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ORIGINAL ARTICLE

Risk scores for occult cancer in patients with unprovoked venous thromboembolism: Results from an individual patient data meta-analysis

Frits I. Mulder[1,2] | Marc Carrier[3] | Frederiek van Doormaal[1] | Philippe Robin[4] | Hans-Martin Otten[5] | Pierre-Yves Salaun[4] | Harry R. Büller[1] | Grégoire Le Gal[3,6] | Nick van Es[1]

[1]Department of Vascular Medicine, Amsterdam University Medical Centers, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

[2]Department of Internal Medicine, Tergooi Hospitals, Hilversum, The Netherlands

[3]Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada

[4]Service de Médecine Nucléaire, Centre Hospitalier Régional et Universitaire de Brest, EA 3878 (GETBO), Université de Bretagne Occidentale, Brest, France

[5]Department of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands

[6]Département de Médecine Interne et Pneumologie, Centre Hospitalier Régional et Universitaire de Brest, Université de Bretagne Occidentale, Brest, France

Correspondence
Frits I. Mulder, Department of Vascular Medicine, Amsterdam Cardiovascular Science, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: f.i.mulder@amsterdamumc.nl

Abstract

Background: The Registro Informatizado de Pacientes con Enfermedad TromboEmbólica (RIETE) score and the Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) risk scores aim to identify patients with acute unprovoked venous thromboembolism (VTE) at high risk of occult cancer, but their predictive performance is unclear.

Methods: The scores were evaluated in an individual patient data meta-analysis. Studies were eligible if enrolling consecutive adults with unprovoked VTE who underwent protocol-mandated screening for cancer. The primary outcome was a cancer diagnosis between 30 days and 2 years of follow-up. The discriminatory performance was evaluated by computing the area under the receiver (ROC) curve in random-effects meta-analyses.

Results: The RIETE score could be calculated in 1753 patients, of whom 63 (3.6%) were diagnosed with cancer. The pooled area under the ROC curve was 0.59 (95% confidence interval [CI], 0.52-0.66; $I^2 = 0\%$). Of the 427 patients (24%) classified as high risk, 25 (5.9%) were diagnosed with cancer compared with 38 of 1326 (2.9%) low-risk patients (hazard ratio [HR], 2.0; 95% CI, 1.3-3.4). The SOME score was calculated in 925 patients, of whom 37 (4.0%) were diagnosed with cancer. The pooled area under the ROC curve was 0.56 (95% CI, 0.46-0.65; $I^2 = 46\%$). Of the 161 patients (17%) classified as high risk (≥2 points), eight (5.0%) were diagnosed with cancer compared with 29 of 764 (3.8%) low-risk patients (HR, 1.2; 95% CI, 0.55-2.7).

Conclusions: The predictive discriminatory performance of both scores is poor. When used dichotomously, the RIETE score is able to discriminate between low- and

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high-risk patients. Because this is largely driven by advanced age, these results do not support the use of these scores in daily clinical practice.

KEYWORDS

cancer, diagnosis, early detection of cancer, neoplasms, venous thromboembolism

1 | BACKGROUND

Venous thromboembolism (VTE), comprising pulmonary embolism and deep vein thrombosis, can be the first manifestation of cancer. The risk of a cancer diagnosis in the 12 months following unprovoked VTE is about 5%.[1] Therefore, current guidelines suggest to perform cancer screening in this group consisting of medical history, physical examination, limited laboratory investigations, chest X-ray, and age- and gender-specific testing.[2]

Several studies evaluated a more extensive cancer screening strategy, which can include computed tomography (CT) or fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scanning.[3-5] A systematic review and individual patient data meta-analysis showed that, compared with limited screening, such extensive screening is associated with a higher probability of cancer detection at initial screening (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.2-3.4) but not at 12 months (OR, 1.4; CI, 0.89-2.1).[1] Moreover, in none of the studies that compared both strategies, extensive screening led to a significant reduction of cancer-related mortality.[4-8] Two post hoc analyses of these studies also indicated that extensive screening may not be cost-effective.[9,10] Taken together, these observations indicate that routine use of extensive screening in all patients is not beneficial.

The clinical benefit of extensive screening may be increased by applying it only to patients at high risk for (occult) cancer. Therefore, the Registro Informatizado de Pacientes con Enfermedad TromboEmbólica (RIETE) score[11] and the Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) score[12] were recently introduced. International guidance statements calls for validation of these scores and subsequent evaluation of extensive screening strategies in high-risk patients.[2] Therefore, we aimed to evaluate the predictive performance of these risk scores in an individual patient data meta-analysis from prospective studies that evaluated cancer screening in patients with unprovoked VTE.

