Original article

The Predictors of Acute Lower Limb Ischemia on the Background of the Recommended Prophylaxis

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Abstract

Objective: Acute limb ischemia (ALI) manifests as sudden lower limb ischemia that, regardless of the underlying cause, can lead to amputation unless there is an appropriate treatment.The study aims to analyze predictors of the lower limb occlusive thrombosis with the acute ischemia development (ALLI), depending on the localization under specifically recommended prophylaxis. ***Materials and methods:*** The researchers performed a retrospective analysis of clinical cases with a confirmed diagnosis of acute lower limb ischemia (ALLI) for 2019. During this period, 20 patients met the study criteria. ***Results and Discussion:*** A multivariate analysis (predictors with a $p<0.1$) established hyperglycemia as a significant predictor of ALLI development under specific prophylaxis (RR 2.2; 95% CI -8.2; 8.4; $p = 0.097$). It indicates a double risk of ALLI for patients with hyperglycemia. ***Conclusion:*** The results indicate the need to correct glycemic parameters to reduce the risk of acute lower limb ischemia, even under antiplatelet or anticoagulant prophylaxis. It is also necessary to analyze the management protocols currently used for such patients to correct the recommended antiplatelet or anticoagulantschemes.

Keywords: arterial thrombosis; arterial thrombosis predictors; ischemia; occlusive thrombosis; smoking.

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Introduction

The lower limb diseases are characterized by gradual arteries occlusion and cause the development of chronic lower limb ischemia (CLI).[1,2]

Peripheral artery disease (PAD) causes 12-15% of deaths in Europe. The complications range from asymptomatic or intermittent claudication to necrosis and loss of limbs.[3]

Acute limb ischemia (ALI) manifests as sudden lower limb ischemia that regardless of the underlying cause and without appropriate treatment can lead to amputation. This disease hasa poor prognostic recovery scenario. Overall, due to comorbidities such as cardiovascular or cerebrovascular disease ALI has a reported mortality rate of 15-20%.[4-6]

ALI decreases limb viability very fast because there is not enough time for new blood vessels to grow to compensate for the loss of perfusion. Sudden ischemia affects all metabolically active tissues of

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the limb: skin, muscles, and nerves. Thus, to preserve the limb viability, there should be a timely diagnosis with rapid revascularization.[2,4,5]

The ALI incidence is approximately 1.5 out of 10,000 people per year.[1]Also, patients with ALI have a high risk of side complications, including myocardial infarction, heart failure exacerbation, kidney function exacerbation, and respiratory complications.[7]

A prospective population-based study includes the assessment of risk factors (all P<0.001) for the acute peripheral vascular ischemia development: arterial hypertension (RR for age and sex, 2.75; 95% CI, 1.95-3.90), smoking (adjusted RR, 2.14; CI 95%, 1.37-3.34), and diabetes (adjusted RR 3.01; 95% CI 1.69-5.35), especially in case of critical limb ischemia (adjusted RR5, 96; 95% CI 3.15-11.26).[4]

Emergency diagnosis primarily includes imaging techniques. Duplex ultrasound (DUS) is the first-line diagnostic test to detect ALI. This method is widely available, low cost, non-invasive, and takes a relatively short time to complete. DUS helps to assess the anatomical location and the obstruction degree (complete or incomplete). Also, DUS provides important information about hemodynamics (proximal and distal to obstruction) and is very useful for revascularization monitoring.[8]

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are high-resolution imaging tests, but they weremostly for patients with CLI or intermittent claudication.

In a meta-analysis, multidetectorcomputed tomography (MDCT) had a sensitivity and specificity of 96 and 98-99%, respectively, for the significant (>50%) aortoiliac stenosis detection. Similar sensitivity and specificity wererelevant for the femoral and popliteal arteries. The CTA'sbiggest advantage is the calcifications, stents, and shunts visualization.[9,10]

After diagnosed ALI, if there are no contraindications, there is a need for an emergency unfractionated heparin treatment (50-100 units/kg, intravenous) to prevent the proximal and distal development of secondary thrombosis. Systemic use of thrombolytic drugs is not recommended, but local use is justified.[11] Then it is important to determine the severity and treatment plan: conservative, revascularization, or amputation.[2,12]

To prevent the ALI onset or recurrence or the CLI development, long-term use of antiaggregant – in case of vessel atherosclerosis – or anticoagulant prophylaxis in case of cardiac arrhythmias or previous episodes of thrombosis.[2,13]

The study aims to analyze predictors of the occlusive thrombosis with the acute lower limb ischemia development (ALLI), under the specifically recommended prophylaxis.

