Original Article

Incidence and risk factors for inferior vena cava filter thrombosis detected at time of filter retrieval in patients with lower extremity deep vein thrombosis: a multicenter retrospective cohort study

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Background: Inferior vena cava filter (IVCF) thrombosis is an uncommon complication of IVCF utilization. The aims of this study were to investigate inferior vena cava (IVC) venography before filter retrieval to determine the incidence relative to filter dwell time and risk factors of IVCF thrombosis based on the clinical data and imaging findings in patients with lower extremity deep vein thrombosis (LEDVT).

Methods: The clinical data from a multicenter randomized trial conducted between October 2017 and March 2019 were reviewed to determine the incidence of IVCF thrombosis in preretrieval venography and the associated risk factors. The correlation between filter dwell times (within 90 days) and incidence was assessed. Baseline demographics, LEDVT presentation, laboratory examination, thrombus characteristics, concurrent pulmonary embolism (PE), comorbidities and risk factors for LEDVT, and IVCF-relevant information were analyzed using the independent samples *t*-test, chi-squared test, Fisher exact test, and regression analysis to determine the univariable and multivariable associations in assessing the risk factors of IVCF thrombosis.

Results: A total of 178 eligible patients were included, of whom 58 were in the IVCF thrombosis group and 120 were in the IVCF nonthrombosis group, and the mean filter dwell time was 22.07±27.91 days (range, 4–190 days). The overall incidence of IVCF thrombosis in patients with LEDVT who received IVCFs was 32.58% (58/178). The incidence of IVCF thrombosis was 35.25% (49/139) in the first 30 days after the IVCF placement and decreased to 22.73% (5/22) between 30 to 60 days of dwell time and to 18.18% (2/11) between 60 and 90 days of dwell time, indicating a decreasing trend within the first 90 days. The risk factors for the occurrence of IVCF thrombosis were concurrent PE [odds ratio (OR) =2.59; 95% confidence interval (CI): 1.27–5.28; P=0.01], rheumatic diseases of the immune system (OR =14.42; 95% CI: 1.52–136.41; P=0.02), IVC:filter radial ratio >0.587 (OR =0.25; 95% CI: 0.10–0.65; P<0.01), and percutaneous angioplasty (PTA) (OR =2.50; 95% CI: 1.09–5.70; P=0.03).

Conclusions: The incidence of IVCF thrombosis at the time of filter retrieval appears to decrease with dwell time within 90 days. Concurrent PE, rheumatic diseases of the immune system, and PTA were taken into account as risk factors. An IVC:filter radial ratio of 0.587 was a protective factor against developing IVCF thrombosis. These findings require further validation in a well-designed study since the present study lacked a close follow-up.

Keywords: Inferior vena cava (IVC); inferior vena cava filter (IVCF); venous thromboembolism (VTE); incidence; risk factors

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Introduction

Inferior vena cava filters (IVCFs) are common intravascular devices that are widely applied to prevent fatal pulmonary embolism (PE) from occurring in high-risk patients with lower extremity deep vein thrombosis (LEDVT). Despite IVCFs being first introduced in 1967, many controversies regarding their utilization and net benefit remain (1-3). IVCF can reduce the incidence of PE in the short term, but it does not come without its own risks (2,3). Insertion-site thrombosis is one of the uncommon adverse events of IVCF placement, with other complications being filter migration, fractures, and inferior vena cava (IVC) wall or adjacent organ perforation (3-5). Moreover, the indwelling IVCF may predispose patients to secondary thrombosis below or above the IVCFs or progressive LEDVT, which may result in venous stasis or leg swelling (6) or may even trigger recurrent PE, which is closely related to the dysfunction of IVCFs resulting from extended clotting above the IVCFs (7,8). In addition, the occurrence of IVCFs thrombosis may prolong the length of hospital stay, which imposes increasing financial burdens and demands on time (9).

Despite these challenges, there is currently an overall paucity of specific guidelines to aid with screening, and alternative predictive programs for IVCF thrombosis remain ambiguous (1). The clinical signs and symptoms of IVCF thrombosis are insidious, nonspecific, and frequently concealed and confused in patients with LEDVT (1,6). A previous study reported a follow-up of 1,718 patients with IVCF placement by computer tomography venography (CTV) and found that about 18% of these patients underwent IVCF thrombosis, but only 2% of had clinical manifestations of complete obstruction of the IVC (3,8). Therefore, the detection of IVCF thrombosis according to clinical features alone is problematic. CTV has been widely used in the diagnosis of IVCF thrombosis. The venography of IVC is typically used at the time of filter retrieval to assess the filter position, tilt, penetration of the IVC, clots within or cephalad to the IVCF, and IVC thrombosis (4,8). However, the incidence of IVCF thrombosis in relation to IVCF dwell time has only been reported in a few randomized trials (2,4,9). Hence, evaluating the incidence at the time of filter removal and identifying relevant risk factors may be of considerable clinical benefit.

The objectives of this study were to investigate the incidence and risk factors for acute IVCF thrombosis following filters placement in patients with LEDVT based on the data of a multicenter randomized controlled trial (RCT). This may assist in developing individualized plans and better identifying higher risk patients in whom IVCFs have been implanted and providing preventive intervention for high-risk patients with potential thrombosis after IVCF placement. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-724/rc).

