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ORIGINAL ARTICLE

Risk factors for post-thrombotic syndrome in patients with deep vein thrombosis: from the COMMAND VTE registry

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Abstract

Post-thrombotic syndrome (PTS) is the most common chronic complication of deep vein thrombosis (DVT). Identifying high-risk patients for the development of PTS might be useful for its prevention. The COMMAND VTE Registry is a multicenter registry that enrolled 3027 consecutive patients with acute symptomatic venous thromboembolisms (VTEs) in Japan between January 2010 and August 2014. The current study population consisted of 1298 patients with lower extremities DVTs who completed 3-year follow-up for those who developed PTS and those without PTS. We investigated risk factors for the development of PTS at the time of DVT diagnosis, using a multivariable logistic regression analysis. Of the entire 1298 study patients, 169 (13%) patients were diagnosed with PTS within 3 years. The rate for anticoagulation discontinuation during follow-up was not significantly different between those with and without PTS. Chronic kidney disease (OR 2.21, 95% CI 1.45–3.39, $P<0.001$), leg swelling (OR 4.15, 95% CI 2.25–7.66, $P<0.001$), absence of transient risk factors for VTEs (OR 2.39, 95% CI 1.55–3.67, $P<0.001$), active cancer (OR 3.66, 95% CI 2.30–5.84, $P<0.001$), and thrombophilia (OR 2.07, 95% CI 1.06–4.04, $P=0.03$) were independent risk factors for the development of PTS. In this real-world Japanese DVT registry, we could identify several important risk factors for the development of PTS at the time of DVT diagnosis.

Keywords Deep vein thrombosis · Venous thromboembolism · Post-thrombotic syndrome · Risk factors

Introduction

Deep vein thrombosis (DVT) is a major health problem in the world and has a long-term risk of recurrence, which could be prevented by anticoagulation therapy [1, 2]. To investigate the optimal treatment strategies for DVTs, previous clinical trials have focused on the prevention of recurrent venous thromboembolisms (VTEs) after a DVT. Post-thrombotic syndrome (PTS), the most common chronic complication of DVTs, causes chronic limb pain, swelling and leg ulcers, which increases the healthcare costs and reduces the quality of life [3, 4]. Previous studies reported that 20–50% of patients with DVTs developed PTS [5–10].

Anticoagulation therapy with an appropriate intensity and duration is thought to be essential for the prevention of PTS, although PTS is still a common complication despite anticoagulation therapy [11]. In addition to anticoagulation therapy, those treatment options such as thrombolysis or elastic compression stockings (ECSs) could be useful to reduce the risk of the development of PTS. However, the routine use of such additional treatments is not recommended because the usefulness of them in all patients with DVTs is still controversial. Identifying high-risk patients for the development of PTS at the time of DVT diagnosis could be useful for selecting good candidates for additional preventive treatment as an initial therapy; however, the risk factors have not yet been adequately studied and validated [6, 8, 9, 12–14]. Thus, we

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aimed to investigate the risk factors for the development of PTS at the time of DVT diagnosis in a large observational study in Japan.

Materials and methods

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 VTEs objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy among 29 centers in Japan between January 2010 and August 2014 before the introduction of direct oral anticoagulants (DOACs) for VTEs in Japan [15]. 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 was concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

We searched the hospital databases for clinical diagnoses and imaging examinations, and enrolled consecutive patients who met the definition of acute symptomatic VTEs diagnosed within 31 days from the symptom onset during the study period [16]. The symptoms of VTEs were defined as follows; sudden onset of dyspnea, pleuritic chest pain, substernal chest pain, cough, fever, hemoptysis, and syncope for a pulmonary embolism (PE), and erythema, warmth, pain, swelling, tenderness, and pain upon dorsiflexion of the foot for a DVT [17, 18]. Additionally, sudden onset abnormalities in the vital signs such as a decrease in the arterial oxygen saturation and hypotension were also regarded as symptoms of a PE. The presence or absence of symptoms was evaluated at the time of the imaging studies.

