Deep Vein Thrombosis as a Harbinger of Malignancy in the Emergency Department

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ABSTRACT

Objective: To determine whether malignancy was discovered within one year of follow-up in patients with deep vein thrombosis (DVT) in the emergency department (ED).

Study Design: Descriptive study.

Place and Duration of the Study: Department of Emergency Medicine, School of Medicine, Duzce University, Duzce, Turkiye, from November 2019 to November 2022.

Methodology: All patients diagnosed with lower limb DVT on venous Doppler ultrasound were included in this study. Patients with a confirmed diagnosis or suspicion of malignancy were excluded. The study outcome was the discovery of malignancy within a year. DVT patients subsequently diagnosed with malignancy were grouped as secondary or idiopathic.

Results: A total of 224 DVT patients without malignancy were studied. The median age of patients diagnosed with DVT was 65.5 years (47-77), of which, 51.8% were females. Malignancy was detected in 5.4% (12/224) of the patients within one year. Malignancy discovery was significantly higher in the secondary DVT group (OR = 4.52, 95% CI = 1.31-11.55; p = 0.021). Ten of 12 patients (83.3%) diagnosed with malignancy were from the genitourinary or gastrointestinal systems.

Conclusion: In patients without known malignancy who were diagnosed with DVT in the ED, the rate of malignancy discovery in a one-year follow-up was 5.4%. EDs, where DVT is frequently diagnosed, are a hub of opportunities for early detection of malignancy. Arranging primary care follow-up of patients with DVT will contribute to better early diagnosis and survival rates, especially for genitourinary and gastrointestinal malignancies.

Key Words: *Deep vein thrombosis, Malignancy, Emergency department, Venous Doppler ultrasound.*

How to cite this article: Demir MC, Selki K. Deep Vein Thrombosis as a Harbinger of Malignancy in the Emergency Department. *J Coll Physicians Surg Pak* 2024; **34(12)**:1534-1538.

INTRODUCTION

There is a two-way relationship between deep vein thrombosis (DVT) and malignancy. It is a well-established fact that malignancy is the most potent risk factor for DVT suggesting that patients with underlying malignancy are at a higher risk of developing DVT.[1] Interestingly, the presence of DVT one year before a malignancy diagnosis has also been associated with advanced-stage malignancy and worse survival.[2] The first documented study on the discovery of malignancy after DVT was performed by Armand Trousseau a century and a half ago, in 1865.[3] Unfortunately, Trousseau, who first described this connection, was diagnosed with DVT in 1866 and had a gastric neoplasm about a year later.[4]

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Received: April 02, 2024; Revised: August 02, 2024; Accepted: September 05, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.12.1534

DVT is detected in 2.1 out of every 1,000 patients in the emergency department (ED).[5] In a study including inpatient wards and outpatient clinics, the rate of DVT detection in patients undergoing diagnostic tests with suspicion of DVT was around 10.3%, while this rate was up to 25% in EDs.[6,7]

Although there are many studies on the predisposition of malignancy for DVT, there are not enough studies on DVT as a harbinger of malignancy. This research aims to highlight the importance of a thorough investigation of patients presenting with DVT to the ED for early identification of any potentially underlying malignancy. The primary aim of this study was to determine if DVT could be a hidden sign of malignancy.

METHODOLOGY

This study was conducted between November, 2019 and October 2022 in the Department of Emergency Medicine, Duzce University, School of Medicine, Duzce, Turkiye, with approximately 90,000 patient visits per year. Patients admitted to the ED between these dates and diagnosed with lower limb DVT by Doppler ultrasound (US) were retrospectively screened. All data were obtained from the hospital's electronic database and ED records. The study was initiated after approval from the local ethics committee (Approval Number: 2023/184, Dated: 4 December 2023).

Eight hundred and eighty-one patients who presented to the ED in the study duration and underwent lower extremity Doppler US with a clinical suspicion / diagnosis of lower limb DVT were examined. The patients with symptoms such as leg swelling, redness, and increased temperature in the foreground of the ED presentation suggestive of DVT were included.[6] Since the incidence of malignancy after DVT is usually high within the first year,[8,9] it was considered appropriate to measure the 1-year follow-up of patients in this study.

