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Age- versus clinical pretest probability-adjusted D-dimer to rule out lower-extremity deep vein thrombosis in ambulatory patients with active cancer

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ABSTRACT

Background: In patients with suspected deep vein thrombosis (DVT), D-dimer thresholds adjusted to age or clinical pretest probability (CPTP) increase the proportion of patients in whom DVT can be safely excluded compared to a standard approach using a fixed D-dimer threshold. Performance of these diagnostic strategies among cancer patients is uncertain.

Aim: To compare the performance of age- and CPTP-adjusted D-dimer approaches among cancer outpatients with clinically suspected DVT, and derive a cancer-specific CPTP rule.

Patients and methods: Consecutive ambulatory patients with active cancer and clinically suspected DVT of the lower extremity underwent CPTP assessment using the Wells rule, D-dimer testing, and whole-leg compression ultrasonography. Patients with normal ultrasonography were followed-up for 3 months for the occurrence of symptomatic venous thromboembolism.

Results: Upon referral, DVT was diagnosed in 48 of 239 (20.1 %) patients. The age-adjusted approach showed higher specificity and efficiency than the standard approach. Compared to the standard and age-adjusted strategies, the CPTP-adjusted approach had 35 % and 21 % higher specificity, and 34 % and 21 % higher efficiency, respectively. Failure rate, sensitivity, and predictive values were similar across strategies. A simplified CPTP score derived from the Wells rule reduced unnecessary imaging with similar accuracy and efficiency, but higher failure rate.

Conclusions: In this prospective cohort of ambulatory cancer patients with clinically suspected DVT, the CPTP-adjusted D-dimer approach held the highest specificity and efficiency, potentially safely reducing unnecessary ultrasonography examinations compared to other approaches. Additional studies are warranted to evaluate the use of a simplified clinical prediction rule in this setting.

1. Introduction

Diagnosis of deep vein thrombosis (DVT) of the lower extremity based solely on clinical signs and symptoms is unreliable because of their poor specificity. This is underscored by a relatively low proportion of patients with clinically suspected lower-extremity DVT being actually diagnosed with DVT [1].

To overcome these challenges, diagnostic strategies that include the sequential use of clinical pretest probability (CPTP) assessment and measurement of D-dimer levels have been developed to identify patients in whom compression ultrasonography can be safely avoided [1].

Further diagnostic tests can be withheld in patients who have a

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negative D-dimer result in combination with a low or unlikely CPTP at initial presentation. However, this combination occurs in only about one third of patients with clinically suspected DVT [1]. In patients with cancer, the clinical usefulness of this approach appears to be even lower since D-dimer levels are often higher, and the presence of active cancer is included in all CPTP assessment rules, thereby decreasing patient's chances of being classified at low or unlikely CPTP [2–4]. In a large individual patient data meta-analysis, the combination of an unlikely CPTP and a negative D-dimer test result occurred in only 9 % of cancer patients with suspected DVT, and it exhibited relatively low safety and efficiency in this patient population [5].

Different strategies using distinct D-dimer thresholds to define a negative test result have been evaluated in individuals from the general population with a clinical suspicion of DVT. The aim of these strategies was to increase the proportion of patients in whom DVT could be excluded by means of combined use of CPTP assessment and D-dimer testing. In the age-adjusted D-dimer approach, a progressively higher D-dimer threshold is adopted with increasing age after 50 years, whereas the CPTP-adjusted D-dimer approach uses a different D-dimer threshold based on CPTP. Both strategies increase the specificity and the proportion of patients in whom DVT can be excluded by D-dimer testing as compared to the standard approach, which adopts a fixed D-dimer threshold in all patients [6–9]. However, these strategies have not been compared head-to-head in cancer patients. As a result, it remains unclear which is the optimal D-dimer approach that should be preferentially used in clinical practice to rule out DVT in patients with active cancer and clinically suspected DVT.

The aim of this study was therefore to evaluate the sensitivity, specificity, negative and positive predictive values, efficiency, and failure rate of the age-adjusted, CPTP-adjusted, and standard D-dimer approaches in patients with cancer and clinically suspected DVT. As a secondary aim, we then tested which items of the Wells score and additional patient- and disease-related characteristics were associated with DVT, and whether a modified clinical prediction rule could be potentially used to implement the diagnostic work-up in this clinical setting.

