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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Subacute lower extremity arterial thrombosis; early outcomes of catheter directed thrombolysis with alteplase and importance of malnutrition assessed by CONUT score

Subakut alt ekstremite arteriyel trombozu; Alteplaz ile kateter aracılı trombolizin erken dönem sonuçları ve CONUT skoru ile değerlendirilen malnutrisyonun önemi

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ABSTRACT

Objective: In this study, we aimed to report early outcomes of catheter-directed thrombolysis (CDT) with alteplase in patients with subacute limb ischemia and to assess whether there is a link between malnutrition (determined by Controlling Nutritional Status [CONUT] score) and response to thrombolysis and bleeding.

Methods: This was a retrospective study conducted between 2007 and 2020 with 118 patients with Rutherford class 3 (34.7%), class 4 (40.7%), and class 5 (24.6%) symptoms owing to infraaortic subacute thrombotic occlusion who were treated with catheter-directed thrombolysis.

Results: Immediate technical success (Thrombolysis in Myocardial Infarction [TIMI] grade 2/3) was achieved in 56%, overall technical success after all adjunctive procedures was seen in 83.9%. Clinical success was obtained in 74.5% within 30 days. Major bleeding occurred in 11.8%. When we excluded access site hematomas, the rate of major bleeding was 5.1%. In-hospital mortality rate was 5.1%, and the amputation rate within 30 days was 12.7%. Any-degree malnutrition was detected in 48.3% according to CONUT score (≥2). Any-degree malnutrition was associated with failed thrombolysis and bleeding. The CONUT score predicted insufficient lytic response even after adjustment for confounding factors; however, serum C-reactive protein or neutrophil/lenfosit ratio did not. Other predictors of immediate technical failure after thrombolysis were symptom duration, Rutherford class 4/5 symptoms, and worsened distal runoff.

Conclusion: In patients with subacute limb ischemia, CDT combined with adjunctive interventions was effective in many patients at the expense of a substantial risk of bleeding and death. Malnutrition was associated with insufficient lytic response and bleeding. Physicians should be aware of malnutrition and consider the nutritional status of patients with limb ischemia when selecting appropriate treatment.

ÖZET

Amaç: Bu çalışmanın amacı subakut alt ekstremite iskemisi olan hastalarda alteplaz ile kateter aracılı intra-arteriyel trombolitik tedavinin erken sonuçlarını yayınlamak ve CONUT (Controlling Nutritional Status) skoru ile değerlendirilen malnütrisyonun trombolitik tedaviye yanıt ve kanama ile ilişkili olup olmadığını belirlemektir.

Yöntemler: Bu, 2007-2020 yılları arasında, infraaortik subakut trombotik oklüzyon nedeniyle Rutherford sınıf 3 (%34.7), sınıf 4 (%40.7) ve sınıf 5 (%24.6) semptomları olan ve kateter aracılı tromboliz ile tedavi edilen 118 hasta ile yürütülen retrospektif bir çalışmadır.

Bulgular: Hemen tromboliz sonrası teknik başarı (TIMI grade 2/3) oranı %56, ilave tüm girişimlerden sonra genel teknik başarı oranı %83.9 olarak görüldü. Hastaların %74.5'inde klinik başarı elde edildi. Major kanama %11.8'inde meydana geldi. Ancak, giriş yeri hematomlarını çıkardığımızda major kanama oranı %5.1 idi. Hastane içi ölüm oranı %5.1 ve 30 günluk amputasyon oranı %12.7 idi. CONUT skoruna göre (≥2) hastaların %48.3'ünde malnütrisyon tespit edildi. Herhangi bir seviyedeki malnütrisyon, başarısız tromboliz yanıtı ve kanama ile ilişkiliydi. Diğer faktörler için ayarlama yapıldıktan sonra bile, CONUT skoru yetersiz litik yanıtı öngördü, ancak serum CRP veya nötrofil/lenfosit oranı litik tedaviye yanıt ile ilişkili bulunmadı. Yetersiz litik yanıtın diğer belirleyicileri semptom süresi, Rutherford sınıf 4/5 semptom ve kötü pedal akım olarak saptandı.

Sonuç: Subakut bacak iskemisi olan hastalarda, kateter aracılı intra-arteriyel trombolitik tedavi tek başına olmasa da ek müdahalelerle birlikte, önemli kanama ve ölüm riskine karşın birçok hastada etkiliydi. Malnütrisyon, yetersiz litik yanıt ve kanama ile ilişkiliydi. Hekimler uygun tedaviyi seçerken malnütrisyonun farkında olmalı ve ekstremite iskemisi olan hastaların beslenme durumunu dikkate almalıdır.

