



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Buntine, P;Thien, F;Stewart, J;Woo, YP;Koolstra, M;Bridgford, L;Datta, M;Gwini, SM

Title:

Effect of a clinical flowchart incorporating wells score, PERC rule and age-adjusted D-dimer on pulmonary embolism diagnosis, scan rates and diagnostic yield

Date:

2019-04-01

Citation:

Buntine, P., Thien, F., Stewart, J., Woo, Y. P., Koolstra, M., Bridgford, L., Datta, M. & Gwini, S. M. (2019). Effect of a clinical flowchart incorporating wells score, PERC rule and age-adjusted D-dimer on pulmonary embolism diagnosis, scan rates and diagnostic yield. *EMA Emergency Medicine Australasia*, 31 (2), pp.216-224. <https://doi.org/10.1111/1742-6723.13125>.

Persistent Link:

<https://hdl.handle.net/11343/285013>

i) Title

The effect of a clinical flowchart incorporating Wells score, PERC rule and age adjusted D-dimer on pulmonary embolism diagnosis, scan rates and diagnostic yield.

(ii) the full names, titles and degrees of the authors;

Authors:

Dr Paul Buntine, MBBS, FACEM. Emergency Physician, Eastern Health, Monash University
Professor Francis Thien, MD, RACP. Director of Respiratory Medicine, Eastern Health, Monash University
John Stewart, Medical Imaging Technologist, Eastern Health, Monash University
Ms Yee Ping Woo, Medical Imaging Technologist
Dr Martin Koolstra, MBBS, FACEM. Emergency Physician, Eastern Health, Monash University
Dr Lindsay Bridgford MBBS FACEM. Emergency Physician, Eastern Health, Monash University
Dr Mineesh Datta, MBBS, RANZCR. Director of Radiology, Box Hill Hospital, Monash University
Dr Stella May Gwini, School of Public Health & Preventive Medicine, Monash University

Acknowledgements:

Jo-Anne McShane, RN, Research Assistant, Box Hill Hospital Emergency Department
Associate Professor Paul Coughlin, MBBS, RACP, PhD. Clinical Haematologist, Eastern Health, Monash University

(iii) each author's contribution

PB conceived the idea for the study, which was then designed with assistance from FT, JS, YW, MK, LB, MD and PC. PB supervised overall conduct of the study. Local sites were coordinated by PB, MK and LB. PB and JM were responsible for data collection from site A whilst JS was responsible for data collection from sites B and C. PB and JM performed all data entry. PB analysed the data, with statistical analysis performed by SG. All authors contributed to the final manuscript. PB takes overall responsibility for paper as a whole.

iv) Short running title

A flowchart consisting of Wells, PERC and age adjusted DD

(v) the addresses of the institutions at which the work was carried out

Box Hill Hospital, 8 Arnold Street, Box Hill, Victoria 3128
Maroondah Hospital, Davey Dr, Ringwood East Victoria 3135
Angliss Hospital, Albert St, Upper Ferntree Gully VIC 3156

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/1742-6723.13125](https://doi.org/10.1111/1742-6723.13125)

(vi) the full postal and email address, plus telephone numbers, of the author to whom correspondence about the manuscript should be sent

Dr Paul Buntine

Emergency Department, Box Hill Hospital, 8 Arnold Street, Box Hill, Victoria 3128

paul.buntine@easternhealth.org.au

03 997 56043

0425 749936

(vii) word count:

Word Count: 5062

Abstract

Objective

To assess the association between the use of a flowchart incorporating Wells score, PERC rule and age-adjusted D-dimer and subsequent imaging and yield rates of Computed Tomography Pulmonary Angiogram and Nuclear Medicine Ventilation Perfusion scans being ordered in the Emergency Department for the assessment of pulmonary embolism.

Methods

A flowchart governing Emergency Department pulmonary embolism investigation was introduced across three Emergency Departments in Melbourne, Australia for a twelve month period. Comparison of pulmonary embolism imaging rates and yield with the preceding twelve months was performed.

Results

1815 pre-implementation scans were performed compared with 1116 scans post implementation. Due to growth in patient attendances over this time, this equated to an imaging rate of 14.5 per 1000 presentations pre implementation and 8.6 per 1000 presentations post implementation ($p<0.001$).

Overall PE imaging yield rates rose from 9.9% to 16.5% ($p<0.001$).

A total of 179 pre-implementation pulmonary embolisms were identified, with an incidence of 1.4 per 1000 presentations. This compared to 185 pulmonary embolisms post implementation, with an incidence of 1.4 per 1000 presentations ($p=0.994$).

Conclusions

The introduction of a clinical flowchart incorporating Wells score, PERC rule and age-adjusted D-dimer was associated with an increase in Emergency Department Computed Tomography Pulmonary Angiogram and Nuclear Medicine Ventilation Perfusion yield rate from 9.9% to 16.5% across the three enrolment hospitals when investigating possible pulmonary embolism. This corresponded to a 40% relative reduction in pulmonary embolism imaging. Diagnosis rates remained unchanged and no cases of missed pulmonary embolism attributable to the flowchart were identified.

Key Words: pulmonary embolism, computed tomography pulmonary angiogram, ventilation perfusion scan, emergency department, d-dimer

Introduction

Over recent years, literature has amassed regarding Emergency Department (ED) investigation for pulmonary embolism (PE). In 1998, Wells devised a three point clinical scoring system classifying patients as low, intermediate

or high risk of having a PE¹. This was supplemented in the early 2000s by D-dimer measurement², with a negative result safely negating further investigation in most patients³. Over recent years it has been proposed that an age-adjusted cut-off for patients 50 years and older could increase yield even further^{4,5,6}. Parallel to these developments other clinical scoring systems emerged, such as the Pulmonary Embolism Rule-out Criteria (PERC) rule—a validated supplementary decision rule for low risk patients^{7,8}. There has been considerable discussion but little published literature around a strategy to specifically combine these three tools into a single flowchart.

This study aimed to assess whether the introduction of a clinical flowchart incorporating Wells score, PERC rule and age-adjusted D-dimer would be associated with a decrease overall imaging rates and increase the positive yield of Computed Tomography Pulmonary Angiogram (CTPA) and Nuclear Medicine Ventilation Perfusion (VQ) scans being ordered to assess for PE at one of the three EDs in Eastern Health (EH), Melbourne.