2. Methods

2.1. Study population

Consecutive ambulatory patients with active cancer who had signs or symptoms suggestive of lower-extremity DVT were eligible for the study. Patients were referred to the Service of Vascular Medicine and Thromboembolic Diseases, "SS. Annunziata" University Hospital, Chieti, Italy from the emergency room, medical oncology department, and other outpatient services of the same Center, or by local family physicians. Cancer status was determined at the time of referral. Active cancer was defined as histologically-confirmed malignancy in patients receiving cancer treatments or palliative care, or who received cancer treatments within 6 months prior to referral.

Exclusion criteria were: age <18 years, prior DVT in the same leg without documented vein recanalization, D-dimer levels measured before CPTP assessment, full-dose anticoagulant treatment for >24 h or need for chronic anticoagulant therapy for any indication, life expectancy <3 months, and inability to attend follow-up visits. The study was approved by the local ethics committee, and all patients provided informed consent. As per study protocol, all included patients underwent a standardized diagnostic DVT work-up that included sequential CPTP assessment, D-dimer testing, and whole-leg compression

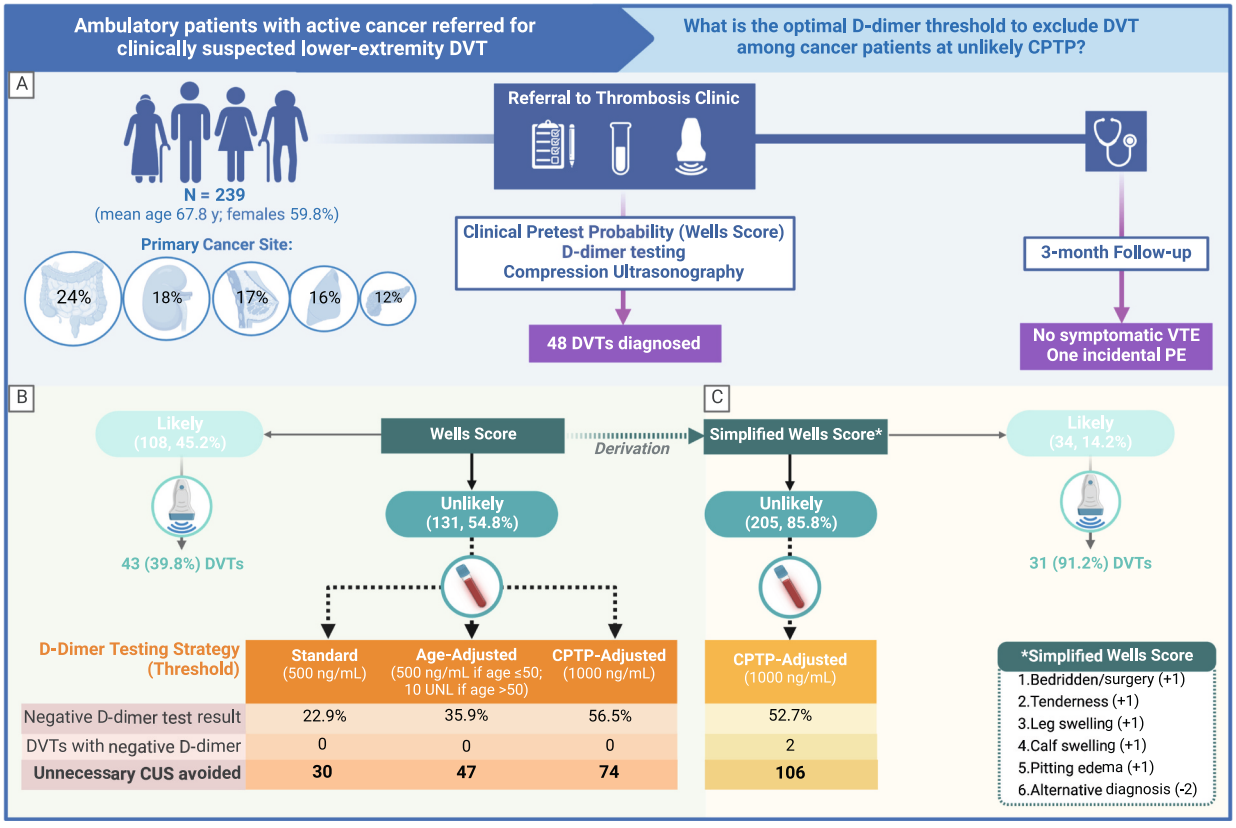

Fig. 1. Study design and main results.
Panel A shows the sequential diagnostic work-up for DVT that the study participants underwent together with main patient characteristics at baseline (i.e., day of referral to thrombosis clinic). Panel B shows the main findings for the different D-dimer strategies. Panel C shows the proposed simplified Wells score, together with its performance in the study population.
Figure created with BioRender.com.

ultrasonography (Fig. 1, Panel A).

