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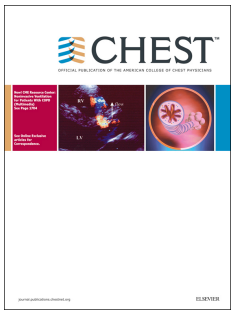

Development of a risk prediction score for occult cancer in patients with venous thromboembolism

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ABBREVIATION LIST

VTE= venous thromboembolism.

DVT= deep vein thrombosis.

PE= pulmonary embolism.

RIETE= Registro Informatizado de Enfermedad TromboEmbólica.

ABSTRACT

BACKGROUND: The benefits of a diagnostic workup for occult cancer in patients with venous thromboembolism (VTE) are controversial. Our aim was to provide and validate a risk score for occult cancer in VTE patients.

METHODS: We designed a nested case-control study within a cohort of VTE patients included in the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry from 2001-2014. Cases: cancer detected beyond the first 30 days after VTE and up for 24 months. Controls: VTE patients with no cancer in the same period.

RESULTS: Of 5,863 eligible patients, 444 (7.6%; (95%CI: 6.8 to 8.2%) were diagnosed with occult cancer. On multivariable analysis, variables selected were: male gender, age>70 years, chronic lung disease, anaemia, raised platelet count, prior VTE and recent surgery. We built a risk score assigning points to each variable. Internal validity was confirmed using bootstrap analysis. Proportion of patients scoring ≤2 points who had cancer was 5.8% (241/4,150) and in those scoring ≥3 points of 12% (203/1,713). We also identified score dividing by gender and age subgroups.

CONCLUSIONS: This is the first risk score that identified VTE patients at increased risk for occult cancer. Our score needs to be externally validated.

KEYWORDS: Neoplasm; Venous thromboembolism; Screening; Pulmonary embolism; Risk.

Introduction

The association between venous thromboembolism (VTE) and cancer has been frequently observed. Although usually developing in advanced stages of the disease, VTE may also appear before the cancer has become symptomatic and may lead to an early diagnosis of cancer.[1-2] One clinical implication of a high risk of occult cancer in patients with acute VTE could be an extensive diagnostic workup at the time of presentation. The usefulness and extension of such screening has been long debated: while several investigators advise only a basic screening including a thorough clinical history, physical examination, simple laboratory tests and a chest X-ray,[3-6] others advocated a more extensive workup.[7-9] From a theoretical point of view, early discovery of cancer should improve the potential for cure, not merely advance the date of diagnosis. However, the potential benefits and harms of such screening are controversial, partly because there is little evidence on what patients should be investigated and what cancer sites should be screened for.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia and Switzerland) observational registry of consecutive patients with objectively confirmed acute VTE. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for such outcomes.[10-13] In the current study, we assessed the most common sites of occult cancer according to age and gender, and built a

prognostic score that might help clinicians to select the most appropriate workup for each patient.

Patients and methods

Inclusion criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements (Authorization of clinical research ethics committee Germans Trias i Pujol and Institut Catalá de la Salud. 05122006).

Physicians participating in the RIETE registry ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits

to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study design

We performed a nested case control study within a cohort of VTE patients included in the RIETE Registry.[14] For diagnosing cancer, tissue biopsy was always required. Patients diagnosed with cancer beyond the first 30 days after VTE were identified as cases, and those with no cancer detected during the first two years after VTE were identified as controls. We assessed the most common sites of cancer according to gender and age subgroups. Then, we compared their clinical characteristics and built a prognostic score aimed to identify those patients at increased risk for occult cancer.

Baseline variables

Patients enrolled in the RIETE registry had data collected from around the time of VTE diagnosis that included but was not limited to: age; sex; weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days before VTE) major bleeding; presence of risk factors for VTE, including recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for >4 days in the 2 months before VTE diagnosis); surgery (defined as those who had undergone major surgery in the 2 months before VTE); extent of the venous thrombosis (distal thrombosis was thrombosis confined to the infra-popliteal veins); clinical signs and symptoms on admission, including heart rate and systolic blood pressure; and laboratory results at baseline that included

haemoglobin levels, platelet count, and serum creatinine at baseline. Creatinine clearance levels were measured according to the Cockcroft and Gault formula.[15] Anemia was defined as hemoglobin levels<13 g/dL for men and <12 g/dL for women.