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Most patients with a recent history of lower limb ischemia (<six months) have a fresh and/or varying degree of organized thrombotic component in their occlusions.[1-4] Clinical presentation of limb ischemia can be classified as acute (≤14 days), subacute (>14 days to three months), chronic (>three months), and acute/subacute deterioration on chronic disease.[2,5,6] Thrombotic occlusions are associated with multiple complications, including distal macro-embolization, prolonged procedure times, amputation, death, re-occlusion, urgent/emergent need for surgery, and bleeding risk because of anticoagulation or thrombolysis.[5,6] Therefore, standard endovascular interventions are strongly avoided, and the treatment of these thrombotic occlusions is a challenge. Surgery, catheter-directed thrombolysis (CDT), percutaneous thrombus aspiration, pharmaco-mechanical thrombectomy (PMT), and hybrid treatment are potential options.[1-13] CDT with alteplase (recombinant tissue plasminogen activator [rtPA]) is an accepted first line of treatment for patients with acute limb ischemia (ALI) who have salvageable limb ischemia.[7,14,15] However, better results were observed in patients treated with surgery in >14 days of ischemia in the Surgery versus Thrombolysis for Ischemic Lower Extremity (STILE) trial.[15] Owing to high perioperative mortality risk, 25%-40% residual thrombus and incomplete restoration of distal runoff after surgical embolectomy, and presence of a significant number of underlying steno-occlusive lesion, CDT combined with endovascular intervention is also a valuable option for patients with subacute lower limb ischemia (SLI).[2-4,6,7,12-14,16-18] The reported success rates with CDT are 52%-85% in patients with SLI; however, it is associated with bleeding risk and ongoing ischemia (distal embolization).[2-4,6,15,16-18] Risk stratification for patients with SLI is essential to improve clinical decision making and to determine the most appropriate therapy, by identifying not only high-risk patients but also determining which patients will do well with CDT.

Malnutrition is a common finding and an important predictor of poor outcomes in patients with cardiovascular and peripheral arterial disease (PAD).[19-27] Controlling nutritional status (CONUT) score was recently defined as a simple, efficient, and relatively comprehensive tool for malnutrition. The CONUT score reflects protein reservation, caloric repletion, and immune defence.[19,24] Up to 79% of patients who undergo vascular surgery can be classified as malnourished.[22,23] However, the clinical significance of the CONUT score with regard to outcomes in patients with SLI who underwent CDT has not been examined. In this study, we aimed to display the early outcomes of CDT in patients with subacute presenting limb ischemia and to assess the relationship between malnutrition, which determined by the CONUT-score, and CDT results and bleeding complications.

Abbreviations:

ALI	*Acute limb ischemia*
CDT	*Catheter-directed thrombolysis*
CK	*Creatine kinase*
CONUT	*Controlling Nutritional Status*
CRP	*C-reactive protein*
NLR	*Neutrophile/lymphocyte ratio*
PAD	*Peripheral arterial disease*
PMT	*Pharmaco-mechanical thrombectomy*
rtPA	*Recombinant tissue plasminogen activator*
SLI	*Subacute lower limb ischemia*
STILE	*Surgery versus Thrombolysis for Ischemic Lower Extremity*
TIMI	*Thrombolysis in Myocardial Infarction*

METHODS

In this retrospective study, 118 patients with SLI, subacute deterioration of chronic disease (>14 days and <three months symptom duration), or distal embolism during angioplasty in subacutely symptomatic patients, who underwent CDT with alteplase between March 2007 and April 2020 were enrolled. Patients with ALI and those who had a contraindication to thrombolytic therapy were excluded from the analysis.[14] Severity of the disease was stratified according to the Rutherford classification, and patients with Rutherford class 3 (severe claudication, 41/118 [34.7%]), class 4 (ischemic rest pain, 48/118 [40.7%]), and class 5 (minor tissue loss, 29/118 [24.6%]) were included. Before catheter angiography and CDT, many patients were evaluated with color Doppler ultrasonography or computed tomography angiography. The study was approved by the Ethics Committee of Kartal Koşuyolu Training and Research Hospital (Approval Date: May 23, 2017; Approval Number: 2017/4/22). The international ethical guidelines for research involving humans were followed.

Demographic and clinical characteristics, treatments, complications, and laboratory data were obtained from the patients' files and the registered hospital information management system used in our hospital. In addition, the pre-procedural and control angiographic data of the patients were obtained from the registered images on the online database system. A modified Thrombolysis in Myocardial Infarction (TIMI) classification was used in evaluating lower extremity perfusion immediately after CDT and after all adjunctive interventions.[9,28] TIMI classification was defined as grade 0 - no perfusion (no significant lysis), grade 1 - penetration without perfusion (contrast passes beyond the obstruction but fails to opacify the segments distal to the obstruction), grade 2 - partial perfusion (contrast passes across the obstruction but is substantially slower than in the collaterals or comparable arteries), and grade 3 - complete reperfusion (prompt antegrade flow into the segments distal to the obstruction). Achievement of complete or near-complete revascularization (TIMI grade 2/3) was considered as procedural success.

