Clinical and Applied Thrombosis/Hemostasis
2018, Vol. 24(8) 1352-1357

DOI: 10.1177/1076029618779143
journals.sagepub.com/home/cat
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The Prevalence of Concomitant Deep Vein Thrombosis, Symptomatic or Asymptomatic, Proximal or Distal, in Patients With Symptomatic Pulmonary Embolism

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Abstract

Patients with pulmonary embolism (PE) may have symptomatic or asymptomatic concomitant deep vein thrombosis (DVT). The reported prevalence of PE-associated DVT is variable, and thus, the utility of routine testing is controversial. The aim of our study was to analyze the prevalence of DVT and the factors associated with proximal DVT/whole-leg DVT in patients with symptomatic PE. In 428 consecutive patients (mean age: 59 $\pm$ 16.4 years; 52.3% men), we performed clinical examination and complete bilateral compression ultrasound and ascertained medical history and risk factors for DVT/PE. χ^2 and *t* tests were used. Deep vein thrombosis was found in 70.6%; proximal DVT in 49.5%. Sensitivity/specificity of DVT symptoms was 42.7%/93.7% for whole-leg DVT and 47.6%/83.3% for proximal DVT. Male gender significantly prevailed among those with whole-leg DVT and with proximal DVT (58.9% and 61.8%). Active malignancy was significantly more frequent in the patients with proximal DVT than without proximal DVT (10.4% vs 3.7%). In conclusion, the prevalence of PE-associated DVT is quite high but clinical diagnosis is unreliable. In our group, male gender and active malignancy were significantly associated with the presence of concomitant proximal DVT.

Keywords

deep venous thrombosis, prevalence, pulmonary embolism, compression ultrasound

Introduction

Venous thromboembolism (VTE) encompasses 2 main clinical forms—deep vein thrombosis (DVT) and pulmonary embolism (PE). Clinical presentation may include signs and symptoms of both forms or those of isolated DVT/PE only. In patients with proven symptomatic PE, the concomitant presence of DVT may be verified by venous compression ultrasound (CUS), an easily available and noninvasive test. However, the utility of CUS in patients with PE has not been clearly established. Moreover, the reported prevalence of PE-associated DVT varies substantially—from 10% to 93% in an older meta-analysis[1] and from 25% to 63% in more recent studies.[2,3] Some authors found an association of the presence of DVT with a worsened outcome in patients with PE.[4] This finding was not consistent across studies, but in a recent meta-analysis, concomitant DVT was significantly associated with increased 30-day all-cause mortality in nearly 7868 patients with PE.[5]

Searching for DVT in patients with PE may play a role in several aspects:

- in thrombotic load evaluation and, consequently, in risk stratification;
- if the use of computed tomography (CT) pulmonary angiography in a patient with PE symptoms is problematic (ie, in pregnancy or allergy to iodine), then finding proximal DVT with CUS means confirmation of PE and enables to avoid exposition to radiation and contrast material[6];

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- diagnosing DVT (even asymptomatic) may prompt timely prevention of postthrombotic syndrome (PTS); and
- baseline testing may theoretically enable better assessment of possible subsequent VTE recurrences (or treatment failure).

The aim of our study was to evaluate the prevalence of DVT, both symptomatic and asymptomatic in patients with symptomatic PE, and to identify factors associated with the presence of DVT.

Materials and Methods

Study Design and Patients

The study had been conducted in the setting of a tertiary university hospital as a single-center retrospective study of prospectively collected data. Since September 2003 to December 2015, 907 consecutive patients, older than 18 years, visited thrombosis clinic shortly after an objectively confirmed VTE—1 to 3 weeks after the event. Only those with diagnosed symptomatic PE, with or without objectively confirmed DVT of the legs, were included. All the patients provided a written informed consent.

Data were obtained from paper and electronic records of eligible patients and completed during personal visit in the clinic by a structured interview. We focused on the following information: symptoms at the time of VTE presentation—symptoms of PE (dyspnea, chest pain, cough, hemoptysis, or syncope), symptoms of DVT (unilateral leg swelling, pain, and color changes); personal history of previous VTE; potential provoking factors of an index VTE event; type and extent of VTE; and comorbidities. We measured patients' anthropometric characteristics and calculated body mass index (BMI) as weight divided by the square of height, in kilograms per square meter (kg/m^2).

