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The prevalence of upper extremity deep venous thrombosis

Üst ekstremite derin ven trombozu prevalansı

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Background: This study aims to determine the prevalence and characteristics of symptomatic upper extremity deep venous thrombosis (UEDVT) and its association with symptomatic pulmonary embolism (PE) in a tertiary care hospital.

Methods: Between January 2001 and December 2003, the prevalence of symptomatic UEDVT at a university hospital within the past three-years was evaluated retrospectively. Patients were identified by hospital records, and a computer-recorded list of all color Doppler ultrasonograms, venograms, and magnetic resonance angiograms of upper extremities was also used. Data were obtained from medical records and follow-up patient questionnaires.

Results: Symptomatic UEDVT was diagnosed in 91 of 100.942 patients of all ages (0.09%) [or 89 of 70.751 of adult patients ≥20 years of age; 0.13%]. Seventy three (80%) of 91 patients with UEDVT had multiple risk factors; 33 patients (36%) had malignancy, 34 patients (37%) had central venous catheters (CVCs), peripheral venous lines (PVLs) and cardiac pacemaker (n=1), 36 patients (40%) had chronic disorders (chronic obstructive pulmonary disease, cardiac disease, chronic renal failure with hemodialysis), 12 patients (13%) had trauma or surgery, 13 of 53 patients (24%) had UEDVT secondary to thrombophilia. Symptomatic PE developed prior to thrombosis being treated in 32 patients (35%). All patients received anticoagulant therapy except 13 patients (5 with thrombolytic therapy; 8 with thrombectomy) who were treated with other methods initially.

Conclusion: Upper extremity deep venous thrombosis is not a rarely seen pathology. Its etiology is usually multifactorial and secondary to thrombophilia, CVC, PVL, chronic diseases and cancer. As PE resulting from UEDVT is a common complication, patients with risk factors should be diagnosed and treated early.

Key words: Axillary vein; brachial vein; deep venous thrombosis; pulmonary thromboembolism subclavian vein; upper extremity deep venous thrombosis.

Amaç: Bu çalışmada, üçüncü basamak bir sağlık kurumunda semptomatik üst ekstremite derin ven trombozlarının (ÜEDVT) prevalansı, özellikleri ve semptomatik pulmoner emboli (PE) ile birlikteliğinin belirlenmesi amaçlandı.

Çalışma planı: Bir üniversite hastanesinde Ocak 2001 ve Aralık 2003 tarihleri arasında son üç yıllık dönem içindeki semptomatik ÜEDVT prevalansı geriye dönük olarak değerlendirildi. Hastalar hastane kayıtlarından tespit edildi ve üst ekstremitelerin manyetik rezonans anjiyografileri, venografileri ve renkli Doppler ultrasonografileri ise bilgisayarda kayıtlı listelerden elde edildi. Veriler, tıbbi kayıtlar ve hasta takip anketlerinden elde edildi.

Bulgular: Tüm yaş grupları için semptomatik ÜEDVT tanısı 100.942 hastanın 91'inde (%0.09) [veya 20 yaş ≥70.751 erişkin hastanın 89'unda; %0.13] kondu. Üst ekstremite derin ven trombozları olan 91 hastadan 73'ünde (%80) çoklu risk faktörleri var idi; 33 hastada (%36) malignansi, 34 hastada (%37) santral venöz kateter (SVK), periferik venöz yol (PVY) ve kardiyak pacemaker (n=1), 36 hastada (%40) kronik hastalıklar (kronik obstrüktif akciğer hastalığı, kalp hastalığı, hemodiyaliz tedavisi gören kronik böbrek yetmezliği, 12 hastada (%13) travma veya cerrahi, 53 hastanın 13'ünde (%24) trombofili ile ilişkili sekonder ÜEDVT var idi. Semptomatik PE 32 hastada (%35) tromboz tedavisinden önce gelişti. Başlangıçta diğer yöntemler ile tedavi edilen 13 hasta (5; trombolitik tedavi, 8 trombektomi) dışındaki tüm hastalar antikoagülan tedavi aldı.

Sonuç: Üst ekstremite derin ven trombozu nadir görülen bir patoloji değildir. Etyolojisi sıklıkla multifaktöriyel olup, trombofili, SVK, PVY, kronik hastalıklar ve kansere sekonderdir. ÜEDVT'den kaynaklanan PE sık görülen bir komplikasyon olduğundan, risk faktörlü hastalar erken tanılanmalı ve tedavi edilmelidir.

Anahtar sözcükler: Aksiller ven; brakiyal ven; derin ven trombozu; pulmoner tromboemboli; subklaviyan ven; üst extremite derin ven trombozu.

