The diagnostic performance of renal function-adjusted D-dimer testing in individuals suspected of having venous thromboembolism

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SUPPLEMENTAL APPENDIX

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Text S1. Methodology

Patients and setting

We analyzed data from the VTEval project (NCT02156401),[1] an investigator-initiated, observational, single-center, prospective cohort study of clinically suspected VTE patients based in the University Medical Center Mainz, Germany. All individuals aged 18 years or over presenting with at least one clinical sign or symptom of VTE, and for whom imaging was indicated, were fully examined until diagnosis was achieved via compression Doppler ultrasonography (CDUS) for deep vein thrombosis (DVT), and computed tomographic pulmonary angiogram (CTPA) or ventilation-perfusion (VQ) scan for PE. All diagnoses were independently confirmed by board-certified senior angiologists. Approval for the VTEval project was obtained from the local data safety commissioner as well as from the ethics committee (medical association of the federal state of Rhineland-Palatinate, Germany; reference no. 837.320.12(8421-F)). All study participants provided written informed consent before study enrolment. All study procedures were conducted in line with the principles outlined in the Declaration of Helsinki and according to Good Epidemiological Practice. The rationale and design of the VTEval project are described in more detail in its published protocol.[1]

Measurement of laboratory markers

Laboratory markers were measured in blood samples collected on the day of patient enrolment. D-dimer was measured in citrate plasma, using both an INNOVANCE assay (Siemens Healthcare Diagnostics, Marburg, Germany) on a Behring Coagulation System (BCS) XP analyzer and a HemosIL assay (Instrumentation Laboratory, Lexington, MA, USA) on an ACL TOP analyzer. We previously demonstrated high agreement between these two assays (r=0.97).[2] Creatinine was determined from frozen ethylenediaminetetraacetic acid (EDTA) plasma samples, which were once thawed for the measurements using a photometric assay on the Abbott Architect c8000 (Abbott Diagnostics, Abbott Park, IL, USA). CRP was immunoturbidimetrically measured in blood serum, also on the Abbott Architect c8000.

Estimation and categorization of renal function

We used the 2009 CKD-EPI equation[3] to estimate the GFRs of patients. For visualization purposes, we constructed a categorical variable reflecting categories of eGFR that correspond with stages one through four of chronic kidney disease (CKD), as promoted by the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for CKD.[4] Starting in order from stage one, these categories are defined as follows:

eGFR≥90mL/min/1.73m^2; eGFR 60-89mL/min/1.73m^2; eGFR 30-59mL/min/1.73m^2, and eGFR<30mL/min/1.73m^2.

D-dimer thresholds

Existing D-dimer thresholds that were evaluated for this study are the conventional cutoff of 500µg/L[5] and the age-dependent threshold introduced in 2010 by Douma et al.[6] The latter threshold is equal to 500µg/L for all individuals below 50 years of age, and takes the value of age×10 for individuals aged 50 years or over. Renal function-adjusted thresholds were also evaluated. All results related to threshold performance are included in this supplemental appendix.

Statistical analysis

D-dimer and CRP were log-transformed to approximate normality prior to analysis. D-dimer threshold values were tested in the abovementioned categories of renal function along the following diagnostic performance metrics (accompanied by according 95% confidence intervals): sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

We constructed a generalized linear model with logit link function incorporating both (ln) D-dimer and eGFR as predictors, and VTE diagnosis as the binomial outcome. We computed receiver operating characteristic (ROC) curves for this model in different categories of renal function. To circumvent improper curves induced by low sample size, we merged the two lowest renal function categories into one group (eGFR below 60 mL/min/1.73m^2) for ROC analyses. Area under the ROC curve (AUC) comparisons were performed using DeLong et al.'s method.[7]

Scatterplots and boxplots were generated to visualize the impact of adjusting (ln) D-dimer by age and (ln) CRP. The scatterplots show Pearson's product-moment correlation coefficients and associated p-values; the p-values depicted in the boxplots were derived with the Mann-Whitney U test. All significance tests were two-sided, using a significance threshold (α) of 0.05.

The robustness of the results was tested by performing a number of pre-planned sensitivity analyses. We repeated our analyses in the subgroups men vs women, young vs old, isolated distal vs proximal DVT, DVTs of provoked vs unprovoked aetiology, inpatients vs outpatients, low vs high thrombotic burden (based on the number of contiguous segments containing thrombi), and low-to-moderate vs high pre-test probability (PTP).

