ORIGINAL RESEARCH

The application of clinical variables and models to predict pulmonary embolism in cancer patients: a comprehensive single cancer center experience

Asem Mansour[1]
Yousef Ismael[2]
Mahmoud Abunasser[2]
Emad Hammode[2]
Rim Turfa[2]
Hikmat Abdel-Razeq[2]

[1]Department of Radiology, King Hussein Cancer Center, Amman, Jordan; [2]Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan

Introduction: Prompt diagnosis and treatment of pulmonary embolism (PE) can help reduce its associated morbidity and mortality. Computed tomography chest angiography (CTA) scanning is the most widely used diagnostic modality. In noncancer patients, only 10% of such studies are positive for PE. Clinical variables, individual or in combination, that can predict test positivity are highly needed.

Materials and methods: All CTAs requested to confirm or exclude a diagnosis of PE in a single comprehensive cancer center were reviewed. In addition to the Wells score, other clinical variables known to increase the risk of PE were analyzed.

Results: A total of 778 adult cancer patients were treated at King Hussein Cancer Center (Amman, Jordan) and were included in this study; the majority of patients (64.2%) had stage 4 disease. Overall, 129 (16.6%) patients had positive scans for PE, while alternative diagnoses were made in 308 (39.6%) patients. Cancer stage and anticancer treatment had no impact on positive PE rates. However, Wells criteria classified patients into three risk groups with PE rates of 10.2%, 16.1%, and 62.5% among the patients with low, moderate, and high risk, respectively ($P < 0.0001$). Duration of cancer diagnosis (<12 months versus >12 months) had a significant impact on positive PE studies (22.0% versus 12.4%, respectively, $P = 0.007$).

Conclusion: The rate of positive PE studies in cancer patients is higher than previously reported in noncancer patients. Positivity for PE was higher during the first 12 months of cancer diagnosis and in those with high probability score according to the Wells criteria. Factors like primary tumor stage and anticancer therapy had no significant impact on PE-positive studies.

Keywords: pulmonary embolism, thromboembolism, cancer, CT angiography

Correspondence: Hikmat Abdel-Razeq
Department of Internal Medicine,
King Hussein Cancer Center,
202 Queen Rania Al Abdulla Street,
PO Box 1269, Amman, Jordan
Tel +962 6 530 0460
Email habdelrazeq@khcc.jo

Introduction

Pulmonary embolism (PE) is not an uncommon diagnosis in clinical practice, especially in high-risk patients like those with known malignancies.[1] Cancer and its treatment are recognized risk factors for venous thromboembolism (VTE).[2] Active cancer accounts for almost 20% of all new VTE events occurring in the community.[3] The risk of VTE varies by cancer type and is especially high among patients with malignant brain tumors, or with adenocarcinoma of the ovary, pancreas, colon, stomach, lung, and prostate.[4]

The clinical diagnosis of PE is difficult to make.[5,6] The clinical presentation is variable and nonspecific, especially in cancer patients.[7] Many of the presenting symptoms and signs detected in patients with acute PE can be attributed to disease progression, malignant pleural effusions, or infection.[8] In addition to proper VTE prophylactic strategies, early recognition, diagnosis, and prompt treatment are expected to lower the high mortality rates associated with PE.

Spiral (helical) computed tomography (CT) scanning with intravenous contrast (ie, CT pulmonary angiography [CTA]) is widely used as a diagnostic modality for patients with suspected PE.[9] In addition to confirming or excluding a diagnosis of PE, CTA can offer alternative pulmonary abnormalities that may explain the patient's symptoms and signs. Given the high rate of CTA-negative tests, as well as the cost, time, and efforts in performing such tests, it is important to find out if certain clinical variables, individual or in combination (models or scoring systems), can predict at least a subgroup of patients in whom the chance of a positive test is low enough to avoid unnecessary imaging studies.

