

Retrospective Study on the Validity of Age Adjusted D-Dimer

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Abstract

The Trust current guidance for the management of patients with possible Pulmonary Embolism (PE) is that any patient presenting with low probability and a D-Dimer level above 500 µg/L is to be considered as positive and therefore referred for a CT Pulmonary Angiogram (CTPA). Authors need to provide assurance to clinicians and the Trust that by making the change in practice to match the recommended NICE guidance of age adjusted D-Dimer (AAD) that there will be no harm to the patients under the care. This would bring the authors in line with other Trusts across the country and the NCEPOD (National Confidential Enquiry into Patient Outcome and Death) guidance.

Other elements to consider are working with the Radiology department to review the implications that the current practice has on radiation exposure. Authors currently refer all patients for a CTPA when there is a raised D-Dimer, if authors were working to AAD then some of these patients would not be referred. The opinion is that this would prevent a radiation exposure, risks associated with the administration of iodinated contrast agents and reduce the number of referrals into radiology, with these factors being considered there is also the potential for reduced bed stay. Due to these factors, there is a potential cost saving for the Trust.

Keywords: Age adjusted D-Dimer; Pulmonary Embolism; Venous thromboembolism; Pre-test probability; CTPA; Disseminated Intravascular Coagulation.

Abbreviations: CTPA: CT Pulmonary Angiogram; AAD: Age Adjusted D-Dimer; NCEPOD: National Confidential Enquiry into Patient Outcome and Death; VTE: Venous thromboembolism; DIC: Disseminated Intravascular Coagulation; ED: Emergency Departments.

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Background

D-Dimer is a protein that is left over after fibrinolysis dissolves a clot. It is made up of two D fragments of the fibrin protein that are connected by a cross-link. The D-Dimer is nonspecific and whilst is a valuable diagnostic test must be considered at point of order and consideration must be taken as to the following. Venous thromboembolism (VTE), cancer, sepsis, and disseminated intravascular coagulation (DIC) can all have elevated D-Dimers. According to American Thoracic Society guidelines, D-Dimer should not be used to rule out PE during pregnancy because it is known to increase throughout the second and third trimesters of pregnancy [1].

Research on the efficacy of AAD in excluding PE has been reported in recent years. This is a common clinical presentation within Emergency Departments (ED) and results in patients often having multiple diagnostic tests to rule out PE. Additionally, research has shown that a revised Geneva score or Wells score with a negative D-Dimer level that indicates a low clinical probability of PE can safely rule out the diagnosis of PE without requiring additional imaging [2-4].

When a patient is 50 years of age or older and has suspected PE, the D-Dimer test result is deemed negative if the value is less than the patient's age multiplied by 10 (e.g., a cut-off of 600 in patients 60 years of age), whereas PE was excluded in those with a low clinical probability and a D-Dimer level lower than 500 µg/L [5].

A large retrospective multicenter cohort study of more than 5000 patients shows that an age adjusted cut-off level for the D-Dimer test doubles the proportion of older patients

(>70 years) in whom PE can be safely excluded in comparison with the conventional cut-off value of 500 µg/L. This concluded that PE could be safely ruled out in 25% and 30% of those patients reducing the risk of unnecessary anticoagulation, risk of iodine contrast injection reactions and radiation risk [6].

NICE guidelines suggested that AAD tests had marginally reduced sensitivity to unadjusted tests (96% versus 98%). Age-adjusted testing, on the other hand, appears to have better specificity and may be able to lower the frequency of false positive results, which can affect patients and resources.

NICE agree that increased specificity of age-adjusted testing in those patients aged over 50 years old came at only a very marginal reduction in sensitivity. Therefore, they recommend that age adjustment be considered for PE exclusion in patients aged over 50 years due to the absence of evidence for other age groups [7].

Goodwin AJ, et al., expressed worry about the condition of D-Dimer testing at the moment [8]. The authors contend that the lack of standardization in D-Dimer tests can make it difficult to use AAD cut-offs safely. The age adjusted cut-off shouldn't be interpreted using several tests that haven't been thoroughly studied. This may have been one of the factors for NICE's first recommendation against the point-of-care D-Dimer test.

