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Usefulness of Clinical Prediction Rules, D-dimer, and Arterial Blood Gas Analysis to Predict Pulmonary Embolism in Cancer Patients

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ABSTRACT

Objectives: Pulmonary embolism (PE) is seven times more common in cancer patients than non-cancer patients. Since the existing clinical prediction rules (CPRs) were validated predominantly in a non-cancer population, we decided to look at the utility of arterial blood gas (ABG) analysis and D-dimer in predicting PE in cancer patients. ***Methods***: Electronic medical records were reviewed between December 2005 and November 2010. A total of 177 computed tomography pulmonary angiograms (CTPAs) were performed. We selected 104 individuals based on completeness of laboratory and clinical data. Patients were divided into two groups, CTPA positive (patients with PE) and CTPA negative (PE excluded). Wells score, Geneva score, and modified Geneva score were calculated for each patient. Primary outcomes of interest were the sensitivities, specificities, positive, and negative predictive values for all three CPRs. ***Results:*** Of the total of 104 individuals who had CTPAs, 33 (31.7%) were positive for PE and 71 (68.3%) were negative. There was no difference in basic demographics between the two groups. Laboratory parameters were compared and partial pressure of oxygen was significantly lower in patients with PE (68.1 mmHg vs. 71 mmHg, $p = 0.030$). Clinical prediction rules showed good sensitivities (88–100%) and negative predictive values (93–100%). An alveolar-arterial (A-a) gradient > 20 had 100% sensitivity and negative predictive values. ***Conclusions:*** CPRs and a low A-a gradient were useful in excluding PE in cancer patients. There is a need for prospective trials to validate these results.

Pulmonary embolism (PE) is a complication of venous thromboembolism (VTE) most commonly, deep vein thrombosis (DVT). It is the third most common cause of death in hospitalized patients and remains an important preventable cause of mortality and morbidity. Approximately 30–40% patients with VTE present with symptomatic PE.[1,2] Patients with malignancy have a high risk of developing venous thrombosis; a population based study showed a two year cumulative incidence of VTE in cancer patients (0.8–8.0%).[2] Cancer patients account for up to 15–20% of all VTE events.[3] The risk of venous thrombosis in patients with cancer is increased with administration of chemotherapy, hormone therapy, surgical procedures, repeated hospital admissions, and immobilization.[4,5] Certain malignancies such as brain, ovarian, pancreatic, and colorectal cancers have been shown to increase the risk for venous thrombosis. Consequently, symptomatic VTE has been shown to be seven times higher in cancer patients when compared with non-cancer patients.[6]

Early diagnosis and treatment of PE has been demonstrated to reduce mortality from 30.0% to 1.5%.[5] Clinical assessment is used to estimate a patient's pretest probability and risk stratification of PE, which is then combined with result of an objective diagnostic test to determine whether the patients have PE.[7,8] This empirical and unstructured approach is probably dependant on a physician's experience, and cannot be standardized, hence, it is not reproducible.[6] As a consequence, investigators of prospective investigation of PE diagnosis (PIOPED II) recommended the use of objective clinical assessment tools for the diagnosis of PE.[8]

For this purpose, several published clinical prediction rules (CPRs) are available, such as Wells score, Geneva score, and revised Geneva

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score.[5,8–10] Using these CPRs, studies have shown the prevalence of confirmed PE to be 10% in low probability category patients, 30% in moderate probability category patients, and 70% in high probability category patients.[7] However, few researchers have specifically looked at the accuracy of these CPRs in patients with malignancy. There is a need to evaluate the usefulness of these CPRs in cancer patients because of high prevalence of VTE, different characteristics of thrombus, increase tendency of clinical deterioration, and increased incidence of central PE in cancer patients. Therefore, we performed a retrospective review of all computed tomography pulmonary angiograms (CTPAs) done for suspicion of PE in cancer patients in our hospital and assessed the utility of the three above mentioned CPRs in predicting PE in this group of patients.

METHODS

The electronic medical records of Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC) were reviewed from December 2005 to November 2010. We identified 177 CTPAs performed during that period. The patients selected were registered to SKMCH & RC with any type of malignancy, suspected of having PE, had complete data available to reconstruct the CPR retrospectively, and received CTPA to confirm the diagnosis.

Of the 177 CTPAs performed, we selected 104 individuals who met the inclusion criteria. The computed tomography (CT) angiograms were performed on admitted patients, patients presenting to the emergency room, and outpatients.

