The Clinical Characteristics of Pulmonary Embolism in Patients with Malignancy: A Single Medical Institutional Experience

The venous thromboembolic complication, pulmonary embolism (PE), is an important cause of death in cancer patients.[1-3] Depending on the clinical presentation, the case fatality rate for acute pulmonary embolism ranges from about 60% to less than 1%.[4] The in-hospital mortality for general medical and surgical patients with PE is up to 6% with a 30-day mortality of 9.3% and a 3-month mortality of up to 15.3%.[5]

Trousseau in 1865 hypothesized that the procoagulant activity generated by tumor cells, macrophages, platelets, and vascular endothelial cells contributed to a thrombophilic state in cancer patients.[6]

Since then, it has been demonstrated that venous thromboembolism (VTE) is three-fold more common in cancer patients compared to patients without cancer.[7-9] The use of newer and more aggressive chemotherapeutic agents has also been associated with an increased risk for thrombosis.[4]

Previous studies have shown that the risk of death is three-fold higher in VTE patients with cancer than VTE patients without cancer and this has been attributed to the fact that malignancies associated with VTE are usually diagnosed at later stages and hence appear to follow a more aggressive course.[10] Another contributing factor to the observed higher mortality is the increased risk of bleeding complications related to the long-term anticoagulation that is typically indicated in malignancy-related VTE.

Anatomically, a PE is characterized as central or peripheral, depending on the location or the arterial branch involved. Central vascular zones include the main pulmonary artery, the left and right main pulmonary arteries, the anterior trunk, the right and left interlobar arteries, the left upper lobe trunk, the right middle lobe artery, and the right and left lower lobe arteries. Peripheral vascular zones include the segmental and subsegmental arteries of the right upper lobe, the right middle lobe, the right lower lobe, the left upper lobe, the lingula, and the left lower lobe. We hypothesize that another potential factor that contributes to the fatal outcomes in PE patients with malignant disease is that they are more likely to suffer from more extensive PEs involving the central vascular zones. It is clear they have a more thrombophilic state and are hence more likely to develop more extensive DVTs than patients without cancer. This phenomenon can potentially results in hemodynamic instability and poorer clinical outcomes.

To verify this hypothesis that cancer patients are more likely to suffer from extensive pulmonary embolism and hence have worse clinical outcomes, length of stay (LOS) and mortality, we retrospectively analyzed PEs, in both cancer and non-cancer patients, detected by CT angiograms.

This retrospective study was conducted at St. Joseph's Regional Medical Center, a 750-bed inner city tertiary-care medical center in Paterson, New Jersey (population 146,199). The study qualified as minimal risk or exempt activity by the St. Joseph's Institutional Review Board who waived the informed consent requirement for individual patients due to the retrospective nature of the study. The medical records and CT scans of hospitalized patients with PEs that were diagnosed from January 2003 to December 2007 were reviewed.

We enrolled 118 adult inpatients (ages ≥ 18) who were hospitalized with symptomatic acute pulmonary embolism and patients were deemed eligible for inclusion provided they had a CT angiogram at the time of diagnosis. Data collection included age, gender, race, hypercoagulable risk factors (prolonged hospitalisation, presence of lupus anticoagulant, morbid obesity, oral contraceptive pills, myeloproliferative disorders, recent surgery), type of malignancy if present, hemodynamics (heart rate, oxygen saturation, respiratory rate, presence, or absence of arrhythmias) and laboratory tests which were documented at the time of diagnosis. In-hospital data with regards to anticoagulation, inferior vena cava filter placement etc. and patient outcomes for up to 1 year after the event were also collected. The Wells score could not be determined in light of the retrospective nature of this study.

Exclusion criteria included pulmonary embolism diagnosed by radiology imaging techniques other than CT angiogram. Therefore, 88 of the 118 screened patients were included in the study.

An experienced radiologist made the initial diagnosis of pulmonary embolism and it was confirmed by another equally experienced radiologist. Hence, all CT scans were interpreted by two experienced radiologists at the time of the initial clinical presentation. Only CT angiography (Siemens Medical Solutions, Iselin, NJ) with 1 mm sections were utilized and in all the cases, the images were obtained in a caudocranial direction, starting at the level of the lower hemidiaphragm and ending at the top of the aortic arch. The CT scans were evaluated using parameters derived on the axial plane. The measurements of the maximum minor axis of the right ventricle and the maximum minor axis of the left ventricle (LV) were taken. The right ventricle (RV) was considered dilated if the RV cavity was wider than the LV cavity along the short axis. The transversal diameter of the central pulmonary artery (on the CT image passing through the pulmonary trunk just before its branching off into left and right pulmonary arteries) was also measured. The criterion used to diagnose PE consisted of direct visualization of a thrombus or of a complete vessel occlusion by thrombus. A patient was assigned to the "central" group if there was radiologic evidence of a PE in the pulmonary arteries or the main stem alone with or without concomitant peripheral vessels involvement. All the other patients with filling defects in one or more peripheral vessels were assigned to the "peripheral" group.