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Upper extremity deep venous thrombosis (UEDVT) is a thrombus in any of the deep veins, such as the radial, ulnar, axillary, subclavian, internal jugular, and brachiocephalic veins, in the upper extremities.[1] They account for 4-10% of all cases of deep venous thrombosis (DVT).[1-7] Although once considered rare, the incidence rates have risen dramatically over the past several decades as the use of central venous catheters (CVCs) and the placement of pacemakers and implantable cardioverter defibrillator devices have increased.[1-4,6-11]

This type of thrombosis can be classified as primary or secondary and is associated with one or more inherited or acquired risk factors.[1-5,10-13] Central venous catheters, underlying neoplastic diseases, primary thrombosis related to exertion, and hypercoagulability are the most frequent risk factors.[1-8,10-13] Upper extremity deep vein thrombosis was once believed to have benign consequences, but more recent data has suggested that this is not the case,[6,9] and it has potential morbidity and mortality similar to DVT of the leg.[1-7] Major morbidity from pulmonary embolism (PE), superior vena cava (SVC) syndrome, and post-thrombotic syndrome have been reported to follow UEDVT.[1-6,9,12,14,15] The prevalence of PE in patients with UEDVT is controversial with rates ranging from 0-33%,[12,4,8,9,10,14] and the overall mortality rate is between 10% and 50%.[1-5,15,16] For these reasons, it is imperative that physicians understand the prevalence of UEDVT along with its pathogenesis and risk factors. They should also be familiar with the diagnostic and treatment considerations for this disease.[1]

To our knowledge, the prevalence of symptomatic UEDVT among hospitalized patients has been previously evaluated. Two cases were reported per 1.000 hospital admissions by Kröger et al.[17] in 1998. Also, Mustafa et al.[8] recently reported that 0.19% of hospitalized adult patients had symptomatic UEDVT.

We recently observed a substantial number of patients presenting with UEDVT who had chronic obstructive pulmonary disease (COPD) associated with PE, and these patients had a significant rate of morbidity and mortality. In our series,[18-21] the patients with COPD were admitted to the hospital with acute respiratory exacerbation (ARE).

Both earlier and more recent reports have confirmed the association of cardiac disease and UEDVT,[7,22] but COPD as a risk factor of UEDVT has not been reported in the literature to date.[1-6,8-10,12,14] However, COPD as a comorbidity of UEDVT, either with or without CVCs, was reported in the study by Joffe et al.[7] in 2004.

There is still substantially less information available on the epidemiology, actual incidence, management, and prognosis in UEDVT within the hospital population. The aims of this retrospective study were to investigate patients with UEDVT who had been admitted to a tertiary care hospital within a specified three-year period and to determine its prevalence, risk factors, and association with symptomatic acute PE.

PATIENTS AND METHODS

We conducted a retrospective study in order to evaluate the frequency of diagnosis in patients with UEDVT at the Erciyes University Medical School during the three-year period between January 1, 2001 and December 31, 2003. In order to identify patients with UEDVT, hospital records and computer-generated lists of all patients who had undergone color Doppler ultrasonography (CDU), contrast venography, or magnetic resonance angiography (MRA) were used. The reports of each patient were reviewed, and cases with positive findings were included in the study. If the patient had been hospitalized on more than one occasion for UEDVT, only the relevant data from the first hospitalization was included.

We also searched the hospital records and computer-generated lists for the presence of concomitant thrombosis of brachiocephalic veins (innominate) and/or SVC[23] along with coincidental symptomatic lower extremity deep venous thrombosis (LEDVT). An objective verification of the diagnosis was required for all patients, and all diagnoses of LEDVT were confirmed by CDU.

Data was recorded suing medical records, office charts, databases from the Erciyes University Medical Center Radiology Department, telephone interviews with the patients or patients' relatives (in cases of patient death), follow-up patient questionnaires, and clinical examination. We used standardized data collection forms to gather information from the charts (Table 1).

The UEDVT patients who received a CVC or a peripheral venous line (PVL) within 30 days of the DVT diagnosis were classified as having CVC- or PVL-associated UEDVT. Patients with a history of vigorous or unusual exercise within 21 days of the thrombosis developing in the affected arm comprised the effort-related UEDVT group. When no forceful activity of the limb occurred before the onset of symptoms and no underlying disease or predisposing factor was initially found, UEDVT was classified as either spontaneous or idiopathic.

