CLINICAL AND LABORATORY BIOMARKERS OF VTE RISK IN CANCER PATIENTS

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DISCLOSURES

- CONSULTING: PfIZER, BMS, JANSSEN, RIGEL, AMGEN, NOVARTIS, SANOFI, GENZYME

- RESEARCH SUPPORT: JANSSEN, PROTOLEX, SYNTIMMUNE

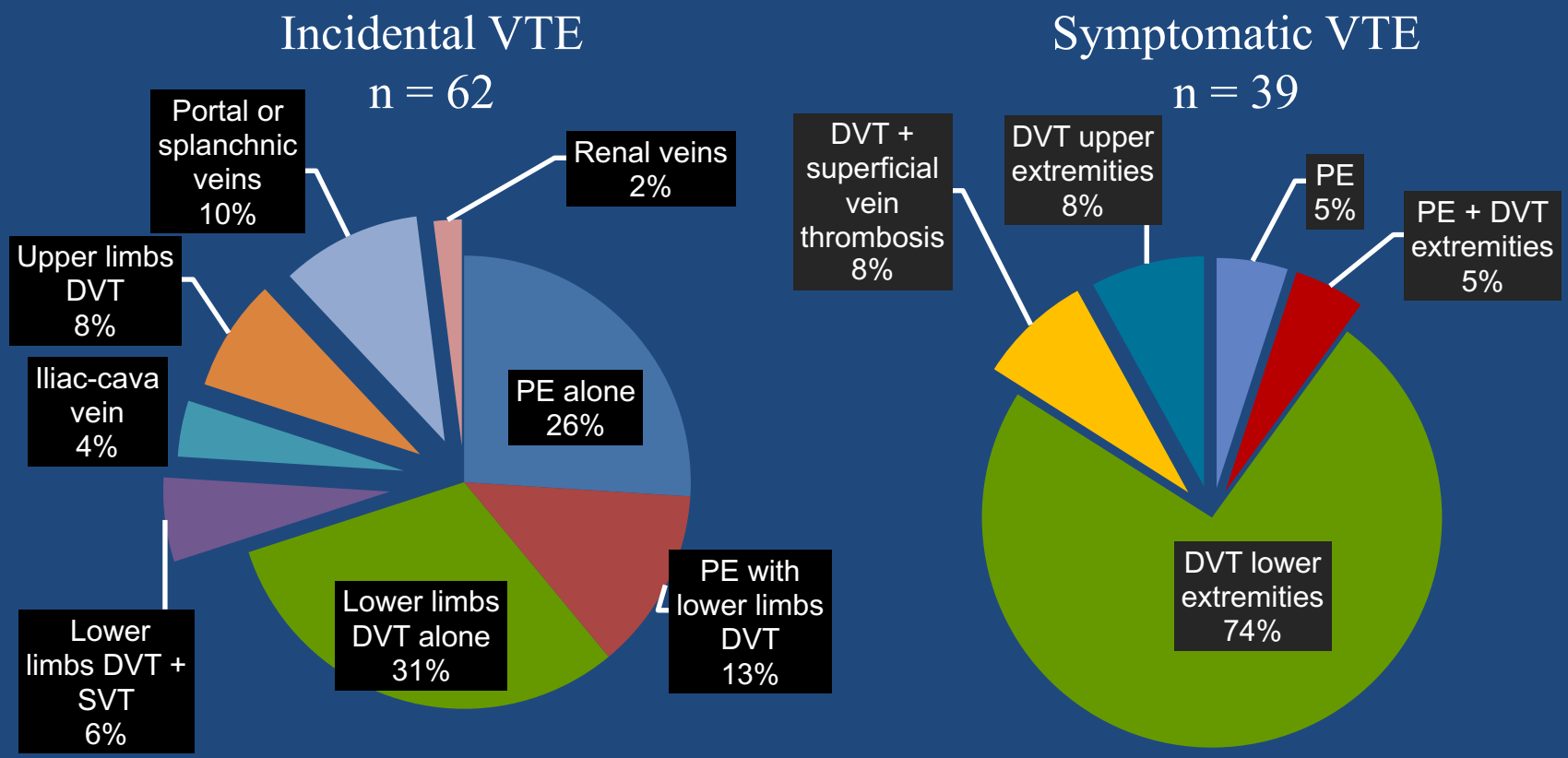
Incidence of Thrombosis in Carcinoma of Various Organs

Organ in which tumor arose	Total No. Cases	Cases With Thrombosis		Cases With Multiple Thromboses	
		No. Cases	Per cent of Total	No. Cases	%Total
Anywhere in pancreas	47	14	29.7	8	17
Head of pancreal	31	5	16.1	3	9.7
Body or tail of pancreas	16	9	56.2	5	31.3
Lung	81	12	14.8	2	2.5
Liver	22	6	27.2	0	
Gallbladder	30	5	16.6	0	
Stomach	147	32	21.8	2	1.3
Duodenum	16	3	18.7	0	
Colon	94	15	15.9	0	
Kidney	27	7	25.9	0	
Prostate	43	7	16.3	0	
Uterus	27	6	22.2	0	
Ovary	17	4	23.5	0	

E.E.Sproul Am J Med. Sci. 1938; 34: 566-570

Where do incidental VTE occur in cancer patients?

Retrospective single institution cohort study: solid tumour and chemotherapy (N = 1,921)



SVT = superficial vein thrombosis.

Di Nisio M, et al. Thromb Haemost. 2010;104:1049-54.

Laboratory abnormalities of hemostasis are common in 431 cancer patients

Test (patients studied)	Abnormal (%)	
aPTT (275)	10/275 (3.6)	
FDPs* (264)	21/264 (7.6)	
PT† (403)	57/403 (14.4)	
Increased platelet count (412)	148/412 (35.9)	IL-6
Increased fibrinogen (262)	125/262 (47.7)	IL-6
FPA‡ (72)	48/72 (66.7)	Thrombin

*FDPs = fibrin degradation products; †PT = prothrombin time; ‡FPA = fibrinopeptide A

Edwards RL et al. Am J Clin Path 1987;88:596–602.