Methods

Patients and study design

This retrospective cohort study was conducted using data from a multicenter RCT (9). The study was prospectively carried out in 188 patients with LEDVT, and the efficacy and safety of PE prevention were compared between the Octoparms filter {Kossel MedTech [Suzhou] Co., Ltd., Suzhou, China} and the Celect filter (Cook Medical, Bloomington, IN, USA) in 10 clinical centers from 6 provinces in mainland China from October 2017 to March 2019 (10). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board of Nanjing First Hospital (No. QX20170714-02). The requirement for written informed consent was waived due to the retrospective nature of the study.

A total of 188 patients with identified acute LEDVT were enrolled in this multicenter RCT. The inclusion and exclusion criteria are provided in the Table S1. In this multicenter, retrospective cohort study, 10 patients were subsequently excluded due to the lack of complete records regarding the venography of IVC because the IVCFs were left *in situ* as permanent filters (the flowchart of this study is shown in *Figure 1*). Of the remaining 178 eligible patients, 58 patients with IVCF thrombosis were classified into an IVCF thrombosis group, and 120 patients without IVCF thrombosis were placed into an IVCF nonthrombosis group. The data concerning these eligible patients were obtained from medical database systems and/or study records. The following information was analyzed: baseline demographics

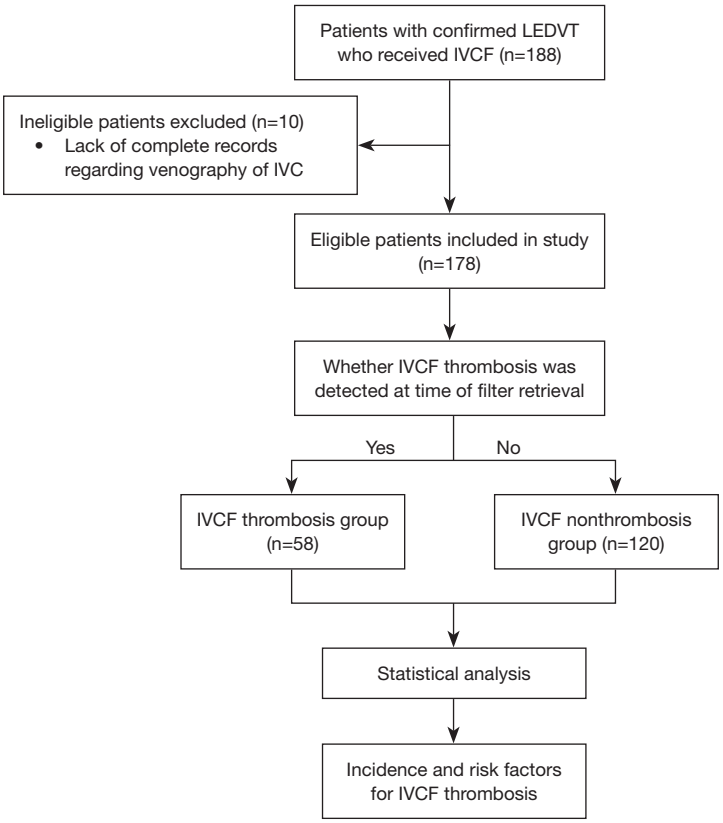

Figure 1 The study flowchart of the inclusion and exclusion criteria of patients with LEDVT. LEDVT, lower extremity deep vein thrombosis; IVCF, inferior vena cava filter; IVC, inferior vena cava.

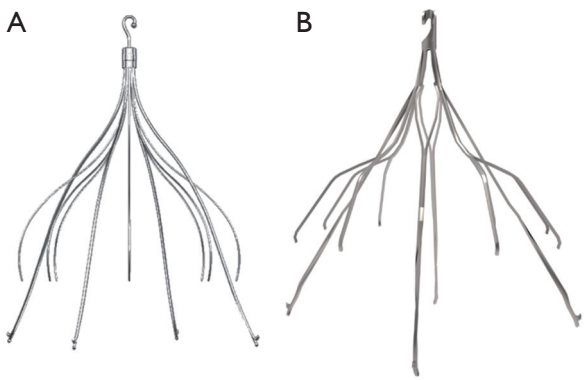

Figure 2 A schematic representation of the Octoparms filter and the Celect filter. (A) The Octoparms filter. (B) The Celect filter. The permission to reuse these images are obtained.

[comprising age, gender, nation, marital status, and body mass index (BMI)]; the presentation of LEDVT [including symptoms and signs, time from symptom onset to admission (if ≤7 days)]; the relevant abnormal laboratory results prior to IVCF placement [including red blood cell counts, white blood cell counts, hematocrit, platelet counts, urine leukocytes, urine erythrocyte, urine proteins, electrocardiography (ECG), and D-dimer value] within the first 48 h; the thrombus characteristics, including the thrombus segment [proximal LEDVT coupled with/without IVC, isolated distal deep vein thrombosis (IDDVT), saphenous vein thrombosis], numbers of involved vessels in the IDDVT, and thrombus limbs (left side, right side, bilateral side, or isolated IVC thrombosis); concurrent PE; comorbidities, including hypertension, diabetes mellitus, cardiologic artery disease (CAD), history of cerebral vascular disease, hyperlipemia, cancer, bronchitis, penicillin anaphylaxis; the risk factors for LEDVT, including trauma, major surgery history, immobilization, rheumatic diseases of immune system (e.g., antiphospholipid antibody syndrome, systemic lupus erythematosus, and rheumatoid arthritis), previous venous thromboembolism (VTE), cancer, and smoking; IVCF-relevant information (the Octoparms and Celect filters are shown in *Figure 2*), including IVCF place