The inclusion criteria for the study were being 18 years of age or older and having undergone lower extremity venous Doppler US imaging with a clinical suspicion / diagnosis of lower limb DVT in the ED. The exclusion criteria were patients who were not diagnosed with DVT in the US, with suspected malignancy on imaging at the time of admission, with symptoms suggestive of malignancy, and patients with a current diagnosis of malignancy, or those previously treated with malignancy (completed treatment, no residual signs, and symptoms).

Lower extremity venous Doppler US is a non-invasive diagnostic method with high sensitivity preferred for diagnosing DVT.[10] In the centre where the study was performed, Radiology and ED units were located together, and imaging was performed by or under the supervision of an expert radiologist with at least five years of lower extremity venous Doppler US experience. The final diagnosis of DVT was made by the real-time B-mode venous Doppler US of the lower extremities using a HDI 5000 (Philips, ATL Ultrasound, Bothell, WA, USA) with 5-8 MHz broadband sector probe and 8-13 MHz broadband linear probe.

Patients were grouped into two categories: Group 1 with idiopathic DVT and Group 2 with DVT, secondary to other underlying pathology. Secondary DVT was defined as the presence of a strong family history, lupus anticoagulant or antithrombin III deficiency, protein C or protein S deficiency, lower limb trauma, prolonged immobilisation, surgical procedures, DVT after pregnancy or puerperium. DVT occurring in the absence of these predisposing conditions was considered idiopathic.

Data were analysed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY). Descriptive statistics were presented as numbers and percentages. Histogram and Kolmogorov-Smirnov were used for normal distribution of the data. Demographic data were presented as mean ± standard deviation (SD) for normally distributed variables and median, interquartile range (IQR) (25-75%) for non-normally distributed variables. Pearson's Chi-square test and Fisher's exact test (when the expected number in the cells was less than five) were used for independent categorical variables. Mann-Whitney U test was used to compare independent two-group numerical variables that did not show normal distribution. The incidence of malignancy during patient follow-up was calculated separately for patients with secondary and idiopathic DVT. The incidences in the two-patient groups were compared, and the odds ratio with a 95% confidence interval (CI) was calculated. A p-value less than 0.05 was considered statistically significant.

RESULTS

Over three years, 881 patients who presented to the ED with clinical suspicion of lower limb DVT and underwent venous Doppler US imaging were screened. DVT was detected in 259 (29.4%) of these patients, of which 35 patients with a current diagnosis of malignancy were excluded. Two hundred twenty-four (n = 224) patients with DVT and no previous diagnosis of malignancy were included in the study. During the follow-up period, 39 (17.4%) patients died from various causes, including malignancy. Malignancy was detected in 12 (5.4%) of 224 patients within one year (Table I).

Table I: Characteristics of patients diagnosed with deep vein thrombosis in the emergency department.

Features	n (%), N = 224
Aetiology of DVT	
Idiopathic	151 (67.4%)
Secondary	73 (32.6%)
Gender	
Female	116 (51.8%)
Male	108 (48.2%)
Age	65.5 (47-77)
Median (interquartile range 25-75) in years	
Side	
Unilateral	219 (97.8%)
Bilateral	5 (2.2%)
Previous history of DVT	
Yes	21 (9.4%)
No	203 (90.6%)
Anticoagulant / antiplatelet use	
Yes	68 (30.4%)
No	156 (69.6%)
Diagnosis of malignancy within 1 year of DVT	
No	212 (94.6%)
Yes	12 (5.4%)
Mortality within 1 year from any cause	
Yes	39 (17.4%)
No	185 (82.6%)

DVT: Deep vein thrombosis.

Within one year, patients with and without malignancy were compared with each other in terms of independent variables. Malignancy occurrence was statistically significantly higher in the secondary DVT group (OR = 4.52, 95% CI = 1.31-11.55; p = 0.021). There were no significant differences between the groups in terms of age, gender, and mortality (p = 0.697, p = 0.641, and p = 0.230, respectively, Table II).

During the 1-year follow-up of the 224 patients, 12 patients were diagnosed with malignancy. Of these, 4 (33.3%) patients died from advanced malignancy. Of the 12 patients diagnosed with malignancy, 10 (83.3%) suffered from genitourinary or gastrointestinal tumours of various stages (Table III).

