Update from the clinic: what's new in the diagnosis of cancer-associated thrombosis?

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Malignancy is associated with a high risk of venous thromboembolism (VTE), and treatment with anticoagulant therapy is associated with a high risk of bleeding. Thus, accurate and timely VTE diagnosis in cancer patients is essential for identifying individuals who would benefit from anticoagulant therapy and for avoiding unnecessary treatment that can cause anticoagulant-related bleeding. The approach to the diagnosis of VTE in non-cancer patients involves a stepwise process beginning with an assessment of the pretest probability (PTP) of VTE using a validated clinical prediction rule (CPR) followed by D-dimer testing and/or diagnostic imaging. In patients with a low PTP and a negative D-dimer result, VTE can be excluded without additional imaging. However, published data suggest that CPRs and D-dimer testing may not be as accurate or as useful in patients with cancer. Studies have shown that the combination of a low PTP and negative D-dimer result is not efficient for exclusion of deep vein thrombosis (DVT) or pulmonary embolism (PE) in the cancer patient population because the vast majority of patients still require radiologic imaging. We propose that cancer patients with suspected VTE should proceed directly to radiologic imaging to confirm or exclude a diagnosis of DVT or PE.

Learning Objectives

- Review the evidence for the use of CPRs in cancer patients with suspected lower-limb DVT or PE
- Understand the limitations of D-dimer testing to rule out VTE in the cancer patient population

Case 1

Patient A is a 52-year-old female with recently diagnosed diffuse large B-cell lymphoma. She is currently undergoing her first cycle of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. She is known to have a large intra-abdominal mass and malignant lymphadenopathy in the pelvis and inguinal regions. She presented to her oncology follow-up before cycle 2 with a 4-day history of left leg pain centered in the thigh and groin. She had noted an increase in pain over the last 24 hours which was impairing her ability to ambulate. She reported chronic bilateral lower extremity edema over the last 2 months. There were no respiratory symptoms. There was no history of surgery, immobility, leg trauma, casting, or hospitalization within the last 3 months. She has a history of hypertension and hypothyroidism for which she takes amlodipine and levothyroxine. On examination, there was bilateral lower-extremity edema up to the knees. The swelling was worse on the left side, and on measurement of the calf circumference at 10 cm below the tibial tuberosity, there was a 2-cm difference. There was no erythema and there were no dilated superficial veins. There was tenderness to palpation in the left medial thigh and groin. In the left groin, there were multiple lymph nodes that were tender to palpation and measured up to 5 cm. The oncologist believed that a deep vein thrombosis (DVT) in the left leg could explain the patient's symptoms. Assessment of pretest probability (PTP) using the Wells DVT clinical prediction rule (CPR) (Table 1) yielded a score of 1 (1 point for active cancer, 1 point for localized tenderness along the deep venous system, 1 point for pitting edema greater in the symptomatic leg, and −2 points for alternative diagnosis given the significant left-sided inguinal lymphadenopathy), placing the patient in the "DVT unlikely" (2-level classification) or intermediate probability category (3-level classification). The oncologist ordered a D-dimer assay, which showed elevated D-dimer at 950 μg/L (normal range, <500 μg/L). Is the use of a CPR such as the Wells DVT score and D-dimer testing efficient and cost-effective in cancer patients? Should Patient A have proceeded directly to imaging?

Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and/or DVT of the upper and lower extremities or splanchnic vasculature, is a common complication of cancer. Although cancer patients have an overall fourfold increased risk of VTE compared with the general population, the incidence of cancer-associated VTE is variable depending on the cancer type, disease stage, time since cancer diagnosis, concurrent treatments, and individual baseline risk as a result of age, ethnicity, and comorbidities, with observed VTE rates of 8% to 19%.[1,2] The management of VTE in cancer patients is challenging because despite appropriate management, such patients are at higher risk of recurrent VTE and anticoagulant-related bleeding than patients without cancer.[3] Furthermore, VTE is a leading cause of death in cancer patients receiving chemotherapy and is an independent predictor of mortality in cancer patients.[4,5] Given the poor outcomes associated with cancer-associated VTE, accurate and timely diagnosis of DVT and PE is particularly important for preventing fatal thrombotic complications and avoiding unnecessary treatment that can cause anticoagulant-related bleeding.