The registry enrolled 3027 consecutive patients with acute symptomatic VTEs after screening for eligibility in 19634 consecutive patients with suspected VTEs through chart reviews by the physicians at each institution. In the present analysis, we excluded 482 patients without lower extremities DVTs, 499 patients who died within 3 years without PTS, and 748 patients who did not complete 3-year follow-up without PTS. Therefore, the current study population consisted of 1298 patients with lower extremities DVTs who completed 3-year follow-up for those who developed PTS and those without PTS (Fig. 1).

Data collection and definitions of the 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.

Hypertension was diagnosed if the peripheral blood pressure was>140/90 mmHg or if the patient was taking medication for hypertension. Chronic kidney disease was diagnosed if there was persistent proteinuria or if the estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m^2 for more than 3 months. The values of the eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [male: $194*Scr^{-1.094}*age^{-0.287}$, female: $194*Scr^{-1.094}*age^{-0.287}*0.739$]. A proximal DVT was defined as a venous thrombosis, which was located in the popliteal, femoral, or iliac veins. Transient risk factors for VTEs included recent surgery (within 2 months prior to VTE), recent immobilization (defined as non-surgical bed-ridden patients with bathroom privileges for>4 days within 2 months prior to the VTE), long-distance travel (travel lasting ≥6 h in the previous 3 weeks), central venous catheter use, pregnancy or puerperium, recent leg trauma, fracture or burn (any events requiring immobilization in the past 2 months), severe infection, and estrogen use [19]. 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. Thrombophilia included a protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome. Initial anticoagulation therapy was defined as a parenteral anticoagulation therapy in the acute phase (heparin or fondaparinux) for ≤10 days after the diagnosis, whereas anticoagulation therapy beyond the acute phase was defined as anticoagulation therapy (warfarin, DOAC, or heparin) that was continued beyond 10 days after the diagnosis. The detailed definitions of other patient characteristics are described in Supplementary Appendix 2.

