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Prevalence and Prognostic Significance of Deep Venous Thrombosis in Pulmonary Embolism

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ABSTRACT

Background: Deep venous thrombosis (DVT) and pulmonary embolism (PE) are regarded as 2 distinct clinical presentations of the same illness. Up to 90% of symptomatic PEs are caused by thrombi in the venous system of the lower extremities. There is a great deal of uncertainty regarding the precise frequency of DVT in individuals with PE and the clinical importance of concurrent DVT. **Objective:** The aim of the current study was to evaluate the prevalence and prognostic significance of DVT in patients with PE.

Patients and methods: A retrospective study included 100 patients with confirmed PE. CT pulmonary angiography (CTPA) was used to diagnose all PEs. Using duplex ultrasonography, all patients were evaluated for the existence of DVT in the lower or upper extremities. Patients were classified into concomitant DVT and non-DVT groups.

Results: DVT was detected in 44% of PE cases (16 of them had subclinical DVT without evident symptoms "36.4% of DVT cases"). Proximal lower limb DVT was found in 36 patients and 6 cases suffered distal lower limb DVT. Upper limb DVT was shown in only 2 cases. Bilateral DVT was found in only 4 cases. Wells and modified Wells scores were significantly different among the 2 groups, where DVT confirmed cases presented more with likely or high-risk cases than DVT negative group. Mortality was proved to be insignificantly different between both groups with 22.3% mortality in DVT positive cases and 25% mortality in DVT negative cases, with overall mortality of 24%.

Conclusions: Nearly half of PE cases had concomitant DVT and that associated DVT had no effect on mortality. Post-operative period and cancer are two comorbidities that could be risk factors for PE without DVT.

Keywords: Pulmonary embolism, DVT, Prevalence, Prognostic significance.

INTRODUCTION

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are viewed as two distinct clinical symptoms of the same illness. Because of sharing similar etiology, the concept of venous thromboembolism (VTE) was introduced several years ago [(1)].Almost 90% of individuals with symptomatic PEs had the source of the emboli in the venous system of the lower limbs [(2)]. Despite of the advances in the diagnostic and therapeutic modalities, there is still considerable mortality rate of VTE during the first 3 months with reported range of 1.4% to 17.4% [(3)].

Many studies demonstrated that some patients with symptomatic DVT had asymptomatic PE. Meanwhile many patients with PE had clinically silent DVT [(4)]. Nonetheless, little is known about the actual frequency of DVT in individuals with PE and its clinical importance [(5,6)]. Also, there is a lack of information about the prognostic value of concurrent DVT in PE patients [(7)].The aim of the current study was to evaluate the prevalence and prognostic significance of DVT in patients with PE.

PATIENTS AND METHODS

A retrospective study included 100 patients with confirmed PE. Data were collected from records of inpatients admitted in the Chest Department and Respiratory Intensive Care Unit of Minia University Hospital.

For all patients detailed history regarding risk factors for VTE was recorded. Also, assessment of clinical probability for PE was done using wells and simplified wells scores.

CT pulmonary angiography was used to diagnose all PEs (CTPA). The localization of the thrombus in the major pulmonary arteries, lobar pulmonary arteries, and segmental or sub segmental branches was further assessed for each confirmed PE on CTPA.

Duplex ultrasonography was used to determine if DVT was present in the lower or upper extremities. Duplex ultrasonography results led to the classification of DVT into proximal and distal DVT. Proximal DVT is defined as thrombosis that affects the common and external iliac veins, common femoral vein, femoral vein, and popliteal vein without respect to calf vein thrombosis. The thrombosis exclusively affects the calf veins in distal DVT [(7)].

Patients were classified into concomitant DVT and non-DVT groups. Chest plain radiography, and some laboratory tests (PaO2, A-a oxygen gradient, lymphocytic count) were done and compared between both groups, as well as comparison regarding the location of the embolus in the multidetector CTPA. Mortality was also compared between both groups.

