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Research Article

Retrospective Study on the Validity of Age Adjusted D-Dimer

Tamer Shalaby Boutrus[1], Ibrahim Benshaban[2], Joby Landa[3], Shaheryar Khan[4], and Joshua Wortelhock[5]

[1]Consultant Acute and Internal Medicine, Royal Liverpool Hospital, Liverpool, UK

[2]GPST1 doctor at Wrexham Maelor Hospital, Wrexham, Wales, UK

[3]Specialist nurse AECU at Wrexham Maelor Hospital, Wrexham, Wales, UK

[4]Doctor at Wrexham Maelor Hospital, Wrexham, Wales, UK

[5]Doctor at Royal Liverpool University Hospital, Wrexham, Wales, UK

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Abstract

Our 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). We 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 our care. This would bring us 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. We current refer all patients for a CTPA when there is a raised D-Dimer, if we 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 the potential cost saving to the Trust.

Key words: Age adjusted D-Dimer, Pulmonary Embolism, Venous, thromboembolism, pre-test probability, CT PA

Background

D-Dimer is a fibrin degradation product, a protein present in the blood after a clot is dissolved by fibrinolysis, it contains two D fragments of the fibrin protein joined 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. D-Dimers can be raised in sepsis, malignancy, Venous Thromboembolism (VTE) or Disseminated Intravascular Coagulation (DIC). D-Dimer levels in pregnancy are known to increase especially in the second and third trimester and, the American Thoracic Society guidelines recommend against the use of D-Dimer to exclude PE in pregnancy [1].

Over recent years a number of studies have been published on the effectiveness of AAD in excluding PE. This is a common clinical presentation within Emergency Departments (ED) and results in patients often having multiple diagnostic tests to rule out PE. Studies have also concluded a low clinical probability for PE based on Wells score or revised Geneva score with a negative D-Dimer level can safely exclude the diagnosis of PE without the need for further imaging [2–4].

In patients with suspected PE and younger than 50 year old, PE was excluded in those with a low clinical probability and a D-Dimer level lower than 500 µg/L, while those 50 years or older, the D-Dimer test result was considered negative in those with a value lower than their age multiplied by 10 (for example a cut-off of 600 in patients age 60 year old) [5].

A large retrospective multicentre 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%). However, evidence suggested that age-adjusted tests had greater specificity and can reduce the number of people receiving false positive results which has impact on patients and resources.

NICE agreethat 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].

A concern was raised by A. J. Goodwin et al, regarding the current state of D-Dimer testing [8]. Their argument is that D-Dimer assays are not standardized and this can create challenges in safely implementing AAD cut-offs. Some assays that have not been sufficiently investigated should not be used in the interpretation of the age adjusted cut-off. Perhaps this was one of the reasons that NICE did not recommend point of care D-Dimer test yet.

Reasons for this divergence among D-Dimer assays include monoclonal antibodies with varying specificities for D-Dimer, different methodology and instrumentation, different values used to discriminate between positive and negative test. All these factors make standardization difficult. Therefore, clinicians need to be aware of the characteristics of the assay used at their institution [9].

Further recommendation for optimal management of patients with query PE comes from NCEPOD (2018) who noticed the lack of documentation around pre-test probability in clinical notes and the lack of mentioning the presence or absence of right ventricular strain in the radiologist report in cases with confirmed PE [10].

Audit Proposal

Aim

The aim in our Trust is to change the cut-off from 500 µg/L to AAD in patients who are 50 or above, improve the documentation of pre-test probability in clinical notes and encourage our radiology department to mention the presence or absence of right ventricular heart strain in their reports.

Method

Our quality improvement project aims to collect retrospectively 400 Computed Tomography Pulmonary Angiogram (CTPA) scansfor patients age 50 or more. We aim to include the age, sex, laboratory D-Dimer, AAD, CTPA result and pre-test probability. Our local Picture Achieving and Communication systems (PACS) department provided us withthe list of patients. Radiology results should be reported by consultant radiologists.

We hope to raise the validity of AAD by the end of the study and do a sub analysis to check the percentage of patients we could have avoided prescribing unnecessary anticoagulation, risk of contrast induced complications and unnecessary radiation exposure.

The D-Dimer result will be interpreted according to our conventional cut-off (500 µg/L) In addition, an age-adjusted cut-off will be analysed, which is considered negative if D-Dimer was lower than a patient's age (in years) x10.

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

Covid positive patients as there is a strong evidence that covid has been associated with raised D-Dimer levels due to either or both a degree of thromboembolism or severe covid infection.

*Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-Dimer might be associated with the disease progression of COVID-19 and patients who admitted to ITU due to covid pneumonitis had very high levels of D-Dimer [11].

We 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 around the right ventricular strain.

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

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

"Calculate the clinical probability of pulmonary embolism in all patient presenting to hospital with a suspected new diagnosis of pulmonary embolism using a validated score, such as the 'Wells' Score'. Record the score in the clinical notes [11].

Plan

It is aimed that by the end of this project there will be six monthsdata 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 organisation.

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.
- Second stage will be presenting the findings in our grand round and provide local departmental teaching.
- 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 we noticed in stage one we decided to focus on the AAD validity in the last stage of our 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

First stage: May -September 2021

Data gathered from 300 scans showed; 127 males (lowest age 50, eldest 94 years) and 173females (lowest age 58 years eldest 98 years). Pre-test probability was documented in 50/300 (16.6%) and D-Dimer was checked in 173 of 300 patients (57.6%).

From the 173 patients, 36(20.8%) patients had a finding of PE, From the 36 all should have had the scan in accordance with Age adjusted D-Dimer (100%).

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-Dimerwas 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

We presented the findings in Grand Round and delivered multiple teaching sessions to junior doctors and specialist nurses. We 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. We agreed to reaudit the documentation of pre-

test probability score in our Ambulatory Emergency Care Unit (AECU).

We 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 we have agreed to reaudit a different sample of 100 CTPAsin 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 morewere 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.

11 patients (11%) were negative for PEand under AAD and would not have been referred for imaging if the principals of the age adjusted D-Dimer guidelines had been applied (assuming low probability score).

Conclusion

This audit has highlighted the importance of documentation and full consideration of the patient prior to referring for imaging. 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%.

Overall there is poor written documentation regarding pre-test probability score and low assurance within the Radiology reports regarding Right Heart Strain in keeping with the NCEPOD report [10].

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-Dimerlevel while scanning patients with a low probability score depends on a positive D-Dimer level.

We 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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***Corresponding author:** Dr. Tamer Shalaby Boutrus, Consultant Acute and Internal Medicine, Liverpool, Prescot Street, Liverpool, L7 8XP, UK;

Phone: 07957772597;

Email: Dr.tamershalaby@hotmail.com