access (right or left femoral, right internal jugular vein), filter location (infrarenal vein or suprarenal vein), IVC diameter, IVC:filter radial ratio (whether ratio >0.587), filter oblique angle (>15°), and the dwell time (i.e., duration of time between filter placement and initial retrieval attempt); and the conjunctive endovascular treatments, including catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT), percutaneous angioplasty (PTA), and percutaneous stents (PTS).

Definition, diagnosis, and details of IVCF thrombosis

The decision and timing for retrieval were individualized in each case by the referring clinician and the interventional radiologist. The diagnosis of IVCF thrombosis was determined with venography or CTV before IVCF retrieval. Interpretation of the diagnosis was based on the initial radiologist's reading and subsequently verified by the operators. IVCF thrombosis was defined as the existing filling defect in the IVCF at the venous phase of CTV or venography. The strategic selections of retrieval were left to the discretion of the endovascular operator team, with the size of thrombus usually being the principal consideration (3). If necessary, thrombolysis or percutaneous aspiration was performed prior to retrieval. IVC diameter was measured on venography under a single inspiratory breath-hold and a nonshock status. The proximal LEDVT and IDDVT were defined according to the clinical practice guidelines (11).

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and R statistical language software (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria). The continuous data are presented as the mean ± standard deviation (SD), and categorical data are expressed as count and percentage. The independent samples *t*-test was used to assess the correlation between the 2 groups and to compare continuous data, including age, BMI, IVC diameter, IVC:filter radial ratio, and time to IVCF retrieval. The significance of categorical data was tested with a chi-squared test or Fisher exact test. The risk factors for IVCF thrombosis were assessed with using logistic regression, and the univariate approach was followed by multivariate analysis. The predictive cutoff value of IVC:filter radial ratio value for a suspected diagnosis was evaluated with receiver operating characteristic (ROC) curve using R software, and the area under the curve (AUC) was calculated. Findings with a P value <0.05 (2-tailed) were deemed statistically significant.

Results

Patients and the incidence of IVCF thrombosis

Among the 178 eligible patients in the present study, 32.58% (58/178) of patients (mean age: 58±17 years; 43.10% male; 94.83% Han nationality; 91.38% married) with IVCF thrombosis were placed into an IVCF thrombosis group, and 67.42% (120/178) of patients (mean age: 57±14 years; 56.67% male; 98.33% Han nationality; 96.67% married) were placed into an IVCF nonthrombosis group. As for the symptoms and signs of LEDVT, more than half of the patients (58.62% *vs.* 59.17%; P=0.95) experienced limb swelling, the majority of the time from symptom onset to admission in both groups was ≤7 days (86.21% *vs.* 72.50%; P=0.04), and the D-dimer value was ≤10 μg/mL (81.03% *vs.* 70.83%; P=0.15). In addition, patients from the 2 groups underwent comparable abnormal laboratory tests (all P values >0.05), the majority of whom underwent proximal LEDVT (91.38% *vs.* 78.33%; P=0.03); however, the subgroup (including those with IVC, IDDVT, and saphenous vein thrombosis) as well the numbers of IDDVT involved vessels were not statistically significant (all P values >0.05). The distribution of thrombus favored the left limbs (65.52% *vs.* 66.67%; P=0.88). Of note, 56.90% of those patients with IVCF thrombosis and 40.00% of those with IVCF nonthrombosis experienced concurrent PE as identified with computed tomography (CT) angiography imaging (P=0.03). The comorbidities and risk factors for patients in the 2 groups were similar and included hypertension (31.03% *vs.* 27.50%; P=0.63) and recent major surgery history (37.93% *vs.* 30.00%; P=0.29). Regarding the IVCF-relevant information, the filters used were "umbrella" IVCFs, including the Octoparms and Celect (P=0.16), which were placed mainly in the infrarenal vein (96.55% *vs.* 98.33%; P=0.83) via the right femoral vein (70.69% *vs.* 58.33%; P=0.36). In both groups, conjunctive endovascular treatments (including PMT, PTA, PTS, and CDT) were performed, and the patients with IVCF thrombosis had a higher rate of PTA (32.76% *vs.* 15.83%; P=0.01).

