Ten years of imaging for pulmonary embolism: too many scans or the tip of an iceberg?

Clinical Radiology

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--Manuscript Draft--

Manuscript Number:	CRAD-D-15-00283R1
Full Title:	10 years of Imaging for Pulmonary Embolism - Too Many Scans, or the Tip of an Iceberg?
Article Type:	Original Paper
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Abstract:	Aim: This study examines the number and nature of investigations performed for suspected PE in a large teaching hospital and the change in incidence and severity of PE over a decade. With availability of CT pulmonary angiography (CTPA), the number of imaging investigations for suspected acute pulmonary embolism (PE) has been increasing steadily. It has been hypothesised that this leads to increased detection of small emboli and effective over-diagnosis. Materials and methods: In this retrospective study, all patients investigated for suspected PE using CTPA or lung scintigraphy during 10 years to March 2012 were identified and their records reviewed. In the final year, all reportedly positive CTPA cases were reviewed and PE severity calculated, for comparison with similar historical data. Results: From 2002 to 2012, total annual investigations for suspected acute PE increased by 163% (805 to 2 121). CTPA increased by 325% (475 to 2 019). Detection of PE increased by 121% (193 to 426 per annum), with stable distribution of severity scores. The positive scan rate decreased from 24% to 20%. The mean age of patients being investigated for PE increased from 56 to 63 years. Conclusions: Increased detection of PE is not due to disproportionate increase in small PEs, but to increased detection of PE of all severities. This finding supports the hypothesis that PE is more common in the general population than previously appreciated, which may represent an iceberg phenomenon of previously undetected disease.

10 years of Imaging for Pulmonary Embolism - Too Many Scans, or the Tip of an Iceberg?

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Professor Edwin J.R. van Beek is supported by the Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE).

No competing interests.

Suggested MeSH Key Words:

- Pulmonary Embolism
- Embolism and Thrombosis
- Diagnostic Imaging
- Diagnostic Techniques, Respiratory System
- Health Services Needs and Demand

Author Contributions

Please list the following phrases and beside each indicate the name(s) of the author(s) to whom they apply:

1 guarantor of integrity of the entire study	NM
2 study concepts and design	JM, EvB, SM, NM
3 literature research	JM, EvB, SM, KM
4 clinical studies	NM, KM
5 experimental studies / data analysis	n/a
6 statistical analysis	NM
7 manuscript preparation	NM, KM
8 manuscript editing	NM, KM, SM, EvB, JM

Reviewer #1: A well written interesting study.

a. I think it would be useful to give the figures for decreased use of Q scans over the ten years and the percentage now investigated by Q vs CTPA.

Numbers now included in text, line 107.

b. Was there any difference in diagnosis rate between Q and CT?

Insert at line 115: In the final year 9% of 102 Q scans and 20% of 2 019 CTPAs were positive.

c. You state the your catchment population increased by only 7% during the study but what happend to patient attendences during the period. They may have increased by more than 7%

There are many different types of hospital attendance and it is difficult to give a useful answer here. We understand that A&E attendances, for instance, are increasing month on month. We feel that the most important observation is the relationship of incidence to the population. All acute admissions for the catchment population were admitted to the hospitals studied and consequently we consider that the catchment population is the most appropriate denominator.

No change made.

d. In terms of factors that might have driven increased referral for investigation was there any change in care pathway e.g was d-dimer used througout period and did institution roll out any care pathway changes which may have contributed to increased investigation?

Alteration beginning line 206:

In a hospital setting, there is easier access to PE diagnostic imaging, and the way in which patients with suspected primary PE are looked after and investigated is changing which could partially explain the increase in radiological referrals. For instance there are new 'ambulatory care' pathways whereby patients can be anticoagulated and return the following day for CTPA.

Reviewer #2:

a. The paper has looked at a decade of investigations for acute PE (both CTPA and VQ) and compared the numbers of scans performed, the number of positive scans and the'severity' of the PE with historical data primarily to test the hypothesis that the number of increase in positive scans is due to the increased detection of smaller PEs.

b. They concluded that there has been an increased incidence of PE but this cannot be attributed to increased detection of smaller PEs with the overall 'severity' score remaining similar to historical data.

c. The paper discusses well why there may be an increase in the number of PE diagnosis (ultimatetly presumbably becasue we are doing more investigations) and argues that there the management of 'smaller PEs' remains unclear and perhaps anticoagulation for this group could be withheld - this would be a more powerful argument if there was any outcome data between the periods studied (?)- although it is mentioned in the introduction that a systematic review showed no includable studies in this regard, this may be worth reiterating in the discussion - was outcome worse when we weren't diagnosing all these PEs?

