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Research letter

Extended D-dimer Cut-offs and Machine Learning for Ruling Out Pulmonary Embolism in individuals undergoing CTPA

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To the Editor,

Pulmonary embolism (PE) is a major cause of morbidity and mortality.[1] Computed tomography pulmonary angiography (CTPA) is the gold standard for diagnosing PE[2] and a common investigation which contributes to potentially avoidable radiation exposure. CTPA use has quadrupled in the past two decades,[3] and this has been associated with lower rates of PE detection[4] and possible overdiagnosis.[5]

Despite efforts to make judicious use of CTPA, PE is typically only detected in 5-15% of scans.[6] Numerous clinical decision rules (CDRs) have been developed to aid clinicians, including the Wells[7] and Geneva scores[8], the Pulmonary Embolism Rule-out Criteria [9], YEARS[10] and PEGeD[11]. Clinician *gestalt* is heavily weighted in these CDRs. Conversely, D-dimer measurement is advised as a follow-up test, to be considered after CDRs have been applied, despite the fact that D-dimers below the upper limit of normal (ULN) are the most robust predictor of absence of PE, typically ruling out PE in ≥98% of individuals.[10, 11] Furthermore, D-dimers increase with age, leading to the validation of “age-adjusted D-dimer” (aaD-dimer) thresholds.[12, 13] Recent studies suggests that extending D-dimer thresholds to 1pg/mL in low-risk individuals, effectively rules out PE at 3-months follow-up.[10, 11]

We hypothesised that combining D-dimers and risk factors in a model which removes the subjective likelihood of PE could provide robust PE rule-out performance. Furthermore, we sought to explore extended D-dimer thresholds to identify novel cut-offs for PE-prediction in moderate-risk patients. We performed a single-centre, retrospective, proof-of-concept study to develop a PE rule-out algorithm. We trained a machine learning model for PE-prediction in a PE-enriched training dataset (a discovery set of real-world consecutive scans, combined with a set of exclusively PE-positive scans to balance outcomes and improve model training), testing performance in a validation dataset of consecutive CTPAs.

Training and validation scans were performed between January 1st 2017 and May 30th 2020, and between January 1st and December 31st 2016, respectively. Age and sex were documented. CTPA requests were reviewed to identify the presence of risk factors: Wells score components[7] (excluding "*PE is the most likely diagnosis*"), hormone replacement therapy/oral contraceptive pill (HRT/OCP), peri-partum status, chest pain, loss of consciousness and hypoxaemia. CTPA-reported PE was recorded as a binary outcome. CTPAs performed to confirm/monitor previously identified PEs and those deemed non-diagnostic were excluded. D-dimer level (HemosIL® D-dimer HS 500 assay, Instrumentation Laboratory, Bedford, MA, USA) was documented if measured within 24hours prior to CTPA. aaD-dimer thresholds were calculated for patients >50-years-old, using the formula $({}^{Age}/_{100})$pg/mL. Only data from CTPAs accompanied by D-dimers measured within the prior 24 hours were included.

We assessed the performance of a gradient boosting classifier (GBC) (*xgboost*), a generally high-performing algorithm for classification tasks, examining the role of D-dimer thresholds (ULN, 1.5xULN, 2xULN) in combination with Wells components and relevant co-variables as predictors in the model. A model training pipeline was created, with predictor variables assessed in several combinations using age, Wells score components and D-dimer. We proposed a model incorporating a given D-dimer threshold (*Θ)*, where the decision rule of any model *M*, given a set of features *F*, and D-dimer threshold (*Θ)* would be:

$$f(M, F, \Theta) = \begin{cases} f(M, F) \; if \; \textit{D-dimer} < \Theta \\ Predict \; PE \; otherwise \end{cases}$$

Performance and comparison to simple pre-defined D-dimer thresholds (ULN, 1.5xULN, 2xULN and aaD-dimer) was assessed in the validation cohort.