Table 1. Data collection form

Patient's name:
Age:
Gender:
Patient's file number:
Patient's phone number:
Right-sided UEDVT:
Left-sided UEDVT:
Previous/later LEDVT:
Coincident LEDVT:
Underlying disease and/or risk factors:

Chronic lung disease:
COPD:
Bronchiectasis:
Others:
Congessive heart failure (CHF):
Delivery:
Other chronic medical diseases:
Chronic renal failure (CRF):
Hemodialysis dependence:
By CVC:
By A-V fistule:

Malignancy:
Thoracic malignancy:
Lung cancer:
Malign mesothelioma:
Head-neck cancer:
Breast cancer:
Metastatic thoracic lymphadenopathy:
Occult malignancy:
Extrathoracic malignancy:
Abdominal cancer:
Other extrathoracic malignancy:
Ongoing radiation:
Ongoing chemotherapy:

A history of vigorous/unusual exercise within 21 days prior to the thrombosis:

Underlying invasive devices/procedures/surgery/inmobization within 30 days of the UEDVT:
Iatrogenic vein manipulation:
Use of CVC:
Peripheral venous lines (PVL):
Cardiac pacemakers:
Recent trauma:
General anesthesia:
Major surgery:
Immobilization:
Hospitalization:

The presenting symptoms and signs of UEDVT:
Edema:
Pain:
Tenderness:
Erythema over affected site:
Palpable venous cord:
Neck and face edema:
Breast edema:
None (incidendal finding)

Location of thrombosis in upper extremity veins:
Brachiocephalic vein:
Superior vena cava:
Subclavian vein:
Internal jugulary vein:
Axillary vein:
Brachial vein:
Ulnar vein:
Radial vein:
Superficial veins:
Basilic vein:
Cephalic vein:

Past medical and/or familiy history:
Personal history for thromboembolic diseases:
UEDVT:
LEDVT:
PE:
Stroke:
Family history for thromboembolic diseases:
UEDVT:
LEDVT:
PE:
Stroke:

Diagnostic method of UEDVT and/or PE:
Upper extremity CDU:
Contrast venography:
MR angiography:
Contras enhanced chest CT:
Spiral CT:
V/P lung scan:

Physical findings due to PTE
Acute dyspnea:
Acute exacerbation in chronic dyspnea:
Tachypnea:
Pleuretic chest pain:

Initial treatment
(SC) LMWH:
(IV) UDAH:
TT:
Surgery:

Complications
PE:
Post-thrombotic syndrome:
Recurrent thrombosis
LEDVT:
UEDVT:
Stroke:
PE:
Paradoxical arteriel embolism:

Prognosis
PTE'den exitus:
Exitus from underlying diseases:
Mortality:
One-month mortality:
Three months mortality:

Outcome
Follow-up duration:

COPD: Chronic obstructive pulmonary diseases; CVC: Central venous catheter; PVL: Peripheral venous line; CDU: Color Doppler ultrasonography; MR: Magnetic resonance; V/P: Ventilation/perfusion; (SC) LMWH: Subcutanously low molecular weight heparin; TT: Thrombolytic therapy; (IV) UFDH: Intravenously unfractioned dose-adjusted heparin.

All the patients with UEDVT were identified by CDU scanning using a commercially available scanner (Toshiba Power Vission 6000) with a 7.5-MHz sector imaging transducer. The internal jugular, subclavian, axillary, brachial, antecubital, basilic, cephalic, radial, and ulnar veins were evaluated for upper extremity thrombosis. The technique of CDU has previously been described in detail.[24] In addition to CDU, 30 patients (32%) were evaluated by a different test, including 24 patients (26%) by contrast venography (Figure 1), and six patients (7%) by MRA for diagnosis of central thoracic venous thrombosis or thrombolytic therapy via catheter. The venography and MRA findings were used as the final arbiter. Patients with thrombophlebitis of only superficial veins of the upper extremities (i.e. antecubital, basilic, and cephalic) were excluded from the study.

Contrast-enhanced chest computed tomography (CT) or spiral CT was performed on 58 patients (64%) with the aim of showing any intraluminal filling defect in the brachiocephalic vein and/or SVC, adjacent diseases (PE, occult malignancy), or other abnormalities causing pressure on the venous system in the thoracic outlet.

A diagnosis of PE was made on the basis of a high-probability interpretation of the ventilation/perfusion (V/P) lung scan or positive spiral CT findings in patients with symptoms which were suggestive of PE.

During the three-year study period, patients were re-invited for a follow-up investigation which was performed in a prospective manner according to a standard protocol and which included a clinical reevaluation. Furthermore, the patients' thrombophilia status was evaluated. This reevaluation was performed while paying special attention to the signs of upper extremity post-,thrombotic syndrome and its frequency along with the time interval of recurrence of ipsilateral or contralateral UEDVT, LEDVT, PE, and stroke. At least a three-month follow-up was done for the entire study group, except for the patients who died early.