   It is difficult to answer this, as we have started with people being scanned. We are not aware of accurate death rates due to TED for our population. This is specifically discussed by Wiener et al. for USA population data.
   We highlight this topic cautiously in our introduction to illustrate some of the controversy and ongoing investigation in the field. No change made.

d. I challenge some of the text regarding 'CTPA being better than V/Q at diagnosing subsegemental PE' (eg Intro 22-25 and discussion 158-162) - I believe the literature on this is not entirely as clear cut especially in the current climate with SPECT VQ which has shown good results and is perhaps better than CTPA at smaller PE. While not especially relevant to the study itself I think SPECT VQ should be discussed and referenced more to reflect emerging modern clinical practice.

   We agree that SPECT VQ is an important development and we are grateful for your prompt to include this in the discussion.
   Change to line 224: CTPA is currently the first line…
   Change to line 257: SPECT V/Q scanning techniques are becoming established elsewhere and we believe that this will play an increasing part in investigation of suspected PE. (28, 29)

   Lines 22-25 refer specifically to historic published work, central to the arguments in the Weiner paper. No change made.

e. The Modified Miller Score needs explanation. I maybe wrong but I think this reflects scoring of segmental PE. What happens to the scoring in isolated sub-segmental PEs?
You're correct - the modified Miller score is not explicit regarding this. Referring back to the Miller Score, involvement of a vessel (or segment) was sufficient to incurr 1 point.
Added, line 55: With specific regard to subsegmental emboli, each bronchopulmonary segment containing an embolus (or emboli) would contribute one point to the score, analogous to 'involvement' in the Miller Score(19), unless superceded by a more proximal embolus.

Abstract

Aim: This study examines the number and nature of investigations performed for suspected PE in a large teaching hospital and the change in incidence and severity of PE over a decade. With availability of CT pulmonary angiography (CTPA), the number of imaging investigations for suspected acute pulmonary embolism (PE) has been increasing steadily. It has been hypothesised that this leads to increased detection of small emboli and effective over-diagnosis.

Materials and methods: In this retrospective study, all patients investigated for suspected PE using CTPA or lung scintigraphy during 10 years to March 2012 were identified and their records reviewed. In the final year, all reportedly positive CTPA cases were reviewed and PE severity calculated, for comparison with similar historical data.

Results: From 2002 to 2012, total annual investigations for suspected acute PE increased by 163% (805 to 2 121). CTPA increased by 325% (475 to 2 019). Detection of PE increased by 121% (193 to 426 per annum), with stable distribution of severity scores. The positive scan rate decreased from 24% to 20%. The mean age of patients being investigated for PE increased from 56 to 63 years.

Conclusions: Increased detection of PE is not due to disproportionate increase in small PEs, but to increased detection of PE of all severities. This finding supports the hypothesis that PE is more common in the general population than previously appreciated, which may represent an iceberg phenomenon of previously undetected disease.

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Introduction

Objective: To assess the impact of a putative increase in detection of small PEs, we have measured the rate and outcomes of investigation for suspected acute PE in our institution over the decade 2002-2012.

Venous thrombo-embolism (VTE), including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) is a frequent and important diagnosis.(1, 2) Despite routine prophylaxis, it also remains a leading cause of secondary mortality and morbidity in many common healthcare scenarios, for example maternity,(3) and lower limb arthroplasties.(4)

As VTE is prevalent, dangerous and treatable, it is not surprising to encounter controversy regarding its diagnosis and management.(5, 6) A recent article argues that modern CTPA makes increasingly sensitive detection of ‘small emboli’, and so alters the spectrum of diagnosis.(7) Figure 1 shows some example CTPA images. The authors hypothesised that additional inclusion of small emboli (previously undetectable) effectively causes overdiagnosis and overtreatment. They highlighted an experimental study reported in 2007,(8) in which patients with suspected PE were randomised to either V/Q scanning or CTPA. Appropriate patient selection, sufficient numbers and modern techniques made this a robust comparison. More PE were detected in the CTPA arm, but no significant differences in outcome were observed. In the CTPA group, 7% of those with PE had isolated, subsegmental emboli, less likely to be detected with a V/Q scan.

In combination, the findings above support the hypothesis: 'It is not beneficial to anticoagulate patients with small PEs'. This was the topic of a systematic review,(9, 10) which found no includable studies and a multicentre trial in North America is currently recruiting to test it.(11) However it is worth considering that treatment of PE is partly secondary prevention. A PE causing presentation might be the forerunner of a preventable secondary event. In addition to dissolution of the embolus causing the presentation, the treatment also targets the thrombotic source of emboli.

Pulmonary embolism is a difficult clinical diagnosis with varied and sometimes minimal symptoms and signs. As a result, patients being investigated for suspected PE may have various other serious illnesses. Patients with clinically suspected PE in whom the diagnosis is refuted show a higher mortality than those in whom the diagnosis is confirmed (17% vs 11% at 6 months).(12) In a more recent study, patients with negative CTPA had a 14% 3-month mortality.(13) It is also relevant to consider that sub-clinical PE is a common incidental finding on CT scans performed for other reasons,(14) and also at *post mortem*.(15) In summary, patients being referred with suspected acute PE are a heterogeneous population with many other potential diagnoses and there is a recognised prevalence of sub-clinical VTE.

