ORIGINAL RESEARCH

Raising the D-dimer threshold for ruling out pulmonary embolism: A single-site, observational study with a historical comparison

Colin BANKS [1,2], Vinay GANGATHIMMAIAH,[1,2] Theophilus I EMETO [3,4,5] Leonie JONES[1] and Jeremy FURYK [2,6,7]

[1]Emergency Department, Townsville University Hospital, Townsville, Queensland, Australia, [2]College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia, [3]College of Public Health, Medical and Veterinary Sciences, James Cook University, Townsville, Queensland, Australia, [4]World Health Organization Collaborating Centre for Vector-borne and Neglected Tropical Diseases, James Cook University, Townsville, Queensland, Australia, [5]Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia, [6]Emergency Department, University Hospital Geelong, Geelong, Victoria, Australia, and [7]School of Medicine, Deakin University, Geelong, Victoria, Australia

Abstract

Objective: The objective of this study was to assess the impact of introduction of a new pulmonary embolism (PE) diagnostic guideline with a raised D-dimer threshold.

Methods: This is a single-site, observational, cohort study with a historical comparison. The new guideline raised the D-dimer threshold to 1000 ng/mL for most patients with a Wells' score of 4 or less. Patients investigated for PE with a D-dimer level and/or definitive imaging in 6-month periods before and after the introduction of the guideline were eligible. Patients with D-dimers of 500–1000 ng/mL were prospectively followed up at 3 months for missed PE.

Results: During the pre-intervention period, 688 patients were investigated for PE, 366 (53.2%) received definitive imaging and 39 PE were diagnosed (5.7% overall, 10.7% of those imaged). For the 121 patients with D-dimers ≥500 and <1000 ng/mL, 87 (71.9%) were imaged with 7 (5.8%) having a PE diagnosed. Post intervention there were 930 patients, of which 426 (45.8%) received definitive chest imaging and there were 50 patients with PE diagnosed (5.4% overall, 11.7% of those imaged). For the 185 patients with D-dimers ≥500 and <1000 ng/mL, 60 (32.4%) were imaged with 5 (2.7%) having PE diagnosed. No cases of missed PE were identified at 3 months.

Conclusion: The introduction of the new guideline was associated with a reduction in overall imaging rates without evidence of missed PE. Further evaluation in other settings is recommended.

Key words: *computed tomography pulmonary angiogram, D-dimer, emergency department, pulmonary embolism, ventilation perfusion scan.*

Key findings

- Raising the D-dimer threshold to 1000 ng/mL to exclude pulmonary embolism for most patients with a Wells' score of 4 or less was associated with a reduction in imaging rates.
- There were no cases identified of missed pulmonary embolism in those excluded using the higher threshold.

Introduction

Evaluation of ED patients with suspected pulmonary embolism (PE) remains a challenge.[1] Assessment of clinical pre-test probability (PTP) followed by clinical prediction rules, D-dimer testing or definitive imaging (either CT pulmonary angiography [CTPA] or ventilation perfusion [VQ] scans) are established elements of common PE diagnostic approaches.[2,3] The reported yield (proportion with a PE) of definitive imaging varies significantly from 3.1% in the USA and 9.3–25.3% in Australasia to 38% in Germany.[4–6] Overtesting with increasing use of definitive imaging in PE diagnosis, and overdiagnosis of PE are ongoing concerns highlighted by several recent studies.[5,7,8]

Research has yielded several validated approaches to limit the use of definitive imaging in ED patients with

suspected PE. The Pulmonary Embolism Rule-out Criteria (PERC) rule enables identification of a cohort of patients who do not need further testing.[9] A plasma D-dimer threshold of 500 ng/mL has been traditionally used to safely exclude PE in patients with a low clinical PTP in whom the diagnosis cannot be ruled out by the PERC rule. However, multiple studies have found that a higher D-dimer threshold is safe in this patient cohort. The ADJUST-PE study revealed that a D-dimer threshold of 10 times the age was safe in patients aged over 50 years.[10] The YEARS study demonstrated that a D-dimer threshold of 1000 ng/mL was acceptable for patients with no YEARS criteria (PE the most likely diagnosis, signs or symptoms of a deep vein thrombosis [DVT] or haemoptysis).[11] Buntine et al. reported a reduction in imaging rates without an increase in missed PE after introducing a pathway where patients with a moderate PTP (defined as Wells' score of 2 to 6) had PE excluded if D-dimer values were below the age-adjusted threshold.[12] The PEGeD study showed that a D-dimer threshold of 1000 ng/mL appeared safe for patients with a low clinical PTP defined as a Wells' score of 4 or less.[13] Freund et al. reported that combining YEARS rule with the age-adjusted threshold did not result in an inferior rate of venous thrombo-embolism.[14]