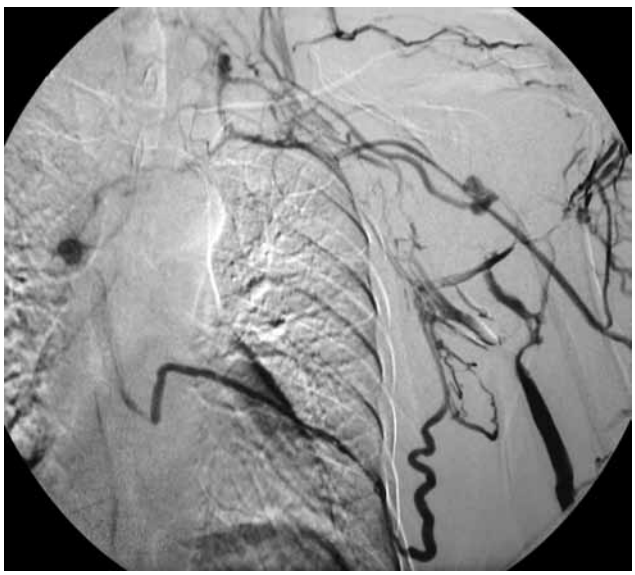

Figure 1. On venography performed with contrast administration through left brachial vein shows that the contrast material passes through collateral veins and that there is no filling in left subclavian, left axillary, left basilic and left brachiocephalic veins.

A risk-factor assessment was performed by taking a detailed history and conducting a follow-up patient questionnaire. The determination of hypercoagulability tests for antithrombin III, protein C and S, activated protein C (APC) resistance (the Leiden mutation of factor V), the anti-phospholipid antibody, and the lupus anticoagulant taken at a mean of three months after the episode of thrombosis were performed according to standard methods. Fifty-three patients (58%) with UEDVT were willing and able to undergo a hematological profile. Protein C and protein S plasma levels were evaluated only if the patient was not under oral anticoagulation treatment at the time of evaluation. None of these patients were undergoing any type of chemotherapy or had a known liver disease. There were no statistical differences in age or gender distributions, incidence of history of neoplasm, percentage of CVCs or PVLs, or presence of LEDVT among the group who underwent the hypercoagulable work-up and those who did not.

Erciyes University Medical School Hospital is a university hospital with a reported capacity of 1.305 patients. It has a Cancer Center which holds 90 patients and a Renal Dialysis and Transplantation Center which can handle 105 patients.

Statistical analysis

Statistical analysis was performed through the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 12.0 software. Descriptive statistics (mean ± standard deviation, and proportion) were applied to summarize the data.

RESULTS

During the three years of the study, 100.942 patients were admitted to the hospital, including newborns. We identified 623 patients with DVT during this period. Lower extremity deep venous thrombosis was diagnosed in 525 (0.52%) of the total number of patients, and 12 of these were under 20 years of age. During the same period, LEDVT was diagnosed in 513 (0.72%) out of 70.751 adult patients, and seven

of these (0.01%) had thrombosis of the SVC or brachiocephalic vein unaccompanied by UEDVT or LEDVT.[23]

Ninety-one out of the 623 patients with DVT had UEDVT during this period, which accounted for 0.09% of the total number of patients admitted. Two patients were 17 years old. One of these had left subclavian vein thrombosis associated with lymphoma and CVC, and the other had meningioma with brachial vein thrombosis due to intravenous (i.v) anesthetic drug injection. The incidence of UEDVT in adults was 89 out of 70.751 patients (0.13%). Fifteen adult patients with UEDVT also had symptomatic LEDVT.

The demographic characteristics of the patients are shown in Table 2. Of all the patients with UEDVT, 49 (54%) were male, and 42 (46%) were female. The mean age was 49.5±15.9 (range 16-80) years. The left side was involved in 41 patients (45%), the right side in 38 patients (42%), and bilateral involvement occurred in 12 patients (13%). Two patients experienced an ipsilateral recurrent UEDVT, and three patients experienced a contralateral UEDVT that occurred during the follow-up interval.

The location of thrombosis in the patients with UEDVT is shown in Table 2. Proximal UEDVT involved the subclavian vein in 62 patients (68%), the axillary