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Table 1. Wells CPR for assessment of PTP of DVT

Wells score	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within the last 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm greater than on asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Dilated superficial veins (nonvaricose)	1
Previous documented DVT (or PE)*	1
Alternative diagnosis as likely or greater than that of DVT	−2
3-level classification	
Low	≥3
Intermediate	1 or 2
High	≤0
2-level classification	
PE unlikely	≥2
PE likely	≤1

*Initial Wells score was for assessment of a first DVT and did not include a score for previous VTE.

Validated diagnostic pathways for lower-extremity DVT and PE that involve PTP assessment using a CPR followed by laboratory testing (D-dimer assay) and/or diagnostic imaging are recommended for diagnosing VTE.[6] However, such strategies may not be as accurate or useful in the cancer patient population. Factors affecting the performance of CPRs in cancer patients include the high incidence of nonspecific symptoms in cancer patients which may mimic symptoms of DVT and PE and the increased prevalence of VTEs in the cancer patient population; in addition, cancer-related risk factors (eg, metastatic disease) that can affect the PTP of VTE were not included as variables in the CPR. Furthermore, D-dimer levels may be elevated in patients with malignancies in the absence of VTE and thereby lower its specificity and utility. Here, we review the challenges and updates in diagnosing symptomatic cancer-associated VTE, focusing on the evidence that evaluated the use of CPRs and D-dimer testing in the cancer patient population with suspected lower-extremity DVT and PE.

Diagnosis of suspected lower-extremity DVT and PE in the general population

Over the last 20 years, the diagnosis of DVT and PE has evolved. Instead of relying on gestalt clinical assessment followed by ad hoc conventional radiologic imaging, the use of validated stepwise algorithms is encouraged. Contemporary diagnostic strategies begin with a formal assessment of the PTP of VTE by using a CPR to estimate whether patients have a low, moderate, or high probability (3-level classification) or a likely vs unlikely (2-level classification) likelihood of having a DVT or PE. The PTP then guides the selection of additional confirmatory tests (imaging studies) to rule in VTE in patients with a high or likely PTP or exclusionary tests (highly sensitive D-dimer assay) to rule out VTE in patients with a low or intermediate or unlikely PTP.[6] This stepwise approach is recommended because it allows clinicians to avoid imaging tests and radiation exposure for patients with suspected DVT or PE when the combination of low PTP and normal D-dimer results can exclude DVT or PE.

Because no diagnostic test or algorithm for VTE is perfectly accurate, the optimal strategy for VTE diagnosis must take into account (1) the potential harms of testing (eg, radiation exposure from ventilation perfusion [VQ] or computed tomography pulmonary angiography [CTPA] scans, and contrast nephropathy or anaphylactic reaction to iodinated contrast material), (2) the cost and feasibility of the involved diagnostic tests, and (3) an acceptable misdiagnosis rate (defined as the combined rates of false negatives [FNs] and false positives [FPs]). Guidelines recommend a misdiagnosis rate (FN + FP) of 5% with an FN rate of 2% or less as an acceptable threshold for a diagnostic pathway.[6] This threshold for FN, also known as the failure rate, is derived from the observed rate of VTE over 3 months of follow-up in studies that used the gold standard tests of intravenous contrast venography (for DVT) or invasive contrast pulmonary angiography (for PE) to confirm or exclude VTE.[7,8]

Although multiple CPRs have been developed, the most commonly used and best validated scores include the Wells score for DVT (Table 1) and the Wells score, Geneva score, and Revised Geneva scores for PE (Table 2).[9,10] Multiple management studies have demonstrated that a low or unlikely PTP in conjunction with a negative result using a highly sensitive D-dimer assay can reliably rule out DVT or PE, obviating the need for radiologic imaging.[11] A recent individual patient data meta-analysis that included data from 13 studies assessing the accuracy of the Wells rule for exclusion of DVT demonstrated that an unlikely Wells DVT score (≤1) combined with a negative D-dimer result was associated with a failure rate of 1.2% (95% confidence interval [CI], 0.7%-1.8%). The efficiency of this strategy, defined as the proportion of patients with an unlikely Wells score and negative D-dimer result in whom VTE can be excluded without imaging, was 28.9% (95% CI, 20.3%-39.5%).[12] Similar results were observed in a meta-analysis of individual patient data that included 6 prospective diagnostic management studies examining the Wells rule in suspected PE; a failure rate of 0.65% (95% CI, 0.38%-1.11%) and an efficiency of 28% (95% CI, 21%-37%) for excluding PE were reported.[13] Overall, there is strong and robust evidence showing that validated diagnostic pathways using a CPR followed by D-dimer testing and/or diagnostic imaging are sufficiently accurate, safe, and efficient for diagnosing VTE in general outpatients with suspected VTE.[6]