A new PE diagnostic guideline (Appendix S1) with a raised D-dimer threshold of 1000 ng/mL was introduced at Townsville University Hospital ED in August 2020. According to this guideline, adult patients with suspected PE had an initial assessment of clinical PTP based on history and examination. PE was excluded in patients with low clinical PTP if they were PERC negative. Patients unable to be cleared by the PERC rule had a Wells' score calculated. If the Wells' score was 4 or less a D-dimer was performed. PE was excluded if the D-dimer level was <1000 ng/mL, except for post-surgical patients (defined as surgery requiring hospitalisation in the preceding 3 weeks). Post-surgical patients were assessed for YEARS criteria. PE was excluded if D-dimer threshold was <500 ng/mL in the

presence of any of the YEARS criteria or <1000 ng/mL in their absence. Patients with a high clinical PTP of PE (as defined by a Wells' score of 4.5 or more) had definitive imaging. In the previous iteration of the guideline, PE was excluded if the D-dimer level was <500 ng/mL in patients aged 50 years or less, or <10 times the age for those over 50 years. Guideline deviations were permitted with senior clinician judgement in both versions. The main objectives of this study were to observe the effect of introduction of a new PE diagnostic guideline on imaging rates for the cohort of patients with D-dimers of ≥500 to <1000 ng/dL and the rate of missed PE at 3 months.

Methods

This was a single-site, prospective observational study with an historical cohort comparison. It was conducted at Townsville University Hospital ED, a mixed major referral ED in Queensland, Australia, with an annual census of 91 997 in 2020–2021. Ethics approval was granted, with a waiver of consent, as a low-risk study.

The study periods of interest were 6-month periods before and after the introduction of the new PE diagnostic guideline. It was introduced in August 2020 which marked the start of the post-intervention period. The pre-intervention period was from May to October 2019 and was chosen to ensure that the results of this study were not influenced by the publication of the PEGeD study in November 2019.[13]

Adult ED patients (age ≥18 years) investigated with a D-dimer, CTPA or VQ scan for suspected PE were included. Exclusion criteria were performance of D-dimer testing for reasons other than PE (DVT and snakebite) and pregnancy. As COVID-19 was not prevalent in the community during the study period, D-dimer testing was not performed for this reason. It was assumed that all CTPA and VQ scans were performed as part of a PE investigative work-up.

The outcomes were the imaging rate, missed PE at 3 months, mortality and ED length of stay (LOS) for patients with a D-dimer level of

≥500 and <1000 ng/mL in the post-intervention component, and imaging rates for the pre-intervention period.

For both phases of the study, patients were identified using the Queensland Laboratory Information System and Picture Archiving and Communication Systems. Patients were assessed for eligibility criteria using electronic health records (integrated electronic medical record; Cerner Inc., North Kansas City, MO, USA). Consecutive patients meeting eligibility criteria were included.

For the post-intervention prospective component, patients with a D-dimer level of ≥500 and <1000 ng/mL were followed up 3 months after the index visit to determine if they had been diagnosed with a PE. Follow-up was by phone. If patients could not be contacted after five attempts, this outcome was assessed by reviewing electronic health records for subsequent presentations, contacting the patient's general practitioner or reviewing publicly available death records.

Data were extracted from the electronic health records using standard chart review methods including precise definitions of eligibility criteria and data variables, training of data abstractors with practice medical records, use of a standardised data abstraction form and periodic meetings for performance monitoring.[15] Data abstractors could not be blinded as they were part of the investigative team. Disputes regarding ambiguous or conflicting data were resolved by consensus between study investigators.

Descriptive summaries for both periods before and after guideline adoption including CTPA, VQ scan, D-dimer concentration, sex, and LOS are presented as counts and percentages or median and interquartile range (IQR). Absolute reductions and 95% confidence intervals (CI) are reported. Data summaries were computed in STATA (StataCorp LLC, 2021, Stata Statistical Software: Release 17.0, College Station, TX, USA).