Materials and methods

This study was conducted at the King Hussein Cancer Center (Amman, Jordan), a tertiary care, teaching, Joint-Commission International accredited cancer center. The study population consisted of all patients for whom a CTA was done to rule out a diagnosis of PE in all clinical care units including the emergency department, medical and surgical units, intensive care unit and outpatient clinics. Patients were identified through a computerized database in the department of radiology that registers all radiologic studies performed. Patients were enrolled during the period of January 2006 to September 2011. The CTAs were obtained with a Philips Brilliance-64 slice scanner (Koninklijke Philips NV, Amsterdam, Netherlands) with a 3.0 mm slice thickness. The contrast volume was 100 mL infused at a rate of 3.0 mL per second.

The CTA was read as positive for PE if filling defect(s) were noted in the pulmonary arterial tree. Findings that provided an alternative explanation or diagnosis were also reported.

The protocol entailed a review of existing medical and radiological records with minimal risk to patients, so the requirement of informed written consent was waived by our local institutional review board. On the day that the test was requested, the existence of the following clinical variables was reviewed using patients' medical records: alternative diagnosis, symptoms suggestive of deep vein thrombosis, tachycardia, immobilization, prior history of deep vein thrombosis or PE, and presence of hemoptysis.

Using these variables, a Wells score was calculated and the clinical probability of PE was characterized as high, moderate, or low (Table 1). Other clinical variables were collected including primary disease, stage and time since cancer diagnosis, active treatment with chemotherapy or hormonal therapy, body mass index (BMI), blood counts including white blood counts, hemoglobin (Hb), and platelets.

Statistical analysis

Descriptive statistics were performed for all variables. Results for continuous variables are expressed as the mean (standard deviation) or median (interquartile range). Categorical variables are expressed as number (percentage). All statistical analysis was carried out using SAS software (version 9.1; SAS Institute Inc, Cary, NC, USA). A P-value <0.05 was considered to be statistically significant, and was measured using the Chi-square test.

Results

During the 4-year study period, 778 adult cancer patients were included. The mean (standard deviation) age of patients at the time of CT was 52.0 (15.6) years and 55.8% were females. Breast, lung, lymphomas, and colorectal cancers were the most frequent cancers accounting for 53% of the whole study group. Among the 667 patients with diseases that can be staged by the Tumor, Node, Metastases staging system, 428 (64.2%) patients had stage 4 disease, whereas only 101 (15.1%) patients had stage 1 or 2 disease. Patients' characteristics are detailed in Table 2.

Overall, 129 (16.6%) patients had positive scans for PE, while alternative diagnoses were given in another 308 (39.6%); such alternative diagnoses included collapse/consolidation, disease progression, pleural effusion, and infection. Another 41 (5.3%) had a ground glass appearance on chest CT that mandated further workup to reach a specific diagnosis (Table 3).

Factors that might affect PE-positive studies were reviewed. The rate of PE-positive studies varied with the

Table 1 Wells score

Clinical criteria	Points
Symptoms of DVT	3
No alternative diagnosis better explains the illness	3
Tachycardia with pulse >100	1.5
Immobilization ($\geq$3 days) or surgery in the previous 4 weeks	1.5
Prior history of DVT or pulmonary embolism	1.5
Presence of hemoptysis	1
Presence of malignancy	1
Risk level	**Total score**
Pulmonary embolism risk score interpretation	
Low probability	0–1
Moderate probability	2–6
High probability	7–12

Abbreviation: DVT, deep vein thrombosis.

