Validation study of age-adjusted D-Dimer cutoff levels to exclude venous thromboembolic disease

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Rationale
- D-dimer levels are useful in screening for venous thromboembolism (VTE) in patients for whom the clinical suspicion is low.
- Conventionally, a value of below 500 µg/L can be used to safely rule out VTE with a low false negative rate.
- Imaging studies, including ultrasound Doppler and CT pulmonary angiography are normally indicated in patients investigated for venous thromboembolism in whom D-dimers values higher than the cut-off value.
- However, D-dimer concentrations rise with age.
- Therefore, in the older population, this may lead to a high proportion of people undergoing unnecessary investigations.
- Recently, a large systematic review and multicentre prospective study both concluded that the use of age-adjusted D-dimer level (age×10 µg/L) for patients aged above 50 years could correctly rule out VTE, demonstrating significantly increased specificity without modifying sensitivity when compared with its normal use.\(^1,2\)
- Our study aimed to validate the strength of the above studies’ results in our local population.

Methods
- We performed a retrospective cohort study of patients who were seen in deep venous thrombosis (DVT)/pulmonary embolism (PE) clinic at QEQM Hospital.
- All patients had routine blood work-up, including D-dimer levels, and an appropriate imaging study as either an ultrasound (US) scan for possible DVT, or CT pulmonary angiogram (CTPA) for possible PE, depending on the presentation.
- Data were collected using a Microsoft Excel spreadsheet on age at clinic attendance/blood test, gender, d-dimer value, US Doppler or CTPA result, re-admission date if within 90 days and reason, and 90-day outcome.
- Data were also analysed using Microsoft Excel.
- Patient aged 50 years and younger were excluded from analysis.

Results
- Of 203 patients aged above 50 years presenting to the DVT/PE clinic during a consecutive two-month period, 9 cases of VTE was seen in patients aged 70-79, closely followed by 8 cases in patients aged 80-89 with patients aged 50-59 and 60-69 both accounting for 7 cases while patients aged 90-99 produced only 3 cases of VTE.
- The prevalence of VTE was 16.7% (34/203). Specificity of age-adjusted D-dimer cut-off was significantly higher compared with conventional D-dimer cut-off of 500µg/L (42.6% vs 30.8%), with a small decrease in sensitivity (94.1% vs 97.1%) caused by one extra false negative. Negative predictive values remained similar (97.3% vs 98.1%) while the positive predictive values showed a slight increase (24.8% vs 22%).
- 21 of the 293 patients (10%) were re-admitted into hospital within 90 days of initial admission, with 5 (2.5%) of those re-admissions being due to possible VTE and subsequently, only 3 (1.5%) of them being confirmed cases of VTE.
- 90-day outcome from initial admission of the 203 patients also recorded 5 (2.5%) cases of death, none of which were related to VTE.
- Figure 1 illustrates a significant reduction in the number of false positive results with the age adjusted d-dimer value when compared with the conventional d-dimer value.

Discussion
- This study reflects the validity of the age-adjusted D-dimer cut-offs as evidenced in larger trials (Adjust PE study) and from meta analysis of multiple study cohorts in USA & Europe.
- Our study did show that the specificity increased from 30.8% to 42.6% as evidenced in the global meta-analysis data, with minimal reduction in sensitivity.
- In this regard, our study achieved its aim to validate the evidence in our own cohort of patients, which may not be represented in the existing data.
- For this reason, it gives further strength to the consideration of redesigning VTE diagnostic pathways for patients above 50 years with low to moderate probability of VTE.
- This is of clinical importance since its use can potentially negate the use of further imaging investigations thus freeing up these resources for other patients in whom these tests are truly indicated, not to mention the avoidance of undue anxiety and radiation incurred by patients.
- The adoption of age-adjusted D-dimer cut-off values in routine practice represents a straightforward, cost-saving intervention in a safer manner.

Limitations
- Our study has several limitations.
- Firstly, the sample size of 203 patients is relatively small when compared with larger studies cited above.
- Secondly, no pretest probability assessment tools (e.g. Wells’ score) were explicitly used and as such it is possible that D-dimer tests were not used correctly in its capacity as a rule out test, though patients seen in the DVT/PE clinic are likely to be of non-high clinical probability of VTE.
- Finally, this study functions at best to validate existing knowledge about the use of this age-adjusted D-dimer cut-off values in the work-up of VTE.

Conclusions
- Our findings echo the conclusions of the high-powered studies published recently.
- We propose that the use of age-adjusted D-dimer cutoff values should be used to safely exclude VTE with low clinical likelihood and aged above 50 years.
- Ultimately, it represents a simple change to practice that can prevent unnecessary imaging in a larger proportion of the population, which itself is associated with increased financial burden to trusts and risk of harm to patients.