Catheter-directed thrombolytic therapy protocol

A minimum of 6 French sheath was inserted into the contralateral common femoral artery for diagnostic peripheral angiography of the affected limb. We also rarely used left brachial artery or ipsilateral common femoral artery for access. Initial angiography was performed to determine the occlusion. The pedal runoff was also evaluated angiographically at the initiation and completion of CDT by assessing patency of the infrapopliteal vessels. Once thrombotic occlusion on angiography or distal embolism during the endovascular procedure for SLI was detected, the occlusion was passed intraluminally with a hydrophilic guidewire. All the patients underwent CDT with alteplase with and without percutaneous aspiration thrombectomy. An infusion catheter (Multipurpose, Judkins right guiding catheter or pigtail catheter) was advanced directly into the thrombosed segments. A 70-100 IU/kg unfractionated heparin was then administered. Before the procedure, all the patients were on 81-150 mg acetylsalicylic acid and clopidogrel 75 mg per day. As there is no standard dose and technique of CDT, the decision regarding the alteplase dose and whether to give a bolus was at the discretion of the physician, and it was usually given as a bolus of 5-10 mg through the thrombotic lesion followed by continuous infusion at 1 mg/hr for 24 hours for a maximum of 48 hours. In some patients, simultaneous subtherapeutic heparin (400-500 IU/hr) infusion was given. The patients were monitored in the intensive care unit during CDT. Comprehensive laboratory tests were measured on admission. Thereafter, hemogram levels were measured every eight hours during CDT. Serum creatinine, electrolytes, C-reactive protein (CRP), and creatine kinase (CK) were measured daily. A control angiography was performed next day at the end of CDT. After CDT, adjunctive endovascular procedures were performed to correct underlying lesions, or surgical treatment was recommended in eligible patients. Stenting was only performed in the case of suboptimal balloon angioplasty results and/or flow-limiting dissection. Thrombolysis was discontinued in case of complete lysis and in case of complications such as progressive ischemia requiring immediate surgical intervention or major hemorrhagic complications. After the procedure, unfractionated heparin (activated partial thromboplastin time 50-70 s) was continued for at least 24 hours; and if there were no side effects, low-molecular weight heparin twice daily was provided until discharge. Antiaggregants and/or anticoagulants and other medical treatments were prescribed on discharge as indicated on a patient-to-patient basis and were determined by the physician who performed the intervention. Dual antiplatelet treatment was given for at least one month, followed by lifelong aspirin in many patients. During the follow-up, no imaging test was performed routinely; however, the presence of restenosis was evaluated within one year with Doppler ultrasonography or computed tomography angiography if symptoms or abnormal conditions were detected on examination.

Definitions

Immediate technical success of CDT was defined as restored patency of the formerly occluded arterial segment and achievement of TIMI grade 2/3 flow immediately after CDT.

Overall technical success was defined as achievement of TIMI grade 2/3 antegrade flow in the affected limb after CDT and all adjunctive interventions.

Clinical failure was defined as death, any degree of lower extremity amputation, need for surgical embolectomy owing to failed thrombolysis, or persistence or worsening of symptoms within 30 days.

Major bleeding events were defined as those that contributed to death, resulted in hemodynamic compromise, intracranial hemorrhage, requirement of intervention or blood transfusion, or a drop in baseline hemoglobin >2 g/dL.[29]

The CONUT score involves serum albumin, total cholesterol level, and lymphocyte count. Prefixed ranges of each parameter were assigned scores, and the sum of the scores of the three parameters represented the CONUT score on admission. A score of 0 to 1 reflected normal; 2 to 4 mild, and ≥5 moderate to severe malnutrition as described.[19-21,24-26] A CONUT score ≥2 was considered to be any-degree malnutrition.

Statistical analysis

Shapiro Wilk normality test was used to evaluate the distributions of variables. Independent sample t-test or Mann-Whitney U test were used to compare the continuous variables in patients with and without immediate technical success with CDT, dependent on distribution. Non-normally distributed continuous variables were presented as median and interquartile range (quartile 1 to quartile 3). We preferred to use median IQR as almost all data were distributed non-normally. Categorical variables were presented as a count and percentage. Categorical variables were compared using chi-squared test and Fisher's exact test. Predictors of immediate technical failure after CDT were analyzed with binary logistic regression analysis. It is important that candidate predictors included in models are clinically and biologically plausible and that their association has been demonstrated in previous studies.[2-4] The odds ratios (hazard ratio) in the regression models for continuous variables represents an increase from the 25th to the 75th percentile. Models 1, 2, and 3 was created to show whether there was added value with inclusion of CONUT score, serum CRP, or neutrophile/lymphocyte ratio (NLR) in predicting immediate technical failure of CDT. The propensity score was generated to eliminate the bias of concurrently heparin administration adjusted by age, symptom duration, previously known PAD, Rutherford class of symptoms, total tPA dose, and distal pedal runoff status. The calculated propensity score was added to each model, and it was evaluated whether the CONUT score, CRP, and NLR predicted immediate technical failure after CDT, respectively. Predictors of any-bleeding were analyzed using binary logistic regression analysis. All the statistical analyzes were performed using "rms," "Hmisc," and "ggplot2" packages with R version 4.01 (R Project, Vienna, Austria). A p value <0.05 was considered statistically significant.