Ethical Approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, El-Minia University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of

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the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS Inc., Chicago) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Of the studied 100 patients, DVT was detected in 44 (44%) patients. Sixteen of them had subclinical DVT without evident symptoms; 36.4% of DVT cases. **Table 1** summarizes the characteristics of DVT in the studied patients.

Table (1): Prevalence and description of DVT in the studied patients.

DVT	PE Positive (N=100)
No **Yes**	56 (56%) 44 (44%)
Upper limbs **Lower limb**	2 (4.5%) 42 (95.5%)
Unilateral **Bilateral**	40 (90.9%) 4 (9.1%)
Proximal **Distal**	36 (81.8%) 6 (13.6%)

DVT: Deep Venous Thrombosis. PE: Pulmonary Embolism.

Table 2 showed that Wells and modified Wells score were significantly different among the 2 groups (DVT positive versus DVT negative).

Table (2): Simplified Wells and Wells score in DVT positive and DVT negative cases.

Variable	DVT Positive (N=44)	DVT Negative (N=56)	P-value
Simplified Wells PE unlikely PE likely	0 (0%) 44 (100%)	9 (16.1%) 47 (83.9%)	0.04* *
Wells score Low Intermediate High	0 (0%) 16 (36.4%) 28 (63.6%)	4 (7.1%) 41 (73.2%) 11 (19.6%)	0.004*

DVT: Deep Venous Thrombosis. N: number. PE: Pulmonary Embolism. *: Significant if P value <0.05.

Regarding demographic data and comorbidities, **Table 3** showed statistically significant difference between both groups regarding the previous history of DVT. On the other hand, postoperative cases were found more in the DVT negative group than the DVT confirmed group. Moreover, cancer was also presented in 16.1% of DVT negative cases and was completely absent in DVT confirmed cases (P=0.04).

Table (3): Demographic characteristics, baseline data and comorbidities of PE patients with and without DVT.

Variable	DVT Positive (N=44)	DVT Negative (N=56)	P-value
Age	(21-70) 44.95 ± 14.5	(22-78) 48.68 ± 17.17	P=0.41
Sex Males Females	 16 (36.4%) 28 (63.6%)	 24 (42.9%) 32 (57.1%)	P=0.68
Smoking Non smoker Mild smoker Moderate smoker Severe smoker	 22 (50%) 4 (9.1%) 4 (9.1%) 14 (31.8%)	 31 (55.4%) 11 (19.6%) 9 (16.1%) 5 (8.9%)	P=0.19
Orthopedic surgery	8 (18.2%)	13 (23.2%)	P=0.70
Previous history of DVT	44 (100%)	5 (8.9%)	P=**0.001***
Pregnancy	6 (13.6%)	2 (3.6%)	P=0.16
Immobility	16 (36.4%)	33 (58.9%)	P=0.12
Postoperative	8 (18.2%)	25 (44.6%)	**P=-0.04***
Diabetes mellitus	8 (18.2%)	5 (8.9%)	P=0.37
Hypertension	4 (9.1%)	7 (12.5%)	P=0.67
Cancer	0 (0%)	9 (16.1%)	**P=0.04***
Oral contraceptive	2 (4.5%)	5 (8.9%)	P=0.49

*: Significant if P value <0.05.

Table 4 showed that there was no statistically significant difference between both groups regarding Chest X ray findings distribution. The most common finding found in both groups is free Chest X ray, followed by Hampton hump sign and raised diaphragmatic copula, then pleural effusion and lastly consolidation.

Table (4): Distribution of Chest X-ray findings in DVT positive and DVT negative cases.

Variable	DVT Positive (N=44)	DVT Negative (N=56)	P-value
Free	20 (45.5%)	26 (46.4%)	0.2
Consolidation	14 (31.8%)	14 (22.6%)	0.2
Pleural effusion	16 (36.3%)	24 (38.7%)	0.2
Raised copula	18 (40.9%)	24 (38.7%)	0.4
Hampton hump sign	18 (40.9%)	28 (43.7%)	0.1

A shown in **Table 5**, both groups were insignificantly different as regards the location of the embolus in CTPA, with sub segmental lesions proved to be the most frequent lesions in both groups.