Three CPRs (Wells criteria, Geneva score, and revised Geneva score) were evaluated for each patient based on the available data whenever possible. Variables recorded included basic demographics, type and stage of cancer, status of cancer (i.e., active on chemotherapy, metastatic, cured, or relapsed), and findings on CTPA including documentation of extent of pulmonary artery occlusion by the thrombus. In addition, we also recorded hemoglobin (Hb), white blood cells (WBC) count, platelet count, arterial blood gas (ABG), alveolar-arterial (A-a) gradient, and D-dimer, which were drawn within 24 hours of the CT scan, where available.

Patients were divided into two groups, CTPA positive (patients with PE) and CTPA negative (PE excluded), and risk factors were analyzed by calculating medians and percentages, where appropriate. Primary outcomes of interest were the sensitivities, specificities, positive and negative predictive values, for all three CPRs, abnormal D-dimer, partial pressure of oxygen (PO_2) < 71 mmHg, partial pressure of carbon dioxide (PCO_2) < 36 mmHg, heart rate (HR) > 100 beats/minute, and A-a gradient to evaluate their utility for excluding PE in our patient population.

The records of all patients were followed-up for four months post scan for documentation of PE, DVT, or sudden death. Comparisons were made with unpaired *t*-test and chi-squared analysis, and the Fisher's exact test, where appropriate, for normally distributed data. A *p*-value of < 0.050 was considered significant.

The study was reviewed by the Institution's Scientific Review Board (IRB) who granted it waiver from a formal IRB review given the retrospective nature of the research.

RESULTS

Out of the 104 CTPA's performed, 33 (31.7%) were positive for PE and 71 (68.3%) were negative. Basic characteristics of patients with positive and negative CTPAs are mentioned in Table 1. No significant difference was noted between the two groups. None of the patients in our cohort received DVT prophylaxis treatment.

Other parameters including WBC, Hb, platelets, peripheral capillary oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), PCO_2, and PO_2 values were compared with unpaired *t*-test and only PO_2 showed statistically significant difference between the two groups, although in absolute terms there was only a difference of 3 mmHg [Table 2].

Table 3 describes the accuracy of CPR's, ABG's analysis, and D-dimers in excluding PE. All three CPRs had high sensitivities and negative predictive values (NPV's). Modified Geneva had 100.0% NPV, but its specificity was the lowest (1.4%, 95% confidence interval (CI) 0.26–7.76).

A-a gradient had 100% sensitivity and NPV with low specificity. Other parameters of ABGs included PO_2 < 71 mmHg and PCO_2 < 36 mmHg, and tachycardia showed neither good NPV nor specificities. D-dimer assay was sensitive but NPV was lower (91.6%) than what has been described for non-cancer patients (97.3%).

Table 1: Basic characteristics of the patients in the two groups.

Characteristics	Total	CTPA positive, n = 33	CTPA negative, n = 71	*p*-value
Male	38	15	23	0.273
Female	66	18	48	
Age range (median)	15–79 (47.0)	25–70 (47.5)	15–79 (47.0)	0.540
Body mass index range (median)	13.6–50.3 (23.7)	13.6–37.0 (24.3)	14.9–50.3 (23.7)	0.763
Hematological malignancy	9	1	8	0.164
Solid organ malignancy	95	32	63	
Risk of thrombosis				**0.319**
Very high risk cancer (gastric and pancreatic)	1	1	0	
High risk cancer (lung, lymphoma, gynecological, genitourinary except prostate)	28	8	20	
Low risk cancer (others)	75	24	51	
Metastatic malignancy	45	12	33	0.330
On medical management	59	13	46	0.035
On surgical management	14	8	6	
Receiving radiation	2	0	2	0.330
Receiving no treatment	27	11	16	0.240

CTPA: computed tomography pulmonary angiogram.

Table 2: Laboratory variables of the two groups.

Variables	CTPA, positive	CTPA, negative	*p*-value
WBC 10^3 /µL (median)	8.12 (0.8–33.67)	8.12 (0.22–397)	0.815
WBC > 11x 10^3 /µL	46.9%	25%	0.187
Platelets10^3/µL (median)	194.5	181	0.330
Platelets > 350 x 10^3/µL	4/32 (12.5%)	12/68 (17.6%)	0.575
Hb g/dL (median)	11.1	10.85	0.082
Hb < 10 g/dL	28.1%	39.7%	0.372
O_2 sat (median)	95%	95%	0.132
FiO_2 (median)	26%	26%	0.974
PCO_2 mm Hg (median)	32	32	0.308
PO_2 mmHg (median)	68.1	71	0.038
A-a gradient (median)	70.2	70.5	0.547
Abnormal D-dimer	21	28	0.041

WBC: white blood cell; Hb: hemoglobin; O_2 sat: oxygen saturation; FiO_2: fraction of inspired oxygen; PCO_2: partial pressure of carbon dioxide; A-a: alveolar-arterial; CTPA: computed tomography pulmonary angiogram.

