THE LANCET
Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol* 2017; published online June 6. http://dx.doi.org/10.1016/S2352-3026(18)30063-2.

Supplementary Web Appendix,

Pabinger et al, Lancet Haematology 2018

Variable	Levels or Unit of measurement	Laboratory assay / Method of measurement
Tumor site category	0=Breast, Prostate 1=Lung, Colorectal, Kidney, Lymphoma, Others 2=Pancreas, Gastric	Prospective documentation
Female sex	0=Male, 1=Female	Prospective documentation
Tumor grade	0=G1+G2, 1=G3+G4	Prospective documentation
Lymph node metastasis	0=TNM N0, 1=TNM N1-3	Prospective documentation
Distant metastasis	0=TNM c/pM0, 1=TNM c/pM1	Prospective documentation
ESA use	0=No documented ESA use within first 3 months of F/U, 1=Documented ESA use within first 3 months of F/U	Retrospective documentation
Age at entry	Years	Prospective documentation
Haemoglobin		CATS: Sysmex XE systems (varying models over time from XE-2000 to XE-5000), MICA: N/A
Absolute Leukocyte count	10^9/liter (i.e. G/L)	CATS: Sysmex XE systems (varying models over time from XE-2000 to XE-5000), MICA: N/A
Absolute Neutrophil count	10^9/liter (i.e. G/L)	CATS: Sysmex XE systems (varying models over time from XE-2000 to XE-5000), MICA: N/A
Platelet count	10^9/liter (i.e. G/L)	CATS: Sysmex XE systems (varying models over time from XE-2000 to XE-5000), MICA: N/A
Mean Platelet Volume	fL	CATS: Sysmex XE systems (varying models over time from XE-2000 to XE-5000), MICA: N/A
Body mass index (BMI)	kg/m²	Prospective documentation
Fibrinogen	mg/dL	CATS: Clauss method; MICA: N/A
FVIII	% activity (as compared to reference plasma)	CATS: Coagulometry; MICA: N/A
D-Dimer	µg/mL	CATS: STA-LIAtest D-DI assay (Diagnostica-Stago, Asnieres, France); MICA: INNOVANCE, Siemens
Soluble P-selectin	ng/mL	CATS: Soluble P-selectin ELISA (R&D Systems, Minneapolis, MN, USA); MICA: Soluble P-

		selectin ELISA (R&D Systems, Minneapolis, MN, USA)
Prothrombin Fragment 1·2		CATS: Enzygnost F 1+2 (Dade-Behring, Marburg, Germany); MICA: N/A
TGA – Peak of Curve	nM of Thrombin	CATS: Technothrombin TGA kit (Technoclone, Vienna, Austria); MICA: N/A
TGA – Velocity Index	nM of Thrombin / minute	CATS: Technothrombin TGA kit (Technoclone, Vienna, Austria); MICA: N/A

Supplementary Table 1. Variables included in the clinical prediction model development process in CATS. The first column reports all variables that were used for development of the clinical prediction model in CATS. The second columns reports corresponding variable levels (for categorical variables) or units of measurement (for continuous variables). The third column reports the laboratory assays or ascertainment method used for biomarker assessment or variable measurement. TNM – Tumor node metastasis classification, c/p – either clinically or pathologically assessed, ESA – Erythropoiesis-stimulating agents, CATS – Vienna Cancer and Thrombosis Study, MICA – Multinational Cohort Study to Identify Risk Factors for Venous Thromboembolism in patients with Cancer, G/L – Giga/Liter, fL – femtoliter, FVIII – Coagulation factor VIII, TGA – Thrombin generation assay.