Diverse D-Dimer assays can be attributed to a variety of factors, such as varied instrumentation and methodology, monoclonal antibodies with differing D-Dimer specificities, and different values utilized to distinguish between positive and

negative test results. It is challenging to standardize because of all these issues. As a result, physicians must be knowledgeable about the features of the assay that is employed at their facility. [9]. NCEPOD (2018) made additional recommendations for the best way to treat patients with query PE after observing that clinical notes did not adequately document pre-test probability and that radiologist reports did not specifically address whether right ventricular strain was present or absent in cases of confirmed PE [10].

Audit proposal

Aim

The Trust aims to improve the documentation of pre-test probability in clinical notes, move the cut-off point from 500 µg/L to AAD in patients 50 years of age or older, and encourage our radiology department to report on the presence or absence of right ventricular heart strain in their reports.

Method

The objective of our quality improvement project is to gather 400 CTPA scans (computed tomography pulmonary angiography) from patients who are 50 years of age or older in the past. Authors want to incorporate the pre-test probability, age, sex, laboratory D-Dimer, AAD, and CTPA result. Authors received the patient list from the local Picture Archiving and Communication Systems (PACS) department. Radiology results should be reported by consultant radiologists.

By the end of the trial, authors aim to increase the validity of AAD and perform a sub analysis to determine the proportion of

patients for whom we could have avoided prescribing needless anticoagulation, the risk of sequelae from contrast-induced hyperemia, and needless radiation exposure.

The D-Dimer result will be interpreted according to our standard cut-off point of 500 µg/L. Furthermore, an analysis will be conducted using an age-adjusted cut-off, which is deemed negative if the patient's D-Dimer is less than their age (in years) x 10.

Inclusion criteria

- Patients with suspected PE
 - Age >50 years of age
 - Low clinical probability for PE.
- Exclusion criteria:
- Patients with known DVT
 - Age below 50 or pregnant women
 - Patients on anticoagulation at time of test

Patients who test positive for COVID-19 because there is compelling evidence linking the virus to elevated D-Dimer levels brought on by either a severe COVID-19 infection or a degree of thrombosis. Elevated D-Dimer may be linked to the progression of COVID-19, according to recent studies that record laboratory abnormalities in patients with confirmed COVID-19. Patients who were referred to the intensive care unit (ICU) due to COVID pneumonitis had extremely high D-Dimer levels [11].

Authors would like to involve Radiology in the audit to review the impact the change in practice would have on the department and patient flows for the AAD and also if it would be possible to build in the standard comments. Second stage will be presenting the findings in our grand round and provide local departmental teaching.

The third stage will involve another 100 CTPA scans, inclusion criteria include a negative covid status, presence of laboratory D-Dimer and age 50 or above. Due to the poor documentation of pre-test probability and unsatisfactory reports for RHS noticed in stage one, authors decided to focus on the AAD validity in the last stage of the project while delivering ongoing teaching sessions to raise the awareness and importance of pre-test probability score and improve radiology reports to ensure optimum management of patients with query PE.

Results

This has implications for further management as mentioned in the NCEPOD report recommendations.

"Standardise CT pulmonary angiogram reporting. The proforma should include the presence or absence of the right ventricular strain. The completion of these proformas should be audited locally to monitor compliance and drive quality improvement.

"Using a validated score, like the 'Wells' Score, determine the clinical probability of pulmonary embolism in every patient who presents to the hospital with a suspected new diagnosis of pulmonary embolism." In the clinical notes, record the score [11].

Plan

It is aimed that by the end of this project there will be six months of data covering an anticipated 400 scans. If the audit supports the change this can be presented at the Trust board with an outlook to changing patient management and implementation across the organization.

This will require monitoring to ensure compliance and sustainability and may

involve patients with query Deep Venous Thrombosis (DVT) in future audits.

The project will have 3 stages:

- First stage aims to collect and analyse 300 scans looking at AAD validity, pre-test probability documentation and comment on Right Heart Strain (RHS) in scans with confirmed PE.

