Acute Lower Limb Ischemia in Antiphospholipid Syndrome: A Retrospective Cohort Study

Xiaoqiang Li (flytsg@163.com)
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Tao Tang
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Chuang Wang
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Wendong Li
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Tong Mei
Enze Hospital of Zhejiang Province

Shilong Han
Shanghai Tenth People's Hospital

Nan Hu
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Xiaolong Du
The Affiliated Drum Tower Hospital, Medical School of Nanjing University

Research Article

Keywords: ALI, APS,anticoagulant,hormonotherapy,intravenous immunoglobuli

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1415528/v1

Acute Lower Limb Ischemia in Antiphospholipid Syndrome: A Retrospective Cohort Study

Tao Tang[a1],Chuang Wang[a1],Wendong Li[a1],Tong Mei[b], Shilong Han[c],Nan Hu[a],Xiaolong Du[a], Xiaoqiang Li[a]*

[a]Department of Vascular Surgery, The Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China.

[b]Department of Vascular Surgery, Enze Hospital of Zhejiang Province, Taizhou, Zhejiang, China

[c]Department of Interventional and Vascular surgery, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China

∗**Correspondence** to: Xiaoqiang Li,Department of Vascular Surgery, The Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China.

E-mail addresses: flytsg@163.com.

[1] Tao Tang, Chuang Wang and Wendong Li have contributed equally to this work.

Competing Interests

1. This work was supported by National Natural Science Foundation of China(Number: 82070496, 81770483).
2. The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval

This is an observational study. The Hospital Research Ethics Committee has confirmed that no ethical approval is required.

Abstract

Acute lower limb ischemia (ALI) with antiphospholipid syndrome (APS) is a potentially fatal disease. We performed retrospective analysis of prospectively collected data from patients examined from January 2015 to January 2021 that were diagnosed with definite APS and ALI, and tested positive for antiphospholipid antibodies; had undergone computed tomographic angiography or color doppler ultrasound, and showed clinical manifestations. In total, 72 APS-ALI patients were enrolled in this cohort study. The patients were divided into two groups: the delayed

APS diagnosis group (APS-d) (n=40) and the timely APS diagnosis group (APS-t) (n=32).72.2% patients showed relieved ischemia symptoms (APS-d vs APS-t, p=0.035), 27.8% patients showed recurrence of thrombosis, and 23.6%patients needed further surgery (APS-d vs APS-t, p=0.042). 37.5% APS patients were administered intravenous immunoglobulin (IVIG) (APS-d vs APS-t, p<0.01) and 34.8% were administered hormonotherapy (APS-d vs APS-t, p<0.01). The rate of amputation was 19.4% (APS-d vs APS-t, p=0.049) and the mortality rate was 16.6% (APS-d vs APS-t, p=0.033).Delayed diagnosis of APS in ALI patients was associated with a high risk of amputation and mortality. ALI patients who were diagnosed with APS early and underwent timely initiation of hormonotherapy, IVIG and anticoagulation, showed improved amputation and mortality.

KEYWORDS

ALI, APS,anticoagulant,hormonotherapy,intravenous immunoglobulin

Introduction

Acute lower limb ischemia (ALI) is characterized by a sudden reduction in lower limb perfusion that threatens limb viability, constituting a vascular emergency[1]. It is one of the common reasons for major amputation, which affects approximately 0.15% of the population each year[2]. The sudden threat to lower limb viability occurs quickly in ALI patients, not allowing sufficient time for the collateral circulation to

compensate for missed perfusion. ALI compromises metabolic activity in the skin, muscle tissue, and nervous system of the limb[3], and rapid initiation of revascularization is necessary to save limb viability. It has been reported that among ALI patients the rate of major amputation is 10%–15% and the 30-day mortality rate is 5%–15%[4]. The recrudescent events of arterial or venous thrombosis and/or miscarriage, for which antiphospholipid (aPL) antibodies are detected by immune-related indicators, in the absence of any underlying disease, characterizes antiphospholipid syndrome (APS)[5-6]. APS patients include cases of venous and/or arterial thromboses in the presence of aPL antibodies without obvious disease symptoms[7-8]. Approximately 4.3% of APS patients suffer from arterial thrombosis in the lower limbs[9]. ALI can be classified as embolic (30%), thrombotic (60%), or thrombosis of artery stents or blood vessel grafts, with the exception of traumatic ALI[10-11]. In clinic, some ALI patients with thrombotic symptoms of unknown cause are diagnosed with APS. Here, we characterized a group of APS patients with ALI according to their clinical signs and symptoms, therapeutic modalities, and clinical outcomes.