Treatment and Follow-up

Patients were managed according to the current clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose, and duration of anticoagulant therapy were recorded. In order to compare adequately both subgroups, we selected only patients with 24 months follow up. During each visit, any signs or symptoms suggesting cancer, symptomatic VTE or major bleeding was noted. In patients with suspected malignancy, the attending doctors decided what diagnostic tests to be performed.

Statistical analysis

We used Student's t test and X^2 test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. Then, we carried out a multivariable analysis through a logistic regression model using the Wald method (step back) trying to identify independent predictors for the occurrence of cancer detected beyond the first 30 days of VTE. Covariates entering in the model were selected by a significance level of p <0.20 on univariable analysis, or by a well–known association reported in the literature. Then, we built a prognostic score assigning points to each independent variable according to regression coefficients β, rounding to the nearest integer. We assigned a risk score to each patient by adding

up points for each independent variable. Performance was quantified in terms of calibration, using the Hosmer-Lemeshow test.[16] Model discrimination was assessed using the C-statistic. Internal validity of the score was confirmed using bootstrap analysis.[17] For the statistical analysis we used the IBM SPSS Statistics program (version 19; SPSS Inc., Chicago, IL), and a two-sided $p<0.05$ was considered to be statistically significant.

Results

As of June 2014, 52,289 patients with acute VTE were enrolled in RIETE. Of these, 9,114 (17%) had previously known cancer and 1,845 (3.5%) were diagnosed with cancer within the first 30 days after VTE (Figure 1). Of the remaining 41,330 patients, 5,863(14%) were followed-up for 24 months. Half of them (51%) were women, and their mean age was 63±18 years. One in every three such patients (33%) initially presented with PE, 18% with DVT and PE concomitantly, and 48% presented with DVT alone. In all, 444 patients (7.6%; 95%CI: 6.90%-8.28%) were diagnosed with cancer beyond the first 30 days (occult cancer) and 5,419 were not (controls).

Patients with occult cancer were most likely male, significantly older, weighed less, most likely had chronic lung disease, raised platelet count or anaemia, but less likely had prior VTE, recent surgery, hormonal use or varicose veins than those with no cancer (Table 1). On multivariable analysis, male gender, age >70 years, chronic lung disease, raised platelet count (≥350,000x1000/mm^3), anaemia, prior VTE and recent surgery were independently associated with the risk for occult

cancer (Table 2). Using these variables, we built a prognostic score assigning one point to male gender, chronic lung disease or raised platelet count, two points to age >70 years or anaemia and two negative points to postoperative VTE or prior VTE. C-statistic was 0.64 (95% CI, 0.61-0.66). The proportion of patients scoring ≤2 points with occult cancer was 5.8% (241 of 4150), and 12%in those scoring ≥3 points (203 of 1713). The cumulative incidence of occult cancer in patients scoring ≤2 points was significantly lower than in those scoring ≥3 points (Figure 2),

The proportion of patients with occult cancer progressively increased with age, from 3.5% (in men) and 2.4% (in women) among those aged <50 years to 12% and 8.8%, respectively in those aged >70 years (Table 3). Among 246 men with occult cancer, the most frequent sites were the lung (26%), prostate (17%) and colorectal (10%). Among 198 women with occult cancer, the most common sites were colorectal (19%), breast (12%), uterine (9.1%), hematologic (8.6%), pancreas (7.6%) and stomach (6.1%). We compared score ≤2 vs. ≥3 attending sex and age subgroups (Table 4).

Discussion

Our study, obtained from a large series of consecutive patients with acute VTE, reveals that one in every 12 (7.6%; 95% CI: 6.8-8.2%) patients with unknown cancer at baseline was diagnosed with cancer beyond the first 30 days after VTE. The amount of patients with occult cancer in our series is consistent with that reported in previous studies.[3,10,18,19] Most of the occult cancers were detected within the first 6 months after VTE diagnosis, as also reported.[10,17-21] Recently,

Carrier et al.[10] found a lower proportion of patients with occult cancer (3.9%; 95%CI: 2.8-5.4%), but their mean age was lower than in our study (54 vs. 63 years old).If we only would consider young patients in our series, the proportion of them with occult cancer would also be lower.