Diagnosis of suspected DVT and PE in cancer patients

Limitations of CPRs in cancer patients. Although currently available CPRs have been shown to accurately risk stratify unselected patients with suspected VTE, the validity of these rules in important patient subgroups, such as cancer patients, is not well established.[9] Although the derivation and validation studies for the most widely used CPRs did include cancer patients, these studies made up only a small percentage of the total patient population (generally <15% to 20%), and no available CPRs have been specifically developed or prospectively validated in a population with malignancies.[10] Most commonly used CPRs do include cancer as one of the predictor variables in their scoring system because cancer is a known independent risk factor for VTE; however, the inclusion of a single cancer-related predictor is insufficient for proper assessment of PTP in cancer patients. Other individual variables in common CPRs may not have the same predictive values in cancer patients compared with non-cancer patients, and current scoring systems do not

Table 2. CPRs for assessment of PTP of PE

Geneva	Points	Revised Geneva	Points	Simplified Revised Geneva	Points	Wells	Points
Recent surgery	3.0	Age >65 y	1.0	Age >65 y	1.0	Clinical signs of DVT	3.0
Previous DVT or PE	2.0	Previous history of PE or DVT	3.0	Previous history of PE or DVT	1.0	Recent surgery or immobilization	1.5
Heart rate >100 bpm	1.0	Surgery or fracture within 1 month	2.0	Surgery or fracture within 1 month	1.0	Heart rate >100 bpm	1.5
		Active malignancy	2.0	Active malignancy	1.0	Previous history of PE or DVT	1.5
						Hemoptysis	1.0
Age, y		**Heart rate (bpm)**		**Heart rate (bpm)**		Malignancy	1.0
60-79	1.0	75-94	3.0	75-94	1.0	Alternative diagnosis less likely	3.0
≥80	2.0	≥95	5.0	≥95	1.0	than PE	
Chest radiograph findings							
Atelectasis	1.0	Pain on leg venous palpation and	4.0	Pain on leg deep vein palpation and	1.0		
Elevated hemidiaphragm	1.0	unilateral edema		unilateral edema			
		Unilateral leg pain	3.0	Unilateral leg pain	1.0		
PaO_2 (mmHg)		Hemoptysis	2.0	Hemoptysis	1.0		
<49 (6.5 kPa)	4.0						
49-59 (6.5-7.99 kPa)	3.0						
60-71 (8-9.49 kPa)	2.0						
72-82 (9.5-10.99 kPa)	1.0						
$PaCO_2$ (mmHg)							
<36 (4.8 kPa)	2.0						
36-38.9 (4.8-5.2 kPa)	1.0						
Probability categories	**Total score**	**Probability categories**	**Total score**	**Probability categories**	**Total score**	**Probability categories**	**Total score**
Low	<5	Low	<4	Low	0-1	**3-Level**	
Intermediate	5-8	Intermediate	4-10	Intermediate	2-4	Low	<2
High	≥9	High	≥11	High	≥5	Intermediate	2-6
						High	>6
						2-Level	
						PE unlikely	≤4
						PE likely	>4

bpm, beats per minute; $Paco_2$, partial pressure of carbon dioxide; Pao_2, partial pressure of oxygen.

take into account VTE risk factors specific to cancer patients. For example, unilateral leg swelling in an otherwise well patient has a limited list of differential diagnoses, but this list is greatly expanded in patients with cancer. A single study examining the performance of the Wells score for PE in cancer and non-cancer patients demonstrated that its discriminatory performance was significantly lower in cancer patients.[14] The odds ratios (OR) for all variables in the Wells score were assessed using multivariate logistic regression to determine the diagnostic value or relative weight of each item. In cancer patients, the only variable that was discriminative for PE was the "other diagnosis less likely than PE" item (OR, 3.7; 95% CI, 2.2-6.3).[14] All other items in the Wells score were less diagnostic with the 95% CI of the OR crossing 1.0. Furthermore, unlike the general population, cancer patients are exposed to unique risk factors (eg, chemotherapy) that increase the risk of VTE. However, none of the current CPRs include risk factors specific to cancer (eg, chemotherapy, tumor type, disease burden, time since diagnosis) that can highly influence the PTP of thrombosis. Thus, the development of CPRs that include cancer-specific risk factors would be of value in the assessment of PTP in this group of patients.

