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Full Length Article

Deep vein thrombosis in upper extremities: Clinical characteristics, management strategies and long-term outcomes from the COMMAND VTE Registry

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ABSTRACT

Introduction: There is a paucity of data on patients with deep vein thrombosis (DVT) in upper extremities.
Materials and methods: The COMMAND VTE Registry is a retrospective multicenter registry enrolling 3027 consecutive patients with acute symptomatic venous thromboembolism (VTE) in Japan. The current study population included 2498 patients with upper or lower extremities DVT.
Results: There were 74 patients (3.0%) with upper extremities DVT and 2424 patients with lower extremities DVT. Patients with upper extremities DVT more often had active cancer (58%) and central venous catheter use (22%). The proportion of concomitant pulmonary embolism at diagnosis was lower in patients with upper extremities DVT than in those with lower extremities DVT (14% and 51%, $P < 0.001$). Discontinuation of

Abbreviations: CI, confidence interval; CT, computed tomography; DVT, deep vein thrombosis; HR, hazard ratio; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism

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anticoagulation therapy was more frequent in patients with upper extremities DVT (63.8% and 29.8% at 1-year, P < 0.001). The cumulative 3-year incidence of recurrent VTE was not different between the 2 groups (9.8% and 7.4%, $P = 0.43$). After adjusting confounders, the risks of upper extremities DVT relative to lower extremities DVT for recurrent VTE remained insignificant (HR 0.94, 95%CI 0.36–2.01, $P = 0.89$).
Conclusions: The prevalence of patients with DVT in upper extremities was 3.0% in the current large-scale real-world registry. Patients with DVT in upper extremities more often had active cancer at diagnosis and central venous catheter use as a transient risk factor for VTE, and less often had concomitant PE. Patients with DVT in upper extremities had similar long-term risk for recurrent VTE as those with DVT in lower extremities despite shorter duration of anticoagulation.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major health problem in the world [1,2]. PE is caused by blockage of pulmonary arteries by thrombus, which is developed in veins and travels through the blood stream. The sources of thrombus are thought to be mostly veins in lower extremities, whereas DVT in upper extremities, which usually refers to thrombosis of the axillary or subclavian veins, rarely occurs spontaneously and sometimes develops as a complication of central venous catheter placement or cancer [3,4]. Historically, DVT in upper extremities was considered as a rare self-limited disease [5,6]. However, recent studies reported that DVT in upper extremities might have significant complications, including PE, loss of vascular access, superior vena cava syndrome, and post-thrombotic syndrome [7,8]. Furthermore, DVT in upper extremities could be increasing, due to widespread

