Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 114; No. 4; P319

Generation of an Age-adjusted D-dimer Cut-off Value in Elderly Patients to Exclude Suspected Venous Thromboembolism

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Abstract

Introduction
The D-Dimer assay is an essential diagnostic tool used in the clinical workup of suspected VTE patients. However, its high sensitivity far exceeds the assays specificity as age increases. This study aimed to generate an age-adjusted D-Dimer cut-off value in a local elderly population, which would potentially lead to increased specificity of the D-Dimer assay, thus reduce the number of false positive results.

Methods
Using the Stago STA Liatest D-Dimer assay, 61 patients ≥70 years which presented to the Emergency Department or Acute Medical Unit UHL were tested and assessed for the presence of VTE. Existing and locally derived D-Dimer cut-off values were examined to determine optimal specificity without infringement on assay sensitivity.

Results
With an assay specificity of <2%, results indicated that this population did not benefit diagnostically using the conventional D-Dimer cut-off value of 0.5µg/ml FEU. From the potential age-adjusted values investigated, the receiver operating characteristic (ROC) curve derived cut-off of 1.025 µg/ml FEU would have safely excluded 64% of this population from unnecessary imaging studies by increasing the specificity of the D-Dimer assay to 66.1%.

Conclusions
The combination of the ROC derived cut-off value of 1.025 µg/ml FEU in combination with an “unlikely” Wells score was associated with a higher number of “negative” VTE cases when compared to the conventional cut-off of 0.5µg/ml FEU.

***Keywords**:* D-dimer, age adjusted cut-off values, venous thromboembolism

***Abbreviations**:*

AUC Area Under the Curve
CI Confidence Interval
CLSI Clinical and Laboratory Standards Institute
COPD Chronic Obstructive Pulmonary Disease
CTPA Computerised Tomography Pulmonary Angiogram
CV Coefficient of Variation
DIC Disseminated Intravascular Coagulation
DVT Deep Vein Thrombosis
FDP Fibrin Degradation Product
FEU Fibrinogen Equivalent Units
NPV Negative Predictive Value
PE Pulmonary Embolism
PTP Pre-Test Probability
PPV Positive Predictive Value
ROC Receiver Operator Characteristics
SD Standard Deviation
UHL University Hospital Limerick
VTE Venous Thromboembolism

Introduction

Venous thromboembolism (VTE) is a potentially fatal yet treatable medical condition comprising of both deep vein thrombosis (DVT) and pulmonary embolism (PE)[1]. VTE has an annual incidence of approximately 0.1% in the general population however this increases 10-fold in individuals 75 years or older [2]. Diagnosing VTE provides a challenging task for the physician as signs and symptoms of VTE also share common symptoms with other potentially fatal disease states [3]. For this reason, a sequential diagnostic strategy is used. This involves a clinical pre-test probability (PTP) risk assessment or Wells score, a D-Dimer diagnostic test result and if necessary, diagnostic imaging [4, 5, 6, 7].

Currently, there is no single accurate diagnostic test for VTE. D-Dimer levels are elevated in acute VTE; however, the specificity of the D-Dimer assay is not exclusive to venous thrombosis. Other non-thrombotic conditions result in elevated D-Dimer levels such cancer, recent surgery, inflammation, pregnancy and aging [3]. For this reason, the diagnostic workup involves the use of a clinical pre-test probability (PTP) risk assessment in combination with the D-Dimer diagnostic assay due to its high false positive result rate. It is recognised that aging is associated with naturally elevated levels of D-Dimers in the blood [8, 9].

D-Dimer assays are highly sensitive (≥97%) and also have a high negative predictive value (NPV), meaning that D-Dimer levels below a predetermined cut-off value can safely exclude a suspected VTE case once an "unlikely" Wells score is applied [2,3]. However, this high sensitivity (negative predictive value) far exceeds the specificity (positive predictive value) as age increases [10].

