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Original Article

Risk and Prognosis of Upper Extremity Deep Vein Thrombosis

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Objectives: We aimed to investigate the clinical features of upper extremity deep vein thrombosis (UEDVT).
Methods: We retrospectively reviewed the background, thrombus site, treatment, and outcome of 76 UEDVT patients.
Results: Of the 76 UEDVT patients, 44 (57.9%) were men, and 51 (67.1%) were complicated by malignancy, 44 (57.9%) had an indwelling central vein (CV) catheter, 8 (10.5%) had concomitant pulmonary embolization (PE), and 33 (43.3%) were symptomatic. Regarding the thrombus site, the right internal jugular vein was the most common, with 30 cases (35.3%). As regards the treatment method, 53 patients (69.7%) received oral anticoagulants. In 2015, when direct oral anticoagulants (DOACs) was covered by insurance, there were 44 UEDVT cases, of which 34 (77.3%) received DOACs. Outcomes at a mean observation period of 37.5±41.5 months included 40 deaths (52.6%) with a mean survival of 16.3±21.3 months. The most common cause of death was malignancy, with 33 cases (82.5%).
Conclusion: In the background of UEDVT, the combination of indwelling CV catheter placement and malignancy was frequently observed. While the risk of recurrence or PE complications is low, the prognosis of UEDVT complicated by malignancy is extremely poor.

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Introduction

Upper extremity deep vein thrombosis (UEDVT) is rare, accounting for 2%–4% of all cases of deep vein thrombosis,[1] and has been considered to have relatively few complications, such as pulmonary embolism, postthrombotic syndrome, and mortality.[2–4] Recently, however, with the increasing use of central venous catheters, UEDVT is on the rise,[5] and some studies reported that UEDVT has a poorer prognosis than lower extremity deep vein thrombosis (LEDVT).[6] Furthermore, evidence for UEDVT in Japanese guidelines and an established treatment for the disease are still lacking. Under these circumstances, UEDVT treatment is currently conducted in accordance with the treatment policy for LEDVT. Therefore, to understand the pathogenesis of UEDVT in daily practice, we retrospectively reviewed UEDVT cases at our hospital and assessed their clinical characteristics.

Methods

Patients

This study included 76 patients diagnosed with UEDVT by the Division of Vascular Surgery at Hamamatsu University Hospital who underwent contrast-enhanced computed tomography (CECT) scan, ultrasonography, and other imaging examinations between January 2008 and December 2021. Patient background, thrombus site, treatment, and outcome were retrospectively reviewed. The outcome was based on the patients' history of visits to our hospital.

Study approval

This study was conducted in accordance with the ethical guidelines for medical research involving human subjects. It was also approved by the Ethics Review Committee of

Hamamatsu University School of Medicine (Approval No. 17-129).

Statistical analysis

Data were analyzed using IBM SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). $p<0.05$ was considered to indicate a significant difference. Survival differences were determined using the Kaplan–Meier method.

Results

As presented in **Table 1**, the mean age of the patients was 59.1 (±16.3, 17–88) years, and 44 and 32 of them were men and women, respectively. Of the patients, 51 (67.1%) had a malignancy at the time of UEDVT diagnosis, 44 (57.9%) had an indwelling central venous (CV) catheter, and 23 (30.3%) had overlapping cases of both. Of the malignant tumors, 12 (23.5%) were esophageal cancer, 8 (15.7%) lung cancer, 7 (13.7%) gastric cancer, and 7 (13.7%) malignant lymphoma. A total of 51 cancer-bearing patients were included in the study. Of them, 14 (27.5%) were diagnosed incidentally before surgery, and 32 (62.7%) were undergoing chemotherapy. The patients were classified according to cancer type: 12 (23.5%) had Stage 0–I, 8 (15.7%) Stage II, 7 (13.7%) Stage III, and 24 (47.1%) Stage IV. Each patient's malignancy stage and the duration of survival together with 5-year survival rate based on the Japanese Cancer Classification are presented in **Supplementary Table**. The primary diseases of UEDVT cases without malignancy included severe infections, cardiac diseases, and inflammatory bowel diseases, such as ulcerative colitis. Six patients (7.9%) had a predisposition to thrombosis, including protein C deficiency or decreased activity in four, protein S deficiency in one, and decreased AT III activity in one. Thrombophilia was discovered after the UEDVT diagnosis. However, not all the UEDVT patients without malignancy were tested for thrombophilia. Furthermore, only two cases were considered idiopathic (Paget–Schroetter syndrome). Regarding concomitant catheterization, 42 (95.5%) cases were due to CV lines for infusion or dialysis and 2 (4.5%) due to pacemaker catheters or Swan–Ganz catheters for the cardiovascular diseases. Pulmonary thromboembolization (PE) occurred in eight patients (10.5%), but only one patient had symptoms of chest pain and respiratory distress. Symptomatic cases, such as swelling and pain in the upper extremities, were observed in 33 cases (43.3%). Asymptomatic cases were incidentally detected by CECT scan. With the exception of four patients with significant poor renal function (estimated Glomerular Filtration Rate (eGFR) <30 mL/min) or history of contrast allergy, 47 of 51 patients (92.2%) with malignancy were diagnosed with UEDVT by CECT, with imaging range of cervical to pelvic to monitor the cancer and check for recurrence and metastasis (**Table 1**).