METHODS

Patient selection

From 2015 to 2021, we treated 72 patients with ALI and APS that had

been referred to Nanjing Tower Hospital(Nanjing,China), Shanghai Tenth People's Hospital(Shanghai,China), and Zhejiang Taizhou Enze Hospital(Taizhou,China). This is an observational study. The Research Ethics Committee has confirmed that no ethical approval is required.All patients were examined and initially treated prior to the onset of ALI-related health problems. For 40 of the patients, APS diagnosis was delayed after suffering from ALI for more than 5 days. None of the patients had systemic lupus erythematosus (SLE), an SLE-like disease, or had previously taken lupus-inducing medicines. Lower extremity vascular doppler, computed tomographic angiography (CTA), and cardiac color ultrasound were implemented to assess the potential cardiac source of the artery embolization and the extent of lower limb thrombosis[12-13]. Therapy was performed in accordance with each patient's symptoms, classification of limb ischemia, and imaging detection. This retrospective analysis of prospectively collected data considered ALI patients with definite APS and positive diagnoses in aPL antibody tests (LA, aCL and anti-β2GPIA)[14]. Patients were included in the cohort if they tested positive for both LA and anti-β2GPIA, and aCL antibodies exceeded 40 IgG phospholipid and/or 40 IgM phospholipid units[15]. The baseline patient characteristics are presented in Table1.

Study procedures

First, we needed to identify the grade of ALI through TASC II[16]

(Table2) and then select appropriate surgery for the APS-ALI patients. Because of the high amputation and mortality rates in ALI patients, emergency vascular surgery and drug therapy are required[17]. Urgent anticoagulation with unfractionated heparin restricts thrombosis progression and improves limb microcirculation. Conventional blood and coagulation detection should be implemented[18]. Regional microcirculation acidosis should be evaluated during adverse events and reperfusion injury in ALI patients with critically endangered limbs. Maintaining acid-base and electrolyte equilibrium is important in APS-ALI patients[17]. Circumspective monitoring of renal function before and after revascularization is also suggested, especially in older patients or those with underlying renal disease[19].

Various revascularization methods, including endovascular (catheter-directed thrombolysis (CDT), percutaneous transluminal angioplasty (PTA))[20-21] and surgical (thrombectomy, bypass)[22-23], could be performed. This study evaluated the currently available therapeutic options and the corresponding clinical outcomes. Several options are available for rethrombosis, including thrombectomy, percutaneous catheterization with or without thrombolysis treatment, and endovascular therapy, such as PTA.

Patients with an immediately threatened or nonviable limb, a bypass graft with a suspected infection, or contraindication to thrombolysis,

should undergo open revascularization[17]. Surgical procedures in ALI patients include thrombectomy with a balloon catheter (Fogarty), bypass surgery, and adjuncts such as endarterectomy, patch angioplasty, and intra-operative thrombolysis[17]. It is recommended by current guidelines that all subjects receive pre- and post-procedure antiplatelet or antithrombotic therapy[24]. However, in APS-ALI patients, the clinical situation is complicated by thrombocytopenia or catastrophic antiphospholipid syndrome (CAPS), which are incompatible with thrombolysis and anticoagulation[25]. Early hormone therapy or intravenous immunoglobulin (IVIG) to improve thrombocytopenia is necessary in APS patients. We divided APS-ALI patients into two groups: the delayed APS diagnosis group (APS-d; confirmed APS > 5 days) and the timely APS diagnosis group (APS-t; confirmed APS ≤ 5 days).(5 days is the key stage for treatment ALI)[4].

Follow-up evaluations

Because ALI is an emergency event, the follow-up visits at 15 days included the evaluation of clinical ischemia symptoms, amputation rate, calculation of the ankle-brachial index (ABI), recurrence of thrombosis, reoperation rate bleeding events, CAPS, and death.After acute stage,over a mean follow-up of 17.3 ± 5.9 months, amputation, ABI,thrombosis,bleeding and death events were observed at the 12-month follow-up. Ischemic site, therapeutic modalities,adverse events and

follow-up outcomes are shown in Table 3.

Statistical analysis

Collected data were expressed as the mean ± standard deviation. Categorical variables were expressed as counts and percentages. Statistical comparisons were performed using the Fisher exact test for categorical data and the Student t-test for continuous variables. Comparisons were evaluated using the Wilcoxon signed-rank test. Groups were compared using the Mantel–Cox log-rank test. The significance level for entry of independent variables from the univariate model into the multivariate model was 0.1. Results are presented as the odds ratio (OR) or hazard ratio (HR), as appropriate, with 95% confidence intervals (CI). All tests were 2-sided, and $p<0.05$ was deemed statistically significant. All statistical analyses were performed using SAS for Windows (version 9.1; SAS Institute Inc., Cary, NC, USA).