Clinically, a predetermined D-Dimer threshold value of 0.5 µg/ml FEU has been validated by numerous studies [2, 11, 12]. As the consequences of missing a VTE are potentially fatal, this conventional threshold is used universally for all age groups, even though D-Dimer levels increase naturally with age. This means the percentage of elderly patients with D-Dimer levels lower than the conventional cut-off (0.5 µg/ml FEU) in which VTE can be excluded is reduced [11]. This prevents a fragile population group from benefiting from a non-invasive diagnosis [3]. By raising the threshold value which determines a positive result, numerous studies have increased the specificity of the D-Dimer assay resulting in fewer false positive results while still maintaining assay sensitivity [13, 14].

This study aims to generate an age adjusted D-dimer cut-off value for elderly patients (over 70 years of age) with suspected VTE using the STA® Liatest D-Di Kit on the Stago STA-® coagulation analyser (Diagnostica Stago, France). This study will also compare this threshold to other recommended D-dimer cut-off values which are utilised in relevant age-adjusted D-dimer studies [8, 15, 16].

Methods

This observational study investigated patients 70 years or older in which the clinical suspicion of VTE required exclusion. All these patients were out-patients and presented to either the Emergency Department or the Acute Medical Unit in the University Hospital Limerick. Over a 4-month period, 116 patients (56 males and 60 females) were included in the study. Exclusion criteria included a "likely" Wells score, anticoagulants, previous VTE, active cancer, recent surgery immobilisation and severe Chronic Obstructive Pulmonary Disease (COPD). All patients had a "positive" D-Dimer result ranging from 0.53-1.3 µg/ml FEU. Ethics approval was granted by the Research Ethics Committee in UHL on the 26th of February 2018 in accordance with the 'The Code of Ethics of the World Medical Association' (Declaration of Helsinki). Informed consent for the study was obtained from each subject.

Each patient was assessed using the Wells scoring system. A Sarstedt® S-Monovette Sodium Citrate 9 NC/2.9ml specimen was obtained from each patient which had a D-Dimer test requested based on the clinician's suspicion for either DVT or PE. All samples tested were <8 hours old and centrifuged at 2000g at room temperature upon arrival into the haematology laboratory. Samples were quantitatively analysed for the D-Dimer molecule using the Stago STA-R Evolution® (Diagnostica Stago, France). Since all patients had a "positive" D-Dimer result using the conventional cut-off value of 0.5 µg/ml FEU, each patient should have received the necessary imaging technique. This was Doppler ultrasound for DVT and a Computerised Tomography Pulmonary Angiogram (CTPA) for PE. This provided an end-result of "positive" or "negative" for VTE.

Numerous cut-off values were then applied to the study population group. They included the conventional cut-off value of 0.5 µg/ml FEU for the STA® Liatest D-Di assay which is applied to all patients regardless of age, and the age adjusted algorithm proposed by Douma and colleagues (Age (in years) X 10 µg/l) [13]. This study also examined the use of the ROC curve derived cut-off value. This value will maintain 97% sensitivity and exhibit the best available specificity [12]. Finally, this study examined the fixed cut-off value of 1.0 µg/ml FEU proposed by Sharp et al. (15). These comparisons provided calculations of sensitivity, specificity, Negative Predictive Value (NPV) and Positive Predictive Value (PPV). The percentages of patients safely excluded using these various cut-offs were also investigated.

Statistical analysis of the data in this study was performed using SPSS (version 23). For the generation of cut-off values, ROC curves were prepared for each population at a 95% CI, with the area under the curve being calculated also.

Results

Of the 116 patients recruited, 55 were excluded from the study due to failure of performing the required imaging technique (CTPA for PE and Ultrasound for DVT). Of the remaining 61 patients, 44.3% were male (n=27) with a mean age of 77.7 years (70-88, 95% CI). Females accounted for the remaining 55.7% (*n*=34) with a mean age of 78.3 years (70-94, 95% CI). All these patients fulfilled the three stages of the study method as previously described. Patients in this study had a D-Dimer result between 0.5-1.3 µg/ml FEU, with males having a mean value of 0.87 µg/ml FEU and females having a slightly higher mean value of 0.97 µg/ml FEU. The breakdown of positive and negative patient results for VTE are illustrated in Table 1.