RESULTS

The study included 118 patients with SLI treated by CDT, median age 61 (49-70) years, and 71% of patients were men. The median duration of tPA infusion was 24 hours (18.25-24), and the median total dose of alteplase was 34 mg (25-34). Immediate technical success was achieved in 66 (56%) patients, and overall technical success was seen in 99 (83.9%) patients. Clinical success was obtained in 88 (74.5%) patients at 30 days. Clinical failure included six in-hospital deaths, 15 any-degree lower extremity amputation within 30 days, six patients needed surgical embolectomy owing to failed thrombolysis, and 10 patients had persistent or worsening of symptoms. Major bleeding occurred in 14 (11.8%) patients, including eight with access site hematoma, two with retroperitoneal bleeding, two with gastrointestinal

Table 1. **Demographic and clinical characteristics of patients with SLI who underwent CDT with and without immediate technical success**

Characteristics	Immediate technical success after CDT n=66	Immediate technical failure after CDT n=52	*p*
Age (years)	59 (51-67)	62 (48-70)	0.600
Female sex, n (%)	15 (22.7)	19 (36.5)	0.100
Hypertension, n (%)	44 (66.7)	37 (71.2)	0.600
Hyperlipidemia, n (%)	33 (50)	28 (53.8)	0.680
Diabetes mellitus, n (%)	28 (42.4)	21 (40.4)	0.820
Coronary artery disease, n (%)	31 (47)	20 (38.5)	0.350
Heart failure, n (%)	6 (9.1)	4 (7.7)	0.790
Renal failure, n (%)	11 (16.7)	10 (19.2)	0.720
Cerebrovascular disease, n (%)	3 (4.5)	3 (5.8)	0.760
Previously peripheral artery disease, n (%)	32 (48.5)	19 (36.5)	0.190
Smoking history, n (%)	39 (59.1)	23 (44.2)	0.110
Atrial fibrillation, n (%)	5 (7.6)	5 (9.6)	0.630
Symptom duration (days)	35 (20-60)	45 (20-75)	0.530
Rutherfold classification, n (%)			
3, severe claudication	28 (42.3)	13 (25)	0.020
4, rest pain	28 (42.4)	20 (38.5)	
5, ulcer or necrotic	10 (15.2)	19 (36.5)	

CDT: catheter-directed thrombolysis; SLI: subacute lower limb ischemia.

Table 2. **Angiographic, laboratory characteristics, and treatment details in patients with SLI who underwent CDT with and without immediate technical success**

Characteristics	Immediate technical success after CDT n=66 (56%)	Immediate technical failure after CDT n=52 (44%)	*p*
Affected lower limb vessels, n (%)			
Iliofemoral	8 (12.1)	5 (9.6)	0.660
Femoropopliteal	58 (87.9)	47 (9.4)	
Stent thrombosis, n (%)	8 (12.1)	3 (5.8)	0.410
Graft thrombosis, n (%)	4 (6.1)	2 (3.8)	
Bolus alteplase administration, n (%)	61 (92.4)	46 (88.5)	0.460
Total dose of alteplase, mg	34 (29.3-34)	34 (23.6-34)	0.210
Duration of alteplase infusion, hours	24 (20-24)	24 (15-24)	0.160
Concomitant Heparin Infusion, n (%)	27 (4.9)	15 (28.8)	0.170
After CDT, antegrade TIMI flow, n (%)			
Grade 0	0	35 (67.3)	<0.001
Grade 1	0	17 (32.7)	
Grade 2	34 (51.5)	0	
Grade 3	32 (48.5)	0	
Number of patent distal pedal vessels, n (%)			
0	3 (4.5)	10 (2.8)	0.004
1	25 (37.9)	21 (43.8)	
2	20 (3.3)	14 (29.2)	
3	18 (27.3)	3 (6.3)	
Popliteal aneurysm, n (%)	7 (1.6)	2 (3.9)	0.170
Adjunctive endovascular interventions before CDT, n (%)			
No intervention	45 (68.1)	33 (63.5)	0.720
Percutaneous thrombus aspiration	11 (16.7)	10 (19.2)	
Balon angioplasty	10 (15.1)	9 (17.3)	
Adjunctive interventions after CDT, n (%)			
Percutaneous thrombus aspiration	3 (4.5)	10 (19.2)	<0.001
Balon angioplasty	15 (22.7)	30 (57.7)	
Stenting	3 (4.5)	6 (11.5)	
Surgery (embolectomy/graft interpostion)	3 (4.5)	13 (25)	
Serum CRP, before CDT, mg/L	2.30 (.58-7.90)	4.42 (1.25-14.5)	0.047
Serum CRP, after CDT, mg/L	5.67 (1.88-17.2)	8.75 (4.49-18.8)	0.060
NLR, before CDT	3.2 (2.47-5.12)	3.80 (2.54-6.48)	0.290
NLR, after CDT	4.29 (2.74-6.0)	5.5 (3.3-11.4)	0.030
Serum CK, before CDT, U/L	72 (45-133)	83 (47.5-157)	0.430
Serum CK, after CDT, U/L	75.5 (49.5-148)	289 (61.5-1416)	0.002
Serum albumin, g/dL	3.8 (3.42-4.11)	3.49 (3.07-3.9)	0.010
Lenfosit count	1700 (1400-2575)	1650 (1200-2200)	0.200
Total cholesterol level, mg/dL	204 (183-231)	185 (170-211)	0.010
CONUT score	1 (0-2)	2 (0-5)	0.004
Any-degree malnutrition, n (%)	23 (34.8)	34 (65.4)	<0.001

