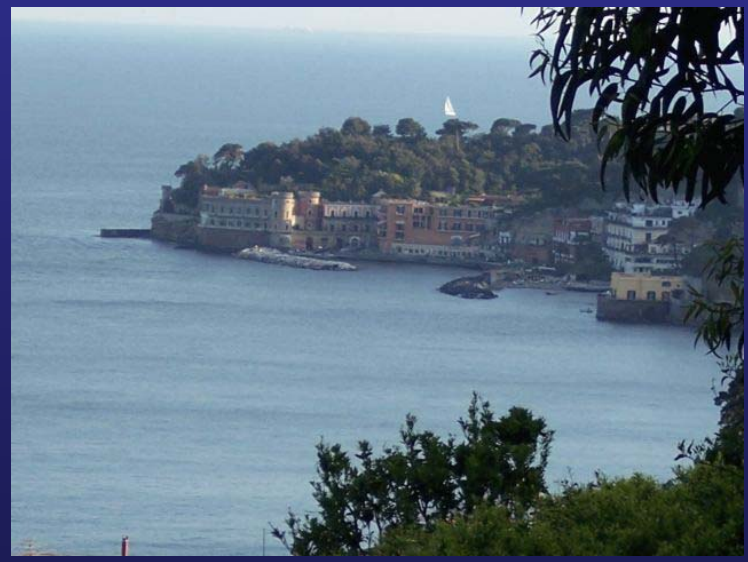
? Para què sirve el recuento de leucocitos en los pacientes con cancer ?



Dr. Pierpaolo Di Micco
Internal Medicine and Emergency Room
Fatebenefratelli Hospital of Naples, Italy

? Para què sirve el recuento de leucocitos en los pacientes con cancer ?

Cancer and thrombophilia and venous thromboembolism

Leukocytosis and mortality in oncological patients

Leukocytes and thrombophilia

Leukocytes and thrombosis

Leukocytosis and venous thromboembolism and malignancy

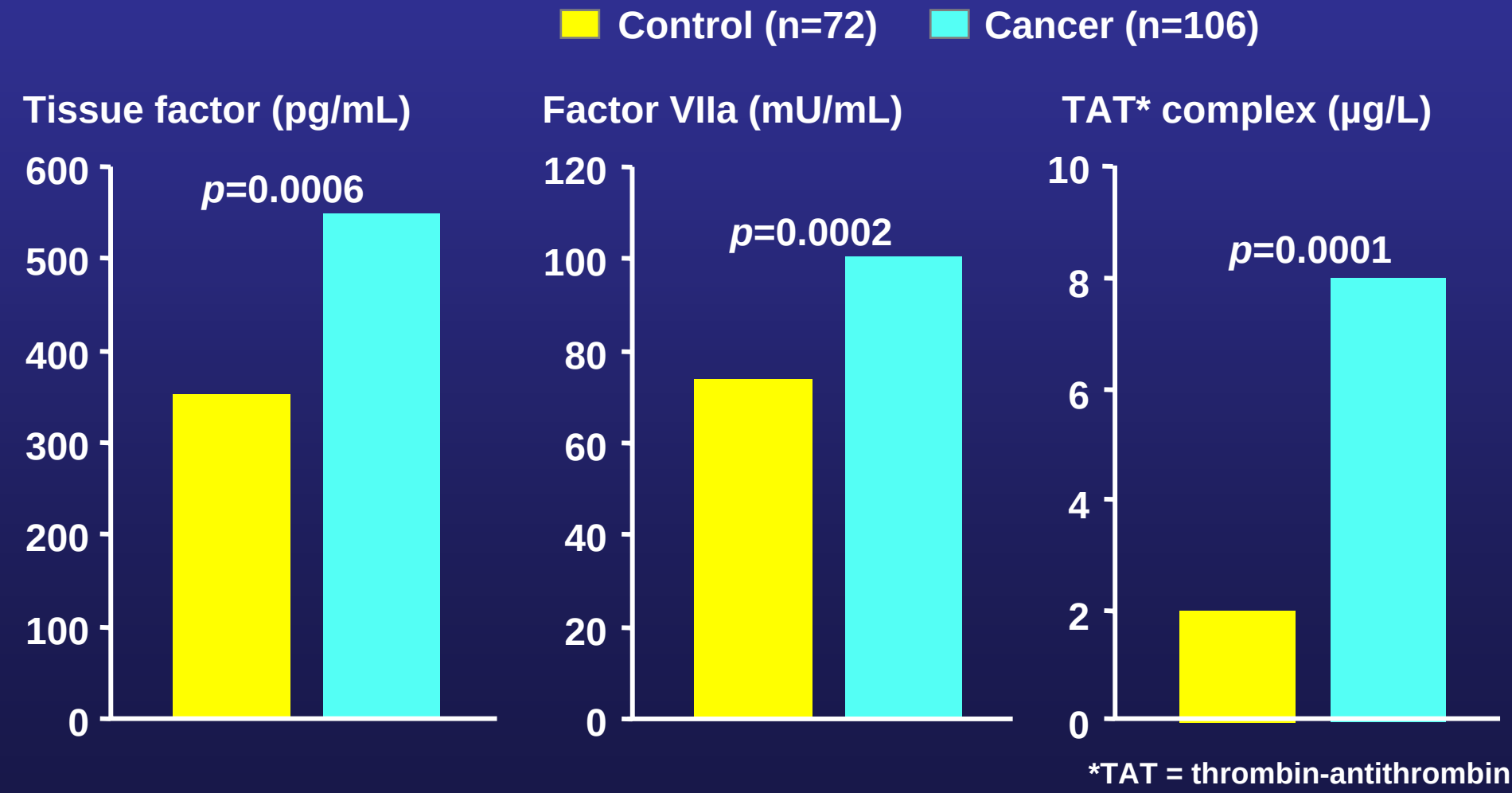
P Dí Mícco

Cancer and thrombosis – a complex relationship

- Cancer may increase the risk of thrombosis through multiple mechanisms[1]
  - tumour-induced hypercoagulability, both direct and through expression of tissue factor[2]
  - damage to the endothelium
  - venous stasis caused by immobility or bulky tumour
- Idiopathic (no known cause) venous thromboembolism (VTE) may be a sign of occult malignancy[3]
- VTE is more likely to recur in cancer patients than in those without malignancy[4]

[1]Prandoni et al (1999)
[2]Kakkar et al (1995)
[3]Prandoni et al (1992)
[4]Levitan et al (1999)

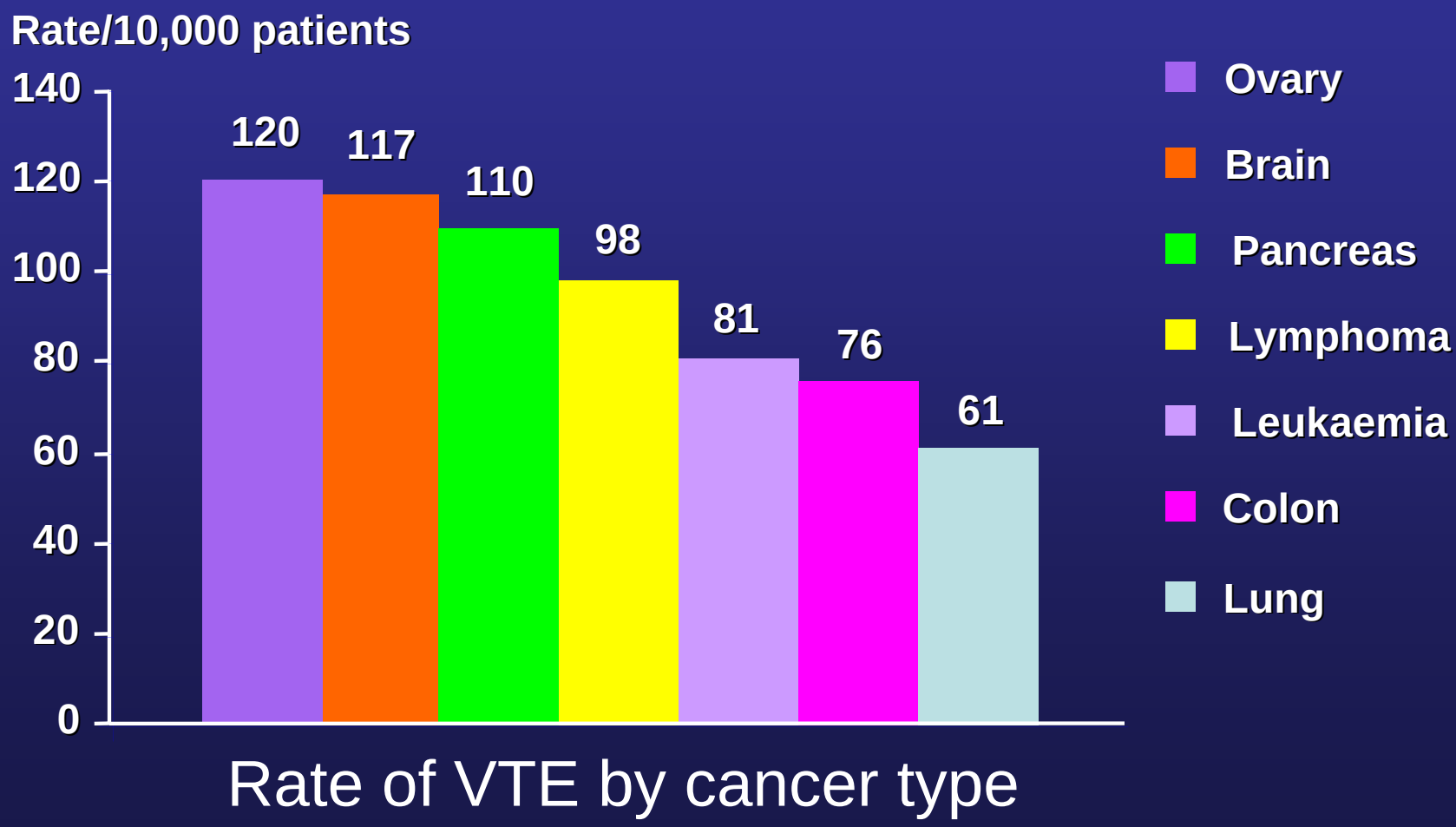
Activation of coagulation in cancer patients