Data on baseline demographics, LEDVT presentation, laboratory examination, thrombus characteristics, concurrent PE, comorbidities and risk factors for LEDVT, and IVCF-relevant information for patients with LEDVT with IVCFs are summarized in *Table 1*. The anticoagulant

Table 1 Baseline demographics, presentation of LEDVT, laboratory examination, thrombus characteristics, concurrent PE, comorbidities and risk factors, and IVCF-relevant information for patients with LEDVT who received IVCFs

Characteristic	IVCF thrombosis group (n=58)	IVCF nonthrombosis group (n=120)	P value
Age (years)	58±17	57±14	0.67
Gender			
Male	25 (43.10)	68 (56.67)	0.10
Female	33 (56.90)	52 (43.33)	
Nation			
Han nationality	55 (94.83)	118 (98.33)	0.40
Other nationality	3 (5.17)	2 (1.67)	
Marital status			
Married	53 (91.38)	116 (96.67)	0.13
Unmarried	5 (8.62)	3 (2.50)	0.07
Divorced	0 (0.00)	1 (0.83)	>0.99*
BMI (kg/m^2)	24.91±3.83	25.47±3.84	0.43
Symptoms and signs			
Limb swelling	34 (58.62)	71 (59.17)	0.95
Strong respiratory sounds	3 (5.17)	8 (6.67)	0.70
Time from symptom onset to admission			
≤7 days	50 (86.21)	87 (72.50)	0.04
>7 days	8 (13.79)	33 (27.50)	
Abnormal laboratory tests			
Red blood cell count	19 (32.76)	26 (21.67)	0.11
White blood cell count	19 (32.76)	54 (45.00)	0.12
Hematocrits	23 (39.66)	62 (51.67)	0.13
Platelet counts	12 (20.69)	28 (23.33)	0.69
Urine leukocytes	12 (20.69)	29 (24.17)	0.61
Urine erythrocyte	10 (17.24)	19 (15.83)	0.81
Urine protein	13 (22.41)	27 (22.50)	0.99
ECG test	31 (53.45)	63 (52.50)	0.91
D-dimer value (μg/mL)			
>10	11 (18.97)	35 (29.17)	0.15
≤10	47 (81.03)	85 (70.83)	
Thrombus segment			
Proximal LEDVT†	53 (91.38)	94 (78.33)	0.03
Coupled with IVC	4 (6.90)	7 (5.83)	0.78
Coupled with IDDVT	36 (62.07)	76 (63.33)	0.87
Coupled with saphenous vein thrombosis	6 (10.34)	14 (11.67)	0.79
IDDVT‡	5 (8.62)	26 (21.67)	0.03

Table 1 *(continued)*

Table 1 *(continued)*

Characteristic	IVCF thrombosis group (n=58)	IVCF nonthrombosis group (n=120)	P value
Number of DDVT involved vessels			
1 involvement	16 (27.59)	50 (41.67)	0.07
2 involvements	11 (18.97)	13 (10.83)	0.14
3 involvements	4 (6.90)	8 (6.67)	0.95
4 involvements	2 (3.45)	4 (3.33)	>0.99*
Thrombus limb			
Left	38 (65.52)	80 (66.67)	0.88
Right	16 (27.59)	27 (22.50)	0.46
Bilateral	4 (6.90)	12 (10.00)	0.95
Isolated IVC thrombosis	0 (0.00)	1 (0.83)	>0.99*
Concurrent PE	33 (56.90)	48 (40.00)	0.03
Comorbidity			
Hypertension	18 (31.03)	33 (27.50)	0.63
Diabetes mellitus	9 (15.52)	13 (10.83)	0.37
CAD	3 (5.17)	7 (5.83)	0.86
History of cerebral vascular disease	5 (8.62)	13 (10.83)	0.65
Hyperlipemia	1 (1.72)	4 (3.33)	0.90
Bronchitis	0 (0.00)	4 (3.33)	0.31*
Penicillin anaphylaxis	5 (8.62)	5 (4.17)	0.23
Risk factors for LEDVT			
Trauma	13 (22.41)	16 (13.33)	0.12
Recent major surgery history[§]	22 (37.93)	36 (30.00)	0.29
Immobilization	7 (12.07)	6 (5.00)	0.09
Rheumatic diseases of immune system	5 (8.62)	1 (0.83)	0.02
Previous VTE	6 (10.34)	11 (9.17)	0.80
Cancer	2 (3.45)	0 (0.00)	0.11*
Smoking	11 (18.97)	22 (18.33)	0.92
Filter type			
Octoparms	24 (41.38)	63 (52.50)	0.16
Celect	34 (58.62)	57 (47.50)	
IVCF placement access			
Right femoral vein	41 (70.69)	70 (58.33)	0.36
Left femoral vein	7 (12.07)	19 (15.83)	0.51
Right internal jugular vein	10 (17.24)	31 (25.83)	0.20

Table 1 *(continued)*

Table 1 *(continued)*

Characteristic	IVCF thrombosis group (n=58)	IVCF nonthrombosis group (n=120)	P value
Filter location			
Infrarenal vein	56 (96.55)	118 (98.33)	0.83
Suprarenal vein	2 (3.45)	2 (1.67)	
IVC diameter (mm)	19.34±2.47	20.92±3.52	<0.001
IVC:filter radial ratio	0.52±0.08	0.56±0.10	0.02
>0.587	7 (12.07)	46 (38.33)	<0.001
≤0.587	51 (87.93)	74 (61.67)	
Filter oblique angle (°)	5.00±3.09	4.91±3.84	0.88
>15°	0 (0.00)	3 (2.50)	0.55*
Time to IVCF retrieval (days)	17.57±26.79	24.25±28.30	0.14
Conjunctive endovascular treatment			
PMT	7 (12.07)	8 (6.67)	0.22
PTA	19 (32.76)	19 (15.83)	0.01
PTS	5 (8.62)	2 (1.67)	0.07
CDT	33 (56.90)	64 (53.33)	0.66