We found that some variables easily available at baseline may help to identify patients at increased risk for occult cancer. Most studies in the literature found occult cancer to be more likely in patients with unprovoked VTE. In our study, occult cancer was less likely to appear in patients with recent surgery, use of hormonal treatment or leg varicosities, but not in those with recent immobility. This is important since most studies on the risk for occult cancer considered only patients with unprovoked VTE, and thus did not consider patients with recent immobility as potential candidates for screening for occult cancer. Additionally, we found that some non-previously reported variables (male gender and chronic lung disease) may also influence the risk of having an occult cancer, and some variables (anaemia[22] or raised platelet count[23]) have been identified in other works.

We identified the most common sites of cancer according to the patient's age and gender. One in every two men with occult cancer (54%) had either lung, prostate or colorectal cancer. Two in every three women with occult cancer had colorectal, breast or abdominal cancer. These data agree with what has been previously reported.[18,24] This is important because screening is not necessary in all VTE patients, but any information suggesting what patients are at increased risk and what cancer sites are more common may be of help to decide the most appropriate workup for each individual patient. Our score could be useful in patients with a low

scoring, because they could avoid discomfort in unnecessary complementary tools and psychological impact looking for cancer. On the other hand, patients scoring high could obtain benefit from a guided screening according to the patient's age and gender.

Recommendations to screen for occult cancer in patients with VTE are not different from the suggestions and/or recommendations issued by most national and international guidelines for the whole population.[24-35] On this way, in patients with anaemia rectal exam and testing for occult blood in faeces should be done, and women with an average risk of breast cancer should undergo regular screening mammography beginning at age 45 years. [35] But according to our data, we suggest that most men with VTE scoring ≥3 points may benefit from a rectal exam, PSA levels, testing for occult blood in faeces and a chest CT-scan, to rule out prostate, lung and/or colorectal cancer. If negative, those aged >50 years might also benefit from an abdominopelvic CT-scan (to rule out pancreatic, bladder, kidney or other tumours). As for women, those scoring ≥3 points may potentially benefit from faecal occult blood testing, a mammography and an abdominopelvic CT-scan.

Evidence from large randomized trials has consistently found reduction in mortality due to colorectal cancer screening using fecal occult-blood tests,[25-30] obtaining an average reduction in mortality of 12% in meta-analyses.[31] Screening for prostate cancer is more controversial. Guidelines do not recommend screening in men aged over 70-75 years old but in those aged 55 to 69 the decision involves weighing the benefits of preventing prostate cancer mortality against the potential harms

associated with screening and treatment.[32-34] Considering breast cancer, a number of randomized trials have shown that mammography screening may reduce breast cancer mortality by 25-30% after 7 to 12 years from entry in the trials.[36, 37] Usefulness of tumor markers is also controversial, because determination of tumor markers did not seem to be cost-effective and is accompanied by a high rate of false-positive results.[21] However, among patients with VTE the prevalence of occult cancer is higher than in those without VTE,[18] and thus the benefits of looking for occult cancer might be higher.

There are a number of limitations in the present study. First, this study was a retrospective analysis of patients that were recruited consecutively, thereby subject to possible selection bias. Second, most patients in RIETE were followed-up for less than 12 months, particularly from 2001 to 2009. In fact, only 12% of patients with no cancer at VTE presentation were included in this study. However, the proportion of patients presenting later with occult cancer and the most common sites of cancer agree with those reported in previous studies. Third, the area under the curve of our prognostic score was mild (0.64; 95%CI: 0.61-0.66). Fourth, we found an association between chronic lung disease and occult cancer. Chronic lung disease is a surrogate for smoking, and smoking has been recently associated with an increased risk for occult cancer in patients with VTE.[19] Hence, the higher risk for occult cancer in patients with chronic lung disease might likely be related to tobacco consumption. Unfortunately, we do not gather information on tobacco consumption in RIETE. Fifth, external validation of score is crucial, and will

let us optimizing screening through personalized work-up, as National Cancer Institute-funded consortium propose.[38]

Conclusions

This is the first risk score to identify what patients with acute VTE are at an increased risk for occult cancer (develop and internal validity). With this study we select a target population as the first step in the screening process, as National Cancer Institute-funded consortium propose. This score can be used easily in global terms or distinguish by sex or age subgroups. However, these results should be externally validated.