Results

A total of 72 APS patients with ALI examined between January 2015 and January 2021 were included in this study. The median age was 47.1 ± 8.3 years and 45.8% were male. In total, 17 patients had a history of APS before ALI and for 40 patients, the diagnosis of APS was delayed by more than 5 days. Generally, aPL, anti-b2GPI, and aCL antibody levels are not tested initially, except when a patient has a history of APS. Patients were divided into the delayed APS diagnosis group (APS-d, 40

patients) (confirmed APS>5 days) and the timely APS diagnosis group (APS-t, 32 patients) (confirmed APS≤5 days). According to the Rutherford classification, there were 26 cases (36.1%) in IIa stage, 35 cases (48.6%) in IIb stage, and 11 cases (15.2%) in III stage. The average platelet count was 87.4±33.6×10^9/L, and there was no significant difference between the APS-d and APS-t groups (86.3 ± 34.7 × 10^^{9}/L vs 88.7 ± 32.4 × 10^9/L, p =0.723). There was a low rate of administration of antiplatelet/anticoagulant (8.3%) medicine in APS patients before ALI diagnosis. In total, 61 (84.7%) patients tested positive for aCL antibodies, 57 (79.2%) patients tested positive for LA antibodies, and 52 (72.2%) patients tested positive for anti-b2GPI antibodies.

All of the 72 patients underwent emergency surgery and among these cases the artery thrombosis lesions were located in the iliac artery (11.1% of patients), iliacofemoral artery (29.2%), femoral artery (38.9%), and popliteal/below-knee artery (20.8%). The different types of ALI are shown in Figure.1. Successful surgery was achieved in 100% of the patients and of the 12 (16.7%) patients with CDT alone, 21 (29.2%) patients had CDT plus PTA, 31 (43.1%) patients had a thrombectomy, and 8 (11.1%) patients had a bypass for the target lesion. Within 5 days of hospitalization, 25 (34.8%) patients had undergone hormonotherapy (APS-d 15% and APS-t 59.4%, p<0.01) and 27 (37.5%) patients had been injected with intravenous immunoglobulin (APS-d 17.5% and APS-t

62.5%, p<0.01). Because of thrombocytopenia and the risk of bleeding, only 39 (54.2%) patients had effective anticoagulants and thrombolysis, and there was a significant difference between the APS-d and APS-t groups (40% vs 71.8%,p=0.04). Of the APS patients, 16 (22.2%) progressed to CAPS (APS-d 32.5% and APS-t 9.4%, p =0.018).

On the day of diagnosis, the APS-ALI patients showed thrombocytopenia, with a mean platelet count of 87.4 ± 33.6 × 10^9/L. The number of platelets continuously increased in the APS-t group, but this rise was delayed in the APS-d group (Figure. 2). The number of platelets in the APS-t group increased within 5 days, reaching an average value of 95.2±14.6×10^9/L compared with 83.1±32.3×10^9/L in the APS-d group(p<0.01), with both groups using hormonotherapy and immunoglobulin therapy.

After emergency surgery within 15 days, 52 (72.2%) patients experienced pain relief (APS-d 62.5% vs APS-t 84.4%,p=0.035), 17 (23.6%) patients had an ABI < 0.8 (APS-d 30% vs APS-t 15.6%,p=0.125), 20 (27.8%) patients thrombosed again (APS-d 37.5% vs APS-t 15.6%p=0.039), and 17 (23.6%) patients needed another operation (APS-d 32.5% vs APS-t 12.5%,p=0.042); the rate of amputation was 19.4% (APS-d 27.5% and APS-t 9.4%, p=0.049) and 12 (16.6%) patients died (one from cerebral hemorrhage, two from septic shock, and nine from CAPS) (APS-d 25% and APS-t 6.2%, p=0.033). Regarding adverse

events, there were seven (9.7%) major bleeding events (two cerebral hemorrhages, two gastrointestinal hemorrhages, and three hematomas in the puncture site) and 19 (27.1%) minor bleeding events during thrombolysis and anticoagulant therapy. In total, 17 (23.6%) patients suffered myocardial ischemia (APS-d 30% and APS-t 15.6%, p=0.175) and 19 (26.3%) patients suffered lacunar cerebral infarction (APS-d 27.5% and APS-t 25%, p=0.525). These complications were treated by medication. In all APS patients administered long-term antiplatelet/anticoagulant treatment, 50% patients received vitamin k antagonists (VKAs) + aspirin, 18.9% received VKAs only, 13.7% received aspirin, and 10.3% received direct oral anticoagulants (DOACs). Among the patients, the 1-year thrombosed rate was 8.6%(compare acute stage $p<0.01$), the reoperation rate was 6.9% ($p<0.01$), and the amputation and death rate was 1.7% ($p<0.01$).

Discussion

Thrombotic events in APS patients are far more frequent in the venous system than in the arterial system[26]. The most frequent arterial thrombotic manifestations are transient ischemic attacks and strokes, while involvement of other large arteries, such as those supplying the lower limbs, are rare[26]. In the Euro-Phospholipid Project, 4.3% of patients with APS cumulatively presented with arterial lower extremity thrombosis[27]. This study, however, did not differentiate atherosclerosis

from thromboembolic events in APS patients. Therefore, the true incidence of primary arterial thrombosis affecting peripheral extremities in APS is unknown. Strong clinical evidence supports this approach for the treatment of APS-associated venous thrombosis, yet there is limited data on primary or recurrent arterial events. When APS patients are suffering with ALI, artery embolization or atherosclerotic-thrombosis are often the first considerations[4], often delaying the diagnosis of APS-ALI patients under emergency conditions.