Statistical analysis was performed in R v4.0.4 (the R Foundation for Statistical Computing) and Jupyter Lab v2.2.6 running Python 3.8 (scikit-learn v0.24.1, pandas v1.2.3). All comparative tests were two-sided with p-values <0.05 considered significant.

Of 1047 CTPAs screened in the discovery dataset, 572 with D-dimers were included (mean age 44.6 years, 39.5% male). 2688 CTPAs were screened for inclusion in the PE-enrichment, with 367 were positive for PE (13.7%), of which 190 with D-dimers were included (mean age 47.3 years, 44.2% male). These two sets formed the PE-enriched training set (n=762). 1314 scans were screened for the validation cohort and 634 (48.2%) with D-dimers were included (mean age 43.6 years, 36.8% male). PE prevalence did not differ between CTPAs included or excluded based on D-dimer availability (discovery cohort: 15.7% vs 14.3%, p=0.59; validation cohort: 14.5% vs 15.5%, p=0.69). PE prevalence did not differ between the discovery and validation cohorts (15.7% vs 15.5%, p = 0.96). Median D-dimer did not differ between discovery and validation cohorts (1.17pg/mL, IQR [0.74, 2.24] vs 1.15pg/mL, IQR [0.70, 2.40], p = 0.87) but was markedly higher in the enrichment (PE-positive) cohort (3.54pg/mL, IQR [1.76, 7.10], p <0.001).

Among the models trained we found that a model incorporating a D-dimer threshold of 1.5xULN (0.75pg/mL), Wells Score components and age as predictors performed best in validation (NPV 99.3%, Sensitivity 99.0%, Specificity 27.4%). The performance of the model compared to the ULN and aaD-dimer for rule-out of PE was 99.3% vs 98.1% vs 98.2% respectively for NPV (p=ns), 98.9% vs 98.9% vs 97.96% respectively for sensitivity (p=ns), and 23% vs 8% vs 16% respectively for scans predicted negative for PE (p<0.0001 by McNemar test)(Figure 1).
We describe the results of a proof-of-concept study investigating novel approaches to PE-prediction based on the analysis of 1396 CTPAs of individuals deemed clinically to be at least at moderate risk of PE who underwent CTPA scans during usual care. Using easily available

clinical predictors we demonstrate that a gradient boost classifier (*xgboost*) model outperformed traditional and exploratory D-dimer thresholds for ruling out PE. This model achieved a high NPV (99.3%), sensitivity of 98.98%, and would outrule significantly more CTPAs than using ULN or aaD-dimer thresholds.

In 2017 the ISTH Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease suggested that the historically accepted failure rate of 2.7% for venous thrombo-embolism may not be valid and that a lower failure threshold of 1.8-2% should be used to calculate power for future prospective studies.[14] Our model achieved the target NPV suggested by the ISTH and performed better than the ULN cut-off, tripling the number of CTPAs predicted negative.

Our study has some limitations, including the retrospective single-centre design, though the ~15% PE prevalence in all cohorts suggests reasonable CTPA use. Secondly, CTPA outcome was determined by real-world reports, and not by re-interpretation of the images. Additionally, clinical factors were drawn from unstructured clinician CTPA requests, meaning the presence of a variable can be assumed to be reliable, but the absence of a risk factor in the request cannot as some features may have been inadvertently omitted by referring physicians. Moreover, only positive predictors of PE (e.g., malignancy, immobility), and not factors associated with a negative likelihood of PE, were considered. Collectively, these issues suggest that greater performance could be achieved in future prospective studies adopting similar approaches. Furthermore, while the included CTPAs were deemed clinically necessary during clinical care, systematic prospective risk scoring was not available and selection bias due to the exclusion of CTPAs without D-dimer must be considered. Nonetheless, the similarity in PE prevalence between scans included and the excluded cohorts suggests that no bias in PE-risk was introduced by exclusion based on absence of D-dimer.