Table 1 Characteristics of patients with UEDVT

Mean age (SD, range): year	59.1±16.3 (17–88)
Sex (Male : Female)	44 : 32
Malignancy	51 (67.1%)
Esophageal cancer	12 (23.5%)
Lung cancer	8 (15.7%)
Gastric cancer	7 (13.7%)
Malignant lymphoma	7 (13.7%)
Colorectal cancer	5 (6.6%)
Pancreatic cancer	2 (2.6%)
Uterine cancer	2 (2.6%)
Others	8 (15.7%)
Catheter-associated	44 (57.9%)
CV catheter	42 (95.5%)
Pacemaker/Swan–Ganz catheter	2 (4.5%)
Thrombophilia	6 (7.9%)
Pulmonary embolization	8 (10.5%)
Symptomatic DVT	33 (43.3%)

UEDVT patients tend to be slightly more common in men, with more patients having malignancy complications and indwelling CV catheter placement. Gastrointestinal cancer is the most common malignancy complication. The incidence of pulmonary thromboembolization complication is low.

CV catheter: central venous catheter; DVT: deep vein thrombosis; UEDVT: upper extremity deep vein thrombosis

The thrombus sites are presented in **Table 2**. The right internal jugular vein was the most common site (35.3%), followed by the left internal jugular vein in 19 (22.4%), left subclavian vein in 11 (12.9%), right subclavian vein in 10 (11.8%), superior vena cava in 8 (9.4%), right upper extremity in 3 (3.5%), and left upper extremity in 3 (3.5%). CV lines were implanted in 21 of 30 (70%) right internal jugular vein thrombi and 8 of 19 (42.1%) left internal jugular vein thrombi. On the other hand, 12 of 30 (40%) right internal jugular vein thrombi and 17 of 19 (89.5%) left internal jugular vein thrombi were associated

Table 2 Proximal site of DVT

Rt. IJV	30 (35.3%)
Lt. IJV	19 (22.4%)
Lt. SCV	11 (12.9%)
Rt. SCV	10 (11.8%)
SVC	8 (9.4%)
Rt. UE	3 (3.5%)
Lt. UE	3 (3.5%)

About half of the UEDVTs occurred in the internal jugular vein. More than 90% of the cases were of central type; peripheral types are rare.

DVT: deep vein thrombosis; IJV: internal jugular vein; SCV: subclavian vein; SVC: superior vena cava; UE: upper extremity; UEDVT: upper extremity deep vein thrombosis

with malignancy.

The treatment used is presented in **Table 3**. Of the 76 patients, 53 (69.7%) received oral anticoagulants and 19 received warfarin (**Table 3**). All 19 patients who received warfarin followed the guidelines[7] and had a controlled PT-INR: 1.5–2.5. Due to their general condition, 9 patients (11.9%) were followed up without therapeutic intervention. In 2015, when direct oral anticoagulants (DOACs) were covered for venous thromboembolism, there were 44 cases of UEDVT, of which 34 (77.3%) were treated with DOAC (edoxaban, apixaban, rivaroxaban). The mean duration of anticoagulation after UEDVT diagnosis for the 51 cancer patients was 710.9±1058.9 days, whereas the mean duration of anticoagulation for the 25 noncancer patients was 55.04±48.7 days.

