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Comparison of Acute Pulmonary Embolism Cases Diagnosed in the Inpatient Setting Versus Those in the Outpatient Setting

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Abstract

Objective: Previous investigations on Acute Pulmonary Embolism (APE) have rarely made a comparison of those diagnosed in inpatient settings with those diagnosed in the outpatient settings. This study aimed to compare risk factors, symptoms and outcomes between APE cases on the basis of settings where they were diagnosed.

Methods: This is a single center retrospective review of all hospitalized patients who were diagnosed with APE over a 5 year period. We used the ICD codes to extract data on patients diagnosed with APE. Patients diagnosed with APE at the time of admission or within 48 hours of hospital admission were grouped as outpatient. Patients who were diagnosed with APE after 48 hours of hospital admission were grouped as inpatient.

Results: The sample included 82 APE cases diagnosed in inpatient settings and 95 APE cases diagnosed in the outpatient settings. Compared to APE cases diagnosed in the outpatient settings, cases diagnosed in the inpatient settings were more likely to be immobilized for 3 days or more (odds ratio [OR]=8.02, 95% confidence intervals [95% CI]=2.94-21.88), had central venous catheterization (OR=10.91, 95% CI=3.05-39.01), and have thrombocytosis (OR=5.23, 95% CI=1.19-23.02). Hospital length of stay (LOS) following the diagnosis of APE in the inpatient APE cases was longer compared to diagnosis in outpatient settings. Adverse outcome including death or major bleeding after the diagnosis of APE was significantly higher in the inpatient group.

Conclusions: These findings emphasize the need for vigilance in the management of APE diagnosed in two different settings, and warrant a review of decision-making approach to the diagnosis and treatment of APE in patients who develop it in the inpatient setting.

Keywords: Acute pulmonary embolism; Inpatient; Outpatient; Outcomes

Abbreviations

APE: Acute Pulmonary Embolism

CP: Chest pain

DVT: Deep venous thrombosis

ICU: Intensive Care Unit

ICD: international classification of diseases

IVC: Inferior vena cava

LOS: Length of stay

PE: Pulmonary Embolism

RIETE: The Computerized Registry of Patients with Venous Thromboembolism

SAS: Statistical Analysis Software

SOB: Shortness of breath

UFH: Un-fractionated heparin

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VTE: Venous thrombo-embolism

Introduction

Acute Pulmonary Embolism (APE) is the third most common cause of death from cardiovascular disease after myocardial infarction and stroke [1]. The vast majority (94%) of APE related deaths are because of a failure of diagnosis [2]. This is partly because of the non-specific symptoms and physical signs that the patients with APE have. To assist health care providers to make correct and timely decisions various prediction scores have been developed which can estimate the probability of APE based on patient characteristics. These commonly applied clinical prediction rules have been extensively validated in outpatients, however, only the Wells rule and the Miniati rule have been applied to hospitalized patients, albeit on small numbers of patients [3,4].

No surprise that the APE is a frequent clinical problem in hospitalized patients and in particular those undergoing major orthopedic surgery, in patients with malignancy and cirrhosis [5-7]. Although a number of risk factors for developing APE have been identified and heparin prophylaxis along with early mobilization proposed to reduce the incidence, APE remains an important clinical problem with Intensive Care Unit (ICU) mortality of 27% and in-hospital mortality of 31% [8,9]. There have been a number of studies that have described the characteristics and outcomes of patients with APE [10-16] however, most focused only those where APE is diagnosed in the outpatient setting. To our knowledge, there have been only three studies that have compared the characteristics and outcomes of patients who are diagnosed with APE in the inpatient setting versus those who are diagnosed with it in the outpatient setting [17-19]. One study focused exclusively on the elderly, [18] another compared both medical and surgical patients with massive or sub-massive APE [19], and the RIETE registry included patients with Deep Vein Thrombosis (DVT) [17].

This study aims to investigate the above mentioned difference in adult medical patients who are diagnosed in outpatient versus the inpatient setting. Distinguishing between these two settings may lead to further research on in hospital diagnosis of APE with ultimate goal of having specific prediction scores for identifying inpatients at high risk of developing APE.