Continuous data are expressed as the mean ± standard deviation; categorical data are expressed as the count (percentage). *, Fisher exact test; †, proximal LEDVT included thrombus in the common iliac vein, external iliac vein, common femoral vein, proximal and distal segments of the femoral vein, and/or popliteal vein; ‡, IDDVT included thrombus in distal veins, including the anterior tibial vein, posterior tibial vein, peroneal vein, gastrocnemius muscle vein, and soleus muscle vein; §, occurred within 30 days before filter implantation. LEDVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; IVCF, inferior vena cava filter; BMI, body mass index; ECG, electrocardiogram; IVC, inferior vena cava; IDDVT, isolated distal deep vein thrombosis; DDVT, distal deep vein thrombosis; CAD, cardiologic artery disease; VTE, venous thromboembolism; PMT, percutaneous mechanical thrombectomy; PTA, percutaneous angioplasty; PTS, percutaneous stents; CDT, catheter-directed thrombolysis.

treatment was initiated immediately when LEDVT was identified using subcutaneous low-molecular weight heparin at a bolus dose of 100 units/kg, administered twice daily. Following heparin treatment, a combination of oral warfarin therapy was deployed for 3 to 5 days, with the dosage adjusted thereafter to maintain an international normalized ratio within the range of 2.0 to 3.0. Alternatively, rivaroxaban was initiated directly at a dosage of 20 mg once daily. The overall incidence of IVCF thrombosis in patients with LEDVT who received IVCFs was 32.58% (58/178), with a mean filter dwell time of 22.07±27.91 days (range, 4–190 days). The incidence of IVCF thrombosis was 35.25% (49/139) in the first 30 days after IVCF placement and decreased to 22.73% (5/22) between 30 and 60 days dwell time and to 18.18% (2/11) between 60 and 90 days dwell time, implying a decreasing trend within 90 days (*Figure 3*). An IVCF dwell time interval of longer than 90 days encompassed an extensive period (range, 90–190 days) in 6 patients, 2 of whom were found to have experienced IVCF thrombus (representing 33.33% of those cases with IVCF thrombosis). These patients were not included in this analysis.

IVC diameter and predictive value of IVC:filter radial ratio

The mean IVC diameter of the included patients with IVCF thrombosis was 19.34±2.47 mm, which was shorter than the 20.92±3.52 mm of patients with IVCF nonthrombosis (P<0.001). Based on the diameter of IVCFs examined *in vitro*, the IVC:filter radial ratios were 0.52±0.08 and 0.56±0.10 (P=0.02) in the IVCF thrombosis and IVCF nonthrombosis groups, respectively. After univariable analysis, predictive the value of the IVC:filter radial ratio was analyzed with ROC curves to identify the optimal cutoff value. A radial ratio >0.587 was discriminant

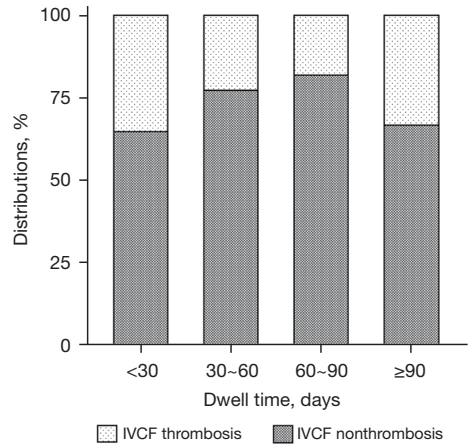

Figure 3 Distributions of patients with IVCF thrombosis and IVCF nonthrombosis in relation to dwell time. IVCF, inferior vena cava filter.

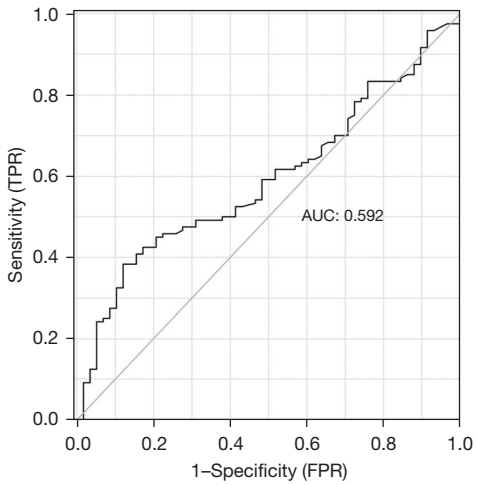

Figure 4 The ROC curve was used to identify the optimal cutoff value of the IVC:filter radial ratio for IVC filter thrombosis in patients with lower extremity deep vein thrombosis who received a filter. The cutoff value was 0.587, and the AUC was 0.59 (95% CI: 0.51–0.68). FPR, false positive rate; TPR, true positive rate; AUC, area under the curve; ROC, receiver operating characteristic; IVC, inferior vena cava; CI, confidence interval.

[AUC =0.59; 95% confidence interval (CI): 0.51–0.68; P<0.05] for predicting IVCF thrombosis (ROC curves are shown in *Figure 4*). The corresponding Youden index was 0.26, and this indicator had a sensitivity of 38.33% and a specificity of 87.93%. Positive predictive value for the IVC:filter radial ratio >0.587 was 86.79%, and the negative predictive value was 40.80%.

