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Role of Thrombophilia in Premature Peripheral Arterial Obstructive Disease – Experience of a Vascular Centre in China☆

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WHAT THIS PAPER ADDS

- In our study, we reviewed 150 young patients with peripheral arterial obstructive disease (PAOD) but not Buerger's disease and assessed the aetiologies, risk profiles and surgical outcomes. Though it was a retrospective study, it represents one of the largest series of premature PAOD in which thrombophilia was consecutively assessed. The key finding was that patients with thrombophilia had the worst prognosis and that they needed more re-interventions than patients with undisturbed coagulation. The results encourage vascular specialists to screen carefully and pay more attention to medical therapy for thrombophilia to get better long-term patency for these patients.

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ABSTRACT

Objective: To evaluate aetiology profile and role of thrombophilia in patients with premature peripheral arterial obstructive disease (PAOD) in China.
Methods: Between January 2000 and January 2010, among 368 patients presenting with PAOD, but not Buerger's disease, at an age of less than 45 years, 150 patients have been screened for thrombophilia and the data analysed retrospectively. Aetiologies of thrombophilia which involved in premature PAOD were assessed and surgical outcomes were stratified for presence of thrombophilia.
Results: In 57 of 150 patients (38%), laboratory assay results suggested thrombophilia, and the rest of them presented with other aetiology (62%). A total of 108 patients, including 38 patients with thrombophilia (35%), needed some type of revascularisation. At 30 days, recurrent thrombosis (29% vs. 9%; $p = 0.005$) and major amputations (11% vs. 1%; $p = 0.032$) were more common in patients with thrombophilia. At 1 year, primary patency (56% vs. 75%, $p = 0.043$), secondary patency (68% vs. 92%, $p = 0.036$) and limb salvage (74% vs. 96%, $p = 0.038$) were significantly lower in patients with thrombophilia.
Conclusion: Thrombophilia is frequently diagnosed among premature PAOD in China and adversely affects outcome after revascularisation. Clinicians should be aware of its high prevalence and aim at screening and sustained thrombophilia treatment.

Peripheral arterial obstructive disease (PAOD) is commonly associated with atherosclerotic arterial lesions that occur within the context of typical cardiovascular risk factors such as arterial hypertension, hyperlipidaemia, diabetes mellitus and smoking in an elderly population.[1] However, in some patients, symptomatic PAOD is diagnosed before the age of 45 years and is not associated with such obvious risk factors.[2] Thus, aetiology of premature PAOD

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is not limited to a typical cardiovascular risk profile but may include other factors such as inherited or acquired thrombophilia, traumatic or anatomical factors.[3] The outcome of patients with premature PAOD has been reported to be worse than that of their older counterparts based on rapid progression of the disease and a higher incidence of early bypass failures and amputations.[2] This may, in part, be due to an insufficient awareness of the importance of correctable aetiological factors which could lead to a significant delay of diagnosis and causative treatment of premature PAOD.

In particular, hypercoagulable states may be easily overlooked in clinical practice, but are likely to affect outcome after surgical revascularisation adversely.[4] Thrombophilic abnormalities may arise in the context of a variety of inherited or acquired immunological, myeloproliferative, inflammatory or coagulation cascade disorders,[5–10] all of which need to be looked for since these patients with thrombophilia are at increased risk for early bypass failure, frequently require multiple vascular interventions and have relatively low limb salvage rates compared to patients with peripheral vascular disease but without thrombophilia.[10,11] This retrospective analysis was undertaken to better understand aetiology profile of thrombophilia involved in premature PAOD in China, and to evaluate the influence of thrombophilia on the patency of the revascularisations done in these young patients.

Materials and Methods

The medical records of all patients, less than 45 years of age and presenting with symptomatic PAOD, but not attributed to Buerger's disease, to the vascular surgery department of Beijing Peking Union Medical College between January 2000 and January 2010 were reviewed. Patients were identified from the in-hospital and outpatient database of Peking Union Medical College Hospital. According to our institutional protocol, patients who underwent serologic evaluation for hypercoagulability were included in this study. The following information was recorded for each patient: demographic characteristics and vascular history including previous arterial thrombo-embolic events or previous arterial reconstructions; cardiovascular risk factors profile including smoking, arterial hypertension, hyperlipidaemia, diabetes mellitus, coronary artery disease, cerebrovascular disease and other co-morbidities. In addition, PAOD symptoms and vascular laboratory results at admission including thrombophilia-screening results and characteristics of arterial lesions were noted. Aetiology results and risk factor profiles were evaluated in all patients including surgical and endovascular techniques used, complications and outcomes of surgical reconstruction. Patients suffering from thrombophilia were compared to those with normal coagulation function. End points of the study were primary and secondary patency rates of the arterial reconstruction and limb salvage. The present observational post-hoc analysis was approved by the local ethics committee, and the need for informed patient consent was waived as analysis was anonymised.