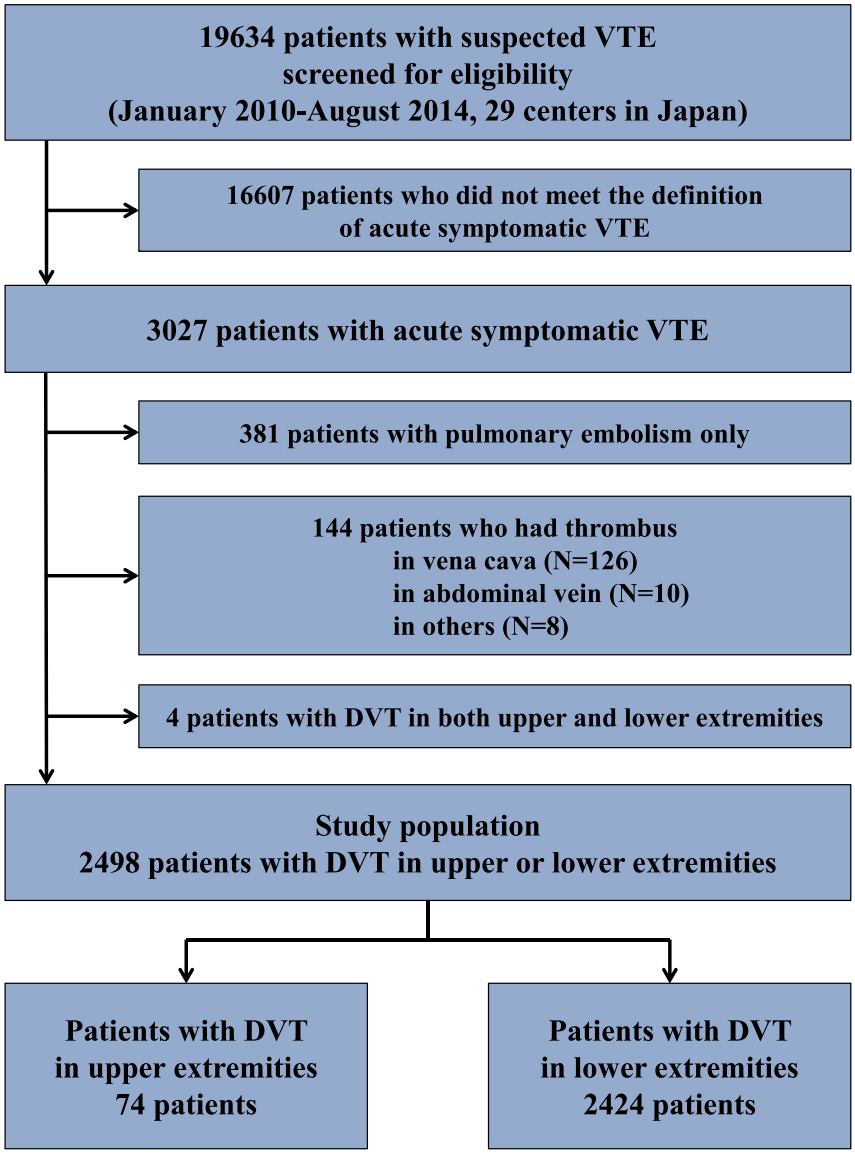


Fig. 1. Study flow chart.
VTE included PE and/or DVT.
DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 1
Patient characteristics.

	Patients with DVT in upper extremities (N = 74)	Patients with DVT in lower extremities (N = 2424)	P-value
Baseline characteristics			
Age (years)[a,b,c]	60.7 ± 14.9	67.4 ± 15.3	< 0.001
Women[a,b,c]	30 (41%)	1499 (62%)	< 0.001
Body weight (kg)	56.0 ± 12.8	57.7 ± 13.3	0.30
Body mass index (kg/m^2)	21.1 ± 3.4	23.2 ± 4.3	< 0.001
Body mass index ≥ 30 kg/m^2[a]	0 (0.0%)	127 (5.2%)	0.04
Comorbidities			
Hypertension[c]	12 (16%)	931 (38%)	< 0.001
Diabetes mellitus[c]	5 (6.8%)	315 (13%)	0.11
Dyslipidemia	8 (11%)	508 (21%)	0.03
Chronic kidney disease[b,c]	9 (12%)	459 (19%)	0.14
Dialysis	0 (0.0%)	20 (0.8%)	0.43
History of cancer	47 (64%)	718 (30%)	< 0.001
Active cancer at diagnosis[a,b,c]	43 (58%)	527 (22%)	< 0.001
Chronic lung disease	4 (5.4%)	196 (8.1%)	0.40
Heart failure	3 (4.1%)	81 (3.3%)	0.74
History of myocardial infarction	0 (0.0%)	43 (1.8%)	0.25
History of stroke[c]	5 (6.8%)	201 (8.3%)	0.64
Atrial fibrillation	5 (6.8%)	91 (3.8%)	0.19
Liver cirrhosis[b,c]	1 (1.4%)	21 (0.9%)	0.66
Connective tissue disease[c]	3 (4.1%)	217 (9.0%)	0.14
Varicose vein[a,c]	0 (0.0%)	125 (5.2%)	0.045
History of VTE[a,c]	3 (4.1%)	142 (5.9%)	0.51
History of major bleeding[b,c]	3 (4.1%)	182 (7.5%)	0.26
Transient risk factors for VTE[a,b,c]	34 (46%)	837 (35%)	0.04
Central venous catheter-related	24 (32%)	26 (1.1%)	< 0.001
Presentation			
Concomitant PE[a,b,c]	10 (14%)	1242 (51%)	< 0.001
Laboratory tests at diagnosis			
Anemia[b,c]	45 (61%)	1325 (55%)	0.30
Thrombocytopenia (platelet count < 100 × 10^9/L)[b,c]	5 (6.8%)	133 (5.5%)	0.64
D-dimer (μg/mL) (N = 2845)	3.3 (1.3–10.0)	10.3 (5.0–20.5)	< 0.001
Thrombophilia[a,c]	1 (1.4%)	118 (4.9%)	0.16