*TAT = thrombin-antithrombin

Kakkar et al (1995)

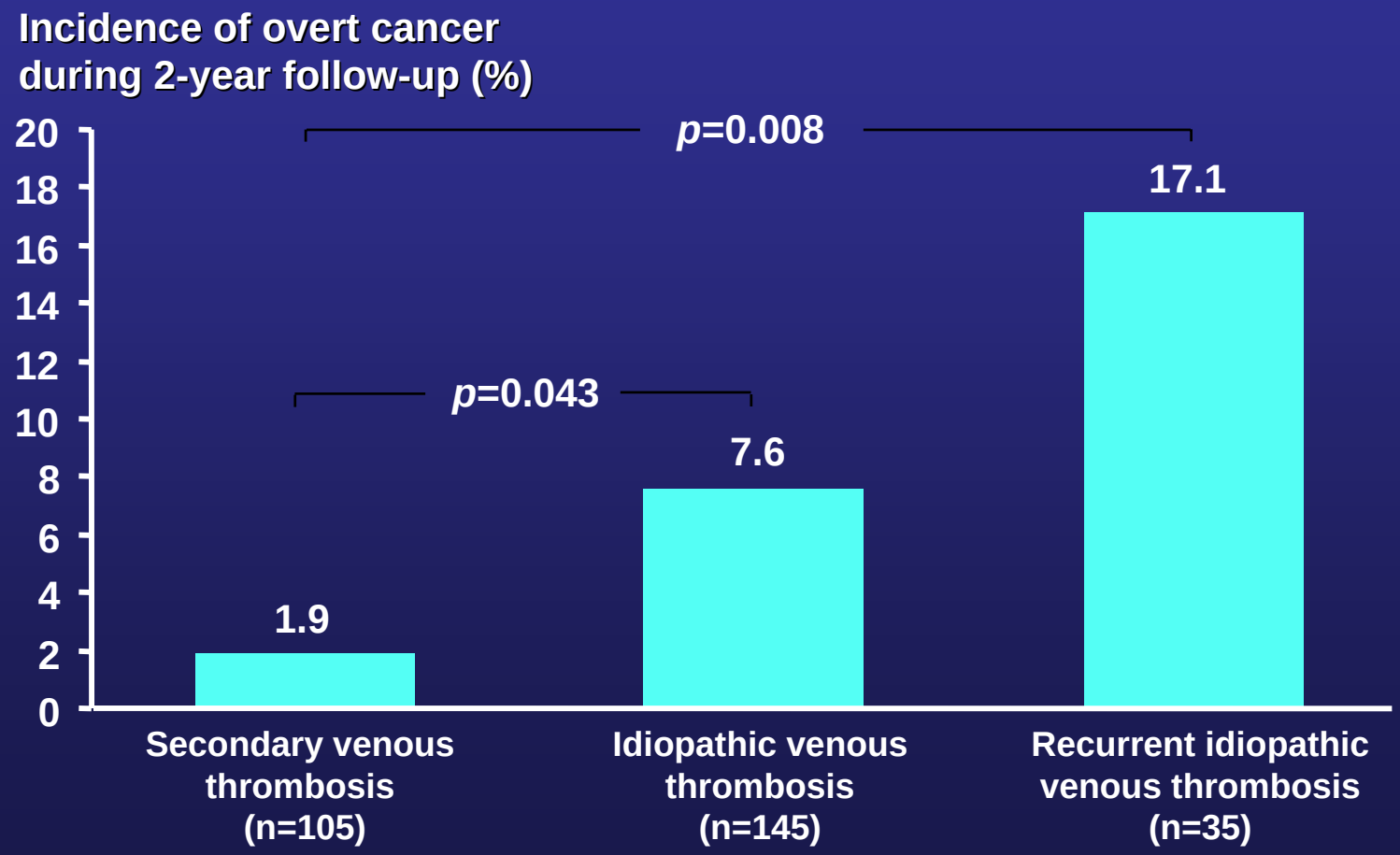
Thrombosis in cancer patients: the risk varies with tumour type



Rate of VTE by cancer type

Levitan et al (1999)

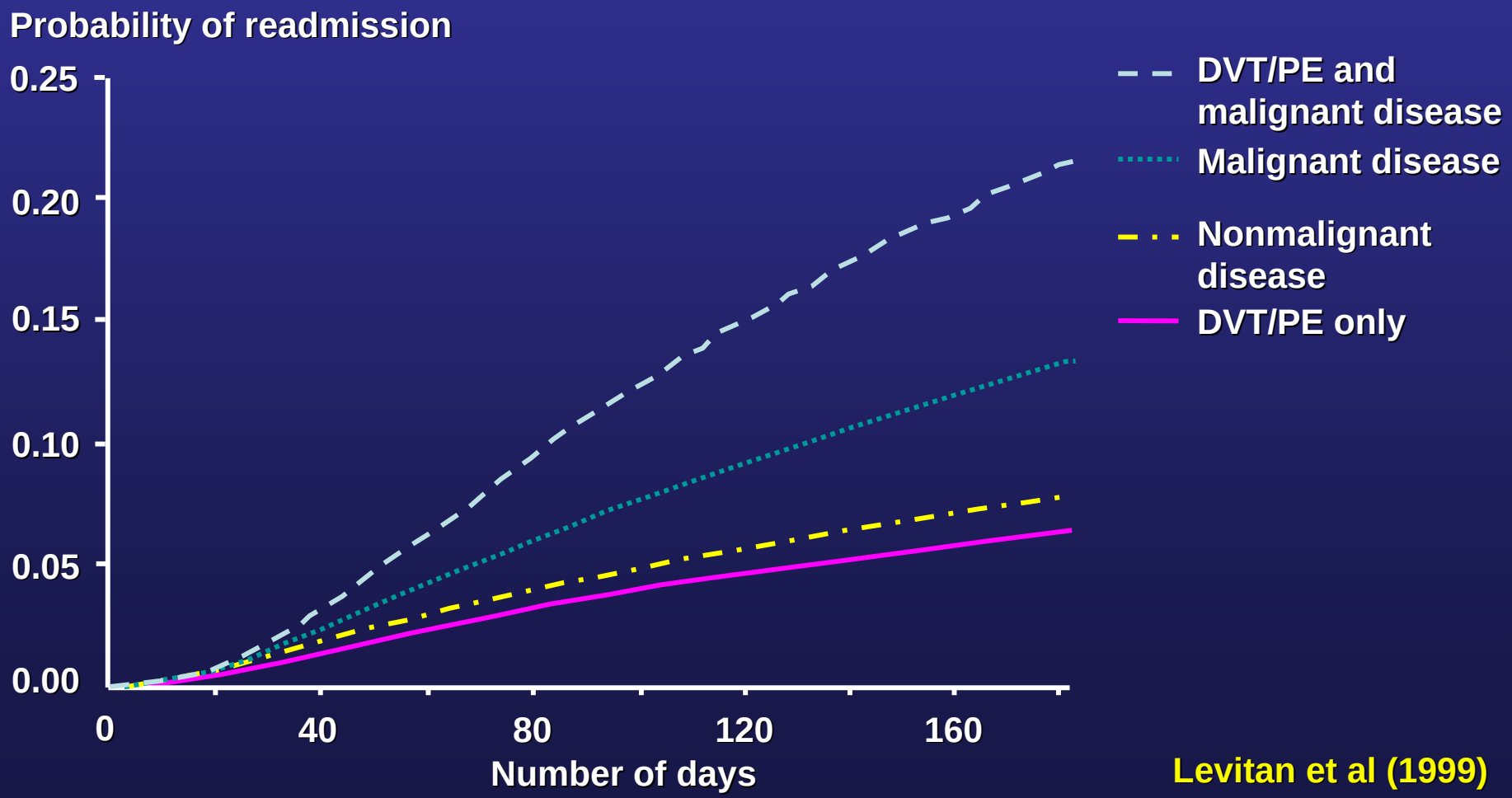
Incidence of newly diagnosed malignancy in patients with VTE