Patients with clinically suspected ALI require the immediate attention of a professional vascular team for diagnosis and therapy. Emergency anticoagulation with unfractionated heparin, which prevents the proliferation of thrombosis and maintains microcirculation, is necessary[28]. In our study, 55.6% of APS-ALI patients exhibited thrombocytopenia, which is associated with a high risk of bleeding during anticoagulation and thrombolysis therapy. After emergency surgery, anticoagulation and thrombolysis therapy was only effective in 54.2% of APS-ALI patients because of thrombocytopenia. For APS-d ALI patients, the cause of thrombocytopenia during emergency treatment was unknown. Conventional tests for antithrombin III, and protein C or protein S were performed[29] and none of our patients showed any evidence of inherited or acquired deficiency of antithrombin III, protein C or protein S. Plasma and platelet infusion resulted in little improvement in thrombocytopenia

in APS-d ALI patients. This delayed improvement in thrombocytopenia resulted in APS-d ALI patients having a low rate of effective anticoagulant/thrombolysis (40%), and a high rate of rethrombosis (37.5%) and reoperation (32.5%). However, for APS-t ALI patients, the early confirmation of APS allowed for timely use of hormonotherapy and IVIG to improve thrombocytopenia. These patients showed a high rate of effective anticoagulant/thrombolysis (71.8%), and a low rate of rethrombosis (15.6%) and reoperation (12.5%). APS-ALI is an emergency state, and this disease is defined as complex and progressive. In total, 22.2% of APS-ALI patients progressed to CAPS (APS-d 32.5% vs APS-t 9.4%,p=0.018) and this was associated with an 16.6% higher mortality rate than ALI alone(p=0.033). Early conformation of APS is key for APS-ALI patients. The diagnosis of APS is based on the presence of aPL antibodies, as well as clinical manifestations of arterial or venous thrombosis, recurrent fetal loss, or thrombocytopenia[30,31] . In our research, the patients showed no bias in terms of sex or age, but a percentage had a history of DVT. CTA images revealed no signs of atherosclerosis in the peripheral artery and cardiac ultrasonography excluded artery embolism from heart thrombus. To diagnose APS-ALI in a timely manner, other immune system-related indicators in addition to antithrombin III, and protein C or protein S, should be tested[32] .

None of our patients had known underlying diseases and all met the

criteria defined for APS. APS patients may display different clinical manifestations and aPL features[33]. Varying types of aPL (LA, aCL, and anti-β2GPIA) and combined positive detections (single, double, or triple positives comprise the aPL spectrum), antibody homotypes (IgG or IgM), antibody titers (low, medium, and high), and persistence of aPL affect the risk of thrombosis to different grades[34]. The aPL characteristics, or the number of positive aPL tests, have been shown to be associated with the thrombotic risk[35]. A retrospective study showed that patients with triple positive aPL (LA, aCL, and anti-β2GPIA positive) have an increased risk of a first thrombotic event and rethrombosis[36]. Among our patients, 65.3% had triple-positive aPL tests, indicating a high risk of thrombotic events. To the best of our knowledge, our report is the most detailed description of a group of APS patients suffering from ALI. Conceivably, anticardiolipin is the cause of the clinical manifestations observed in our group and other APS patients, but it is likely that its presence may merely be a marker for an already established thrombotic tendency. Myocardial ischemia (23.6%) and lacunar cerebral infarction (30.5%) observed in our patients, are commonly detected in APS-ALI patients, particularly when the syndrome is manifested by peripheral arterial thrombosis. Endothelial damage may explain local peripheral arterial thrombosis. The mechanism responsible for arterial thrombosis in APS remains unknown. However, several hypotheses have been proposed including: inhibition of

prostacyclin release by endothelial cells, impaired fibrinolysis manifested by increased levels of plasminogen activator inhibitor, and decreased levels of tissue plasminogen activator in plasma[37,38]. Other theories involve the inhibition or impaired function of protein C, protein S, or antithrombin III, as reported in some APS patients[39,40].

We found that the rate of postoperative thrombosis and reoperation in APS-ALI patients was high. Surgery may hasten limb loss, with an amputation rate of 19.4% among patients (APS-d 27.5%), which may be partly caused by the low rate of effective anticoagulant and thrombolysis. However, performing a vascular surgical procedure accelerates thrombotic events, possibly due to endothelial injury or by interfering with the balance between vasoactive substances, such as endothelin and endothelium-derived relaxing factor. Since the disease is caused or mediated by autoantibodies, a trial of steroid therapy might be considered. In our patients, the early use of hormonotherapy and IVIG could reduce the thrombotic tendency in APS-ALI.