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's t-test or Wilcoxon's rank sum test based on distribution.
Chronic kidney disease was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate (eGFR) was < 60 mL/min/1.73 m^2 for > 3 months. The values of eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [man: $194*Scr^{-1.094}*age^{-0.287}$, woman: $194*Scr^{-1.094}*age^{-0.287}*0.739$]. Anemia was diagnosed if the value of hemoglobin was < 13 g/dL for men and < 12 g/dL for women. Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.
[a] Potential variables for the multivariable Cox regression model to estimate the risk for recurrent VTE.
[b] Potential variables for the multivariable Cox regression model to estimate the risk for major bleeding.
[c] Potential variables for the multivariable Cox regression model to estimate the risk for all-cause death.

use of central venous catheters and increase in cancer survivors.

To date, no randomized controlled trials have evaluated treatment strategies of patients with DVT in upper extremities, leading to uncertainty in optimal treatment strategies including anticoagulation therapy. Furthermore, few studies have evaluated long-term clinical outcomes of patients with DVT in upper extremities. Therefore, we sought to evaluate the clinical characteristics, management strategies, and long-term outcomes of patients with DVT in upper extremities in a large observational database in Japan.

2. Materials and methods

2.1. Study population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) registry is a physician-initiated, retrospective, multicenter cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography (CT), ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy among 29 centers in Japan between January 2010 and August 2014. The design of the registry was previously reported in detail [9,10]. We searched the hospital databases for clinical diagnosis and imaging examinations, and enrolled consecutive patients who met the definition of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period [11]. The presence or absence of symptoms was evaluated at the time of the imaging studies.

The relevant review boards or ethics committees in all 29 participating centers (Supplementary Appendix 1) approved the research protocol. Written informed consent from each patient was waived, because we used clinical information obtained in routine clinical practices, and no patients refused to participate in the study when contacted for follow-up. This method is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

We enrolled 3027 consecutive patients with acute symptomatic VTE after screening of the consecutive 19,634 patients with suspected VTE for eligibility through chart review by the physicians at each institution. The current study population consisted of 2498 patients with DVT in upper or lower extremities, after excluding 381 patients with PE only, 144 patients who had thrombus in locations other than upper or lower extremities, and 4 patients with DVT in both upper and lower extremities (Fig. 1). The study patients were divided into 2 groups: patients with DVT in upper extremities and patients with DVT in lower extremities. We compared the clinical characteristics, management strategies and long-term outcomes between the 2 groups.

2.2. Data collection and definitions for patient characteristics

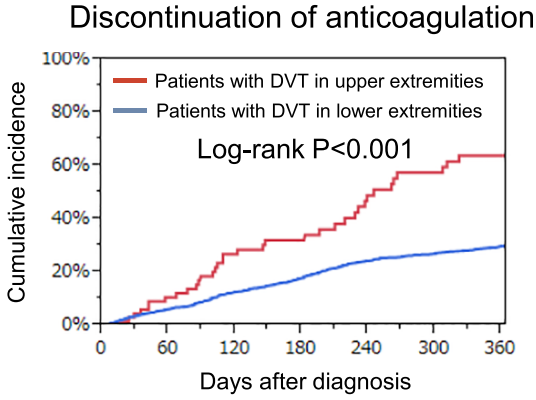
Data for the baseline characteristics were collected from the hospital charts or hospital databases according to the pre-specified definitions. The physicians at each institution were responsible for data entry into an electronic case report form in a web-based database system. Data were automatically checked for missing or contradictory input and values out of the expected range. Additional monitoring for the quality of data was performed at the general office of the registry.