Essentials

- The RIETE and SOME scores aim to detect patients at risk of cancer after venous thromboembolism.
- We evaluated their predictive performance in an individual-patient data meta-analysis.
- The continuous predictive discriminatory performance of both scores is poor.
- When used dichotomously the RIETE score can discriminate between low- and high-risk patients.

2 | METHODS

For the present analysis, individual patient data were used from patients with objectively confirmed unprovoked VTE that were previously obtained in a systematic review (Table S1).[1] The design and detailed methods of this systematic review were reported previously.[1] Briefly, adults with unprovoked deep vein thrombosis or pulmonary embolism were enrolled in randomized controlled trials or prospective cohort studies evaluating protocol-mandated screening strategies for occult cancer. Patients were followed for at least 12 months for cancer diagnoses missed by the initial screening strategy.

2.1 | Study description

The definition of unprovoked VTE was consistent across studies. In general, the studies excluded patients if the index VTE was related to known cancer, recent surgery or immobilization, known thrombophilia, pregnancy or puerperium, or if it was a recurrent unprovoked event. Follow-up durations ranged between 1 and 3 years. Patients in whom VTE was not objectively confirmed and patients who were enrolled more than 90 days after the index VTE diagnosis were excluded from the dataset. Risk of bias assessment is shown in Tables S2 and S3. Detailed characteristics of the included studies and of their population are presented in Tables S4-S6.

2.2 | Prediction scores

Two clinical prediction scores for occult cancer in patients with VTE were evaluated: the RIETE score[11] and the SOME score.[12] We were unable to evaluate the risk score proposed by Ferreyro and colleagues[13] given that the Charlson Comorbidity Index was not routinely collected in any of the studies.

The RIETE score was derived in 5863 patients with provoked or unprovoked VTE who were enrolled in the international RIETE registry. The primary outcome was a cancer diagnosis between 30 days and 2 years of follow-up, hence excluding cancers diagnosed early

after the index VTE. The score comprises seven clinical items, which are assigned −2 to 2 points (Table 1). The range of the sum score is −3 to 7 points. Patients with a sum score of 2 points or less are classified as low risk and those with 3 points or more as high risk. In the present analysis, the item "chronic lung disease" was replaced by "current or former smoker" because information on chronic lung disease was not available in the majority of the included studies.

The SOME score was derived using data from a multicenter, randomized, controlled trial in Canada (SOME), which compared limited occult-cancer screening with extensive occult-cancer screening in 854 patients with unprovoked VTE.[5] In a post hoc analysis, three variables were identified as independent predictors of cancer over the 1-year follow-up period: age 60 years or older, current smoking, and previous provoked VTE. Because the adjusted hazard ratios (HR) for these three items were very similar (ie, 3.1, 2.8, and 3.2, respectively), a simple score was used by assigning 1 point to each item (Table 1), as suggested previously.[14] Patients with 2 or 3 points were classified as high risk and those with 0 or 1 point as low risk. The item "current smoker" was replaced by "current or former smoker" to enable calculation of the score in all studies. Data from the SOME study, which were included in the dataset, were not used for the evaluation of this score.

2.3 | Outcomes

The primary outcome was a confirmed cancer diagnosis between 30 days and 2 years of follow-up, identical to the outcome used in the derivation study of the RIETE score. This outcome predominantly captures cancers that are diagnosed after the initial screening period, while excluding cancers that are readily detected at initial presentation by limited screening tests, such as medical history, physical examination, or basic laboratory tests. A sensitivity analysis was performed for which the outcome was restricted to cancers that were detected by extensive screening tests or during follow-up, hence excluding all cancers detected by limited screening tests. Analyses were performed in the complete study group, as well as in the subgroup of patients of 50 years or older because the risk of a cancer diagnosis is higher in elderly patients.

TABLE 1 Risk prediction scores for occult cancer

RIETE Score	Points
Male	+1
Age older than 70 y	+2
Chronic lung disease	+1
Anemia[a]	+2
Platelet count 350 × 10^9/L or higher	+1
Previous venous thromboembolism	-1
Postoperative venous thromboembolism	-2
Classification	
Low risk	≤2
High risk	≥3
SOME score	**Points**
Age 60 y or older	+1
Current smoking	+1
Previous provoked venous thromboembolism	+1
Classification	
Low risk	≤1
High risk	≥2

[a]Hemoglobin concentration < 13 g/dL in males or < 12 g/dL in females.