Candidate Biomarkers

- **Blood counts** [1]
  - Platelet count
  - Leukocyte count
  - Hemoglobin
- **D-dimer** [2]
- **Tissue factor** [3,4]
- **Soluble P-selectin** [5]
- **C-reactive protein** [6]
- **Factor VIII** [7,8]
- **Neutrophil nets** [9]

1. Khorana AA, et al. *Blood* 2008; 2008;111:4902-4907
2. Ay, C, et al. *J Clin Oncol*; 2009; 27:4124-4129
3. Khorana AA, et al. *Clin Cancer Res.* 2007;13:2870-2875
4. Zwicker J I, et al. *Clin Cancer Res* 2009;15:6830-6840
5. Ay C, et al. *Blood.* 2008;112:2703-2708
6. Kroger K, et al. *Ann Oncol*. 2006, 17:297-303
7. Minnema MC, et al. *J Thromb Haemostas* 2003; 1: 45-49
8. Vormittag R, et al. Arteroscler Thromb Vasc Biol 2009; 29: 2176-2181
9. van Montfoort ML et al. Arterioscler Thromb Vasc Biol. 2013;33:147-151

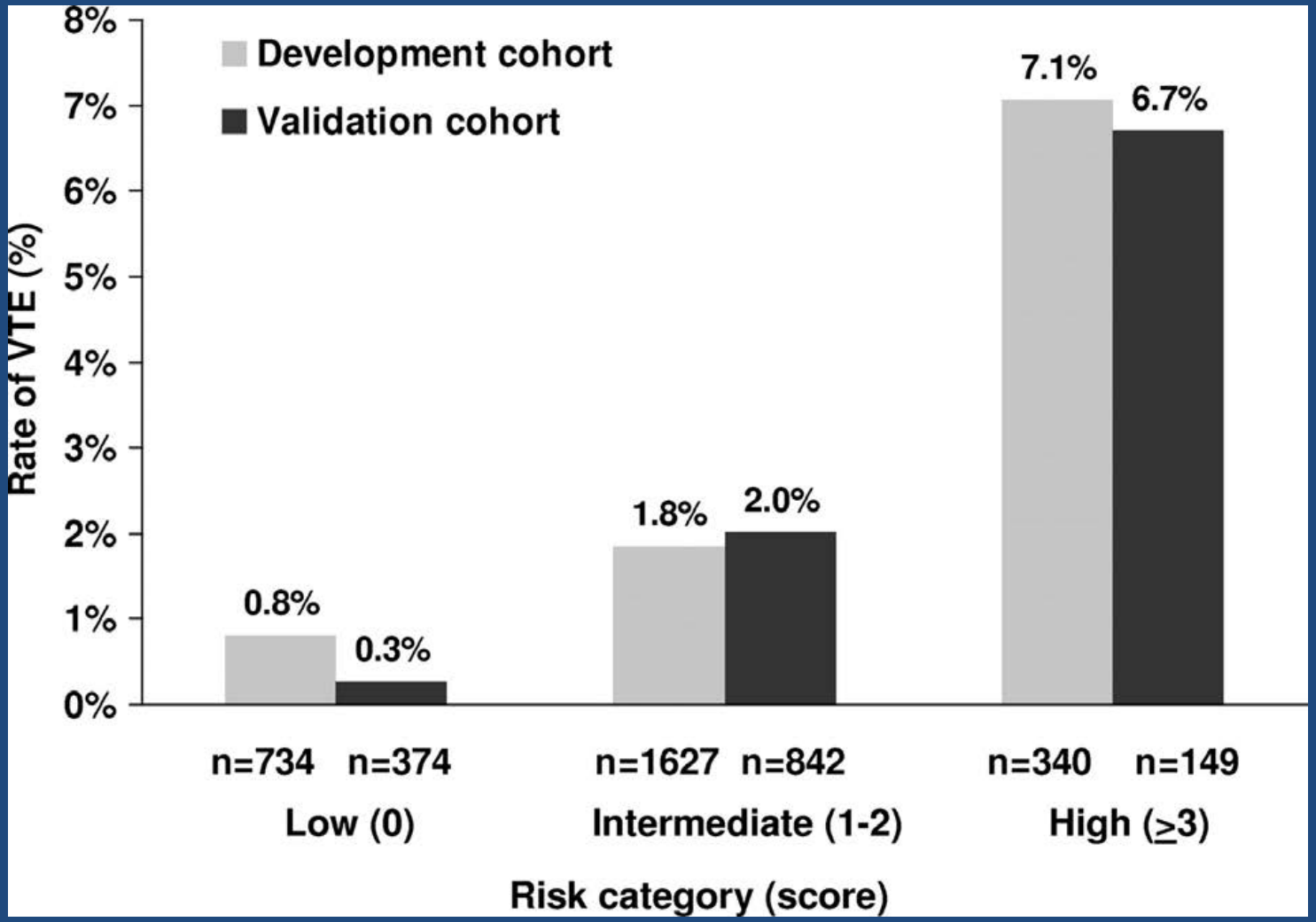
The Khorana Clinical Risk Model

Patient Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

*Risk for patients receiving systemic chemotherapy

Khorana AA et al. *Blood* 2008

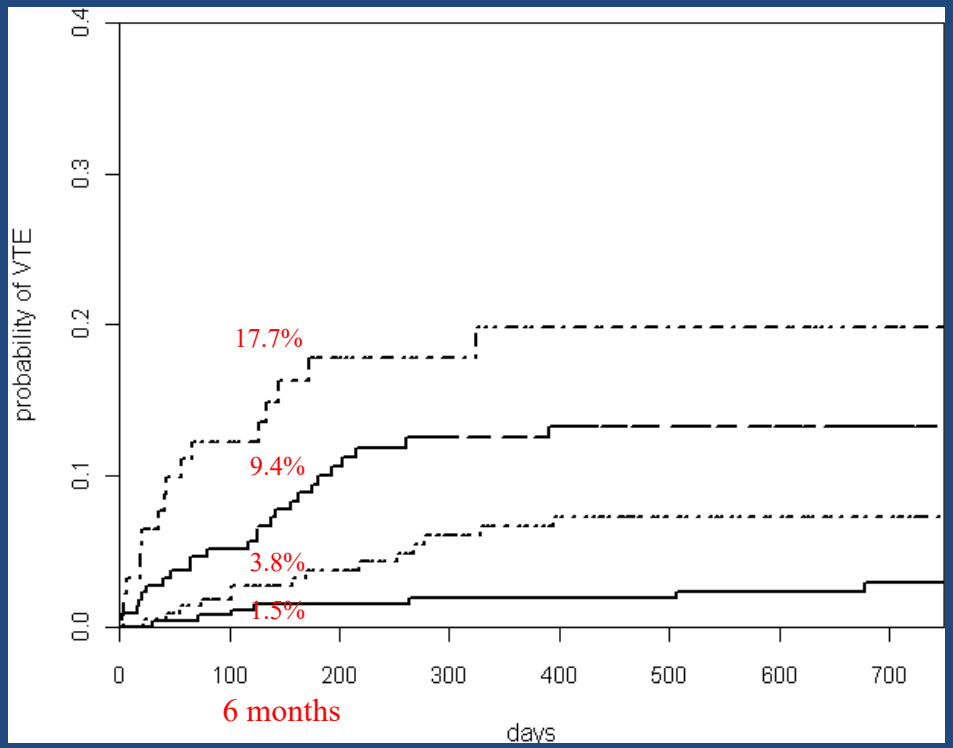
Rates of VTE according to scores from the risk model in the derivation and validation cohorts.



Khorana A A et al. Blood 2008;111:4902-4907

Vienna CATS validation

- Full data available in 839 patients
- Median observation time/follow-up: 643 days



		Number of Patients n	Number of Events n (%)
Score ≥3	Score ≥3	96	16 (17%)