	Univariable analysis			Standardized Univariable analysis	
Variable	**HR**	**95% CI (p)**		**Stand. HR**	**95% CI (p)**
Clinical Variables					
BMI (per doubling)	1·76	0·87-3·56 (p=0·12)		1·16	0·96-1·39 (p=0·12)
Female sex	0·93	0·64-1·34 (p=0·68)		N/A	N/A
Use of erythropoiesis-stimulating agents (ESAs)	2·77	1·40-5·48 (p=0·003)		N/A	N/A
Tumor site category					
---Low/Intermediate Risk of VTE	Ref.	Ref.		N/A	N/A
---High Risk of VTE	2·79	1·55-5·04 (p=0·001)		N/A	N/A
---Very High Risk of VTE	6.48	3·36-12·50 (p<0·0001)		N/A	N/A
Tumor characteristics					
Tumor grade G3/G4	1·48	1·02-2·15 (p=0·04)		N/A	N/A
Lymph node metastasis	2·11	1·34-3·34 (p=0·001)		N/A	N/A
Distant metastasis	1·67	1·15-2·42 (p=0·007)		N/A	N/A
Laboratory Parameters & Biomarkers					
Haemoglobin (per doubling)	0·51	0·22-1·17 (p=0·11)		0·87	0·72-1·03 (p=0·11)
Absolute Leukocyte count (per doubling)	1·07	0·90-1·29 (p=0·44)		1·07	0·91-1·25 (p=0·44)
Absolute Neutrophil count (per doubling)	1·28	1·01-1·62 (p=0·04)		1·19	1·01-1·40 (p=0·04)
Platelet count (per doubling)	1·37	0·98-1·93 (p=0·07)		1·22	0·99-1·50 (p=0·07)
Mean platelet volume (per doubling)	0·64	0·15-2·70 (p=0·54)		0·94	0·78-1·14 (p=0·54)
D-Dimer (per doubling)	1·43	1·29-1·59 (p<0·0001)		1·75	1·48-2·06 (p<0·0001)
sP-Selectin (per doubling)	1·40	1·02-1·93 (p=0·04)		1·25	1·01-1·53 (p=0·04)
Fibrinogen (per doubling)	1·54	0·99-2·39 (p=0·06)		1·21	1·00-1·47 (p=0·06)
Factor VIII activity (per doubling)	2·21	1·53-3·18 (p<0·0001)		1·53	1·26-1·87 (p<0·0001)

Prothrombin fragment 1·2 (per doubling)	1·50	1·19-1·88 (p<0·0001)		1·38	1·15-1·66 (p<0·0001)
Peak of Thrombin Generation (per doubling)	1·03	0·87-1·23 (p=0·73)		1·03	0·86-1·25 (p=0·73)
Velocity Index of Thrombin Generation (per doubling)	1·04	0·93-1·17 (p=0·51)		1·07	0·88-1·29 (p=0·51)

Supplementary Table 2. Cause-specific hazards of VTE for variables included in the clinical prediction model development process in CATS – Univariable and Standardized Univariable analysis. Results were derived with univariable Cox regression models ("cause-specific hazards analysis"). Continuous variables were log2-transformed prior analysis (hence, they can be interpreted as the relative increase in the cause-specific hazard of VTE per doubling of the respective variable). Only continuous variables with a standardized hazard ratio below 0·80 or above 1·25 were considered for further model development with the LASSO method. Abbreviations: HR – Hazard Ratio, 95%CI (p) – 95% confidence interval (p-value), Stand. HR – Z-standardized hazard ratio (only applicable for continuous variables), N/A – not applicable (i.e. for categorical variables Z-standardization is not applicable), VTE – Venous Thromboembolism, sP-Selectin – Soluble P-Selectin.

VTE event	n (%) in CATS	n (%) in MICA
Pulmonary embolism (PE)	30 (37·5%)	22 (45·8%)
Deep vein thrombosis (DVT)	26 (32·5%)	16 (33·3%)
DVT+PE	7 (8·8%)	3 (6·3%)
Fatal PE	5 (6·3%)	2 (4·2%)
Upper arm DVT	3 (3·8%)	5 (10·4%)
Others	9 (11·3%)	0 (0·0%)

Supplementary Table 3. Distribution of VTE events in CATS (n=80 events) and MICA (n=48 events). Event types are sorted by decreasing proportion in the CATS study (with "others" reported at the bottom of the table). Abbreviations: VTE – Venous Thromboembolism, CATS – Vienna Cancer and Thrombosis Study, MICA – Multinational Cohort Study to Identify Risk Factors for Venous Thromboembolism in patients with Cancer, DVT – Deep vein thrombosis, PE – Pulmonary embolism.

Supplementary Paragraph 1. Externally-validated equation for predicting 6-month risk of VTE in outpatients with solid cancer. The nomogram reported in the main manuscript (Figure 3) is based on the equation below, where cancersite=(0 for "low/intermediate risk of VTE" tumor sites, 1 for "high risk of VTE" tumor sites, and 2 for "very high risk of VTE" tumor sites) and D-Dimer has the unit μg/mL:

$$6monthVTErisk(\%) = 100 * (1 - (1 - 0.02137053)^{e(0.6709158 \times cancersite + 0.2793001 \times \log_2(d\,\dim er + 1))})$$