Using the current CPRs, cancer patients have a different PTP distribution compared with non-cancer patients because CPRs tend to risk stratify fewer cancer patients into low or unlikely risk groups. This effect is partly due to the point score given for malignancy and partly because symptoms mimicking VTE are far more prevalent in patients with cancer. In 2 studies assessing the Wells criteria for DVT, cancer patients were significantly less likely to be categorized as low risk, with threefold fewer patients in the low or unlikely probability groups.[15,16] In these studies, less than 20% of cancer patients were categorized as low risk, compared with 58% to 62.9% of patients without cancer. Thus, the utility of the low PTP in identifying patients who may be managed without imaging is limited by the small numbers of cancer patients in this category.

The prevalence of VTE within each risk group also differs between patients with cancer and those without cancer because of the higher risk of VTE in malignancies. In a meta-analysis that included >10 000 patients with suspected DVT, an intermediate PTP (defined as a Wells score of 1-2) was associated with an observed DVT prevalence of 8.1% to 13.3%.[12] In contrast, cancer patients in this same risk group had a twofold higher prevalence (19.0% to 26%).[12] Thus, although patients with and without cancer may be classified in the same risk group using a CPR, the prevalence of VTE is different. CPRs have not been extensively studied in patient populations with higher VTE prevalence such as cancer and should therefore be used with caution in populations in which the model has not been specifically validated. This recommendation also applies to cancer patients admitted to the hospital because hospitalized patients have a higher risk of thrombosis, and most CPRs were developed and validated in outpatients with suspected thrombosis.

Limitations of D-dimer testing in cancer patients. Because D-dimer is a degradation product resulting from the breakdown of a cross-linked fibrin clot by plasmin cleavage, D-dimer levels are almost always elevated in patients with acute VTE. However, because increased D-dimer levels are also seen in a variety of other clinical conditions such as cancer, pregnancy, surgery, trauma, hemorrhage, and infection, D-dimer elevation is not specific for VTE. Consequently, the utility of D-dimer testing resides in its ability to exclude VTE when the levels are normal. Unfortunately, because >50% of cancer patients have elevated D-dimer levels, the D-dimer test has lower specificity and higher FP rates in this group of patients compared with the general population.[17-19] A large number of commercial D-dimer assays have been developed that differ with respect to the manufacturer's cutoffs for a normal test (range, <120 to 500 <μg/L).[20] Thus, it is critical to be aware of the manufacturer's specific cutoff for any D-dimer assay being used.

Data that examine the accuracy (as defined by sensitivity, specificity, negative predictive value [NPV]), safety, and clinical utility of D-dimer testing in cancer patients are limited. Published studies are either retrospective or subgroup analyses of larger trials, and most included small numbers of cancer patients. Studies using high and moderate sensitivity D-dimer assays generally demonstrate high NPVs in cancer patients (Table 3).[16,21-28] In contrast, the specificity of D-dimer testing for the diagnosis of both DVT and PE was consistently lower in the cancer patient subgroups in these studies (Table 3).[16,21-28] As expected, the proportion of cancer patients with a negative D-dimer result in these studies was also low, ranging from 8.5% to 30% (Table 3). Thus, the clinical utility of D-dimer testing, defined by the proportion of patients in which VTE can be ruled out by a negative D-dimer result, is much lower in the cancer than the non-cancer patient population.

Aging also reduces the specificity of D-dimer testing, because D-dimer levels increase with age, even in healthy patients.[29] To offset the decrease in specificity associated with age-related increases in D-dimer levels, investigators have examined alternative ways of interpreting D-dimer results to help increase the specificity of D-dimer testing while retaining a high NPV. Proposed strategies include using an age-adjusted D-dimer cutoff (defined as age × 10 in patients older than age 50 years), varying the D-dimer threshold for all patients and changing the D-dimer threshold in patients with low PTP.[25,30,31] These strategies have been examined in cancer patients to improve the clinical utility of D-dimer testing. In an analysis combining data from 2 prospective multicenter outcome studies in patients with suspected PE, raising the D-dimer cutoff in cancer patients from 500 μg/L to 1000 μg/L improved specificity from 16% to 37% while retaining high NPV at 98% (95% CI, 85%-99%).[25] With this strategy, the percentage of patients with a negative D-dimer increased from 11% to 26%. These results must be interpreted with caution because the CIs surrounding the NPV are quite wide. In a post hoc subgroup analysis of the ADJUST-PE study that assessed the usefulness of an age-adjusted D-dimer cutoff, the proportion of cancer patients with a negative D-dimer increased from 9.9% with the traditional threshold of <500 μg/L to 19.7% with the age-adjusted cutoff.[32] Although the proportion of cancer patients with a negative D-dimer did double with the age-adjusted cutoff, it remained lower than in non-cancer patients (19.7% vs 41.9%; $P < .001$). These studies indicate that a higher D-dimer threshold may increase the clinical utility of D-dimer testing in cancer patients, but prospective data in a cancer patient population are needed to confirm these findings and ensure that the increased D-dimer thresholds retain a high NPV.