Score 2	Score 2	231	25 (11%)
Score 1	Score 1	233	14 (6%)
Score 0	Score 0	279	7 (3%)

Ay et al ISTH 2009 Abs

KHORANA SCORE OF ≥2 IS PREDICITIVE OF HIGH RISK OF VTE IN PROSPECTIVE CLINICAL TRIALS

AVERT TRIAL[1]

- Venous thromboembolism — no. (%) 28/275 (10.2)*
- Deep-vein thrombosis — no. (%) 12 (4.4)
- Pulmonary embolism — no. (%)16 (5.8)

* No pre-enrollment lower limb ultrasound performed.

CASSINI TRIAL[2]

- Venous thromboembolism — no. (%) 37/421 (8.8)*
- Deep-vein thrombosis — no. (%) 22 (5.2)
- Pulmonary embolism — no. (%)15 (3.6)

* Of 1080 enrolled patients, 49 (4.5%) excluded due to baseline DVT on screening ultrasound.

[1] Carrier M, et al. NEJM 2019; 380: 711-719. 2 Khorana AA, et al. NEJM 2019; 380: 720-728

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BIOMARKERS FROM THE VIENNA CAT STUDY

- D-Dimer (≥ 1.44 µg/ml)[1]: HR 1.8 (95% CI: 1.0 to 3.2; *P* = .048)

- PT F 1.2 (>358 pmol/L)[1]: HR 2.0 (95% CI: 1.2 to 3.6; *P*= .015)

1. Ay, C, et al. *J Clin Oncol*; 2009; 27:4124-4129

ELEVATED D-DIMER IS A MAJOR RISK FACTOR FOR VTE IN CHINESE CANCER PATIENTS

Univariate analysis

Preoperative risk factors	t/χ^2	*P*
Age	2.70	.007
PLT	2.93	.004
Tumor diameter	1.97	.048
Tumor diameter >10 cm	4.259	.039
Cardiovascular complications	6.264	.012
D-dimer >0.5 μg/mL	41.84	<.001
Age >55 y	11.30	.001
PLT $>300 \times 10^9$/L	4.727	.030