Prandoni et al (1992)

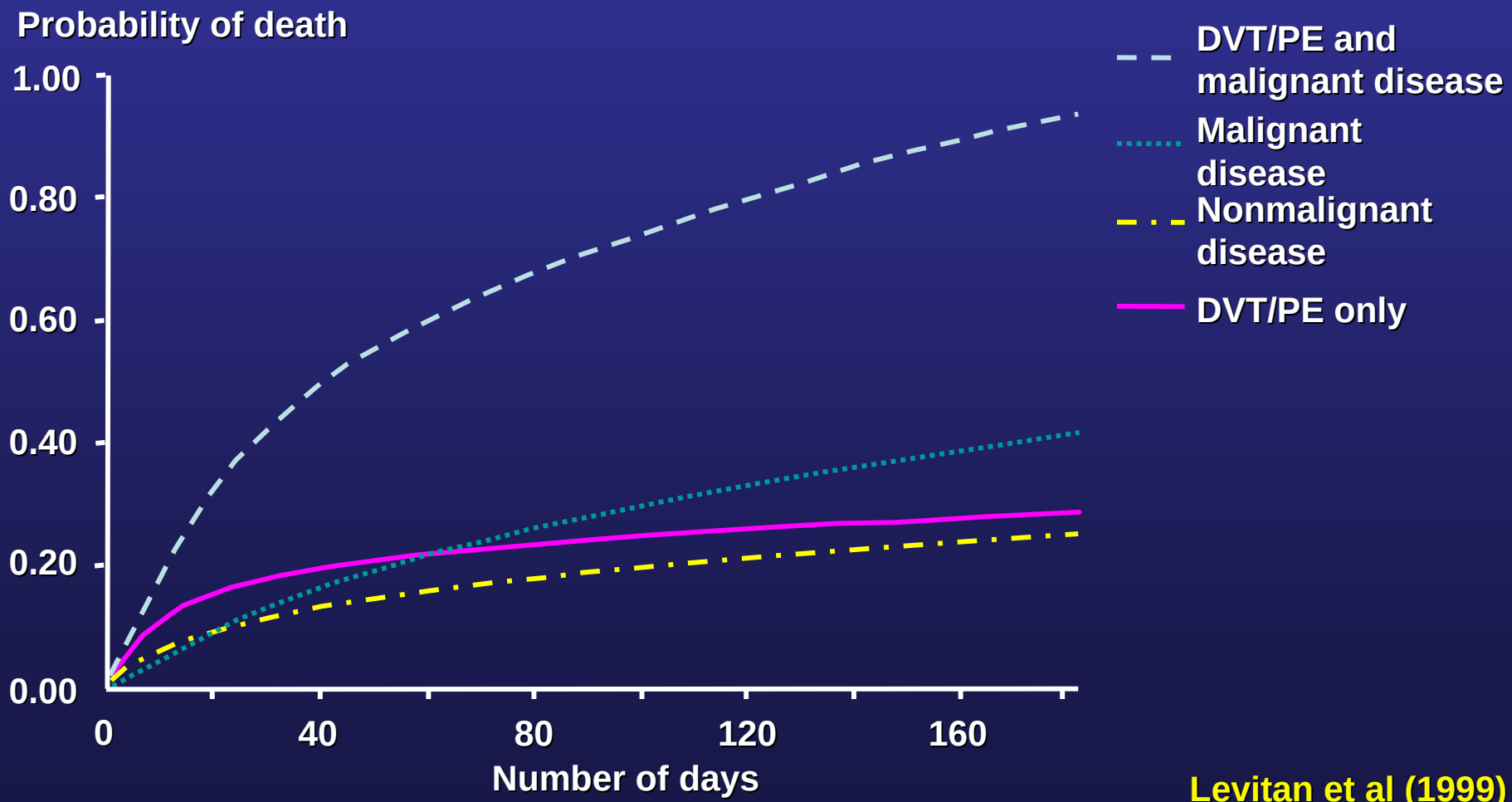
The risk of recurrence of VTE is increased in cancer patients

Probability of hospital readmission with DVT/PE within 183 days of initial hospital admission



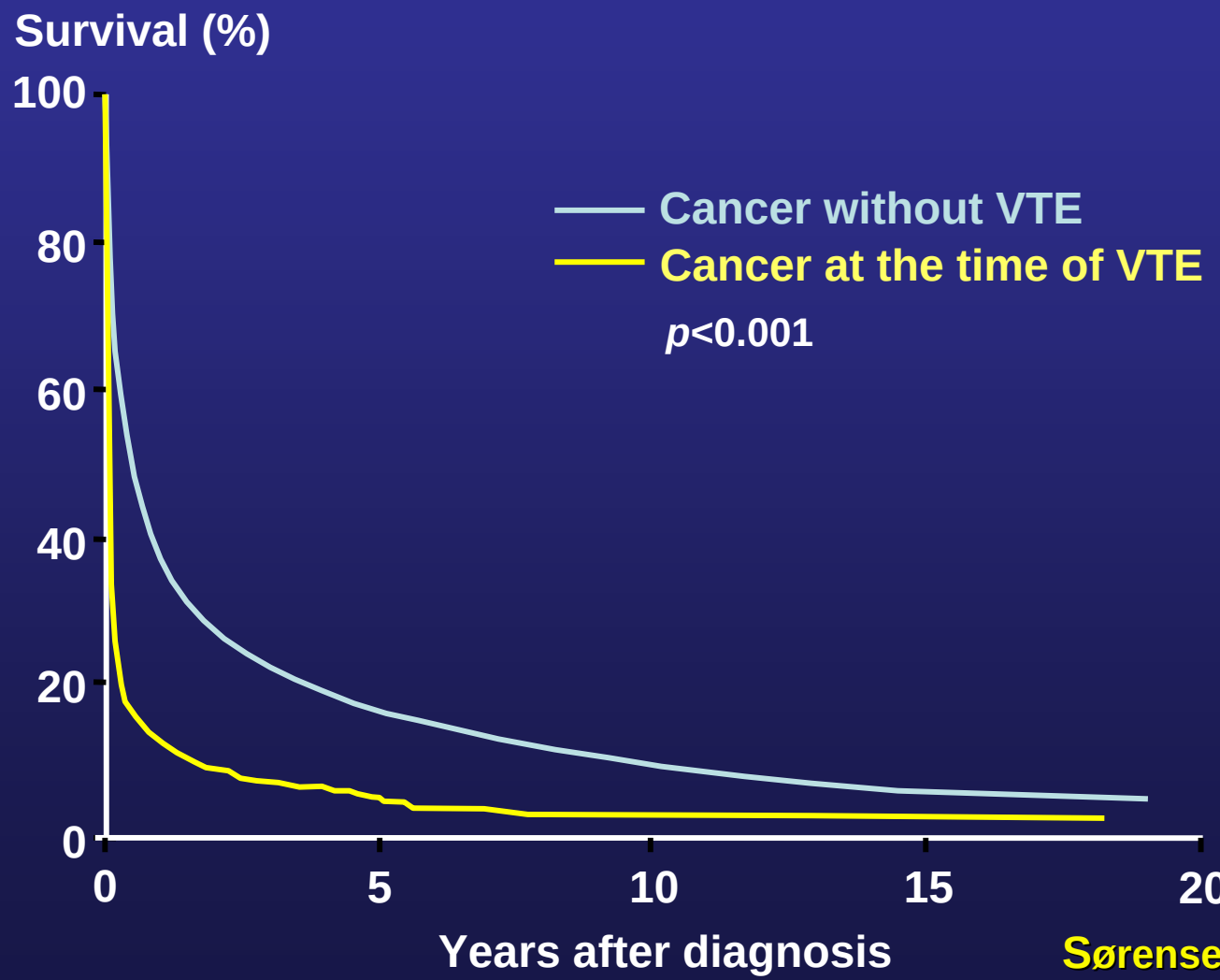
Levitan et al (1999)

Concurrent VTE and cancer increases the risk of death
Probability of death within 183 days of initial hospital admission



Levitan et al (1999)

Survival rate for patients with a diagnosis of cancer at the time of VTE



Sørensen et al (2000)

Leukocytosis and cancer

Several recent articles reported a significant association between elevated white blood cell (WBC) count and mortality in patients with cancer, but the influence of elevated WBC count on outcome in cancer patients with VTE has not been explored

Shankar A et al. Arch Intern Med 2006; 166: 188-194

Kasuga I e t al. Cancer 2001; 92: 2399-2405.