Table 2. Demographic characteristics, distribution of vessels showing thrombosis, and physical findings in the study population

	n	%	Mean±SD	Range
Patient, characteristics (n=91)			49.5±15.9	16-80
Gender				
Male	49	54		
Female	42	46		
Right-sided	38	42		
Left-sided	41	45		
Bilateral	12	13		
Previous/later LEDVT	7	8		
Coincident LEDVT	8	9		
Location of thrombosis in upper extremity veins (n=91)				
Subclavian + internal jugulary	24	26		
Brachial + axillary + subclavian vein	16	17		
Brachiocephalic + subclavian and/or axillary	14	15		
SVC + brachiocephalic + subclavian and/or axillary	11	13		
Subclavian + axillary vein	7	8		
Internal jugular vein only	7	8		
Subclavian vein only	5	6		
Ulnar vein only	3	3		
Brachial vein only	2	2		
Axillary vein only	2	2		
Physical findings of upper limbs (n=91)				
Arm swelling	86	95		
Upper extremity pain	36	40		
Prominent veins on chest	33	36		
Palpable cord	15	18		
Erythema over affected site	13	14		
Neck and face edema	12	13		
Breast edema (only women)	8/42	19		
None (incidental finding)	0	0		
Physical findings due to PE (n=32)				
Acute dyspnea	12	38		
Acute exacerbation in chronic dyspnea	20	62		
Tachypnea	32	100		
Pleuretic chest pain	19	60		
Hemoptysis	9	28		

LEDVT: Lower extremity deep venous thrombosis; SVC: Superior vena cava; PE: Pulmonary embolism.

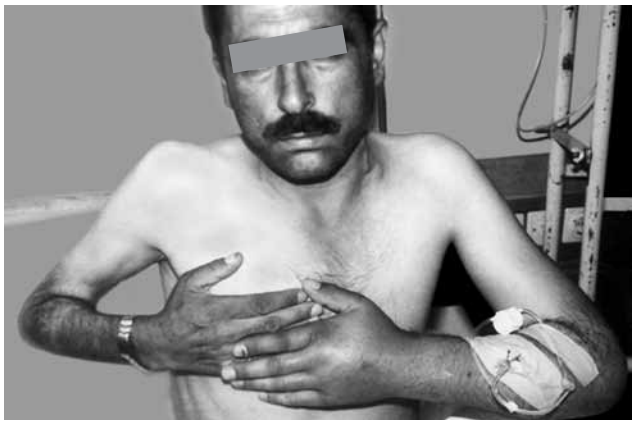

Figure 2. The chronic obstructive pulmonary disease patient's picture, showing non-pitting swelling in his left arm from shoulder to the fingers, left sided prominent venous cord on neck.

vein in 36 patients (40%), the internal jugular vein in 31 patients (34%), the brachial vein in 18 patients (20%), and the ulnar vein in three patients (3%). Venography or MRA revealed that in 25 patients (27%), UEDVT extended to the brachiocephalic veins and in 11 patients (12%), it extended to the SVC (Figure 1).[23]

The duration of symptoms before treatment was 9.0±9.5 days (between 1 and 30 days). The physical examination findings are shown in Table 2. All patients had symptoms due to UEDVT. In 86 patients (95%), edema of the upper limb (Figure 2) was the most common complaint. Eight women with UEDVT had prominent ipsilateral breast edema.[18] Twelve patients (13%) with UEDVT extending to the brachiocephalic vein and/or the SVC had face and neck edema.[23]

Thirty-two patients (35%) had symptomatic PE while four patients had fatal PE (one with cerebral hemorrhage after thrombolytic therapy; three with severe COPD and ARE). Pulmonary embolism occurred before the venous thrombosis was treated in all patients. Except for two patients with PE, CDU for LEDVT excluded the presence of the newly formed thrombi. Seven patients with PE also had brachiocephalic vein or SVC thrombosis, and three had right atrial thrombus. Two patients with PE also had coincidental LEDVT. Fourteen patients (42%) with PE were diagnosed by V/P lung scans, and 18 patients (58%) were diagnosed by contrast-enhanced spiral CT.

The clinical variants and etiologic risk factors of the patients with UEDVT are shown in Table 3. Seventy-three patients (80%) had secondary UEDVT associated with various diseases and conditions, and all of them had at least two or more (acquired and/or inherited) risk factors.

Eighteen patients (20%) were initially classified as primary UEDVT (Table 3). Effort thrombosis (Paget-Schroetter syndrome; PSS), identified in four patients (4%), developed after strong efforts with the arms. There were two patients with anti-phospholipid antibody syndrome, two patients with APC resistance, either alone or with lupus anticoagulant activity, and 10 patients with occult cancer among the 18 patients with primary UEDVT.

Thirty-four (37%) patients with secondary UEDVT were associated with either a cardiac pace maker (only one patient), CVC, or PVL. The CVC and PVL were inserted on the side of the UEDVT in 33 patients (36%) with chronic medical diseases (CMD) or malignancy (Table 3).

Thirty-three patients (36%) with secondary UEDVT were associated with malignancy. Eighteen patients (19%) with cancer had lung carcinoma and mesothelioma, and 11 patients (12%) had head-neck and breast carcinoma due to previous surgery, radiotherapy, or i.v chemotherapeutic drugs.