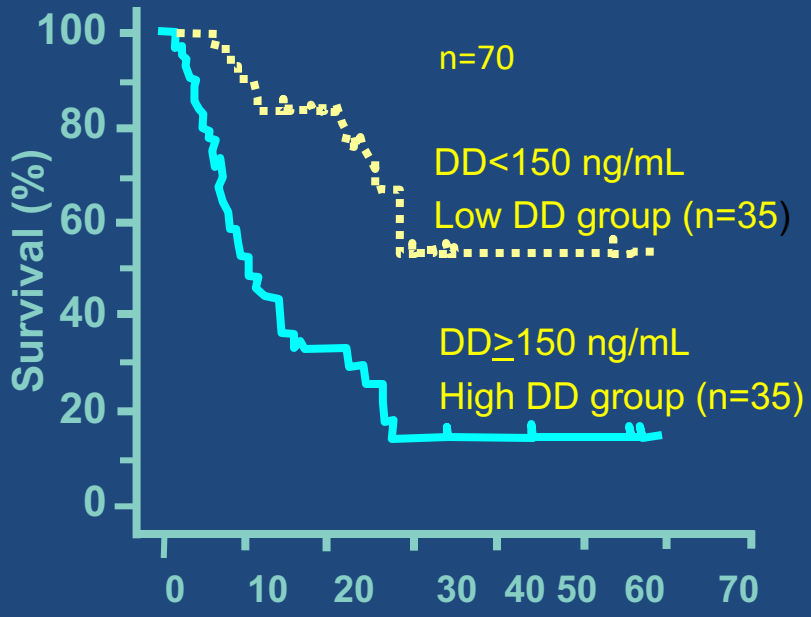
Multivariate analysis

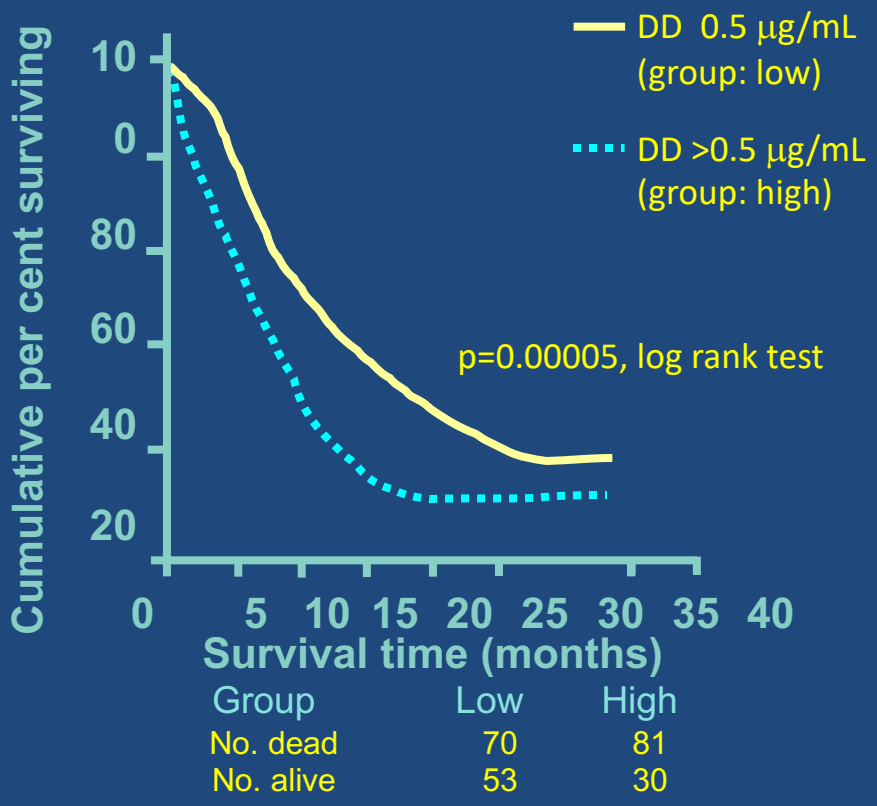
Risk factors	*P*	OR	95%CI
Age >55 y	.003	13.110	2.451–70.133
PLT $>300 \times 10^9$/L	.037	3.987	1.085–14.657
D-dimer >0.5 μg/mL	<.001	17.317	3.485–86.057
Tumor diameter >10 cm	.015	4.930	1.364–17.819

CI = confidence interval, OR = odds ratio, VTE = venous thromboembolism.

Zhang W et al. Medicine 2018; 97: 31 (e11758)

Elevated levels of D-dimer are predictive of survival in lung cancer





- **Pre-treatment plasma levels of D-dimer predicted survival independent of stage, tumour size, performance status or histology**

- **Pre-treatment levels of D-dimer predicted survival on multivariate analysis**

Taguchi O. et al. *Thorax* 1997;**52**:563–5. Buccheri G et al. *Eur J Cancer* 1997;**33**:50–5.

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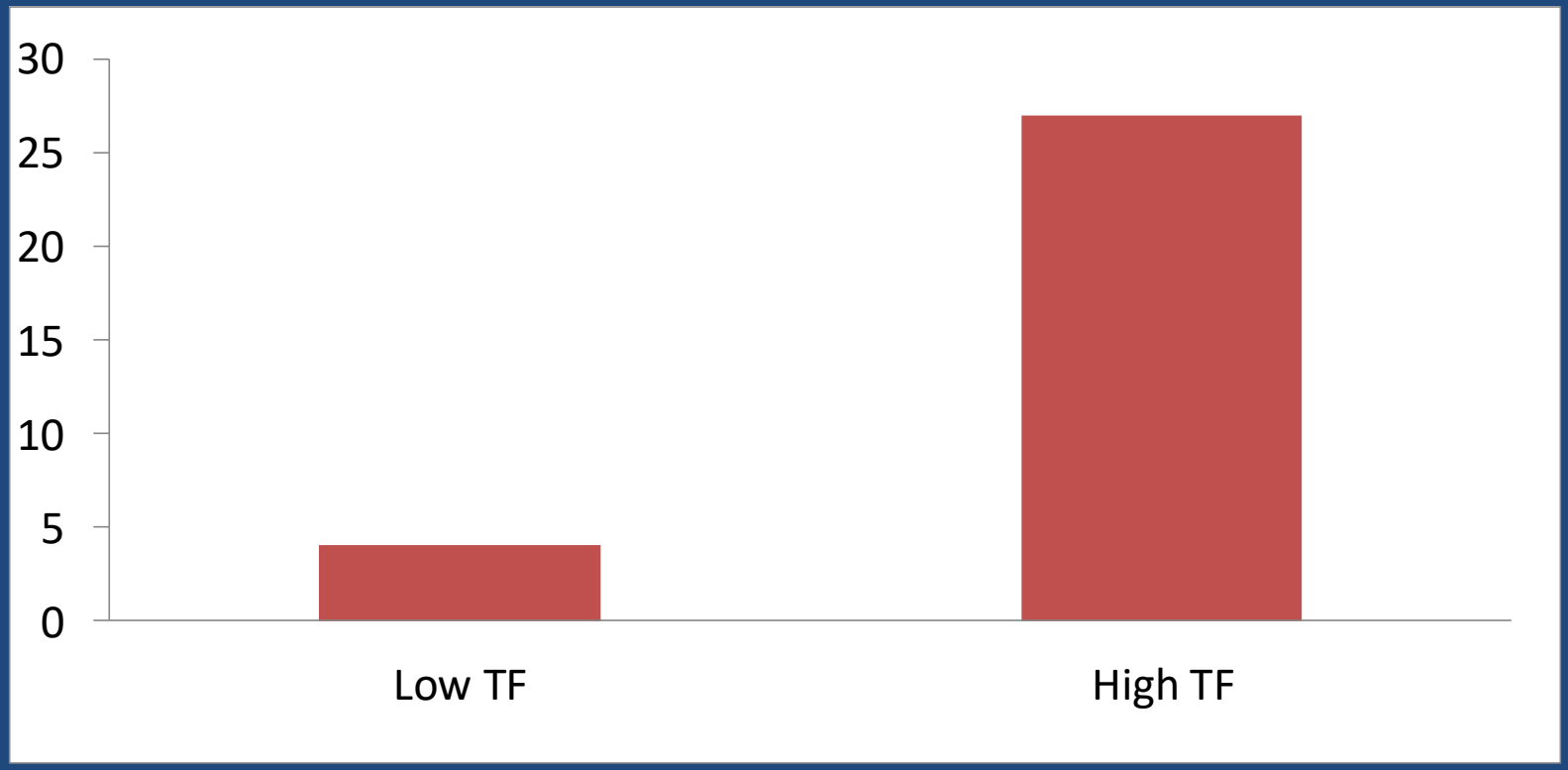
Tissue Factor (TF) in Cancer: Lack of standardized assays