First stage: May -September 2021

Data gathered from 300 scans showed: 127 males (lowest age 50, eldest 94 years) and 173 females (lowest age 58 years eldest 98 years). Out of 300 patients, 173 had a D-Dimer test (57.6%) and 50 had documentation of pre-test likelihood (16.6%).

Out of the 173 individuals, 36 (20.8%) had a PE finding. All 36 of the patients should have received a scan in accordance with the 100% age-adjusted D-Dimer.

137 patients had D-Dimer over 500 but negative for PE and 24 (17.5%) patients with D-Dimer over 500 but below age adjusted D-Dimer were all negative on imaging for PE (100%).

D-Dimer was not checked in 127/300 and 22 patients had finding of PE (18.6%).

58 out of 300 patients had imaging findings of PE, only 37(63.7%) patients had a mention of right heart strain within the imaging report. No scans showed changes of covid.

Second stage: October 2021

Authors presented the findings in Grand Round and delivered multiple teaching sessions to junior doctors and specialist nurses. Authors have raised the importance of reviewing and documenting pre-test probability score as a high probability is an indication for direct imaging while a low one

requires a review of the D-Dimer levels before further imaging. Authors agreed to reaudit the documentation of pre-test probability score in our Ambulatory Emergency Care Unit (AECU). Authors were advised to liaise with our Radiology department to improve the reporting of CTPA scans to include a comment on RHS status in scans with PE and agreed to reaudit once there is an agreement regarding the inclusion of RHS within the radiology reports.

Finally, Authors have agreed to reaudit a different sample of 100 CTPAs in covid negative patients with documented D-Dimer and age 50 or more to recheck validity.

Third stage: November 2021

100 CTPA scans for non-covid patients 50-year-old or more were reviewed, from the scans reviewed 23 (23%) were found to be positive on imaging for PE. Of the 23, 3 patients (13%) would not have been suitable for imaging if the age adjusted D-Dimer was the only factor considered when referring the patient for imaging. However, the pre-test probability was not reviewed for these patients, and this could have been the indications for referring these patients for imaging.

If the low likelihood score and age-adjusted D-Dimer criteria had been followed, 11 individuals (11%) who tested negative for PE and under AAD would not have been referred for imaging.

Conclusion

The significance of thorough patient evaluation and documentation before recommending a patient for imaging has been brought to light by this audit. Stage 1 found that application of AAD theory would have

prevented 24 patients from having a CTPA therefore would not have had a radiation exposure, administration of iodinated contrast agent and could have potentially been sent home earlier assuming that their pre-test probability was also low (which was not documented robustly within their notes). However, stage 3 provided further information when 23 patients would have not fit the criteria for AAD, although 3 patients were positive for PE on imaging. Overall, 47 patients out of 273 had D-Dimer over 500 and below the AAD, 44 did not show evidence of PE on imaging 93.6%. Fifty-nine patients out of 273 showed evidence of PE on imaging, 56 had D-Dimer level over the AAD cut off 94.9%.

According to the NCEPOD report [10], there is generally inadequate written documentation about the pre-test probability score and low assurance in the radiology results regarding right heart strain.

Management of PE is assessed clinically and based on pre-test probability scores; high probability score is an indication for direct referral for imaging ignoring D-Dimer level while scanning patients with a low probability score depends on a positive D-Dimer level.

Authors have concluded in our audit, in accordance with the referenced studies and NICE guidelines, the validity of AAD; however, the downside is the lack of documentation of pre-test probability scores within the patient records which would have provided further assurance as to the impact of pre-test probability and AAD.

Learning Points

- Pre-test probability score must be the first approach for patients. PE.

- Patients with low probability, age 50 or over we can safely apply the concept of AAD.
- The importance of the imaging reports to provide whether right heart strain is absent or present as this will impact on the staging of the PE from low risk (if absent) to high-intermediate risk (if present) with raised Troponin levels.

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Authors contribution

- Tamer Shalaby Boutrus, Supervising Consultant
- Ibrahim Benshaban, data collection and delivery of teaching
- Joby Landa, data collection and delivery of teaching
- Shaheryar Khan, data collection and delivery of teaching
- Joshua Wortelhock, data collection and delivery of teaching

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