Methods

A three site before and after study was designed to compare ED CTPA and VQ ordering rates and yield before and after implementation of a flowchart governing PE investigation. To allow for possible seasonal variation we used 12 month data collection periods, with a pre implementation period from October 27 2014 to October 25 2015, and an implementation period from October 26 2015 to October 24 2016. Stakeholders from emergency medicine, radiology, respiratory medicine and haematology developed the flowchart and low risk ethics approval from EH ethics committee was obtained. **The enrolment sites were Box Hill hospital, Maroondah hospital and Angliss hospital with annual ED attendances for 2016 of approximately 64 000, 58 000 and 40 000 respectively . All three EDs are mixed adult/paediatric Level 3 Emergency Departments academically affiliated with the Eastern Health Clinical School, Monash University.** All CTPA and VQ scans on patients aged 16 and over who attended one of these three EH EDs based in Melbourne (~~Box Hill hospital, Maroondah hospital, Angliss hospital~~) during the study period were included in data analysis but it was left to the discretion of the senior treating ED doctor whether to ultimately

adhere to the flowchart. This was particularly emphasised in specific clinical situations where individual components of the flowchart lack validation (eg. patients aged under 18 years, pregnancy). Due to local differences in imaging test availabilities between the three enrolment hospitals two versions of the flowchart were introduced (figure 1), which differed only in their recommendation to proceed with CTPA vs VQ scan should imaging be required.

The implementation phase commenced upon integration of the flowchart into the ED Information System (EDIS) in use across all sites. This was configured to print out whenever a D-dimer, CTPA or VQ were requested. All medical imaging departments were instructed to proceed with imaging only after receiving the flowchart, unless specifically advised by a senior ED doctor to override it. Hard copies were also made available for cases where non-EDIS generated test requests were received. In the two weeks prior and immediately after implementation, staff were educated regarding these changes via one-on-one and group tutorials plus email communication.

For the duration of this study the D-dimer assay used at all three sites was D-Di Plus (Stago)⁹, reported as mg/L FEU.

During the pre-implementation phase, results reported on our pathology system flagged an abnormal D-dimer greater than 0.3 mg/L by displaying this value in bold. Coinciding with the commencement of the implementation phase, this value was increased to 0.5 mg/L, however for patients with suspected PE clinicians were instructed to use 0.5 mg/L for patients aged less than 50 years, and an age adjusted D-dimer ($\text{age} \times 0.01$) if aged 50 years or greater.

All imaging data for the duration of the study period was obtained from the EH Radiology Information System database. To ensure familiarity with the project during the first 6 months of the implementation phase, regular audits were performed using both clinical notes from the EDIS and printed flowcharts. Individual clinicians were contacted by local site coordinators where there was a clear deviation from the flowchart.

All radiological results were reported by consultant radiologists. These were read by a research nurse, with any ambiguity flagged for further review by the lead researcher. A final diagnostic decision was then made after

consideration of all subsequent investigation and management decisions, either on discharge home from the ED or on discharge from the ward (for patients admitted from the ED). Only CTPA and VQ scans performed during an ED visit or Short Stay admission were included, with the exception of a small number of patients who had their imaging booked in ED and performed shortly after admission to a ward bed.

Results were entered into Microsoft Excel 2010, which was also used for descriptive analysis. Rates and their 95% confidence intervals (CI) were estimated using Stata Statistical Software version 14.2. Two-samples test of proportions were used to compare pre-implementation and implementation rates and yield.

Interrupted Time Series (ITS, also known as segmented regression) was used to analyse change in yield rates post-intervention. This method uses time series methods, accounting for autocorrelation between variables and the pre-intervention period serves as a control period. Time lags were included in the ITS analysis to highlight possible differences in post implementation effect onset between the three sites. Newey-West standard errors for coefficients were estimated and the Cumby-Huizinga test for autocorrelation was conducted to determine optimum number of lags. This lead to inclusion of autocorrelation with a maximum of three lags in analysis of Sites A and B data while Site C and overall data were analysed without lags. The unit of analysis was month which ran from the 26th to the 25th of the following month.

Results

Basic demographic information and ED details are shown in Table 1. Comparisons of pre and post CTPA/VQ scan rates are shown in Table 2. In all tables and figures Site A refers to Box Hill hospital, site B refers to Maroondah hospital and site C refers to Angliss hospital.

Overall CTPA and VQ numbers at all 3 EDs

A total of 1815 scans (675 VQ scans and 1140 CTPAs) were performed during the pre-implementation period, compared with 1116 scans (446 VQ scans and 670 CTPAs) post implementation. Due to growth in patient attendances over this time, this equated to an imaging rate of 14.5 per 1000 presentations pre implementation and 8.6 per 1000 presentations post implementation. This difference was statistically significant ($p<0.001$) at all three sites. Confidence intervals and individual ED results are shown in Table 2.

CTPA and VQ yield rate at all 3 EDs

Combined PE yield rates for the three EDs rose from 9.9% to 16.5%. This result was also statistically significant ($p<0.001$) (Table 2).

Using ITS, there was no significant change in the imaging yields from pre- to post-intervention periods (Table 3) although a small change was observed for one site. The results presented in Table 3 and Figure 2 also suggest that there was a lag in uptake of the intervention. Two sites showed no significant changes in yield rates immediately following intervention, however significant increases were then observed in the second and/or third month.

Number of PEs identified

A total of 179 PEs were identified during the pre-implementation period, with an incidence of 1.4 per 1000 presentations. This compares to 184 PEs post implementation, with an incidence of 1.4 per 1000 presentations ($p=0.994$) (Table 2).

Inter-hospital comparison of results

Chi-squared analysis showed pre-implementation imaging rates and yield to differ significantly between sites ($p<0.001$, $p=0.015$), however this effect was no longer observed post implementation ($p=0.780$, $p=0.762$).

D-dimer sub analysis

A comparison of the subset of patients who proceeded to imaging after D-dimer is shown in Table 4. **233 fewer patients with a normal D-dimer received imaging post implementation. Of these, 126 had a D-dimer between 0.3-0.5 mg/L FEU and 91 had a D-dimer >0.5 mg/L FUE but less than the age adjusted cut off.**

Analysis of possible missed PEs

Interrogation of the EDIS was performed for patients who presented post implementation and had a PE diagnosed within three months of a previous presentation to one of the three EH EDs. No instances were discovered where a PE had been considered but not imaged during the initial visit. Likewise, there were no coronial reports received by EH relating to a missed PE from ED post implementation. A search of the EH adverse events database showed one patient who represented to an EH ED with a PE two days after a previous presentation, however there was no clinical suspicion of PE during this earlier attendance and the flowchart was therefore not applied.