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Table 1. Clinical characteristics of patients with vs. without occult cancer.

	Occult cancer	No cancer	OR (95%CI)	p
Patients, n	***444***	***5,419***		
Clinical characteristics,				
Gender (male), n (%)	246 (55)	2,644 (49)	1.30 (1.07-1.58)	0.007
Age > 70 years, n (%)	265 (60)	2,355 (43)	1.93 (1.58-2.35)	<0.001
Weight (kg), mean (SD)	73.9 (14)	76.5 (15)	1.33 (1.04-3.97)	0.001
BMI, mean (SD)	27.6 (4.8)	28.5 (5.2)	0.31 (0.36-1.56)	0.002
Co-morbid diseases, n (%)				
Chronic lung disease	74 (17)	568 (10)	1.71 (1.31-2.23)	<0.001
Chronic heart failure	30 (6.8)	314 (5.8)	1.18 (0.80-1.74)	0.407
Recent major bleeding	9 (2.0)	94 (1.7)	1.17 (0.59-2.34)	0.652
Laboratory findings, n (%)				
Anaemia	154 (35)	1,315 (24)	1.66 (1.35-2.03)	<0.001
Leucocytes >11,000 x 1,000/mm^3	123 (28)	1,321 (24)	1.19 (0.96-1.48)	0.118
Platelet count ≥350,000 x 1,000/mm^3	55 (12)	509 (9.4)	1.36 (1.01-1.83)	0.040
Raised fibrinogen levels	27 (39)	1,029 (41)	0.89 (0.55-1.45)	0.642
Positive D-dimer levels	75 (68)	2,199 (66)	1.09 (0.34-3.52)	0.922
Initial VTE presentation, n (%)				
• DVT	219 (49)	2625 (48)	1	
• Pulmonary embolism	142 (32)	1800 (33)	0.95 (0.76-1.18)	0.868
• DVT / pulmonary embolism	83 (19)	994 (18)	1.01(0.77-1.30)	
Proximal DVT	257 (84)	3113 (86)	0.86 (0.62-1.19)	0.359
Bilateral DVT	20 (6.2)	156 (4.1)	1.54 (0.95-2.49)	0.108
Upper extremity DVT	6 (1.4)	137 (2.5)	0.46 (0.20-1.08)	0.161
Risk factors for VTE, n (%)				
Recent surgery	28 (6.3)	564 (10)	0.58 (0.39-0.86)	0.006
Recent immobility ≥4 days	90 (20)	1094 (20)	1.01 (0.79-1.28)	0.967
Hormonal therapy	8 (1.8)	324 (6.1)	0.29 (0.14-0.58)	<0.001
Recent travel	8 (1.8)	142 (2.7)	0.68 (0.33-1.40)	0.297
Pregnancy/ puerperium	112 (2.1)	0	-	-
None of the above (unprovoked)	310 (70)	3356 (62)	1.42 (1.15-1.75)	0.001
Varicose veins	77 (18)	1182 (22)	0.77 (0.60-0.99)	0.045
Prior VTE	62 (14)	1036 (19)	0.69 (0.52-0.91)	0.007

Abbreviations: OR, odd ratio; CI, confidence Interval; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; DVT, deep vein thrombosis.

Table 2. Multivariable analysis and score to identify patients with increased risk for occult cancer.