Gripp S et al, J Clin Oncol 2007; 25: 3313-3320.

Leukocytes and Thrombosis

Leukocytes seem to be critical in VTE appearance and resolution,

since neutrophils predominate early in the thrombus

and release elastase and other fibrinolytic proteins,

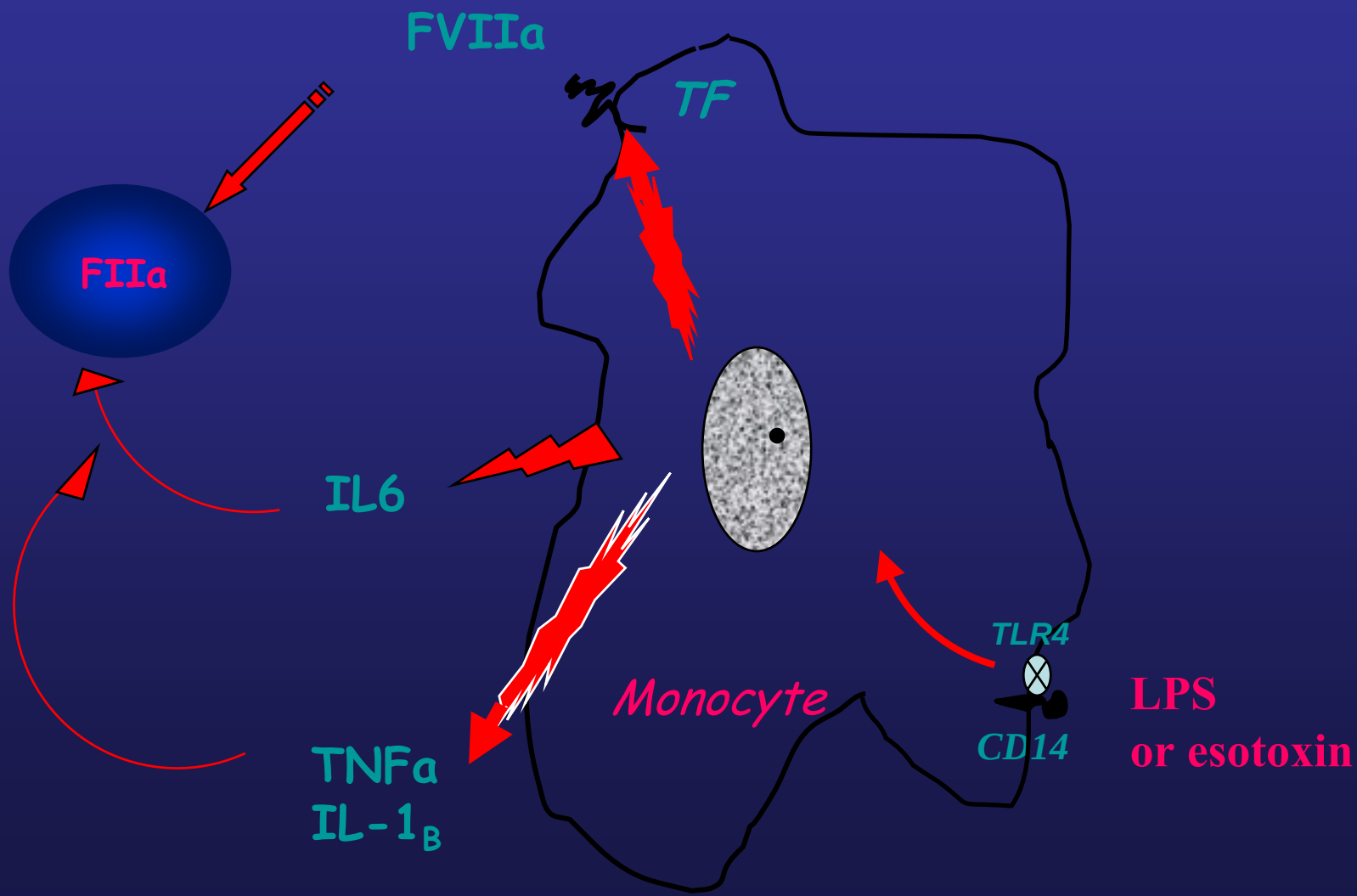
which are believed to lyse the thrombus.

In addition, neutrophil stimulation studies have demonstrated

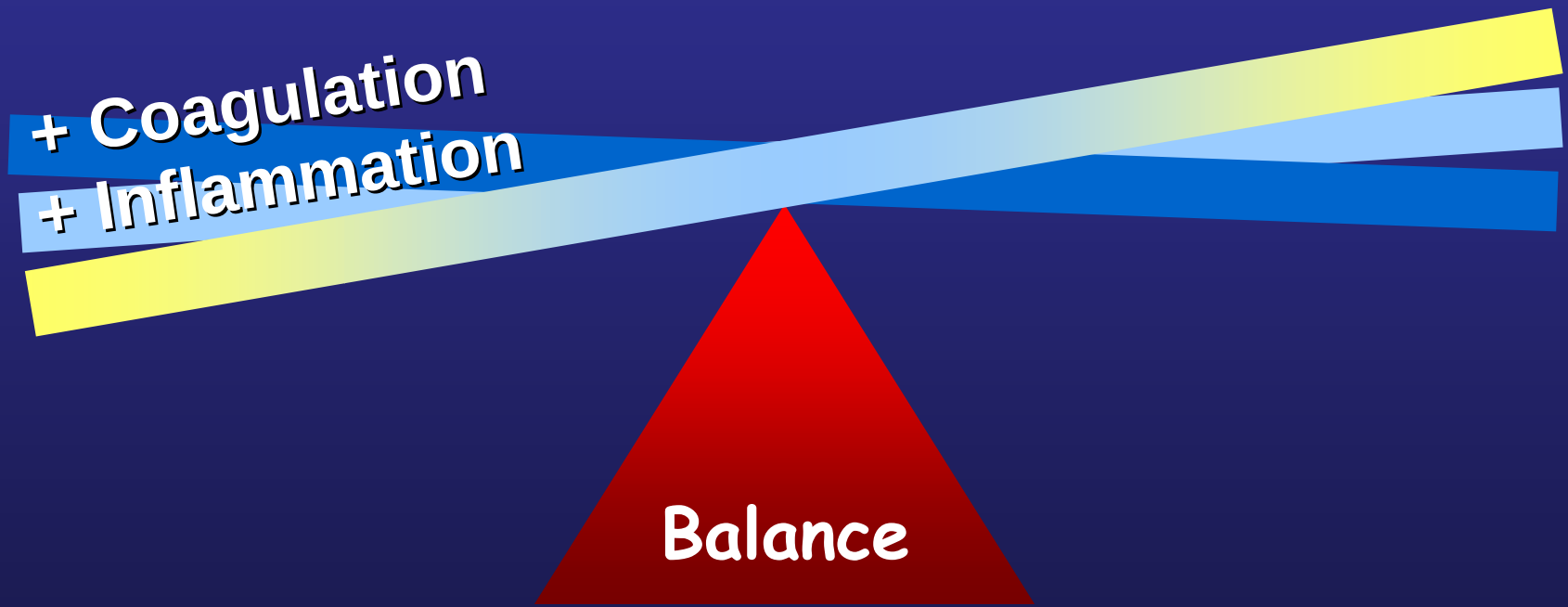
enhancement of thrombus resolution in the rat.

Lin J, Proctor MC, et al. 2003
Henke PK, Wakefield TW, et al, 2001

Generation of pro-inflammatory and pro-coagulant cytokines by monocytes following antigen exposure (e. g. endotoxin, esotoxin …)



Impairement of haemostatic balance during leukocytes activation



Carvalho AC, Freeman NJ. *J Crit Illness.* 1994;9:51-75; Kidokoro A et al. *Shock.* 1996;5:223-8; Vervloet MG et al. *Semin Thromb Hemost.* 1998;24:33-44.

JAK mutation, leukocytes, MPD and thrombosis

Since the discovery of the JAK2V617F mutation, the clinical and pathological consequences of this defect have been investigated to determine whether its presence characterises a distinct subgroup of (MPD).

MPD management remains highly dependent on the patient's thrombotic risk.

Whether the presence of the JAK2V617F mutation modifies the thrombotic risk is currently contentious, although there is
increasing clinical evidence to suggest that the mutation may be variably associated with thrombosis.