Risk factors for IVCF thrombosis

The univariable analysis of baseline demographics, presentation of LEDVT, laboratory examination results, thrombus characteristics, PE occurrence, comorbidities and risk factors, and IVCF-relevant information for patients with IVCFs and LEDVT showed that the factors that predicted the probability of IVCF thrombosis were as follows: time from symptom onset to admission (P=0.04), thrombus segment (P=0.03), concurrent PE (P=0.03), rheumatic diseases of the immune system (P=0.02), PTA (P=0.01), and IVC:filter radial ratio (P<0.001). Moreover, IVCF thrombosis seemed slightly more likely to develop in female (P=0.10) and unmarried patients (P=0.07) in the IVCF thrombosis group compared with those in the IVCF the nonthrombosis group. The remaining baseline demographics, abnormal relevant laboratory tests within the first 48 h, symptoms and signs, numbers of involved vessels in IDDVT, thrombus limbs, the comorbidities and risk factors for LEDVT, filter types, IVCF placement access, conjunctive treatments, filter oblique angle, and dwell time were not significantly different (all P values >0.05). Multivariate logistic regression analysis showed that concurrent PE [odds ratio (OR) =2.59; 95% CI: 1.27–5.28; P=0.01], rheumatic diseases of the immune system (OR =14.42; 95% CI: 1.52–136.41; P=0.02), and PTA (OR =2.50; 95% CI: 1.09–5.70; P=0.03) were risk factors for the occurrence of IVCF thrombosis, while an IVC:filter radial ratio >0.587 was a protective factor (*Table 2*).

Discussion

IVCFs are used to decrease the risk of thrombus migration from LEDVT to pulmonary artery, but may also act as a nidus for the development of IVCF thrombosis (1,2), which can have clinical manifestations varying from symptom-free to phlegmasia or leukophlegmasia. Although its occurrence has been shown to be similarly associated with LEDVT in terms of pathology and clinical spectrum, the predisposing risk factors have not been extensively investigated (11). Therefore, increasing the understanding of IVCF thrombosis and seeking related risk factors may yield important clinical benefit. Previous studies have reported that the types of IVCFs, regular anticoagulants after IVCF placement, oblique angle of IVCFs, and other factors that

Table 2 Multivariate regression analysis of risk factors for IVCF thrombosis in patients with LEDVT

Risk factors	OR	95% CI	P value
Time from symptom onset to admission			
≤7 days	1.65	0.41–6.65	0.48
>7 days	1.00		
Proximal LEDVT	0.90	0.17–4.75	0.90
Concurrent PE	2.59	1.27–5.28	0.01
Rheumatic diseases of the immune system	14.42	1.52–136.41	0.02
IVC:filter radial ratio			
>0.587	0.25	0.10–0.65	<0.01
≤0.587	1.00		
PTA	2.50	1.09–5.70	0.03

IVCF, inferior vena cava filter; LEDVT, lower extremity deep vein thrombosis; OR, odds ratio; CI, confidence interval; PE, pulmonary embolism; IVC, inferior vena cava; PTA, percutaneous angioplasty.

may cause mechanical changes in venous blood flow are related to the occurrence of IVCF thrombosis (2). However, the majority of these assessments have been performed in retrospective studies (1,11). In the present study, baseline demographics, the presentation of LEDVT, laboratory examination results, thrombus characteristics, concurrent PE, comorbidities and risk factors for LEDVT, and IVCF-relevant information from a multicenter, randomized trial were analyzed. We found that concurrent PE (OR =2.59; 95% CI: 1.27–5.28; P=0.01), rheumatic diseases of the immune system (OR =14.42; 95% CI: 1.52–136.41; P=0.02), and PTA (OR =2.50; 95% CI: 1.09–5.70; P=0.03) were risk factors for the occurrence of IVCF thrombosis, while an IVC:filter radial ratio >0.587 was a protective factor against IVCF thrombosis development. Moreover, the abovementioned risk factors are likely to have complex interactions in fostering the occurrence of IVCF thrombosis.

The incidence of IVC thrombosis has been reported to be 4–15%, but depending on the number of IVC filters, the incidence of IVCF thrombosis can range from 1.6% to 33% in the literature (1,2,12). A higher incidence reaching 40% was also reported and was considered to be associated with a relatively short IVCF dwell time (13). Our study similarly showed that 35.25% of patients experienced IVCF thrombosis within 30 days of placement time, with a decreasing trend thereafter, which is in accordance with other studies (3,13). However, this finding needs to be further validated in a well-designed study since the present study lacked a close follow-up at specific time points and since intrafilter thrombosis tends to resolve over time. Moreover, the temporary IVCFs tend to be thrombosed more often, simply because these are discovered at the time of intended retrieval (2,4). Therefore, the true incidence of IVCF thrombosis may be underestimated because IVCF thrombosis sometimes emerges in relative obscurity and is not consistently detected or reported (6). Of note, the shape of IVCFs has also been considered to be associated with the probability of IVCF thrombosis (14), and prevalence of "umbrella" IVCF-related thrombosis has been reported to be as high as 60% (1,4,13). In the present study, the overall incidence of IVCF thrombosis in the umbrella IVCFs was 32.58%, which is significantly lower than that reported in the prior literature (13), which may be partly attributable to an improvement of rationally designed IVCFs (14). Despite the shortcomings of using this nonspecialized, multicenter, randomized trial for IVCF thrombosis, one clinical advantage was the ability to analyze a relatively large sample of patients who received IVCFs and the consideration of a large number of variables as potential risk factors for the development of IVCF thrombosis.