There were 22 patients (24%) with chronic lung disease (18 with COPD, three with bronchiectasis, and one with idiopathic pulmonary fibrosis) and cor pulmonale. Most patients had previously received i.v infusions of medications with PVL (n=9) or CVC (n=5) during acute exacerbation of chronic respiratory failure.[18-21] Their medical histories included severe coughing bouts, severe hypoxia, frequent acute exacerbation, high hematocrit levels, and frequent hospitalization.[18-21]

Ten patients (11%) with UEDVT were associated with chronic renal failure (CRF) which required ongoing hemodialysis. Six patients (7%) with subclavian vein thrombosis had arteriovenous (AV) shunts, and four patients (4%) with UEDVT had CVC for renal dialysis on the side of UEDVT. One patient with CRF also had Buerger's disease. There was no evidence of thrombosis of the shunts.

Thrombophilia was found in 17 (32%) of the 53 patients with UEDVT (Table 4). Of these 53 patients, four had primary UEDVT, and 13 patients with thrombophilia had secondary UEDVT. In six patients (11%), APC resistance was the most common coagulation abnormality among the patients who were administered hypercoagulability tests.

None of the patients with malignancy and CMD, either with or without CVC and PVL, had regularly received anticoagulant prophylaxis before thrombosis. All patients with UEDVT received therapy with anticoagulant agents. Approximately half of the patients were treated with UDAH followed by warfarin sodium, and the other half were treated with

Table 3. Clinical variants and etiologic risk factors of upper extremity deep venous thrombosis in study population

UEDVT variants (n=91)	n	%
Primary	18	20
Effort thrombosis (Paget-Schroetter syndrome)	4	4
Antiphospholipid antibody syndrome	2	2
APC Resistence with/without lupus anticoagulant	2	2
Initially idiopathic (occult malignacy)	10	11
Secondary (initially underlying disease)	73	80
Cancer	33 total (10 occult)	36
Thorocic malignancy	18	23
Extrathoracic malignancy	13	14
Abdominal malignancy	4	4
Mediastinal lymphadenopathy,		
External compression (TOS); with cancer	29	32
CVC, PVL and pacemaker	34	37
Peripheral venous line	17	19
Cancer with CVC	11	12
Radiotherapy	6	6
Chemotherapetic or anesthetic drugs	6	6
CRF with arteriovenous fistula or CVC	10	11
Chronic lung disease and cor pulmonale	22	24
Cardiac disease	4	4
Trauma or/and surgery of upper extremity	12	13
External compression (TOS); with surgery	1	1
Behçet's disease	3	3
Buerger's disease	1	1
Ankylosing spondylitis and Sapho syndrome	1	1
Delivery	1	1
Thrombophilic states	13/53	24

UEDVT: Upper extremity deep venous thrombosis; APC: Activated protein-C; TOS: Thoracic outlet syndrome; CVC: Central venous catheter; PVL: Peripheral venous line; CRF: Chronic renal failure.

low-molecular-weight heparin (LMWH) [deltaparine at a dosage of 200 Unit/kg/daily or enoxaparine 1.5 mg/kg/daily, subcutaneous; (SC)] followed by warfarin sodium for at least three to six months with a mean of 4.4±5.2 months (range 3 to 48 months). Five patients (5%) received i.v streptokinase followed by unfractionated heparin (UFH) and warfarin. A thrombectomy was performed on six renal dialysis patients with subclavian and/or brachiocephalic vein thrombosis, and surgery was performed on two patients with PSS. The surgical procedures were successful in all cases.

Table 4. Thrombophilic states in patients with UEDVT (n=53)

	n	%
Primary (idiopathic)		
Antiphospholipid antibodies	2	4
Activated protein C resistance	1	2
Activated protein C resistance with lupus anticoagulant	1	2
Secondary (underlying disease)		
Activated protein C resistance alone	5	8
Antithrombin-3 deficiency	2	4
Antiphospholipid antibodies and malignancy	1	2
Protein-C deficiency	2	4
Protein-S deficiency	1	2
Lupus anticoagulant activity	2	4
Total	17	34

At least three months of follow-up data was available for the entire study group. The one-month and three-month mortality rates for the entire study group were 12 patients (13%) and 34 patients (37%), respectively. Late thrombotic sequelae developed in 12 patients (13%). Also, 12 patients (14%) experienced an episode of recurrent venous thromboembolism (VTE) [LEDVT, UEDVT, stroke, PE, paradoxical arterial embolism] without anticoagulation during the follow-up period.