DVT in upper extremities included thrombosis in brachial, axillary, subclavian, internal jugular, and brachiocephalic veins [12]. Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo cancer-surgery, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy of 6 months or less) at the time of the diagnosis. Initial anticoagulation therapy was defined as parenteral anticoagulation therapy in the acute phase (heparin or fondaparinux) for ≤ 10 days after the diagnosis, while anticoagulation therapy beyond the acute phase was defined as anticoagulation therapy (warfarin, direct oral anticoagulant, or heparin) continued beyond 10 days after the diagnosis. The detailed definitions of patient

Table 2
Treatment strategies.

	Patients with DVT in upper extremities (*N* = 74)	Patients with DVT in lower extremities (*N* = 2424)	P-value
Treatment in the acute phase			
Initial anticoagulation therapy	56 (76%)	2004 (83%)	0.12
Thrombolysis	3 (4.1%)	316 (13%)	0.02
Vena cava filter use	4 (5.4%)	615 (25%)	< 0.001
Ventilator support	0 (0.0%)	36 (1.5%)	0.29
Percutaneous cardiopulmonary support	0 (0.0%)	18 (0.7%)	0.46
Concomitant medications at discharge			
Corticosteroids	8 (11%)	297 (12%)	0.71
Non-steroidal anti-inflammatory drugs	10 (14%)	246 (10%)	0.35
Proton pump inhibitors/H2-blockers	32 (43%)	1079 (45%)	0.83
Statins	2 (2.7%)	369 (15%)	0.003
Antiplatelet agents	8 (11%)	249 (10%)	0.88
Anticoagulation therapy beyond the acute phase	68 (92%)	2279 (94%)	0.45
Warfarin	63 (85%)	2178 (90%)	0.42
Direct oral anticoagulant	4 (5.4%)	63 (2.6%)	
Heparin	1 (1.4%)	38 (1.6%)	
TTR for INR 1.5–2.5 (%) (N = 2098)	72.1 (28.8–83.0)	72.4 (45.9–91.6)	0.11
TTR for INR 2.0–3.0 (%) (*N* = 2098)	20.5 (4.3–50.0)	30.2 (8.2–56.2)	0.14
Discontinuation of anticoagulation during follow-up	36/68 (53%)	884/2279 (39%)	0.02
Reason for discontinuation			
Physician's judgment	26/36 (72%)	537/884 (61%)	0.38
Bleeding event	5/36 (14%)	160/884 (18%)	
Other	5/36 (14%)	187/884 (21%)	
Interruption of anticoagulation during follow-up period	8/68 (12%)	288/2279 (13%)	0.83

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using Wilcoxon's rank sum test.
DVT, deep vein thrombosis; INR, international normalized ratio; TTR, time in therapeutic range.



	0-day	90-day	180-day	1-year
Patients with DVT in upper extremities				
N of patients with discontinuation		12	20	35
N of patients at risk	68	51	36	18
Cumulative incidence		18.5%	32.0%	63.8%
Patients with DVT in lower extremities				
N of patients with discontinuation		193	380	616
N of patients at risk	2279	1928	1667	1340
Cumulative incidence		8.8%	17.8%	29.8%

Fig. 2. Kaplan-Meier event curves for discontinuation of anticoagulation therapy comparing upper versus lower extremity DVT.
The discontinuation of anticoagulation was estimated in patients who received anticoagulation therapy beyond the acute phase, and defined as withdrawal of anticoagulation therapy lasting > 14 days for any reasons.
DVT, deep vein thrombosis.

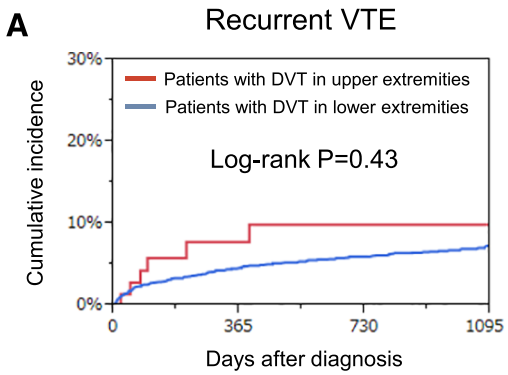
characteristics are described in Supplementary Appendix 3.