Methods

This work builds on previous published data from this institution.(16, 17) An earlier paper reports a cohort of consecutive positive CTPAs (n=504) from 2001 to 2004, with standardised severity scoring. We have performed a retrospective analysis of all CTPA and Q-scan referrals in the year ending 31/03/12, with comparable severity scoring using the

modified Miller score.(18) For some analyses, the Miller scores have been categorised as Mild (1-5), Moderate (6-10), and Severe (11-16). With specific regard to subsegmental emboli, each bronchopulmonary segment containing an embolus (or emboli) would contribute one point to the score, analogous to 'involvement' in the Miller Score(19), unless superceded by a more proximal embolus. The project was approved by the local research ethics authority.

Retrospective Case Reviews

All CTPA and Q scan records in the year ending 31/03/12 were retrieved from the hospital information system, numbering 2 138. Referrals and reports were evaluated by two independent physicians. 17 cases were excluded because the indication was not suspected acute PE, for instance the investigation of pulmonary hypertension. CTPA reports detailing new PEs were identified. These cases were reviewed and PE severity quantified with a Modified Miller score, under supervision of a chest radiologist with 20 years of experience.

Similar hospital record searches were used to identify the rates of referral for Q-scans and CTPAs in the years between 2001 and 2012.

In seeking to quantify the incidence of PE, this study is limited to cases where suspected acute PE has been referred to Clinical Radiology for imaging with Q-scan or CTPA. There may be other clinical routes for diagnosis of PE that are not included in this analysis.

Imaging Protocols

Although our imaging practices have developed over the period of study, the extraction of standardised categorical data means that valid comparisons can be made. Current protocols are described:

CT Pulmonary Angiography

CTPA is performed using a 75ml injection of Intravenous contrast medium (Iomeron 400), given by pump injection at 4.5 ml/s (Dose reduced to 50mls when age >40 and mass <95kg). 64-slice helical CT acquisition from hyoid to costophrenic angles following an inspiratory breath-hold instruction, with arms abducted. The scan is triggered on detection of the leading contrast in the right atrium.

Pulmonary Scintigraphy

Planar images of the thorax are obtained in 8 projections, beginning immediately after intravenous injection of 80 MBq of Tc99 labelled macro-aggregated albumin. Total scan time is approximately 15 minutes using a 2-head gamma camera, and low-energy high-resolution parallel collimators.

Analyses

Statistical and graphical analyses were performed by NM using Microsoft Excel and GraphPad Prism. Each patient's age in complete years was calculated using the date of birth and date of scan. Age distributions were assessed with 10-year histogram bins, centred on each multiple of 10 (i.e. 5-14, 15-24 etc.). In addition to graphical analysis, distribution of PE severity scores was assessed for change using Chi-squared analysis of normalised data, the table having 16 rows and 2 columns, therefore 15 degrees of freedom.

Results

Increased rate of investigation and shift to CTPA

From 2002 to 2012 there was a 163% increase in the annual rate of investigation for suspected acute PE (from 805 to 2 121). In this same period the number of CTPAs performed per year has increased by 325%

(from 475 to 2 019). This is a change from 45% of total investigations to 96% as%. Over the same period, Q-scans have fallen from 566 to 102 per year, from 55% to 4% of investigations. These changes are illustrated in Figure 2. Further analysis of the referrals in the first and last of these years in Figure 3 reveals that Q-scanning is now most commonly performed in younger patients, peaking at approximately 30 years of age.

Increased Detection of PE

Detection of PE increased by 121% (from 193 to 426 per annum). The number of investigations has increased even more, resulting in a slight decrease in PE-positive scan rate from 24% to 20%. In the final year 9% of 102 Q scans and 20% of 2 019 CTPAs were positive. The population served by our hospital has increased by 7% over this period,(20) so a greater rate of diagnosis in our practice represents increased incidence of acute PE diagnosed radiologically.

Distribution of PE Severity Scores

PE severity scores show a stable distribution over the recent decade (Figure 4), with the proportion of severe PEs (modified Miller score 11 or greater) stable at 36% (p=0.85). There is no significant difference between samples on Chi-squared analysis of the categorical data. (Chi-square=9.58, p=0.85). Although variation is not significantly different when considering the distribution of all scores, the proportion of cases with a modified Miller score of 1 has increased from 11% to 16%.

The comparison above uses the cohort previously described by Wong et al.,(17) with data from more than one year in the older set. Subset analysis of the year ending March 31st 2002, is not shown, but a similar pattern is present (Chi-square=17.5, p=0.29). That sample is smaller, n=134, in part because during that year many patients had PE diagnosed

by scintigraphy and so modified Miller scoring of severity is not applicable.