2.2. Clinical pretest probability assessment

The Wells clinical prediction rule, which includes items related to patient history and physical examination, was used to assess CPTP at initial presentation before any other diagnostic testing was performed. The two-level Wells score, which classifies patients as unlikely or likely CPTP for DVT, was calculated applying the same values used in the original study (Supplementary Table 1) [1].

2.3. D-dimer measurement

D-dimer was measured on the day of referral using INNOVANCE D-Dimer (Siemens Healthcare Diagnostics, Newark, DE, USA). According to the standard D-dimer approach, the threshold used to categorize D-dimer result as negative was <500 ng/mL in patients with unlikely CPTP. In the age-adjusted D-dimer strategy, the threshold used to consider D-dimer as negative was <500 ng/mL in patients ≤50 years of age, and <10 times the patient's age in those >50 years old [9]. In the CPTP-adjusted D-dimer approach, the threshold used to consider D-dimer results as negative was <1000 ng/mL in patients with unlikely CPTP [6].

2.4. Imaging testing

All patients underwent whole-leg compression ultrasonography of the symptomatic leg on the day of referral. Compression ultrasonography was performed from the common femoral vein to the popliteal and calf veins assessing vein compressibility on the transverse plane. The examination was considered positive in case of vein non-compressibility, or negative otherwise. Anticoagulant therapy was started only in patients with an ultrasonography positive for DVT. Patients with normal ultrasonography were followed-up for 3 months for the occurrence of symptomatic venous thromboembolic events. Patients were carefully instructed to contact the study personnel, or refer to the emergency department immediately if signs or symptoms of DVT or pulmonary embolism (PE) occurred before the 3-month follow-up visit. During follow-up, subjects with suspected DVT underwent whole-leg compression ultrasonography, while those with suspected PE underwent ventilation/perfusion scintigraphy or computerized tomographic pulmonary angiography. Patients were considered to have DVT if they had a positive ultrasonography at initial referral, or presented with objectively confirmed symptomatic venous thromboembolism during the 3-month follow-up period.

2.5. Statistical analysis

Standard descriptive statistics were used to summarize baseline data. Mean differences between patients with DVT and patients in whom DVT was excluded were tested using Kruskal-Wallis test and Fisher exact test as appropriate. A 2 × 2 contingency table was constructed for each D-dimer strategy according to D-dimer results and DVT diagnosis in individual patients.

Estimates of sensitivity, specificity, negative predictive value, positive predictive value, and efficiency were computed for the standard, age-adjusted, and CPTP-adjusted D-dimer approaches. Corresponding 95 % confidence intervals (CI) were calculated using the Clopper-Pearson method.

The efficiency of a D-dimer strategy was defined as the proportion of patients with unlikely CPTP in whom DVT was considered excluded based on negative D-dimer test results. The failure rate was defined as the proportion of patients with unlikely CPTP and negative D-dimer test results who had DVT at referral or symptomatic venous thromboembolism during the 3-month follow-up.

We estimated the absolute differences for sensitivity, specificity, negative predictive value, positive predictive value, and efficiency between the different D-dimer approaches. Relative 95 % CIs were estimated using the Agresti-Caffo method.

A cancer-specific CPTP rule was built for exploratory purposes. The association between the following patient- and disease-related characteristics and the presence of DVT was explored in univariable logistic regression models calculating crude odds ratios (ORs) with 95 % CIs: items of the Wells score, cancer-specific characteristics (e.g., use of chemotherapy and radiotherapy within the previous month, presence of metastases, cancer history), prior superficial vein thrombosis of the internal or external saphenous veins, and level of patient mobility (e.g., no mobility restriction, mobility restricted to chair or bed for half of the time). Variables with a level of significance <0.05 were fitted in univariable logistic regression models to confirm the association with DVT.