Combining CPRs and D-dimer testing for VTE diagnosis in cancer patients. Few studies have examined the accuracy and safety of combining CPRs and D-dimer testing for diagnosing DVT or PE in cancer patients. In a pooled analysis of databases from 3 prospective studies of 2496 consecutive patients with suspected DVT (including 200 patients with cancer), the combination of a low or unlikely PTP on the Wells CPR and negative D-dimer result was

Table 3. D-dimer test characteristics in cancer and non-cancer patients

Reference	D-dimer assay	Patient type	Sample size	VTE prevalence (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	NPV (%) (95% CI)	Negative test, No. (%)
Diagnosis of DVT								
Lee et al[21]	SimpliRED	No cancer	947	14.6	82.6 (12.4-17.0)	82.2 (79.4-84.8)	96.5 (94.9-97.8)	NR
		Cancer	121	48.8	86.4 (75.0- 94.0)	48.4 (35.5-61.4)	78.9 (62.7-90.4)	NR
ten Wolde et al[28]	SimpliRED	No cancer	1522	22.0	93.0 (90.0-96.0)	64.0 (62.0-67.0)	97.0 (96.0-98.0)	782 (51.4)
		Cancer	217	40.0	98.0 (92.0-100.0)	48.0 (39.0-59.0)	97.0 (89.0-100)	64 (29.5)
Di Nisio et al[16]*	SimpliRED	No cancer	1822	22.0	90.0 (85.0-93.0)	64.0 (61.0-66.0)	97.0 (96.0-98.0)	913 (50.1)
		Cancer	244	41.0	94.0 (80.0-90.0)	51.0 (42.0-60.0)	97.0 (88.0-99.0)	73 (29.9)
Schutgens et al[26]	Minutex	No cancer	508	35.0	99.0 (NR)	30.0 (NR)	98.0 (NR)	100 (19.6)
		Cancer	47	62.0	100.0 (NR)	22.0 (NR)	100.0 (NR)	4 (8.5)
Shitrit et al[27]	Miniquant	All patients	126	27.8	94.0 (NR)	57.0 (NR)	54.0 (NR)	NR
		Cancer	21	61.9	91.0 (NR)	0.0 (NR)	38.0 (NR)	NR
Bates et al[22]†	MDA	All patients	595	19.0	96.0 (90.0-99.0)	45.0 (40.0-49.0)	98.0 (95.0-99.0)	220 (37)
		Cancer	66	43.9	97.0 (82.0-100)	46.0 (30.0-63.0)	94.0 (73.0-100.0)	18 (27.3)
Bates et al[23]	MDA	All patients	556	10.1	98.2 (90.4-100)	60.4 (56.1-64.7)	99.7 (98.2-100)	303 (62.5)
		Cancer	50	34.0	100 (80.5-100)	45.5 (28.1-63.7)	100 (78.2-100)	15 (30)
Diagnosis of PE								
Di Nisio et al[24]	Tinaquant	No cancer	447	19.0	93.0 (87.0-98.0)	53.0 (48.0-58.0)	97.0 (95.0-99.0)	199 (44.5)
		Cancer	72	26.0	100 (82.0-100)	21.0 (10.0-32.0)	100 (72.0-100)	11 (15.3)
Righini et al[25]	VIDAS	No cancer	1554	23.0	100 (99.0-100)	41.0 (39.0-44.0)	100 (99.0-100)	494 (32)
		Cancer	164	33.0	100 (93.0-100)	16.0 (11.0-24.0)	100 (82.0-100)	18 (11)

NR, not reported.
*Sensitivity, specificity, and NPV reported for patients with a low to moderate PTP of DVT.
†Includes patients with suspected DVT and PE.