2.3. Clinical follow-up and endpoints

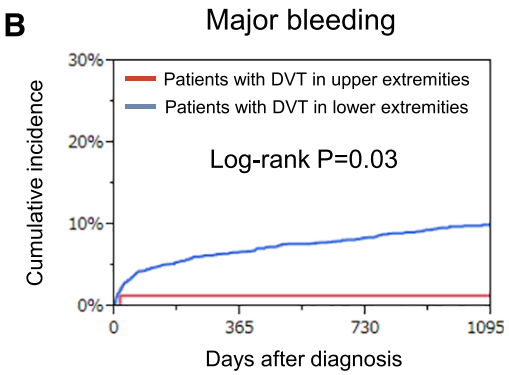
Collection of follow-up information was mainly conducted through review of hospital charts, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by phone and/or mail with questions regarding vital status, recurrent VTE, bleeding, invasive procedure, and status of anticoagulation therapy.

The outcomes measured were recurrent VTE, major bleeding and all-cause death during the entire follow-up period. The recurrent VTE was defined as PE and/or DVT with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined as International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ [13]. The independent clinical event committee (Supplementary Appendix 2) unaware of the patient characteristics reviewed all study outcomes.

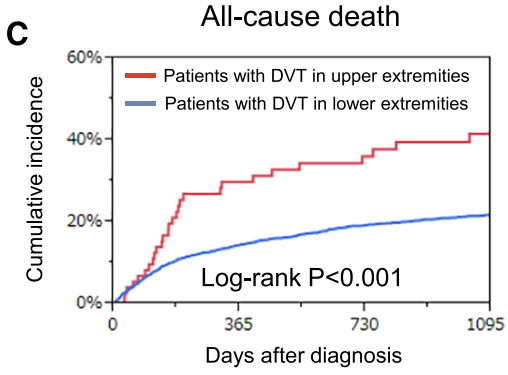
Anticoagulation therapy cessation was classified into discontinuation and interruption according to the pre-specified definitions. Discontinuation of anticoagulation was defined as withdrawal of anticoagulation therapy lasting > 14 days for any reasons such as bleeding events, physicians' judgment in the absence of adverse events, and others. Interruption of anticoagulation was defined as temporary cessation of anticoagulation therapy with reinstitution within 14 days for any reasons including invasive procedure and bleeding events, etc. Scheduled switch from one anticoagulation therapy to another anticoagulation therapy was not regarded as interruption of anticoagulation. Data for international normalized ratio (INR) during follow-up in patients receiving warfarin were collected from the hospital charts of the centers where the index VTE was diagnosed. Time in therapeutic range (TTR) was calculated by the Rosendaal method [14], according to a therapeutic INR range of 1.5 to 2.5, which is recommended in the



	0-day	90-day	1-year	3-year
Patients with DVT in upper extremities				
N of patients with event		3	5	6
N of patients at risk	74	64	45	24
Cumulative incidence		4.2%	7.7%	9.8%
Patients with DVT in lower extremities				
N of patients with event		59	101	146
N of patients at risk	2424	2156	1881	1102
Cumulative incidence		2.5%	4.6%	7.4%



	0-day	90-day	1-year	3-year
Patients with DVT in upper extremities				
N of patients with event		1	1	1
N of patients at risk	74	66	48	26
Cumulative incidence		1.4%	1.4%	1.4%
Patients with DVT in lower extremities				
N of patients with event		105	153	208
N of patients at risk	2424	2123	1859	1097
Cumulative incidence		4.5%	6.7%	10.0%



	0-day	90-day	1-year	3-year
Patients with DVT in upper extremities				
N of patients with event		5	21	28
N of patients at risk	74	67	48	26
Cumulative incidence		6.8%	29.8%	41.6%
Patients with DVT in lower extremities				
N of patients with event		152	339	488
N of patients at risk	2424	2212	1969	1168
Cumulative incidence		6.4%	14.4%	21.7%

Fig. 3. Kaplan-Meier event curves for (A) recurrent VTE, (B) major bleeding and (C) all-cause death comparing upper versus lower extremity DVT.
VTE included PE and/or DVT.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

Japanese guidelines [15], as well as according to a therapeutic INR range of 2.0 to 3.0, which is recommended in the Western guidelines [16–18].