The initial management of an event had been at the treating physician's discretion and had been performed either on inpatient basis, in the Department of Internal Medicine, or on outpatient basis in the clinic of this Department. The diagnostic process of PE had been performed in a standard structured manner, that is, the first step had been the assessment of pretest clinical probability of PE presence. Of the scoring systems commonly used in clinical practice, for example, PE Wells score,[7] revised Geneva rule,[8] simplified Wells score,[9] simplified revised Geneva rule,[10] or Pulmonary Embolism Rule out Criteria,[11] PE Wells score had been used as it had been widely adopted in our institution. In the case of high or moderate PE probability, patients had undergone further examination with an imaging method—helical CT pulmonary angiography or/and perfusion/ventilation lung scan. In those with isolated DVT symptoms, the pretest clinical probability had been assessed by DVT Wells score,[12] and CUS had been further used in the case of high or moderate probability.

In the patients with confirmed PE, within 7 days after diagnosis of PE, complete CUS of both legs had been done (complete CUS means examining leg veins from the groin to the ankle, unlike limited or 2-point ultrasound in which the examiner looks only in the groin and in the popliteal fossa).[13] Venous ultrasound had been performed in all but 10 patients.

Table 1. Characteristics of the Whole Group of Patients With PE (n = 428) and the Prevalence of DVT and SVT.

Age, years	59 ± 16.4
BMI, kg/m^2	29.7
Females, n (%)	204 (47.7)
Unprovoked events, n (%)	260 (60.7)
Active cancer, n (%)	30 (7.0)
Previous VTE (PE and/or DVT), n (%)	92 (21.5)
Previous DVT, n (%)	51 (11.9)
DVT, n (%)	302 (70.6)
Proximal DVT, n (%)	212 (49.5)
SVT, n (%)	16 (3.7)
SVT without DVT, n (%)	10 (2.3)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, superficial vein thrombosis; VTE, venous thromboembolism.

Having excluded the patients with isolated DVT symptoms (ie, those without symptomatic PE), 1 with upper extremity DVT and 10 cases with PE in whom CUS had not been performed, we finally included 428 patients into the analysis.

In the case of confirmed DVT, we distinguished proximal location (thrombus above popliteal fossa) and distal location (calf vein thrombosis). If positive personal history of previous VTE was reported, we obtained further details about the type of the event (DVT, PE, or both) and location in the case of DVT (right/left, proximal/distal).

We labeled the events as provoked if triggered by or associated with injury, plaster cast, surgery within 2 months prior to VTE; acute infection; immobility for at least 3 consecutive days or hospitalization with immobility; active cancer (ie, diagnosed 1 year or less prior to VTE or simultaneously and/or ongoing cancer therapy); pregnancy, delivery, puerperium; estrogen therapy; and long distance travel within a month prior to VTE.

Statistical Analysis

The obtained data were entered into a computerized database and underwent further analysis. For that, we used SAS software version 9.2 (SAS Institute, Cary, North Carolina). We compared means and proportions, using the t test and the χ^2 test, respectively.

Results

The Characteristics of the Whole Group and the Prevalence of Concomitant Thrombosis

The characteristics of the whole group are shown in Table 1. Of all patients with PE, DVT was diagnosed in 302 (70.6%) cases. Left leg was affected in 51.3%, while 39.4% of patients had DVT in the right leg, and in 9.3%, bilateral DVT was found.

Table 2. Characteristics of Patients With PE (n = 428) With Diagnosed DVT and Without DVT.[a]

	DVT Confirmed: n = 302 (70.6%)	DVT Not Confirmed: n = 126 (29.4%)	P
Age, years	60.1 ± 15.9	57.3 ± 17.4	.12
Age ≥70 years, n (%)	103 (34.1)	34 (27.0)	.24
BMI, kg/m^2	29.7 ± 5.2	29.7 ± 7.3	.96
Females, n (%)	124 (41.1)	80 (63.5)	<.0001
Patients with symptoms suggestive of DVT, n (%)	129 (42.7)	8 (6.3)	<.0001
Unprovoked events, n (%)	187 (61.9)	74 (58.7)	.48
Previous VTE (PE and/or DVT), n (%)	66 (21.8)	26 (20.6)	.78
Previous DVT, n (%)	51 (16.9)	16 (12.7)	.32

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]*t* test and χ^2 test were used for comparison.