Results

The pre-intervention search identified 753 patients, of which 688 were investigated for PE after exclusions
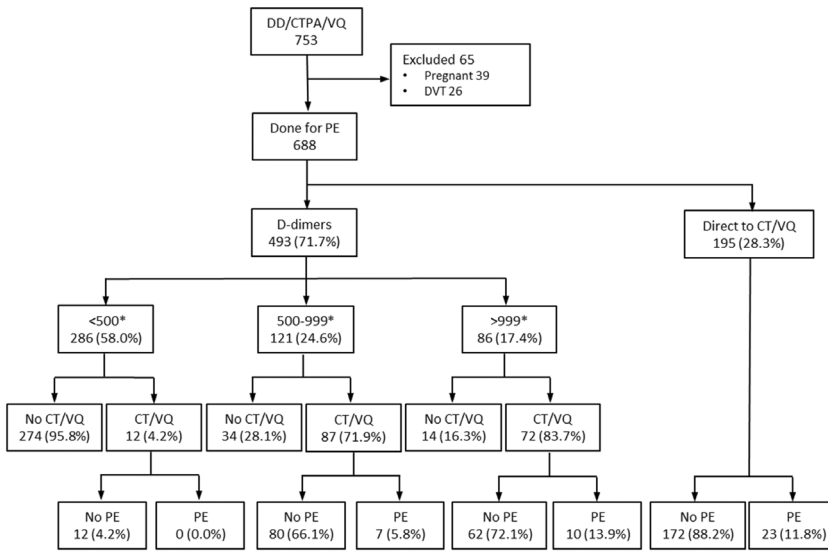
Figure 1. *Pre-intervention patient outcomes. *D-dimer units in ng/mL. CTPA, CT pulmonary angiography; DD, D-dimers; DVT, deep venous thrombosis; PE, pulmonary embolism; VQ, ventilation perfusion scan.*

for DVT and pregnancy. Of these, 61.9% were female and the median age was 53 years (IQR 37–67). The outcomes of the ED presentation in terms of investigations performed and whether PE was diagnosed are presented in Figure 1. The overall number of patients imaged was 366 (53.2%) and the overall number of PE diagnosed was 39 (5.7%

overall, 10.7% of those imaged). For the 121 patients with D-dimers ≥500 and <1000 ng/mL, 87 (71.9%) were imaged with 7 (5.8%) having a PE diagnosed. If the age-adjusted D-dimer threshold was applied to this group, there were 30 patients who would have been excluded from having PE according to the guideline. Of these 30, 13 (43.3%) were imaged with CTPA, and one (3.3%) was positive for PE.

The post-intervention search identified 1004 patients, of which 930 were investigated for PE. The median age was 51 years (IQR 36–66) and 576 (61.9%) were female. The outcomes are shown in Figure 2. Of the 930 patients, 426 (45.8%) received definitive chest imaging. There were 50 (5.4%) patients with PE diagnosed which was 11.7% of those who underwent definitive imaging. Of the 185 patients with D-dimer level of ≥500 and <1000 ng/mL, 60 (32.4%) underwent definitive imaging, despite the guideline recommending that PE was excluded. There were 33 patients out of the 185 who would have had PE excluded by the old guideline incorporating an age-adjusted D-dimer threshold, and 9 (27.3%) were scanned, all negative for PE.

After the intervention, there was an absolute reduction in imaging rate of 7.4%, 95% CI (2.4–12.3) for the overall cohort being investigated for PE and an absolute reduction of 39.5%, 95% CI (29.0–49.9) for the cohort with a D-dimer level of ≥500 and <1000 ng/mL.

For the 185 post-intervention patients with D-dimers ≥500 and <1000 ng/mL, 60 were scanned and 5 (8.3% of 60, 2.7% of 185) were diagnosed with PE. Details of these patients are presented in Table 1. Of the 125 patients who were discharged from ED with no imaging, two declined consent and two were lost to follow up. There were no cases of missed PE in the 121 patients who had follow-up. There were two deaths in this group, one from a small bowel obstruction and the other from end-stage chronic obstructive pulmonary disease. Both these patients underwent definitive imaging during the index presentation.
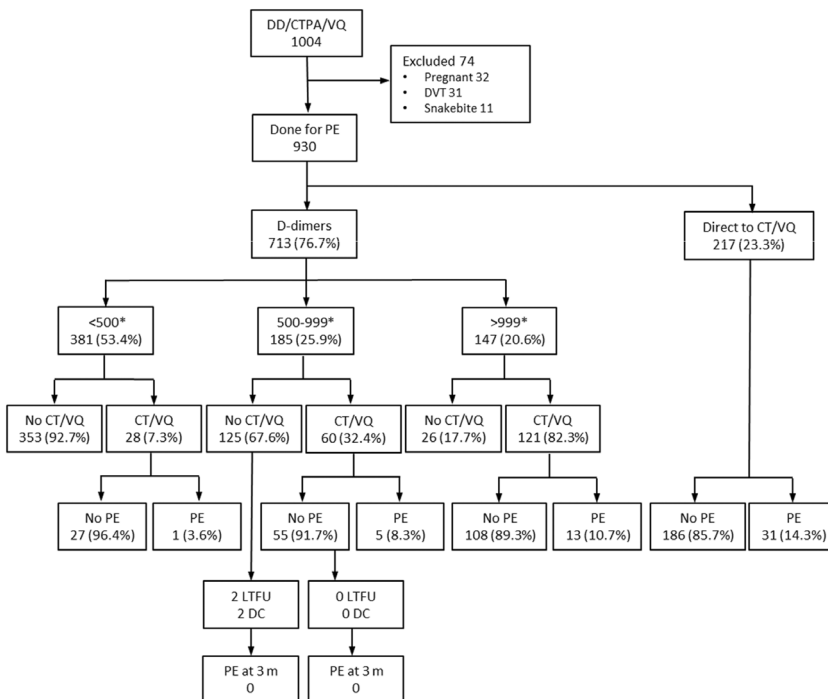