2.4. Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range (IQR) based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's *t*-test or Wilcoxon's rank sum test based on their distributions. We used the Kaplan-Meier method to estimate the cumulative incidences of the endpoint events and assessed the differences with the log-rank test. To adjust for the clinically relevant confounders, we used the multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and their 95% confidence interval (CI) for the risk of patients with DVT in upper extremities relative to patients with DVT in lower extremities for clinical outcomes. Based on the previous reports [15–18] and consideration of clinical relevance, we selected 9 risk-adjusting variables for recurrent VTE, 10 risk-adjusting variables for major bleeding, and

Table 3
Crude and adjusted clinical outcomes.

	Patients with DVT in lower extremities (reference) (N = 2424)	Patients with DVT in upper extremities (N = 74)				
	Number of patients with event during entire follow-up period (cumulative 3-year incidence)	Number of patients with event during entire follow-up period (cumulative 3-year incidence)	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	P value
Recurrent VTE	169 (7.4%)	6 (9.8%)	1.39 (0.55–2.87)	0.45	0.94 (0.36–2.01)	0.89
Major bleeding	230 (10.0%)	1 (1.4%)	0.16 (0.01–0.69)	0.008	0.13 (0.01–0.58)	0.003
All-cause death	556 (21.7%)	30 (41.6%)	2.07 (1.40–2.93)	< 0.001	1.08 (0.72–1.56)	0.71

Cumulative 3-year incidence was estimated using the Kaplan-Meier method. Crude and adjusted HRs and 95% CIs were estimated by the Cox proportional hazard models using the patients with DVT in lower extremities as the reference. Recurrent VTE, major bleeding and all-cause death were adjusted by incorporating the respective risk-adjusting covariates listed in Table 1.
HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism.

17 risk-adjusting variables for all-cause death (Table 1). All statistical analyses were conducted using JMP version 10.0.2 (SAS Institute Inc., Cary, NC, USA). All reported *P*-values were 2-tailed, and P-values < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

In the entire study population, the mean age was 67 years, 61% were women, and mean body weight and body mass index were 57.6 kg and 23.1 kg/m^2, respectively. There were 74 patients (3.0%) with DVT in upper extremities and 2424 patients (97%) with DVT in lower extremities. The baseline patient characteristics were different in several aspects between the 2 groups (Table 1). Patients with DVT in upper extremities were younger, more often had active cancer at diagnosis and central venous catheter use as a transient risk factor for VTE. The prevalence of concomitant PE at diagnosis was lower in patients with DVT in upper extremities than in patients with DVT in lower extremities.

3.2. Anticoagulation therapy

The patients with DVT in upper extremities received anticoagulation therapy beyond the acute phase as often as the patients with DVT in lower extremities. Median TTR among warfarin users was not significantly different between the 2 groups (Table 2). Among patients who received anticoagulation therapy beyond the acute phase, discontinuation of anticoagulation therapy was more frequent in patients with DVT in upper extremities (patients with DVT in upper extremities: 63.8% and patients with DVT in lower extremities: 29.8% at 1-year, $P < 0.001$) (Fig. 2). Most of the reasons for discontinuation of anticoagulation were physician's judgment in both groups (Table 2). The prevalence of interruption of anticoagulation therapy during follow-up period was not significantly different between the 2 groups.

3.3. Clinical outcomes

The median follow-up period was 1225 (IQR: 847–1771) days for surviving patients (95.1% follow-up rate at 1 year). The cumulative 3-year incidence of recurrent VTE in patients with DVT in upper extremities was not significantly different from that in patients with DVT in lower extremities (9.8% and 7.4%, $P = 0.43$) (Fig. 3A). After adjusting confounders, the risks of patients with DVT in upper extremities DVT relative to lower extremities DVT for recurrent VTE remained insignificant (Adjusted HR 0.94, 95%CI 0.36–2.01, $P = 0.89$) (Table 3). Among patients with DVT in upper extremities, 6 patients developed symptomatic recurrent VTE events during follow-up period (Table 4). Except for 1 patient who developed index DVT in upper extremities due to a recent surgery, all other patients had active cancers at diagnosis. Most of recurrent VTE events were developed as recurrent DVT in upper extremities, whereas 1 patient developed vena cava thrombus related to vena cava filter, and 1 patient developed DVT in lower extremities with concomitant PE. Except for 1 patient who discontinued anticoagulation therapy 261 days after diagnosis and developed a recurrent VTE event at 394 days, all other patients had received anticoagulation therapy at recurrence.

