D-dimer level has higher correlation with pulmonary embolism diagnosis than a clinical prediction score

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Abstract

Aim This study aimed to compare the predictive value of D-dimer and a clinical prediction score in diagnosis of pulmonary embolism (PE) as this could improve practice and reduce costs simultaneously. Method To achieve this, medical records of patients who presented to the Emergency Department of a large Australian metropolitan general hospital over 12 months and underwent DD testing were reviewed. The correlation coefficient (CC) was calculated using the Cramer's V method. Results CC between low-, intermediate- and high-risk groups on their own and a final diagnosis of PE on imaging was 0.1332, 0.1278 and 0.0817, respectively. By contrast, the CC when using positive DD was higher for all categories: 0.7527, 0.6256 and 0.4195, respectively. For the age-adjusted DD, the correlations were higher than for the clinical prediction score but less than for the absolute DD; calculated at 0.6490, 0.4987 and 0.3550 for the respective groups. The overall CC for risk category was 0.1107; for a positive DD, it was 0.7033; for the age-adjusted DD, it was 0.5928. Conclusion Positive DD has a higher correlation with PE diagnosis than the clinical prediction score. DD assay, whether positive or negative, is therefore an invaluable test in assessment of patients with suspected PE and can help determine the need for tomographic imaging. The absolute DD is more useful than the age-adjusted value.

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What's known (What's already known about the topic)

- Tomographic imaging to establish a diagnosis of PE is expensive
- Clinical prediction scores are used widely to assist in assessing individuals suspected of having PE
- The major utility of D-dimer is for excluding PE owing to its high negative predictive value

What's new (What does this article add)

- This is the first study to compare the correlation between D-dimer and PE diagnosis with the correlation between a clinical prediction score and PE diagnosis
- This is the first study to account for patients who didn't have imaging after initial clinical assessment
- The utility of absolute and age-adjusted D-dimer levels were compared in terms of correlation with PE diagnosis

Introduction

Pulmonary embolism (PE) is associated with high mortality and morbidity[1] and creates a high financial and efficiency burden on the healthcare system[2]. Diagnostic imaging with tomographic techniques – such as computed tomography pulmonary angiography (CTPA) or ventilation-perfusion (V/Q) scan with single emission computed tomography (SPECT) is expensive[3]. Early diagnosis has been shown to reduce mortality[2]. Thus, the use of clinical decision aids and blood tests may help reduce the resource and economic burdens on our health system.[4] The high negative predictive value of D-dimer assays has been most useful for excluding the diagnosis of PE[4-6], particularly for patients in the Emergency Department (ED)[7, 8]. However, many did not undergo imaging investigations and this needs to be taken into account. Our aim was to compare the ability of a positive DD level (both absolute and age-adjusted) to predict a positive result for PE on imaging and compare it with a conventional clinical risk score – to better justify use of expensive tomographic imaging.

Methods

Patients

Records of patients who presented to the ED of a large Australian metropolitan general hospital within twelve calendar months who underwent D-dimer testing were reviewed. Patients were included if they were over 16 years of age and had a D-dimer assay for suspected PE. Patients who had DD testing for suspected deep vein thrombosis (DVT) without PE, or for explicitly other reasons – such as assessment for disseminated intravascular coagulation after snake bites – were excluded.

Patient records were reviewed to re-calculate a pre-test probability based on the Revised Geneva Score (RGS – as summarised by Wong et al[9]). While the Wells score is more widely used and is well validated[10], it is difficult to calculate post hoc, especially as a major component of this score – that PE is the most likely diagnosis – is subjective. RGS, by contrast, uses objective and quantifiable measures, as summarised in Table 1. Both clinical scoring systems are reported to have similar accuracy[9, 11].

D-dimer assay

Serum D-dimer level was measured with the Stago 'STA-R Evolution' analyser (Stago Diagnostica, Genevilliers, France) using the STA-Liatest D-dimer assay. The reference range (< 0.4 mg/L) was based on previously published literature[12]. The age-adjusted D-dimer level was calculated using the method described by Douma et al[13], in which the so-called "permissible" D-dimer level (in mg/L) for patients aged over 50 years is their age divided by 100.

Imaging

The imaging results were taken from reports generated by specialist radiologists and nuclear medicine physicians. It was recorded whether patients had ventilation-perfusion (V/Q) lung scans, computed tomographic pulmonary angiograms (CTPA), both or neither.

V/Q scans were acquired by single photon emission tomography (SPECT) with a Symbia T6 scanner (Siemens AG, Munich, Germany). It is a large field-of-view, dual-head gamma-camera with a low-energy, all-purpose collimator. The ventilation-phase images were acquired following the inhalation of technetium-labelled ultrafine carbon particles (Technegas, Cyclomedica, Lucas Heights, Australia). The scanner was pre-programmed to 64 positions for 8-15 seconds per position (depending on body habitus). The perfusion phase images were acquired following the peripheral intravenous administration of technetium-labelled macroaggregated albumin (DraxImage MAA, Jubilant DraxImage Inc, Montreal, Canada). In this stage, the scanner was pre-programmed to 64 positions for 8 seconds per position. Iterative reconstruction with ordered subset expectation maximisation (OSEM) was applied and images could be viewed in all tomographic (coronal, transverse and sagittal) planes. Images were interpreted according to the European Association of Nuclear Medicine's 2009 Guidelines[14].