Table 3: Utility of variables and clinical prediction rules in predicting pulmonary embolism.

Variables	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
D-dimer (95% CI)	95.5 (78.20–99.19)	28.2 (16.54–43.78)	42.8	91.6
PCO_2 < 36mmHg (95% CI)	78.6 (60.40–89.79)	35.0 (24.17–47.64)	36.0	77.7
PO_2 < 71mmHg (95% CI)	67.9 (49.30–82.07)	56.6 (44.10–68.42)	42.2	79.1
HR > 100/minute (95% CI)	75.8 (58.90–87.17)	39.1 (28.48–50.92)	37.3	77.1
A-a gradient > 20 (95% CI)	100.0 (87.94–100.00)	5.1 (1.74–13.92)	33.3	100.0
Wells score (95% CI)	97.0 (84.60–99.46)	21.4 (13.40–32.30)	36.7	93.7
Geneva score (95% CI)	88.0 (70.04–95.83)	52.7 (39.79–65.31)	45.8	90.6
Modified Geneva (95% CI)	100.0 (89.57–100.00)	1.4 (0.26–7.76)	32.6	100.0

PCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; HR: heart rate; A-a: alveolar-arterial; CI: confidence interval.

We also calculated diagnostic odds ratio (DOR) for all these variables. D-dimer and all three CPRs showed DORs of around eight, indicating that these tests were eight times more positive in patients with PE.

All of the patients were followed-up for four months. Twenty patients lost to follow-up, two developed DVTs, and none of them had documented recurrent PE. At the end of the four-month period, 27 patients had died, seven of whom had sudden death. These seven patients may have had recurrent PEs, but since repeat CT scans were not performed this cannot be proven.

DISCUSSION

Our study showed that all three CPRs have high sensitivities and NPVs. However, modified Geneva score had 100% NPV, which makes it the best test to exclude PE. A-a gradient and D–dimer also showed high sensitivities and NPVs.

Several CPRs were devised as tools to rule out PE clinically. These rules help in excluding those patients who require no further investigations, based on history, clinical examination, and laboratory findings. American College of Chest Physicians (ACCP) anticoagulation guidelines recommend empiric anticoagulant treatment if clinical probability for PE is high, while waiting for diagnostic imaging.[11] As signs and symptoms of PE are quite variable, a systematic approach is required to manage and prevent mortality. In 1998, Wells et al,[6] devised a clinical model for patients with suspected PE, which along with ventilation perfusion lung scan, reasonably excluded PE. They noted that only 3.4% of the patients in the low probability group had PE. In 2001, Wicki et al,[12] validated the Geneva score, which was based on more objective variables than the Wells criteria. Prevalence of PE in the low probability group was 10%. However, only 13% (138) of the patients in their cohort had malignancy, and separate data for this cohort was not available. Iles et al,[7] evaluated the effect of clinical experience on pretest probability calculated by Wells and Geneva score. They observed that the Geneva score was more consistent in calculating pretest probability and showed least inter-rater variability. The Geneva score was revised in 2006 by Le Gal et al.[3] Eight statistically significant variables were identified and incorporated into the revised Geneva score, including presence of malignancy. Based on these variables, the prevalence of PE was reduced to 8% in the low probability group. Their study population also included only 9.2% (89) cancer patients. In both the Geneva and the revised Geneva scores, clinical variables were noted to be independent of implicit judgment of physicians, however, both were studied in emergency departments only.[13,14] Although all three rules have short comings, but when compared, showed similar performance in excluding acute PE in combination with D-dimer, proved to be even more sensitive and significantly decreased the need for further diagnostic imaging.[5,15]

Kearon et al,[16] demonstrated the utility of D-dimer testing alone in excluding PE in low pretest probability patients, however, that alone cannot be used to exclude PE in patients with moderate to high risk of developing PE. Similarly ABG analysis and A-a gradient alone or in different combinations were not helpful in excluding PE in previous studies, although these parameters are never analyzed in cancer patients.[17,18]