Table 4. Accuracy of PTP assessment and D-dimer testing in cancer and non-cancer patients with suspected DVT

Reference	Patients with cancer		Patients without cancer	
	Low PTP and negative D-dimer	Unlikely PTP and negative D-dimer	Low PTP and negative D-dimer	Unlikely PTP and negative D-dimer
Carrier et al[15]				
N (%)	12 (6.0)	24 (12.0)	557 (22.3)	894 (35.8)
Sensitivity, % (95% CI)	100 (31.0-100)	100 (59.8-100)	95.0 (81.8-99.1)	91.7 (82.1-96.6)
Specificity, % (95% CI)	46.2 (27.1-66.3)	57.1 (41.1-71.9)	62.9 (59.6-66.1)	70.4 (67.8-72.9)
NPV, % (95% CI)	100 (69.8-100)	100 (82.8-99.6)	99.6 (98.6-99.9)	99.3 (98.5-99.7)
Di Nisio et al[16]				
N (%)	22 (9.0)	—	651 (35.7)	—
Sensitivity, % (95% CI)	100 (51.0-100)	—	86.0 (78.0-92.0)	—
Specificity, % (95% CI)	58.0 (42.0-72.0)	—	66.0 (63.0-69.0)	—
NPV, % (95% CI)	100 (85.0-100)	—	98.0 (97.0-99.0)	—

associated with high sensitivity and NPV in patients with and without cancer (Table 4). Although the NPV was high in cancer patients (100% for both the low and DVT unlikely PTP classifications), the CIs were quite broad, ranging as low at 69.8% because of the small sample size. In other words, it is possible that up to 30% of cancer patients could be wrongly diagnosed as not having a DVT on the basis of a low or DVT unlikely PTP and a negative D-dimer result. Specificity was lower in cancer patients with both the low (non-cancer patients, 62.9; 95% CI, 59.6-66.1 vs cancer patients, 46.3; 95% CI, 27.1-66.3) or DVT unlikely (non-cancer patients, 70.4; 95% CI, 67.8-72.9 vs cancer patients, 57.1; 95% CI, 41.1-71.9) categorization for PTP.[15] A second retrospective study in patients with suspected DVT confirmed these findings (Table 4).[16] In these studies only 6% to 9% of cancer patients had a low PTP and a negative D-dimer and did not require further testing. Thus, >90% of cancer patients would require additional imaging to rule out DVT.[15,16] If a 2-level classification system was used, the proportion of patients in whom further testing was not required increased to 12%; however, this still means that 88% of cancer patients would need imaging.[15]

The predicted safety and efficiency of the 2-level Wells score and D-dimer testing for exclusion of DVT in important patient subgroups, including patients with cancer, was examined in a large meta-analysis of individual patient data from 13 studies and 10 002 patients.[12] In the overall population, the predicted failure rate of an unlikely Wells PTP and negative D-dimer was 1.2% (95% CI, 0.7%-1.8%), which falls under the acceptable failure threshold of ≤2% for a diagnostic pathway. The efficiency of the strategy, defined by its ability to exclude DVT with no further testing, was 28.9% (95% CI, 20.3%-39.5%). However in cancer patients, the failure rate was 2.2% (95% CI, 0.5%-8.6%) and the efficiency was 9.1% (95% CI, 5.5%-14.7%) (Table 5). This predicted failure rate of 2.2% not only exceeds the standard acceptable safety margin, but the upper limit of the 95% CI is as high as 8.6%. Moreover, DVT could be excluded in only a small proportion of cancer patients (<10% cancer patients vs 30% non-cancer patients) without further imaging testing using this strategy.

A meta-analysis of individual patient data from 6 prospective management studies in 7268 patients with suspected PE examined the performance of a 2-level Wells score and either fixed or age-adjusted D-dimer testing.[13] With a fixed D-dimer cutoff set at ≤500 μg/L, the failure rate and efficiency in the overall population were 0.65% (95% CI, 0.38%-1.11%) and 28% (95% CI, 21%-37%), respectively.[13] Using an age-adjusted D-dimer threshold, the efficiency increased by 5% (33%; 95% CI, 25%-42%) while maintaining a failure rate below the acceptable safety threshold (0.94%; 95% CI, 0.58%-1.5). In patients with active cancer, the failure rate and efficiency of the Wells rule and fixed D-dimer cut off for exclusion of PE were 2.6% (95% CI, 0.57%-11.0%) and 9.1% (95% CI, 6.8%-12.0%), respectively (Table 5). As observed for the exclusion of DVT, the use of a 2-level Wells score and fixed D-dimer cutoff for exclusion of PE is neither safe nor efficient in those with cancer. If an age-adjusted D-dimer threshold is used, the failure rate in the cancer patient subgroup is 1.4% (95% CI, 0.15%-12.6%). The estimated failure rate falls within acceptable safety thresholds, but the upper bound of the wide CI at 12.6% raises concerns. By using an age-adjusted D-dimer threshold, the efficiency of the algorithm in cancer patients is increased by 4%, such that 13.1% of patients would not have to undergo further testing to exclude PE.