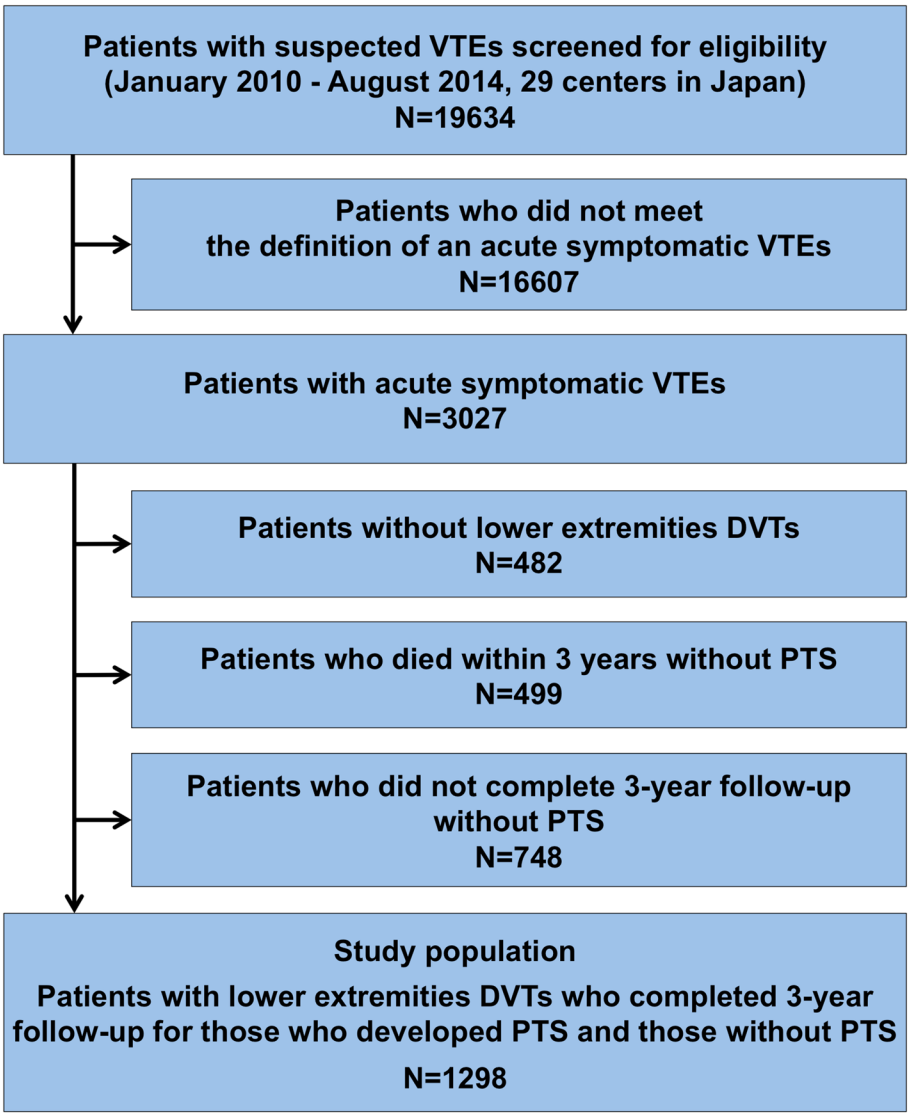

Fig. 1 Study flow chart. VTE included both PE and/or DVT. DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

Clinical follow-up and definitions of the endpoints

Collection of the follow-up information was mainly conducted through review of hospital charts. In this retrospective cohort study, the data collection for follow-up events was performed between July 2016 and March 2017.

The outcome measure in the current study was the development of PTS within 3 years. PTS was defined as the presence of subjective venous symptoms and/or objective venous signs in the lower extremity that developed the index DVT, which persisted beyond the acute phase or occurred newly. Subjective venous symptoms and objective venous signs included the followings: pain, leg swelling, eczema, skin induration, pigmentation, ulcer, or venous claudication [20]. Those with any new thrombus or exacerbation of the thrombus by ultrasound examinations were not regarded as PTS. Those with other specific causes of them than PTS were not also regarded as PTS. The members in independent clinical event committee, who were unaware of the patient characteristics, reviewed all study outcomes (Supplementary Appendix 3).

Discontinuation of anticoagulation was defined as a withdrawal of anticoagulation therapy lasting >14 days for any reasons including bleeding events, drug side effects, non-adherence of the patient, or the physician's judgment in the absence of adverse events. Data on the international normalized ratio (INR) during the follow-up in patients receiving warfarin were collected from the hospital charts of the centers where the index VTE was diagnosed. The time in a therapeutic range (TTR) was calculated by the Rosendaal method [21], according to a therapeutic INR range of 1.5–2.5, which is recommended in the Japanese guideline [22].

Statistical analysis

We presented categorical variables as numbers and percentages, and continuous variables as the mean with standard deviation or the median with interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, a 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 constructed multivariable logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (CI) of the variables for the development of PTS within 3 years after the DVT diagnosis. We selected 15 variables at the time of DVT diagnosis, which consisted of 11 clinically relevant variables consistent with the previous reports (age, sex, obesity, history of DVT, 3 types of DVT symptoms at the time of the diagnosis [leg swelling, pain/tenderness upon dorsiflexion of the foot for DVT, and erythema/warmth], proximal DVT, varicose vein, absence of transient risk factors for VTEs, and thrombophilia) [20], and 4 variables with *P* values <0.1 in univariate models in the current study population (hypertension, chronic kidney disease, connective tissue disease, and active cancer) (model 1). Furthermore, to adjust for the variables related to therapeutic intervention, we included additional 5 variables related to therapeutic intervention with *P* values <0.1 in univariate models (initial anticoagulation therapy, inferior vena cava filter use, anticoagulation therapy beyond the acute phase, corticosteroids at discharge, and non-steroidal anti-inflammatory drugs at discharge) together with the 15 variables at the time of DVT diagnosis (model 2). All statistical analyzes were conducted using R software packages (version 3.2.4; R Development Core Team). All the statistical analyzes were two tailed and *P* values <0.05 were considered statistically significant.