Table 2 Patients' characteristics

Gender	
Male	344 (44.2%)
Female	434 (55.8%)
Total	778
Age	
Range (years)	18.0–85.0
Mean (±SD)	52.0 (±15.6)
Median	54.3 (±17.6)
Primary cancer	
Breast	163 (21.0%)
Lung	98 (12.6%)
Lymphoma	77 (9.9%)
Colorectal	74 (9.5%)
Acute leukemia	47 (6.0%)
Sarcoma	30 (3.9%)
Multiple myeloma	27 (3.5%)
Stomach	26 (3.3%)
Cervix and endometrium	23 (3.0%)
Ovary	22 (2.8%)
Prostate	16 (2.1%)
Bladder	16 (2.1%)
Brain	16 (2.1%)
Chronic leukemia	15 (1.9%)
Head and neck	15 (1.9%)
Pancreas	14 (1.8%)
Others	99 (12.7%)
Stage*	
1	43 (6.4%)
2	73 (10.9%)
3	123 (18.4%)
4	428 (64.2%)
Clinical unit	
Outpatient clinic	127 (16.3%)
Emergency room	186 (23.9%)
Regular units	380 (48.8%)
Intensive care unit	85 (10.9%)
Active treatment	
Chemotherapy	401 (51.5%)
Hormonal therapy	47 (6.0%)
Thalidomide	15 (1.9%)

Note: *Out of 667 stageable patients by the Tumor, Node, Metastasis staging system.
Abbreviation: SD, standard deviation.

primary cancer; it was highest in patients with colorectal cancers where there were 18 of 74 (24.3%) positive studies compared to 13 of 163 (8.0%) positive studies in patients with breast cancer ($P = 0.006$). Patients with lung cancer and lymphoma had positive rates in 17.3% (17/98) and 15.6% (12/77), respectively.

Disease stage had no impact on positivity rate; PE was diagnosed in 14.0% of patients in stage 1, 12.3% of patients in stage 2, 17.1% of patients in stage 3, and 18.7% of patients in stage 4 disease ($P = 0.53$). Active treatment (chemotherapy, radiotherapy, and hormonal therapy) that patients were receiving at the time of CTA was also reviewed;

Table 3 Prevalence of pulmonary embolism and alternative diagnoses

Findings	Number (%)
Pulmonary embolism	129 (16.6)
Alternative diagnosis	349 (44.9)
Pleural effusion	80 (10.3)
Disease progression	91 (11.7)
Significant atelectasis/consolidation/collapse	98 (12.6)
Infection	12 (1.5)
Nonspecific ground glass appearance	41 (5.3)
Others*	27 (3.5)
No diagnosis	300 (38.6)

Note: *Others include: pneumothorax, lung fibrosis, bronchitis oblitrans, pericardial effusion, hiatal hernia, superior vena cava thrombosis, bronchiectasis, pulmonary edema.

among 461 (59.3%) patients who were on active treatment, positive studies were reported in 70 (15.2%) compared to 59 (18.7%) among the 317 (40.7%) who were on observation ($P = 0.19$).

The site of the clinical patients' assessment at the time of CTA study had an impact on PE rates; the highest positive studies were seen in those requested from medical outpatient clinics (30 of 127 [23.6%]) and emergency departments (37 of 186 [19.9%]) compared to 48 of 380 (12.6%) in regular medical units and 14 of 85 (16.5%) in studies requested from the intensive care unit ($P = 0.02$).

The application of the Wells criteria classified our study patients into three risk groups: low, 246 (31.6%); moderate, 492 (63.2%); and high-risk, 40 (5.1%) with PE diagnosed in 10.2%, 16.1%, and 62.5%, respectively ($P < 0.0001$). Additionally, time since cancer diagnosis had a significant impact on positive PE studies; 77 (22.0%) of 350 patients who had the CTA done during the first 12 months had positive studies compared to 37 (12.4%) of 298 who had the CTA done beyond the first 12 months since cancer diagnosis ($P = 0.007$).

In univariate analysis, the following covariants were not associated with positive PE: prechemotherapy platelet count of 350×10^9/L or more, hemoglobin level less than 10.0 g/dL, leukocyte count more than 11×10^9/L, and a BMI of 35 kg/m^2 or more (Table 4).

Discussion

This study reviewed a single cancer center's experience to determine if certain clinical variables, with or without a combined scoring system, can possibly predict a subgroup of cancer patients in whom the chance of a positive test is low enough to avoid unnecessary imaging studies.