Effect on all of hospital ordering

Total CTPA and VQ ordering rates for EH during the study periods are shown in Figure 3.

Discussion

Like all diagnostic testing, the “ideal” yield for PE imaging in the ED is a balanced consideration¹⁰. A low yield increases risks such as radiation exposure^{11,12} and contrast nephropathy,¹³ whilst increasing the rate of false positive findings and incidental findings¹⁴, with an associated risk of treatment associated harm^{15,16}. A yield that is too high will have a statistically corresponding increase in false negatives, with associated harm from missed diagnosis of PE.

There is considerable evidence that a structured approach to ED diagnosis of PE can increase yield rates. In 2013, Ong et al¹⁷ showed an increased yield in positive CTPA scans from 9% to 14% at Box Hill Hospital, Melbourne that corresponded with the introduction of a flowchart based on a combination of Wells score and D-dimer with a flat cut off of 0.3 mg. Similar recent work by Mills et al¹⁸ demonstrated an increase in CTPA from 8.1% to 10.6% with Wells

score based clinical decision support while Jimenez et al demonstrated a significant decrease in CTPA use via the introduction of computer based diagnostic decision support although they did not see a corresponding increase in imaging yield¹⁹. Internationally, adoption of an age adjusted D-dimer compared with a flat cut-off of 0.5 mg/L has been shown to safely increase the diagnostic yield of D-dimer testing and overall imaging yield^{4,5,6,20}, although Jones et al²¹ highlighted potential issues with the upfront use of D-dimer in undifferentiated ED patients. In 2017 the YEARS tool²² was demonstrated to achieve a 8.7% reduction in CTPA numbers over the use of Wells + age adjusted D-dimer by simply stratifying patients into two discrete D-dimer cut off groups depending on the presence or absence of three clinical features associated with PE.

Direct comparison of our findings with any of these studies is difficult, due to varying patient settings, differences in enrolment procedures and pathway elements, and large differences in baseline diagnostic yields. Nevertheless, multiple sources, such as the American College of Physicians²³, have recommended the adoption of a structured approach to PE diagnosis. The pathway examined in this paper draws heavily from many sources, all of which have demonstrated an improvement in PE imaging yield but there is little existing literature regarding the use of a single flowchart specifically combining Wells score, PERC rule, and age-adjusted D-dimer, nor the expected yield from such a strategy.

In the RESPECT-ED study²⁴, Mountain et al recently showed that diagnostic yield from CTPA in Australian EDs ranged from 9.3% - 17%, with a mean of 13.6%. The use of local guidelines was not explored in this paper; however this variation in yield suggests that current practice differs significantly between sites. Comparison with these results also shows that our mean combined implementation yield rate of 16.5% is higher than that which they experienced. Furthermore, our dataset also included VQ scans, for which all three of our sites experienced a lower implementation yield (12.9%) than for CTPA alone (19.1%). Of the 13 Australian sites included in RESPECT-ED, the highest CTPA yield was 17.0%.

Whilst the results showed an increase in yield of 6.6%, interrupted time series analysis suggests that there may already have been a small pre-existing trend towards increased yield at the three sites. Also, despite the described intervention occurring simultaneously across all three sites at the go live date, there was considerable variation in uptake tempo, with changes at sites B and C only becoming statistically significant when a two month delay is considered. This is not unexpected, given the lack of a run-in period and logistical complexity in changing practice amongst a large group of ED physicians across three different sites.

In addition to analysis of overall results, attempts have been made to quantify what effect on yield the various components had. Pre-post comparison of patients who had both a D-dimer test and imaging (Table 4) shows that 233 fewer patients with a normal D-dimer received imaging post implementation. Of these, 126 could be attributed to the increase in D-dimer reference range from 0.3-0.5 mg/L FEU, and a further 91 to use of the age adjusted cut-off. Somewhat surprisingly, a fall in associated PE diagnosis from 15% to 0% was also seen post implementation in patients with a normal D-dimer. **In addition to the reduced imaging attributable to changes in D-dimer cut off parameters shown in Table 4, it can also be seen that 12 patients with a normal D-dimer were diagnosed with PE pre-implementation but none were identified post implementation.** A possible explanation for this could be a greater proportion of pre-implementation patients with a high Wells score also having a D-dimer measured before imaging, and its inadequate sensitivity in this sub-group²⁵⁻²⁷. The post implementation increase in patients with an elevated D-dimer and PE diagnosis also suggests a more discriminatory approach to post-implementation patient selection for D-dimer testing.

In the pre-implementation period Site A already had some basic PE decision support in place¹⁷, in contrast with Sites B and C, where no particular practice guidance existed. This contrast is highlighted by the significant difference in pre-implementation yield and imaging rates between site A compared with sites B and C. This difference disappeared during the implementation phase. With this in mind, EDs with existing PE decision support processes in place,

especially if already using a D-dimer cut off of 0.5 mg/L, are unlikely to see an increase in yield of the same magnitude as was experienced in this study. Nevertheless, we believe that our results demonstrate that a combined CTPA/VQ yield rate of over 15% is achievable in comparable Australian EDs performing a mix of CTPA and VQ scans, whilst for sites predominantly performing CTPA this is may be higher.

Accounting for the adjusted presentation numbers pre and post implementation, we estimate that use of the flowchart was associated with 772 fewer ED scans during the intervention period. As figure 3 illustrates, comparison of raw imaging numbers for the whole network between the two time periods shows a growth in non-ED scans by 189. Adjusting this for total organisational activity is problematic, especially as there was a 4.5% growth in occupied bed days recorded across the three campuses between the two periods. Nevertheless, even if a small portion of the imaging not performed in the ED was moved to an inpatient setting there is a potential for patient and organisational benefit, measured in terms of ED flow and ~~NEAT~~ performance **against the National Emergency Access Target (NEAT) of 90% of patients leaving the ED within 4 hours of arrival**²⁸, although this must be weighed up against the potential for increased morbidity from delayed PE diagnosis²⁹⁻³¹.

Whilst it is possible that use of the flowchart resulted in an increase in missed PE diagnosis, investigation of hospital records, adverse event registers and coronial reports showed no evidence of this. There was also no statistical difference in the number of patients diagnosed with PE between the two periods and during the implementation phase no PEs were identified in the 86 patients who had a negative D-dimer but still proceeded to imaging.