Results

Patient characteristics

In the current study population, the mean age was 65.6 ± 15.4 years, 62% was female, and the mean body weight and body mass index were 59.2 ± 13.6 kg and 23.7 ± 4.3 kg/m^2, respectively. Of the entire 1298 patients, 169 (13%) patients had diagnosis of PTS within 3 years. The mean age, proportion of women, and the mean body weight were not significantly different between patients with and without PTS (Table 1). Patients with PTS more frequently had chronic kidney disease, connective tissue disease, and active cancer, but less frequently had transient risk factors for VTEs. Proximal DVTs at the time of the presentation and symptoms at the time of the diagnosis were significantly more prevalent in the patients with PTS. The prevalence of anticoagulation therapy beyond the acute phase, median TTR for warfarin users, and the prevalence of discontinuation of anticoagulation during the follow-up were not significantly different between the patients with and without PTS (Table 1).

Risk factors for the development of PTS

The multivariable logistic regression model not including variables related to therapeutic interventions (model 1) demonstrated that chronic kidney disease (OR 2.25, 95% CI 1.49–3.41, $P < 0.001$), connective tissue disease (OR 1.88, 95% CI 1.15–3.07, $P = 0.01$), leg swelling (OR 4.52, 95% CI 2.47–8.27, $P < 0.001$), absence of transient risk factors for VTEs (OR 2.29, 95% CI 1.51–3.47, $P < 0.001$), active cancer (OR 4.03, 95% CI 2.57–6.32, $P < 0.001$), and thrombophilia (OR 2.16, 95% CI 1.12–4.15, $P = 0.02$) were independently associated with the development of PTS among the variables at the time of DVT diagnosis (Table 2). The multivariable logistic regression model adding variables related to therapeutic interventions (model 2) demonstrated that chronic kidney disease (OR 2.21, 95% CI 1.45–3.39, $P < 0.001$), leg swelling (OR 4.15, 95% CI 2.25–7.66, $P < 0.001$), absence of transient risk factors for VTEs (OR 2.39, 95% CI 1.55–3.67, $P < 0.001$), active cancer (OR 3.66, 95% CI 2.30–5.84, $P < 0.001$), thrombophilia (OR 2.07, 95% CI 1.06–4.04, $P = 0.03$), inferior vena cave filter use (OR 1.99, 95% CI 1.34–2.96, $P < 0.001$), and non-steroidal anti-inflammatory drugs at the time of discharge (OR 2.29, 95% CI 1.41–3.72, $P < 0.001$) were independently associated with the development of PTS (Table 2). Independent risk factors for the development of PTS at the time of DVT diagnosis identified in model 1 were consistent with those identified in model 2 except for connective tissue disease.

Discussion

The main findings of the current study from the real-world registry were as follows: (1) PTS occurred in 13% of patients with DVTs in whom the presence or absence of PTS was ascertained throughout 3-year follow-up; (2) Independent risk factors for the development of PTS at the time of DVT diagnosis were chronic kidney disease, leg swelling, absence of transient risk factors for VTEs, active cancer, and thrombophilia.

Several previous studies reported the risk factors for the development of PTS, although those were not consistent across the studies [12–14]. This is partly due to the differences in diagnostic criteria, patient populations, and study designs across the studies. The risk factors may also vary depending on the ethnicity. The prevalence of homozygous