The association between cancer and thrombosis has been well established since the first observation made by

Table 4 Rates of positive PE studies (N = 778)

Clinical variables	Total N (%)	Positive N (%)	P-value for Chi-square
Gender			
Female	434 (55.8%)	68 (15.7%)	0.42
Male	344 (44.2%)	61 (17.8%)	
Stage			
1	43 (6.4%)	6 (14.0%)	0.53
2	73 (10.9%)	9 (12.3%)	
3	123 (18.4%)	21 (17.1%)	
4	428 (64.2%)	80 (18.7%)	
Total score*			
High probability	40 (5.1%)	25 (62.5%)	
Moderate probability	492 (63.2%)	79 (16.1%)	<0.0001
Low probability	246 (31.6%)	25 (10.2%)	
Blood counts			
WBC			
$<11 \times 10^9$/L	538 (69.2%)	84 (15.7%)	0.29
$\geq11 \times 10^9$/L	240 (30.8%)	45 (18.8%)	
PLT			
$<350 \times 10^9$/L	623 (80.1%)	101 (16.3%)	0.59
$\geq350 \times 10^9$/L	155 (19.9%)	28 (18.1%)	
Hb			
<10 gm/dL	235 (30.2%)	32 (13.7%)	0.15
≥10 gm/dL	543 (69.8%)	97 (17.9%)	
BMI (kg/m²)			
<35	671 (86.2%)	113 (16.9%)	0.62
≥35	107 (13.8%)	16 (15.0%)	
Treatment			
Active treatment	461 (59.3%)	70 (15.2%)	0.19
No active treatment	317 (40.7%)	59 (18.7%)	
Clinical units			
Outpatient clinics	127 (16.3%)	30 (23.6%)	
Emergency room	186 (23.9%)	37 (19.9%)	0.02
Regular units	380 (48.8%)	48 (12.6%)	
ICU	85 (10.9%)	14 (16.5%)	

Note: *High (7–12 points), moderate (2–6 points), low (0–1 points).
Abbreviations: PE, pulmonary embolism; N, number; WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; BMI, body mass index; ICU, intensive care unit.

Armand Trousseau more than 100 years ago.[10] Cancer and its treatment are recognized risk factors for VTE, including PE. In a population-based case-control study of 625 Olmsted county patients, the risk of VTE was six-fold higher in cancer patients compared to those without.[11] Additionally, PE is associated with substantial morbidity and mortality; both tend to be higher among cancer patients, and those who survive such events may develop chronic complications like pulmonary hypertension.[12,13] In a large study, Sørensen et al[14] examined the survival of patients with cancer and VTE compared to those without VTE matched for many factors including the type and duration of cancer diagnosis; the 1-year survival rate for cancer patients with VTE was 12% compared to 36% in the control group (P < 0.001).

Furthermore, the risk of VTE recurrence was higher in cancer patients compared to those without.[14] Given these points, every effort should be made to prevent and detect PE early on.

The risk of VTE varies by cancer type; it is higher in patients with malignant brain tumors, as well as for adenocarcinoma of the pancreas, colon, stomach, ovary, lung, prostate, and kidney,[15–17] but it is lower in sites like skin and breast.[18,19] In addition to primary tumor type, other cancer-related factors play an important role in VTE rates; the risk of VTE is highest during the first 3–6 months after the initial diagnosis of cancer.[20] Such risk also varies with the stage of the disease; it is much higher with advanced-stage compared to early-stage disease.[20] Our study, however, showed that such disease-related factors cannot be utilized to help predict a diagnosis of PE in cancer patients who present with suggestive clinical features.

Even the well described higher risk of VTE in cancer patients on active treatment with chemotherapy, hormonal therapy, or antiangiogenesis drugs like thalidomide failed to predict higher positivity rates for PE.[21–24]

The application of Wells criteria,[25] however, was useful in predicting the diagnosis of PE in a group of 40 patients who were categorized as high risk; 62.5% of them had positive studies, compared to a rate of 10.2% in a group of 219 patients who were felt to be at low risk for PE and a rate of 16.1% among a group of 492 patients who were classified as a moderate-risk group based on the Wells criteria. However, the number of patients in the high-risk group was not high enough to make firm conclusions.