	β	Odds ratio	95% CI Lower	95% CI Upper	*p*	**Points**
Underlying conditions						
Male gender	.378	1.46	1.19	1.79	<0.001	**+1**
Age >70 years	.642	1.90	1.55	2.33	<0.001	**+2**
Chronic lung disease	.338	1.40	1.07	1.84	.015	**+1**
Anaemia	.539	1.71	1.38	2.13	<0.001	**+2**
Platelets $\geq 350x10^6/mm^3$	.334	1.40	1.03	1.90	.034	**+1**
Risk factors for VTE						
Postoperative	-.722	.49	.32	.73	<0.001	**-2**
Prior VTE	-.392	.68	.51	.89	.006	**-1**

Hosmer-Lemeshow test: χ^2=4.33,degree of freedom (df):8, p=0.826.
C-statistic: 0.64 (95% CI, 0.61-0.66)
List of variables included in the multivariable regression analysis: age >70 years, body mass index, chronic lung disease, platelet count ≥350,000 x 1000/mm, anaemia, recent surgery, hormonal therapy, unprovoked, varicose veins, prior VTE.
Anaemia was defined as: Haemoglobin levels <12 g/dL in women, <13 g/dL in men.
Abbreviations: CI, confidence intervals; DVT, deep vein thrombosis; VTE, venous thromboembolism.

Table 3. Sites of occult cancer according to sex and age subgroups.

Site of cancer	Total	<50 years	50-70 years	>70 years
Men, all patients	***2,890***	***662***	***1,057***	***1,171***
Men, occult cancer, n (%)	***246 (8.51)***	***23 (3.47)***	***81 (7.66)***	***142 (12.1)***
Lung	63 (2.18)	8 (1.21)	21 (1.99)	34 (2.90)
Prostate	42 (1.45)	1 (0.15)	13 (1.23)	28 (2.39)
Colorectal	29 (1.00)	1 (0.15)	7 (0.66)	21 (1.79)
Bladder	17 (0.59)	0	5 (0.47)	12 (1.02)
Hematologic	13 (0.45)	4 (0.60)	5 (0.47)	4 (0.34)
Stomach	12 (0.42)	0	2 (0.19)	10 (0.85)
Unknown origin	12 (0.42)	0	6 (0.57)	6 (0.51)
Kidney	9 (0.31)	0	5 (0.47)	4 (0.34)
Brain	8 (0.28)	5 (0.76)	1 (0.09)	2 (0.17)
Billiard tract	8 (0.28)	1 (0.60)	2 (0.19)	5 (0.43)
Liver	6 (0.21)	1 (0.60)	3 (0.28)	2 (0.17)
Pancreas	5 (0.17)	0	1 (0.09)	4 (0.34)
Oral/pharyngeal /Larynx	5 (0.17)	0	2 (0.19)	3 (0.26)
Oesophagus	4 (0.14)	0	2 (0.19)	2 (0.17)
Other	13 (0.45)	2 (0.30)	6 (0.57)	5 (0.43)
Site of cancer	**Total**	**<50 years**	**50-70 years**	**>70 years**
Women, all patients	***2,973***	***695***	***679***	***1,599***
Women, occult cancer, n (%)	***198 (6.66)***	***17 (2.45)***	***40 (5.89)***	***141 (8.82)***
Colorectal	38 (1.28)	3 (0.43)	6 (0.88)	29 (1.81)
Breast	23 (0.77)	1 (0.14)	6 (0.88)	16 (1.00)
Uterus	18 (0.61)	3 (0.43)	2 (0.29)	13 (0.81)
Hematologic	17 (0.57)	0	3 (0.44)	14 (0.88)
Unknown origin	15 (0.50)	1 (0.14)	2 (0.29)	12 (0.75)
Pancreas	15 (0.50)	0	3 (0.44)	12 (0.75)
Stomach	12 (0.40)	0	2 (0.29)	10 (0.63)
Ovary	12 (0.40)	3 (0.43)	6 (0.88)	3 (0.19)
Lung	9 (0.30)	3 (0.43)	1 (0.15)	5 (0.31)
Bladder	9 (0.30)	0	1 (0.15)	8 (0.50)
Kidney	8 (0.27)	1 (0.14)	3 (0.44)	4 (0.25)
Brain	5 (0.17)	0	2 (0.29)	3 (0.19)
Billiard tract	4 (0.13)	0	0	4 (0.25)
Other	13 (0.44)	2 (0.29)	3 (0.44)	8 (0.50)

Table 4. Incidence of occult cancer according to sex, age subgroups and scoring.