Table 1 Patient characteristics

	Total ($N=1298$)	PTS ($N=169$)	No PTS ($N=1129$)	P value
Baseline characteristics				
Age (years)	65.6 ± 15.4	65.3 ± 16.1	65.6 ± 15.3	0.77
Women	807 (62%)	101 (60%)	706 (63%)	0.54
Body weight (kg)	59.2 ± 13.6	59.8 ± 15.4	59.1 ± 13.3	0.57
Body mass index (kg/m^2)	23.7 ± 4.3	23.9 ± 4.8	23.6 ± 4.2	0.40
Body mass index ≥30 kg/m^2	87 (6.7%)	16 (9.5%)	71 (6.3%)	0.17
Hypertension	505 (39%)	55 (33%)	450 (40%)	0.08
Diabetes mellitus	163 (13%)	17 (10%)	146 (13%)	0.35
Dyslipidemia	289 (22%)	38 (23%)	251 (22%)	1.00
Chronic kidney disease	226 (17%)	46 (27%)	180 (16%)	< 0.001
Dialysis	10 (0.8%)	0 (0.0%)	10 (0.9%)	0.38
Liver cirrhosis	5 (0.4%)	0 (0.0%)	5 (0.4%)	1.00
Chronic lung disease	108 (8.3%)	16 (9.5%)	92 (8.1%)	0.67
Connective tissue disease	139 (11%)	29 (17%)	110 (9.7%)	0.006
History of heart failure	29 (2.2%)	4 (2.4%)	25 (2.2%)	0.78
History of DVT	79 (6.1%)	16 (9.5%)	63 (5.6%)	0.07
History of major bleeding	79 (6.1%)	8 (4.7%)	71 (6.3%)	0.54
Absence of transient risk factors	834 (64%)	135 (80%)	699 (62%)	< 0.001
Active cancer	148 (11%)	43 (25%)	105 (9.3%)	< 0.001
Varicose vein	76 (5.9%)	12 (7.1%)	64 (5.7%)	0.57
Presentation				
Proximal DVT	967 (75%)	137 (81%)	830 (74%)	0.04
Symptoms at the time of the diagnosis	1048 (81%)	162 (96%)	886 (79%)	< 0.001
Leg swelling	959 (74%)	156 (92%)	803 (71%)	< 0.001
Pain/Tenderness upon dorsiflexion of the foot for DVT	364 (28%)	47 (28%)	341 (30%)	0.59
Erythema/Warmth	55 (4.2%)	15 (8.9%)	69 (6.1%)	0.23
Laboratory testing at the time of the diagnosis				
Anemia (N = 1293)	636 (49%)	84 (50%)	552 (49%)	0.87
Thrombocytopenia (N = 1293)	62 (4.8%)	8 (4.8%)	54 (4.8%)	1.00
Estimated glomerular filtration rate (mL/min/1.73m^2) (N = 1288)	70.6 (54.1–87.0)	66.5 (53.4–86.8)	71.1 (54.3–87.0)	0.30
D-dimer (μg/mL) (N = 1224)	9.7 (4.8–19.1)	11.1 (5.1–19.5)	9.5 (4.7–18.9)	0.23
Thrombophilia	79 (6.1%)	15 (8.9%)	64 (5.7%)	0.15
Treatment in the acute phase				
Initial anticoagulation therapy	1087 (84%)	133 (79%)	954 (85%)	0.07
Heparin	1030 (79%)	116 (69%)	914 (81%)	< 0.001
Fondaparinux	76 (5.9%)	19 (11.2%)	57 (5.0%)	0.003
Thrombolysis	221 (17%)	29 (17%)	192 (17%)	1.00
Inferior vena cava filter use	353 (27%)	64 (38%)	289 (26%)	0.001
Treatment beyond the acute phase				
Anticoagulation therapy	1258 (97%)	160 (95%)	1098 (97%)	0.09
Warfarin	1218 (94%)	152 (90%)	1066 (94%)	0.10
TTR for INR 1.5–2.5 (%) (N = 1178)	76.6 (51.8–92.0)	72.3 (52.6–88.1)	76.5 (51.6–92.4)	0.19
Discontinuation of anticoagulation during follow-up	508 (40%)	68 (40%)	440 (39%)	0.75
Concomitant medications at the time of the discharge				
Corticosteroids	148 (11%)	30 (18%)	118 (11%)	0.008
Non-steroidal anti-inflammatory drugs	130 (10%)	36 (21%)	94 (8.3%)	<0.001
Proton pump inhibitors/H_2 blockers	562 (43%)	67 (40%)	495 (44%)	0.35
Statins	228 (18%)	30 (18%)	198 (18%)	1.00
Antiplatelets	133 (10%)	16 (9.5%)	117 (10%)	0.82