Age of Population Being Investigated

The mean age of patients being investigated for PE (both Q-scan and CTPA) has increased from 56 years in 2001/02 to 63 years in 2011/12 (95% CI +6.1 to +8.9 years). The proportion of patients being investigated who are over 80 years of age has increased from 12% to 21%. Increasing age is represented in the Figure 3 histograms, where the mode changes from 65 to 80.

The population of patients being investigated with CTPA is also older, as seen in Figure 5. The mode has changed from 70 to 80, and the mean from 61 to 65 (95% CI +1.6 to +5.2).

Incidence of PE in all age groups

To further investigate the increased incidence of PE, and the relationship to the changing age of the population, relative frequency plots are given for comparison in Figure 6. The positive results in each severity bracket are distributed across the age range, and reflect the age distribution of all CTPAs. There does not appear to be any anomalous increase in positive cases or severe cases associated with the increase in older patients.

Discussion

The incidence of PE diagnosed radiologically has more-than-doubled in a decade. This is a surprising finding, and might reasonably lead to the hypothesis that the ‘Increased number of emboli is due to detection of smaller emboli’, as advanced by Wiener, Schwartz and Woloshin.(7) However that hypothesis is refuted by our analysis of PE severity. The

proportion of patients diagnosed with massive PE, within the group of patients with CTPA confirmed emboli, remains the same. This refutes the hypothesis that modern CTPA has caused a particular increase in diagnosis of small PE. The incidence of small PE has increased, but in proportion to the overall incidence.

We do not contest that replacing isotope scintigraphy with CTPA in imaging for suspected PE has resulted in a greater number of smaller emboli being diagnosed, as demonstrated by Anderson et al. 2007.(8) Our data primarily relates to a continuing rise in the diagnosis of PE within patients investigated with CTPA.

The size of PE that a scanner is able to identify is limited by the spatial resolution of CT, and this has remained fairly static at around 1mm over the decade under investigation. Greater number of detectors and decreased acquisition times do improve co-ordination with the contrast bolus and breath hold to reduce artefacts from contrast dilution and respiratory motion respectively, but when the technique was satisfactory these were not restricting factors. The small increase in the proportion of PE with a severity score of 1 (from 11% to 16%, see Figure 4) may represent an effect of increased sensitivity to detection of smaller emboli but it does not account for the increased rate of detecting PE.

A number of factors may underlie the increase in incidence during the study period. Although the population being investigated contains a greater proportion of older people, the age distribution of PE has changed in a similar fashion, without any major discrepancy in the age distribution of PE. Younger patients still have a similar proportion of positive studies, with no gross change in severity categorisation (Figure 6). The increased

number of studies being performed means that the rate of diagnosis in each category has increased proportionally.

We know from other reports that incidental PE are identified on CT scans investigating other diseases in both inpatients,(14) outpatients,(21) and on post mortem examinations.(15) Thus sub-clinical PE is a real entity and there may be an iceberg phenomenon, where we see only the tip and a significant proportion of disease remains undiagnosed. Increased suspicion of relevant symptoms by patients and clinicians could lead to an increased referral rate for imaging and thereby increased diagnosis, transferring subclinical PE to clinical PE. Because we are observing this increase in investigations that have been targeted to symptomatic PE, this would require a historical context when symptoms were previously not investigated, or were given an alternative (incorrect) diagnosis.

It is possible that public awareness has increased causing more patients to present to medical care with their symptoms. We are anecdotally aware of recent media exposure of VTE and the emotive, politically polarised name ‘economy class syndrome’ has helped to raise its profile, although it is not necessarily accurate.(22) Another change may be that patients more often present directly to an emergency department rather than to primary care. In a hospital setting, there is easier access to PE diagnostic imaging, and the way in which patients with suspected primary PE are looked after and investigated is changing which could partially explain the increase in radiological referrals. For instance there are new ‘ambulatory care’ pathways whereby patients can be anticoagulated and return the following day for CTPA.

We are also aware of recent activity to develop new injected and oral anticoagulants(23, 24) which contributes to a high awareness of thrombo-

embolic disease among medical professionals. Prescription of prophylaxis means that thrombo-embolic disease is routinely considered when admitting inpatients.

The increasing rate of pulmonary emboli may reflect a decrease in the health of our population. Prevalence of chronic illness is increasing,(25) and the ensuing 'multimorbidity' is now seen as a significant challenge to healthcare providers.(26, 27) Successful management of previously fatal diseases (including thrombo-embolic disease) may be increasing the prevalence of chronic illness, and increasing the risk of secondary VTE. This may be a paradoxical effect of improved healthcare.