Materials and Methods

The local ethical committees of the Federal State Budgetary Educational Institution of Higher Education "Irkutsk State Medical University" of the Ministry of Health of the Russian Federation and the Regional State Budgetary Institution of Healthcare "Irkutsk Clinical Hospital No. 1" approved the clinical trial. The retrospective study took place at a surgical hospital of the Irkutsk Clinical Hospital No. 1.

The clinical part of the study includes the analysis of the ALLI examination and treatment results for 2019.

The inclusion criteria for the study:

- The diagnosed ALLI;
- A standard examination – blood and urine tests within a year before the detected case of ALLI;
- DUS of the lower limb vessels;
- Theverified diagnosis before the operation according to the MDCT of the lower limb vessels;
- The patient is over 18 years old;
- The patient receives prophylactic doses of antiplatelet and/or anticoagulants;

Non-inclusion criteria:

- The patient has an aortic aneurysm, thrombophilia;
- Due to various reasons, the patient did not meet the examination standard.

Study Group Characteristics

The study incorporates a retrospective analysis of clinical cases with an established diagnosis of acute lower limb ischemia (ALLI) for 2019. During this period, 20 patients met the study criteria.

Analysis / Diagnostic and Treatment Methods

The obligatory examination included the complaints and anamnesis, clinical blood and urine tests, biochemical blood test, coagulogram, analysis of the electrolyte composition of blood, the abdominal cavity organs, genitourinary system X-ray and ultrasound, the lower limb MDCT, and DUS. The blood and urine parameters analysis should beno

more than one year before the ALLI development.

Data Analysis

The initial data and surgical treatment results analyzed using "STATISTICA for Windows 10.0" (Statsoft, Inc, USA), "SPSS Statistics 23.0" (IBM, USA), and "Stata 14.2" (StataCorp, USA).

Ethical Clearance: This study was approved by Ethics committee of Irkutsk State Medical University, Irkutsk, Russia.

Results

Initial Parameters

The patients' average age was 71.8 ± 12.0 years. The gender division was equal: ten men and a similar number of women. Four patients (20%) applied on the first day after the disease onset, the rest (n = 16; 80%) – later. The median duration of the disease was seven (2; 14) days. Tables 1 and 2present the patients' preoperative parameters.

Table 1. Occlusion Localization According to MDCT and DUS

Occlusion Localization	N = 20	%
External iliac artery	2	10
Internal iliac artery	1	5
Common femoral artery	10	50
Deep femoral artery	7	35
Superficial femoral artery	6	30
Popliteal artery	13	65
Posterior tibial artery	13	65
Anterior tibial artery	13	65
Peroneal artery	6	30

Table 2. Patients Initial Parameters the Year before ALLI

Parameter	(n = 20)
Height, cm	169.2±6.9
Weight, kg	73.9±10.3
Smoking, N (%)	16 (80%)
Alcoholism, N (%)	1 (5%)
Myocardial infarction, N (%)	5 (25%)
Stroke, N (%)	3 (15%)
Vascular atherosclerosis, N (%)	17 (85%)
Heart rhythm disorder, N (%)	18 (90%)
Hypertonic disease, N (%)	18 (90%)
Stomach ulcer, N (%)	4 (20%)
Duodenal ulcer, N (%)	2 (10%)
Diabetes, N (%)	6 (30%)
Cholelithiasis, N (%)	2 (10%)
Chronic pancreatitis, N (%)	2 (10%)
Chronic urinary tract infections, N (%)	2 (10%)
Urolithiasis disease, N (%)	1(5%)
Erythrocytosis, N (%)	1(5%)
Erythropenia, N (%)	4(20%)
Anemia, N (%)	10 (50%)
Leukocytosis, N (%)	10 (50%)
Coagulopathy, N (%)	3(15%)
Proteinuria, N (%)	12(60%)
Leukocyturia, N (%)	19(95%)
Hyperglycemia, N (%)	9(45%)
Hyperamilasemia, N (%)	7(35%)

Logistic Analysis

Univariate and multivariate logistic regression analysis determinedthe predictors of ALLI development. The researchers selected predictor variables according to the initial parameters (partially displayed in Table 2). Table 3 presents the information on predictor factors (univariate and multivariate logistic regression analysis).

The results helped to build a model for predicting the risk of the iliac, lower leg, and popliteal arteries occlusion. Univariate analysis revealed no reliable ($p<0.05$) predictors. A multivariate analysis of predictors with a significance level of $p <0.2$ also revealed no reliable predisposing variables. Thus, for this localization, there were no predictors of occlusion.