A strength of this study is the way in which it was integrated into standard patient care across three discrete EDs. All patients scanned during the comparison periods were included, regardless of their treating physician or whether there was adherence to the flowchart. This is likely to enhance both reproducibility and sustainability. Our implementation also drew heavily from our experiences with existing evidence based change management strategies, which was an additional potential reason for the effect size that we saw³².

Limitations

A limitation of this study was our inability to capture patients where PE was considered but neither D-dimer or imaging were performed, either due to a negative PERC score or failure to follow the flowchart. Whilst we encouraged clinicians to use the flowchart whenever PE was considered, differential diagnoses may have been considered and excluded without documentation. Similarly, although data were captured for all patients who had their D-dimer measured but did not proceed to imaging, they were excluded from final analysis due to the difficulty in determining whether D-dimer was being measured for PE as a differential diagnosis, or for alternative reasons (such as aortic dissection, DVT exclusion). Including these factors would have required a different study design.

Compliance with use of the flowchart was not formally assessed. The regular audits during the first 6 months of the implementation period were performed as part of the overall change management process rather than to measure this aspect of the study.

This was an uncontrolled before and after study, and it is possible that the observed effect was from factors other than the pathway introduction. Despite this, we feel that interrupted time series analysis shows a strong association between increased imaging yield and adoption of the pathway. The similarity in effect observed across the three sites and use of symmetrical twelve-month time periods also suggest that factors other than those described in this intervention were unlikely to have played a significant role.

Conclusions

The introduction of a clinical flowchart incorporating Wells score, PERC rule and age-adjusted D-dimer was associated with an increase in ED combined CTPA/VQ imaging yield rate from 9.9% to 16.5% across the three

enrolment hospitals when investigating possible PE. This corresponded to a 40% relative reduction in PE imaging. PE diagnosis rates remained unchanged and no cases of missed PEs attributable to the flowchart were identified. A larger, randomised, multi-centre study could identify whether such a strategy is transferable across all Australian EDs.

Acknowledgments

This project was supported by a research grant from the EH Foundation, which was kindly donated by House Husbands (9 Network). We are also grateful for the support of Jo-Anne McShane, Research Assistant at Box Hill Hospital ED, and Associate Professor Paul Coughlin, Clinical Haematologist, EH.

Competing interests

None declared

References

- 1 Wells P, Ginsberg J, Anderson D, Kearon C et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med.* 1998; 129(12): 997-1005.
- 2 Schreiber D. Your lab focus: science. The role of D-Dimer in the diagnosis of venous thromboembolism. *Lab Med.* 2002; 33(2): 136-141.

3 Wells PS, Anderson D, 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 Righini M, Van Es J, Den Exter P, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA.* 2014; 311(11): 1117-1124.

5 Woller S, Stevens S, Adams D et al. Original Research: Pulmonary Vascular Disease: Assessment of the Safety and Efficiency of Using an Age-Adjusted D-dimer Threshold to Exclude Suspected Pulmonary Embolism. *Chest.* 2014; 1444-1451.

6 Schouten HJ, Geersing GJ, Koek HL et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. *BMJ.* 2013; 346:f2492

7 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.

8 Singh B, Mommer S, Erwin P, Mascarenhas S, Parsaik A. Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism--revisited: a systematic review and meta-analysis. *Emerg Med J.* 2013; 30(9): 701-706.

9 STA®-Liatest® D-Di Plus, Less interferences for even More Confidence. Available from URL: <https://www.stago.com/products-services/new-products/detail/article/staR-liatestR-d-di-plus-less-interferences-for-even-more-confidence/> [Accessed June 26, 2017]

10 Cronin P, Kelly A. Influence of population prevalences on numbers of false positives: an overlooked entity. *Acad Radiol.* 2011; 18(9): 1087-1093.

11 Edwin A. T, Hyo-Chun Y. Four-Year Cumulative Radiation Exposure in Patients Undergoing Computed Tomography Angiography for Suspected Pulmonary Embolism. *Radiology Research And Practice*, 2013; Volume 2013 Article ID 482403, 5 pages

12 Malone J, Guleria R, Craven C, et al. Justification of diagnostic medical exposures: some practical issues. Report of an International Atomic Energy Agency Consultation. *Br J Radiol.* 2012; 85(1013): 523-538.

13 Mitchell A, Jones A, Tumlin J, Kline J. Prospective study of the incidence of contrast-induced nephropathy among patients evaluated for pulmonary embolism by contrast-enhanced computed tomography. *Acad Emerg Med* 2012; 19(6): 618-625.

14 Anjum O, Ohle R, Bleeker H, & Perry, J. (2017). MP20: Prevalence of incidental findings on chest computed tomography in patients with suspected pulmonary embolism in the ED. *CJEM*, 19(S1), S71-S72.

15 Kakkos S, Kirkilesis G, Tsolakis I. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg.* 2014; 48(5): 565-575.

16 Hutchinson B, Navin P, Marom E, Truong M, Bruzzi J. Overdiagnosis of Pulmonary Embolism by Pulmonary CT Angiography. *Am J Roentgenol* 2015; 205(2): 271-277.

17 Ong C, Malipatil V, Lavercombe M et al. Implementation of a clinical prediction tool for pulmonary embolism diagnosis in a tertiary teaching hospital reduces the number of computed tomography pulmonary angiograms performed. *Internal Medicine Journal*. 2013; 43(2): 169-174.

18 Mills A, Ip, I, Langlotz C et al. Clinical decision support increases diagnostic yield of computed tomography for suspected pulmonary embolism. *Am J Emerg Med*. 2017 Sep 6. pii: S0735-6757(17)30727-1.

19 Jiménez D, Resano S, Otero R for the IRYCIS Pulmonary Embolism Study Group, et al Computerised clinical decision support for suspected PE. *Thorax* 2015;70:909-911

20 Mahmood A, Durrans C, Naik S et al. P259 Cost analysis of implementing a pe pathway incorporating 3-level wells scoring, perc rules and age-adjusted d-dimers. *Thorax* 2016;71:A228.

21 Jones P, Elangbam B, Williams NR. Inappropriate use and interpretation of D-dimer testing in the emergency department: an unexpected adverse effect of meeting the “4-h target”. *Emergency Medicine Journal* 2010;27:43-47.

22 Van der Hulle T, Cheung W, Kooij S et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017; 390: 289–97

23 Raja A, Greenberg J, Qaseem A, Denberg T, Fitterman N, Schuur J. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med* 2015; 163(9): 701-711.