Table 1: Illustrating the number of positive and negative VTE patients for the study group (≥70 years)).

Group	**No. of patients**	**No. of positive imaging results**	**No. of negative imaging results**
70-79 years	37	2	35
80 years or older	24	0	24
Whole population	**61**	**2**	**59**

Number of positive and negative VTE cases for each age group. Only two positive results were observed, both in the 70-79 age category. The first patient was positive for PE, with a D-Dimer result of 1.28 µg/ml FEU with a history of chronic bronchitis. The second patient was positive for DVT with a D-Dimer result of 1.03 µg/ml FEU with no previous history.

Performance criteria of the various D-Dimer cut-offs can be seen on Table 2. The optimal manufacturer sensitivity of 97% was maintained for all cut-off values. The most significant increase in specificity was seen in the ROC derived cut-off value of 1.025 µg/ml FEU with an Area Under the Curve (AUC) of 0.822 (95% CI, 0.607-1.0). Applying this value to the population, increased assay specificity to 66.1% while maintaining 97% sensitivity was observed.

Table 2: Performance criteria of the various D-Dimer cut-offs in the whole study population.

	Whole population			
	Conventional cut-off (0.5 µg/ml)	Age adjusted cut-off (Age (in years) X 10 µg/l)	Fixed cut-off of 1.0 µg/ml (Sharp et al)	ROC derived cut-off (1.025 µg/ml; AUC, 0.822, 95% CI, 0.607-1.0)
Sensitivity	97%*	97%*	97%*	97%*
Specificity	<2%	32.2%	61%	66.1%
NPV	100%	100%	100%	100%
PPV	3.3%	4.8%	8%	9.1%

Table 3 assesses the percentage of patients in this study who would be considered negative for VTE when applying these various cut-off values. Since the study only selected patients with a positive D-Dimer result, the conventional cut-off (0.5 µg/ml FEU) failed to exclude VTE in all of these patients. The remaining three cut-offs performed well, with the best results seen in the ROC derived cut-off. Using this cut-off, 39 patients (64%) would have produced a negative D-Dimer result, thus preventing the need for unnecessary imaging techniques in over half of the population group. Table 4 illustrates the mean, standard deviation, and the analytical D-Dimer range of the study population. The most common explanation for patients not scanned was “scan request cancelled/denied by team” and accounted for approximately 30-40% of cases.

Table 3: VTE negative patients when D-Dimer results are applied to the various cut-off values for the whole population.

Group	**No. of patients**	**% neg with standard cut-off (0.5 µg/ml FEU)**	**% neg with age adjusted cut-off (Age x 0.01µg/ml FEU)**	**% neg with cut-off of 1.0 µg/ml FEU**	**% neg with ROC derived cut-off (1.025 µg/ml FEU)**
Whole population (≥70 years)	61	0/61 (0%)	20/61 (33%)	36/61 (59%)	39/61 (64%)

Table 4: Comparison in mean, standard deviation, minimum and maximum D-Dimer value of patients who received scans versus patients who did not.

Group	No. of patients	Mean D-Dimer result µg/ml FEU	Minimum D-Dimer result µg/ml FEU	Maximum D-Dimer result µg/ml FEU	SD
Scanned population	61	0.93	0.53	1.3	0.22
Not scanned population *	55	0.81	0.52	1.3	0.24

**Primary reasons for non-scanning: Scan result denied by radiology (30-40%), symptoms of VTE resolved, lack of availability of scan, alternative diagnosis found/suspected, D-Dimer ordered by on-call team, clinical plan changed by supervising consultant, patient RIP, patient discharged.*

Discussion

The D-Dimer assay is an essential diagnostic tool used in the initial clinical workup of suspected VTE patients [11]. However, its high sensitivity far exceeds the assays specificity as age increases [10]. It is widely documented that D-Dimer levels increase naturally with age often without any underlying thrombotic disease [8, 9, 11]. The most logical solution to this problem is to raise the conventional D-Dimer cut-off in elderly patients. Studies reported the increased utility of the D-Dimer assay when applying an age adjusted D-Dimer cut-off, which resulted in the increased specificity of the D-Dimer assay [8, 13, 14].