CK: creatine kinase; CRP: C-reactive protein; NLR: neutrophile/lymphocyte ratio; CDT: catheter-directed thrombolytic therapy; CONUT: Controlling Nutritional Status; SLI: subacute lower limb ischemia.

Table 3. Complications in patients with SLI who underwent CDT with and without immediate technical success

Characteristics	Immediate technical success after CDT n=66 (56%)	Immediate technical failure after CDT n=52 (44%)	*p*
Interruption of thrombolysis, n (%)	5 (7.6)	8 (15.3)	0.070
Distal embolism, n (%)	9 (13.6)	12 (23.1)	0.060
Any bleeding complication, n (%)	24 (36.4)	8 (12.1)	0.840
Minor bleeding	16 (24.2)	12 (23.1)	0.880
Major bleeding	18 (34.6)	6 (11.5)	0.920
Contrast induced acute kidney injury, n (%)	7 (10.6)	11 (21.2)	0.110
Amputation within 30 days, n (%)	4 (6.1)	11 (21.2)	0.004
In-hospital mortality, n (%)	1 (1.5)	5 (9.6)	0.010
Restenosis within one year, n (%) (among 107 patients)	14 (21.5)	18 (42.8)	0.040

CDT: catheter-directed thrombolytic therapy; SLI: subacute lower limb ischemia.

bleeding, one with intracranial hemorrhage, and one with compartment syndrome and fasciotomy. When we excluded access site hematomas, the rate of major bleeding was 5.1%. In-hospital mortality rate was 5.1%, and lower extremity amputation rate within 30 days was 12.7%.

Demographic, clinic, and angiographic characteristics of the patients with SLI who underwent CDT with and without immediate technical success are presented in Tables 1 and 2. Patients with immediate technical failure after CDT had more frequent Rutherford class 4/5 symptoms (75% vs 57.5%) than those with immediate technical success after CDT (p=0.020). In patients with immediate technical success after CDT, the distal pedal runoff status was better than those with immediate technical failure after CDT. After CDT, adjunctive interventions were performed in 64.4% of the patients (Table 2). Both endovascular and/or surgical adjunctive interventions were required in all the patients with immediate technical failure after CDT. At follow-up, proven restenosis within one year was more common in patients with immediate technical failure after CDT than patients with successful thrombolysis (21.5% vs 42.8%, p=0.040). Moreover, although serum CK and NLR before CDT were similar between the groups, serum CRP on admission was significantly higher (4.42 mg/L [1.25-14.5] vs 2.30 mg/L [0.58-7.90], p=0.047) in patients with immediate technical failure after CDT. Serum CK and NLR after CDT were higher in patients with immediate technical failure after CDT; however, serum CRP tended to be higher in these patients. Among the patients, 57 (48.3%) had any-degree malnutrition according to the CONUT-score (≥2). Interestingly, the CONUT-score was higher, and any-degree malnutrition was more frequent in patients with immediate technical failure after CDT (65.4% vs 34.8%, p<0.001), mainly owing to lower serum albumin and lower total cholesterol levels (Table 2).

Complications in patients with SLI who underwent CDT with and without immediate technical success are presented in Table 3. Although major/minor bleeding rates were similar between the groups after CDT, in-hospital death and any-degree amputation was more frequent in patients with immediate technical failure after CDT. In addition, distal embolism was more likely observed in patients with immediate technical failure after CDT (13.6% vs 23.1%, p=0.060).