2.4 | Analysis and statistical methods

Overall discrimination of the continuous RIETE and SOME scores was assessed by calculating the area under the receiver operating characteristic (ROC) curve in each study, with 95% confidence intervals (CI) computed with DeLong's method.[15] These estimates were transformed to the logit scale before meta-analysis to improve the validity of the underlying assumptions.[16,17] A two-stage random effects meta-analysis with inverse variance weighting was performed on the logit scale. The DerSimonian-Laird random effects model was used to obtain summary estimates.[17,18] Summary estimates obtained in meta-analysis were transformed back to the probability scale.

Because the follow-up durations varied across the studies, we also calculated the area under a time-dependent ROC curve at 365 days (the minimum follow-up duration) in each study, using the method proposed by Heagerty.[19] Standard errors were obtained using 500 bootstrap samples. Estimates were summarized in a two-stage meta-analysis in the same way as for the conventional area under the ROC curves.

The discriminatory performance of the dichotomized scores was evaluated by estimating a hazard ratio (HR) with 95% CI using a mixed-effects Cox regression model (ie, a frailty model). To account for the clustering of observations within studies, a random intercept was specified in the model for the study level. Patients were censored if they deceased without a preceding cancer diagnosis, were lost to follow-up, or were alive after 2 years. The conditional association between cancer and the various score items was evaluated in a multivariable mixed-effects Cox proportional hazards regression model. The proportionality assumption was checked by visual inspection of the log-minus-log survival plots.

Missing values were not imputed because the proportion of patients with a missing risk score appeared to be low (3%). A significance level of 0.05 was used in statistical testing. Statistical analyses were performed in R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org), using the *pROC*, *survivalROC*, *meta*, and *coxme* packages.

3 | RESULTS

The individual patient dataset comprised 2371 patients with unprovoked VTE from 10 studies. Patients enrolled in five of these studies

(N = 396) were excluded because no information of chronic lung disease or smoking was recorded. Two small studies (N = 90) were excluded because only one patient was diagnosed with cancer beyond 30 days, which was insufficient to analyze discrimination or perform multivariable analyses.

3.1 | Included studies

Data from the remaining three studies were used for the present analysis. The Trousseau study was a Dutch multicenter, nonrandomized, concurrently controlled trial between 2002 and 2007 in which participating centers applied limited screening or limited screening plus mammography and thoraco-abdominal CT scanning.[3] A total of 630 patients with unprovoked VTE were followed for a median of 2.5 years, during which 50 (7.9%) patients were diagnosed with cancer. Standard Diagnostic Procedures With or Without Fludeoxyglucose F 18 Positron Emission Tomography in Finding Cancer in Patients With a Blood Clot in a Vein (MVTEP) was a French multicenter, randomized controlled trial that randomly allocated 394 patients with unprovoked VTE to limited screening or limited screening plus a whole-body 18-FDG PET/CT-scan between 2009 and 2012.[4] Twenty-five patients (6.3%) were diagnosed with cancer in the 24-month follow-up period. SOME was a Canadian multicenter randomized controlled trial conducted between 2008 and 2014, in which 854 patients with unprovoked VTE were randomized to limited screening or to limited screening plus abdominopelvic CT scanning.[5] During the 12-month study period, 33 (3.9%) patients were diagnosed with cancer.

3.2 | Individual patient dataset

The individual patient dataset based on the three studies comprising 1878 patients, of whom 48 (2.6%) were excluded because they were enrolled more than 90 days after the VTE event or because the VTE was not objectively confirmed. All three studies were considered at low risk of bias in all domains (Table S2). The final dataset comprised 1830 patients who were enrolled after a median of 7 days (interquartile range [IQR], 2, 12) following the VTE diagnosis. During a median follow-up of 397 days (IQR, 361, 730), 98 patients (5.4%) were diagnosed with cancer, 33 (1.8%) were lost to follow-up, and 61 (3.3%) died. Sixty-four patients (3.5%) were diagnosed with cancer at the initial screening, of whom 16 (25%) were detected by extensive screening procedures, such as CT or ultrasonography of the abdomen or whole-body FDG PET/CT. Cancer was diagnosed in another 26 patients (1.4%) in the first 12 months and in 8 patients (0.4%) between 12 and 24 months. Cancer was diagnosed in 6 of 550 patients (1.1%) younger than 50 years and in 92 of 1280 patients (7.2%) age 50 years or older. Baseline characteristics of the patients in the final dataset are shown in Table 2.