Extending D-dimer cut-offs beyond the upper limit of normal may be applicable even in populations with moderate-to-high pre-test probability of PE, potentially extending the insights

from YEARS and PeGed and improving pre-test-prediction and resource utilisation. These results provide insights into possible future of PE risk-stratification strategies.

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Contributions

ANF conceptualised the study and design, performed data analysis, wrote the manuscript and is the co-lead author. NMcC co-designed the study, performed data analysis, performed machine learning analyses and is the co-lead author. BG, JD, ES and NOC performed data collection, preliminary data coding and participated in study design. KM, FN, MWB, JD, MPK and DM consulted on study design, performed internal review, and edited the manuscript. KC and CMcC participated in study design, performed internal review, edited the final manuscript. CMcC is the senior author.

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Conflict of Interests

The authors report no conflict of interests.

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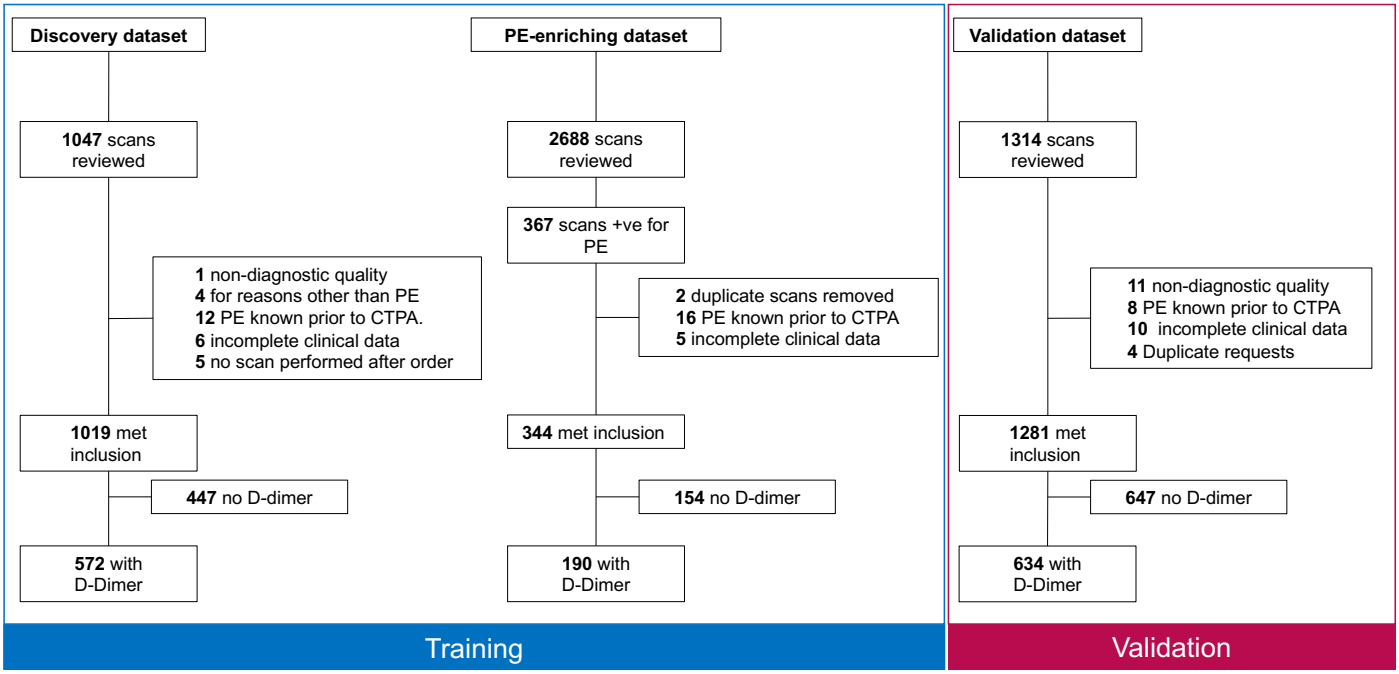
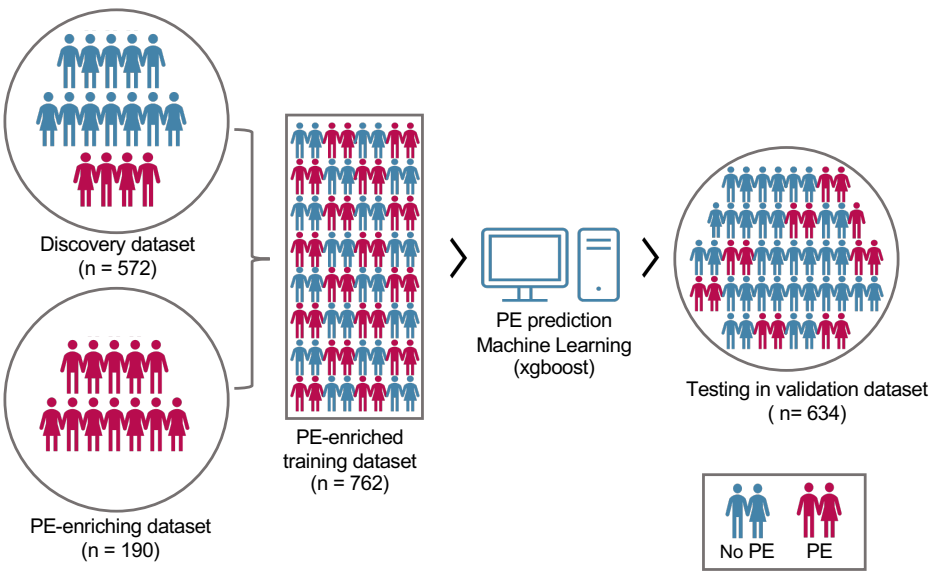
a)