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean and standard deviation, or median and interquartile range based on the distributions. Categorical variables were compared with the Chi-square test when appropriate; otherwise, we used a Fisher's exact test. Continuous variables were compared using the Student's t test or Wilcoxon's rank sum test based on the distributions. Anemia was diagnosed if the value of hemoglobin was <13 g/dL for men and <12 g/dL for women. Thrombocytopenia was diagnosed if the value of platelet was $<100\times10^9$/L. Thrombophilia included a protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome

DVT deep vein thrombosis, *PTS* post-thrombotic syndrome, *TTR* time in therapeutic range, *INR* international normalized ratio

Table 2 Multivariable logistic regression analysis to identify the independent risk factors for the development of PTS within 3 years after a DVT diagnosis

	Model 1			Model 2		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (per year)	1.00	0.99–1.01	0.92	1.00	0.99–1.02	0.80
Women	0.95	0.66–1.37	0.79	0.95	0.65–1.37	0.78
Body mass index ≥30 kg/m^2	1.76	0.93–3.34	0.08	1.74	0.91–3.34	0.09
Hypertension	0.80	0.54–1.18	0.26	0.78	0.52–1.15	0.21
Chronic kidney disease	2.25	1.49–3.41	<0.001	2.21	1.45–3.39	<0.001
Connective tissue disease	1.88	1.15–3.07	0.01	1.69	0.87–3.28	0.12
History of DVT	1.11	0.59–2.10	0.74	1.17	0.60–2.28	0.64
Varicose vein	1.38	0.69–2.76	0.36	1.28	0.63–2.62	0.50
Symptom at the time of the diagnosis						
Leg swelling	4.52	2.47–8.27	<0.001	4.15	2.25–7.66	<0.001
Pain/tenderness upon dorsiflexion of the foot for DVT	0.97	0.66–1.44	0.89	0.96	0.65–1.44	0.86
Erythema/warmth	1.39	0.74–2.60	0.30	1.36	0.72–2.58	0.35
Proximal DVT	1.08	0.69–1.69	0.74	1.06	0.65–1.75	0.81
Absence of transient risk factors	2.29	1.51–3.47	<0.001	2.39	1.55–3.67	<0.001
Active cancer	4.03	2.57–6.32	<0.001	3.66	2.30–5.84	<0.001
Thrombophilia	2.16	1.12–4.15	0.02	2.07	1.06–4.04	0.03
Initial anticoagulation therapy				0.77	0.47–1.27	0.31
Inferior vena cava filter use				1.99	1.34–2.96	<0.001
Anticoagulation therapy beyond the acute phase				0.49	0.20–1.18	0.11
Medications at the time of the discharge						
Corticosteroids				0.94	0.50–1.77	0.84
Non-steroidal anti-inflammatory drugs				2.29	1.41–3.72	<0.001

We presented categorical variables as numbers and percentages, and continuous variables as the mean with standard deviation or the median with interquartile range based on their distributions. Categorical variables were compared using the Chi-squared test when appropriate; otherwise, a 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 constructed multivariable logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (CI) of the variables for the development of PTS within 3 years after the DVT diagnosis. We selected 15 variables at the time of DVT diagnosis, which consisted of 11 clinically relevant variables consistent with the previous reports (age, sex, obesity, history of DVT, 3 types of DVT symptoms at the time of the diagnosis [leg swelling, pain/tenderness upon dorsiflexion of the foot for DVT, and erythema/warmth], proximal DVT, varicose vein, absence of transient risk factors for VTE, and thrombophilia) [20], and 4 variables with *P* values <0.1 in a univariate models in the current study population (hypertension, chronic kidney disease, connective tissue disease, and active cancer) (model 1). Furthermore, to adjust for the variables related to therapeutic intervention, we included additional 5 variables related to therapeutic intervention with *P* values <0.1 in a univariate models (initial anticoagulation therapy, inferior vena cava filter use, anticoagulation therapy beyond the acute phase, corticosteroids at discharge, and non-steroidal anti-inflammatory drugs at discharge) together with the 15 variables at the time of DVT diagnosis (model 2). Thrombophilia included a protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome

CI confidence intervals, *DVT* deep vein thrombosis, *OR* odds ratio, *PTS* post-thrombotic syndrome

factor V Leiden or homozygous prothrombin G20210A, which could predispose PTS development, was lower in Asians than in Caucasians [23]. However, all the previous studies were reported from Western countries, and evidence from Asian countries is currently lacking.