Definitions

The following definitions were used: symptomatic PAOD was defined as lower limb ischaemia with clinical manifestation including intermittent claudication, rest pain or ischaemic tissue loss, and details of the arterial lesions were identified by duplex ultrasound or computer tomography angiogram (CTA). Symptoms were considered acute, if symptoms appeared within 2 weeks preceding admission in our institution. Conversely, symptoms that persisted longer than 2 weeks were considered chronic PAOD.[1] Definition of thrombophilia encompassed a series of inherited and acquired hypercoagulable states including auto-immune disorders, myeloproliferative states and others (Table 1).[12]

Table 1
Aetiology profile of premature PAOD in 150 young Chinese adults.

Aetiology or risk factors	*n*	%
Thrombophilia	57	38.0
Hypercoagulable states	33	22.0
Hyperhomocysteinemia	14	9.3
PC/PS deficiency	6	2.0
Eosinophilia[a]	7	4.7
Polycythemiavera	1	0.7
Acutemyelocytic leukaemia	1	0.7
Essential thrombocythemia	3	1.0
Nephrotic syndrome with cholesterol embolism	1	0.1
Immunological disease	24	16.0
Antiphospholipid syndrome (APS)[b]	5	3.3
Systematic lupus erythematosus (SLE)	2	1.3
Takayasu's arteritis	10	6.7
Other systematic vasculitis[c]	7	4.7
Other causes of PAOD without thrombophilia	93	62

PAOD, Peripheral arterial obstructive disease.
[a] 1 case complicated with APS.
[b] 1 case complicated with systematic vasculitis.
[c] 1 case complicated with hyperhomocysteinemia.

Diagnosis was based on laboratory screening test results including coagulation function assays such as prothrombin and activated partial thromboplastin time; blood cell counts; erythrocyte sedimentation rates (ESRs) and level of C-reactive protein (CRP); levels of protein C and S, antithrombin III, factor V Leiden, prothrombin 20210A and homocysteine; as well as assays for lupus anticoagulant, antiphospholipid and antinuclear antibodies (ANAs).

Perioperative management

Indication for treatment was based on the clinical evaluation done by the vascular specialists in charge. In general, interventions were considered for the patients with critical limb ischaemia (CLI) or severe intermittent claudication (i.e., Rutherford category 3–6). Patients with mild symptoms were managed by best medical treatment, as long as symptoms responded satisfactorily. Patients, in whom an immunological disorder has been detected, first received immunosuppressive therapy using oral prednisone and cyclophosphamide for 1–3 weeks before surgery until inflammatory markers (including ESR and CRP) returned to normal. In case of acute limb-threatening ischaemia, immunosuppressive therapy was started in the operating room. Patients with hyperhomocysteinaemia received routinely folic acid and vitamin B_{12} supplements. In patients with myeloproliferative disorders such as polycythaemia vera (PCV) or essential thrombocythaemia (ET), hydroxyurea was administrated to reduce red blood cell mass and platelet counts. Lastly, all patients received antithrombotic treatment perioperatively according to the American College of Chest Physicians (ACCP) guidelines.[13] In brief, aspirin (100 mg d^{-1}) or clopidogrel (75 mg d^{-1}) were used in patients without thrombophilia who underwent percutaneous transluminal angioplasty with or without stenting. Patients with a hypercoagulable state, long-segment occlusive lesions, poor distal outflow and those receiving a below-knee surgical bypass received, in addition, warfarin. Low-molecular-weight heparin (1 mg kg^{-1} d^{-1}) was given until patients reached the international normalised ratio (INR) long-term target level between 2 and 3. All patients with hypercoagulability or immunological disorders were advised to maintain on specific drug therapy for at least 1 year.

Follow-up

Patients were followed at 1, 3, 6 and 12 months after discharge and then on a yearly basis in an outpatient clinic. Interval history,

clinical examination and duplex ultrasound or CTA were used to assess patency of the arterial reconstructions, limb salvage and compliance with medication.