Figure 2. *Post-intervention patient outcomes. *D-dimer units in ng/mL. CTPA, CT pulmonary angiography; DC, declined consent; DD, D-dimers; DVT, deep venous thrombosis; LTFU, lost to follow up; m, months; PE, pulmonary embolism; VQ, ventilation perfusion scan.*

TABLE 1. *Characteristics of patients with D-dimers ≥500 and <1000 ng/mL and pulmonary embolism (PE)*

Age	Sex	D-dimer (ng/mL)	Imaging	Type of PE	Comments
71	Male	920	CTPA	Segmental	Presented with chronic back pain and dyspnoea
31	Female	530	VQ	Subsegmental	Previous PE
61	Female	760	CTPA	Lobar	Right-sided PE in a patient with left-sided chest pain
51	Male	600	CTPA	Segmental	Uncertain clinical significance, not anticoagulated
20	Female	660	VQ	Segmental	Factor V Leiden positive

CTPA, computed tomography pulmonary angiography; VQ, ventilation perfusion scan.

Patients with a D-dimer level of ≥500 and <1000 ng/mL who did not undergo imaging had a shorter ED LOS than those who did. Details are presented in Table 2.

Discussion

The absolute reduction in overall imaging rate of 7.4% in this study was similar to that reported in the YEARS (8.7%) and PEGeD (8.6%) studies, where reduction was calculated in comparison to an age-adjusted strategy.[11,13] The reduction was noted in this study despite nearly one-third (32.4%) of patients with D-dimers ≥500 and <1000 ng/mL undergoing imaging contrary to the guideline. This deviation from the guideline may have been due to several reasons. The clinical PTP of PE may have changed following discussion with a senior ED clinician or following review by admitting inpatient clinicians. Patient referral to ED with a D-dimer level of ≥500 ng/mL and an expectation of definitive imaging could have influenced clinical decision making. Lack of awareness of the new guideline or reluctance to follow it, may have also contributed.

Of the 125 patients with D-dimers ≥500 and <1000 ng/mL who were discharged from the ED with no imaging, two declined consent and two were lost to follow up. If both patients lost to follow up had PE diagnosed within the 3 months that would be a miss rate of 1.6%, which is less than the calculated test threshold of 1.8% for investigating for PE and close to the false negative rate of 1.2% for a CTPA.[16,17]

The proportion of patients who were scanned despite having a D-dimer value of ≥500 and <1000 ng/mL and had a PE was 8.3% (5/60) in our study compared to 7.5% (3/40) in the YEARS study and 1.6% (2/127) in the PEGeD study.[11,13] Despite the positivity rate of 8.3% for scans performed contrary to the guideline, there were no cases of missed PE in the 121 patients who did not get scanned. This discrepancy may well have been due to clinical features that prompted a revised clinical risk stratification by a more senior clinician. Another possible explanation is overdiagnosis, defined as identification of problems that were never going to cause harm. This is an area of controversy for PE with some researchers speculating that some PE may be physiological and may not need to be diagnosed or treated.[8,18]

This study showed a shorter LOS for patients who did not undergo imaging. This reduction in LOS was noted in patients who were discharged from ED as well as in those who were admitted under an inpatient team. Overcrowding is a major issue for most EDs and any measure that can safely shorten the LOS would have a positive effect. The reduction in imaging would also result in collateral benefits of reduced radiation exposure, reduced incidence of contrast allergic reactions and reduced healthcare costs.

This study has limitations. The single-centre design limits external validity. The sampling strategy might have missed eligible patients and it is possible that some patients had D-dimer testing based on a suboptimal or erroneous clinical assessment. The reasons for guideline deviation could not be determined with certainty using this methodology. However, prospective follow-up of patients and minimal loss to follow-up are strengths of this study.

