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Predicting short term mortality after investigation for venous thromboembolism ☆

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ABSTRACT

Introduction: Deaths following diagnosis of venous thromboembolism (VTE) often result from another concurrent illness. The specificity of mortality markers predicting death from pulmonary embolism is unknown. The aim of this analysis was to compare blood predictors of death in patients with confirmed VTE to patients with negative investigations for VTE.

Materials and methods: Consecutive patients investigated for VTE were prospectively consented from a single hospital over 9 months. VTE was diagnosed and excluded with a standard diagnostic algorithm. Blood was drawn for biomarker analysis and analyzed in batches for NT-proBNP, high sensitivity troponin T, C-reactive protein (CRP), fatty acid binding protein (FABP) and ischemia modified albumin (IMA). Participants were followed for 3 months. The cohort was analyzed in two groups: those diagnosed with VTE and those who had thrombosis excluded. Regression analysis for 3-month mortality was performed for each group.

Results: 16/153 patients diagnosed with VTE died within three months (10.5%) as did 23/606 patients who had negative investigations for VTE (3.8%). Predictors for death following VTE included cancer, NT-proBNP, troponin T, FABP, and Hb<95 g/L. NT-proBNP>500 pg/ml in acute cancer associated VTE predicted death with C-statistic of 0.89 (0.80-0.99). Cancer, NT-proBNP and troponin T also predicted death in patients with negative investigations for VTE.

Conclusion: Several blood markers are not specific for death from PE and may be surrogate markers of global declining health.

Introduction

Venous thromboembolism (VTE) is a common disease affecting one person in every 1000 person years [1]. Certain comorbidities such as cancer, sepsis, surgery, and trauma predispose patients to develop thromboembolism. The cumulative three month, all-cause mortality following diagnosis of VTE is around 9% to 15% [2,3]. However, patients diagnosed with VTE are frequently ill with cancer, heart disease or other comorbidity which have an associated mortality risk. Death could result from these coexistent conditions rather than from fatal pulmonary embolism (PE). The three month cumulative mortality from fatal embolism following diagnosis of PE is 2% [2]. Fatal PE occurs in around 0.5% of cases of deep vein thrombosis (DVT) [4].

In recent years, much work has attempted to identify factors that predict death following PE diagnosis. Research has focused on three areas: bedside assessment, diagnostic imaging and blood test results. The Geneva score [5] and the pulmonary embolism severity index [6] were derived to establish a low risk group of PE patients, who might be treated at home. Echocardiogram [7], leg doppler [8] and right ventricle CT volume [9] findings correlate with poor outcome and death following pulmonary embolism. Brain natriuretic peptide (BNP) [10] and troponin blood levels [11] are both associated with increased mortality post PE. There has been almost no research on prognosis following DVT. Blood testing to predict poor outcome in thrombosis is an attractive option, since it is rapid, avoids the application of sometimes complex risk scores, and does not depend on the availability of out-of-hours diagnostic imaging. Information on prognosis is generally used to inform decision making on level of inpatient care (intensive care, high dependency care or routine ward admission), home treatment of VTE and the timing of outpatient follow up.

Patients diagnosed with VTE may have other medical illnesses, and mortality predictors may relate to their comorbidity rather than venous thrombotic disease. For example, serum BNP levels predict death in nursing home residents [12], sudden cardiac death [13], death following an episode of syncope [14] and death during hospital admission for sepsis [15]. BNP is secreted from the myocardium and has classically been used to diagnose cardiac failure. It is unclear whether the association with death is directly mediated through

Abbreviations: VTE, Venous thromboembolism; DVT, Deep vein thrombosis; PE, Pulmonary embolism; BNP, Brain natriuretic peptide; H-FABP, Heart-type fatty acid binding protein; IMA, Ischemia modified albumin; CRP, C-reactive protein; hs troponin T, High sensitivity troponin T.

☆ Parts of this analysis were presented at the XXIII ISTH Congress, Japan 2011 and 14th ICEM Ireland, 2012.

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myocyte stretch in premorbid acute cardiac failure secondary to other conditions. Likewise, troponin, heart-type fatty acid binding protein (H-FABP) and ischemia modified albumin (IMA) are specifically released from the myocardium. All have been associated with VTE, however, like BNP, they might also predict death from unrelated conditions. If these markers are useful in predicting death in patients who have had negative investigations for VTE, the results might help inform physicians on further testing for serious alternative diagnoses, or else indicate which patients could be safely discharged without further investigation.

This was a hypothesis generating study. We aimed to assess multiple blood biomarkers in prediction of all-cause death and PE related death in a cohort of consecutive patients diagnosed with PE and DVT. The study aimed to compare mortality predictors following diagnosis of VTE to mortality predictors in patients who had had negative investigation for VTE.