The latter two subgroups were operationalized by separately analyzing patients with a Wells' score for DVT of ≤2 or >2, respectively, or a Wells' score for PE of ≤4 or >4, respectively. Rows containing missing values were omitted from analyses depending on the variables contained therein.

All statistical analyses were carried out in the R environment, version 3.4.0. Analyses of threshold performance criteria (sensitivity, specificity, PPV, NPV) were computed with the caret package. ROC curves were constructed and analyzed using the pROC package.

Table S2. D-dimer threshold definitions.

Threshold*	Definition
Conventional[5]	$Threshold = 500\mu gL^{-1}$
Age-adjusted[6]	$Threshold = \begin{cases} 500\mu gL^{-1}, & age < 50 \\ age \times 10, & age \geq 50 \end{cases}$
Lindner et al.[8†]	$Threshold = \begin{cases} 500\mu gL^{-1}, & eGFR^{\ddagger} \geq 60 \\ 594\mu gL^{-1}, & 30 \leq eGFR < 60 \\ 1738\mu gL^{-1}, & eGFR < 30 \end{cases}$
Xi et al.[9†]	$Threshold^{\S} = \begin{cases} 501\mu gL^{-1}, & eGFR^{\ddagger} \geq 90 \\ 612\mu gL^{-1}, & 60 \leq eGFR < 90 \\ 876\mu gL^{-1}, & 30 \leq eGFR < 60 \end{cases}$
Pfortmueller et al.[10†]	$Threshold = \begin{cases} 333\mu gL^{-1}, & eGFR \geq 60 \\ 1306\mu gL^{-1}, & 30 \leq eGFR^{\dagger} < 60 \\ 1663\mu gL^{-1}, & eGFR < 30 \end{cases}$

* Threshold identifier, as used throughout this supplement; † Renal function-adjusted; ‡ Unit: mL/min/1.73m^2. § These thresholds are to be applied to D-dimer values that were first normalized by (age/50).

Table S3. Diagnostic performance of validated D-dimer thresholds in suspected VTE patients, by stage of kidney dysfunction.

	Total Sample*	Stages of chronic kidney disease by eGFR [mL/min/1.73m^2]			
		≥90	60-89	30-59	<30
Sample size, n	1,082	410	417	140	29
Conventional D-dimer threshold[†]					
Sensitivity	0.92 (0.89-0.94)	0.83 (0.76-0.89)	0.94 (0.90-0.97)	0.98 (0.90-1.00)	1.00 (0.72-1.00)
Specificity	0.24 (0.20-0.28)	0.35 (0.28-0.42)	0.21 (0.15-0.27)	0.07 (0.02-0.17)	0.09 (0.00-0.41)
Positive predictive value	0.52 (0.48-0.56)	0.51 (0.45-0.58)	0.53 (0.48-0.59)	0.46 (0.36-0.55)	0.52 (0.30-0.74)
Negative predictive value	0.76 (0.68-0.82)	0.71 (0.61-0.80)	0.80 (0.66-0.90)	0.83 (0.36-1.00)	1.00 (0.02-1.00)
Age-adjusted D-dimer threshold[‡]					
Sensitivity	0.90 (0.87-0.93)	0.83 (0.76-0.88)	0.92 (0.87-0.96)	0.94 (0.84-0.99)	1.00 (0.72-1.00)
Specificity	0.33 (0.29-0.37)	0.39 (0.32-0.46)	0.35 (0.28-0.42)	0.21 (0.12-0.33)	0.27 (0.06-0.61)
Positive predictive value	0.55 (0.51-0.58)	0.53 (0.46-0.59)	0.57 (0.51-0.63)	0.49 (0.39-0.59)	0.58 (0.33-0.80)
Negative predictive value	0.78 (0.72-0.84)	0.73 (0.63-0.81)	0.83 (0.72-0.90)	0.82 (0.57-0.96)	1.00 (0.29-1.00)

* Creatinine available in 92.1% (n=997) of the sample; D-dimer in 85.5% (n=925) of the sample; both in 79.4% (n=859) of the sample.

Table S4. Diagnostic performance of renal function-adjusted D-dimer thresholds in suspected VTE patients, by stage of kidney dysfunction.