We conducted blood tests (D-dimer) and ultrasound examinations every 3 months to check for UEDVT recurrence. There were no cases of recurrent thrombosis during the follow-up period. Regarding the outcome, 40 patients (52.6%) died. Majority of the deaths were caused by malignancy (33 cases, 82.5%), followed by myocardial infarction (2 cases, 5%), ileus (1 case, 2.5%), and interstitial pneumonia (1 case, 2.5%), with no deaths related to blood clots. The mean follow-up period of all 76 patients was 37.5±41.5 months with a mean 3-year survival rate of 56.6%. The survival of patients with UEDVT complicated by malignancy was extremely poor, with an average 3-year survival rate of 35.3% with malignancy cases and 84% without malignancy cases (**Fig. 1a**). On the other hand, a comparison of survival rates between patients with and without catheters revealed that the 3-year mean survival rate with central venous catheters was 59.1%, whereas the 3-year mean survival rate without catheters was 40.6%, with no significant difference between the two groups. No significant difference was observed in the 3-year mean survival rates between UEDVT patients complicated by malignancy with and without CV catheters (**Figs. 1b** and **1c**). Similarly, no significant difference was observed in the 3-year mean survival rates between UEDVT patients without malignancy with and without CV catheters (**Fig. 1c**). Taken together, CV catheter placement itself may be a risk factor for UEDVT development but has little impact on life expectancy.

Table 3 Treatment

No oral anticoagulants	Heparin	6 (7.9%)
	Enoxaparin	4 (5.3%)
	Argatroban	1 (1.3%)
	CDT*	3 (3.9%)
Oral anticoagulants	Warfarin	19 (25.0%)
	Edoxaban	30 (39.5%)
	Apixaban	2 (2.6%)
	Rivaroxaban	2 (2.6%)
No treatment		9 (11.9%)
Total		76

Oral anticoagulants were the treatment of choice in 53 (69.7%) patients. Due to their general condition, 9 patients (11.9%) were followed up without therapeutic intervention.
CDT: catheter-directed thrombolysis

Discussion

Although there have been few previous studies of UEDVT in Japan and it has been considered a relatively rare disease, the number of cases encountered in clinical practice is increasing due to the increased number of patients with CV catheter and the advances in imaging modalities.[8]

UEDVT is categorized into primary or secondary. Primary includes Paget–Schroetter syndrome, which is triggered by excessive upper extremity motion and is idiopathic. Regarding frequency, some studies reported that primary cases were more common and secondary ones less common,[9] but most studies reported that secondary cases were more common, with primary cases being 2.1%,[10] 9.7%,[11] about 1/3[12] and varied by report. The results of the present study indicated that only 2 (2.6%) of the 76 patients had primary UEDVT. The risk factors for secondary UEDVT include catheter-related conditions, such as CV catheters and pacemakers, and malignancy.[4,13]

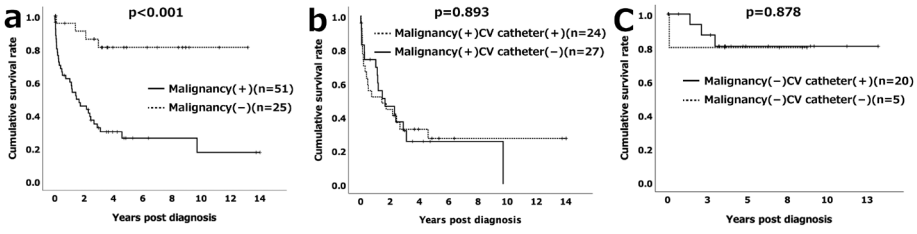

Fig. 1 Cumulative survival in UEDVT patients. (**a**) Comparison of survival between UEDVT patients with and without malignancy. (**b**) Comparison of survival between patients with UEDVT complicated by malignancy with and without CV catheters. (**c**) Comparison of survival between UEDVT patients without malignancy with and without CV catheters.
CV catheter: central venous catheter; UEDVT: upper extremity deep vein thrombosis