In patients with SLI or subacutely worsening symptoms on chronic disease, the independent predictors of immediate technical failure (TIMI grade 0-1 antegrade flow at the end of CDT) were symptom duration (p=0.020), Rutherford class 4/5 symptom (p=0.020), poor distal runoff (p=0.002), and any-degree malnutrition (p<0.001) (Table 4). Furthermore, it was statistically significant when we incorporated it as CONUT score (from 0 to 3) in Model 1 (OR: 2.21 (1.22-3.98), p=0.008). When the malnutrition status was classified as normal, mild, and moderate to severe on the basis of the CONUT score, the rate of immediate technical success (TIMI 2/3 flow) after CDT decreased as the degree of malnutrition worsened

Table 4. **Predictors of immediate technical failure after CDT in patients with SLI**

	Model 1 (CONUT score)		Model 2 (Admission CRP)		Model 3 (Admission NLR)	
	OR and 95% CI	*p*	OR and 95% CI	*p*	OR and 95% CI	*p*
Age (years) (50.25-68.75)	0.60 (0.28-1.23)	0.160	0.73 (0.38-1.42)	0.360	0.87 (0.45-1.65)	0.670
Symptom duration (20-65) days	2.99 (1.20-7.43)	0.020	2.56 (1.09-6.06)	0.030	2.66 (1.13-6.26)	0.020
Diabetes mellitus	0.94 (0.39-2.28)	0.900	0.91 (0.39-2.1)	0.830	0.91 (0.40-2.08)	0.820
Previously known PAD	0.55 (0.21-1.42)	0.220	0.50 (0.20-1.24)	0.130	0.50 (0.20-1.23)	0.130
Rutherford class (Class 4-5 vs 3)	3.29 (1.17-9.22)	0.020	3.04 (1.11-8.34)	0.030	3.62 (1.34-9.78)	0.010
Number of patent pedal vessels (0 vs 1, 2, 3)	7.01 (2.06-23.78)	0.002	4.91 (1.65-14.62)	0.004	4.72 (1.61-13.8)	0.004
Concomitant UFH infusion	0.55 (0.22-1.39)	0.200	0.59 (0.24-1.45)	0.250	0.60 (0.25-1.45)	0.260
Total alteplase dose (25-34 mg)	0.72 (0.51-1.03)	0.080	0.76 (0.54-1.07)	0.120	0.78 (0.55-1.09)	0.150
Distal embolization	1.78 (0.72-4.41)	0.210	1.76 (0.75-4.13)	0.190	1.82 (0.78-4.23)	0.160
*Any-degree malnutrition	5.16 (1.97-13.51)	<0.001	-	-	-	-
Admission CRP (0.84-9.34 mg/L)	-	-	1.25 (0.90-1.72)	0.170	-	-
Admission NLR (2.47-6.15)	-	-	-	-	0.96 (0.79-1.16)	0.680

*This was still statistically significant when we incorporated it as CONUT score (from 0 to 3) in Model 1 (OR : 2.21, 95% CI: 1.22-3.98, p=0.008).
The OR (hazard ratio) for continuous variables represents an increase from the 25th to the 75th percentile.
CDT: catheter-directed thrombolytic therapy; CI: confidence interval; CONUT: Controlling Nutritional Status; CRP: C-reactive protein; NLR: neutrophile/lymphocyte ratio; OR: odds ratios; PAD: peripheral artery disease; SLI: subacute lower limb ischemia; UFH: unfractionated heparin.

Table 5. **Multivariate logistic regression analysis after covariates adjustment using the propensity score for predicting immediate technical failure after CDT**

	Model 1 (CONUT score)		Model 2 (CRP on admission)		Model 3 (NLR on admission)	
	OR and 95% CI	*p*	OR and 95% CI	*p*	OR and 95% CI	*p*
Propensity score* (0.31-0.39)	1.40 (0.79-2.47)	0.230	1.18 (0.69-2.02)	.520	1.10 (0.65-1.88)	0.710
Any-degree malnutrition†	3.96 (1.78-8.82)	<0.001	-	-	-	-
CRP on admission (0.84-9.34 mg/L)	-	-	1.25 (0.96-1.63)	0.090	-	-
NLR on admission (2.47-6.15)	-	-	-	-	0.98 (0.84-1.16)	0.880

*Adjusted by concurrent heparin administration, age, symptom duration, previously known PAD, Rutherford class of symptom, total alteplase dose, and pedal runoff status.
The OR (HR) for continuous variables represents an increase from the 25th to the 75th percentile.
†Still statistically significant when we incorporated it as CONUT score (from 0 to 3) in Model 1 (OR: 1.80, 95% CI: 1.13-2.88, p=0.01).
CDT: catheter-directed thrombolytic therapy; CI: confidence interval; CONUT: Controlling Nutritional Status; CRP: C-reactive protein; NLR: neutrophile/lymphocyte ratio; OR: odds ratios; SLI: subacute lower limb ischemia.

(70% vs 44% vs 33%) (Figure 1). Multivariate logistic regression analysis after covariates adjustment using the propensity score (adjusted by concurrent heparin administration, age, symptom duration, previously known PAD, Rutherford class of symptom, total alteplase dose, and pedal runoff status) revealed that any-degree malnutrition was still associated with immediate technical failure after CDT; however, serum CRP or NLR on admission was not associated with immediate technical failure after CDT (Table 5). Although age, female sex, concurrent administration of heparin with alteplase, and Rutherford class were not associated with bleeding complications, any-degree malnutrition was associated with bleeding complications (OR 2.28 (1.01-5.21), p=0.045) (Table 6).