TABLE 2 Baseline characteristics

	N = 1830
Age	
Mean, years (SD)	58 (15)
≥50 y, n (%)	1280 (70)
≥60 y, n (%)	837 (46)
>70 y, n (%)	424 (23)
Male sex, n (%)	1142 (62)
Index venous thromboembolism, n (%)	
PE with or without DVT	842 (46)
DVT only	988 (54)
Previous venous thromboembolism, n (%)	163 (8.9)
Unprovoked	46 (2.5)
Provoked	81 (4.4)
Unknown whether provoked	36 (2.0)
Anemia, n (%)	318 (17)
Missing	12 (0.7)
Platelet count ≥ 350×10^9/L, n (%)	210 (12)
Missing	20 (1.1)
Smoking, n (%)	
Current smoker	199 (11)
Current or former smoker[a]	281 (15)
Former smoker	387 (21)
Never smoked	934 (51)
Missing	29 (1.6)

[a]The Trousseau study did not distinguish between former or current smoking.[3]

3.3 | RIETE score

The RIETE score could be calculated for 1781 patients (97%), of whom 28 (1.6%) were excluded because they were diagnosed with cancer within 30 days. Of the remaining 1753 patients, 63 (3.6%) were diagnosed with cancer between 30 days and 2 years of follow-up. The median RIETE score was 2 points (IQR, 1, 2; range, −1 to 7). The most frequent items were male sex (N = 1089; 62%) and current or former smoking (N = 841; 48%), which was used a proxy for chronic lung disease. Because all VTE events were unprovoked, none of the patients were assigned points for postoperative venous thromboembolism.

The area under the ROC curve of the RIETE score, reflecting overall continuous discrimination, ranged from 0.59 (95% CI, 0.48-0.69) to 0.63 (95% CI, 0.42-0.81) across the three studies. The pooled area under the ROC curve was 0.59 (95% CI, 0.52-0.66; $I^2 = 0\%$), which was consistent with the pooled area under the time-dependent ROC curve at 365 days (0.59; 95% CI, 0.51-0.66; $I^2 = 0\%$).

The dichotomized RIETE score classified 427 patients (24%) as high risk (≥3 points) and 1326 patients (76%) as low risk (≤2 points). During a median follow-up of 398 days (IQR, 362, 730), cancer was diagnosed in 25 high-risk patients (5.9%) and in 38 low-risk patients

(2.9%), corresponding to an HR of 2.0 (95% CI, 1.3-3.4; Figure 1). The cancer types that occurred in the high-risk group are shown in Table S7. Among patients aged 50 years or older, the HR was 1.5 (95% CI, 0.87-2.5). In the multivariable analysis, only the item "age 70 years or older" was significantly associated with cancer (adjusted HR, 2.2; 95% CI, 1.3-3.8; Table S8).

In the sensitivity analysis in which the outcome was restricted to cancers detected either by extensive screening tests or during follow-up (N = 50), the pooled area under the ROC curve was 0.60 (95% CI, 0.51-0.68; I^2 = 0%) and the pooled HR for the dichotomous score was 2.6 (95% CI, 1.5-4.7).

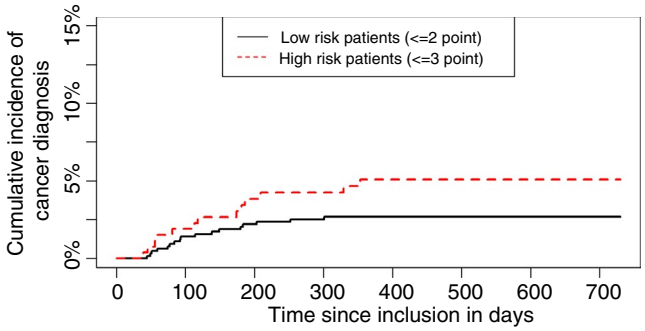

FIGURE 1 Risk of cancer diagnosis in low- and high-risk patients according to RIETE score

3.4 | SOME score

The SOME score could be calculated in 948 of 977 patients (97%) enrolled in the Trousseau and MVTEP studies. Twenty-three patients (2.4%) were diagnosed with cancer within 30 days and were excluded from this analysis. Of the remaining 925 patients, 37 (4.0%) were diagnosed with cancer between 30 days and 2 years of follow-up. The median SOME score was 1 point (IQR, 0, 1; range, 0-2). The most frequent item was "age 60 years or older" (N = 492; 53%).