Table 3. The Differences Between Patients With PE (n = 428) With Proven Proximal DVT and Without Proximal DVT.[a]

	Proximal DVT: n = 212 (49.5%)	No Proximal DVT: n = 216 (50.5%)	P
Age ≥70 years, n (%)	74 (34.9)	63 (29.2)	.29
Obesity, n (%)	98 (46.2)	94 (43.5)	.68
Females, n (%)	81 (38.2)	123 (56.9)	.005
Males, n (%)	131 (61.8)	93 (43.1)	.007
Patients with symptoms suggestive of DVT, n (%)	101 (47.6)	36 (16.7)	<.0001
Unprovoked events, n (%)	130 (61.3)	130 (60.2)	.88
Previous VTE (PE and/or DVT), n (%)	49 (23.1)	43 (19.9)	.47
Cardiac and/or pulmonary disease, n (%)	39 (18.4)	41 (19.0)	.89
Current smoking, n (%)	33 (15.6)	33 (15.3)	.94
Active cancer, n (%)	22 (10.4)	8 (3.7)	.009

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]*t* test and χ^2 test were used for comparison.

The DVT location was proximal in 212 cases (70.2% of DVTs). Of those, 11 patients had iliofemoral thrombosis (3.6% of DVTs).

In 16 patients, superficial vein thrombosis (SVT) was found, in 6 cases with concomitant DVT and in 10 cases as isolated SVT. Concerning isolated SVTs, most of them (6 cases) were located in great saphenous vein (GSV) above the knee (one of them bilaterally) while in 2 cases in GSV below the knee, and in 2 cases, small saphenous vein was affected.

The Characteristics of Patients With PE With and Without DVT

The comparison of the groups with diagnosed DVT and without DVT is shown in Table 2. There were no significant differences in age or BMI. However, female patients were significantly less represented in the group with concomitant DVT than in the group with isolated PE (41.1% vs 63.5%, $P < .0001$).

Not surprisingly, symptoms suggestive of DVT were significantly more often present in the patients with confirmed DVT (42.7%). Accordingly, in 57.3% cases, DVT was asymptomatic. On the other hand, 8 patients (6.3% of the whole group) had symptoms suggestive of DVT, but DVT was not found. The causes of those symptoms were heterogeneous—posttraumatic leg pain, chronic venous disease, recent sclerotherapy of varicose veins, recent saphenectomy, and SVT—all these represented by 1 case, while in 3 cases, we were not able to identify any potential explanation of complaints. Taken together, the sensitivity of DVT symptoms was 42.7% (95% confidence interval [CI]: 37.1%-48.5%), while the specificity reached 93.7% (95% CI: 87.9%-97.2%).

Unprovoked events were comparably represented in the group with isolated PE and the group with PE and DVT (about 60% in both groups). Between the 2 groups, there was significant difference neither in the positive history of previous VTE (PE and/or DVT) nor in the positive history of previous DVT only. Most of recurrent DVTs (ie, newly diagnosed DVTs in patients with the history of DVT in the past) were ipsilateral (37 cases, ie, 72.5% of recurrent DVTs).

Factors Associated With the Presence of Proximal DVT

In further analysis, we focused on proximal DVT only and we compared the group of patients with PE with and without proximal DVT (accordingly, patients without proximal DVT might have had no DVT or distal DVT). The results are presented in Table 3.

Similar to whole-leg thrombosis, proximal DVT was significantly more frequent in men. Deep vein thrombosis symptoms were significantly more often present in the patients with proximal DVT than in those without. However, the sensitivity and specificity of DVT symptoms for proximal DVT differ in comparison with those characteristics for DVT of the entire leg (ie, including distal DVT). Sensitivity of DVT symptoms for proximal DVT was still quite low, that is, 47.6% (95% CI: 40.8%-54.6%), while the specificity decreased to 83.3% (95% CI: 77.7%-88.1%).

Provoked and unprovoked cases were similarly distributed in the group with and without proximal DVT. We tried to look in detail at the respective provoking factors and comorbidities and their potential association with the presence or absence of proximal DVT. We proved neither an association with cardiopulmonary diseases nor with smoking. Patients with cancer represented only a small group in our study (30 patients, ie, 7.0%). However, active malignancy was significantly more frequent in patients with proximal DVT than in patients with PE without proximal DVT (10.4% vs 3.7%; $P = .009$).

Discussion

In the literature, the reported prevalence of concomitant DVT in patients with PE is highly variable,[3,14,15] probably due to substantial heterogeneity among studies that included various population and used various methods (venography in older studies, CUS—either limited or complete—in more recent ones). Some authors focus on proximal DVT exclusively, while others do not specify. The prevalence of detectable DVT in patients with symptomatic PE has varied from 21% to 93% in the studies.[4] Some researchers have reported higher proportion of proximal DVT,[15] others the same proportions of distal and proximal DVT.[16] Our findings are in agreement with a review, reporting about 70% of patients with symptomatic PE having DVT, about two-thirds of those proximal.[17]