DISCUSSION

There are three obvious reasons that may account for the apparent increased incidence of inpatient UEDVT during the last decade: *(i)* the widespread use of long-term i.v catheters; *(ii)* the more liberal use of CDU; and *(iii)* the increased awareness of this condition by the clinician.[10]

We diagnosed UEDVT in 89 out of 70,751 adult patients ≥20 years (0.13%), and we identified UEDVT, which represented 12% of all cases of DVT during this period, in hospitalized patients at an approximate rate of 1.3 per 1000 patients per year. The prevalence of UEDVT that we observed among hospitalized patients was slightly lower than that reported by Kröger et al[17] and Mustafa et al.[8]

A possible explanation for the lower UEDVT prevalence in our study could be that we reported only symptomatic UEDVT in a rather low number of patients with CVC. The frequency of UEDVT we reported probably grossly underestimates the true number of cases because imaging tests for UEDVT were always performed on symptomatic patients in our series. Many patients with UEDVT may be completely asymptomatic, as was the case in other prospective studies.[6,9,11,15]

As the use of CVC and pacemaker wires has increased, their role in the etiology of UEDVT has become more prominent.[6-8,10-12,14,17] This association was clearly evident in the present study in which only 19% of our patients had CVC. In contrast, Kröger et al.[17] and Mustafa et al.[8] reported the use of CVC in 33% and 60% of patients with UEDVT, respectively.

The signs and symptoms of UEDVT are also non-specific. It is important to confirm or exclude UEDVT in all symptomatic patients.[1-5,10,23] Using compression ultrasonography or CDU as the preferred initial diagnostic test may fail to detect central thrombus below the clavicle.[8,23,24] In the present study, venography and/or MRA were preferred over CDU if there was a suspicion of central thoracic vein thrombosis.[23] This is similar to what has been found in other studies.[2,8,18,23]

Pulmonary embolism is an important complication of UEDVT in up to one-third of patients and may even be the presenting manifestation of this disorder.[6,9,10-12,15] We diagnosed symptomatic PE in 32 patients (35%) with UEDVT, and similar data was found by Prandoni et al.[12] Pulmonary embolism in patients with UEDVT who received early therapy was rare.[8,14] It occurred before the venous thrombosis was treated in our series. Some patients with PE in our series also had brachiocephalic and SVC thrombosis,[23] which Mustafa et al.[8] also found, or right atrial thrombus, which was in accordance with previous reports.[25]

The clinical presentation of symptomatic UEDVT includes swelling of the arm, neck, and face, pain, a palpable tender cord, and prominent veins over the chest or upper arm.[3,4,6,12,18-20] Swelling along with pain in the upper extremity were the most common presenting complaints in our study. Thirteen percent of all patients also presented with symptoms of SVC syndrome.[23] This is similar to what Mustafa et al.[8] found in their series. Breast edema was observed in eight (19%) out of 42 women in our study. This is a physical finding which has previously been discussed in central thoracic vein obstructions,[18,23,26] although it has not been clearly mentioned in other series on UEDVT.[2,4,5,8,12,25]

The UEDVT can be classified as primary or secondary.[1-5,6,10] Primary UEDVT occurs in patients without obvious predisposing causes.[1-5,12,13,27] Approximately one-third of UEDVT are primary (2 per 100.000 persons per year),[28] and these include either idiopathic thrombosis or thrombosis related to anatomical abnormalities [the thoracic outlet syndrome (TOS) or effort (PSS)].[1-5,10,13,27] Paget-Schroetter Syndrome with strong effort was identified in four patients (4%) with primary UEDVT. Similar to previous series,[12,13,28] there were four patients (5%) with thrombophilia among primary UEDVT. Idiopathic primary UEDVT occurs with no identifiable trigger and raises the concern of occult malignancy.[1-5,31] Ten patients with idiopathic UEDVT were associated with occult malignancy in our series.

Secondary UEDVT accounts for the majority of cases of UEDVT (80%) and is related to temporary risk conditions such as insertion of CVCs for chemotherapy, parenteral nutrition, administration of antibiotics, blood products, malignancy, arm surgery or trauma, immobilization (plaster cast), and pregnancy.[1-5,11,27,29] Most (80%) of the patients in our series had secondary UEDVT associated with at least two or more inherited or acquired risk factors, which supports Rosendaal's hypothesis.[29] Among the various factors, we found that the combination of CVC or PVL, malignancy,

thrombophilic state, CMDs, and trauma were the prominent causes of UEDVT in most cases. This has also been noted in other series.[4,6,8,12,15]

Cancer, either overt or occult,[2,30] is quite common in patients with UEDVT (more than 40% of cases).[1-8,9,12] Independent of catheter placement, malignancy is an independent risk factor for VTE.[1-5] Recently, a large population-based case-control study showed approximately an eight-fold increased risk of UEDVT in patients with cancer.[4] An association of malignancy with UEDVT, which was observed in 36% of patients in our series, was reported in 30% of patients by Isma et al.,[28] and in 45% of patients by Mustafa et al.[8] Some patients had thrombophilia and malignancy in the present study, which has also been seen in other studies in the medical literature.[28,31] Upper extremity deep vein thrombosis is sometimes a harbinger of occult cancer.[30] Ten patients with occult cancer were admitted with signs suggestive of SVC syndrome and/or UEDVT, and the malignancy was detected later. This also occurred in the series by Girolami et al.[30]