Methods

Study design

We performed a retrospective chart review of all hospitalized patients from a single institute who were diagnosed with APE over a period of 4 years. The study was approved by the institutional review board (Reference: UFJ 2012-109). All patients in the hospital discharge registry with international classification of diseases (ICD-9) codes, APE (415.19), iatrogenic PE (415.11) and multiple PE (415.19) were considered for inclusion in this study. These patients were then divided into two groups based on the timing of diagnosis of APE. All the patients who developed APE more than 48 hours after admission (which was for unrelated reason) were considered as inpatient APE. Those patients who presented to the hospital and were found to have APE within 48 hours of admission were assigned to the outpatient APE cases. We excluded patients younger than 18 years of age, patients with only previous diagnosis of APE, and those with medical records having missing or incomplete information (see Figure 1). To have a more uniform patient population for this study we also excluded patients who were admitted to the surgical and trauma services.

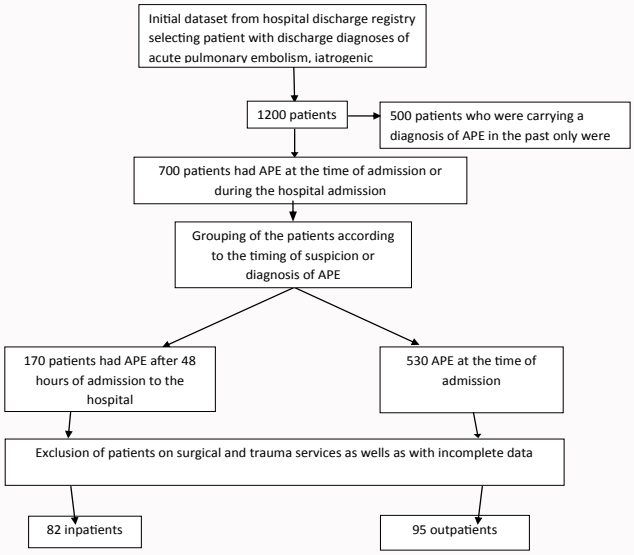

Figure 1: The scheme utilized to select patient's data for analyses.

Data collection

The data which was acquired from the medical records was arranged as demographic profile of the patients, risk factors for development of APE in these patients, patients' clinical presentation and treatment, and final outcome of that particular hospitalization. Demographic profile included information on age, gender and race of the patients. Data were collected on commonly known risk factors as well as care-related factors which predispose them to develop APE. The additional risk factors assessed in this study were cancer with or without treatment in the last six months prior to the diagnosis of APE, central venous catheterization and lower limb paralysis at the time of diagnosis of APE. Information on both the number and type of co-morbidities closely related to development of APE was collected as well. Patient's clinical presentation at the time of admission to the hospital or on the day of diagnosis of APE was extracted in addition. This encompassed both symptoms and vital signs. Information about treatment with anti-coagulants, thrombolytics or inferior vena cava filter was also collected. Similarly, the information about the final outcomes of the hospitalization in which the patient was diagnosed to have APE was collected which included: Length of Stay (LOS) following the diagnosis of APE, major bleeding requiring blood transfusion of blood product and death.

Statistical analysis

Each group was characterized using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Bivariate comparisons between the variables of interest and the groups were tested for associations using a chi-square test or quantitative differences using an independent two-sample student's *t*-test or a Wilcoxon signed rank test. A p value ≤ 0.05 was considered statistically significant. Four separate logistic regression models were constructed to show significant differences between APE cases diagnosed in the inpatient settings compared to those diagnosed in outpatient settings. The model 1 compared only risk factors as determined in the patient's history, model 2 included clinical symptoms and findings, model 3 tested for comorbidities, whereas model 4 included all factors shown to be significantly associated with APE cases diagnosed in inpatient settings in models

Table 1: Inpatient vs. outpatient pulmonary embolism cases from 2007 to 2011.