TABLE 2. *ED length of stay (LOS) for patients with D-dimers ≥500 and <1000 ng/mL*

	Number	Average LOS (min)
Home with no imaging	106	340
Home with imaging	36	533
Admitted† with no imaging	19	390
Admitted† with imaging	24	652

†Admission to an inpatient unit, not to ED short stay.

Conclusion

The introduction of a new PE diagnostic guideline with a raised D-dimer threshold was associated with a reduction in imaging rates of 53.2% to 45.8% for all patients being investigated for PE, and for patients with D-dimers ≥500 and <1000 ng/mL, from

71.9% to 32.4%. In patients from this cohort who did not undergo imaging, there were no cases of missed PE and there was an associated reduction in ED LOS. Further research is required to prospectively validate these findings in other settings.

Acknowledgements

Competing interests

None declared.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Geersing GJ, Takada T, Klok FA *et al*. Ruling out pulmonary embolism across different healthcare settings: a systematic review and individual patient data meta-analysis. *PLoS Med.* 2022; **19**: e1003905.
2. Stals MAM, Takada T, Kraaijpoel N *et al*. Safety and efficiency of diagnostic strategies for ruling out pulmonary embolism in clinically relevant patient subgroups: a systematic review and individual-patient data meta-analysis. *Ann. Intern. Med.* 2022; **175**: 244–55.
3. Wells PS, Anderson DR, Rodger M *et al*. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann. Intern. Med.* 2001; **135**: 98–107.
4. Mountain D, Keijzers G, Chu K *et al*. RESPECT-ED: rates of pulmonary emboli (PE) and sub-segmental 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* 2016; **11**: e0166483. Erratum in: *PLoS One* 2017; **12**: e0184219.
5. Kline JA, Garrett JS, Sarmiento EJ, Strachan CC, Courtney DM. Over-testing for suspected pulmonary embolism in American emergency departments: the continuing epidemic. *Circ. Cardiovasc. Qual. Outcomes* 2020; **13**: e005753.
6. Al-Zaher N, Vitali F, Neurath MF, Goertz RS. The positive rate of pulmonary embolism by CT pulmonary angiography is high in an emergency department, even in low-risk or young patients. *Med. Princ. Pract.* 2021; **30**: 37–44.
7. Wang RC, Miglioretti DL, Marlow EC *et al*. Trends in imaging for suspected pulmonary embolism across US health care systems, 2004 to 2016. *JAMA Netw. Open* 2020; **3**: e2026930.
8. Dobler CC. Overdiagnosis of pulmonary embolism: definition, causes and implications. *Breathe* 2019; **15**: 46–53.
9. Kline JA, Courtney DM, Kabrhel C *et al*. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J. Thromb. Haemost.* 2008; **6**: 772–80.
10. Righini M, Van Es J, Den Exter PL *et al*. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA* 2014; **311**: 1117–24. Erratum in: *JAMA* 2014; **311**: 1694.
11. van der Hulle T, Cheung WY, Kooij S *et al*. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017; **390**: 289–97. Erratum in: *Lancet* 2017; **390**: 230.
12. Buntine P, Thien F, Stewart J *et al*. Effect of a clinical flowchart incorporating Wells score, PERC rule and age-adjusted D-dimer on pulmonary embolism diagnosis, scan rates and diagnostic yield. *Emerg. Med. Australas.* 2019; **31**: 216–24.
13. Kearon C, de Wit K, Parpia S *et al*. Diagnosis of pulmonary embolism with D-dimer adjusted to clinical probability. *N. Engl. J. Med.* 2019; **381**: 2125–34.
14. Freund Y, Chauvin A, Jimenez S *et al*. Effect of a diagnostic strategy using an elevated and age-adjusted D-dimer threshold on thromboembolic events in emergency department patients with suspected pulmonary embolism: a randomized clinical trial. *JAMA* 2021; **326**: 2141–9.
15. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: where are the methods? *Ann. Emerg. Med.* 1996; **27**: 305–8.
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. Thromb. Haemost.* 2004; **2**: 1247–55.
17. Mos ICM, Klok FA, Kroft LJM, de Roos A, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. *J. Thromb. Haemost.* 2009; **7**: 14918.
18. Swan D, Hitchen S, Klok FA, Thachil J. The problem of under-diagnosis and over-diagnosis of pulmonary embolism. *Thromb. Res.* 2019; **177**: 122–9.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Townsville University Hospital ED pulmonary embolism diagnostic guideline.