Heparin introduced perioperatively, followed by long-term VKAs, with or without antiplatelet therapy (APT), is currently recommended for arterial thrombosis patients with APS[41]. In our study, 18.9% of APS-ALI patients received VKAs, 50% received VKAs + APT, 13.7% received APT, and 10.3% received DOACs. Among our patients treated long term with antiplatelets/anticoagulants, the occurrence of major

bleeds (3.4%) and rethrombosis (8.6%) was low. This combined treatment should be independently validated for each patient according to the presence of vascular risk factors and the patient's risk of bleeding. In patients with a stroke and a moderate or high-risk aPL profile, the addition of low-dose aspirin (75–100 mg) should be considered[42]. In older patients with a low-risk aPL profile and a high bleeding risk, low-dose aspirin alone may be considered. The TRAPS[43] study reported that triple-positive aPL patients on rivaroxaban showed significantly higher rates of occurrence of arterial events compared with warfarin-treated patients. Therefore, the use of DOACs is controversial in APS patients with previous arterial thrombosis or triple-aPL positivity. Our study had some shortcomings, including its retrospective design, relatively small sample size, and incomplete follow-up data. In the future, prospective studies and randomized controlled trials are needed in APS-ALI patients.

conclusion

In conclusion, Our findings suggest that young patients presenting with ALI, particularly those with a history of thrombotic events, should be screened for APS. APS-ALI manifests as a sudden decrease in limb perfusion resulting in a threat to the viability of the lower extremity and the need for a life-saving emergency operation. The early confirmation of APS using hormonotherapy and IVIG may improve thrombocytopenia.

Full anticoagulation should be started prior to surgery and continued postoperatively with anticoagulation/thrombolysis and then VKAs, with or without APT, over the long term.

References:

1. Hess CN, Huang Z, Patel MR,et al. Acute Limb Ischemia in Peripheral Artery Disease. Circulation. 2019; 140: 556-65. 10.1161.
2. McNally MM, Univers J. Acute Limb Ischemia. Surg Clin North Am. 2018; 98: 1081-96. 10.1016.
3. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. N Engl J Med. 2012; 366: 2198-206. 10.1056.
4. Patel NH, Krishnamurthy VN, Kim S,et al. Quality improvement guidelines for percutaneous management of acute lower-extremity ischemia. J Vasc Interv Radiol. 2013; 24: 3-15. 10.1016.
5. Rahman A. Management of antiphospholipid syndrome. Clin Rheumatol. 2020; 39: 2111-4. 10.1007.
6. de Carvalho JF, Levy RA, Shoenfeld Y. Antiphospholipid syndrome and antibodies. J Immunol Res. 2014; 2014: 942869. 10.1155
7. Chighizola CB, Raimondo MG, Meroni PL. Management of Thrombotic Antiphospholipid Syndrome. Semin Thromb Hemost. 2018; 44: 419-26. 10.1055.
8. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012; 157: 47-58. 10.1111.
9. Cervera R, Boffa MC, Khamashta MA, Hughes GR. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus. 2009; 18: 889-93. 10.1177.
10. Chang Z, Yan H, Zhen Y, Zheng J, Liu Z. Lower Limb Arterial Calcification and Acute Thrombosis Risk in Patients with Peripheral Artery Disease. Ann Vasc Surg. 2020; 63: 227-33. 10.1016.
11. Alonso-Coello P, Bellmunt S, McGorrian C, et al, Spencer FA. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141: e669S-e690S. 10.1378.
12. Fukuda I, Chiyoya M, Taniguchi S, Fukuda W. Acute limb ischemia: contemporary approach. Gen Thorac Cardiovasc Surg. 2015; 63: 540-8. 10.1007.
13. Santistevan JR. Acute Limb Ischemia: An Emergency Medicine Approach. Emerg Med Clin North Am. 2017; 35: 889-909. 10.1016.
14. Polytarchou K, Varvarousis D, Manolis AS. Cardiovascular Disease in Antiphospholipid Syndrome. Curr Vasc Pharmacol. 2020; 18: 538-48. 10.2174.
15. Zuo Y, Shi H, Li C, Knight JS. Antiphospholipid syndrome: a clinical perspective. Chin Med J (Engl). 2020; 133: 929-40. 10.1097.
16. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007; 45 Suppl S: S5-67.