DISCUSSION

There are no specific recommendations for the management of SLI in the current guidelines, and patients presenting with >14 days ischemia are considered chronic, and CDT is recommended with class IIb in non-acute symptomatic limb ischemia.[12,14] The op-

Table 6. **Predictors of any bleeding complication in patients with SLI who underwent CDT with alteplase**

	OR and 95% CI	*p*
Age, years (50.25-68.75)	0.89 (0.50-1.62)	0.720
Female sex	1.11 (0.46-2.67)	0.820
Concomitant heparin infusion	1.27 (0.57-2.84)	0.560
Rutherford class (3-5)	0.64 (0.23-1.80)	0.400
Any-degree malnutrition	2.28 (1.01-5.21)	0.045

CDT: catheter-directed thrombolytic therapy; CI: confidence interval; OR: odds ratios; SLI: subacute lower limb ischemia.

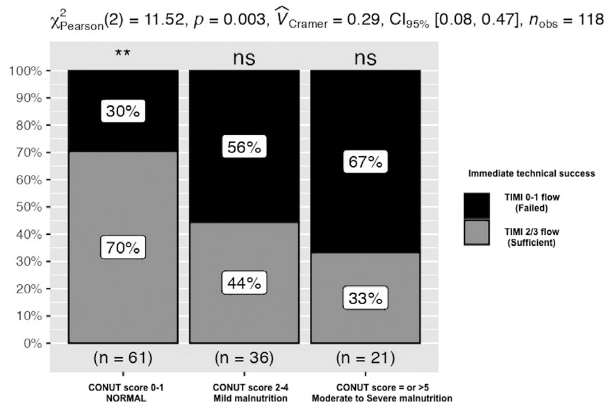

Figure 1. The rates of immediate technical success or failure after catheter-directed intraarterial thrombolysis according to the grade of malnutrition. Degree of malnutrition is classified as normal, mild, and moderate to severe malnutrition on the basis of the CONUT score. The rate of immediate technical success (Thrombolysis in Myocardial Infarction 2/3 flow) after catheter-directed thrombolysis decreased as the degree of malnutrition worsened (70% vs 44% vs 33%). Any-degree malnutrition was associated with technical failure after catheter-directed intraarterial thrombolysis.
CONUT: Controlling Nutritional Status; TIMI: thrombolysis in myocardial infarction.

timal initial treatment for patients with SLI remains undefined. Wholey et al.[2] reported that complete thrombolysis was achieved in 86% of the acute, 77% of the subacute, and 75% of the chronic occlusions. However, overall patency rates following dethrombosis in chronic occlusions (>three months) has been reported to be less than in SLI and ALI. Therefore, removal of the thrombotic component in chronic occlusions has less of an impact on overall outcomes than on those with SLI. Subacute presentation represents different clinical and imaging characteristics from ALI and chronic limb ischemia.[2-5] Dethrombosing approach to a thrombotic occlusion depends on multiple factors but generally requires a combination therapy.[5,6] We observed that in patients with SLI, thrombolysis alone was not effective enough. Kuhn et al.[17] found that CDT with rtPA was more effective in ALI than in SLI (82.4% vs 52.6%), consistent with the STILE trial.[1-4,5,15,17] A symptom of long duration suggests more organized thrombi in the occlusion. Non-acute occlusions are likely to contain multilayered fresh and organized thrombi and also thrombus attached to the vessel wall that might be responsible for insufficient response to CDT.[5,6,11-13] Thrombus organization begins approximately five days after thrombus formation and promotes endothelial dysfunction, which further aggravates thrombogenity.[13] We noticed that CDT combined with complementary interventions, which were mainly endovascular, provided sufficient early recanalization in many patients (83.9%). Adjunctive interventions were performed after CDT in 64.4% of the patients.

Similar to previous data, Rutherford class 4/5 symptom and poor distal runoff indicate the most advanced stage of PAD and high atherosclerotic burden that influenced early and late outcomes of patients with SLI treated with CDT.[2-4] This study showed that symptom duration, Rutherford class-4/5 symptom, poor distal runoff status, and any-degree malnutrition were associated with immediate technical failure after CDT. The CONUT score, as a continuous or categorical variable, predicted insufficient response to CDT even after adjustment for confounding risk factors.

Given the high prevalence of malnutrition in patients with atherosclerosis and PAD, a comprehensive nutritional assessment of all patients is advised. Yokoyama et al.[27] reported that CONUT score was more strongly associated with major adverse cardiovascular and leg events in patients with PAD. In this study, 48.3% of patients with SLI were at least mildly malnourished as determined with the CONUT score. Advanced age, the disease process, associated comorbidities, atherosclerotic disease burden, limited mobility, lower socio-economic status, and poor quality oral intake might contribute to undernutrition and muscle atrophy in patients with PAD.[22] Sarcopenia or sarcopenic obesity (low muscle and high fat mass) may be encountered in some patients, where malnutrition is masked by overweight. Approximately 44% of patients with PAD could be sarcopenic, which is associated with increased mortality, limb loss, and cardiovascular events.[22] Therefore, body mass index alone is not sufficient to determine the nutritional status of patients.[20-22] The CONUT score has been reported to be associated with poor ulcer healing (with > 4 score), long-term mortality, and poor amputation-free survival in patients with PAD.[22-27] It was demonstrated for the first time in this study that any-degree malnutrition was associated with insufficient thrombolytic response and bleeding complications in patients with SLI treated by CDT. In an attempt to select the potential responders for CDT and avoid bleeding complications, clinicians should consider the nutritional status of the patients with limb ischemia when selecting appropriate treatment.