		Total Sample*	Stages of chronic kidney disease by eGFR [mL/min/1.73m^2]			
			≥90	**60-89**	**30-59**	**<30**
	Sample size, n	1,082	410	417	140	29
Renal function-adjusted thresholds	**Lindner et al. (2014)**					
	Sensitivity	0.90 (0.87-0.93)	0.83 (0.76-0.89)	0.95 (0.90-0.97)	0.98 (0.90-1.00)	0.73 (0.39-0.94)
	Specificity	0.26 (0.22-0.30)	0.35 (0.28-0.42)	0.21 (0.15-0.27)	0.09 (0.03-0.18)	0.55 (0.23-0.83)
	Positive predictive value	0.51 (0.48-0.55)	0.51 (0.45-0.58)	0.53 (0.48-0.59)	0.46 (0.37-0.56)	0.62 (0.32-0.86)
	Negative predictive value	0.75 (0.67-0.81)	0.71 (0.61-0.80)	0.80 (0.66-0.90)	0.86 (0.42-1.00)	0.67 (0.30-0.93)
	Xi et al. (2015)					
	Sensitivity	0.89 (0.85-0.92)	0.86 (0.79-0.91)	0.90 (0.84-0.94)	0.94 (0.84-0.99)	0.91 (0.59-1.00)
	Specificity	0.34 (0.30-0.39)	0.29 (0.23-0.37)	0.43 (0.36-0.51)	0.21 (0.12-0.33)	0.36 (0.11-0.69)
	Positive predictive value	0.53 (0.50-0.58)	0.50 (0.44-0.56)	0.60 (0.54-0.66)	0.49 (0.39-0.59)	0.59 (0.33-0.82)
	Negative predictive value	0.78 (0.71-0.83)	0.71 (0.60-0.81)	0.81 (0.72-0.88)	0.82 (0.57-0.96)	0.80 (0.28-0.99)
	Pfortmueller et al. (2017)					
	Sensitivity	0.93 (0.89-0.95)	0.90 (0.85-0.94)	0.98 (0.95-1.00)	0.79 (0.66-0.89)	0.91 (0.59-1.00)
	Specificity	0.22 (0.19-0.26)	0.21 (0.16-0.28)	0.10 (0.06-0.15)	0.55 (0.43-0.67)	0.55 (0.23-0.83)
	Positive predictive value	0.51 (0.47-0.55)	0.49 (0.43-0.55)	0.51 (0.46-0.56)	0.58 (0.46-0.70)	0.67 (0.38-0.88)
	Negative predictive value	0.77 (0.69-0.84)	0.73 (0.59-0.84)	0.86 (0.65-0.97)	0.77 (0.63-0.88)	0.86 (0.42-1.00)

* Creatinine available in 92.1% (n=997) of the sample; D-dimer in 85.5% (n=925) of the sample; both in 79.4% (n=859) of the sample.

Table S5. Evaluation of the additive information provided by eGFR in D-dimer testing by category of renal function in clinically relevant subgroups.