The cumulative 3-year incidence of major bleeding was significantly lower in patients with DVT in upper extremities (1.4% and 10.0%, $P = 0.03$) (Fig. 3B). After adjusting the confounders, the lower risk of upper extremities DVT relative to lower upper extremities DVT for major bleeding remained significant (Table 3). The cumulative 3-year incidence of all-cause death was significantly higher in patients with DVT in upper extremities (41.6% and 21.7%, $P < 0.001$) (Fig. 3C). However, after adjusting the confounders, the excess mortality risk of patients with DVT in upper extremities relative to patients with DVT in lower extremities was no longer significant (Table 3).

4. Discussion

The main findings of the current study were as follows; 1) Among patients with DVT in upper or lower extremities, the prevalence of patients with DVT in upper extremities was 3.0%; 2) Patients with DVT in upper extremities more often had central venous catheter placement and active cancer, and less often had concomitant PE; and 3) The risk for recurrent VTE was not significantly different between patients with DVT in upper extremities and those in lower extremities.

DVT in upper extremities is a relatively rare disease, and only some studies reported the data on DVT in upper extremities with little data on long-term clinical outcomes. The proportions of DVT in upper extremities among patients with DVT were reported to range from 4% to 11% [8,19–21]. The difference in the prevalence of DVT in upper extremities could be partly due to the difference in the study population and study design. The prevalence of patients with DVT in upper extremities trended to be higher in the studies which included patients with DVT confirmed by imaging examinations irrespective of clinical symptoms, and lower in the studies that only included acute symptomatic VTE, suggesting that the proportion of patients with non-acute or asymptomatic DVT would be greater in upper extremities. The current retrospective study showed relatively-low prevalence (3.0%), which was in line with the results from the studies enrolling acute symptomatic VTE only [8].

Previous studies reported that strong risk factors for DVT in upper extremities were prior central venous catheter placement, cancer, and hospitalization [8,19]. Approximately 50% and 40% of patients with DVT in upper extremities were reported to have prior central catheter placements and cancers, respectively. Consistent with previous reports, the current study showed high proportions of central venous catheter placement (32%) and active cancer (58%). In the current study, the prevalence of active cancer was remarkably high compared with

Table 4
Cases of symptomatic recurrent VTE during follow-up among patients with DVT in upper extremities.

No.	Age (years)	Sex	Active cancer at diagnosis	Central venous catheter at diagnosis	Time to recurrent VTE (days)	Diagnosis of recurrent VTE	Location of recurrent DVT	Anticoagulants at recurrent VTE	Central venous catheter at recurrent VTE	
1	73	Woman	No	No	20	DVT	Upper	DOAC	No	Recent surgery due to trauma at diagnosis
2	69	Woman	Yes	Yes	48	DVT	Vena cava	Warfarin	No	Vena cava filter insertion at diagnosis
3	66	Woman	Yes	Yes	77	PE + DVT	Lower	Warfarin	No	
4	69	Man	Yes	No	98	DVT	Upper	Warfarin	No	
5	67	Woman	Yes	Yes	211	DVT	Upper	Warfarin	Yes	
6	69	Man	Yes	No	394	DVT	Upper	None	No	

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; DOAC, direct oral anticoagulant.

previous reports. This observation might suggest that the number of patients with cancer-related DVT in upper extremities has been increasing in the real-world, partly due to increase in cancer survivors with rapid progress of cancer treatment [22].