Table (5): Location of embolus in MDCTPA in DVT positive and DVT negative groups

Affected artery	DVT Positive (N=44)	DVT Negative (N=56)	P-value
Main pulmonary artery only	4 (9.1%)	6 (10.7%)	0.8
Main pulmonary artery with lobar, segmental or sub-segmental affection	12 (27.3%)	14 (25%)	
Isolated lobar	2 (4.5%)	6 (10.7%)	
Segmental	10 (22.7%)	10 (17.9%)	
Subsegmental	16 (36.4%)	19 (33.9%)	
Lobar and sub segmental	0 (0%)	1 (1.8%)	

Comparing some laboratory parameters of the 2 groups, **Table 6** revealed non-statistically significant differences between them.

Table (6): Laboratory findings in DVT positive and DVT negative cases

Variable	DVT Positive (N=44)	DVT Negative (N=56)	P-value
PaO_2	67.8 ± 12.9	66.1 ± 12.8	0.09
A-a Gradient	6187.8 ± 1147.2	6169.1 ± 1147.2	0.9
Lymphocyte count	3.04 ± 0.71	2.1 ± 0.43	0.05
D-dimer	652.3 ± 100.6	646.2 ± 110.4	0.8

DVT: Deep Venous Thrombosis. PE: Pulmonary Embolism. N: Number. PaO_2: Arterial blood oxygen tension. A-a gradient: Alveolar arterial oxygen gradient. Hs-CRP: high sensitivity C reactive protein.

Mortality was proved to be insignificantly different between both groups, with 22.3% mortality in DVT positive cases and 25% mortality in DVT negative cases, with overall mortality of 24% (**Table 7**). Hospital mortality was not significantly different between both groups

Table (7): Survival in DVT positive and DVT negative cases.

Variable	DVT Positive (N=44)	DVT Negative (N=56)	P-value
Survivors	34 (77.3%)	42 (75%)	0.7
Non survivors	10 (22.3%)	14 (25 %)	

DVT: Deep Venous Thrombosis. PE: Pulmonary Embolism. N: Number.

DISCUSSION

The majority of the patients, DVT in the lower limbs that is symptomatic or asymptomatic will result in PE as a side effect [(8)]. According to recent data PE can present without DVT, which is termed de novo (DNPE) [(9)]. The diagnosis of peripheral or abdominal vein thrombosis in a considerable proportion of PE patients is somewhat challenging despite thorough and sensitive testing [(10,11)].

The occurrence of PE without peripheral DVT could be attributed to several reasons. Sometimes total dislodgement of a thrombus from its original site of formation can happen [(8)]. Moreover, thrombus can develop in other unexpected places, such as the heart, jugular vein, or abdominal vein (especially right-sided intra-cardiac thrombosis). In-situ pulmonary thrombus development is a possibility at last.

Many years ago, believed that DVT and PE were to the same disease group but had distinct clinical presentations. Few studies, however, looked at the total prevalence of DVT in PE patients. According to several researches, the reported prevalence of concurrent DVT in individuals with PE ranges widely, from 10% to 93% [(12,13,14,15)]. The substantial heterogeneity of patients among studies and using different methods for DVT detection (venography in older studies and compression ultrasonography in more recent ones) could be responsible for the wide range of variability.

The current study elucidated 44% prevalence of DVT in PE cases, with most thrombi found in lower limbs (95.5%) and 81.8% of the thrombi were proximal.

Similar to these results, **Lee Colleagues** [(3)] discovered that 45.5% of PE patients had concurrent DVT. **Yamaki Colleagues** [(7)] discovered that proximal DVT was present in 30% of their patients, and that 58.1% of PE patients also have concurrent DVT. Up to 60% of patients with CTPA-proven symptoms of PE have concurrent DVT, according to **Girard Colleagues** [(15)].

In the current study, 16 (36.4%) patients were proven to have subclinical DVT without any clinical manifestations of it.