The area under the ROC curve of the continuous SOME score was 0.60 (95% CI, 0.52-0.68) in the Trousseau study and 0.50 (95% CI, 0.38-0.62) in the MVTEP study. The pooled area under the ROC curve was 0.56 (95% CI, 0.46-0.65; I^2 = 46%). The pooled area under the time-dependent ROC curve at 365 days was 0.57 (95% CI, 0.49-0.65).

The dichotomized SOME score classified 161 patients as high risk (17%) and 764 patients (83%) as low risk. Over a median follow-up of 730 days (IQR, 638, 730), cancer was diagnosed in 8 (5.0%) high-risk patients and 29 low-risk patients (3.8%), corresponding to a pooled HR of 1.2 (95% CI, 0.55-2.7; Figure 2). The cancer types that occurred in the high-risk group are shown in Table S7. Among patients of 50 years or older, the HR was 0.95 (95% CI, 0.43-2.1). In the multivariable analysis, only "age of 60 years or older" was significantly associated with a cancer diagnosis between 30 days and 2 years of follow-up (adjusted HR 2.5; 95% CI, 1.2-5.2; Table S9).

Results of the sensitivity analysis, in which the outcome was restricted to cancers detected either by extensive screening tests or during follow-up (N = 29), were comparable to the main analysis; the pooled area under the ROC curve was 0.55 (95% CI, 0.40-0.69) and the pooled HR for the dichotomous score was 1.1 (95% CI, 0.44-2.5).

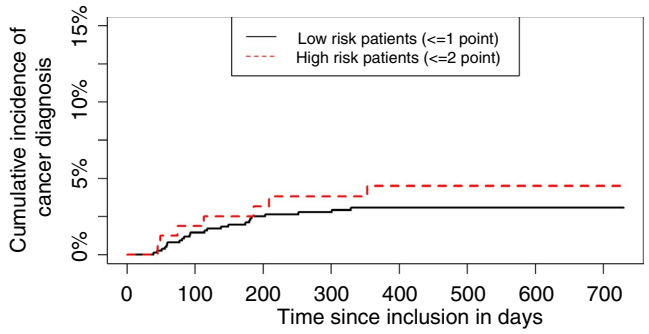

FIGURE 2 Risk of cancer diagnosis in low- and high-risk patients according to SOME score

4 | DISCUSSION

The present individual patient data meta-analysis combined data of three prospective studies with a low risk of bias to evaluate the predictive performance of the RIETE and SOME scores for occult cancer in patients with unprovoked VTE. The pooled area under the ROC curve was 0.59 for the continuous RIETE score and 0.56 for the SOME score, indicating modest discrimination. When used dichotomously, the RIETE score was able to distinguish between low-risk and high-risk patients (HR 2.0; 95% CI, 1.3-3.4), but not the SOME score (HR 1.2; 95% CI, 0.55-2.7). Discriminatory performance was lower in patients aged 50 years or older.

Strengths of this study include the availability of patient-level data from large, prospective, multicenter trials, allowing for detailed evaluation of the scores including time-to-event and subgroup analyses. The proportion of patients in whom the scores could not be calculated was low (3%). Because the included trials enrolled patients in both secondary and tertiary centers, we believe that the current findings are representative of daily clinical practice. Several limitations also need to be acknowledged. We were unable to include only three of 10 available studies because either the scores could not be calculated or the number of events was too few for the analyses. The included studies varied in extensive screening strategies and follow-up duration. The low I^2 in most analyses indicated little between-study heterogeneity, but it has to be noted that this test is less powerful when only a few studies are meta-analyzed.

Discrimination of the RIETE score was lower in the present study (pooled area under the ROC curve, 0.59) than in the derivation study (0.64),[11] despite using the same outcome definition by excluding cancers diagnosed in the first 30 days after unprovoked VTE. A sensitivity analysis based on cancers missed by limited screening yielded similar poor performance. In addition, we were unable to confirm that the score maintains its performance in elderly patients, as was

shown in the derivation study. A possible explanation for these discrepancies could be differences in included patients. For example, both patients with provoked and unprovoked VTE were included in RIETE and the proportion of patients with an age > 70 years was substantially higher in RIETE (45%) than in the present analysis (23%). Notably, only 12% of patients with VTE in RIETE were used for derivation of the score, which might have caused selection bias. Another possible explanation is the mandated screening for occult cancer at baseline in the included studies in contrast to the observational nature of the RIETE registry. Because no information on chronic lung disease was available, current or former smoking status was used as a proxy in calculating the RIETE score. Consequently, non-heavy smokers with a short smoking history were also regarded as high-risk patients, possibly deflating occult cancer risk in the high-risk group.