For CTPA studies, a routine protocol was utilised after injection of a 50–70-mL bolus of iopromide (300 mg iodine per millilitre, Ultravist; Bayer Schering Pharma, Berlin, Germany), which was followed by injection of 20–30 mL of a saline solution into an antecubital vein through an 18-gauge intravenous cannula (injection rate, 3.0–4.0 mL/sec). By using a bolus-tracking technique, a region of interest was placed in the main pulmonary artery, and image acquisition began 4 seconds after the signal attenuation reached the predefined threshold of 100 HU. The other acquisition parameters were as follows: tube voltages of 80 and 140 kVp and effective tube currents of 177 and 42 mAs for the two x-ray tubes; rotation time, 0.33 second; detector collimation, 32 × 2 × 0.6 mm; pitch, 0.75; and field of view, 500 mm for the large detector array.

Statistics

Since over 60% of patients who underwent D-dimer testing had no imaging for PE, "Cramer's V" method was employed. It is used to calculate correlation coefficient (CC) for categorical variables in a 2x3 matrix, as Phi Coeffient is applicable only for a 2x2 table. Using this statistical method meant that correlation – the degree one variable matched another – rather than sensitivity and specificity was the main consideration. Interpretation was the same as for Phi correlation coefficient; it varies between 0 and 1 without negative values, 0.05-0.09 would be considered weak correlation, 0.1-0.14 would signify moderate correlation, 0.15-0.24 would be considered in the strong range and 0.25 (or above) would be regarded very strong correlation[15].

Ethics

The study was approved as low-risk research by the Human Research Ethics Committee of the hospital, with a waiver of individual consent. Formal trial registration was not mandated.

Results

D-dimer levels were obtained in a total of 2165 individual patients. Hospital records were not available for 37 patients (1.7%); these were excluded from further analysis. A further 103 patients had D-dimer testing for reasons other than suspected PE and 10 were less than 16 years of age. These patients were all excluded. The remaining 2015 patients met the inclusion criteria (Figure 1).

Characteristics of the study population are summarised in Table 2. The mean age of patients was 50.5 years (range 16.0 to 98.4) with 1188 females (59.0%). The mean D-dimer level was 0.93 mg/L (range 0.01 to 20.00). 63% of the study population did not have imaging for PE, while 37% did (V/Q in 14%, CTPA in 23% or both in just under 1%).

The patients were classified according to their clinical probability in Table 3. Approximately 62% were considered to be low probability; intermediate 37.4%; high, less than 1%. The total number of patients who had imaging was tabulated. Those with a final diagnosis of PE was also tabulated. In the low probability cohort (according to the RGS score), just over 32% had imaging. Of those, 7.5 % were diagnosed with

PE. In the intermediate probability cohort, 44% had imaging. This yielded a diagnosis of PE in 13.3% of patients. For the high probability group, the incidence of PE imaging and diagnosis were 66.7% and 30%, respectively. In total, of approximately 36.8% of patients who underwent D-dimer testing, 10.4% were subsequently diagnosed with PE.

The number of patients imaged – and the number who were found to have PE – were gauged according to whether the D-dimer level was positive (as shown in Table 4). These values were also calculated for age-adjusted D-dimer levels (as shown in Table 5).

The clinical risk calculated for each patient (as summarised in Table 3) was derived from the individual components of RGS. The incidence of each component is listed in Table 6.

Prevalence of each component of RGS in the entire study population as well as when PE was diagnosed on imaging, when imaging did not show PE and when imaging was not performed was also calculated and shown in table 6. Correlation (coefficient) with a diagnosis of PE on imaging was calculated for each component of RGS, the overall RGS risk category and a positive D-dimer (absolute or age-adjusted) and summarised in table 7. The correlation of positive D-dimer with positive imaging for PE was 0.7033 and the correlation for a positive D-dimer by age-adjusted criteria was 0.5928. The correlation coefficient (CC) between low, intermediate and high risk group on their own and a final diagnosis of PE on imaging was calculated at 0.1332, 0.1278 and 0.0817, respectively. On the other hand, the CC between a positive absolute D-dimer and a final diagnosis of PE on imaging in patients with low, intermediate and high risk group was calculated at 0.7527, 0.6256 and 0.4195, respectively. For the age-adjusted D-dimer, the correlations were calculated at 0.6490, 0.4987 and 0.3550, respectively. The overall CC for all risk categories on their own was calculated at 0.1107 and for a positive absolute D-dimer at 0.7033 (table 8).

Discussion

While previous studies were unable to account adequately for patients without imaging, this obstacle was overcome with a novel statistical approach. Previous studies have evaluated the sensitivity and specificity of D-dimer for diagnosing or excluding PE - often in comparison to clinical risk scores. This was well reviewed by Weitz et al[16]. However, such methods could only be applied (and sensitivity, specificity and predictive values calculated) if every single patient in the study had V/Q or CTPA imaging subsequently. It would not account for patients who did not have subsequent imaging. To accommodate for this unknown factor, the choice of statistical method had to observe this fact.