In the study by **Kelly and Colleagues [16],** the reported prevalence subclinical DVT in general surgical, stroke and orthopedic patients when heparin prophylaxis was not used was 19 to 84%. Also, their study showed a significant minority of patients who develop subclinical proximal DVT will end in PE. Study of **Hirmerova and Colleagues [17]** elucidated that 57.3% of DVT confirmed cases were asymptomatic.

Wells and modified wells score were shown in the current study to be significantly different among both groups, with all DVT confirmed cases and 83.9% of DVT negative cases showed likely PE in modified wells score. In original wells score, more DVT positive cases revealed high probability 63.6% versus 19.6% in the DVT negative group. While in the DVT negative group, the majority (73.2%) of patients had intermediate probability compared to 34.4% in the DVT positive group. None of the patients in the DVT positive group had low probability for PE, while 7.1 in the DVT negative group had low probability for PE.

Of course, the statistically significant difference can be attributed to the inclusion of DVT as a risk factor in both wells and modified wells classifications, but also intermediate and high risk were present in DVT negative cases due presence of other risk factors. However, the important point to reveal is that in DVT negative patients, about 16% of patients had low clinical probability using modified wells score. Whereas, by using original well score, 7.1% of DVT negative patients had low clinical probability which necessitate a higher degree of clinical suspicion in such group of patients

In the current study, previous history of DVT was significantly presented more in DVT confirmed cases (100%) than in DVT negative cases (9.7% only). **Hirmerova and Colleagues [17]** found that previous DVT was presented more in the DVT positive group but non-significantly (P=0.32) and this may be due to the difference in group numbers. Postoperative PE and cancer were more significantly presented in the DVT negative cases (45.2% and 16.1%, respectively) than in DVT positive cases (18.2% and 0%, respectively). Malignancy was strongly related with isolated PE according to **Schwartz and Colleagues [18].** Moreover, **Palareti and Colleagues [19]** found that active cancer was significantly presented more in idiopathic PE (12.8%) than in DVT associated cases (8.1%) (P=0.03). The Study of **Lee and Colleagues [3]** revealed slight increase in history of surgery or trauma ≤4 weeks in DVT confirmed cases but with no significant value (P=0.824).

Velmahos and Colleagues [20] studied 247 trauma patients and diagnosed PE in 46 of them. They found DVT in only 7 patients; therefore, they concluded that PE might occur de novo in the lungs.

Several studies have shown inconsistencies and contradictions in the data about the clinical importance of concurrent DVT in the course of PE patients. According to the International Cooperative Pulmonary Embolism Registry (ICOPER) research, concurrent DVT in PE patients is unrelated to all-cause death [11]. Nevertheless, **Wicki and Colleagues [21]** showed that patients with concurrent DVT had a greater chance of dying than those without DVT. In addition, a recent meta-analysis revealed that DVT is strongly linked to a higher risk of 30-day death in patients with acute PE [22].

The current study revealed insignificant difference in mortality between DVT positive and DVT negative cases. In accordance to these results, **Lee and Colleagues [3]** found that for patients with PE, the presence of concurrent DVT did not provide a statistically significant difference in 30-day all-cause death (P=0.584).

Overall mortality rate in the current study was 24% and these results are higher than the results of **Surov and Colleagues [23]** who detected mortality rate within 30 days observation time of 17.7%.

Limitations of the current study were the retrospective design and the small number of included patients.

CONCLUSION

Post-operative period and cancer are two comorbidities that could be risk factors for PE without DVT. Absence of DVT could make the diagnosis of PE more challenging by decreasing the clinical probability for PE. Using the original wells score rather than the simplified wells could be more helpful in diagnosis of PE in DVT negative patients. It is recommend conducting more studies on a larger number of cases and more sensitive modalities for diagnosis of DVT in PE confirmed cases. Also future studies should screen for hidden thrombi in PE cases and searching for other risk factors in idiopathic PE, like hidden malignancy or thrombophilia.

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