Continuous variables (age and LOS) were tested for normality by the D'Agostino-Pearson omnibus normality test. Group-wise comparisons were made with a parametric method (*t*-test) for data that were not significantly different than normal and by a non-parametric method (Mann–Whitney test) for data that were not normally distributed.

Categorical associations were evaluated for statistical significance by Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (95%CI) are provided as measures of clinical relevance. For this study, α was set at 0.05; statistical significance required a two-sided *P* value $< \alpha$. To be considered as a covariate, a potentially confounding baseline characteristic was required to have a more rigorous level of significance, i.e. *P* < 0.20. None achieved this level. Univariate OR (odds ratio) and 95% CI are provided, as well as the hazard ratio (HR) and 95%CI from Kaplan–Meier analysis of survival data.

Data were analyzed using Prism™ software from GraphPad Corp., San Diego, CA on a Windows Vista/personal computer platform.

Table 1 displays the baseline characteristics of the 88 patients included in the study. 41/88 (46.6%) patients had an underlying malignancy and 47/88 (53.4%) patients did not. There were 20 males and 21 female patients in the cancer group and 23 males and 24 female patients in non cancer group.

The baseline demographic characteristics including age, gender, and race did not show any significant differences. In both groups, almost all patients presented with shortness of breath and/or chest pain. Hemodynamic instability (as evidenced by vital signs, oxygenation, respiratory compromise, and cardiac arrhythmia) did not show any statistical significance in both groups. The presence of lower extremity DVT was recorded in 13 patients in cancer group and 14 patients in non-cancer group.

Table 2 shows the common types of malignancy associated with VTE. Genito-urinary cancer was most commonly associated with VTE (13/41; 31.7%) followed by gastro-intestinal (10/41; 24.4%), then lung cancer, breast cancer, hematologic malignancies, melanoma, and CNS tumors. Patients in the cancer group were more likely to be present with a central PE (26/41; 63.4%) compared with 15 of 47 (31.9%) in the non-cancer group (OR = 3.70; 95%CI: 1.53 to 8.95; *P* = 0.0051).

There was no significant difference observed in the use of low molecular weight heparin versus warfarin between the two groups. Cancer patients with PE were more likely have an IVC filter placement than non cancer (13/41 *vs* 6/47). Lengths of stay as shown in Figure 1 is significantly greater in the

Table 1: The baseline characteristics of subjects in the study			
Characteristics	**Cancer group**	**Non cancer group**	***P*-value**
N (number)	41	47	
Age (mean ± 1 SD)	64.9±14.1	61.0±18.0	0.2355
Gender (M/F)	20/21	23/24	1.000
Ethnicity			
White	25	24	1.000
Black	8	10	
Others	8	13	
Hemodynamic instability (*n*/total; %)	23/41	19/47	0.1993
Risk factors (*n*/total; %)	12/41	23/47	0.0811

cancer group (median: 9d; IQR: 7-19d) compared to non-cancer group (median: 7d; IQR: 5-11d; *P* = 0.032).

Mortality was calculated with the available information from medical charts and tumor registry. The Kaplan–Meier curve in Figure 2 shows no statistically significant difference in the mortality between the cancer and non-cancer group groups (*P* = 0.17 HR = 1.60 (0.82 − 3.15)). However, the curves tend to separate toward the end of 12 months.

Table 2: Primary sites of tumor in cancer patients

Cancer type	Number of patients
Central nervous system	2
hematologic	3
Gastrointestinal	
Colon cancer	7
Pancreatic cancer	1
Esophageal cancer	1
Cholangiocarcinoma	1
Genito–urinary	
Endometrial cancer	2
Cancer of cervix	1
Prostate cancer	8
Ovarian cancer	2
Lung NSCLC	6
Breast	6
Melanoma	2
Multiple myeloma	1
Total	43

Venous thromboembolism (VTE) is a frequent complication in cancer and can sometimes be a harbinger of occult cancer.[11] Despite improved therapeutic options, the overall in-hospital mortality for major PE is estimated to be at least 22% and as high as 65% in those who require cardiopulmonary resuscitation.[12] There is a hypothesis that since many cancer patients have a low grade disseminated intravascular coagulation (DIC), they would have a higher rate of *in situ* thrombosis of small pulmonary vessels and therefore a relatively lower incidence of central pulmonary emboli.[13] Our study was aimed to disprove this hypothesis and identify patients with malignant disease who develop extensive central PEs and are hence at higher risk for hemodynamic instability and mortality.

Our study shows that cancer patients have high rate of central pulmonary embolism (involvement of main pulmonary arteries). The spectrum of complications for these patients includes right ventricular failure, hypotension, and tachyarrhythmias. However our study did not show an increase in hemodynamic instability with cancer patients.