Delluc et al. reported that 93% of UEDVT cases were associated with CV catheters and malignancy.[11] Our results also showed 71 cases (93.4%) with catheter-related or malignant tumors or both, consistent with the previous report. **Figure 1b** shows that the use of CV catheters does not worsen the life expectancy of UEDVT patients with malignancy. However, an interaction between cancer progression and use of CV catheters is possible. When the 24 UEDVT patients with cancer who had CV catheter placement were examined, 7 (29.2%) were found to have Stage I; 2 (8.3%), Stage II; 5 (20.8%), Stage III; and 10 (41.7%), Stage IV cancer; there was no significant difference in the frequency of the CV catheter placement between the patients with early and advanced cancers ($p=0.371$). As regards the impact of the use of CV catheter in the noncancer patient group, **Fig. 1c** shows that CV catheter placement itself has a negligible impact on life expectancy. Therefore, we speculated that CV catheter placement itself is a risk factor for UEDVT development but has a negligible impact on life expectancy. Other risk factors include prior DVT, surgery, cardiovascular disease, hormone therapy, and hypercoagulable conditions, although the frequency of each as a single factor is not high.[10]

The right internal jugular vein was previously the first choice for CV catheter placement in our hospital. If placement could not be done on the right internal jugular vein due to underlying disease or surgery, the left internal jugular vein was selected. Recently, however, peripherally inserted central venous catheters (PICCs) have become the catheter of choice owing to their relatively low cost, ease of placement and removal, fewer complications (pneumothorax, bleeding, and air embolism), and better patient tolerability. PICCs are increasingly being used. In a systematic review, Chopra et al. reported a 2.6-fold higher risk of thrombosis with PICCs compared with other CV catheters ($p<0.0001$) in approximately 4000 patients.[14] As the use of PICCs is expected to increase in the future, there is a concern that the incidence of UEDVT will also further increase.

To date, no consensus has been reached on UEDVT treatment. The 2017 revised Guidelines for the Diagnosis, Treatment, and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis, issued by The Japanese Circulation Society, do not explicitly state the treatment strategy for UEDVT.[7] The American College of Chest Physicians (ACCP) guidelines recommends at least 3 months of anticoagulation; however, this guideline was set based on LEDVT data.[15] Our treatment policy for UEDVT also conforms to LEDVT. Catheter-related thrombosis is treated with anticoagulation for 3 months, and the patient is reevaluated at the end of the 3-month period to determine whether to continue anticoagulation or not. Patients with malignancy are generally continued with anticoagulation permanently as long as there are no side effects. However, few studies have examined the efficacy of anticoagulation therapy for UEDVT. Vedovati et al. reported that in a prospective cohort study examining the usefulness of DOACs and using the UEDVT recurrence risk classification based on the 2019 European Society of Cardiology guideline, a significant difference was observed in the recurrence risk among the low, intermediate, and high-risk groups, but none in the adverse events of major bleeding.[16] This study is the first to report the utility and safety of DOAC use for UEDVT, and further reports are warranted. Prophylactic anticoagulation in patients with indwelling CV catheter or malignancy is not recommended by the 8th ACCP guideline (Grade 1b).[17] In this study, no cases of recurrent UEDVT were observed. Generally, a lower recurrence risk is reported compared with LEDVT.[18,19] The frequency of PE complications was 10.5%, similar to previous reports of recurrent UEDVT.[20] Given that UEDVT has a low risk of recurrence and a low incidence of PE, continued anticoagulation for longer periods may not be necessary in malignancy-associated UEDVT. We believe that further study is warranted to accumulate more data in the future. In this study, the 3-year survival rate of UEDVT patients with malignancy was as low as 35.3%, suggesting that treatment should be conducted considering the extremely poor prognosis of these patients. On the other hand, the 3-year survival rate of UEDVT patients without malignancy was relatively good at 84%, suggesting that the treatment strategy for UEDVT patients should be divided according to the presence or absence of malignancy.

This study had several limitations: it was a single-center and retrospective study, the sample size was small, and the anticoagulation policy changed due to the emergence of DOAC during the observation period.

Conclusion

The UEDVT cases at our institution were reviewed. The main risk factors were catheterization and malignancy. Although the complication rate of recurrence and PE was low, the prognosis for patients with malignancy was extremely poor.

Conflicts of Interests

All authors declare that no competing interests exist.

Author Contributions

Study conception: YE, NU
Data collection: YE, MS, KK, TK, YY
Analysis: YE, NU, KI
Manuscript preparation: YE

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Supplementary Information

Supplementary material is available at the online article sites on J-STAGE and PMC.

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