Statistical methods

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 17.0 software. Continuous data were expressed as median (interquartile range). Study groups were compared using Mann–Whitney *U* test for continuous data and Pearson chi-square test for categorical data. Survival, patency and limb salvage were analysed using the Kaplan–Meier method and compared by log-rank test. No imputation strategy was applied for missing data points. All tests applied were unpaired and two-sided, and a *p*-value of less than 0.05 was considered to indicate a statistically significant difference between groups.

Results

Of 368 patients, less than 45 years of age, with symptomatic premature PAOD in our hospital database, evaluation records of 53 patients who suffered from Buerger's disease and 165 patients without thrombophilia did not meet the inclusion criteria and were excluded, leaving a total of 150 patients entered into the study. Median age was 36 years (31.5–41.0 years). The median time interval between onset of PAOD symptoms and admission was 3.2 months (1.5–6.0 months). At admission, 82 patients (55%) suffered from severe and progressive claudication (Rutherford category 3), 19 patients (13%) presented with persistent rest pain (Rutherford category 4) and 22 patients (15%) had ulceration or minor tissue loss (Rutherford category 5). In another 27 patients (18%), the indication for arterial reconstruction was acute limb-threatening ischaemia (Rutherford Class 2) in the presence of underlying peripheral arterial disease.

Aetiology, risk factors and location of lesions

Blood assays for thrombophilia were positive in 57 patients (38%) and the remaining 93 patients were found to have no abnormalities in thrombophilia evaluation. Of the 57 patients with thrombophilia, hypercoagulable state mainly linked to haematological disorders was found in 33 patients (58%), 24 patients (42%) suffered from immunological disease (Table 1). Prevalence of risk factors varied according to the aetiology of premature PAOD. By contrast, prevalence of hypertension (2 vs. 20%; $p = 0.001$) and diabetes (2 vs. 11%; $p = 0.040$) was significantly higher in normal coagulation test group (Table 2). Arterial lesions were located in the aorto-iliac segment in 27 patients (18%) and in the femoro-popliteal-tibial segment in 70 patients (47%). Both segments were affected in 53 patients (35%).

Treatment and outcome

A total of 42 patients were managed conservatively with medical treatment only (28%), and the remaining 108 patients (72%) underwent surgical or endovascular revascularisation including 25 emergency procedures and 83 elective procedures (Table 4). In 108 patients who underwent revascularisation, 38 patients (35%) were found with thrombophilia and the remaining 70 (65%) patients were found with normal coagulation test. Types of arterial reconstruction according to study groups are detailed in Table 4. The following comparisons of outcomes were performed between patients with and without thrombophilia. Median length of stay of operated patients was 23 days (13.5–28.0). Previous revascularisation for both limbs salvage was more common in patients with thrombophilia (26% vs. 7%; $p = 0.006$), but redo surgery rate on ipsilateral limb had no significant difference between the two groups (16% vs. 6%; $p = 0.085$; Table 3).

Table 2
Demographics characteristics and risk factors profile of 150 patients with premature PAOD according to thrombophilia and non-thrombophilia.

Characteristics	Thrombophilia ($n = 57$)	Normal coagulation test ($n = 93$)	p[b]
Age (years)[a]	35 (32–41)	37 (30–42)	0.206[c]
Sex ratio (male:female)	48:9	73:20	0.390
Hypertension (%)	1 (2)	19 (20)	0.001
Diabetesmellitus (%)	1 (2)	10 (11)	0.040
Hyperlipidaemia (%)	6 (11)	21 (23)	0.062
Smoking (%)	28 (49)	39 (42)	0.390
Coronary arterial disease (%)	2 (4)	8 (9)	0.225
Cerebrovascular events (%)	2 (4)	6 (6)	0.436
Previous venous thrombo-embolic disease (%)	2 (4)	3 (3)	0.925
Previous arterial revascularization (%)	12 (21)	10 (11)	0.083

PAOD, peripheral arterial obstructive disease.
[a] Values are median (interquartile range).
[b] χ^2 test.
[c] Mann–Whitney *U* test.

There was no perioperative death, and the incidence of minor complications was comparable between the two groups. Similarly, involved arterial level and type of revascularisation were broadly similar in the two groups (Table 4). However, emergency operations occurred more often in the thrombophilia group (39% vs. 14%, $p = 0.003$); and surgical embolectomy was performed more often in the patients with thrombophilia (68% vs. 47%, $p = 0.034$; Table 4). Recurrent thrombosis and major amputation within 30 days after operation occurred more often in the thrombophilia group (29% vs. 9%; $p = 0.005$), and (11% vs. 1%; $p = 0.032$), respectively (Table 4). Even if emergency procedures were excluded, early recurrent thrombosis and major amputation rates remained more frequent in the thrombophilia group (38.5% vs. 8.3%; $p = 0.004$), and (23.1% vs. 1.7%; $p = 0.002$), respectively.