10.1016.
17. Olinic DM, Stanek A, Tataru DA, Homorodean C, Olinic M. Acute Limb Ischemia: An Update on Diagnosis and Management. J Clin Med. 2019; 8. 10.3390.
18. Santistevan JR. Acute Limb Ischemia: An Emergency Medicine Approach. Emerg Med Clin North Am. 2017; 35: 889-909. 10.1016.
19. Ganesh T, Zakher E, Estrada M, Cheng HM. Assessment of microvascular dysfunction in acute limb ischemia-reperfusion injury. J Magn Reson Imaging. 2019; 49: 1174-85. 10.1002.
20. Hage AN, McDevitt JL, Chick J, Vadlamudi V. Acute Limb Ischemia Therapies: When and How to Treat Endovascularly. Semin Intervent Radiol. 2018; 35: 453-60. 10.1055.
21. Lind B, Morcos O, Ferral H, Chen A, Aquisto T, Lee S. Endovascular Strategies in the Management of Acute Limb Ischemia. Vasc Specialist Int. 2019; 35: 4-9. 10.5758.
22. Kolte D, Kennedy KF, Shishehbor MH, et al. Endovascular Versus Surgical Revascularization for Acute Limb Ischemia: A Propensity-Score Matched Analysis. Circ Cardiovasc Interv. 2020; 13: e8150. 10.1161.
23. de Donato G, Setacci F, Sirignano P, Galzerano G, Raucci A, Palasciano G. Hybrid procedures for acute limb ischemia. J Cardiovasc Surg (Torino). 2010; 51: 845-53.
24. Khan S, Hawkins BM. Acute Limb Ischemia Interventions. Interv Cardiol Clin. 2020; 9: 221-8. 10.1016.
25. Carmi O, Berla M, Shoenfeld Y, Levy Y. Diagnosis and management of catastrophic antiphospholipid syndrome. Expert Rev Hematol. 2017; 10: 365-74. 10.1080.
26. Mezhov V, Segan JD, Tran H, Cicuttini FM. Antiphospholipid syndrome: a clinical review. Med J Aust. 2019; 211: 184-8. 10.5694.
27. Arachchillage D, Laffan M. Pathogenesis and management of antiphospholipid syndrome. Br J Haematol. 2017; 178: 181-95. 10.1111.
28. Fluck F, Augustin AM, Bley T, Kickuth R. Current Treatment Options in Acute Limb Ischemia. Rofo. 2020; 192: 319-26. 10.1055.
29. Haapaniemi E, Tatlisumak T, Soinne L, Syrjala M, Kaste M. Natural anticoagulants (antithrombin III, protein C, and protein S) in patients with mild to moderate ischemic stroke. Acta Neurol Scand. 2002; 105: 107-14. 10.1034.
30. Devreese K. Testing for antiphospholipid antibodies: Advances and best practices. Int J Lab Hematol. 2020; 42 Suppl 1: 49-58. 10.1111.
31. Yelnik CM, Kozora E, Appenzeller S,et al. Cognitive disorders and antiphospholipid antibodies. Autoimmun Rev. 2016; 15: 1193-8. 10.1016.
32. Sevim E, Willis R, Erkan D. Is there a role for immunosuppression in antiphospholipid syndrome? Hematology Am Soc Hematol Educ Program. 2019; 2019: 426-32. 10.1182.
33. Sadanand S, Paul BJ, Thachil EJ, Meletath R. Dyslipidemia and its relationship with antiphospholipid antibodies in APS patients in North Kerala. Eur J Rheumatol. 2016; 3: 161-4. 10.5152.
34. Kelchtermans H, Pelkmans L, de Laat B, Devreese KM. IgG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. J Thromb Haemost. 2016; 14: 1530-48. 10.1111.
35. Devreese KM. Antiphospholipid antibodies: evaluation of the thrombotic risk. Thromb Res. 2012; 130 Suppl 1: S37-40. 10.1016.
36. Amory CF, Levine SR, Brey RL, et al. Antiphospholipid Antibodies and Recurrent Thrombotic

Events: Persistence and Portfolio. Cerebrovasc Dis. 2015; 40: 293-300. 10.1159.
37. Ware BD, Eller AG. Antiphospholipid syndrome and thrombosis. Clin Obstet Gynecol. 2006; 49: 861-74. 10.1097.
38. de Groot PG, de Laat B. Mechanisms of thrombosis in systemic lupus erythematosus and antiphospholipid syndrome. Best Pract Res Clin Rheumatol. 2017; 31: 334-41. 10.1016.
39. Chen WH, Lan MY, Chang YY, Chen SS, Liu JS. The prevalence of protein C, protein S, and antithrombin III deficiency in non-APS/SLE Chinese adults with noncardiac cerebral ischemia. Clin Appl Thromb Hemost. 2003; 9: 155-62. 10.1177.
40. Phan AT, Malkoc A, Craig D. An Exceedingly Rare Case of Antithrombin III Deficiency and Catastrophic Antiphospholipid-Like Disease. J Med Cases. 2021; 12: 262-6. 10.14740.
41. Kalmanti L, Lindhoff-Last E. Treatment of Vascular Thrombosis in Antiphospholipid Syndrome: An Update. Hamostaseologie. 2020; 40: 31-7. 10.1055.
42. Garcia D, Erkan D. Diagnosis and Management of the Antiphospholipid Syndrome. N Engl J Med. 2018; 378: 2010-21. 10.1056.
43. Pengo V, Denas G, Zoppellaro G,et al Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018; 132: 1365-71. 10.1182.