Thus, Cramer's V method was used as its major advantage is that it accounts for many patients not having further imaging. Fisher's Exact Test was considered as an alternative, however was felt to be less appropriate as some categories are very large. Thus, using Fisher's Exact Test would be less reliable. We therefore used Cramer's V despite the potential inadequacies of having some small groups - such as those with haemoptysis who eventually diagnosed with PE (just two cases amongst the entire cohort).

Conversely, it can be construed as a drawback of this study design to have results expressed in statistical terms with which some clinicians may not be familiar. The outcomes are not expressed in terms of sensitivity, specificity and predictive values which are used much more commonly in clinical practice and guidelines. However, CC may be a more useful metric in this situation.

Alternatively, some studies on PE have used assessment by respiratory physician at six months after the index event as the gold standard. Obviously, this is equally problematic. For the pragmatic intents of this study, it had to be assumed that CTPA and V/Q are sufficiently and equally accurate. It is known, however, that there is a percentage of indeterminate CTPA studies – reported as up to 6%[17]. This may account for some of the patients listed in table 2 as having undergone both studies. The central finding was that the D-dimer level was superior to RGS in terms of its higher correlation with a diagnosis of PE on subsequent imaging. We demonstrated that the correlation between a positive D-dimer level with a diagnosis of PE was 0.7033 compared to 0.1103 for risk category; the former implying strong correlation in statistical terms, and the latter, moderate.

Unsurprisingly, the correlation between a positive D-dimer result and diagnosis of PE was well short of 100%. However, D-dimer has been shown to have a greater correlation with diagnosis of PE (on imaging). It can, thus, avoid using further tomographic imaging unnecessarily. This would be desirable clinically[6]. This study, as elsewhere[18], clearly showed over-use of tomographic imaging in patients with lower pre-test probability.

If more patients with a high clinical pre-test probability were imaged, how would this have altered results? The group with a high clinical pre-test probability would probably have had a higher correlation with diagnosis of PE but it would be unlikely to bridge the gap from 0.0814 to 0.4195. If all clinically high-probability patients with negative imaging results had positive imaging instead, the correlation would have been 0.2716. How is it possible that the correlation was so low even if the test had relatively high sensitivity, specificity and positive predictive value? The answer is simply because there was such a large proportion (still 33%) with no imaging results. This highlights how calculating correlation better accounts for those without imaging.

If a greater number of patients with negative D-dimer were imaged – and presumed to have no evidence of PE on either CTPA or V/Q – then the correlation would be even higher than that documented. Similarly, if a greater number of patients with positive D-dimer were imaged – and presumed to have PE on either CTPA or V/Q – then the correlation would also be higher than that found.

It has been suggested that age-adjusted D-dimer reference ranges have higher sensitivity and specificity for PE[19-22]. This is particularly in the context of a low pre-test probability[23]. In this study, however, the absolute D-dimer level had a higher correlation with a diagnosis of PE than age adjusted D-dimer. Further, the correlation of D-dimer levels with a subsequent diagnosis of PE - for each category of pre-test probability - were consistently higher for the absolute value than the age-adjusted values (as shown in table 8). Our findings in this regard would be consistent with a minority of studies/publications such as the work of a Canadian group[24].

Conclusion

A positive D-dimer test, absolute or age-adjusted, was found to have a higher correlation with a diagnosis of PE on subsequent V/Q SPECT or CTPA than a clinical risk score. Thus, the relevance of a D-dimer test in the context of suspected PE is no longer limited to a negative result to aid excluding PE and a positive test could be equally valuable. Given a positive D-dimer had a higher correlation with PE diagnosis than a clinical risk score system (like RGS) in our cohort, we conclude that it would be more sensible and reliable to determine if tomographic imaging is further required based on a positive D-dimer than a clinical prediction score on its own and thus, reduce resource and economic burdens in the health system. A validation study, preferably utilising the same statistical method, should be carried out in light of these findings.

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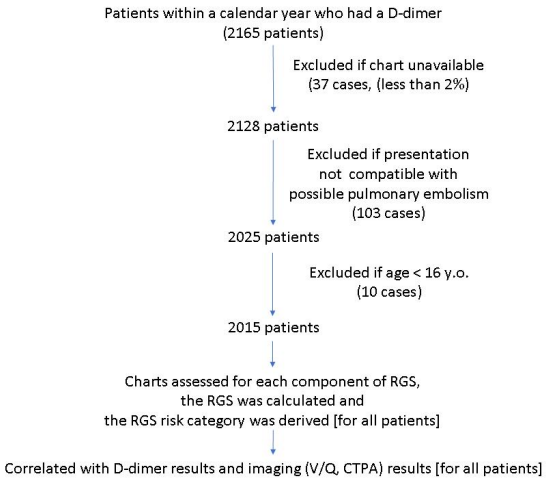

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