DISCUSSION

This study was designed to evaluate the incidence of new malignancy in the 1-year follow-up of patients with DVT diagnosed in the ED. Malignancy developed in 12 (5.4%) of 224 patients diagnosed with DVT, in 1-year follow-up. Of these 12 patients, 8 (66.7%) were in the secondary DVT group. The risk of malignancy was 4.5 times higher in patients with secondary DVT than in patients with idiopathic DVT.

Table II: Comparison of characteristics between deep vein thrombosis patients with and without malignancy.

Parameters	Detection of malignancy		p-value	OR % CI (Lower-Upper)
	Yes	No		
Aetiology of DVT			0.021*	4.52 (1.31-11.55)
Idiopathic	4 (33.3%)	147 (69.3%)		
Secondary	8 (66.7%)	65 (30.7%)		
Gender				
Male	5 (41.7%)	103 (48.6%)	0.641**	
Female	7 (58.3%)	109 (51.4%)		
Age (in years)			0.697***	
Median (IQR 25-75)	64.5 (55.5 - 69.75)	65.5 (46.25 - 77)		
Side			>0.99	
Unilateral	12 (100%)	207 (97.6%)		
Bilateral	0 (0%)	5 (2.4%)		
Previous history of DVT			>0.99	
Yes	1 (8.3%)	20 (9.4%)		
No	11 (91.7%)	192 (90.6%)		
Use of anticoagulants			0.009*	5.06 (1.47-17.45)
Yes	4 (33.3%)	60 (28.3%)		
No	8 (66.7%)	152 (71.7%)		
Mortality within 1 year from any cause				
Yes			0.230*	
No	4 (33.3%)	35 (16.5%)		
	8 (66.7%)	177 (83.5%)		

**The p-value was obtained using Fisher's exact test. **Obtained by Pearson's Chi-Square test. ***Obtained by Mann-Whitney U test. DVT: Deep vein thrombosis. IQR: Interquartile range. Categorical variables are given as n (%).*

Table III: Characteristic features and mortality outcomes of patients diagnosed with malignancy within 1 year after deep vein thrombosis diagnosis.

Age (years)	Gender	Side of DVT	Site of DVT	Type of malignancy	Anticoagulant use	Mortality
73	Female	Unilateral	Right superficial femoral vein and deep femoral vein	Pulmonary carcinoma	Yes	No
37	Female	Unilateral	Right external iliac vein, main / superficial / deep femoral vein, popliteal vein, vena saphena magna	Liver carcinoma	No	No
58	Female	Unilateral	Right external iliac vein, main / superficial / deep femoral vein, popliteal vein, vena saphena magna	Carcinoma of the endometrium	No	No
57	Male	Unilateral	Left external iliac vein, main / superficial / deep femoral vein, popliteal vein	Renal carcinoma	Yes	No
55	Female	Unilateral	Left vena saphena magna	Carcinoma of the endometrium	Yes	No
83	Male	Unilateral	Right external iliac vein, main / superficial / deep femoral vein, popliteal vein, vena saphena magna	Prostate adenocarcinoma	No	Yes
68	Male	Unilateral	Right main / superficial / deep femoral vein, popliteal vein	Gastric carcinoma	Yes	Yes
40	Male	Unilateral	Right main / superficial / deep femoral vein, popliteal vein	Carcinoma of the oesophagus	Yes	No
61	Female	Unilateral	Left popliteal vein, vena saphena magna	Carcinoma of the cervix	Yes	No
68	Female	Unilateral	Right main femoral vein, popliteal vein	Hodgkin lymphoma	Yes	No
69	Male	Unilateral	Left popliteal vein, vena saphena magna	Gastric carcinoma	Yes	Yes
70	Female	Unilateral	Left popliteal vein	Pancreatic carcinoma	No	Yes

DVT: Deep vein thrombosis.

Prandoni *et al*. reported a 5.2% incidence of malignancy in 250 patients with DVT in a two-year follow-up period.[11] A more recent systematic review and meta-analysis reported a 6.3% prevalence of malignancy development within 12 months of venous thromboembolism diagnosis.[12] In a study conducted in the Netherlands in 1998, 13 (4%) new malignancies were detected in 326 patients during a 6-month follow-up period.[13] In a prospective study conducted in 2006, the 2-year incidence of malignancy in patients diagnosed with DVT was 4.4%, and the relative risk of newly diagnosed malignancy was 2.2 (95% CI = 1 - 4.7) times higher in all DVT patients.[8] While the rates in these studies were similar to this study, malignancy was encountered in 150 (11%) of 1,383 DVT patients in a study conducted in the year 1994.[14] The reason why this rate is higher compared to the present study may be because malignancy screening lasted up to 3 years. In the same study, the number of new malignancy diagnoses in the first six months was 66 (4.8%) (OR = 5.3, 95% CI = 4.1 - 6.7, p <0.05).[14] In this study, the malignancy rate in the idiopathic DVT patient group was 2.6% , which is lower than the rates of 7.2 - 7.4% reported in other studies.[8,11,13] The malignancy rate in the secondary DVT patient group was 11% which is relatively high.