TABLE1 Baseline Patient Characteristics

Variables	N=72	APS diagnosed delayed(40)	APS diagnosed timely(32)	p
Age, y	47.1±8.3	47.6±9.2	46.5±7.5	0.868
Men	33/72(45.8)	18/40(45)	15/32(46.9)	0.814
History/risk factors				
Diabetes	11/72(16.7)	6/40(15)	5/32(12.5)	0.597
CVD	9/72(12.5)	4/40(10)	5/32(15.6)	0.498
Stroke	8/72(11.1)	5/40(12.5)	3/32(9.4)	0.725
Hypertension	14/72(19.4)	8/40(20)	6/32(18.8)	0.569
Hyperlipidemia	12/72(16.7)	6/40(15)	6/32(18.8)	0.756
DVT	16/72(22.2)	7/40(17.5)	9/32(28.1)	0.393
Current tobacco use	19/72(26.3)	11/40(27.5)	8/32(25)	0.514
Nephropathy	5/72(6.9)	3/40(7.5)	2/32(6.25)	0.606
Platelets(<100*10^9/L)	40/72(55.6)	22/40(55)	18/32(56.2)	0.553
Platelets(<50*10^9/L)	16/72(22.2)	9/40(22.5)	7/32(21.8)	0.590
Platelets(*10^9/L)	87.4±33.6	86.3±34.7	88.7±32.4	0.723
Rutherford category				
I	0	0	0	
IIa	26/72(36.1)	15/40(37.5)	11/32(34.6)	0.810
IIb	35/72(48.6)	21/40(52.5)	14/32(43.8)	0.487
III	11/72(15.2)	7/40(17.5)	4/32(12.5)	0.744
LA(+)	57/72(79.2)	32/40(80)	25/32(78.1)	0.536
ACL(+)	61/72(84.7)	34/40(85)	27/32(84.3)	0.597
Anti-β2GPI(+)	52/72(72.2)	29/40(72.5)	23/32(71.9)	0.580
LA(+)ACL(+)Anti-β2GPI(+)	47/72(65.3)	26/40(65)	21/32(65.6)	0.578
Antiplatelet/anticoagulant History	6/72(8.3)	3/40(7.5)	4/32(9.4)	0.692

CVD:cardiovascula disease; APS:antiphospholipid syndrome; LA:lupus anticoagulant; ACL:anti-cardiolipin; Anti-β2GPI:andanti-b2-glycoproteinI

TABLE 2 Classification of Acute Limb Ischemia (TASC II)

Stage	Prognosis	Sensory loss	Muscle Weakness	Arterial Doppler	Venous Doppler
I	no immediate limb threat	none	none	audible	audible
IIa	salvageable if promptly treated	minimal	none	often inaudible	audible
IIb	salvageable if treated immediately	Rest pain	mild to moderate	inaudible	audible
III	limb irreversibly damaged	anesthetic	paralysis	inaudible	inaudible

TASC:Transatlantic Inter-Society Consensus

TABLE 3 ALI in APS: Ischemic site,Therapeutic modalities,Adverse events and Outcomes

Variables	N=72	APS diagnosed delayed(40)	APS diagnosed timely(32)	p
Ischemic site				
Iliac artery	8/72(11.1)	4/40(10)	4/32(12.5)	0.512
Iliacofemoral artery	21/72(29.2)	11/40(27.5)	10/32(31.2)	0.797
Femoral artery	28/72(38.9)	15/40(37.5)	13/32(40.6)	0.812
Popliteal/below-knee artery	15/72(20.8)	8/40(20)	7/32(21.9)	0.536
CDT	12/72(16.7)	7/40(17.5)	5/32(15.6)	0.522
CDT+PTA	21/72(29.2)	13/40(32.5)	8/32(25)	0.604
Thrombectomy	31/72(43.1)	17/40(42.5)	14/32(43.7)	0.552
Bypass	8/72(11.1)	5/40(12.5)	3/32(9.4)	0.725
IVIG(Within 5 days in hospital)	27/72(37.5)	7/40(17.5)	20/32(62.5)	<0.01
Hormonotherapy(Within 5 days in hospital)	25/72(34.8)	6/40(15)	19/32(59.4)	<0.01
Effective anticoagulant and thrombolysis	39/72(54.2)	16/40(40)	23/32(71.8)	0.04
Adverse events				
Major bleeding	7/72(9.7)	4/40(10)	3/32(9.4)	0.625
Minor bleeding	19/72(27.1)	11/40(27.5)	8/32(25)	0.514
ischemia reperfusion injury	22/72(30.5)	13/40(32.5)	9/32(28.1)	0.799
myocardial ischemia	17/72(23.6)	12/40(30)	5/32(15.6)	0.175
Lacunar cerebral infarction	19/72(26.3)	11/40(27.5)	8/32(25)	0.525
CAPS	16/72(22.2)	13/40(32.5)	3/32(9.4)	0.018
Outcomes after emergency surgery with 15 days				
Pain relieved	52/72(72.2)	25/40(62.5)	27/32(84.4)	0.035
ABI<0.8	17/72(23.6)	12/40(30)	5/32(15.6)	0.125
Rethrombosis	20/72(27.8)	15/40(37.5)	5/32(15.6)	0.039
Reoperation	17/72(23.6)	13/40(32.5)	4/32(12.5)	0.042
Amputation	14/72(19.4)	11/40(27.5)	3/32(9.4)	0.049
Death	12/72(16.6)	10/40(25)	2/32(6.2)	0.033
Outcomes after emergency surgery with 1 year				Compare acute Stage(p)
Pain relieved	55/58(94.8)	/	/	0.01
ABI<0.8	4/58(6.9)	/	/	0.08
Rethrombose	5/58(8.6)	/	/	<0.01