Expertly interpreted pulmonary vascular imaging, either ventilation-perfusion scan or CTA, is not uniformly available at most hospitals. When evaluating a patient with suspected PE during times when pulmonary vascular imaging is not available, clinicians frequently face the decision of whether to administer anticoagulant therapy while awaiting availability of such imaging studies.

Our positive PE rate of 16.6% on CTAs is higher than rates reported by similar observational studies in noncancer patients. In a cross-sectional study, Hall et al[26] reviewed 589 pulmonary CTAs that were ordered in the emergency department of a tertiary care hospital; PE was found in 55 of 589 CTAs (9%) and another 195 (33%) had findings that supported alternative diagnoses including 141 patients (24%) with new incidental findings that required further diagnostic follow-up. However, our rate is lower than rates reported by the PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis) trial (23%), which involved a highly

selected population, enrolling 824 of 7,284 patients who had suspected PE.[27] Our lower rate can be explained by the higher frequency of nonspecific respiratory symptoms in cancer patients that can mimic PE.

Though the positivity rate among our study patients was not high, CT was a useful test even when clinical suspicion of PE was low, because alternative explanations for symptoms were revealed.[28] Radiographic findings supporting potential alternative diagnoses – especially disease progression, infiltrates, and pleural effusions – were found in almost 40% of our cohort. However, one can argue that a good quality chest X-Ray could have made the diagnosis. In fact, almost all such patients had a prior chest X-ray, the findings of which did not stop physicians from ordering CTs.

Lombard et al[29] also described potential alternative diagnoses and significant incidental findings in 62 patients who underwent CTA at a tertiary care hospital in Canada. The authors' PE rate (11%) was similar to ours, as an additional 57% of the patients in their study had findings categorized as "alternative diagnoses or significant additional findings."[29]

Our significantly larger sample size allowed for more detailed categorization of non-PE findings and a greater focus on the importance of identifying disease progression or infectious process early on.

Several other investigators have tried to establish predictive models – the application of which could identify cancer patients at risk of VTE. In one study, Khorana et al[30] found that primary tumor site, platelet count, leukocyte count, Hb level, use of erythropoiesis stimulating agents, and BMI were predictive factors for occurrence of VTE. The same issue was addressed by the Vienna Cancer and Thrombosis Study group who reported that elevated plasma P-selectin level predicted VTE in 687 newly diagnosed ambulatory cancer patients.[31] The cumulative probability of VTE after 6 months of follow up was 11.9% in patients with serum P-selectin above and 3.7% in those below the 75th percentile ($P = 0.002$).[31] More recently, the same group reported their experience in utilizing D-dimer and prothrombin fragments 1+2 (F1+2), markers that reflect the activation of blood coagulation and fibrinolysis, for the prediction of cancer-associated VTE. In this prospective, observational study, D-dimer and F1+2 levels independently predicted the occurrence of VTE in a group of 821 patients with newly diagnosed cancer or progression of disease who did not recently receive active treatment.[32]

Our study is not without limitations: this study was conducted in a single institution and in cancer patients, thus results may not be generalizable to other clinical settings.

The retrospective study design could have introduced bias in patient selection; however, the radiology database that was used to identify patients captures all imaging studies that are ordered. We used a consecutive patient sampling strategy that minimized selection bias within our population.

Conclusion

In conclusion, CTAs obtained to rule out PE are associated with better yield in cancer patients compared to historical data in noncancer patients; yet, CTAs were more than twice as likely to find an alternative diagnosis as they were to find a PE, even in this high-risk group of cancer patients. In addition to a high-risk score according to the Wells criteria, other clinical factors like recent diagnosis of cancer (<12 months), but not disease stage or active treatment, were associated with higher positive CTA studies. However, the Wells score alone might not be enough of a criterion to be relied upon to exclude a diagnosis of PE.

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Disclosure

The authors report no conflicts of interest in this work.

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