These observations are further supported by laboratory parameters which suggest that the JAK2V617F mutation may confer increased activation of leucocytes and platelets in MPD.

However, the role of screening for the JAK2V617F mutation in patients presenting with thrombosis without overt MPD is still unclear

VTE – Cancer – Leukocytosis -- Prognosis

Registro Informatizado de Enfermedad Trombo Embólica (RIETE)

www.riete.org

Characteristics:

- **multicenter**
- **independent**
- **prospective**
- **available in internet**

Aim:

- **to provide information on what happens in real-life**

sponsored by: Sanofi-Aventis and Spanish Ministery of Health

Registro Informatizado de Enfermedad Trombo Embólica (RIETE)

therapy in special conditions:

- renal insufficiency
- very elderly
- recent bleeding
- oncological patients
- ....

natural history of the disease:

- epidemiology
- diagnosis
- prevention
- risk factors
- treatment
- outcome

Usually understudied in RCT

Registro Informatizado de Enfermedad Trombo Embólica (RIETE)

- symptomatic DVT/PE
- confirmed diagnosis
- follow-up: 3 months

www.riete.org

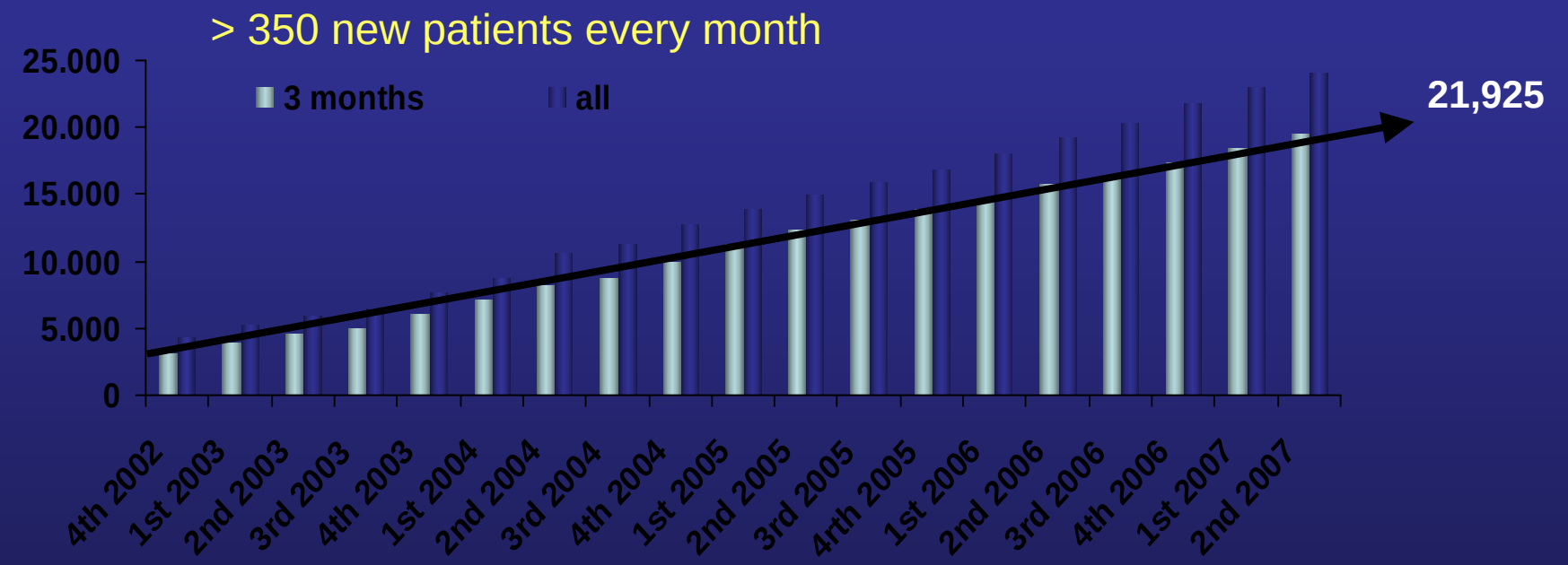
Characteristics of DVT/PE

Diagnosis confirmed by objective methods:

- **Ultrasound scan**
- **Angiography**
- **CT scan**
- **MR scan**
- **Pletismography**
- **Nuclear medicine**

sponsored by: Sanofi-Aventis and Spanish Ministery of Health

Recruitment rate



124 centres

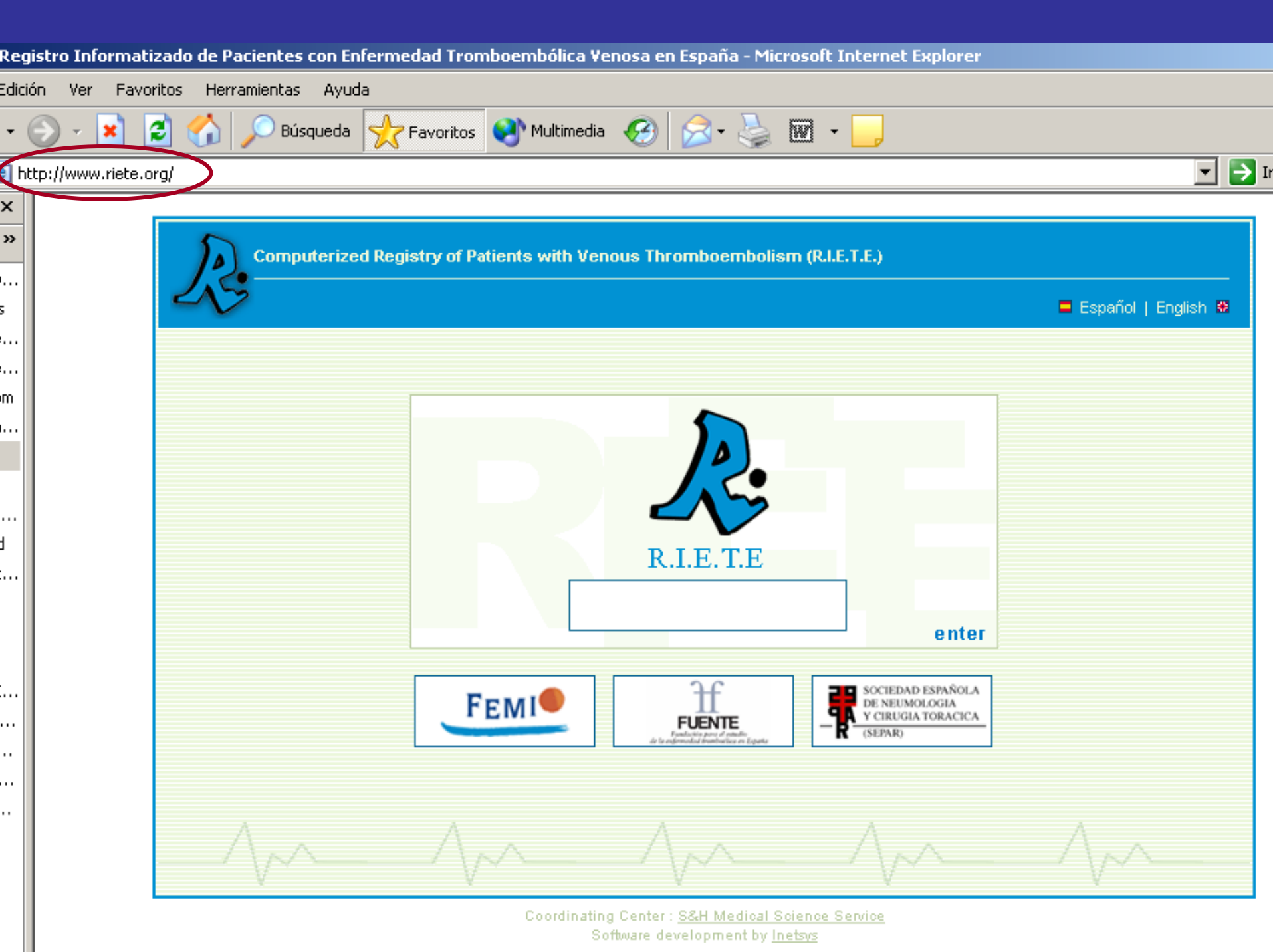
20 centres

4 centres

1 centre

24 centres

2 centres


Registro Informatizado de Pacientes con Enfermedad Tromboembólica Venosa en España - Microsoft Internet Explorer
Edición Ver Favoritos Herramientas Ayuda
Búsqueda Favoritos Multimedia
http://www.riete.org/
Computerized Registry of Patients with Venous Thromboembolism (R.I.E.T.E.)
Español | English
R.I.E.T.E
enter
FEMI
FUENTE
SOCIEDAD ESPAÑOLA DE NEUMOLOGIA Y CIRUGIA TORACICA (SEPAR)
Coordinating Center : S&H Medical Science Service
Software development by Inetsys

System authentication

If you are a member of the Registry or wish to consult the Registry data, you can enter your private area previously identifying yourself in this box.