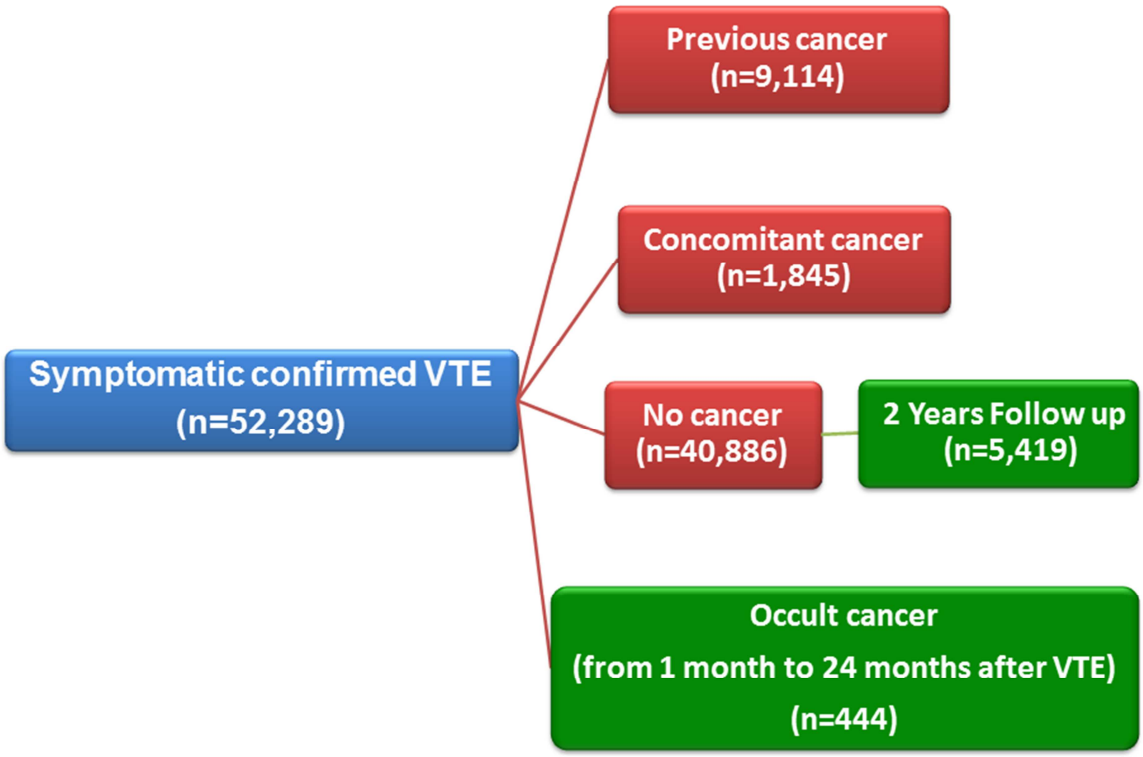
	Men	Women
<50 years	**23/662 (3.5%; 95%CI: 2.2% to 5.2%)***	**17/695 (2.4%; 95%CI: 1.3% to 3.9%)***
≤2 points	18/590 (3.1%; 95%CI: 1.8% to 4.8%)	13/668 (1.9%; 95%CI: 1.0 to 3.3%)
≥3 points	5/72 (6.9%; 95%CI: 2.3% to 15.5%)	4/27 (14.8%; 95%CI: 4.2% to 33.7%)
50-70 years	**81/1,057 (7.7%; 6.1% to 9.4%)***	**40/679 (5.9%; 4.2-7.9%)**
≤2 points	60/923 (6.5%; 95%CI: 5.0% to 8.3%)	37/652 (5.7%; 95%CI: 4.0 to 7.7%)
≥3 points	21/134 (15.7%; 95%CI: 10% to 23%)	3/27 (11.1%; 95%CI: 2.4 to 29.1%)
>70 years	**142/1171 (12.1%; 95%CI: 10.3 to 14.1%)***	**141/1599 (8.8%; 95%CI: 7.5 to 10.3%)**
≤2 points	19/222 (8.6%; 95%CI: 5.2% to 13%)	94/1095 (8.6%; 95%CI: 7.0 to 10.4%)
≥3 points	123/949 (13%; 95%CI: 10.9% to15.2%)	47/504 (9.3%; 95%CI: 6.9% to 12.2%)