24 Mountain D, Keijzers G, Chu K, Joseph A, Read C, Fatovich D, 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(12): e0166483.

25 Ekelund S. Why D-dimer tests cannot be used to exclude venous thromboembolism in patients with high pretest probability. *Acutecaretesting.org*. [January 2015, cited August 8 2017]. Available from <https://acutecaretesting.org/en/articles/why-ddimer-tests-cannot-be-used-to-exclude-venous-thromboembolism-in-patients>.

26 Kearon C, Ginsberg J, Douketis J et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. *Ann Intern Med* 2016; 144(11): 812-821.

27 Kline J, Hogg M, Courtney D, Miller C, Jones A, Smithline H. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. *J Thromb Haemost*. 2012; 10(4): 572-581.

28 Sullivan C, Staib A, Khanna S et al. The National Emergency Access Target (NEAT) and the 4-hour rule: time to review the target. *MJA*. 2016; 204(9): 354.

29 Kline J, Hernandez-Nino J, Jones A, Rose G, Norton H, Camargo CA J. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med* 2007; 14(7): 592-598.

30 Alonso-Martínez J, Sánchez F, Echezarreta M. Original article: Delay and misdiagnosis in sub-massive and non-massive acute pulmonary embolism. *Eur J Intern Med.* 2010 Aug; 21(4):278-82.

31 Smith S, Geske J, Morgenthaler T. Risk factors associated with delayed diagnosis of acute pulmonary embolism. *J. Emerg. Med* 2012; 42(1): 1-6.

32 Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *BMJ Quality & Safety* 2005;14:26-33.

Table 1: Sex and mean age for patients having CTPA or VQ scanning

	Pre-Implementation Phase			Implementation Phase		
	Male n(%)	Female n(%)	Mean age [SD] (yrs)	Male n(%)	Female n(%)	Mean age [SD] (yrs)
Site A	282 (44%)	363 (56%)	61.5 (18.0)	165 (37%)	281 (63%)	62.9 (19.5)
Site B	304 (40%)	458 (60%)	58.1 (18)	167 (41%)	241 (59%)	59.2 (18.4)
Site C	146 (36%)	262 (64%)	53.3 (19)	84 (32%)	180 (68%)	54.8 (19.1)
Combined	732 (41%)	1083 (59%)	58.2 (18.5)	415 (37%)	701 (63%)	59.6 (19.4)

Abbreviations: SD = standard deviation

Table 2: Comparison of pre- and post- PE-related rates

	Pre-implementation Phase				Post-Implementation Phase				Comparison of pre-implementation and implementation phases		
	N	n	Rate (per 1,000 presentations)	95% CI	N	n	Rate (per 1,000 presentations)	95% CI	Diff	95% CI	p-value
Total number of scans (n)											
Site A	49161	645	13.1	12.2, 14.2	52869	443	8.4	7.6, 9.2	-4.7	-6.0, -3.5	<0.001
Site B	45909	762	16.6	15.5, 17.8	46292	408	8.8	8.0, 9.7	-7.8	-9.2, -6.3	<0.001
Site C	30509	408	13.4	12.1, 14.7	30025	265	8.8	7.8, 10.0	-4.5	-6.2, -2.9	<0.001
Combined	125579	1815	14.5	13.8, 15.1	129186	1116	8.6	8.1, 9.2	-5.8	-6.6, -5.0	<0.001

Number of PE's identified (n)

Site A	49161	80	1.6	1.3, 2.0	52869	77	1.5	1.2, 1.8	-0.2	-0.6, 0.3	0.537
Site B	45909	68	1.5	1.2, 1.9	46292	68	1.5	1.2, 1.9	0.0	-0.5, 0.5	0.961
Site C	30509	31	1.0	0.7, 1.4	30025	39	1.3	0.9, 1.7	0.2	-0.3, 0.8	0.363
Combined	125579	179	1.4	1.2, 1.7	129186	184	1.4	1.2, 1.6	0.0	-0.3, 0.3	0.994
	N	n	%	95% CI	N	n	%	95% CI	Diff	95% CI	p-value
Yield rate											
Site A	645	80	12.4	10.1, 15.2	446	77	17.4	14.1, 21.2	5.0	0.6, 9.3	0.022
Site B	762	68	8.9	7.1, 11.1	408	68	16.7	13.3, 20.6	7.7	3.6, 11.9	<0.001
Site C	408	31	7.6	5.4, 10.6	264	39	14.3	11.0, 19.1	6.7	1.8, 11.7	0.005
Combined	1815	179	9.9	8.6, 11.3	1118	184	16.5	14.4, 18.8	6.6	4.1, 9.2	<0.001

N = ED presentations aged 16 years and over
n = number of scans

Table 3: Change in Yield rate after intervention (interrupted-time series)

Hospital Site	Change in yield post-intervention			Change in slope		
	β	95% CI	p-value	β	95% CI	p-value
Site A						
No delay	-0.01	-0.10, 0.07	0.749	0.01	-0.01, 0.01	0.382
Delay = 1 month	0.03	-0.05, 0.12	0.419	0.01	-0.01, 0.02	0.427
Delay = 2 month	0.08	0.03, 0.14	0.007	0.00	-0.01, 0.01	0.767
Delay = 3 month	0.07	0.00, 0.14	0.038	0.00	-0.01, 0.01	0.725
Site B						
No delay	0.10	-0.02, 0.22	0.090	-0.01	-0.02, 0.01	0.413
Delay = 1 month	0.11	0.00, 0.22	0.047	-0.01	-0.03, 0.01	0.176
Delay = 2 month	0.15	0.08, 0.23	<0.001	-0.02	-0.04, 0.00	0.021
Delay = 3 month	0.11	-0.01, 0.22	0.064	-0.03	-0.05, 0.01	0.016
Site C						
No delay	0.06	0.01, 0.11	0.025	-0.01	-0.02, 0.00	0.063
Delay = 1 month	0.01	-0.04, 0.06	0.768	-0.01	-0.02, 0.00	0.063
Delay = 2 month	0.00	-0.05, 0.05	0.990	-0.01	-0.02, 0.00	0.081
Delay = 3 month	-0.01	-0.07, 0.05	0.761	-0.01	-0.02, 0.00	0.151
All sites						
No delay	0.04	-0.02, 0.10	0.171	0.00	-0.01, 0.01	0.572
Delay = 1 month	0.06	-0.01, 0.12	0.105	-0.01	-0.02, 0.01	0.388
Delay = 2 month	0.09	0.05, 0.13	<0.001	-0.01	-0.02, 0.00	0.052
Delay = 3 month	0.06	0.00, 0.13	0.045	-0.01	-0.03, 0.00	0.041