CTPA ~~has become~~is currently the first line test of choice for the investigation of suspected acute PE. For patients with suspected PE, a normal chest radiograph, and no history of asthma or chronic obstructive pulmonary disease, pulmonary perfusion scintigraphy remains the preferred investigation in our institution. When the radiograph is abnormal, or there is a history of chronic lung-disease, patients are referred for CTPA. It is suggested that increasing patient age and co-morbidity mean that a larger proportion of patients are excluded from Q-scans on the basis of chronic respiratory illness or chest radiograph abnormalities.

Investigating suspected PE in pregnancy and the puerperium is a special clinical scenario. Q-scan is the preferred method due to a lesser dose of ionising radiation to maternal breasts.(28) This may, at least in part, explain why the Q-scan age distribution in Figure 3 has a mode of 30 years.

In most cases of suspected PE presenting outside daytime hours, patients are treated with subcutaneous low-molecular weight heparin, and imaging is deferred until the following morning. In cases where anticoagulation is contraindicated (*e.g.* some recent operations or a recent bleeding illness), or when important diagnostic doubt exists, imaging may be required immediately, which favours CTPA.

The widespread use of CT in many other clinical scenarios means that CT services are well established and available. Intravenous contrast medium can be used 'off the shelf' and has a long shelf life, whereas Tc^{99m} labelled Macro-agregated albumin requires on-site expertise for the harvesting and combination of radioisotope, whose mode of action requires instability. With few other indications for emergency radionuclide imaging, this is not available over the weekend in our institution. Meantime CTPA, being available, has become well accepted in emergencies, and imaging suspected PE over the weekend is commonplace. It may follow that Q-scanning has become less familiar as a result of the success of CTPA, to the extent that it is not considered by referring clinicians, or even by some radiologists when prioritising CT referrals. SPECT V/Q scanning techniques are becoming established elsewhere and we believe that this will play an increasing part in investigation of suspected PE. (29, 30)

Conclusions

In our practice, the rate of investigations for acute PE has increased by a factor of 2.6 in the recent decade, with a large increase in CTPA and a reduction in Q-scans.

The incidence of PE has increased by a factor of 2.2. The cause of the increased incidence of PE is not clear. Contrary to expectation, the later

cohort of diagnosed PE shows a similar distribution of severity to the historic comparison. Frequent diagnosis of smaller emboli does not explain the increase in total numbers of PE being diagnosed.

The most likely explanation for our findings is that prevalence of PE is greater than we were previously aware of (either clinically or radiologically). We hypothesise an iceberg phenomenon of undiagnosed disease. In this context, increased investigation will lead to increased detection. This would imply that our understanding of PE could still be improved. Another hypothesis is that our population is becoming less healthy, perhaps as a paradoxical consequence of greater investment in healthcare.

PE is a spectrum of disease and the least severe PE (embolus in a single segmental artery or smaller) do represent a significant proportion of cases (16%). The optimal management of these patients remains unclear and it may be that these patients could be better treated without anticoagulants.

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Figure Legends

FIGURE 1. Axial Images from Positive CT Pulmonary Angiograms

Patients are scanned shortly after injection of intravenous contrast, timed for greatest opacification in pulmonary arteries. **A:** Multiple small emboli are present. Three centri-luminal filling defects are shown in cross-section in lower-lobe segmental arteries. **B:** Another patient with a 'saddle embolus' astride the pulmonary trunk bifurcation and filling defects in the proximal pulmonary arteries. Secondary *cor pulmonale* causes retrograde opacification in the azygous vein and delayed opacification of the aorta.

FIGURE 2. Frequency of Investigations for Acute PE (stacked columns)

FIGURE 3. Referrals for CTPA and Q Scan by Patient Age (stacked bars)

FIGURE 4. Distributions of PE Severity Score

Normalised frequency distributions of PE severity score on positive CTPAs in a previous cohort (n=504) and in 2011/12 (n=400).

FIGURE 5. *Histograms of CTPA Results by Patient Age*

FIGURE 6. Normalised Frequency distributions of CTPA Referrals and Results

Age distribution of all CTPAs is shown as a line. Age distribution of positive cases is shown as bars which are subdivided by severity.