The results of these studies suggest that the combination of an unlikely Wells score and a negative D-dimer test is neither safe nor efficient for the exclusion of DVT or PE in cancer patients. Using an age-adjusted D-dimer cutoff may improve the efficiency of the algorithm, but 87% of cancer patients would still require additional imaging tests. Further studies in a cancer-specific patient population are needed to confirm the safety and efficiency of the age-adjusted D-dimer.

Diagnostic strategy for DVT and PE in cancer patients

For patient A, PTP assessment with the Wells DVT score indicated an intermediate or DVT unlikely probability category with a total score of 1 point (1 point for active cancer, 1 point for localized tenderness along the deep venous system, 1 point for pitting edema that was greater in the symptomatic leg, and −2 points for an alternative diagnosis). The measured D-dimer level was elevated at 950 μg/L (manufacturer cutoff for the assay was <500 μg/L). On the basis of these results, a Doppler ultrasound was ordered which was negative for DVT. This clinical situation illustrates the limitations of CPRs and D-dimer testing in cancer patients. The CPR/D-dimer strategy is known to have a low efficiency in cancer patients with less than 10% of patients with suspected DVT and PE presenting with an unlikely PTP and negative D-dimer.[12,13] Thus, this stepwise approach is unlikely to be cost-effective in the cancer patient population because the majority of patients, as was the case for patient A, will require additional imaging to rule out VTE.

Because of the limitations of CPR in combination with D-dimer testing in terms of efficiency, cost-effectiveness, and safety in the cancer patient population, cancer-specific guidelines recommend

Table 5. Predicted failure and efficiency rates of the Wells score and D-dimer testing for excluding DVT and PE in cancer patients

Reference	Cancer patients	All patients
Geersing et al[12] (DVT)		
N	834	10 002
Failure rate, % (95% CI)	2.2 (0.5-8.6)	1.2 (0.7-1.8)
Efficiency, % (95% CI)	9.1 (5.5-14.7)	28.9 (20.3-39.5)
van Es et al[13] (PE)		
N	938	7 268
Failure rate fixed D-dimer*, % (95% CI)	2.6 (0.57-11.0)	0.65 (0.38-1.11)
Efficiency fixed D-dimer*, % (95% CI)	9.1 (6.8-12.0)	28.0 (20.5-37.0)
Failure rate age-adjusted D-dimer†, % (95% CI)	1.4 (0.15-12.6)	0.94 (0.58-1.5)
Efficiency age-adjusted D-dimer†, % (95% CI)	13.1 (10.6-16.1)	32.6 (24.6-41.7)

Failure rate is defined as the probability of DVT or PE in those with an unlikely Wells score and a negative D-dimer result. Efficiency rate ia defined as the proportion of patients with an unlikely Wells score and a negative D-dimer result.
*D-dimer threshold = 500 μg/L.
†D-dimer threshold = age of patient multiplied by 10 μg/L in patients older than age 50 y.

proceeding directly to imaging (ultrasound for DVT and CTPA for PE) in cancer patients with suspected VTE.[33]

In conclusion, there is insufficient evidence in the cancer patient population to support the use of currently available CPRs in conjunction with D-dimer testing for the diagnosis of suspected DVT and PE. Because the combination of CPRs and D-dimer testing is neither safe nor efficient in cancer patients, the use of current diagnostic algorithms should be avoided. We therefore suggest that cancer patients with suspected VTE proceed directly to diagnostic imaging for confirmation or exclusion of DVT and PE. Further studies to develop cancer-specific CPRs to be used in conjunction with fixed or age-adjusted D-dimer testing are needed to improve the accuracy, safety, and efficiency of these diagnostic tools in the cancer patient population.

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