Patients with indwelling CVCs constitute a particularly high-risk population, especially those suffering from cancer and undergoing chemotherapy or those subjected to invasive hemodynamic monitoring, chronic parenteral nutrition, hemodialysis, or transvenous pacing. These patients with CVCs have an overall prevalence of more than 60% for either symptomatic or asymptomatic UEDVT.[1-5,11,27] According to a recent large cross-sectional study, the presence of an indwelling CVC is the most powerful independent predictor of UEDVT, and the overall risk of UEDVT increases by 18-fold in patients with cancer and CVCs.[4] There were 11 patients with CVC and malignancy in our study.

The cephalic and basilic veins are superficial veins of the upper extremity which are commonly canalized for peripherally-inserted central catheters (PICCs), PVLs, and midlines, and they drain directly into the axillary vein. Lobo et al.[32] reported the largest study to date of the association between PICCs and UEDVT in 2009. In this study of 777 patients undergoing PICC placement in a single medical center, 4.9% of the patients subsequently developed symptomatic UEDVT.[32] Uncommonly, UEDVT developed in carriers of PVL. This was generally due to chemical phlebitis spreading to the deep venous system of the arm, particularly in patients who frequently used i.v drugs with CMDs and malignancy.[2,5,12,27] We observed an association of PVL with the upper extremity in 17 patients (18%).

Eighteen (20%) patients with COPD were admitted with ARE to the hospital in our series, but this contrasted with data from other series.[4,8,12,17] In fact, a hypercoagulable state has been described in patients with COPD.[33,34] Venous thromboembolism also occurs with increased frequency in patients with COPD during ARE.[21,35] Mechanisms underlying the increased risk of VTE in such patients are unknown, but it may be due to reduced mobility or hypercoagulability as a result of worsening hypoxia during ARE.[34]

There were 12 patients (13%) with UEDVT associated with surgery or trauma of the upper extremity in our series. Immobilization of the upper limb and the resultant stasis caused by either surgery or plaster cast placement are associated with a higher risk for UEDVT.[1-7,10,27]

Similar to what was found in the series by Mustafa et al.,[8] there were 10 patients with UEDVT connected with CVC or patent AV shunts who had been undergoing hemodialysis in our study. Daneschvar et al.[36] showed that patients with chronic kidney diseases (CKD) suffered UEDVT more frequently than patients without CKD.

Three patients with UEDVT in our study were diagnosed with Behçet's disease. This is in contrast to previous data found in other studies.[4,7,8,12] Involvement of major veins, including occlusion of the SVC, may be associated either with or without thrombosis of the subclavian veins in Behçet's disease.[23,37]

Inherited hypercoagulable states increase the risk of UEDVT by shifting the hemostatic state of the blood of affected persons closer to the thrombosis threshold.[1-6,9,13,28,38] The role of thrombophilia in causing both primary and secondary UEDVT remains a matter of debate.[27] In the literature, the prevalence of coagulation abnormalities in patients with UEDVT ranges between 8% and 61%.[5,12,13,28,38] The differences can mainly be explained because observational studies report varying results due to different selection criteria for patients and by the limited sample sizes, which varied from 18 to 63 patients.[5,38] Additionally, the studies had different time points for blood collection at the diagnosis of thrombosis which can also influence the assessment of coagulation abnormalities.[5] Fifty-three patients were investigated for thrombophilic state in our study, and of these, it was identified in 13 patients with secondary UEDVT and four patients with primary UEDVT. This is similar to what was found in other series.[13,28,38]

We found the rate of mortality and incidence of PE to be significantly high in the UEDVT patients. The high mortality could be reflective of the high-risk patient population represented by the UEDVT patients, as was the case in other studies.[15,16] Our review revealed that

the comorbid factors for mortality were malignancy along with multisystem organ failure in cases both with and without PE.

In conclusion, our results suggest that UEDVT is not actually as rare and benign as has been previously reported, and the prognosis is closely related to underlying diseases. Symptomatic UEDVT is usually multifactorial and secondary to thoracic malignancy, CVC, PVL, CMDs such as COPD, cor pulmonale, CHF, CRF which requires ongoing hemodialysis, and thrombophilic states. Because PE is a frequent complication of UEDVT, patients with risk factors should be diagnosed early and be treated with anticoagulant drugs.

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