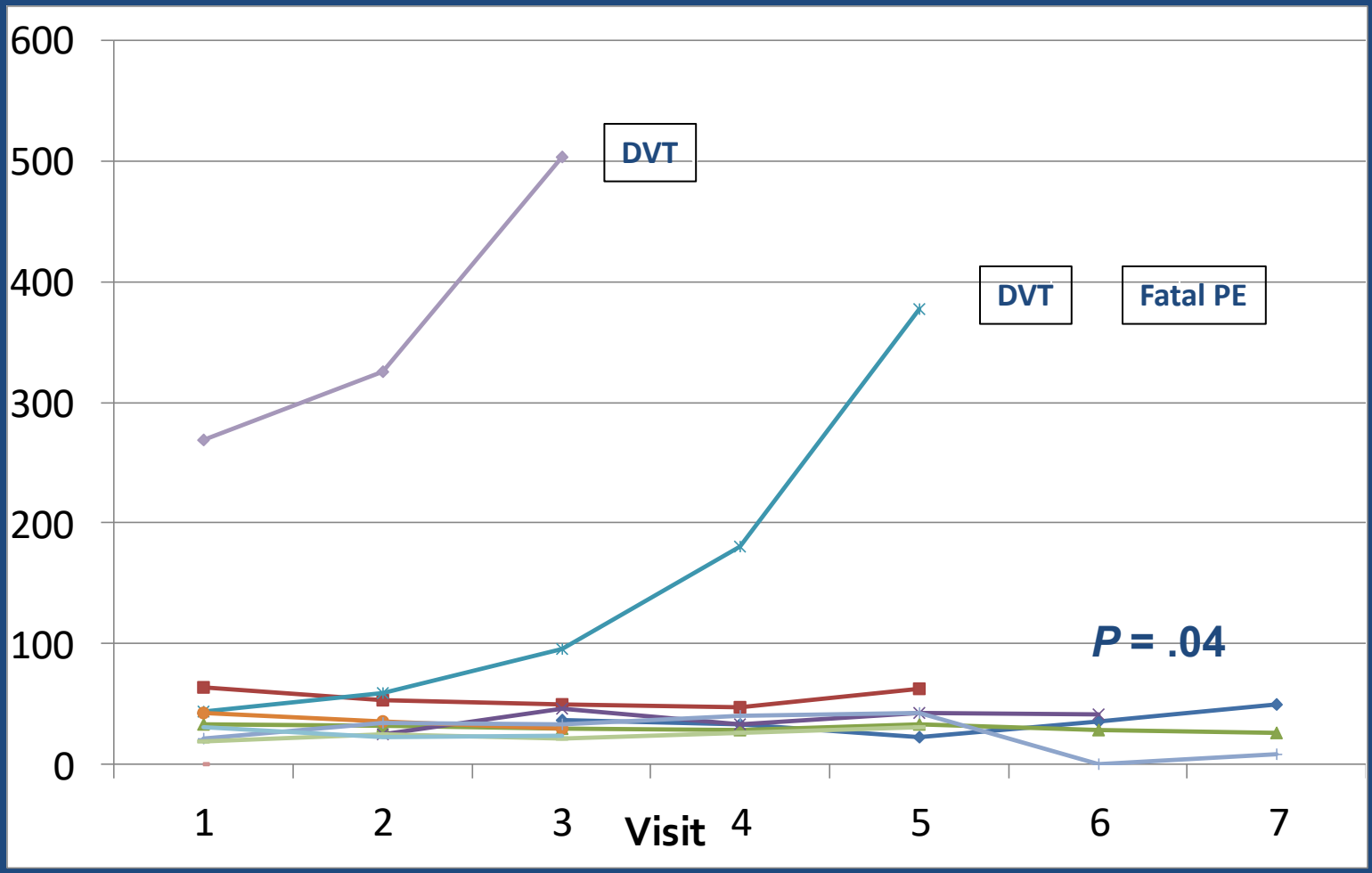
- Immunohistochemistry of tumor specimens
- TF ELISA
- TF MP procoagulant activity assay
- Impedance-based flow cytometry