Median duration of follow-up after revascularisation was 12 months (9–24 months). No patient died during follow-up. At 1 year, the primary patency rates (56% vs. 75%; = 0.043, Fig. 1) and secondary patency rates (68% vs. 92%; = 0.036; Fig. 2) were poorer in patients with thrombophilia. Similarly, limb salvage at 1 year was lower in patients with thrombophilia (74% vs. 96%; $p = 0.038$; Fig. 3). Among the 38 patients with thrombophilia who received a revascularisation, nine (24%) decided to stop the anticoagulant

Table 3
Demographics characteristics and risk factors profile of 108 patients with or without thombophilia undergoing revascularization.

Characteristics	Thrombophilia group ($n = 38$)	Normal coagulation test group ($n = 70$)	p[b]
Age (years)[a]	36 (32.5–41)	39 (32–42)	0.084[c]
Sex ratio	31:7	59:11	0.875
Hypertension (%)	6 (16)	8 (11)	0.519
Diabetes mellitus (%)	0 (0)	7 (10)	0.044
Hyperlipidaemia (%)	4 (11)	11 (16)	0.457
Smoking (%)	24 (63)	32 (46)	0.083
Coronary arterial disease (%)	0 (0)	5 (7)	0.092
Cerebrovascular events (%)	2 (5)	3 (4)	0.817
Previous arterial revascularization (%)	10 (26)	5 (7)	0.006
Ipsilateral limb (%)	6 (16)	4 (6)	0.085
Contralateral limb (%)	4 (10)	1 (1)	0.032

PAOD, peripheral arterial obstructive disease.
[a] Values are median(interquartile range).
[b] χ^2 test.
[c] Mann–Whitney *U* test.

Table 4
Surgical information and early outcomes of 108 patients with or without thombophilia undergoing revascularization.

Variables	Thrombophilia group ($n = 38$)	Normal coagulation test group ($n = 70$)	p[b]
Indication			
Limb salvage (%)	21 (55)	35 (50)	0.601
Claudication (%)	17 (45)	35 (50)	0.601
Location of lesion			
Above-knee (%)	23 (61)	45 (64)	0.699
Below-knee (%)	15 (39)	25 (36)	0.699
Emergency operation (%)	15 (39)	10 (14)	0.003
Surgical procedures			
Thrombectomy (%)	26 (68)	33 (47)	0.034
Bypass (%)	7 (18)	22 (31)	0.145
Endovascular intervention (%)	5 (13)	15 (21)	0.291
Minor complications			
Wound infection (%)	1 (3)	0 (0)	0.173
Haematoma (%)	2 (5)	2 (3)	0.527
30-d reocclusion (%)	11 (29)	6 (9)	0.005
30-d amputation (%)	4 (11)	1(1)	0.032
Length of stay (days)[a]	24.5 (5–63)	21 (3–98)	0.128[c]

PAOD, peripheral arterial obstructive disease.
[a] Values are median (range).
[b] χ^2 test.
[c] Mann–Whitney U test.

and causative medical treatment of thrombophilia during follow-up and eight of them (89%) presented with recurrent thrombosis during follow-up including six who required a major amputation after failed revision. By contrast, among 29 thrombophilia patients who remained compliant with the above treatment, only 11 (38%) suffered recurrent thrombosis and received reoperation with six major amputations during follow-up ($p = 0.008$).

Out of 42 conservatively treated patients, 12 patients (29%) had no condition for revascularisation because of no distal outflow, 13 (31%) refused any intervention, the remaining 17 (40%) who had thrombophilia with active auto-immune or myeloproliferative disorders needed special drug therapy to control the thrombophilia. Overall, 18 patients (43%) improved their symptoms under medical treatment only, 16 (38%) were stable, and eight patients (19%) including seven who had no operative condition and one who refused any operation worsened their symptoms and needed a major amputation.