b)



c)

		Performance (n = 634)													
	D-dimer Threshold	%Predicted negative	% PEs missed	Sens	Spec	PPV	NPV	FNR	FPR	TNR	TPR	TP	FP	FN	TN
D-dimer alone	ULN	8.36	1.02	98.98	9.70	16.70	98.11	0.01	0.90	0.10	0.99	97	484	1	52
	Age-adjusted[a]	16.09	2.04	97.96	18.66	18.05	98.04	0.02	0.81	0.19	0.98	96	436	2	100
	1.5xULN	28.55	4.08	95.92	33.02	20.75	97.79	0.04	0.67	0.33	0.96	94	359	4	177
	2xULN	43.38	10.20	89.80	49.44	24.51	96.36	0.10	0.51	0.49	0.90	88	271	10	265
Machine learning[b]	1.5xULN	23.34	1.02	98.98	27.43	19.96	99.32	0.01	0.73	0.27	0.99	97	389	1	147
	2xULN	35.96	7.14	92.86	41.23	22.41	96.93	0.07	0.59	0.41	0.93	91	315	7	221

Definition of abbreviations: NPV = negative predictive value, FN = false negative, FNR = false negative rate, FP = false positive, FPR = false positive rate, PPV = positive predictive value, PE = pulmonary embolus, Sens = sensitivity, Spec = specificity, TN = true negative, TNR = true negative rate, TP = true positive, TPR = true positive rate.

[a] Age-adjusted D-dimer threshold = $(^{Age}/_{100})$pg/mL,

[b] Gradient Boost Classifier incorporating a given D-dimer cut-off, Wells score components and age.

Figure legend

Figure 1: a) Prisma diagram of study population selection, b) Study design: a discovery set of 572 consecutive CTPAs (PE prevalence 15.7%) was combined with a set of 190 exclusively PE-positive CTPAs to balance outcomes so as to improve classification training. This PE-enriched training set (n = 762) was used to train models and performance was tested in the validation dataset comprised of 634 consecutive CTPAs (PE prevalence 15.5%). c) Performance metrics of the simple D-dimer thresholds and machine learning models in the validation cohort.