Tissue Factor Expression and VTE in Patients with Pancreatic Cancer



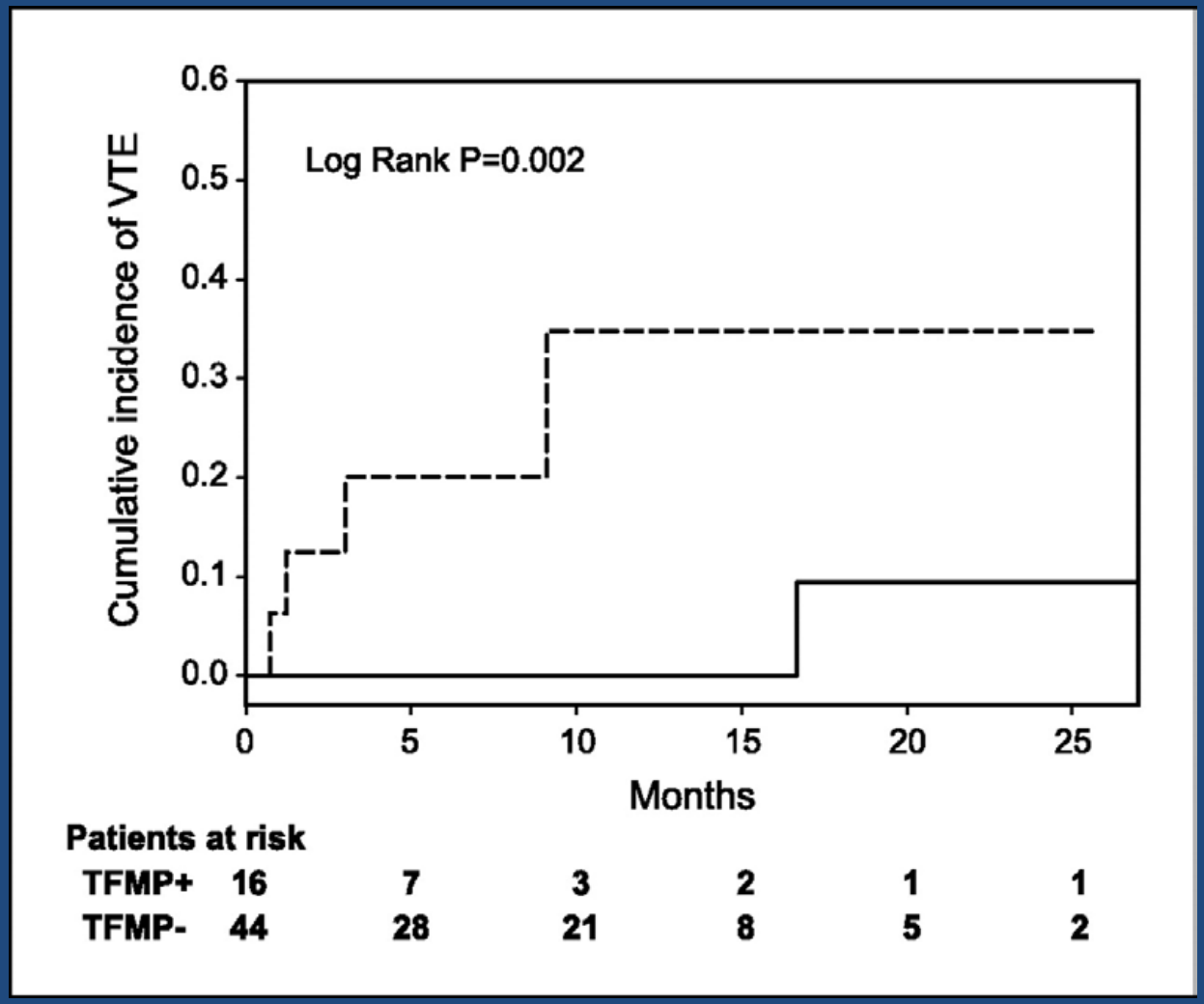
Khorana AA, et al. *Clin Cancer Res.* 2007;13:2870-2875.