Figure 1
Click here to download Figure: Figure 1.tif

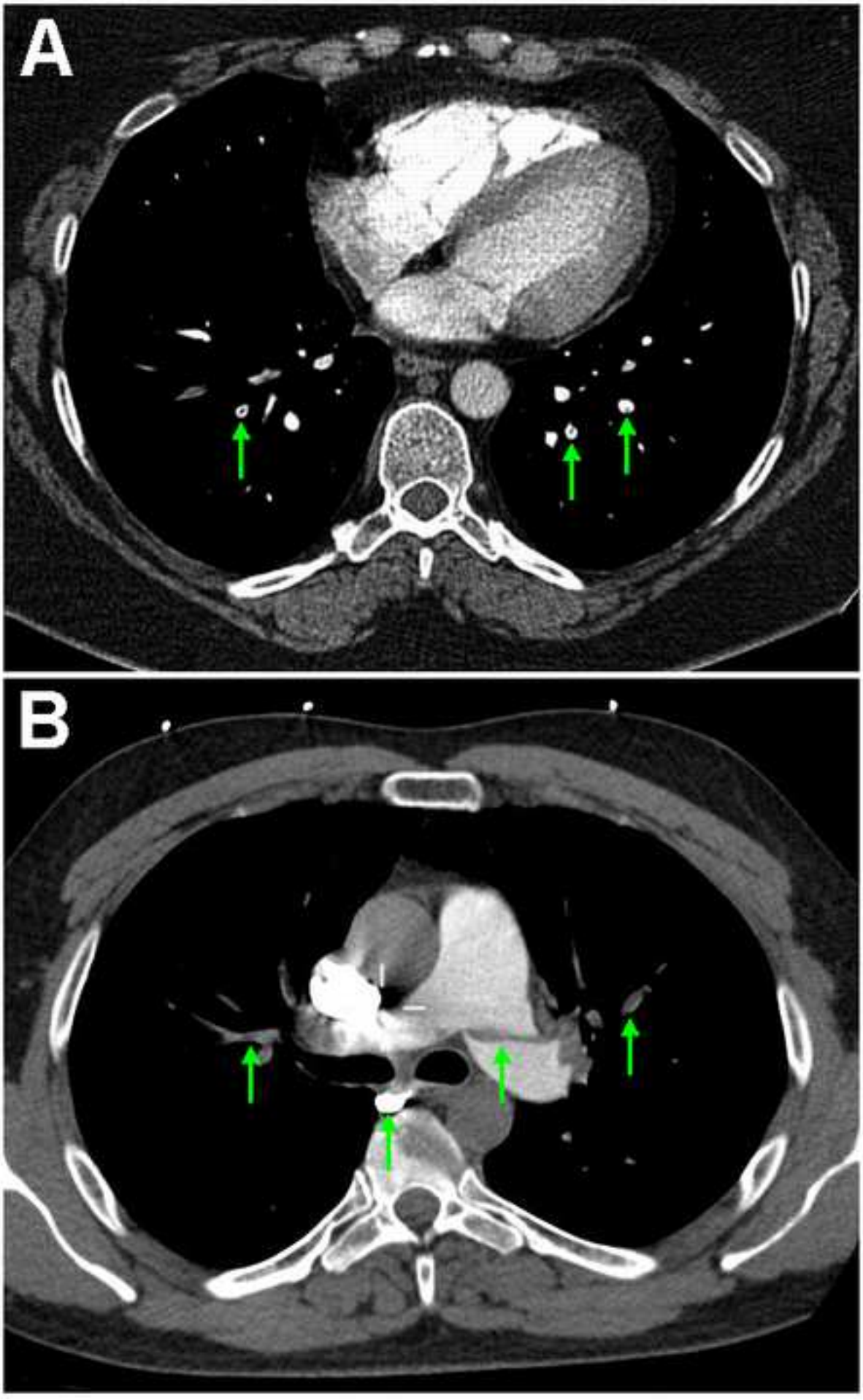


Figure 2

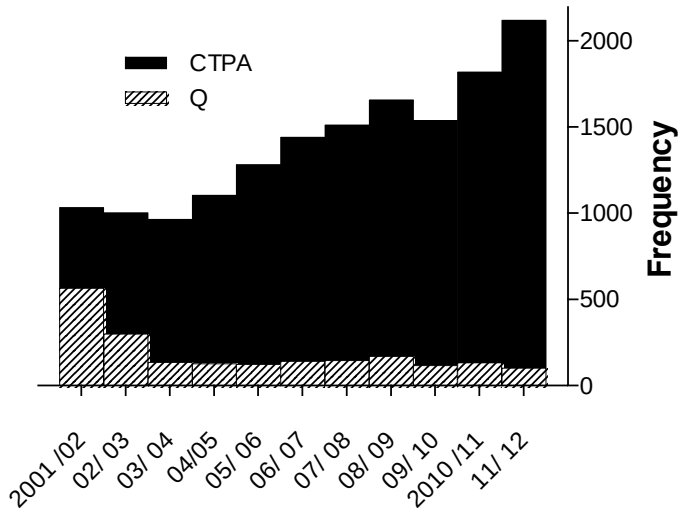

CTPA
Q
2000
1500
1000
500
0
Frequency
2001 /02
02/ 03
03/ 04
04/05
05/ 06
06/ 07
07/ 08
08/ 09
09/ 10
2010 /11
11/ 12