Table 4 – comparison of patients where d-dimer was measured and imaging performed

	Pre-implementation Phase		Implementation Phase		Comparison of yield rate pre-implementation and implementation phases		
	No. of patients	PEs identified	No. of patients	PEs identified	Diff	95% CI	p-value
	N	n(%)	N	n(%)			
d-dimer <0.3 mg/L FEU	39	3 (7.7)	23	0 (0.0)	-7.7	-16.1, 0.7	0.173
d-dimer 0.3 – 0.49 mg/L FEU	162	4 (2.5)	36	0 (0.0)	-2.5	-4.9, 0.0	0.341
d-dimer ≥0.5 mg/L but < age adjusted cut off (for patients aged 50 or older)	141	5 (3.5)	50	0 (0.0)	-3.5	-6.6, 0.0	0.178

d-dimer \geq age adjusted cut off and patient aged >49 yrs	269	49 (18.2)	419	88 (21.0)	2.8	-3.3, 8.8	0.372
d-dimer ≥ 0.5 and patient aged <50 years	125	17 (13.6)	195	30 (15.4)	1.8	-6.1, 9.6	0.660
Total	736	78 (10.6)	723	118 (16.3)	5.7	2.3, 9.2	0.001

Figure Legends:

Figure 1

Investigation pathway for pulmonary embolism – site a

Alternative imaging recommendation - sites b and c

Figure 2: Observed distribution of yield rate over time by hospital site

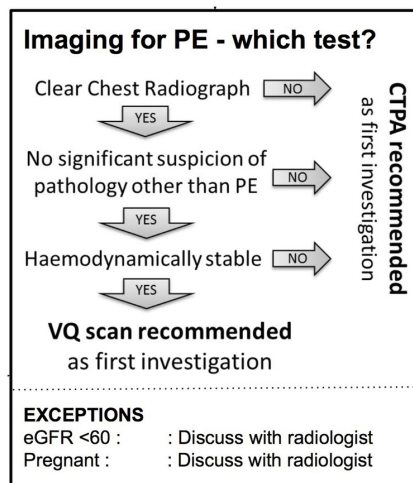
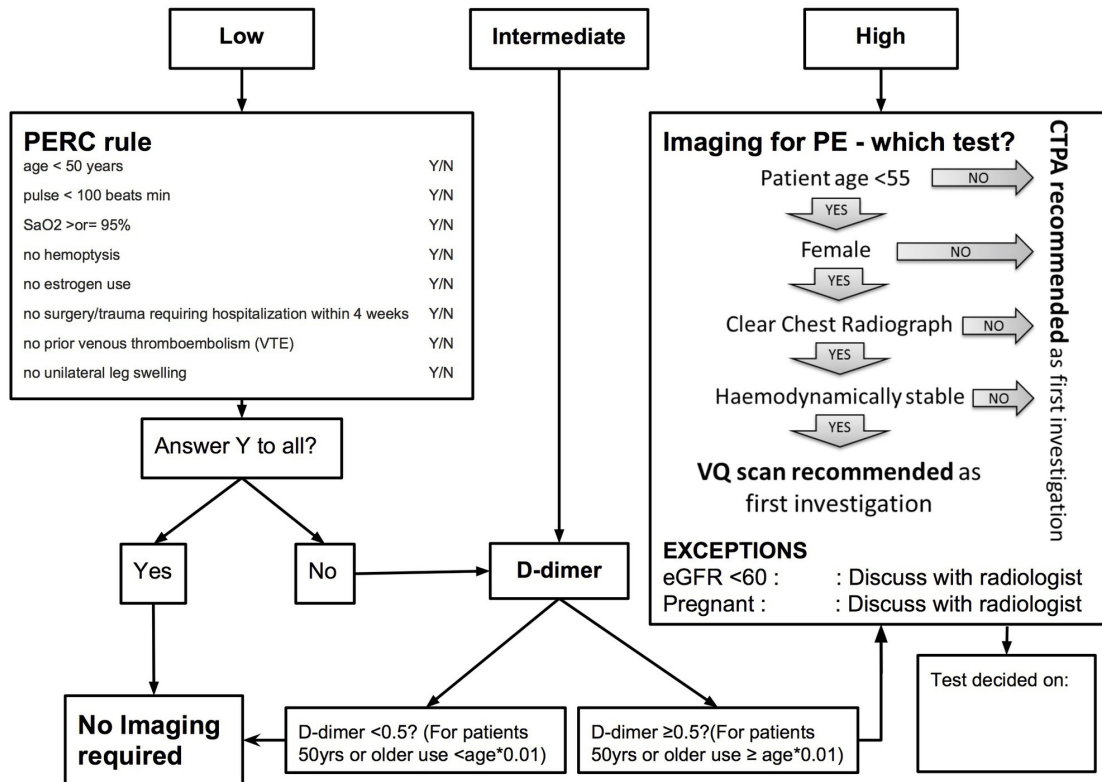
Figure 3: Comparison of total organisational CTPA/VQ numbers