Reoperation	4/58(6.9)	/	/	<0.01
Amputation	1/58(1.7)	/	/	<0.01
Death	1/58(1.7)	/	/	<0.01
Antiplatelet/anticoagulant	54/58(93.1)	/	/	/
VAKs	11/58(18.9)	/	/	/
VAKs+aspirin(75-100mg)	29/58(50)	/	/	/
Aspirin	8/58(13.7)	/	/	/
DOACs	6/58(10.3)	/	/	/
Major bleeding events	2/58(3.4)	/	/	/
Minor bleeding events	9/58(15.5)	/	/	/

ALI:acute lower limb ischemia; APS:antiphospholipid syndrome; CDT:catheter-directed thrombolysis; PTA:percutaneous transluminal angioplasty;IVIG:intravenous immunoglobulin;CAPS:catastrophic antiphospholipid syndrome;ABI:ankle brachial index; VAKs:vitamin k antagonists; DOACs:direct oral anticoagulants

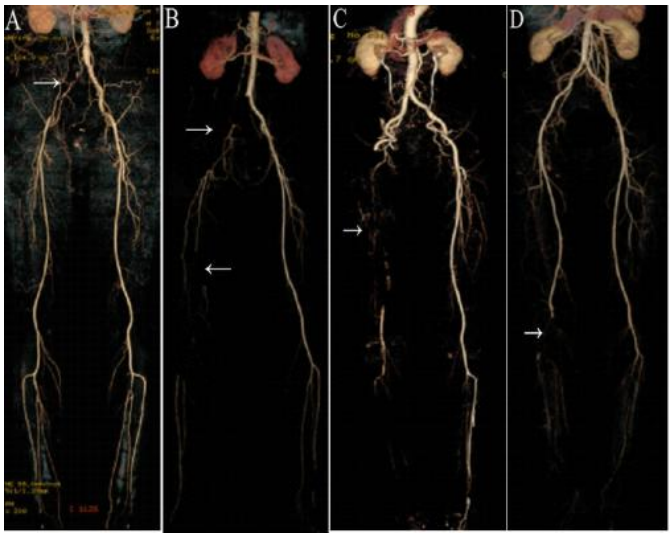

Fig.1 CTA reconstruction of ALI.The different position of arterial thrombosis in APS-ALI. A:iliac artery thrombosis; B:iliacofemoral artery thrombosis; C:femoral artery thrombosis; D:popliteal/below-knee artery thrombosis; There was no obvious atherosclerosis in lower limb artery. (CTA:computered tomograhy angiography; APS:antiphospholipid syndrome;AIL:acute lower limb ischema)

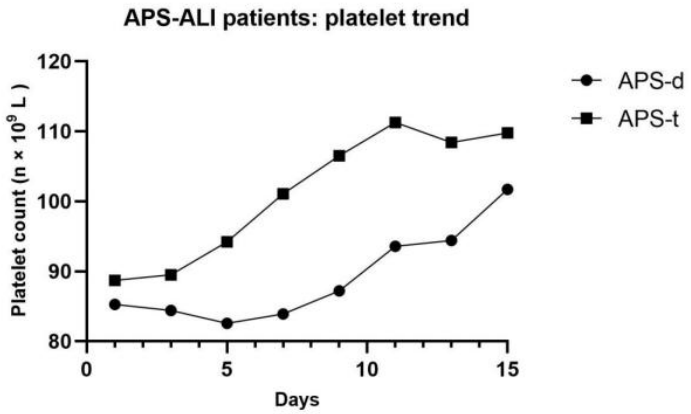

Fig.2 Trend in platelet count during the days in APS-ALI patients. APS-d: the number of platelets had no improving at the time of 5 days,then confirmed APS started increasing platelets count. APS-t: the number of platelets continued to increase during the days. (APS-d: antiphospholipid syndrome-delayed diagnosis; APS-t:antiphospholipid syndrome-timely diagnosis;AIL:acute lower limb ischema).