Username :

Password :

Start

If you wish to consult the Registry and have not yet registered, please do it here and request for your login and password.

Request subscription

If you wish to participate as a Member of the Registry and include your patients' data, please contact :

riete@shmedical.es

Treatment

Check patients with : Any symptoms

- [ ] Thrombocytopenia (platelet count < 80.000 /mm^3)
- [ ] Pregnancy
- [ ] Serum creatinine levels > 3 mg/dl
- [x] Major bleeding in the past month (prior to the diagnosis of thrombosis)
- [ ] Abnormal prothrombin time
- [ ] Haemodynamic instability (systolic blood pressure on admission < 90 mmHg and PE symptoms)
- [ ] None of the above

Analysis

RIETE follow up 90 days from VTE diagnosis until 2006

Analysed variables

Age, weight, gender, in\outpatients, immobility, recent surgery, prior VTE, chronic heart-lung-kidney failure, recent bleeding, metastatic cancer, site of cancer, symptomatic DVT\PE; LEDVT\UEDVT, PaO2, SBP, initial treatment, long term treatment, outcome (bleeding, recurrence, fatal PE, overall death). 3315 patients: 996 with leukocytosis

Cancer, VTE and leukocytosis vs not leukocytosis

	Leukocytosis N=996	No leukocytosis N=2319	Odds ratio (95% CI)	P value
Clinical characteristics,				
Gender (males)	556 (56%)	1261 (54%)	0,9 (0,8-1,09)	**0.447**
Age >70 years	504 (51%)	1133 (49%)	1 (0.9-1.2)	**0.36**
Body weight >70 kg	440 (44%)	1144 (49%)	0.7 (0.6-0.8)	**<0.001**
Outpatients	652 (66%)	1623 (70%)	0.8 (0.7-0.9)	**0.005**
Risk factors for VTE,				
Immobility ≥4 days	272 (27%)	443 (19%)	0.6 (0.5-0.8)	**<0.001**
Surgery <2 months	180 (18%)	362 (16%)	0.8 (0.7-1.02)	**0.082**
Prior VTE	150 (15%)	334 (14%)	0.95 (0.8-1.2)	**0.63**
Underlying diseases,				
Creatinine levels	210 (21.1%)	345 (14.9%)	1,52 (1,2–1,8)	**<0.001**
>1.2ml/min	43 (4.3%)	84 (3.6%)	0,83 (0,5-1,2)	**0,37**
Chronic heart failure	98 (10%)	231 (9.8%)	1,01 (0.8-1.3)	**0,95**
Chronic lung disease	530 (53.2%)	1284 (55.4%)	1.09 (0.9-1.3)	**0.25**
OTHERS	32 (3.2%)	85 (3.7%)	1.15 (0,7-1.7)	**0,61**
Recent major bleeding				
Cancer characteristics	481 (48%)	980 (42%)	0.8 (0.7-0.9)	**0.001**
Metastatic cancer				
Site of cancer	154 (15%)	232 (10%)	0.6 (0,5- 0,7)	**<0.001**
Lung	93 (9.3%)	336 (14%)	1,6 (1,3-2,1)	**<0.001**
Breast	53 (5.3%)	88 (3.8%)	0,7 (0.5-0,9)	**0.030**
Stomach	55 (5.5%)	58 (2.5%)	0,4 (0,3-0,6)	**<0.001**
Pancreas	116 (12)	342 (15%)	1,3 (1,05-1,6)	**0.010**
Colorectal	21 (2.1%)	72 (3.1%)	1,5 (0,9-2,4)	**0.067**
Ovary	79 (7.9%)	156 (6.7%)	0,8 (0,6-1,1)	**0.12**
Bladder	54 (5.4%)	122 (5.3%)	0,97 (0,7-1,3)	**0.45**
Brain	76 (7.6%)	158 (6.8%)	0,8 (0,6-1,17)	**0.22**
Haematologic	28 (2.8%)	79 (3.4%)	1,2 (0,78-1,8)	**0.219**
Uterus	91 (9.1%)	288 (12%)	1,4 (1,1-1,8)	**0.003**
Prostate	19 (1.9%)	41 (1.8%)	0,9 (0,5-1,6)	**0.44**
Kidney	30 (3%)	50 (2.2%)	0,7 (0,4-1,1)	**0.090**
Unknown origin	127 (12.8%)	297 (12.8)	1,0 (0,8-1,2)	**0.507**
Other				

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Cancer, VTE and leukocytosis vs not leukocytosis

	Leukocytosis N=996	No leukocytosis N=2319	Odds ratio (95% CI)	P value
Clinical presentation				
Symptomatic DVT	447 (44.9%)	1380 (59.5%)	1,8 (1.5-2.1)	**<0.001**
Symptomatic PE	332 (33.3%)	561 (24.2%)	0.64 (0.5-0.76)	**<0.001**
Symptomatic DVT-PE	217 (21.8%)	378 (16.3%)	0.7 (0.58-0.84)	**<0.001**
For patients with only DVT				
Proximal DVT	250 (25.1%)	603 (26.0%)	1.05 (0.88-1.2)	**0.309**
Upper-extremity DVT	67 (6.7%)	134 (5.8%)	0.85 (0.63-1.1)	**0.302**
For patients with PE,				
SBP <100 mm Hg	144 (14.5%)	230 (9.9%)	0.6 (0.5-0.8)	**<0.001**
Arterial PO2 <60 mm Hg	135 (13.6%)	381 (16.4%)	1.3 (1.04-17)	**0.011**
Initial therapy				
LMWH	458 (46 %)	1047 (45.1%)	1,1 (0.7-1,6)	**0.64**
UFH	37 (3.7%)	99 (4.3%)	0.85 (0,6-1,3)	**0.43**
Thrombolytics	4 (0.4%)	4 (0.4%)	2,3 (0.6-9,3)	**0.25**
Inferior vena cava filter	38 (3.8%)	89 (3.8%)	1,06(0.7-1,5)	**0.53**
Long-term therapy				
LMWH	142 (14.3%)	311 (13.4%)	1,1 (0.8-1,4)	**0.43**
AVK drugs	348 (34.9%)	842 836.3%)	0.9 (0,7-1,14)	**0.40**
3-month outcome				
Major bleeding	32 (3.2%)	85 (3.7%)	1,1 (0,7-1,7)	**0.29**
Fatal bleeding	20 (2.0%)	22 (0.9%)	0.5 (0.25-0.8)	**0.012**
Recurrent DVT	49 (4,9%)	89 (3,8%)	0.7 (0.5 – 1.1)	**0.156**
Recurrent PE	37 (3.7%)	58 (2.5%)	0.66 (0.4-1.01)	**0.038**
Fatal PE	48 (4.8%)	50 2.2%)	0.4 (0.29-0.65)	**<0.001**
Overall death	435 (44%)	606 (26%)	0.5 (0.4-0.5)	**<0.001**