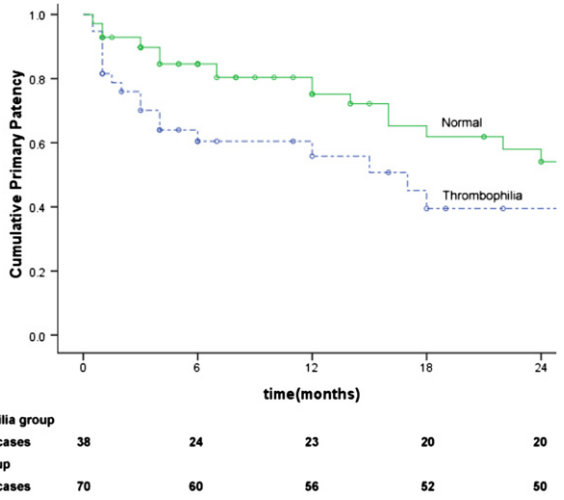

Figure 1. Cumulative primary patency rate in patients undergoing surgical interventions with thombophilia factors (thrombophilia, $n = 38$) and without (normal, $n = 70$). Difference in patency rate was statistically significant with log-rank test ($p = 0.024$). All standard errors <10%.

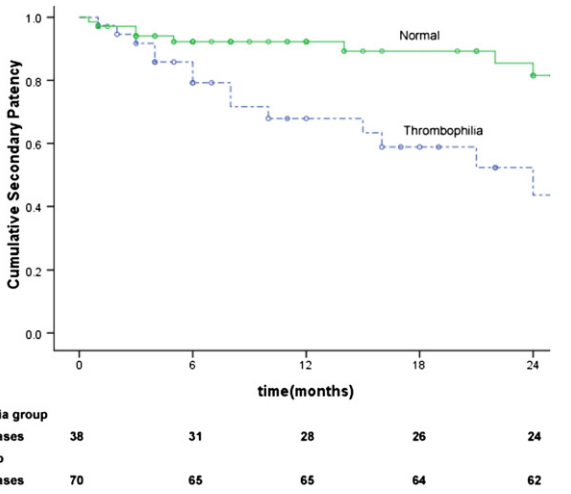

Figure 2. Cumulative secondary patency rate in patients undergoing surgical interventions with thombophilia factors (thrombophilia, $n = 38$) and without (normal, $n = 70$). Difference in patency rate was statistically significant with log-rank test ($p = 0.003$). All standard errors <10%.

Discussion

As in other parts of the world, recognition of premature PAOD in young adults is often missed in China,[3] probably because the aetiology of premature PAOD is variable and may confuse early diagnosis and effective treatment. The present study aimed to lay out the aetiological spectrum of premature PAOD, its clinical features and treatment outcomes with a special focus on the impact of thrombophilia on the prognosis. The key finding was that patients with thrombophilia had the worst prognosis and that they needed more re-interventions than patients with undisturbed coagulation. This is particularly true if they did not adhere to the anticoagulant and medical treatment of this condition.

Other studies have suggested that patients with premature PAOD had rapid deterioration towards CLI due to repeated acute thrombotic events and to a lack of collateral circulation.[14] Therefore, the prognosis of patients with premature PAOD was significantly worse than that of their older counterparts with an increased rate of re-interventions, late amputation and overall poor long-

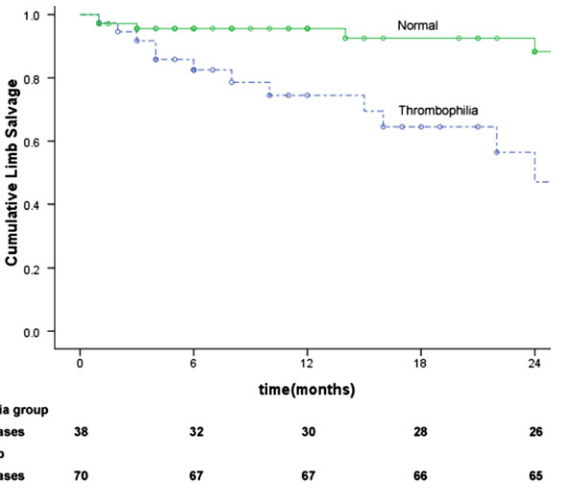

Figure 3. Cumulative limb salvage rate in patients undergoing surgical interventions with thombophilia factors (thrombophilia, $n = 38$) and without (normal, $n = 70$). Difference in limb salvage rate was statistically significant with log-rank test ($p = 0.004$). All standard errors <10%.

term patency.[15] The present study confirms the results of these studies, showing that a specific subset of patients, with a coagulation disorder, might be partly responsible for the impaired outlook.