Materials and Methods

Study Design and Setting

The Thromboembolism Assessment and Diagnosis (THREAD) study was conducted in a UK inner city 900-bed University hospital, providing medical care for around 320,000 patients each year. This was a prospective cohort study and primarily a diagnostic study, designed to assess novel blood tests for VTE. The study was approved by the local Ethics Committee (reference 08/H1014/56).

Selection of Participants

Patients who were suspected of having either DVT or PE were included. Any patient investigated in the emergency department for DVT and any patient investigated for PE either in the emergency department or as an inpatient was eligible to be included in the study. During study planning, a decision was made not to include inpatients (ward patients) investigated for DVT because of wide variation in diagnostic practice between specialties. Although this would limit the generalizability of the study findings, it was not possible to standardize the reference standard diagnostic protocol amongst inpatients investigated for DVT.

The hospital uses an integrated electronic pathway for diagnosing DVT and PE. To ensure identification of all eligible patients, three methods were employed: the researcher was alerted every time a new electronic diagnostic pathway was commenced, hospital staff members could page the researcher, and diagnostic imaging requests were screened. Patients gave written informed consent to participate in the study. To ensure the study cohort reflected the full range of patients investigated for VTE, exclusion criteria were kept to a minimum. Exclusions were inability to consent, refusal to participate and age under 16.

Diagnosis of VTE

Each patient underwent standardized assessment for either DVT or PE. Patients with symptoms of both were investigated for both PE and DVT. PE was diagnosed by an intraluminal filling defect on CT pulmonary angiography or a high probability ventilation-perfusion (VQ) scan in a patient with a high clinical probability of PE. DVT was diagnosed with Doppler ultrasound scan of the legs. Both PE and DVT were excluded by a low probability Wells' score and a normal latex agglutination D-dimer blood test (IL-test D-dimer, Instrumentation Laboratories, Madrid). PE was also excluded by a negative CT pulmonary angiogram, a normal VQ scan or a low probability VQ scan in a patient at low clinical probability of PE. DVT was excluded by two normal serial Doppler ultrasound scans of the leg veins, examining from the trifurcation of the popliteal vein to the iliac veins.

Patient Follow Up

Every patient was followed clinically for three months by hospital record search and direct telephone contact. If the patient could not be contacted by telephone, the family practitioners' records were searched. Death certificates and autopsy results were obtained for all patients who died during follow up. An independent adjudication committee of three experts reviewed the hospital records, family physician records and autopsy results for all patients who died. Cause of death was ascertained when they agreed that PE had or had not contributed to death.

Patient Demographics, Parameters and Blood Tests

The researcher interviewed each patient at the time that consent was obtained. This was done either at the hospital bedside, or by telephone. Risk factors, examination findings and diagnostic test results were recorded.

A sample of the blood drawn at presentation was saved for later analysis in batches. The serum was analyzed for high sensitivity troponin T (hs troponin T) (Roche diagnostics), N-terminal pro-brain natriuretic peptide (NT-proBNP) (Roche Diagnostics), heart-type fatty acid binding protein (H-FABP) (Cambridge Bioscience), C-reactive protein (CRP) (Roche Diagnostics) and ischemia modified albumin (IMA) (Inverness Medical). Each patient had a full blood count drawn as a routine part of their investigation.

This was a hypothesis generating analysis which was conducted *post hoc* on data from a prospective diagnostic cohort study. Each assay was run on serum from the first 400 consecutive patients. The study was designed to assess these biomarkers as diagnostic tests for VTE. Due to funding constraints, only hs troponin T assay was run on every study patient thereafter. In the latter half of the study, CRP and IMA testing was restricted to patients investigated for PE because we hypothesized they might be candidate diagnostic markers for PE and not DVT. In the latter half of the study, only patients who were positive for DVT or PE were tested with BNP and H-FABP, since we expected these biomarkers to function as prognostic indicators following VTE diagnosis.

Statistics

Data were analyzed using SPSS version 20.0. The primary outcome was all cause cumulative mortality within three months of the assessment for VTE.

The initial intention had been to analyze prognostic markers for DVT and PE separately, however there were too few deaths within either cohort to enable separate analysis. Therefore, the patient groups with DVT and PE were combined into one thrombosis group. The second group comprised those patients who had negative investigations for either DVT or PE.

The initial 400 patients (all of whom were tested for the biomarkers) were analyzed alone. Receiver operating characteristics curves (ROC curves) were constructed to assess the prognostic utility of the biomarkers in the group of patients diagnosed with either PE or DVT, and the group of patients who had VTE excluded as a cause for their symptoms. Each biomarker was dichotomized. Univariate logistic regression was used to assess the prognostic utility of the dichotomous variables (symptoms, signs and test results) adjusted for age.

Multivariate analysis was restricted by sample size, and limited to a maximum of two variables per model, using forward stepwise selection. Multivariate analysis was not possible for death from PE, nor was it possible to perform separate analyses of patients treated for DVT and PE. The best model to predict death from any cause within three months of the diagnosis of VTE was identified and reported with the C-statistic.