A univariate analysis of the femoral artery system occlusion as a significant predictor ($p <0.05$) established prior anemia (RR 2.77; 95% CI 0.5; 4.9; $p = 0.013$) and hyperglycemia (RR 2.2; 95 % CI 0.1; 4.2; $p = 0.033$).Other factors were not significant ($p> 0.05$). A multivariate analysis ($p <0.1$) also determined hyperglycemia as a significant predictor (RR 2.2; 95% CI -8.2; 8.4; $p = 0.097$), which indicates a double risk of developing ALLI for the patientswith hyperglycemia.

Discussion

The obtained results were analyzed and compared with the data earlier presented in scientific publications. The comparative analysis is difficult due to the small number of works on the search for occlusion predictors of specific localizations (with ALLI) under the ongoing prophylaxis.

Table 3. Predictors of ALLI development from obstruction localization

Occlusion Localization	Sign	Univariate analysis			Multivariate analysis	
		χ^2	RR (95% CI)	P	RR (95% CI)	P
Iliac artery system	Obesity More than 12 hours Anemia Blood thickening	2.38 3.24 4.77 3.71	-0.11 (-0.04; 0.27) -0.42 (-1.1; 0.3) 0.12 (-0.04; 0.28) 0.3 (-0.1; 0.75)	0.152 0.272 0.142 0.179		
Femoral artery system Multivariate Logit Regression: $\chi^2 = 10.1$; $p < 0.01$	Anemia Low hematocrit (less than 0,3) Chronic kidney disease Hyperglycemia	7.71 3.92 2.03 5.3	2.77 (0.5; 4.9) -0.1 (-0.2; 0.01) 1.3 (-0.5; 3.3) 2.2 (0.1; 4.2)	**0.013** 0.074 0.171 **0.033**	2.1 (-0.8; 5.1) -0.05 (-0.2; 0.1) -2.2 (-8.2; 8.4)	0.163 0.577 - **0.097**
Lower leg artery system	Male gender Age over 70 Smoking Leukocytosis Hyperglycemia	2.03 2.69 1.31 2.03 1.2	-1.3 (-3.3; 0.5) 0.06 (-0.01; 0.15) 1.09 (0.8; 3.0) 1.3 (-0.5; 3.3) 1.0 (-0.8; 3.0)	0.061 0.127 0.258 0.171 0.287		

Several studies confirmed the high value of hyperglycemia as a predictor of acute lower limb ischemia.[4,14] The risk ratio in this case is on average about 1.7-3.0, which correlates with the obtained results (RR 2.2). However, most studies did not study the risk of developing ALI under specific prophylaxis. The results concluded that an isolated risk factor for thrombosis development is hyperglycemia, regardless of the blood coagulation indicators. This is probably due to the influence of the glycemia level on the regulation of hemostasis and, as a result, with its volatile values, a decrease in the effectiveness of preventive measures.[15]

Since diabetes leads to specific changes in primary and secondary hemostasis, such patients require oral anticoagulants.[16] Possibly a more effective combination prescribing approach (COMPASS study)[17], in diabetic patients (n = 10.241), the addition of 2.5 mg rivaroxaban to aspirin resulted in a significantly lower incidence of serious cardiovascular complications (RR 0.74, 95% CI 0.61-0.90; p = 0.68) with higher rates of expected severe bleeding (heart rate 1.70, 95% CI 1.25-2.31). In 3287 patients with peripheral arterial disease and diabetes treated with rivaroxaban plus aspirin, the absolute reduction in the overall endpoint (cardiovascular death, myocardial infarction, and stroke) was twice as high as in patients without diabetes.[18]That is, such patients require a careful choice of a prevention regimen.

It should be added that a large national study in Japan,[19] including an analysis of 1,121,359 cases, demonstrated a predominantly negative effect of diabetes on peripheral vessels (primarily of the lower limb) in comparison with coronary vessels (1.96 times higher, p <0.001).

Conclusions

The results indicate the need to correct glycemic parameters to reduce the risk of acute lower limb ischemia, even during antiplatelet or anticoagulant prophylaxis. It is also necessary to analyze the management protocols currently used for such patients to correct the recommended regimens for taking anticoagulants and antiplatelet agents.

Conflict of interest. The authors declare no conflicts of interest.

Research transparency. The study was not sponsored. Researchers are solely responsible for submitting the final manuscript to print.

Declaration on financial and other interactions. All authors took part in the concept and design of the study and in writing the manuscript. All authors approved the final version of the manuscript. The authors did not receive research fees.

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