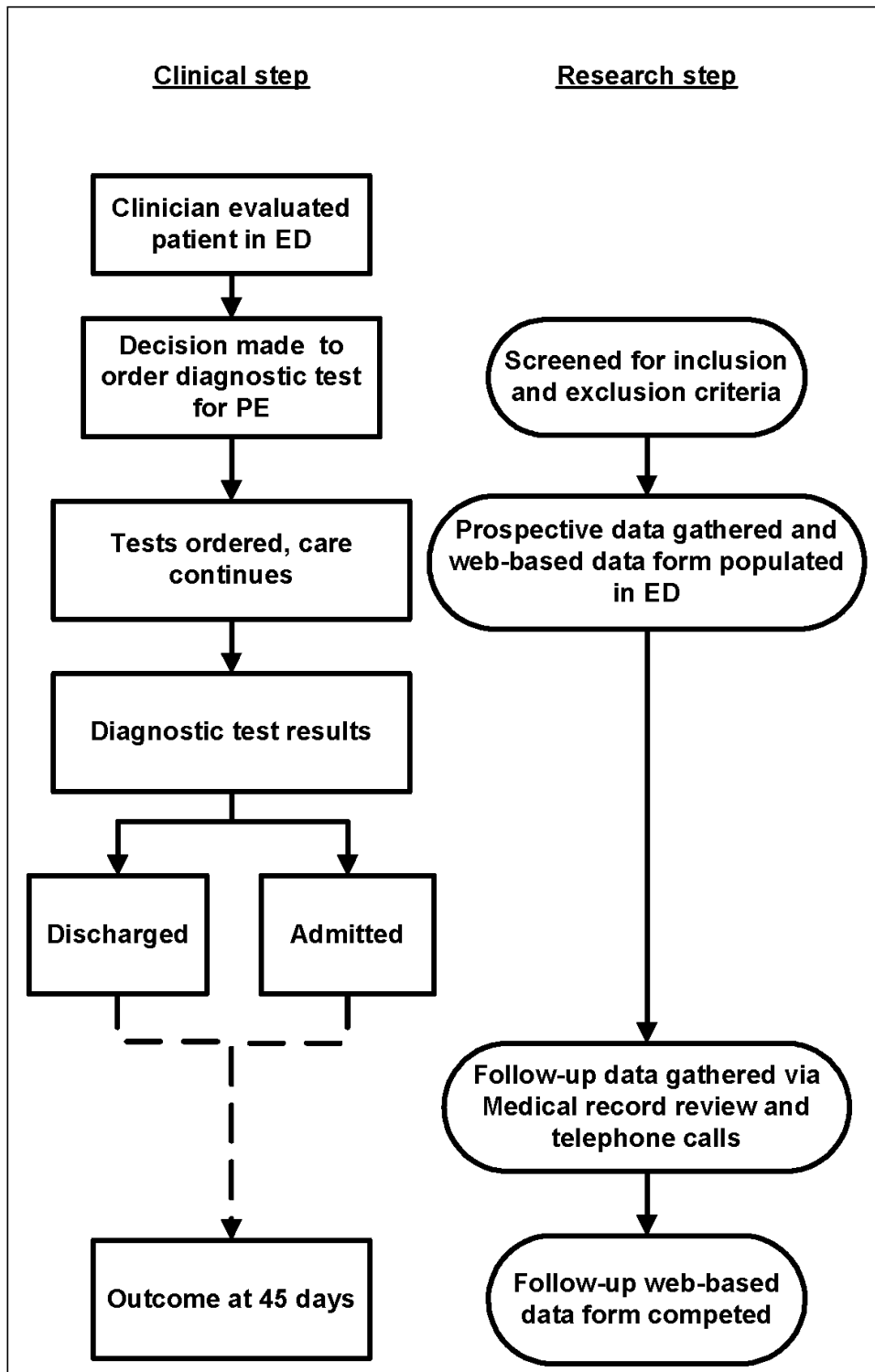


Figure 2. Overview of the diagnostic algorithm used by all 13 study hospitals to exclude the diagnosis of pulmonary embolism in the emergency department. All patients had either a D-dimer, CT angiography or ventilation-perfusion lung scan performed. Solid lines depict primary pathways and dotted lines represent secondary pathways. *Yale University used a qualitative D-dimer.