A cancer-specific CPTP rule was derived assigning points to each variable with a significant association, based on regression's coefficients. The threshold used to categorize patients as unlikely or likely CPTP according to the cancer-specific CPTP rule was determined using the Youden index. The diagnostic performance of the newly-derived cancer-specific CPTP was subsequently compared with that of the other strategies.

The study was registered with ClinicalTrials.gov, number NCT02341937.

All analyses were performed using R, version 4.0.4 (2021-02-15) and R studio, version 1.1.423 – © 2009–2018 RStudio, Inc.

3. Results

A total of 255 consecutive outpatients with active cancer and clinically suspected lower-extremity DVT were prospectively screened. After excluding 16 patients (6.3 %) who had received anticoagulant treatment for >24 h ($n = 5$) or lacked D-dimer test measurement ($n = 11$), 239 patients were eventually included in the present analysis.

Patient mean age was 67.8 (SD 9.50) years, 60 % were females (Table 1). The most frequent primary cancer sites were gastrointestinal

Table 1
Main patient characteristics at referral.

	Overall	No DVT	DVT	*p*-Value
N	239	191	48	
Age, years, mean (SD)	67.8 (9.5)	68.3 (9.1)	65.9 (10.9)	0.33
Sex, males, n (%)	96 (40.2)	78 (40.8)	18 (37.5)	0.74
Previous cancer, n (%)				1
<5 years	9 (3.8)	7 (3.7)	2 (4.2)	
>5 years	7 (2.9)	6 (3.1)	1 (2.1)	
Active cancer type, n (%)				0.03
Gastrointestinal	57 (23.8)	45 (23.6)	12 (25.0)	
Genitourinary	43 (18.0)	30 (15.7)	13 (27.1)	
Breast	41 (17.2)	31 (16.2)	10 (20.8)	
Lung	38 (15.9)	33 (17.3)	5 (10.4)	
Pancreas	29 (12.1)	27 (14.1)	2 (4.2)	
Prostate	14 (5.9)	13 (6.8)	1 (2.1)	
Brain	4 (1.7)	1 (0.5)	3 (6.3)	
Hematologic	4 (1.7)	3 (1.6)	1 (2.1)	
Other	9 (3.8)	8 (4.2)	1 (2.1)	
Metastatic disease, n (%)	187 (78.2)	149 (78.0)	38 (79.2)	1
Chemo-radiotherapy within 1 month, n (%)	201 (84.1)	161 (84.3)	40 (83.3)	0.83
Previous saphenous vein thrombosis, n (%)	15 (6.3)	11 (5.8)	4 (8.3)	0.51
D-dimer, ng/mL, mean (SD)	3184.3 (13,154.3)	1697.2 (2026.5)	9101.6 (28,546.0)	<0.001
Wells rule, mean (SD)	1.67 (1.6)	1.14 (1.0)	3.79 (1.5)	<0.001
Wells CPTP, n (%)				<0.001
Unlikely	131 (54.8)	126 (66.0)	5 (10.4)	
Likely	108 (45.2)	65 (34.0)	43 (89.6)	

CPTP: Clinical Pre-Test Probability. *p*-Values are derived from Kruskal-Wallis test for continuous variables and from Fisher exact test or chi-squared test for categorical variables as appropriate.

(23.8 %), genitourinary (18.0 %), breast (17.2 %), lung (15.9 %), and pancreas (12.1 %). Metastatic disease was present in 187 (78.2 %) patients. Fig. 1 outlines our main study results.

According to the Wells rule, 54.8 % of the patients had unlikely CPTP, and 45.2 % likely CPTP. On the day of referral, compression ultrasonography diagnosed DVT in 48 (20.1 %) patients. DVT involved the popliteal or more proximal veins in 29 patients, distal veins in 4 patients, and both proximal and distal veins in 15 patients. None of the 191 patients without DVT at initial compression ultrasonography developed symptomatic venous thromboembolic events during the 3-month follow-up. A 74-year-old patient with lung cancer who had unlikely CPTP and a D-dimer value of 961 ng/mL, underwent ultrasonography which excluded DVT at the time of referral, but was later diagnosed with incidental subsegmental PE on a computed tomography scan performed for cancer restaging, which also documented cancer progression. Twenty-three (9.6 %) patients died during follow-up due to cancer progression.

The type and distribution of alternative diagnoses considered for the assessment of the Wells score are shown in Supplementary Table 2. The prevalence of DVT according to CPTP categories and D-dimer test results are reported in Supplementary Table 3.