Figure 3

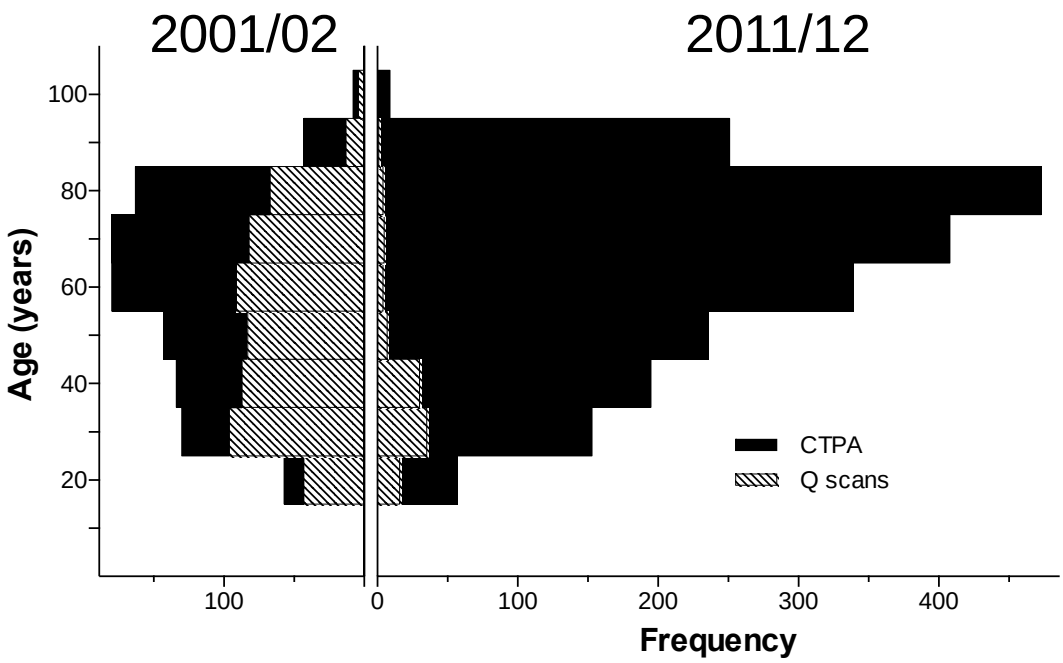

2001/02
2011/12
Age (years)
100
80
60
40
20
100
0
100
200
300
400
Frequency
CTPA
Q scans