A classical hypothesis for the pathogenesis of thrombosis (15), also known as Virchow's triad, proposes that thrombosis occurs due to hypercoagulability of the blood, alterations in hemodynamics, and endothelial/vessel wall injury. IVCF thrombosis is considered a subset of thrombosis and likely has a similar pathogenesis, and the concept of Virchow's triad can be applied to these

patients. However, the underlying pathogenic mechanisms of IVCF thrombosis have not been well elucidated. The risk factors for IVCF thrombosis tend to be multifaceted according to the Virchow's triad. Within this theory, 3 phenomena are assumed to be associated with the IVCF thrombosis process. First, thrombosis may arise unnoticed or with severe IVC vessel/endothelial wall injury in the course of IVCF insertion, secondary inflammatory reaction, leukocyte and platelet aggregation, etc., which may subsequently trigger insertion situ IVC thrombosis. Second, IVCF placement, IVC thrombus in situ, or the trapped clots intercepted by IVCFs may collectively or separately alter IVC hemodynamics. Finally, the manifestation of the hypercoagulable state of the patients' blood may aggravate thrombosis. However, this hypothesis has not been tested, and should be investigated in future research. Moreover, digital subtraction IVC venography remains the gold standard for the diagnosis of IVCF thrombosis. However, it is still difficult to be certain if these manifestations represent insertion situ clots or trapped embolisms produced from LEDVT while filling defects are detected at time of retrieval, and sometimes both entities can overlap. Although intimal hyperplasia can also occur at points of IVCF contact with IVC wall, free-floating filling defects on venography are more likely to be thrombus rather than intimal hyperplasia (2,4). However, the pathologies of clots in these patients have not been confirmed, and further study is required.

Previous research regarding PE demonstrated that the time from symptom onset to admission ≤7 days and proximal LEDVT constitute increased risks for PE (16,17). However, few studies have focused on the relationship between the incidence of IVCF thrombosis and these factors as independent predictors. Clots are likely to dislodge from the primary site and be trapped in IVCFs, increasing the risk of IVCF thrombosis. Therefore, the relationship between IVCF thrombosis and symptom onset time and proximal LEDVT was analyzed in the present study, with the results showing that these factors were associated with a significantly higher risk of IVCF thrombosis ($P<0.05$); however, these factors did not reach statistical significance after the multivariate analysis, implying that the time from symptom onset to admission ≤7 days and proximal LEDVT may be not independent risk factors for IVCF thrombosis. Interestingly, we found that patients with PE had an approximately 2.59-fold increased risk of IVCF thrombosis compared with patients without PE, which is in line with King *et al.*'s study (2). Patients demonstrating a propensity to develop a large clot burden in one anatomic region are conceivably at a higher risk for developing clots within IVCFs, which implies that patients with PE are more likely to experience recurrent PE during the subsequent disease courses. Of note, the rheumatic diseases of immune system were associated with an approximately 14.42-fold increased risk of IVCF thrombosis compared, which is consistent with a previous report that considered inheritable diseases as one of the main risk factors for IVC thrombosis (18,19). However, the effects of rheumatic diseases of the immune system have not been extensively examined, and thus a complete screening of patients with IVCF thrombosis may be insightful (20). Moreover, PTA was associated with a 2.50-fold higher risk for IVCF thrombosis. Hence, the decision-making process regarding aggressive treatment should carefully weigh these risks with the potential benefits. In addition to the factors mentioned above, compression of the iliac vein may be another cause of IVCF thrombosis (18). However, this was observed in too few cases to constitute a significant difference in our cohort; nonetheless, these factors may be worth examining in studies with larger samples.

Although it has been shown that male patients have increased risk of IVCF thrombosis (10,18), analysis of the correlation between IVCF thrombosis and gender and marital status in patients with LEDVT showed that female and unmarried patients were associated with slightly higher risks of IVCF thrombosis, but this was not a statistically significant association. Although the many other factors believed to be predictive of VTEs did not have sufficiently numerous cases to warrant statistical comparisons or do not demonstrate overwhelming rates, the frequency of these factors is worth noting (2,4,10). In a retrospective review of 164 patients with retrievable IVCF, the risk factors for thrombosis were filter tilt ≥15°, hook wall apposition, IVC dilation rate ≥50%, and dwell time >2 weeks (2). However, in the present study, 3 cases with filter tilt ≥15° were observed, and the mean filter oblique angle was not statistically significant. The cause of the lower rate may be directly attributable to properties of the IVCFs themselves (12), which have been proven to have good performances in close to the center condition of IVC (21). Hook wall apposition was not found in the included patients, time to IVCF retrieval was comparable in the 2 groups, and patients with IVCF nonthrombosis had a significantly higher IVC:filter radial ratio than did those with thrombosis. An IVC:filter radial ratio value of 0.587 could predict IVCF thrombosis and was a protective factor. A prior study (4) might have

been influenced by a few confounding variables due to various IVCFs having different filter dilations. Hence, the larger radial ratio is, the larger the IVC dilations. Using IVC:filter radial ratio can reduce the influence of different IVCF diameters and be a more objective means of evaluation. The finding that IVC:filter radial ratio >0.587 was a protective factor suggests that we can choose filters of different diameters depending on the diameter of IVC to reduce the possibility of IVCF thrombosis. Of note, the AUC for IVCF thrombosis was relatively low (AUC =0.59). Hence, further targeted studies may be needed to identify the optimal ratio.