3.1. D-dimer test results

In the standard D-dimer approach, 45 (18.8 %) patients had a negative D-dimer test result, and 194 (81.2 %) had a positive test result. D-dimer was negative in 30/131 patients with unlikely CPTP (efficiency: 22.9 %; 95%CI 16.0 to 31.1), none of whom was diagnosed with symptomatic venous thromboembolism during the 3-month follow-up (failure rate: 0.0 %; 95 % CI 0.0 to 11.6).

In the age-adjusted D-dimer approach, 68 (28.5 %) patients had a negative D-dimer test result, while 171 (71.5 %) had a positive test result. Age-adjusted D-dimer was negative in 47/131 patients with unlikely CPTP (efficiency: 35.9 %; 95%CI 27.7 to 44.7), none of whom was diagnosed with symptomatic venous thromboembolism at 3 months (failure rate: 0.0 %; 95 % CI 0.0 to 7.5).

In the CPTP-adjusted D-dimer approach, 89 (37.2 %) patients had a negative D-dimer test result, and 150 (62.8 %) had a positive test result. CPTP-adjusted D-dimer was negative in 74/131 patients with unlikely CPTP (efficiency: 56.5 %; 95%CI 47.6 to 65.1), none of whom was diagnosed with symptomatic venous thromboembolism at 3 months (failure rate: 0.0 %; 95 % CI 0.0 to 4.9).

When compared to the standard approach, the age-adjusted and CPTP-adjusted D-dimer strategies showed higher efficiency (absolute difference age-adjusted vs standard strategy: 13.0 %; 95%CI 1.9 to 23.7; CPTP-adjusted vs standard strategy: 33.6 %; 95%CI 22.0 to 44.2). The efficiency of the CPTP-adjusted D-dimer was higher compared to that of the age-adjusted approach (absolute difference CPTP-adjusted vs age-adjusted strategy: 20.6 %; 95%CI 8.6 to 32.0).

3.2. Comparative performance of D-dimer strategies

Table 2 shows the accuracy indices for D-dimer using the standard, age-adjusted, and CPTP-adjusted approaches in patients with unlikely CPTP.

Sensitivity and negative predictive values were overall high and similar across the different diagnostic strategies. Specificity varied broadly, ranging from 23.8 % with the standard approach to 58.7 % with the CPTP-adjusted approach. The specificity of the age-adjusted and CPTP-adjusted D-dimer was higher compared to that of the standard approach (absolute differences age-adjusted vs standard strategy: 13.5 %; 95 % CI 2.1 to 24.5; CPTP-adjusted vs standard strategy: 34.9 %; 95% CI 23.1 to 45.7). The specificity of the CPTP-adjusted strategy was higher compared to that of the age-adjusted approach (absolute difference CPTP-adjusted vs age-adjusted strategy: 21.4 %; 95 % CI 9.1 to 33.1).

3.3. Derivation of a modified CPTP rule for ambulatory patients with active cancer and suspected lower-extremity DVT

We found insufficient evidence for an association between DVT and prior saphenous vein thrombosis, reduced mobility, and cancer-specific characteristics, including cancer site, presence of metastasis and cancer treatment. The items of the Wells score associated with DVT were bedridden or surgery, tenderness, leg swelling, calf swelling or pitting edema, or alternative diagnosis possible (Fig. 1, Panel C, and Supplementary Table 4).

Based on the regression coefficients, all these items were assigned one point, except alternative diagnosis which received −2 points, as in the original CPTP rule. According to the Youden test, the threshold for categorizing CPTP as unlikely was an overall score of ≤2 points. Based on this simplified CPTP score comprising six items only, 205 (85.8 %) patients were classified as CPTP unlikely.

In these patients, D-dimer was negative in 44 (21.5 %) using the standard approach, 67 (32.7 %) with the age-adjusted, and 108 (52.7 %) with the CPTP-adjusted approach.

The accuracy indices of the original CPTP rule and simplified CPTP rule in combination with the three different D-dimer approaches are shown in Supplementary Table 5. Performances were similar in terms of specificity, efficiency, and negative predictive values. Albeit not statistically different, the sensitivity of all D-dimer approaches was lower and positive predictive values were higher when D-dimer was used in combination with the simplified CPTP rule.