Although high dose, blousing, and pulse spray techniques achieve vessel patency faster than low dose infusion, they are associated with more bleeding and no increase in patency rate or improvement in limb salvage.[6,7,30] Sebastian et al.[16] showed that CDT with 2-3 mg bolusing followed by 0.5 mg/hr alteplase infusion was safe and effective in patients with limb ischemia. Immediate success of CDT was 81% in native artery occlusion and 78% in grafts with >14 days' symptom duration. Therefore, in patients with SLI and malnutrition, bolusing need not be given, or these low doses could be used to reduce bleeding complications. Surgery, PMT, and hybrid treatment are alternatives. However, preoperative nutritional status significantly affected in-hospital mortality and long-term outcomes of patients who underwent infrainguinal bypass grafting for limb ischemia.[26] Current PMT devices provide a safe and effective alternative to thrombolysis and is associated with a reduced rate of major bleeding and shorter hospitalizations.[5-10] PMT can be considered in patients with SLI and malnutrition; however, PMT devices are expensive, and their use is not widespread.

Reported major bleeding rate was 5%-12%.[6,7] Any-bleeding complication rates were reported as approximately 30%. Most of these were local access site bleedings and simply manageable with compression, vascular sheath upsizing, and adjustment of anticoagulation or thrombolytic therapy. In this study, major bleeding complications occurred in 11.8% of the patients. When we excluded access site hematomas, the rate of major bleeding was 5.1%. Unlike other studies, a >2 g/dL drop in baseline hemoglobin was defined as major bleeding in our study.[29] The effect of concomitant heparin infusion with CDT on efficacy and bleeding is also controversial. Previously demonstrated concomitant continuous heparin infusion during CDT offered no benefit, but major bleeding tended to be more in those given heparin infusion.[30] Subtherapeutic dose heparin might be given to prevent pericatheter thrombosis. Bivaluridine may also be considered in patients with SLI who are at high risk of bleeding and/or have malnutrition instead of heparin.

In this study, serum CRP on admission was significantly higher in patients with insufficient response to thrombolytic therapy. That could be related to the atherosclerotic burden, which is an active inflammatory process. In addition, patients with immediate technical failure after CDT had more frequent malnutrition, which may also be related with high serum CRP. Malnutrition and inflammation are mutually causal and promote each other.[22] However, neither serum CRP nor NLR was a predictor of immediate technical failure after CDT. Previously, postoperative NLR was found to be associated with peripheral graft failure.[31] Taşoğlu et al.[32] also reported that NLR was an indicator of ischemic injury, and therefore, related to amputation in ALI. After CDT, we noticed higher NLR and higher serum CK in patients with failed thrombolysis than in those with successful thrombolysis for SLI, probably owing to ischemic injury.

Limitations

This study was a single-center, retrospective, observational study with an inherent bias and was conducted with a relatively small sample size. In addition, information with regard to body mass indices of the patients could not be given owing to missing data. Cholesterol level, which is used in CONUT score, would change with statin treatment, which is mostly indicated for these patients. Similar to the previous studies in patients with acute coronary syndrome, coronary artery disease, and PAD; more than half of our patients were on statin therapy.[19-21,24-26] However, as in the studies we mentioned, it was thought that this would not affect the results. In this retrospective study, we could not share the data regarding statin usage because there was no clear data on it. As our hospital is a tertiary cardiovascular diseases hospital, amputations could not be specified as major or minor although we did active search for available amputation data.

Conclusion

In patients with SLI, thrombolysis alone was not effective enough; however, CDT combined with adjunctive interventions provides adequate antegrade flow in many patients with an early clinical success rate of 74.5% at the expense of a substantial risk of bleeding and death. Malnutrition, assessed by the CONUT score, was detected in almost half of the patients; and any-degree malnutrition was associated with insufficient lysis and bleeding complications. Healthcare practitioners should be aware of malnutrition in patients with PAD, who are already nutritionally susceptible, and consider the nutritional status of patients with limb ischemia when selecting appropriate treatment. Appropriate medical support should be provided if necessary to improve clinical outcomes across all stages of the disease process.

Ethics Committee Approval: Ethics committee approval was received for this study from the Kartal Koşuyolu Training and Research Hospital (Approval Date: May 23, 2017; Approval Number: 2017/4/22).

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Keywords: Bleeding; catheter directed thrombolysis; malnutrition; peripheral artery disease; thrombosis

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