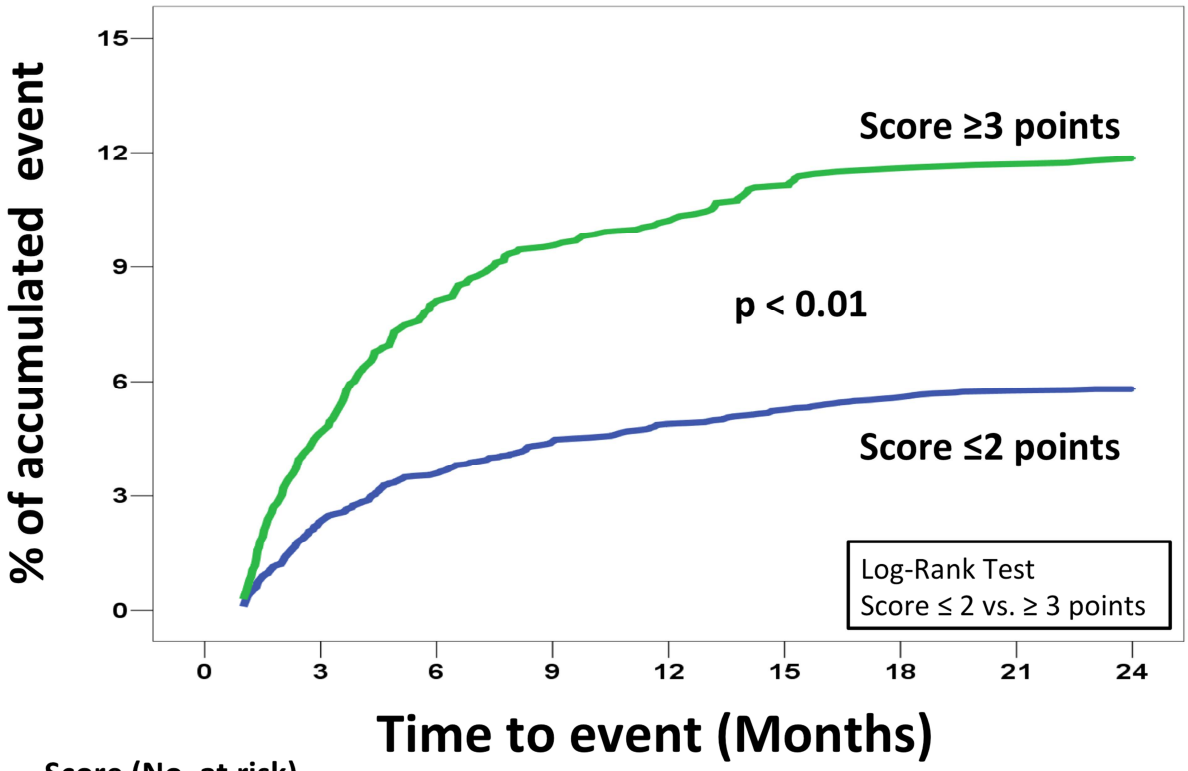
95%CI: 95 % confidence interval, two-tailed exact Clopper-Pearson.
* $p < 0.05$ when we compared score ≤2 vs. ≥3 points, attending sex and age subgroups. We used X^2 test (or Fisher's exact test when appropriate) to compare categorical variables.

Figure legends

Figure 1. Flowchart patients.

Figure 2. Cumulative incidence of occult cancer over 2 years attending score (≤2 vs. ≥3 points). Time-to-event data.


Previous cancer
(n=9,114)
Concomitant cancer
(n=1,845)
Symptomatic confirmed VTE
(n=52,289)
No cancer
(n=40,886)
2 Years Follow up
(n=5,419)
Occult cancer
(from 1 month to 24 months after VTE)
(n=444)



Score (No. at risk)								
≤ 2 points (n= 4,150)	4,053	4,001	3,967	3,947	3,933	3,919	3,911	3,909
≥ 3 points (n= 1,714)	1,634	1,575	1,551	1,539	1,524	1,516	1,514	1,511