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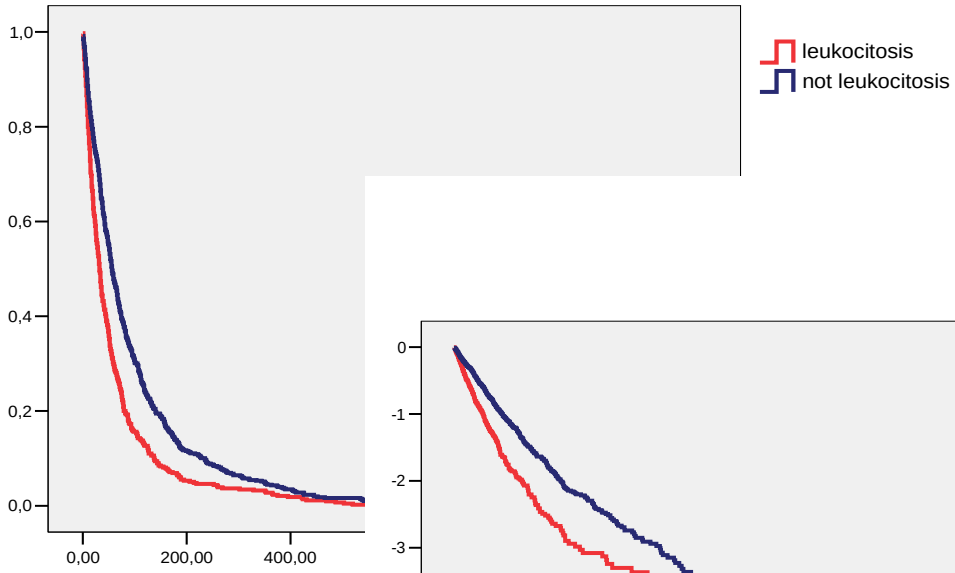
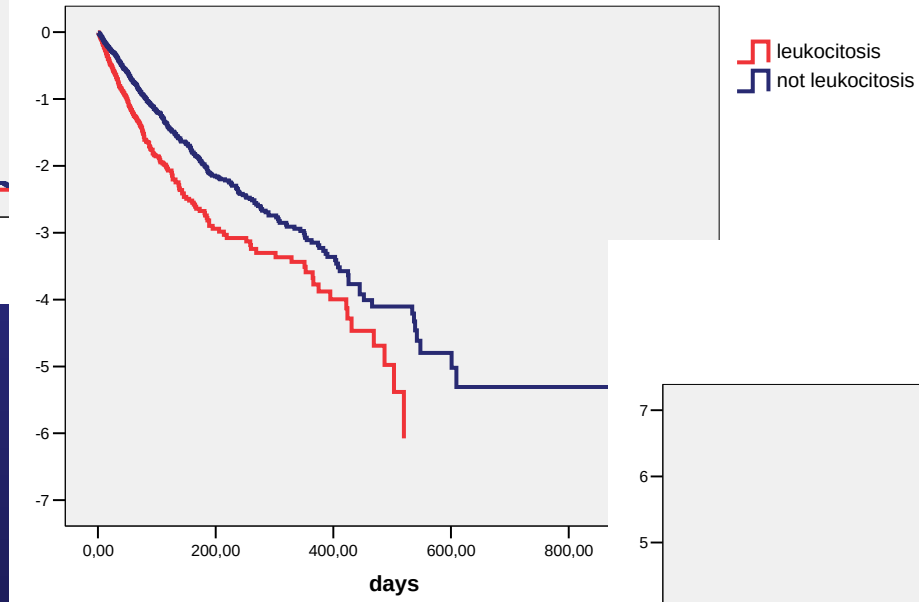
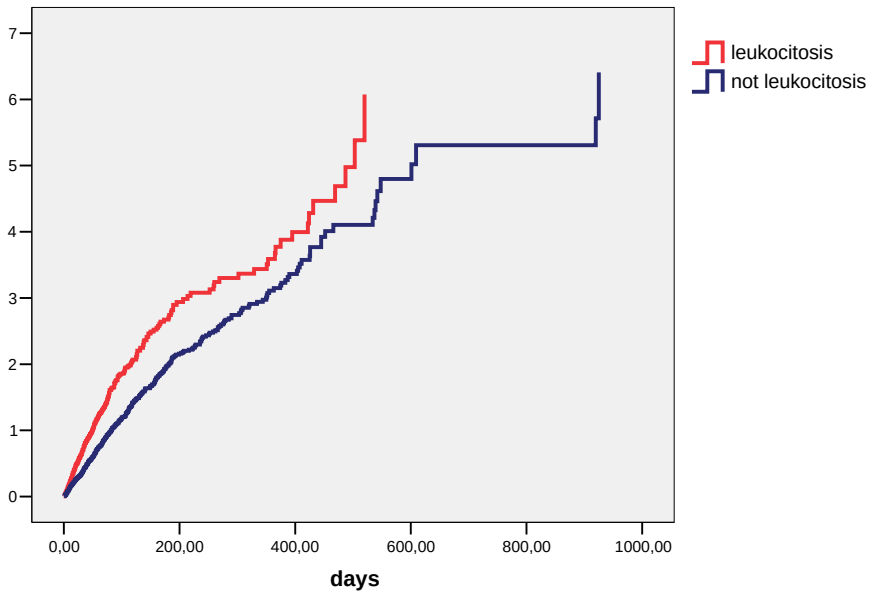
VTE, cancer, leukocytosis and death