Results from this analysis corresponded with other studies which indicated an increase in assay specificity when higher age-adjusted cut-off values were applied to this population group [8, 11, 13, 14]. The performance of the conventional D-Dimer cut-off (0.5 µg/ml FEU) was extremely poor, with a specificity of <2% for this population. This result was somewhat expected as only "positive" D-Dimer results were included in this study (results between 0.53-1.3 µg/ml FEU). Although a small sample size, this result highlights the low prevalence (3.28%) of VTE in this population as only 2 patients were positive for VTE out of 61 individuals.

Utilising the age adjusted algorithm proposed by Douma et al, specificity of the D-Dimer assay increased to 32.2% while maintaining 97% sensitivity [13]. Although, this was a significant increase when compared to the conventional cut-off, other studies reported significantly higher increases in specificity [11, 14, 17]. One possible explanation for such differences may be due to our inclusion of only participants with D-Dimer levels between 0.53-1.3 µg/ml FEU, while these studies had no restriction on D-Dimer values thus a variety of values have been included. For this study, the ROC derived cut-off value performed best. With a value of 1.025 µg/ml FEU, the specificity of the assay increased to 66.1% while maintaining 100% sensitivity.

Similar studies recommending general cut-off values witnessed vastly improved assay specificity. However, they often appeared to affect the sensitivity of the assay. Sharp et al reported 75.4% specificity with 84.2% sensitivity for a general cut-off of 1.0 µg/ml FEU while Granziera et al. reported a sensitivity of >98% and specificity of 39.1% when using a cut-off of 0.98 µg/ml FEU [15, 18].

Focusing on the ROC derived cut-off which provided the highest increase in specificity, 64% of the study population could have been safely excluded for VTE without the requirement of a radiological examination. In contrast, none of the patients were deemed negative using the conventional cut-off. Compared to the literature, the performance of the ROC cut-off appears superior to the age-adjusted algorithm. Righini et al. concluded that the proportion of patients excluded based on D-Dimer result increased from 6.4% to 29.7% while Douma et al. reported 42% of patients could be excluded using the new age-adjusted algorithm versus 36% with the conventional cut-off [8, 13]. In this study, the ROC cut-off could have safely out-ruled 64% of the population, while only 33% would be out-ruled using the age adjusted cut-off algorithm. This increase in assay efficiency offers the potential to limit Emergency department referrals along with unnecessary radiological exposure in the elderly population.

A key secondary finding of this study was the high number of patients with "positive" D-Dimer results (conventional cut-off) that did not receive the necessary radiological examination. Based solely on the D-Dimer result, the necessary scan should have been performed irrespective of the explanations provided on table 4. "Scan request cancelled/denied by team" accounted for the highest proportion of cases (approx. 40%), however further investigations/audits should be performed to recognise the failure to complete the appropriate diagnostic strategy of VTE.

This study confirms that the use of an age-adjusted D-Dimer cut-off significantly can increase the specificity of the D-Dimer assay in elderly patients (70 years or older). Using the conventional cut-off of 0.5 µg/ml FEU, all patients in the study required radiological examination. However, by applying the ROC derived cut-off of 1.025 µg/ml FEU, 64% of the population would have safely been excluded from the diagnosis of VTE while maintaining assay sensitivity, thus minimising the requirement of unnecessary imaging studies. This study provides a practical approach to implementing locally derived ROC cut-off D-Dimer values for small and medium sized laboratories. Given the wide variety of methodologies available on the market, it demonstrates the benefits of D-Dimer ROC cut off values to Irish medical laboratories to replicate the improved specificity findings found in larger age-adjusted D-Dimer publications, systematic reviews and meta-analyses.

Declaration of Conflicts of Interest:

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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