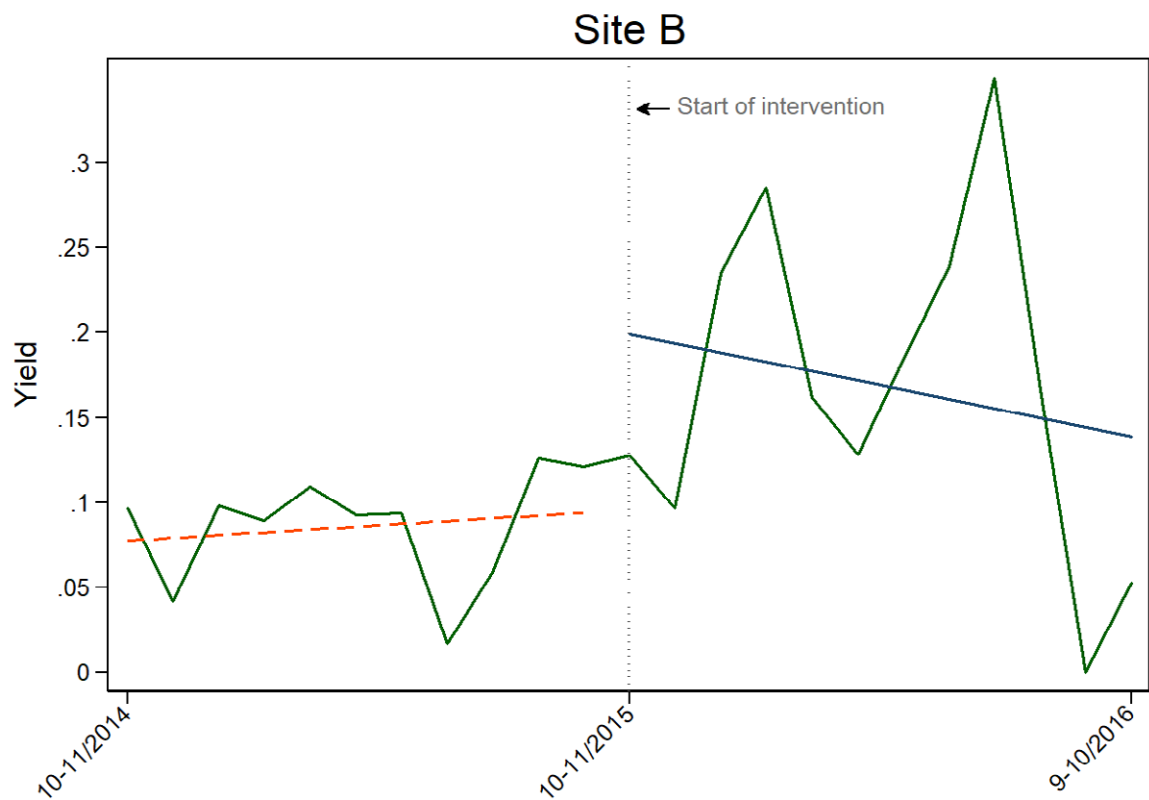
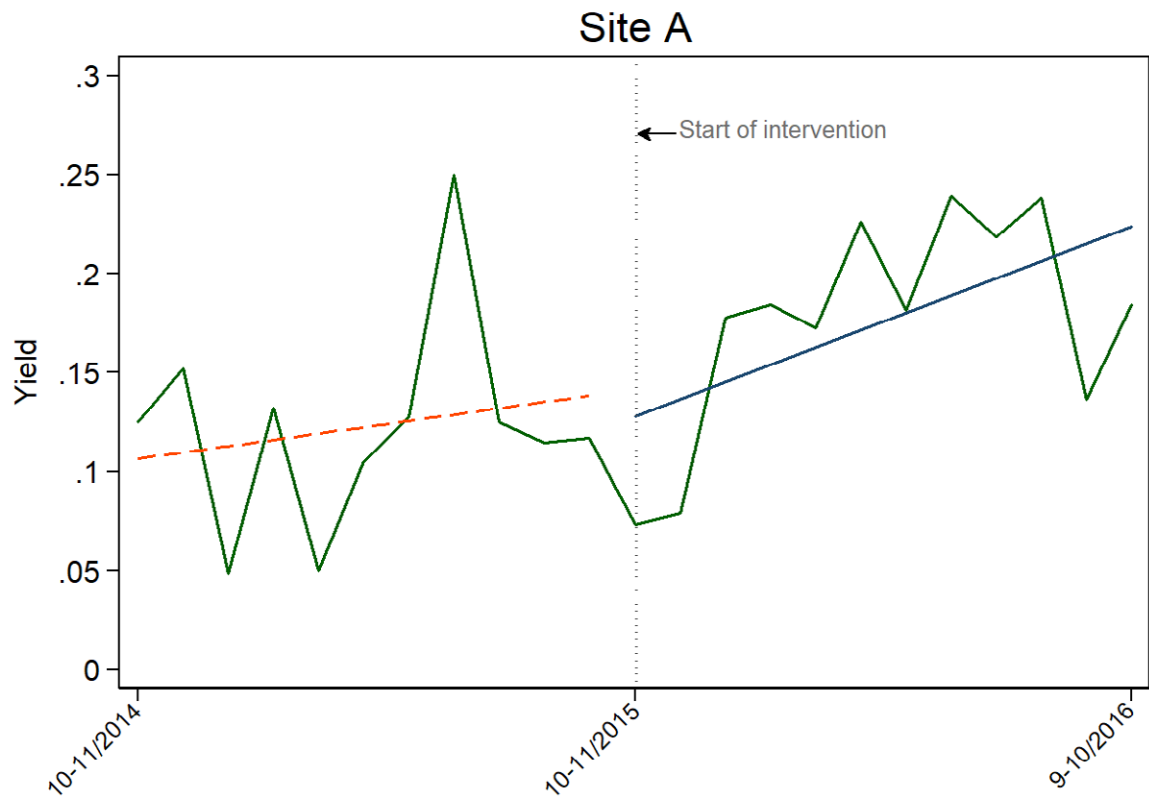
1. Chest X-Ray. Use to determine if another diagnosis is more likely than PE

2. Assess clinical probability for PE using Wells score

- PE is most likely diagnosis (consider history, examination, ECG, CXR)	3	<input type="checkbox"/>
- Suspected DVT	3	<input type="checkbox"/>
- Heart Rate >100/minute	1.5	<input type="checkbox"/>
- Immobilisation or surgery within previous 4 weeks	1.5	<input type="checkbox"/>
- Previous DVT/PE	1.5	<input type="checkbox"/>
- Haemoptysis	1	<input type="checkbox"/>
- Malignancy (on treatment, treated in past 6 months or palliative)	1	<input type="checkbox"/>
TOTAL		<input type="text"/>

Score (circle)	<2	Low Probability (pre-test probability = 3.4%)
	2-6	Intermediate (pre-test probability = 27.8%)
	>6	High (pre-test probability 78.4%)