Cancer is associated with 4.1 times increased risk of thrombosis, and chemotherapy increases this risk 6.5 times that of the general population.[19,20] Moreover, thrombotic event within one year of diagnosis of malignancy have been shown to be associated with a poor prognosis.[21] Surgery in cancer patients also increases the risk of fatal VTE two to three times when compared to non-cancer patients undergoing similar surgery.[20] Hormone replacement therapies like tamoxifen and erythropoeisis stimulating factors are strongly associated with VTE. Other risk factors in chemotherapy patients are pre-chemotherapy platelet count, Hb, and leukocyte count. Finally, certain malignancies show higher predisposition for VTE and can be divided as very high risk (stomach, and pancreas), high risk (lung, lymphoma, gynecological, and genitourinary excluding prostate), and low risk (breast, colorectal, head, and neck). A clinical model based on these factors was proposed by Khorana et al,[22] in 2008 for predicting chemotherapy associated VTE. They suggested considering five variables; site of cancer, platelet count, Hb level (or use of erythropoiesis-stimulating agents), leukocyte count, and body mass index to determine risk of VTE in cancer patients.

Most studies analyzing the utility of CPRs in the general population included a relatively small number of cancer patients.[13,22,23] A meta-analysis of

52 different studies analyzing utility of CPRs and D-dimer combination showed sensitivities between 0.84–0.91 for the different tests, but all these studies contained only 2–30% of cancer patients.[24] The study with 30% of cancer patients had a sample size of 114 patients. A study by Sohne et al,[25] showed 2% incidence of VTE in low probability and D-dimer negative cancer patients after three months of follow-up in comparison, the incidence in non-cancer patients was 0.5%. However, despite the higher prevalence and incidence of elevated D-dimer in cancer patients, it was observed by Ten et al,[21] that the NPV of D-dimer test in cancer patients was as high as non-cancer patients in their cohort of 1 739 patients (217 had cancer).

Van et al,[26] performed a posthoc analysis from a prospective cohort study of patients clinically suspected of having PE. They assessed the performance of CPRs in excluding PE combined with a negative D-dimer test in patients with suspected PE and malignancy. They identified 114 patients who had malignancy noted that 34 (30%) were diagnosed with PE. They observed that the sensitivities for the CPRs were 65% (95% CI 48–95%) for Wells score and 74% (95% CI 57–84%) for the modified Geneva Score; similarly, the NPVs were 82% (95% CI 71–89%) and 76% (95% CI 60–87%), respectively. Although we observed higher NPVs and sensitivities for the CPRs in our study, but since the authors did not have any information on the tumor type, stage or treatment making, a comparison with our cohort was difficult.

Douma et al,[27] performed a posthoc analysis of 475 patients with malignancy from a cohort of 3 306 patients with suspected PE. One hundred and thirty (27%) of the 475 patients had PE. They calculated the receiver operating characteristics curves for Wells score and D-dimer and compared them with non-cancer patients. For the Wells CPR, the area under the curve (AUC) was 0.665 (95% CI 0.612–0.717) for patients with malignancy and 0.743 (95% CI 0.720–0.765) for patients without malignancy (p = 0.004). For D-dimer, the AUC was 0.803 (95% CI 0.734–0.871) for patients with malignancy, which differed significantly from the AUC for patients without malignancy: 0.875 (95% CI 0.865–0.895, p = 0.020).

Our study showed that an elevated D-dimer is very sensitive for PE (95.5%) but has a very low specificity (28.2%). These results are influenced by prevalence of high D-dimer and thromboembolism in these patients. ABG analysis in non-cancer patients had showed no benefit for exclusion of PE and similar results were seen when A-a gradient was used.[20] In contrast, our study shows that in cancer patients A-a gradient has 100% sensitivity and NPV, which is very close to D-dimer, Wells score, and Geneva score. Therefore, our study shows that CPRs and D-dimer are as sensitive for cancer patients as non-cancer patients to exclude PE. Additionally, A-a gradient has equal diagnostic test performance to CPR's and D-dimer.

Limitation to our study includes its retrospective design, as well as the fact that it is a single center study. Additionally, a significant proportion of our patients (20) were lost to follow-up, emphasizing the need for a large prospective multicenter trial that follows these patients for an extended duration of time.

CONCLUSION

Our study found that all three CPRs can be used to help exclude PE in patients with malignancy and modified Geneva score performing the best. However, there is a clear need for a prospective multicenter trial looking at the utility of these CPRs with different malignancies, as we would expect them to perform differently in patients with malignancies and higher predisposition for VTEs compared to those with a lower predisposition. We recommend using the modified Geneva score to help exclude PE in patients with malignancy.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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