Guidelines neither address the necessity of CUS in patients with PE (to screen or not to screen) nor specify the strategy of CUS (to perform limited or complete CUS; to test all patients with PE or only those with DVT symptoms). Both complete (whole-leg) CUS and limited CUS (2-point ultrasound, examining the veins in the groin and the popliteal fossa, thus searching for proximal DVT only) were proven to be equally reliable and safe in diagnostic algorithms for DVT. In our institution, we are used to perform complete CUS, and therefore, we are able to specify the prevalence of all DVTs or that of proximal DVTs only. Other centers may prefer limited CUS. The 2 tests have differing advantages and disadvantages.[18,19] Limited CUS is simple, less time demanding, and less dependent on the experience of the sonographer.[20,21] In PE diagnostic process, only ultrasound-proven proximal DVT is considered sufficient to rule in PE if avoiding CT angiography is desirable.[6,22] Isolated distal DVT is considered more benign in nature, less associated with the risk of subsequent PTS,[23] and theoretically would have lesser influence on the outcome of patients with PE. However, the presence of distal DVT may also have clinical implications. A study of 203 patients with PE who had undergone bilateral complete CUS and had been followed for 12 months proved both the presence of DVT and that of proximal DVT as independent predictors of adverse events.[4] Moreover, complete CUS may be able to reveal alternative diagnosis and thus enable an accurate and specific treatment.[24] So, the use of complete or limited CUS is a matter of choice, depending on the clinical context, patient's needs, available resources, and decision of respective physicians and/or institutions.

Performing CUS only in selected patients with PE, that is, those with a higher probability of the presence of DVT, might theoretically be a more rational approach. However, the selection criteria for CUS testing are not clear. In this sense, we tried to focus on the reliability of symptoms suggestive of DVT. Testing only the patients with potential DVT symptoms may seem reasonable, but in our study, the symptoms were not too reliable indicators of the true presence of DVT. Many of DVTs, including proximal ones, were asymptomatic. On the other hand, some patients had "falsely positive" DVT symptoms. Only in some of them we were able to identify an alternative cause of the complaints. Hypothetically, DVT might have been originally present, but the source thrombus might have embolized completely.

Interestingly, 16 patients had SVT, 10 of those without concomitant DVT. This finding confirms again that SVT is not a negligible condition.[25] According to the literature, 2% to 13% of SVT may be associated with symptomatic PE.[26]

The association of male gender with the presence of concomitant DVT is also noteworthy. We proved this association for all DVTs as well as for proximal DVTs only. This finding is in agreement with the results of one more extensive analysis of gender differences in PE clinical presentation. The authors demonstrated a higher prevalence of PE-associated proximal DVT in men. They considered this finding a possible indicator of greater severity of PE and potential contributor to higher VTE recurrence rate in men.[27] However, this difference has been poorly understood so far.

According to the literature, some conditions may predispose to isolated PE presentation, for example, some cardiac or pulmonary problems.[28-30] However, we have not found such an association.

In one retrospective review, malignancy was also significantly associated with isolated PE.[31] To the contrary, in our study, active malignancy in patients with PE was significantly associated with the presence of proximal DVT. The absolute numbers of patients with cancer were small in our study, but in the mentioned review, the numbers were even smaller.

We are aware of the limitations of our study. Ten patients with PE who had not been examined with CUS were not included, but it probably did not considerably influence the results of the analysis of the remaining 428 patients. Moreover, CUS may have lower specificity for distal asymptomatic DVT. Even though the sonographers were well trained and experienced, this potential limitation should be considered. As our study was single centered and retrospective, the generalizability of the findings is limited, and the results must be interpreted with caution. However, the data of consecutive patients were prospectively collected and very thoroughly evaluated. Moreover, we precisely distinguish symptomatic/asymptomatic and proximal/distal DVT, which is not always the case in other studies of VTE clinical presentation. Our study may be valuable as it presents real-life clinical practice data.

Conclusions

In conclusion, in the group of 428 consecutive patients with PE, we performed complete bilateral venous ultrasound and confirmed a high prevalence of concomitant DVT (70.6%), most of them proximal (70.2%, respectively). Sensitivity of DVT symptoms was quite low (42.7%) and specificity relatively high (93.7%). However, symptom specificity for proximal DVT was lower (83.3%). Pulmonary embolism-associated DVT (in the entire leg) as well as PE-associated proximal DVT was significantly more frequent in males. Active malignancy was significantly associated with the presence of proximal DVT, although the absolute numbers were small. Further studies are needed to specify the role and the optimal strategy of venous ultrasound in patients with PE.

Authors' Note

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. Our institution does not require ethical approval for reporting individual cases or case series.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research was supported by the Charles University Research Fund (project number Q39).

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