The efficiency of the simplified CPTP rule was 21.5 % (95%CI 16.0 to 27.7) in combination with the standard D-dimer approach, 32.7 % (95% CI 26.3 to 39.6) with the age-adjusted D-dimer approach, and 52.7 % (95%CI 45.6 to 59.7) with the CPTP-adjusted D-dimer approach. The failure rates of these approaches were 2.3 % (95%CI 0.1 to 12.0), 1.5 % (95%CI 0.0 to 8.0), and 1.9 % (95%CI 0.2 to 6.5), respectively.

4. Discussion

The present study, that included a prospective cohort of 239 ambulatory patients with active cancer and clinically suspected lower-extremity DVT, suggests that the age-adjusted and CPTP-adjusted D-dimer strategies may perform better than the standard approach using a fixed D-dimer threshold in this specific patient population. In particular, the findings suggest that the CPTP-adjusted approach may hold the highest specificity and efficiency, potentially allowing to safely avoid a larger number of unnecessary compression ultrasonography as

Table 2
Accuracy indices for D-dimer using the standard, age-adjusted, and CPTP-adjusted approaches in patients with unlikely CPTP.

	D-dimer approach			Absolute difference		
	Standard	Age-adjusted	CPTP-adjusted	Age-adjusted vs standard	CPTP-adjusted vs standard	CPTP-adjusted vs age-adjusted
Sensitivity	100 (47.8, 100)	100 (47.8, 100)	100 (47.8, 100)	0.0 (−36.7, 36.7)	0.0 (−36.7, 36.7)	0.0 (−36.7, 36.7)
Specificity	23.8 (16.7, 32.2)	37.3 (28.9, 46.4)	58.7 (49.6, 67.4)	13.5 (2.1, 24.5)	34.9 (23.1, 45.7)	21.4 (9.1, 33.1)
NPV	100 (88.4, 100)	100 (92.5, 100)	100 (95.1, 100)	0.0 (−6.1, 8.3)	0.0 (−4.7, 8.4)	0.0 (−4.0, 5.4)
PPV	5 (1.6, 11.2)	6 (20, 13.3)	8.8 (2.9, 19.3)	1.0 (−5.9, 8.2)	3.8 (−4.6, 13.3)	2.8 (−6.2, 12.6)

CPTP: Clinical Pre-Test Probability; NPV: negative predictive value; PPV: positive predictive value. Data are presented as percentages with 95 % Confidence Intervals.

compared to the other strategies tested.

In a general population of patients with clinically suspected DVT, the combination of unlikely CPTP and negative D-dimer result can safely and efficiently exclude the diagnosis of DVT avoiding unnecessary imaging [1]. This strategy was shown to have limited clinical usefulness in the setting of cancer because only a small proportion of cancer patients present with these features compared to individuals without malignancy [2–5,10,11]. In a large individual participant meta-analysis including 10,002 patients with suspected DVT, the combination of an unlikely CPTP and negative D-dimer test occurred in only 9.1 % of cancer patients compared with 28.9 % of the general population [5]. Importantly, this combination was associated with an almost double failure rate in patients with malignancy (2.2 % vs 1.2 % in the general population). In line with these observations, only 12 % of cancer patients included in our study had unlikely CPTP in combination with negative D-dimer as determined by the standard approach, underscoring the limited usefulness of this strategy to reduce the proportion of unnecessary compression ultrasonography.

A more recent individual patient data meta-analysis including 2554 patients with clinically suspected DVT found that both the age-adjusted and the CPTP-adjusted D-dimer approaches increase the specificity and efficiency compared to the standard approach [6]. Our study seems to confirm these observations derived from the general population, and may extend them to the specific subgroup of ambulatory patients with active cancer.

A potential disadvantage of the age-adjusted D-dimer approach is that it does not apply to patients younger than 50 years of age, in whom the use of imaging cannot be reduced by this approach. In this study, the CPTP-adjusted D-dimer strategy had 21 % higher specificity and 21 % higher efficiency compared to the age-adjusted strategy, which would allow to withhold imaging in 56 % of cases, compared to 36 % of the age-adjusted, and 23 % of the standard D-dimer approaches. Since all patients underwent, as per study protocol, whole-leg compression ultrasonography regardless of D-dimer test results, we could determine a posteriori the safety of these approaches for each patient. Using the CPTP-adjusted D-dimer strategy with the original Wells score may have translated into 74 unnecessary ultrasonography examinations avoided, compared to 47 and 30 tests with the age-adjusted and standard D-dimer strategies, respectively. When using the simplified CPTP-score, application of the CPTP-adjusted D-dimer strategy resulted in a total of 106 unnecessary compression ultrasonography tests avoided (Fig. 1, Panels B and C). It is however worth noting that two out of 108 (1.9 %) patients, in whom imaging should have been withheld based on the simplified CPTP rule and CPTP-adjusted D-dimer, were diagnosed with lower-extremity DVT.