	Outpatient	Settings	Inpatient	Settings	P
	N = 95	%	N = 82	%	
Demographic characteristics					
Age > 55 years	46	48.4	44	53.7	0.48
Male	41	43.2	32	39	0.57
Race					0.44
- Caucasian	31	32.6	25	30.5	
- African-American	64	67.4	57	69.5	
Risk factors from history					
Recent surgery	12	12.6	16	19.5	0.21
History of trauma	3	3.1	2	2.4	0.77
Anticoagulation	2	2.1	2	2.4	0.88
Antiplatelet drugs	27	28.4	29	23.2	0.42
History of pulmonary embolism	17	17.9	1	1.2	<0.001
History of deep venous thrombosis	16	16.8	3	3.7	0.005
Cancer	17	17.9	8	9.8	0.12
Smoking	25	26.3	33	40.2	0.04
Thrombocytosis (Platelet count ≥ 400,000)	5	5.3	15	18.3	0.006
Lower limb paralysis	2	2.1	9	11	0.02
Central Venous catheter	5	5.3	30	37	<0.001
Immobilization for 3 or more days	18	19	54	65.9	<0.001
Symptoms and Findings					
Shortness of breath	70	73.6	28	34.2	<0.001
Chest pain	48	50.5	12	14.6	<0.001
Cough	10	10.6	8	9.8	0.84
Respiratory rate > 18/min	34	35.8	43	52.4	0.03
Heart rate > 100/min	36	37.9	41	50	0.11
Systolic blood pressure < 90 mmHg	77	95	67	93	0.59
Diastolic blood pressure < 60 mmHg	80	84.2	67	81.7	0.66
Temperature > 99°F	15	15.8	21	25.6	0.11
Body mass index (in Kg/m^2)					0.02
- 17- <25	30	31.9	21	25.6	
- 25-<30	18	19.2	19	32.2	
- 30 - <35	12	12.8	24	29.3	
- ≥35	34	36.2	18	21.9	
Glomerular filtration rate (GFR) < 60 ml/min	22	23.9	18	22.5	0.82
Oxygen <90 %	1	1.1	6	7.3	0.03
Location of embolism					0.79
- Central	70	73.7	59	72	
- Segmental	25	26.3	23	28	
Size of pulmonary embolism					0.78
- Small	69	72.6	58	70.7	
- Large	26	27.4	24	29.3	
Comorbidities					
N					0.14
- None	13	13.6	11	13.4	
-1	19	20	27	32.9	
- ≥ 2	63	66.3	44	53.7	

Type					
- Hypertension	59	62.1	58	70.7	0.23
- Diabetes mellitus	22	23.1	27	32.9	0.15
- Dyslipidemia	26	27.4	11	13.4	0.02
-Chronic Obstructive Pulmonary Disease	12	12.6	12	14.6	0.7
- Coronary artery Disease	12	12.6	5	6.1	0.14
- End stage renal or chronic kidney disease	6	6.3	8	9.8	0.4
- Congestive Heart Failure	11	5.9	0	0	0.001
Outcomes					
Final outcome					
- Discharge without event	86	90.5	64	78	0.06
- Bleed	5	5.3	9	11	
- Death	4	4.2	9	11	
Outcome bleed or death	9	9.5	18	22	0.02

1-3 as well as age and gender All statistical analysis was conducted using SAS 9.3 (Cary, NC).

Results

Figure 1 presents an overview of the patients' selection for this study. Out of the sample of 1200 patients identified by their ICD codes, the final sample for analyses included 82 APE cases diagnosed in inpatient settings and 95 APE cases diagnosed with it in the outpatient settings.

Patient demographics

Table 1 presents an overview of all the variables compared between the two groups. There were no differences in age, gender and race between the two groups. Thirty nine percent of the patients in the inpatient group were in the ICU at the time of diagnosis of APE and 21% of the patients in the outpatient group required admission to the ICU after a diagnosis of APE.

Risk factors and Comorbidities

Of all the risk factors evaluated, prior history of a DVT, APE and cancer was more common in the outpatient group compared to those diagnosed in the inpatient settings. Risk factors with higher prevalence in the inpatient group included history of smoking, thrombocytosis, lower limb paralyses, placement of central venous line and immobilization for 3 or more days.

The number of comorbidities between the two groups did not differ significantly. Compared to APE cases diagnosed in outpatient setting, those diagnosed in inpatient settings were more likely to have dyslipidemia.

Clinical presentation

Symptoms such as Shortness of Breath (SOB) and chest pain were more frequently reported in cases that were diagnosed in the outpatient settings as compared to those diagnosed in the inpatient settings. APE cases diagnosed in the inpatient settings were more likely to be tachypneic (respiratory rate of 18 or more per minute) and hypoxic (oxygen saturation in blood <90%) at the time of diagnosis than those diagnosed in the outpatient settings. In the inpatient group the diagnosis of APE was made on an average at the end of second week (11.5 days ± 9 days). No differences in the location or size of the clot on the imaging were observed between the two groups. Models 1-3 showed similar associations as those observed in the univariate analyses (Table 2). Model 4 showed that compared to those diagnosed in outpatient settings, thrombocytosis, placement of central venous catheter and immobilization for 3 or more days were more likely to be present in the APE cases diagnosed in the inpatient settings.