	≥90mL/min/1.73m^2		60-89 mL/min/1.73m^2		<60mL/min/1.73m^2	
	$AUC_{D\text{-}dimer}$	$AUC_{D\text{-}dimer + eGFR}$	$AUC_{D\text{-}dimer}$	$AUC_{D\text{-}dimer + eGFR}$	$AUC_{D\text{-}dimer}$	$AUC_{D\text{-}dimer + eGFR}$
Sex						
Men	0.75 (0.67-0.83)	0.75 (0.67-0.83)	0.82 (0.76-0.88)	0.83 (0.77-0.89)	0.65 (0.51-0.79)	0.67 (0.54-0.81)
Women	0.69 (0.59-0.79)	0.69 (0.61-0.79)	0.73 (0.66-0.81)	0.76 (0.69-0.83)	0.81 (0.72-0.91)	0.84 (0.75-0.93)
Age						
<60 years	0.74 (0.68-0.80)	0.74 (0.68-0.80)	0.80 (0.72-0.89)	0.82 (0.75-0.90)	0.59 (0.32-0.86)	0.66 (0.39-0.92)
≥60 years	0.71 (0.57-0.85)	0.71 (0.58-0.85)	0.77 (0.71-0.83)	0.78 (0.73-0.84)	0.79 (0.71-0.87)	0.79 (0.71-0.87)
Presentation						
Isolated DVT	0.68 (0.61-0.75)	0.69 (0.61-0.76)	0.69 (0.61-0.76)	0.73 (0.66-0.80)	0.65 (0.51-0.79)	0.65 (0.51-0.79)
Isolated PE	0.63 (0.46-0.80)	0.63 (0.47-0.79)	0.78 (0.67-0.89)	0.79 (0.69-0.91)	0.42 (0.23-0.61)	0.69 (0.51-0.88)
Combined VTE	0.89 (0.84-0.94)	0.90 (0.85-0.94)	0.87 (0.82-0.91)	0.87 (0.83-0.92)	0.82 (0.74-0.90)	0.84 (0.76-0.92)
Site of DVT						
Isolated distal	0.67 (0.59-0.75)	0.69 (0.61-0.76)	0.66 (0.58-0.73)	0.69 (0.61-0.76)	0.69 (0.57-0.80)	0.69 (0.57-0.80)
Proximal	0.82 (0.76-0.88)	0.82 (0.76-0.89)	0.88 (0.84-0.92)	0.89 (0.85-0.93)	0.83 (0.74-0.92)	0.84 (0.76-0.93)
Aetiology of VTE						
Provoked	0.74 (0.67-0.81)	0.74 (0.67-0.81)	0.78 (0.73-0.84)	0.80 (0.75-0.86)	0.71 (0.60-0.82)	0.71 (0.60-0.82)
Unprovoked	0.74 (0.66-0.82)	0.75 (0.67-0.83)	0.77 (0.71-0.84)	0.79 (0.73-0.85)	0.78 (0.68-0.87)	0.78 (0.69-0.88)
Outpatient						
Yes	0.74 (0.69-0.80)	0.75 (0.69-0.80)	0.79 (0.74-0.84)**	0.81 (0.76-0.86)**	0.75 (0.66-0.83)	0.76 (0.67-0.84)
No	0.68 (0.43-0.93)	0.67 (0.43-0.92)	0.62 (0.40-0.83)	0.63 (0.42-0.84)	0.73 (0.44-1.00)	1.00 (1.00-1.00)
Thrombotic burden*						
Low	0.67 (0.60-0.75)	0.69 (0.61-0.76)	0.67 (0.60-0.75)	0.69 (0.61-0.76)	0.68 (0.56-0.79)	0.69 (0.58-0.80)
High	0.85 (0.79-0.92)	0.85 (0.79-0.92)	0.90 (0.86-0.94)	0.90 (0.86-0.94)	0.86 (0.79-0.94)	0.87 (0.80-0.94)
Pre-test probability[†]						
Low	0.70 (0.63-0.77)	0.70 (0.63-0.77)	0.75 (0.68-0.81)	0.75 (0.69-0.82)	0.70 (0.59-0.82)	0.70 (0.58-0.81)
High	0.74 (0.58-0.89)	0.73 (0.58-0.89)	0.77 (0.67-0.87)**	0.87 (0.80-0.94)**	0.78 (0.66-0.91)	0.79 (0.67-0.91)