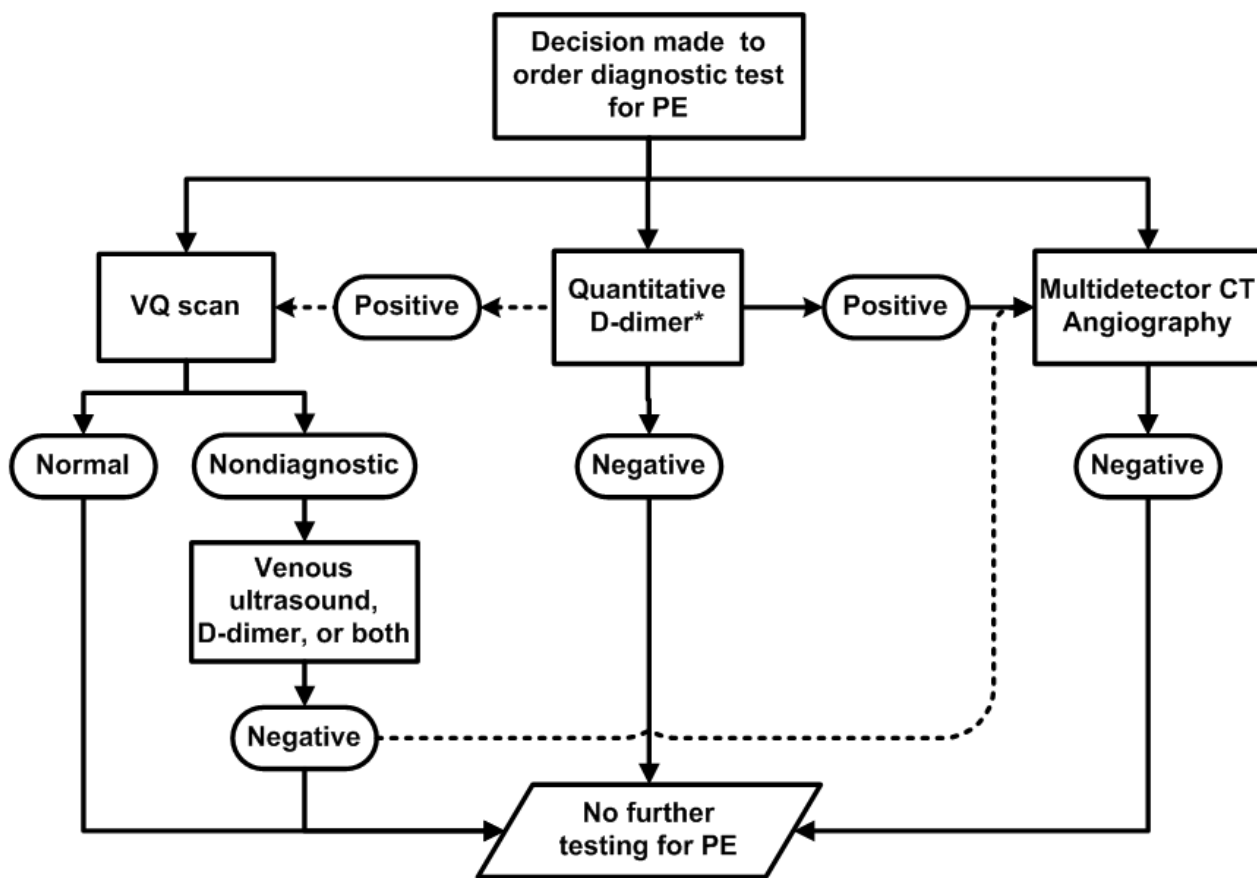
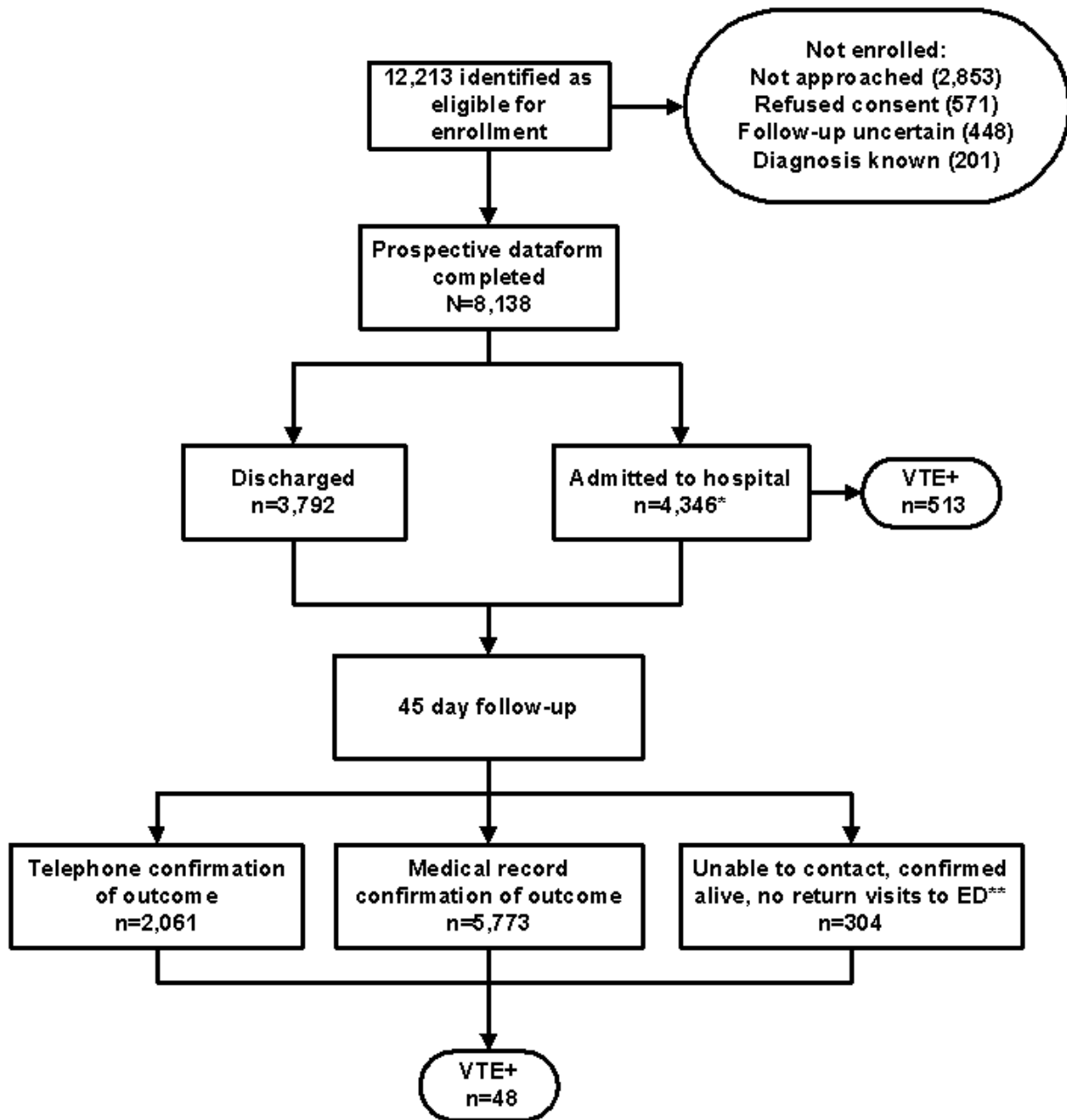