There are several limitations in the present study that merit discussion. First, as with all large multicenter databases, the present study is subject to reporting bias, errors, and the inability to obtain certain case specifics or details. In addition, this study was not specifically designed to investigate the risk factors for IVCF thrombosis, and it did not give a strict definition of IVCF thrombosis nor did it report on patient symptoms. Hence, it has inherent limitations of reporting bias. Second, the timings of IVCF retrieval were limited to be within 90 days, the groups of venography intervals were empirical, which might have affected the findings. Third, the sample sizes included in this study were relatively small for assessing the risk factors. Fourth, the compression of iliac vein may increase the risk of IVCF thrombosis (18); however, the extent of the compression of iliac vein could not be determined due to CTV of the IVC not being conducted in all included patients. Fifth, the indicator of IVC:filter radial ratio was mainly relevant to clinical experience, and IVC measurement may be affected by other variables, but not hydration status or ventilatory moment. Finally, the population examined in this study was predominantly Asian, and our findings may not have external validity in other ethnicities; moreover, many risk factors described in literature related to IVCF thrombosis had very low event rates and thus could not be statistically compared, which might have influenced the results. In addition, a predictive model was not established in the present study. In the future, a study including more factors and excluding confounding factors to overcome these limitations can be designed, and a predictive model can be established.

Conclusions

The present study shows that with increasing dwell time within 90 days, there is a decreasing trend in the incidence of preretrieval venography. Concurrent PE, rheumatic diseases of the immune system, and PTA were found to be risk factors for the occurrence of IVCF thrombosis events, which suggests that intense monitoring of patients with these signs is essential because of the relatively high incidence of IVCF thrombosis in this population. An IVC:filter radial ratio >0.587 was found to be a protective factor against IVCF thrombosis emergence. The conclusions drawn here should be validated in a future study with a close follow-up.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the Nanjing First Hospital (No. QX20170714-02), and the requirement for written informed consent was waived due to the retrospective nature of the study.

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Supplementary

Table S1 The inclusion criteria and exclusion criteria for this multicenter randomized controlled trial

Variables	Indicator details
Inclusion criteria	Patients with 2 or more of the conditions as follows:
	a. Patients with PE or IVC or iliac, femoral, and popliteal vein thrombosis who have 2 of the following conditions
	(i) Have contraindications of anticoagulation therapy, with complications such as bleeding occurrence during anticoagulant period, recurrence of PE after adequate anticoagulation, and failure to achieve adequate anticoagulation for various reasons
	(ii) PE coupled with LEDVT
	(iii) Free-floating thrombi or a large number of thrombi in the iliac and femoral veins or IVC
	(iv) Patients diagnosed with thrombophilia and repeated PE occurrence
	(v) Patients with acute LEDVT intending to undergo thrombolysis or PMT
	b. 15 mm ≤ IVC diameter ≤ 30 mm
	c. Aged 18 years or older, with no restrictions on gender
	d. Voluntarily participation and signed informed consent form; able to cooperate with the whole test process
Exclusion criteria	Patients with one or more of the conditions as follows:
	a. Infection present in the puncture site of filter placement
	b. Patients with severe arrhythmia or myocardial infarction within 1 year
	c. Chronic IVC thrombosis, severe stenosis, or malformation of IVC or the internal jugular vein
	d. Pulmonary fibrosis and PE caused by the loss of embolus from the right heart cavity
	e. Patients with massive PE or with dangerous and life-threatening conditions
	f. Patients with bacteremia or toxemia or purulent embolism
	g. Diameter of IVC greater than or equal to the maximum diameter of the backup filters
	h. Severe liver and kidney dysfunction (ALT and AST more than 3 times the upper limit of normal value; Cr >225 μmol/L)
	i. Patients with blood pressure higher than 180/110 mmHg unable to be controlled by medication
	j. INR >3.0 and APTT more than 5 times the upper limit of normal value in patients with severe coagulopathy
	k. Identified patients who are allergic to the components of contrast agent or filter system
	l. Patients with active cancer or life expectancy <6 months
	m. Patients with mental disease, psychological disorders that cannot be properly expressed, or with alcoholism and drug dependence (e.g., drug addiction)
	n. Participation in clinical trials of other drugs or medical devices within 3 months prior to screening
	o. Pregnant or lactating women, and women planning to give birth shortly who could not take viable contraceptive measures during the trial
	p. Other conditions that the investigator considered inappropriate for participation in the clinical trial

PE, pulmonary embolism; IVC, inferior vena cava; LEDVT, lower extremity deep vein thrombosis; PMT, percutaneous mechanical thrombectomy; ALT, alanine transaminase; AST, amino transferase; Cr, creatinine; INR, international normalized ratio; APTT, activated partial thromboplastin time.

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