As the CPTP-adjusted D-dimer strategy relies on clinical probability assessment, failure of clinical evaluation to adequately stratify the prevalence of DVT across probability subgroups might undermine the usefulness of the CPTP-adjusted strategy. In agreement with previous studies, we found that a relatively small proportion of patients with cancer was classified as having unlikely CPTP, resulting in relatively low numbers of individuals with negative CPTP-adjusted D-dimer results [2,3]. Cancer-specific CPTP rules may incorporate patient- and disease-related characteristics that could be relevant in the setting of cancer, potentially implementing the diagnostic performance of CPTP-based strategies in this population. Several attempts to develop cancer-specific clinical prediction models have been made to date, but failed to significantly improve the DVT diagnostic work-up [12]. In the current study, we found no added diagnostic value of including distinct cancer-specific characteristics to the Wells rule. However, a simplified CPTP rule including only six items of the original Wells rule held similar results compared to the original CPTP rule. In our study, application of this simplified Wells rule appeared to retain similar efficiency as the original Wells rule, but was associated with a considerable net reduction in the number of imaging tests performed (Fig. 1). It is however worth noting that the drop in sensitivity associated with the simplified rule may lead to an increased failure rate which in our study was 1.9 % with an upper limit of the 95 % confidence interval as high as 6.5 %. Larger additional studies are therefore warranted to confirm the clinical usefulness and cost-effectiveness of the CPTP-adjusted D-dimer approach among ambulatory cancer patients, and to evaluate the simplified, six-item CPTP rule in this specific patient population and care setting.

To the best of our knowledge, this is the first study that specifically compares the diagnostic performance of the standard, age-adjusted and CPTP-adjusted D-dimer approaches in ambulatory patients with active cancer. Patients were prospectively evaluated by expert physicians using a standardized protocol, and none was lost to follow-up. Other strengths of the study include determination of CPTP before D-dimer testing to minimize the risk of biased CPTP assessment, and systematic, objective evaluation of cancer diagnosis, characteristics, and treatments.

There are, however, several study limitations that should be taken into consideration when interpreting the current results. For instance, the relatively small sample size may have accounted for the broad confidence intervals around all estimates, reducing the confidence in the precision of diagnostic accuracy indices. The study population consisted mostly of patients with solid cancer, hence results might not apply to patients with hematological malignancies. Since we only included ambulatory cancer patients with a life expectancy >3 months, findings may not extend to hospitalized cancer patients or to those approaching end of life. In addition, the study was conducted at a single academic center, and included subjects of Caucasian ethnicity, which may further reduce the generalizability of the results. CPTP assessment and execution of compression ultrasonography are subjected to inter-operator variability. In this study, they were performed by physicians with long experience in venous thromboembolism diagnosis and management. As one single D-dimer assay was used in the study, it is not possible to exclude that results may differ when using distinct D-dimer assays [13].

In conclusion, in this prospective cohort of ambulatory patients with active cancer and clinically suspected lower-extremity DVT, the age-adjusted and CPTP-adjusted D-dimer strategies appeared to have higher specificity and efficiency compared to the standard approach using a fixed D-dimer threshold. The CPTP-adjusted D-dimer approach seemed to outperform the other strategies and might potentially represent the preferred strategy to safely withhold compression ultrasonography. A modified, six-item CPTP rule derived from the Wells rule might simplify the diagnostic work-up and considerably reduce the number of unnecessary ultrasonography tests, but it was associated with a higher failure rate.