This research found that the rate of malignancy diagnosis within one year in patients diagnosed with DVT was 5.4%,

which is significantly high. The rate of DVT detection in patients undergoing diagnostic tests with suspicion of DVT is higher in the ED than in other departments.[6,7] The lower rates in studies conducted in other clinics compared to the ED may be due to the lower threshold for imaging in other departments. In addition, patients with vague complaints in outpatient clinics present to the ED in case of deterioration in general condition or acute health problems. These rates may increase in EDs due to targeted and rapid diagnostic processes in patients with more prominent symptoms.[15] This may increase the physician's suspicion in the ED regarding diagnosis and contribute to the rate of correct diagnosis.

It is worth noting that this rate was observed in patients diagnosed with DVT in the ED during this retrospective study, where no referrals were being made for malignancy detection. Many prospective and retrospective studies have shown that early detection of malignancies, especially in the pelvis and abdomen, can be achieved by using basic screening methods such as physical examination, computed tomography scans, or targeted laboratory tests, especially in individuals diagnosed with unprovoked or idiopathic DVT.[12,16,17] Routine screening with CT of the abdomen and pelvis did not provide clinically significant benefit.[18] According to a study by Hettiarachchi *et al.*,[13] 77% of newly diagnosed malignancies were related to the genitourinary and gastrointestinal systems. In this study, this percentage was even higher at 83.3%. Based on these findings, if patients are asked about symptoms related to these systems and then referred to the relevant oncologic divisions after presenting at the ED, the chances of early malignancy diagnosis will increase significantly. In addition, it should be remembered that in patient groups where early diagnosis and treatment are critical, such as malignancy, referrals after DVT diagnosis are of vital importance. It is impossible to screen everyone presenting to the ED with an unprovoked DVT. Increasing awareness among EM physicians and obtaining adequate/relevant history to exclude possible malignancies should be encouraged. Furthermore, instituting dedicated DVT clinics for follow-up might be beneficial where thorough history and examination can be carried out, and the service can be extended to screening tests if clinically indicated. However, primary care plays an extremely important role in the early follow-up of these patients. The first follow-up should be within one week of diagnosis and further follow-ups can be as clinically indicated for each patient.

There were some limitations in the study. Being a single-centre retrospective study, the available information was limited and the patient population was restricted to a specific catchment area. Further multi-centre randomised controlled trials are required to validate the findings of this study. Not all information was available. Poor documentation led to incomplete data to study factors common to both DVT and malignancy that could have been picked at the first ED presentation.

CONCLUSION

It was found that 5.4% of patients diagnosed with DVT in the ED were diagnosed with malignancy after one year of follow-up. There is still no consensus on whether suggesting that DVT may be a harbinger of malignancy. Further multi-centre studies are needed to validate this. EDs, where DVT is frequently diagnosed, are a hub of opportunities for early detection of malignancy. Arranging primary care follow-up for DVT patients in the ED can improve early diagnosis and survival rates, especially for genitourinary and gastrointestinal system malignancies. Instituting dedicated DVT clinics can help achieve this.

ETHICAL APPROVAL:
This study was initiated in the Emergency Department, School of Medicine, Duzce University, following the Ethics Committee Approval (Duzce University Non-Invasive Health Research Ethics Committee's approval with decision number 2023/184, on 4 December 2023).

PATIENTS' CONSENT:
Due to the descriptive, retrospective nature of the study, the patient's consent was not obtained.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MCD: Conception and design of the research, supervision, drafting, and critical revision of the manuscript for important intellectual content.
KS: Design of the research, data collection, statistical analysis, interpretation of data, and drafting of the manuscript.
Both authors approved the final version of the manuscript to be published.

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