Prophylaxis and Treatment

More than 70% of patients in the inpatient group were on some form of prophylaxis (subcutaneous unfractionated heparin [UFH], subcutaneous Low Molecular Weight Heparin [LMWH] or sequential compression device) against VTE at the time of diagnosis of APE. As expected no patients in the outpatient group was on any VTE prophylaxis. Additionally we did not find any patient in either group to be on anticoagulation at the time of diagnosis of APE.

The most common form of treatment used for APE in both groups was a combination of subcutaneous LMWH and warfarin. Insertion of IVC filter as a sole treatment was insignificantly higher in the inpatient group. Whereas tissue plasminogen activator (t-PA) was not used in any patient in the inpatient group.

Outcomes

Hospital LOS following the diagnosis of APE was significantly longer ($p<0.001$) in the inpatient group (mean=29.9 days standard deviation [SD]=28.8) compared to those diagnosed in the outpatient setting (mean=6.5 days, SD=4.2). The composite "bad" outcome of major bleeding requiring transfusion of blood products or death during hospitalization was more common in the inpatient group. Four out of the 9 deaths (44.4%) in the inpatient group and 3 out of the 4 deaths (75.0%) in the outpatient group were attributed directly to APE as per physician death summaries. No significant differences were observed when these analyses were adjusted for demographic factors (not shown).

Discussion

Our study reveals that the patients who are diagnosed with APE in the inpatient setting differ from those diagnosed with it in the outpatient setting. This difference is not only in the factors which predispose these two different patient population to APE but also reflective in the subsequent outcomes after the diagnosis of APE. Results of our study may be more applicable on the patients admitted to the medical services as we included adult patients from all age groups, definitive diagnosis of APE (not just DVT) with wide spectrum of APE severity unlike previous studies [17-19].

Table 2: Factors associated with the inpatient diagnosis of pulmonary embolism compared with outpatients in University of Florida Jacksonville teaching hospital (2007 to 2011).

	Models for type of characteristics		Full model	
	OR	95% CI	OR	95% CI
Demographic characteristics				
Age > 55 years*			1.96	0.79-4.91
Male vs. female*			0.96	0.39-2.37
Risk factors from history	**Model 1**			
History of pulmonary embolism†	0.01	0.00-0.24	†	
Cancer	0.29	0.09-0.87	0.28	0.08-1.02
Thrombocytosis (Platelet count ≥ 400 000)	14.28	3.71-54.97	5.23	1.19-23.02
Central Venous catheter	6.49	2.00-21.09	10.91	3.05-39.01
Immobilization for 3 or more days	9.73	4.17-22.73	8.02	2.94-21.88
Symptoms and Findings	**Model 2**			
Shortness of breath	0.09	0.04-0.22	0.09	0.03-0.25
Chest pain	0.09	0.04-0.23	0.13	0.04-0.39
Temperature > 99°F	3.27	1.28-8.44		
Body mass index (in Kg/m^2)				
- 17- <25	1			
- 25-<30	1.94	0.68-5.57		
- 30 - <35	4.99	1.60-15.57		
- ≥35	0.87	0.32-2.41		
Comorbidities	**Model 3**			
- Dyslipidemia	0.41	0.19-0.89	0.09	0.02-0.36

* Variables forced in the analyses
† Variable was strongly associated with outpatient cases and was not considered in the final model
OR – Odds of finding given characteristics in inpatient compared to outpatient cases
95% CI – 95% confidence interval

Patient demographics

This study did not show any significant difference in age, gender, and race between the two groups of patients. We studied patient demographics as there has been a recent increased awareness on ethnic differences in epidemiology of DVT/APE largely as a result of several recent studies conducted in the United States. These studies have shown that incidence rate of DVT/PE is higher in African American patients with predilection for female gender [20-22]. It may be possible that we failed to observe any differences probably because of the small size of the patient populations in this study. It is noteworthy however that there were differences in demographics inside each group, as there was higher number of females and African American patients who were diagnosed with APE in each individual group.

Risk factors and Co-morbidities

Studies in the past have shown that all of the patients with inpatient diagnosis of APE had at least one or more predisposing factors [23] while only about half of the patients with outpatient diagnosis have documented predisposing factors [24]. Our study findings were consistent with the previous studies in the inpatient group but we saw only about 6% of patients in the outpatient group with no clear risk factors for development of APE. Our study also looked into the presence of so called "temporary risk factors" such as recent surgery or trauma, immobilization for more than 3 days, presence of a central venous catheter as well as the "permanent risk factors" such as previous history of DVT/APE, lower limb paralysis and thrombocytosis. In addition, our study also accounted for the co-morbidities.