CRediT authorship contribution statement

Study conception and design: Marcello Di Nisio, Ettore Porreca. Data acquisition: Marcello Di Nisio, Maria Domenica Guglielmi, Camilla Federici. Statistical analysis: Matteo Candeloro, Anne Wilhelmina Saskia Rutjes. Interpretation of the results: Matteo Candeloro, Marcello Di Nisio, Nicola Potere, and Anne Wilhelmina Saskia Rutjes. Drafting of the manuscript: Marcello Di Nisio. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MDN received personal fees as invited speaker from Bayer, Daiichi Sankyo, and Viatris, personal fees for advisory board membership from Leo Pharma and Pfizer, and institutional funding from Leo Pharma. NP received a training fellowship from the International Society on Thrombosis and Haemostasis, and research funding from International Network of VENous Thromboembolism Clinical Research Networks, outside of the present work.

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Appendix A. Supplementary data

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References

[1] M. Di Nisio, N. van Es, H.R. Büller, Deep vein thrombosis and pulmonary embolism, Lancet 388 (10063) (2016) 3060–3073.
[2] M. Carrier, A.Y. Lee, S.M. Bates, D.R. Anderson, P.S. Wells, Accuracy and usefulness of a clinical prediction rule and D-dimer testing in excluding deep vein thrombosis in cancer patients, Thromb. Res. 123 (2008) 177–183.
[3] M. Di Nisio, A.W.S. Rutjes, H.R. Buller, Combined use of clinical pretest probability and D-dimer test in cancer patients with clinically suspected deep venous thrombosis, J. Thromb. Haemost. 4 (2006) 52–57.
[4] M. Di Nisio, M. Sohne, P.W. Kamphuisen, H.R. Buller, D-dimer test in cancer patients with suspected acute pulmonary embolism, J. Thromb. Haemost. 3 (2005) 1239–1242.
[5] G.J. Geersing, N.P.A. Zuithoff, C. Kearon, D.R. Anderson, A.J. Ten Cate-Hoek, J. L. Elf, S.M. Bates, A.W. Hoes, R.A. Kraaijenhagen, R. Oudega, R.E.G. Schutgens, S. M. Stevens, S.C. Woller, P.S. Wells, K.G.M. Moons, Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis, BMJ 10 (348) (2014 Mar), g1340, https://doi.org/10.1136/bmj.g1340.
[6] S. Parpia, S. Takach Lapner, R. Schutgens, J. Elf, G.-J. Geersing, C. Kearon, Clinical pre-test probability adjusted versus age-adjusted D-dimer interpretation strategy for DVT diagnosis: a diagnostic individual patient data meta-analysis, J. Thromb. Haemost. 18 (2020) 669–675.
[7] S.T. Lapner, J.A. Julian, L.-A. Linkins, S.M. Bates, C. Kearon, Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism, Thromb. Haemost. 117 (2017) 1937–1943.
[8] C. Kearon, K. de Wit, S. Parpia, S. Schulman, M. Afilalo, A. Hirsch, F.A. Spencer, S. Sharma, F. D'Aragon, J.-F. Deshaies, G. Le Gal, A. Lazo-Langner, C. Wu, L. Rudd-Scott, S.M. Bates, J.A. Julian, PEGeD Study Investigators, Diagnosis of pulmonary embolism with d-dimer adjusted to clinical probability, N. Engl. J. Med. 381 (22) (2019) 2125–2134.
[9] H.J. Schouten, G.J. Geersing, H.L. Koek, N.P.A. Zuithoff, K.J.M. Janssen, R. A. Douma, J.J.M. van Delden, K.G.M. Moons, J.B. Reitsma, Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis, BMJ 3 (346) (2013 May), f2492.
[10] M. ten Wolde, R.A. Kraaijenhagen, M.H. Prins, H.R. Buller, The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis, Arch. Intern. Med. 162 (2002) 1880–1884.
[11] A.Y.Y. Lee, J.A. Julian, M.N. Levine, J.I. Weitz, C. Kearon, P.S. Wells, et al., Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis, Ann. Intern. Med. 131 (6) (1999) 417–423.
[12] T. Takada, S. van Doorn, S. Parpia, et al., Diagnosing deep vein thrombosis in cancer patients with suspected symptoms: an individual participant data metaanalysis, J. Thromb. Haemost. 18 (2020) 2245–2252.
[13] M.P. de Maat, P. Meijer, W. Nieuwenhuizen, F. Haverkate, C. Kluft, Performance of semiquantitative and quantitative D-dimer assays in the ECAT external quality assessment program, Semin. Thromb. Hemost. 26 (6) (2000) 625–630, https://doi.org/10.1055/s-2000-13218. PMID: 11140799.