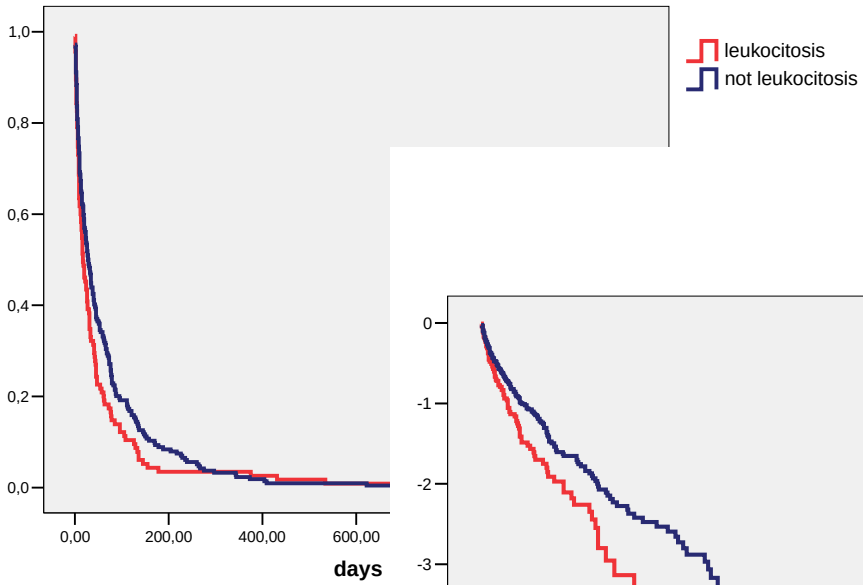


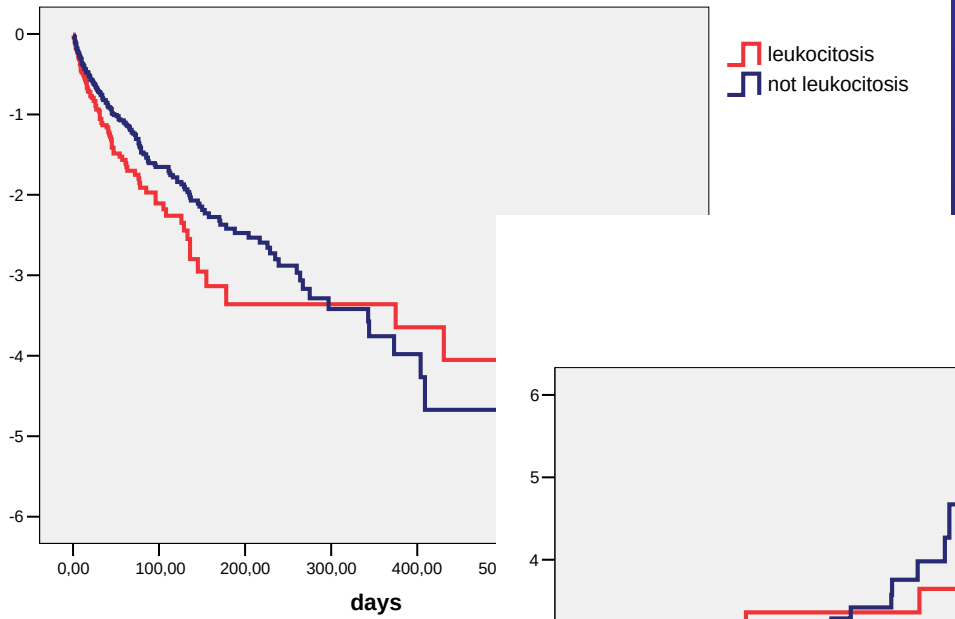


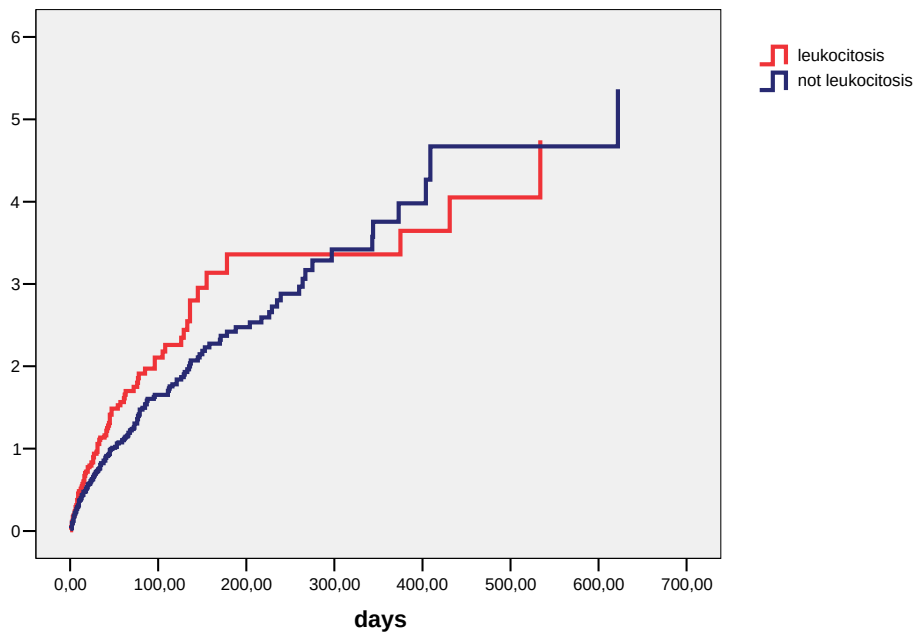


RIETE follow up 90 days from VTE diagnosis

VTE, cancer, leukocytosis and bleeding

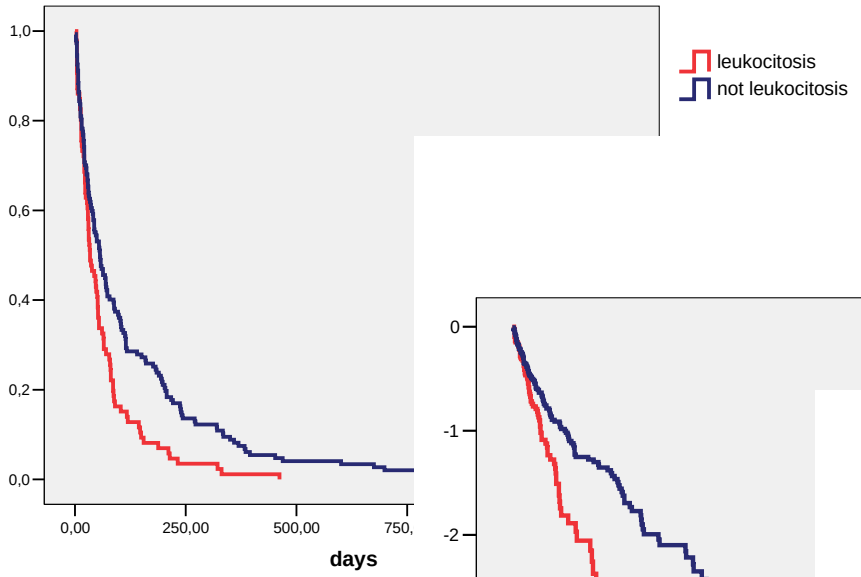


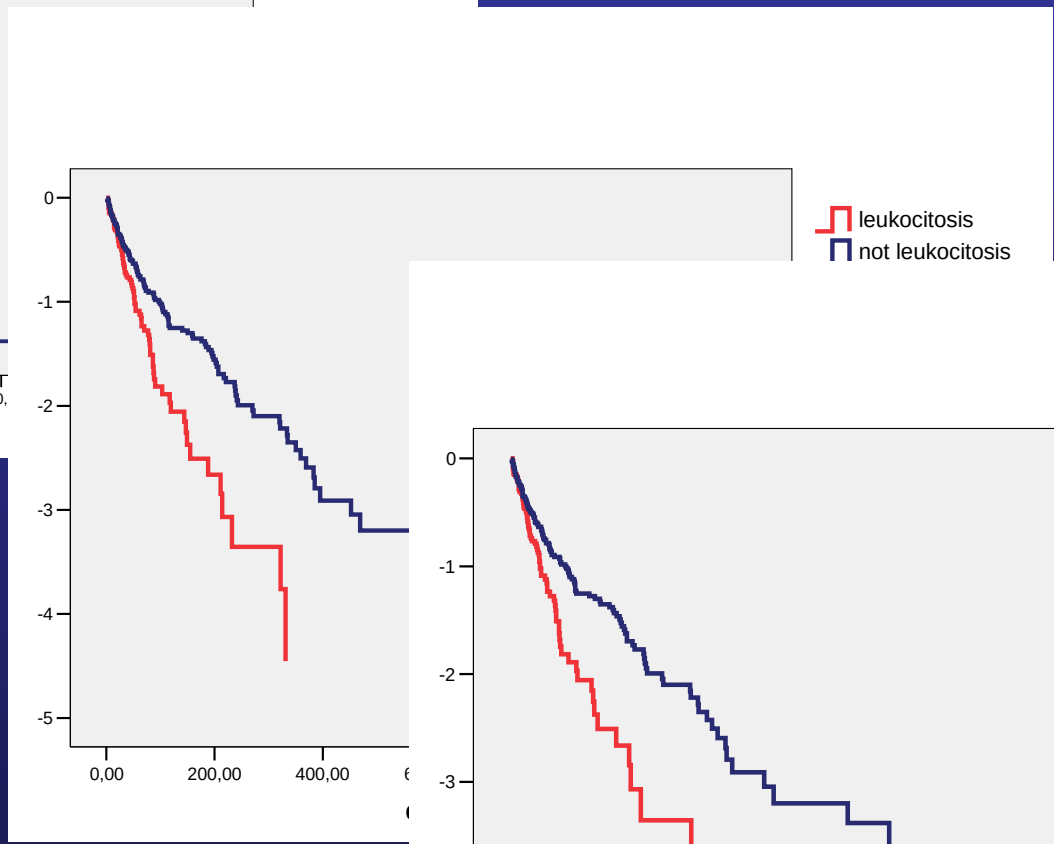


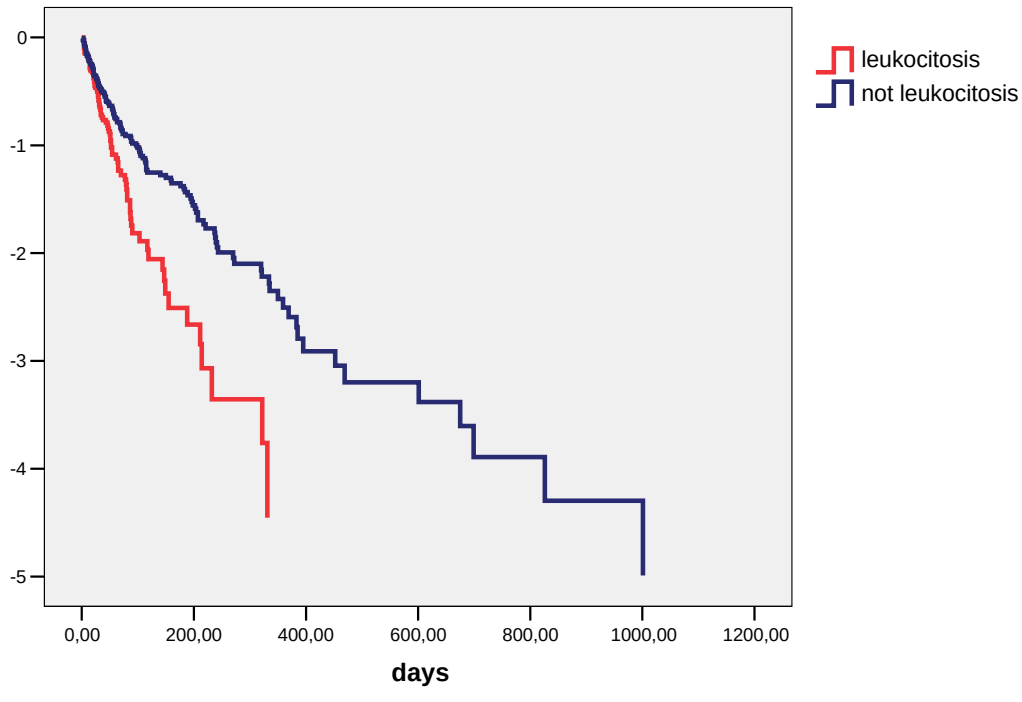


RIETE follow up 90 days from VTE diagnosis

VTE, cancer, leukocytosis and VTE-recurrence







RIETE follow up 90 days from VTE diagnosis

Discussion

Currently we don't have prognostic methods for oncological patients with VTE that already shows worse prognosis after 1 yy (Levitan et al.)

No good results have been obtained by monitoring
-D-dimer
-INR

Data from RIETE seem to offer a new prospective point of view for these patients because the increased rate of complications within 3 months of follow up, related to VTE recurrence, bleeding and overall death in presence of leukocytosis (> 11.000 mm cube) at the moment of VTE diagnosis in oncological patients

Discussion

Cancer patients with VTE and luekocytosis have an increased incidence of VTE recurrences, bleeding complications and death compared with those without cancer.
This poor outcome probably reflect the hypercoagulable state associated with cancer, the multiple comorbidities frequently present in these patients.
Limitations of data offered by RIETE may be related to the use drugs inducing increase of WBC (eg steroids, GCSF and so on)

Induced leukocytosis may induce a poor outcome of these patients and may be related to comorbidities (sepsis, local infection), to drugs administration or to be idiopathic

Identifying those clinical characteristics that put cancer patients with VTE at an increased risk for complications is important also to know or to improve their outcome.
This requires a better recognition of at-risk patients, so that any preventive strategies might be targeted to those who will benefit most also by further studies.