Plasma Tissue Factor Antigen and VTE



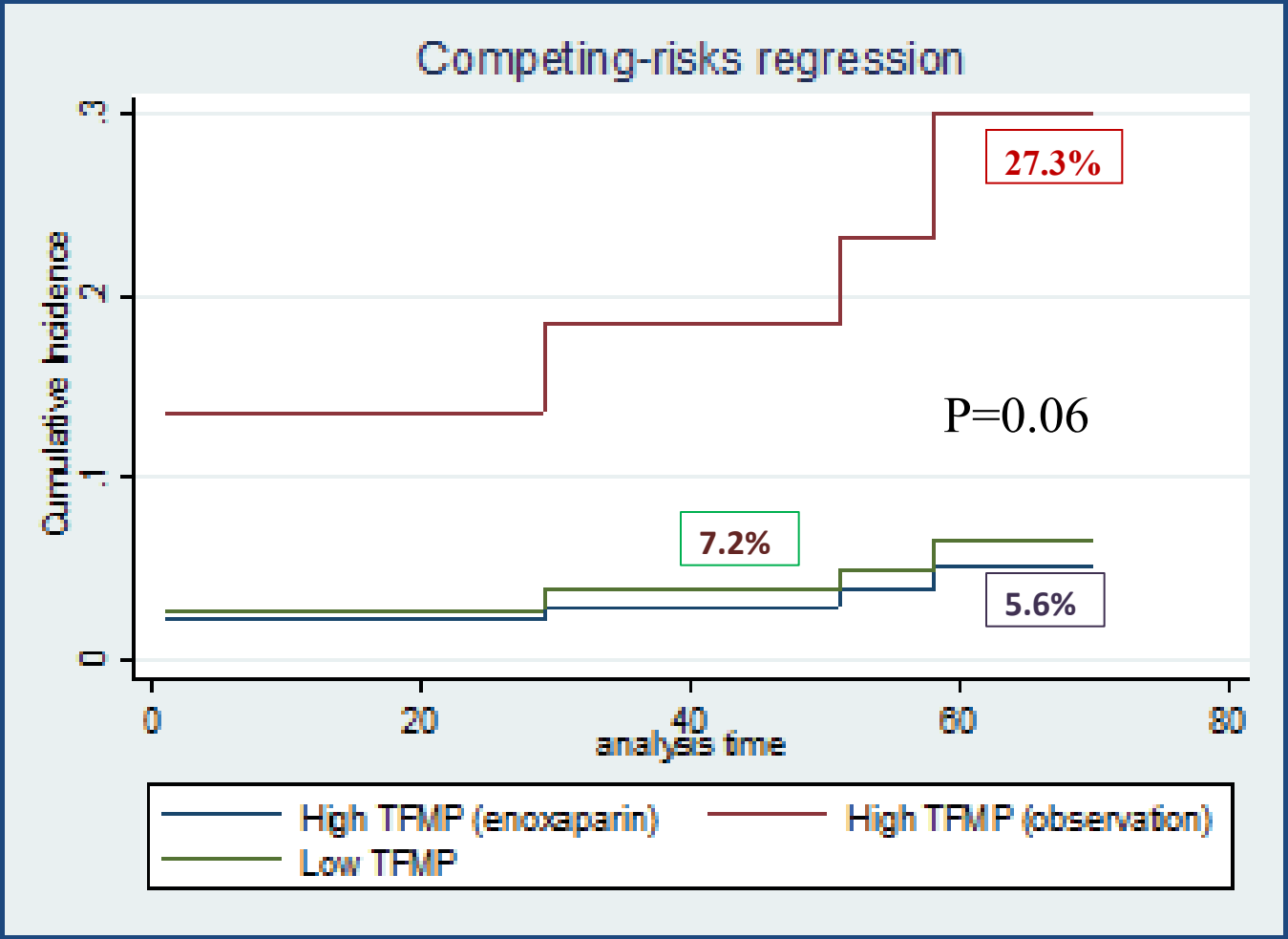
Khorana AA, et al. *J Thromb Haemost.* 2008;6:1983-1985.

Cumulative incidence of VTE for cancer patients according to TF–bearing microparticles



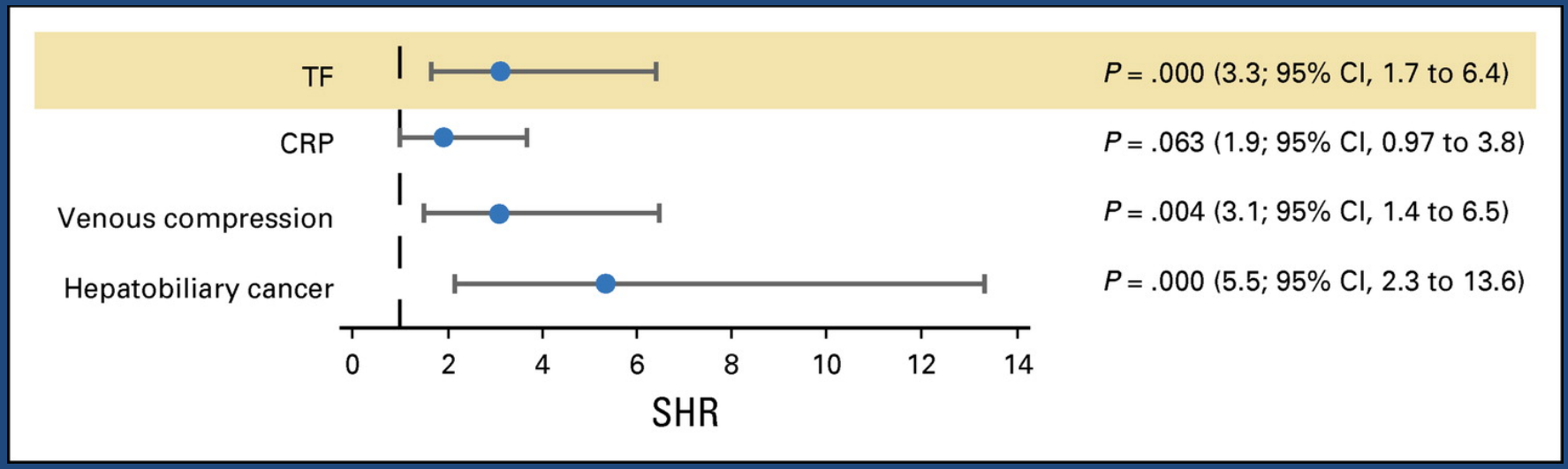
Zwicker J, Liebman HA, Neuberg D et al. Clin Cancer Res 2009;15:6830-6840

MICROTEC OUTCOME



Zwicker J, et al. Br J Haematol 160: 530-537

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial



Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model. Competing risk regression analysis of time to recurrent VTE that accounts for study design variables and significant predictors identified in individual analyses.
CRP, C-reactive protein; TF, tissue factor.