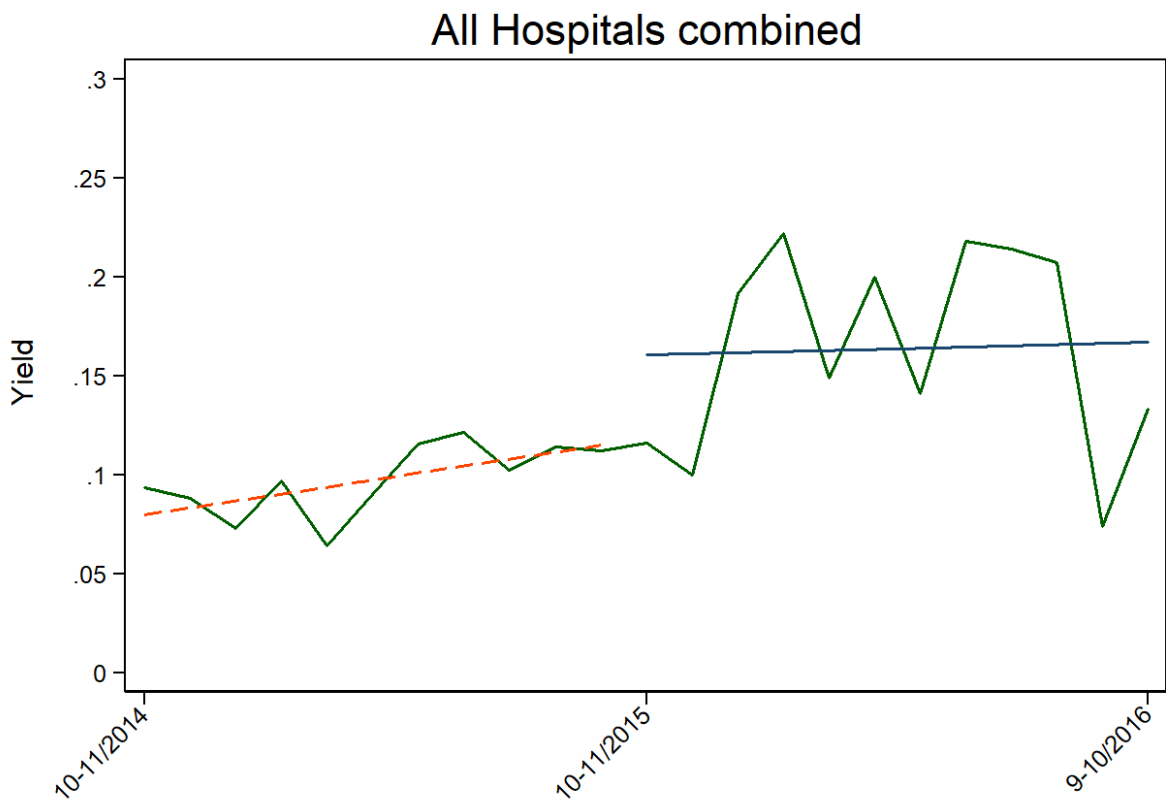
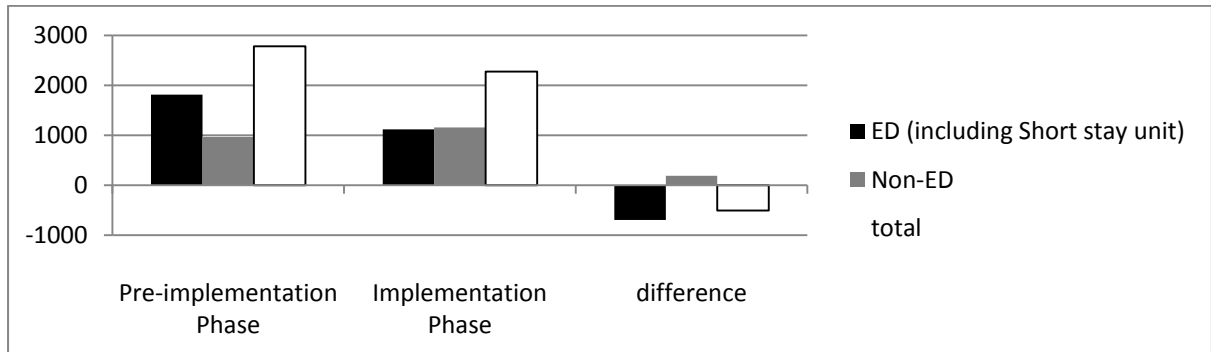


Figure 3. Comparison of total organisational CTPA/VQ numbers



Title Page

i) Title

The effect of a clinical flowchart incorporating Wells score, PERC rule and age adjusted D-dimer on pulmonary embolism diagnosis, scan rates and diagnostic yield.

(ii) the full names, titles and degrees of the authors;

Authors:

Dr Paul Buntine, MBBS, FACEM. Emergency Physician, Eastern Health, Monash University
Professor Francis Thien, MD, RACP. Director of Respiratory Medicine, Eastern Health, Monash University
John Stewart, Medical Imaging Technologist, Eastern Health, Monash University
Ms Yee Ping Woo, Medical Imaging Technologist
Dr Martin Koolstra, MBBS, FACEM. Emergency Physician, Eastern Health, Monash University
Dr Lindsay Bridgford MBBS FACEM. Emergency Physician, Eastern Health, Monash University
Dr Mineesh Datta, MBBS, RANZCR. Director of Radiology, Box Hill Hospital, Monash University
Dr Stella May Gwini, School of Public Health & Preventive Medicine, Monash University

Acknowledgements:

Jo-Anne McShane, RN, Research Assistant, Box Hill Hospital Emergency Department
Associate Professor Paul Coughlin, MBBS, RACP, PhD. Clinical Haematologist, Eastern Health, Monash University

(iii) each author's contribution

PB conceived the idea for the study, which was then designed with assistance from FT, JS, YW, MK, LB, MD and PC. PB supervised overall conduct of the study. Local sites were coordinated by PB, MK and LB. PB and JM were responsible for data collection from site A whilst JS was responsible for data collection from sites B and C. PB and JM performed all data entry. PB analysed the data, with statistical analysis performed by SG. All authors contributed to the final manuscript. PB takes overall responsibility for paper as a whole.

iv) Short running title

A flowchart consisting of Wells, PERC and age adjusted DD

(v) the addresses of the institutions at which the work was carried out

Box Hill Hospital, 8 Arnold Street, Box Hill, Victoria 3128
Maroondah Hospital, Davey Dr, Ringwood East Victoria 3135
Angliss Hospital, Albert St, Upper Ferntree Gully VIC 3156

(vi) the full postal and email address, plus telephone numbers, of the author to whom correspondence about the manuscript should be sent

Dr Paul Buntine
Emergency Department, Box Hill Hospital, 8 Arnold Street, Box Hill, Victoria 3128
paul.buntine@easternhealth.org.au

03 997 56043
0425 749936

(vii) word count:

Word Count: 5062

Author Manuscript