In a previous retrospective study by Hasenberg *et al.*, there was a tendency for patients with malignant disease to have a higher rate of central PEs than patients without malignancies.[14] The odds of a central PE in cancer patients was about twice as high as in patients without a malignant disease. Our results seem to support this study and it appears that the
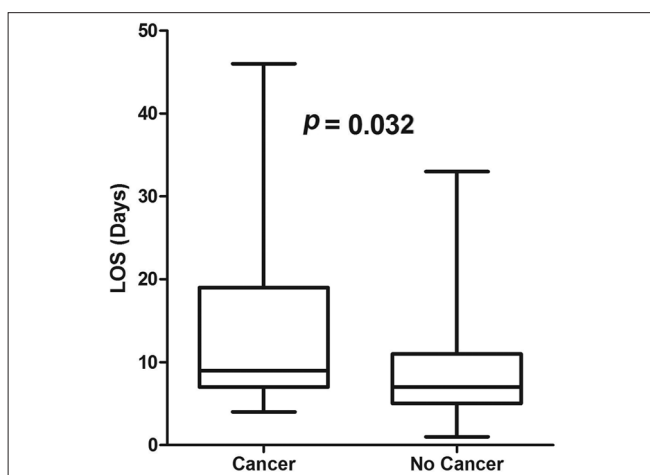

Figure 1: Box plot of the lengths of stay for the pulmonary embolism patients in the cancer and non-cancer groups. The horizontal line represents the median value, the lower and upper limits of the box represent the interquartile range, and the error bars represent the range. Lengths of stay is significantly greater in the cancer group with pulmonary embolism (median: 9d; IQR: 7-19d) compared to non-cancer group with pulmonary embolism (median: 7d; IQR: 5-11d; *P* = 0.032)
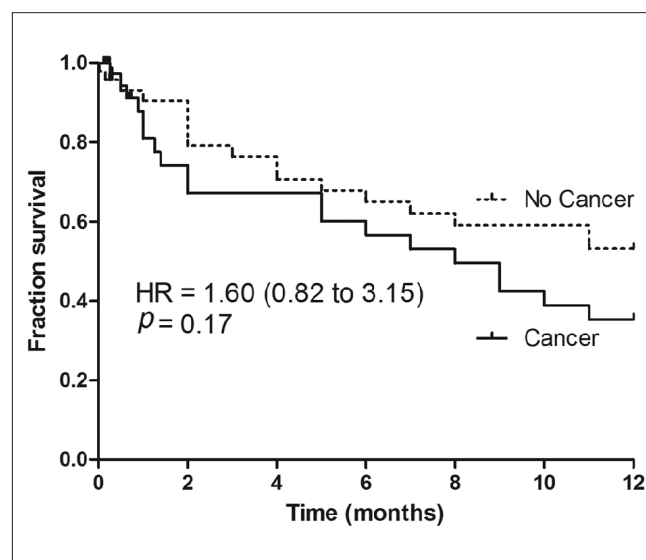

Figure 2: The Kaplan–Meier overall survival curves comparing the outcomes of the pulmonary embolism patients with and without cancer. The curves show no statistically significant difference in the mortality between the cancer and non-cancer group groups (*P* = 0.17 HR = 1.60 (0.82−3.15)

density of the intrapulmonary thrombus is greater in malignant patients than non-malignant patients. These findings are based on the hypothesis that there is an increased procoagulant activity in malignancy and that translates into extensive VTE. Furthermore, age, surgery, immobilization, and other comorbid features will also influence the overall likelihood of venous thromboembolic complications, as they do in patients without malignancy.

Published studies have demonstrated that involvement of the main central pulmonary arteries is associated with a high risk of mortality.[15,16] However, in our study, the mortality rate of the malignant patients with extensive PE's were not significantly different from that of the non-malignant patients.

Hospital LOS was significantly higher in cancer group compared with non-cancer group. Cancer group had an average of 14 days stay whereas the non cancer group had only 9 days on an average. This could most likely be a reflection of the multiple co-morbidities present in cancer patients.

Gastrointestinal cancer, lung cancer, and hematological cancer are associated with a very high risk for venous thrombosis.[17] The most common cancer associated with pulmonary embolism in our study were genitourinary,[13] gastrointestinal[10] followed by lung and breast (6 each). It is an interesting finding that in our study, genitourinary especially prostate cancer is strongly associated with pulmonary embolism and this could be as a result of the increased prevalence of these malignancies in the older African American male population that present to our medical institution.

There are limitations in our study that need to be highlighted. First, its a retrospective study and hence it did not allow us to produce correlations with clinical findings of other diagnostic tests, especially echocardiography that could help identify right ventricular failure. Second, we did not review the venous Doppler ultrasounds of all the patients to identify any potential association with extensive/bilateral lower extremity deep vein thrombosis. Third, the sample size is not very large.

Pulmonary embolism is a common and potentially lethal disease in active cancer patients. They appear to be at a higher risk for central PE and as a result are more likely to have longer stays in the hospital after diagnosis than patients without cancer. Based on the results of our study, specific strategies for the management of acute PE in patients with malignancy seem to be warranted.

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