In the current study, we found that some independent risk factors were consistent with the previous reports, but others were not, suggesting that there might be different risk factors in Japanese patients. Unprovoked VTEs are known to be associated with a higher risk of a recurrence than VTEs provoked by transient risk factors [24]; however, there are conflicting reports regarding whether the absence of transient risk factors for VTEs is a risk factor for PTS [6, 8, 13, 25]. Similarly, whether thrombophilia predisposes PTS development remains unclear [26]. There is a scarcity of data on chronic kidney disease and active cancer as a risk factor for PTS. In the multivariable model including those variables related to therapeutic interventions, inferior vena cave filter use and non-steroidal anti-inflammatory drugs at the time of discharge were independently associated with the development of PTS. A previous systematic review reported that inferior vena cava filter use could be associated with the development of PTS [27], while non-steroidal anti-inflammatory drugs were reported to increase the risk for the development of VTEs, but not for PTS [28].

The pathogenesis of PTS is considered to be venous hypertension due to a persistent venous obstruction and valvular reflux caused by venous valve damage [29–34]. In the current study, the strongest independent risk factor for the development of PTS at the time of DVT diagnosis was leg swelling, presumably caused by venous obstruction by an extensive thrombus. In a previous report, the presence of residual venous symptoms 1 month after the DVT diagnosis was a strong risk factor for PTS [6], suggesting that PTS often develop based on sustained venous obstruction by the thrombus in the first few weeks after a DVT, and early treatment to release the venous obstruction might be important for the prevention of PTS.

Thrombolysis with anticoagulation therapy to treat acute DVTs leads to higher rates of vein patency and better preservation of the valve function than anticoagulation therapy alone, although its role for the prevention of PTS has not yet been established [35]. Catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (PCDT) is likely to be safer and more effective than systemic thrombolysis and could be effective for the prevention of PTS. The current guidelines make a weak recommendation of CDT or PCDT for patients with acute symptomatic extensive proximal DVTs [20, 36]. However, the ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) trial recently reported a disappointing result that the addition of PCDT to anticoagulation therapy in patients with acute proximal DVTs did not reduce PTS, but increased major bleeding [37]. Therefore, routine use of PCDT for acute proximal DVT could not be recommended. ECS is another adjunctive treatment and has been used targeting prevention of PTS and reduction of PTS symptoms. However, recently, the SOX (Compression Stockings to Prevent the Post-Thrombotic Syndrome) trial reported that routine use of ECSs did not reduce PTS occurrence [38]. According to the trial, the current guidelines do not recommend the routine use of ECS for the prevention of PTS [20, 36]. Thus, the risk factors for the development of PTS might be clinically important to identify the highest risk population potentially suitable for adjunctive therapies targeting prevention of PTS and reduction of PTS symptoms.

Study limitations

The current study had several limitations. First, a PTS diagnosis was based on retrospective collection of the follow-up information. Therefore, PTS could be underdiagnosed. Furthermore, clinical tools such as the Villalta scale, the CEAP criteria, or the Ginsberg criteria for a PTS diagnosis and the PTS severity classification were not used in the current study [16]. Second, the patients who seemed to be high-risk for recurrent VTEs could be followed up carefully, which might lead to a frequent PTS diagnosis. Therefore, some risk factors for PTS could be influenced by known risk factors for recurrent VTEs. Third, not all patients were examined by ultrasound examinations for distal parts of the veins in lower extremities, and some distal DVT could be overlooked. Finally, the current study was conducted before the introduction of DOACs for VTEs in Japan. Thus, it should be interpreted with caution whether the present results could be extrapolated in patients treated with DOACs.

Conclusions

In this real-world Japanese DVT registry, chronic kidney disease, leg swelling, absence of transient risk factors for VTEs, active cancer, and thrombophilia were identified as the independent risk factors for the development of PTS at the time of DVT diagnosis.

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