When comparing the individual risk factors between the two groups, our study showed that more patients in the inpatient group had various risk factors which were significantly higher than the patient in the outpatient group. This is not surprising because hospitalization and its associations (immobilization, central venous catheterization) are independent risk factors for VTE [25]. In contrast history of a DVT or APE was significantly more common amongst the patients in the outpatient group. Even though in a previous study [19] there was no significant difference in the history of prior VTE, these findings may be reflecting the tendency for patient in the outpatient group to develop VTE and present with it at the very outset without any provocation.

On detailed comparison of the comorbidities prevalent in the patients in these two groups, this study found no difference in the number of co-morbidities. Multiple individual comorbidities which have direct or indirect co-relation to development of an APE were assessed. It was revealed that patients in the outpatient group had higher prevalence of dyslipidemia. The implication of this risk factor as a part of metabolic syndrome to increase the risk of APE has been shown in a number of recent studies [26-27].

Clinical presentation

Development of an APE in a patient has long been known to cause non-specific symptoms and signs. In a recent study [28] it

was shown that about 7 % of the patients did not have any of the common symptoms and signs associated with diagnosis of APE. SOB, chest pain, and cough are the three common symptoms associated with APE diagnosis [29]. To our surprise, less number of patients in the inpatient group showed SOB and chest pain compared to those diagnosed in the outpatient settings. It might be possible that some of the patients were immobilized and/or intubated and sedated in the ICU and would've complained of SOB or CP more frequently if they had been awake and/or ambulatory. Even though the complaints of symptoms were lesser in the inpatient group, higher number of patients showed tachypnea and hypoxia. We speculate that the oxygen saturation was lower probably because most of the inpatients were immobilized and/or were in the ICU and thus predisposed to atelectasis. On the other hand, insignificant difference in the size and location of APE rules it out as a possible explanation.

There was no difference in the other vital signs between the two groups in our study. This is in contrast to the Japanese study and the RIETE registry both of which found hypotension to be more common in the patients who developed APE in the inpatient setting (21% vs. 0, $p = 0.02$, and 8% vs. 7%, $p = 0.004$, respectively) [17,19]. The higher chance of an adverse outcome in the inpatient group is most likely due to the prevalence of multiple temporary risk factors and severe co-morbidities. The lack of difference between the inpatient and outpatient group in terms of individual adverse outcomes can also be similarly explained by the fact that higher number of inpatients were on VTE prophylaxis in our study. Moreover patients in the outpatient group who had worse hemodynamics or severe presentation might have not made it to the hospital at all. Nevertheless these results reflect the fragility of clinical characteristics of inpatients diagnosed with APE which results commonly in unfavorable outcomes.

Study Limitations

This study was from a single center, small and retrospective in nature. This precluded from evaluating long-term outcomes like death and recurrent VTE within 3 months of diagnosis of APE. The group of patients who developed APE in the outpatient setting did not include patients who were not hospitalized. However, inclusion of such patients would probably not have changed the results since such patients would be healthier than those who were hospitalized. Our study attempted to adjust the two groups to the best of our ability but was limited by the design of the study. A minimal use of thrombolytics was observed in this sample, and a higher use of this treatment option might have led to different outcomes in both the groups opposed to the ones reported here. Due to the retrospective nature of the study it is difficult to entirely rule out the impact of antecedent co-morbidities on the final outcomes in the inpatient group. Although the number of comorbidities did not differ between the two groups, these findings beg the questions whether it is the severity of comorbidities that matter? Also if more patients were on some form of VTE prophylaxis could it have prevented this excess morbidity or mortality? These shortcomings can be addressed in future studies with large samples and more detailed data collection.

Conclusions

Patients who are diagnosed with APE in the inpatient setting differ slightly from those who are diagnosed with it in the outpatient setting. They are symptomatic less often yet have multiple temporary risk factors for VTE more often. APE in such patients is associated with a longer hospital LOS and a significantly higher risk of major bleeding or death. These findings emphasize the need for vigilance in the management of APE in such patients and warrant further research into the reasons behind the difference in outcomes between the two groups of patients in order to improve the approach to the diagnosis and treatment of APE in patients who develop it in the inpatient setting.

Competing Interest

The authors declare that they have no competing interests whatsoever.

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