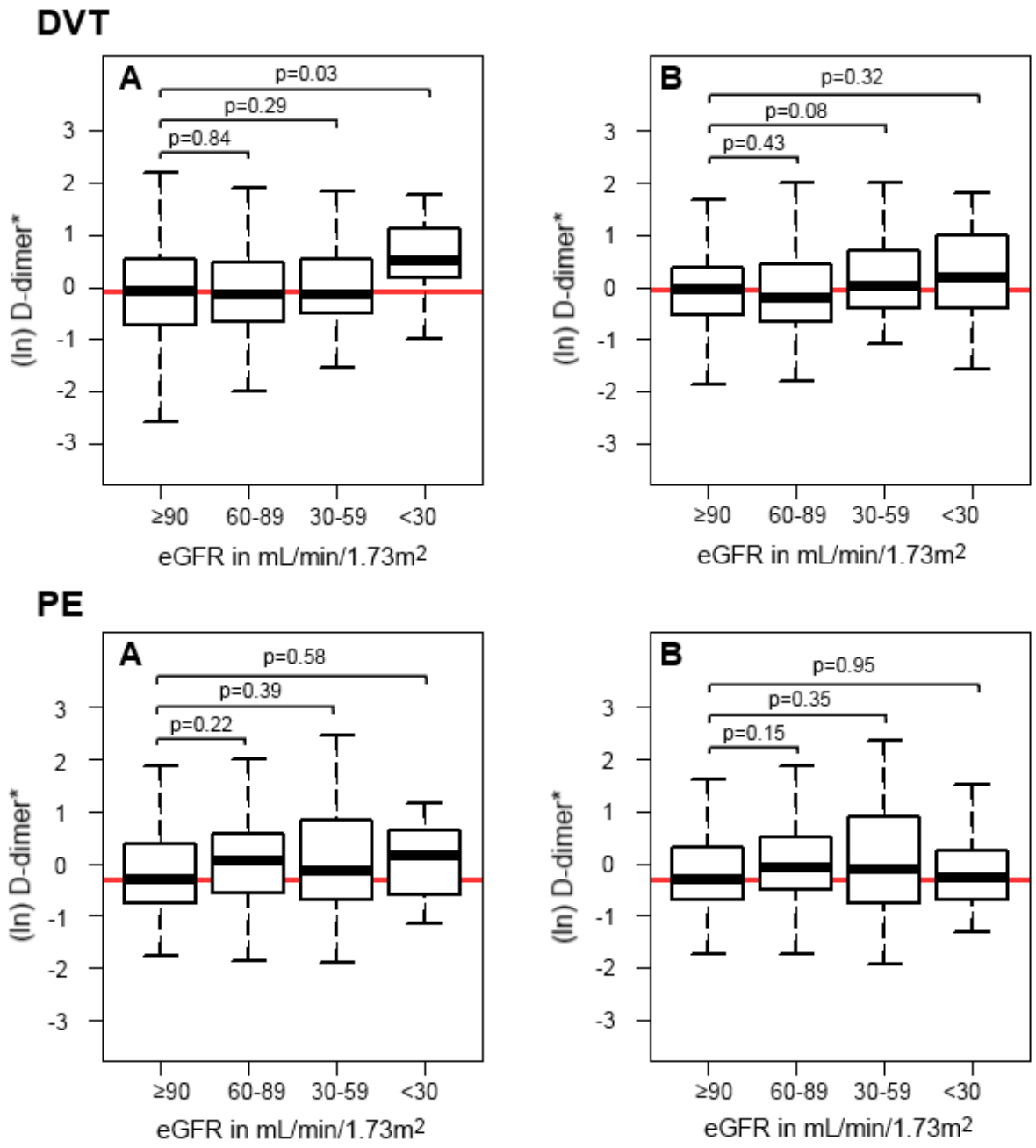
The numeric entries in this table refer to areas under the ROC curves (AUC) of either D-dimer alone or a predictive model combining D-dimer and eGFR. The ranges in brackets indicate their 95% confidence intervals. AUC pairs with double asterisks (**) were significantly different at $P \leq 0.05$. *Low burden is defined as having a thrombus in one venous segment; high burden is defined as thrombi in two or more contiguous venous segments. [†] Based on the Wells' score: a Wells' score of 2 or less (DVT) or 4 or less (PE) is considered a low pre-test probability, while a Wells' score of greater than 2 (DVT) or 4 (PE) constitutes a high pre-test probability. Abbreviations: eGFR, estimated glomerular filtration rate; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table S6. Impact of renal function, age and systemic inflammation on the concentration of D-dimer in individuals with suspected venous thromboembolism.

	Renal function		**Renal function and age**		**Age**		**Renal function, age, systemic inflammation**		**Age and systemic inflammation**	
	β-estimate [95%CI]	*P*	β-estimate [95%CI]	*P*	β-estimate [95%CI]	*P*	β-estimate [95%CI]	*P*	β-estimate [95%CI]	*P*
Predictors										
Renal function (eGFR)	-0.011 [-0.014,-0.007]	<0.001	-0.004 [-0.009,-0.001]	0.08	-	-	-0.004 [-0.008,0.001]	0.11	-	-
Age	-	-	0.014 [0.007,0.020]	<0.001	0.019 [0.014,0.023]	<0.001	0.011 [0.005,0.017]	<0.001	0.015 [0.011,0.019]	<0.001
Systemic inflammation (ln CRP)	-	-	-	-	-	-	0.366 [0.317,0.415]	<0.001	0.361 [0.314,0.408]	<0.001
Model fit										
Adjusted R^2	0.044		0.061		0.064		0.276		0.272	
$\%\Delta R^2$	-		+39.4		+47.4		+534.9		+524.4	

This table shows the β-estimates with accompanying 95% confidence intervals and p-values of different ordinary least squares regression models that all share (ln) D-dimer as the dependent variable. The R^2 for each model denotes how much of the variance in D-dimer is accounted for by the incorporated variables. $\%\Delta R^2$ denotes the percentage change in variance accounted for by a given model compared to the reference model with eGFR as the only predictor. Abbreviations: CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ln, natural logarithm-transformed.

Figure SF1. Age (A) and age and CRP (B) adjusted D-dimer by eGFR in suspected deep venous thrombosis versus suspected pulmonary embolism



*All boxplots were additionally adjusted by VTE phenotype, a categorical variable with the categories no VTE, isolated distal DVT, proximal DVT, isolated PE, and DVT with concomitant PE. The red line indicates the median of the leftmost renal function category (i.e., normal renal function).

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