The predictive performance of the SOME score also appeared to be poor in this analysis. The score only contains three variables: age 60 years or older, current smoking, and previous provoked VTE. Approximately two-thirds of the group in which we were able to evaluate the SOME score consisted of patients from the Trousseau study. Previous VTE was one of the exclusion criteria for that study,[3] and information on smoking was collected as the combined variable "current or former smoker" rather than "current smoking," possibly causing the poor predictive performance of this score in our dataset.

The present results are in line with a recent post hoc analysis of the Hokusai-VTE study, a randomized controlled trial evaluating edoxaban for treatment of acute VTE, which also demonstrated a poor discriminatory performance of the RIETE and SOME scores as reflected by the area under the ROC curve of 0.62 (95% CI, 0.57-0.66) and 0.59 (95% CI, 0.55-0.62), respectively.[14] As in the present study, only older age appeared a significant predictor of cancer in both scores in the multivariable analyses. Two other prospective studies that evaluated the RIETE score, observed a comparable, modest area under the ROC curve (0.61 and 0.63, respectively).[20,21] These studies also confirmed that the risk of occult cancer is significantly higher in those with 3 points or more compared with the lower risk group, as reflected by the OR of 3.2 (95% CI, 1.5-8.3)[21] and HR of 2.6 (95% CI, 1.5-4.3).[21]

Although the predictive performance of the continuous RIETE and SOME scores appeared to be poor, the RIETE score was able to identify patients with a two-fold increased risk of occult cancer when used dichotomously. However, discrimination was mainly driven by age > 70 years as risk factor, which in itself was already associated with a two-fold increased risk of cancer detection. This implies that clinicians should have a lower index of suspicion for occult cancer in the elderly, but that there are clinically no clear additional benefits in using these scores. This observation also implies that future studies evaluating extensive screening strategies could focus on older age groups to reduce the number needed to screen. Finally, anemia and thrombocytosis, which are both included in the RIETE score, will likely lead to additional investigations for cancer anyway when not readily explained by other comorbidities. To the best of our knowledge, neither of the scores are frequently used in current clinical practice. Current guidelines advocate against the use of these scores to make decisions about screening.[2] The modest performance of these score in this study also does not support their implementation.

The present study underscores that prediction of occult cancer in patients with unprovoked VTE is challenging as reflected by the poor performance of both risk scores. Because the types of cancer detected in patients with unprovoked VTE is heterogeneous, currently identified risk factors may not be specific enough to capture the full spectrum of cancers. Whether more detailed clinical variables or tumor-specific biomarkers further improve prediction to select patients for extensive screening deserves further study.

CONFLICT OF INTEREST

Drs. Mulder, Salaun, Robin, Otten, van Doormaal, and Büller declare no conflicts of interest. Dr. van Es: advisory board honoraria from LEO Pharma, Bayer, and Daiichi-Sankyo. Dr. Carrier declares research funding from LEO Pharma, BMS, and Pfizer and advisory board honoraria from Bayer, BMS, LEO Pharma, Servier Sanofi, and Pfizer. Dr. Le Gal reports grants from Portola Pharmaceuticals, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, LEO Pharma, Daiichi Sankyo, and Bayer, and personal fees from Bayer, Pfizer, LEO Pharma, Sanofi, and bioMérieux outside the submitted work.

AUTHOR CONTRIBUTIONS

Nick van Es initiated the study. Nick van Es and Frits I. Mulder wrote the first draft and performed the statistical analyses. Marc Carrier, Frederiek van Doormaal, Philippe Robin, Hans-Marting Otten, Pierre-Yves Salaun, and Grégoire Le Gal collected data. All authors interpreted the data, drafted the final manuscript, approved the final manuscript, and agreed to be accountable for all aspects of the work. This manuscript has been read and approved for submission to JTH by all authors.

ORCID

Frits I. Mulder https://orcid.org/0000-0002-6902-3425

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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