Reports in the European literature have shown that premature PAOD was mostly associated with non-atherosclerotic disease such as Buerger's, collagen vascular disease, popliteal entrapment, thrombo-embolism or vascular trauma.[3] However, the role of thrombophilia in this youngest subset of patients of less than 45 years was unclear. Ray et al.[16] screened for thrombophilia a series of 124 patients with premature PAOD who had previously undergone a lower limb revascularisation and found that 40% of them had some kind of thrombophilia. The incidence of thrombophilia among non-premature PAOD is lower than premature PAOD patients. Evans et al.[17] reported the incidence of thrombophilia in non-premature PAOD patients as 21%. The prevalence seems to be similar in the Chinese population, as almost 40% of patients referred to our hospital for premature PAOD presented with thrombophilia that could be attributed to either hypercoagulable states or immunological disorders. Therefore, although hypercoagulability has been associated primarily with 'idiopathic' venous thrombo-embolic disease in the past,[14,16] it should also be recognised as an important aetiological factor for arterial thrombo-embolism with an increased risk of occlusion after arterial reconstructions.[11,18,19]

Thrombophilia may be inherited or acquired. The most important inherited causes include genetic mutations of factor V Leiden and factor IIG20210A, as well as deficient antithrombin, protein C and protein S, whereas acquired causes include lupus anticoagulant/antiphospholipid antibody syndrome, myeloproliferative disorders, essential thrombocytosis and nephrotic syndrome.[5–9] In our experience, most of the premature PAOD patients had acquired thrombophilia based on myeloproliferative or immunological disorders whereas inherited causes were rare. Vasculitis disorders represent a further form of thrombophilia, in which endothelial damage exposes extracellular matrix and activates the coagulation system, especially during active inflammation.[20,21] Therefore, thrombophilia is a heterogeneous group of disorders and patients with premature PAOD should be investigated thoroughly with complete haematological, coagulation and serological profiles.[22] In our experience, primary serological test such as ESR and CRP should be done in all the patients who had no clear reason for premature PAOD. Furthermore, it is worthwhile to perform systematic and extensive laboratory screening of thrombophilia in the patients who had obvious hypercoagulable tendency such as repeat thrombosis events, especially for the patients with positive results in primary screening.

As shown in the literature, arterial revascularisation done in patients with premature PAOD has been associated with poor results,[1] since PAOD progression is faster and the rate of failure after bypass surgery is higher than in elderly patients. According to Valentine et al.,[2] 29% of PAOD patients remain stable without intervention and 29% remain stable for a mean of 76 ± 13 months after a single intervention. In comparison, 41% of young patients with PAOD required multiple operations or major amputations during the above follow-up period. Similar proportions were observed in the present study. Thrombophilia may play an important role in this context as it triples the risk of thrombotic occlusion following arterial revascularisation.[2] For instance, in our study, every fourth patient with thrombophilia had already had a previous arterial revascularisation in ipsilateral or contralateral limb. Though this series of patients increased the bias of study because they may artificially increase the incidence of patients with thrombophilia, it indirectly reflects that the patients with thrombophilia had higher thrombo-embolism events rate than the normal population. In the thrombophilia group, the incidence of thrombotic occlusions during follow-up was also much higher than in patients without thrombophilia. Interestingly, these two groups of patients with and without thrombophilia were fairly similar with regard to the other risk factors including indications, type of revascularisation and medical treatment. This highlights the need for complete investigations and careful surveillance of patients with premature PAOD.

Potential limitations to our study include its retrospective nature, and that this group of patients presenting with different patterns of PAOD were heterogeneous and subjected to various arterial reconstructive procedures. In addition, this was not a population-based study, but a single-centre experience with the risk of recruitment bias. Another shortcoming is the lack of power for confounder-adjusted analysis and subgroup analysis. Nonetheless, the present study represents one of the largest series of premature PAOD in which thrombophilia was consecutively assessed.

Conclusion

Thrombophilia is an important risk factor for patients with premature PAOD in China. This is reflected by its high prevalence in these young patients and its significant negative impact on their prognosis. This should encourage vascular specialists to screen carefully these patients for thrombophilia, particularly, if the patients had no clear reason for premature PAOD and with obvious hypercoagulable tendency in clinical practice, because these patients are likely to benefit from a close follow-up with long-term anticoagulation or immunotherapy to lessen the risk of failure of any arterial revascularisation.

Conflict of Interest

None.

Funding

None.

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