Alok A. Khorana; Pieter W. Kamphuisen; Guy Meyer; Rupert Bauersachs; Mette S. Janas; Mikala F. Jarner; Agnes Y.Y. Lee; *Journal of Clinical Oncology* 2017 351078-1085. DOI: 10.1200/JCO.2016.67.4564

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BIOMARKERS FROM THE VIENNA CAT STUDY

- sP-selectin (≥53.1 ng/ml)[1]: HR 2.6 (95% CI: 1.4 to 4.9; *P*= .003)
- Factor VIII (≥232%)[2]: HR 2.8 (95% CI: 1.7 to 4.6; *P*=.001)

1. Ay, C, et al. *J Clin Oncol*; 2009; 27:4124-4129
2. Vormittag R, et al. *Arteroscler Thromb Vasc Biol* 2009; 29: 2176-2181

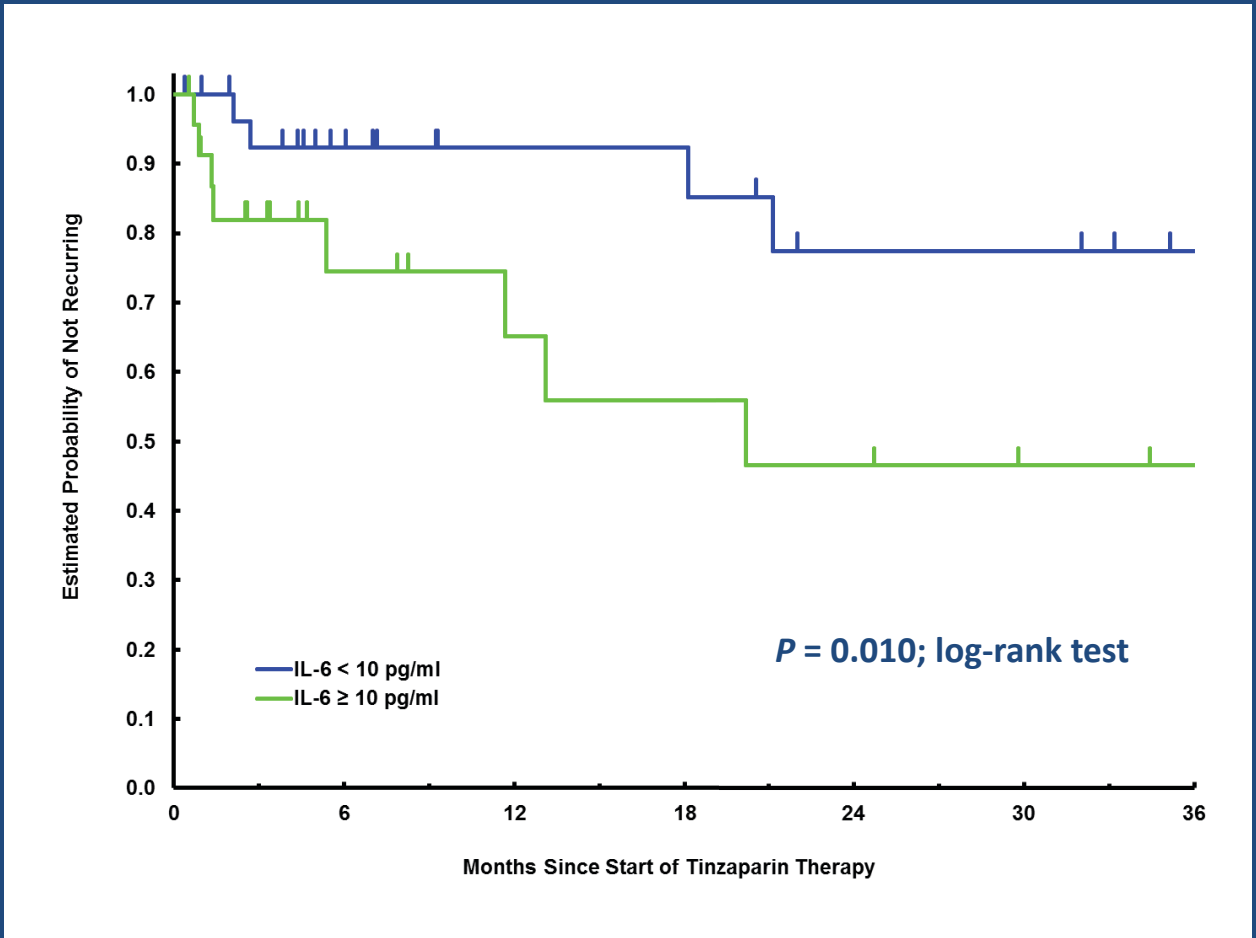
Association between Laboratory Characteristics and Thromboembolic Events.

	Positive			Negative			
Variable	n	Mean	SD	n	Mean	SD	P-value
Hemoglobin (g/dl)	58	10.29	1.92	112	11.05	2.07	0.007
Hematocrit (%)	58	31.38	5.22	112	33.51	5.80	0.007
Platelets (k/mm^3)	58	220.14	97.61	112	258.83	302.99	0.645
Creatinine (mg/dl)	59	1.19	1.40	100	1.01	1.12	0.136
FBN (mg/dl)	52	411.46	149.96	94	435.81	143.01	0.240
TNF-α (pg/ml)	48	14.76	6.48	88	17.85	19.57	0.215
AFXa (%)	52	102.94	25.72	94	106.81	30.35	0.439
hsCRP (mg/l)	49	68.42	73.39	89	43.92	61.70	0.056
IL-6 (pg/ml)	44	24.83	27.02	76	21.72	48.40	0.032
Dimer-D (ng/ml)	45	4,615.38	6,460.54	91	977.52	2,145.50	<0.001
P-selectin (ng/ml)	44	33.60	23.35	73	20.40	6.92	<0.001

SD, standard deviation; FBN, fibrinogen, TNF-α, tumoral necrosis factor-α; AFXa, activated factor Xa; hsCRP, ultrasensitive C-reactive protein; IL-6, interleukin-6.

Barbour Fernandes LF et al. Molecular Clinical Oncology 2017; 8: 188

Cumulative Risk of Recurrent Venous Thromboembolism (VTE) in Patients with Cancer and Pulmonary Embolism (PE) According to Elevated Interleukin-6 (IL-6) Levels



O'Connell, et al. J Thrombosis & Thrombolysis-In press