Figure 4

Wong et.al
2001- 04

2011/12

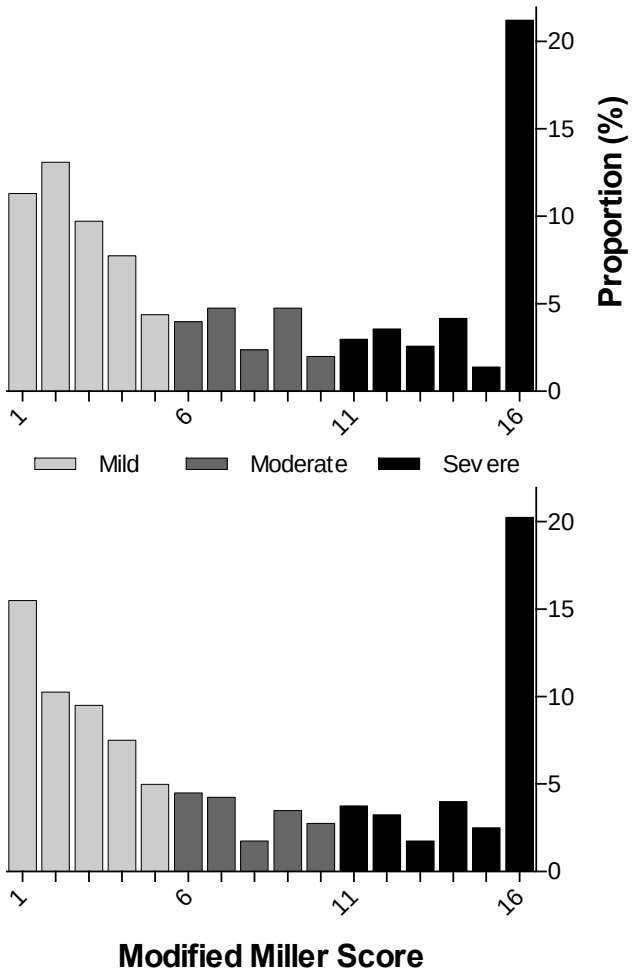


Figure 5

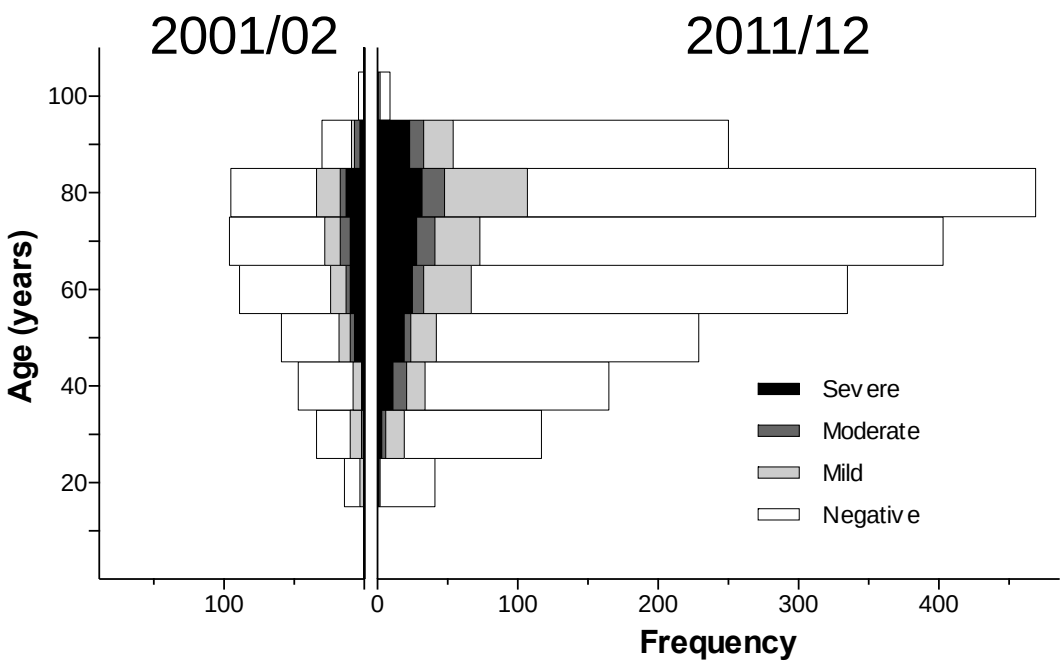
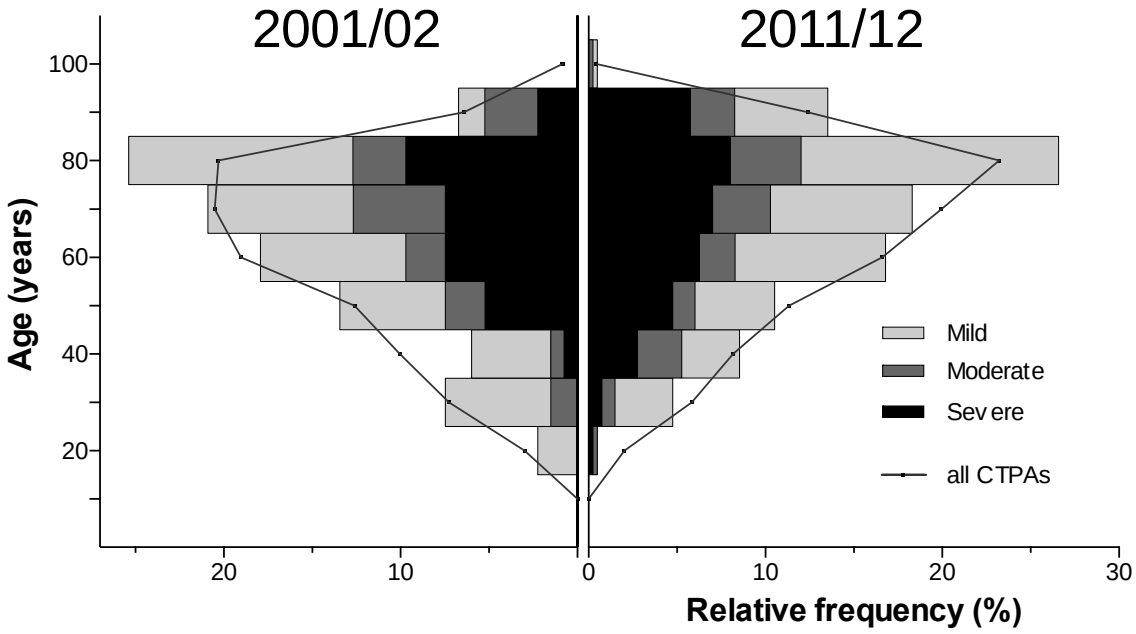

2001/02
2011/12
Age (years)
100
80
60
40
20
100
0
100
200
300
400
Frequency
Severe
Moderate
Mild
Negative

Figure 6


2001/02
2011/12
100
80
60
40
20
Age (years)
Mild
Moderate
Severe
all CTPAs
20
10
0
10
20
30
Relative frequency (%)

Highlights

We have examined PE incidence, severity and rate-of-investigations over a decade.

The rate of investigation has more-than doubled and PE incidence is increasing.

This occurs in all age groups and without change in distribution of severity scores.

This suggests an iceberg phenomenon due to subclinical disease.