Figure 3. Flow diagram showing outcomes of all patients (*telemetry 2,158 unmonitored ward 958, ED Observation 1,015, ICU 215. **All patients indicated that the study hospital was his or her hospital of choice).



Appendix

Table. Enrollment details for the 13 sites

Hospital name	Location	Start date	End date	Method of enrollment	Informed Consent	Number enrolled	Eligible	Computerized system(s) queried
Carolinas Medical Center	Charlotte, NC	5/1/2004	6/30/2006	Consecutive	Written and Waiver*	2609	2838	McKesson Horizon and Star
University Hospital	Charlotte, NC	9/2/2004	9/30/2005	Random	Written	498	641	McKesson Horizon and Star
Northwestern Feinberg School of Medicine	Chicago, IL	10/27/2004	9/14/2006	Convenience†	Written	1081	2285	Cerner powerchart
Yale School of Medicine	New Haven, CT	9/1/2004	3/31/2005	Consecutive	Verbal	551	719	Zixcorp (Dallas TX)
Baystate Medical Center	Springfield, MA	12/2/2004	3/8/2006	Consecutive	Written	500	581	Cerner Millennium Clinical Information System (CIS).
St. Vincent Mercy Medical	Toledo, OH	5/10/2005	8/26/2006	Convenience†	Waiver	458	500	Invision Patient Information Net Access (Siemens)
Exempla St. Josephs	Denver, CO	3/29/2005	9/19/2005	Random	Written	476	627	Meditech for CT/VQ and MiSys Laboratory System for Dimers
University of Colorado	Denver, CO	8/9/2005	4/10/2006	Random	Written	126	202	Pulsecheck (Picis)
Mayo Clinic	Phoenix, AZ	11/4/2004	9/30/2006	Random	Written	432	550	IDX
Pitt County Memorial Hospital	Greenville, NC	2/1/2006	10/30/2006	Random	Written	188	210	McKesson, Wellsoft and SMS
Christchurch Hospital	Christchurch, NZ	9/23/2003	9/30/2004	Consecutive	Written	427	681	Manual tracking
Massachusetts General Hospital	Boston, MA	10/1/2004	2/30/2006	Random	Verbal	492	547	EDIS and IDX
William Beaumont Hospital	Royal Oak, MI	11/17/2005	11/16/2006	Convenience†	waiver	300	1832	Medical record abstract system

*70% waiver.

†Initially started as consecutive, but fell short of 85%