Traditionally, patients with DVT in upper extremities were thought to be at a low risk for development of PE. A previous study reported that patients with DVT in upper extremities less likely presented with PE at diagnosis (10%), compared with those in lower extremities [8]. The current study also showed that patients with DVT in upper extremities less often had concomitant PE at diagnosis (14%), although the proportions of concomitant PE were higher than previously reported, which could be partly due to the relatively large proportion of contrast-enhanced CT examination ($N = 1905$, 76%) [23]. However, the previous studies reported that the rate of recurrent PE in patients with DVT in upper extremities was not lower than the rate in those in lower extremities [8,21]. Another recent study also reported that patients with DVT in upper extremities had a similar outcome than those in lower extremities during the course of anticoagulation therapy [24]. Similarly, the current study showed that the risk for recurrent VTE in patients with DVT in upper extremities was not significantly different compared with that in patients with DVT in lower extremities, and only 1 patient developed a recurrent DVT event with concomitant PE. Due to lack of evidences, the current guidelines make weak recommendations of same initial and long-term anticoagulation therapy for patients with DVT in upper extremities as those in lower extremities [25]. However, in the current study, the duration of anticoagulation therapy in patients with DVT in upper extremities was shorter as compared with that in patients with DVT in lower extremities, suggesting that physicians regarded that the long-term risk for recurrent VTE in patients with DVT in upper extremities was relatively low, although this is partly due to the difference in the patients characteristics, including central venous catheter placement and active cancer. In the current study, it might be important to note that the risk for recurrent VTE was comparable in patients with DVT in upper and lower extremities despite shorter duration of anticoagulation in patients with DVT in upper extremities. Further studies are needed to clarify the optimal treatment strategies in patients with DVT in upper extremities.

5. Study limitations

The current study has several limitations. First and most importantly, the absolute number of patients with DVT in upper extremities was small ($N = 74$), although it was derived in a large observational database of patients with VTE. Due to lack of adequate statistical power, we could not conduct detailed analyses among patients with DVT in upper extremities. Therefore, the results of the current study should be regarded as exploratory and hypothesis generating. Especially, as for major bleeding, only 1 patient in 74 patients with DVT in upper extremities experienced a major bleeding event, and the comparison of major bleeding between the groups was quite underpowered. Second, the current study was an observational study, which can be subject to various biases inherent to observational study design. Especially, the therapeutic decision-making was left to the discretion of the attending physicians, which could have some influence on clinical outcomes. Especially, the difference in duration of anticoagulation therapy between the groups could have some influence on recurrent VTE and major bleeding. Third, the true rate of concomitant PE including asymptomatic PE was unknown, because not all patients were subjected to contrast-enhanced CT examination at diagnosis of DVT unless they have symptoms. Fourth, the inclusion criteria of the COMAND VTE registry are patients with acute symptomatic VTE, consistent with the previous large registry (RIETE Registry) [8]. Thus, we could not evaluate patients with asymptomatic DVT in upper extremities. Furthermore, we evaluated symptomatic recurrent VTE as a recurrent event, consistent with previous reports [8,26–28]. Thus, we could not evaluate incidental asymptomatic recurrent VTE. Fifth, the

current study population showed the high rate of vena cava filter use partly because the Japanese VTE Guidelines at the time allowed the vena cava filter use in a wide range of indications, which could have some influence on clinical outcomes. Sixth, the more recent study, which evaluated symptomatic proximal DVT of the extremities, reported higher proportions of DVT in upper extremities [29]. Because the current study did not specifically target on upper extremity DVT, a cautious interpretation should be made on the prevalence of DVT in upper extremities, and the rates of VTE recurrence in the current study. Finally, the current study was conducted before introduction of direct oral anticoagulants for VTE in Japan. Thus, it should be interpreted with caution whether the present results could be extrapolated to patients treated with direct oral anticoagulants.

6. Conclusions

The prevalence of patients with DVT in upper extremities was 3.0% in the current large-scale real-world registry. Patients with DVT in upper extremities more often had active cancer at diagnosis and central venous catheter use as a transient risk factor for VTE, and less often had concomitant PE. Patients with DVT in upper extremities had similar long-term risk for recurrent VTE as those with DVT in lower extremities despite shorter duration of anticoagulation.

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Conflicts of interest

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston Scientific. Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare and Daiichi-Sankyo. Dr. Kimura serves as an advisory board member for Abbott Vascular and Terumo Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Appendix A. Supplementary data

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