How to Cite:
Abuhadema, A. S., Mohamed, N. A., Hefnawy, E. T., Khairy, H. M., & Mohamed, H. A. (2022). Stratification of predictors of major amputation versus limb salvage in Egyptian patients with critical limb ischemia. *International Journal of Health Sciences*, *6*(S1), 3289–3305. https://doi.org/10.53730/ijhs.v6nS1.5469

Stratification of predictors of major amputation versus limb salvage in Egyptian patients with critical limb ischemia

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***Abstract*---** Aim of the study: To determine major predictors for limb salvage (or major amputation) in chronic limb threatening ischemia (CLTI) in Egyptian people. Design: Pilot study, observational analytical study. Patients and Methods: This study was conducted on 224 cases in the Department of Vascular Surgery in Kasr Al-Ainy Hospital – Cairo University between March 2018 to February 2019. The clinical, radiological and operative variables were collected and detect patients who need major amputation in 30 days and verify predictors of limb salvage, which was subjected to univariate analysis in order to determine the most important factors of failure of limb salvage. Results: The TLC, total CK, serum urea level and incomplete foot arch are independent factors directly proportional to the possibility of major amputation. Open interventions and presence of inline distal runoff enter the foot are independent factors inversely proportional to the possibility of major amputation. Anemia and active cardiac

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
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Manuscript submitted: 18 Jan 2022, Manuscript revised: 09 Feb 2022, Accepted for publication: 27 March 2022

condition are risk factors for major amputation. Conclusion: We obtained factors that predict the limb salvage by using of univariate and multivariate analysis. These factors can help the practitioners to predict the limb salvage and guides the consumption of health care resources and personnel.

***Keywords*---**Major amputation, Revascularization, CLI/CLTI, Predictors for limb salvage.

Introduction

Peripheral artery disease (PAD) includes the diseases of arteries occlusion that can range from asymptomatic to critical requiring interventions such as revascularization or amputation. The prevalence of PAD can be as high as 20% in the general population. [1] The disease causes imbalance in the metabolic needs of distal perfusion to the tissue, in which case it becomes more progressive and symptomatic. Critical limb ischemia (CLI) or chronic limb threatening ischemia (CLTI) is at the extreme of this spectrum, with a prevalence that is hard to calculate and quite variable in the different published research sources. CLI develops when the perfusion becomes insufficient at rest, unlike asymptomatic PAD or exertional claudication. [1] Several publications have used major lower limb amputation as a method of calculating prevalence for CLTI, claiming that CLTI is the cause for the majority of cases (>80%). However, in some administrative records, it might not be clear cutoff limits between minor (below the ankle) and major (above the ankle) amputations. [2]

According to recent literature , the risk of major amputation is very different from one country to another (3.6 to 68.4 per 100,000 per year), The difference is the result of many variables such as ethnicity and diabetes prevalence among different populations . Amputations that are not diabetes related appear to be declining in many countries. However, Diabetes related amputations are rising in other countries. [3]

The decision between limb salvage trial and primary major amputation is the most important in managing CLTI. Amputation of a Lower extremity without open or endovascular limb salvage is considered primary amputation in CLTI. Despite impressive revascularization achievements, there is strong evidence that primary amputation may still be the best option in some patients. Because of differences between surgeon's experiences, the ratio of major primary amputation to revascularization differs between facilities. Diabetes mellitus, end-stage renal disease, tissue loss, and low functional level all results in amputation rather than revascularization as the chosen therapy option. [4]

Current care of CLI/CLTI consists of aggressive attempts for limb salvage. This approach is more lesions focused than it is patient focused. Some CLI patients planned for limb salvage efforts may be served with primary amputation or non-operative management. Currently Modern care of CLI is lacking sufficient data. The comprehension of the natural history of CLI is limited, with little ability to prevent disease progression. Most patients with symptomatic CLI are burdened by the disease tremendously, with decreased baseline function, leading to loss of ability to be ambulant and ability to live independent. Surgical treatment is graft and limb focused, with only little understanding of the effects of treatment on patient morbidity and mortality. While surgical revascularization may prevent loss of limbs, it does not necessarily guarantee ambulation or functional independence. The advantage of revascularization over primary amputation in patients who do not regain independent ambulation is therefore questionable. The extent of ischemic foot lesions on overall outcomes has not been clearly identified. Even when limb ischemia is relieved, a fair concern remains. Which is the high mortality due to cardiovascular diseases in the CLI population? [5]

There are four main goals of primary amputation for CLTI patients:
(1) Ischemic pain relief
(2) Removal of any diseased, necrotic, or grossly infected tissues in the extremities
(3) Achievement of primary healing
(4) Preservation of independent ambulation. [2]

Still, primary amputation is considered best treatment option for patients suffering extensive foot lesions, significant comorbidities, or very unfavourable anatomy. ESKD presents a particularly higher challenge especially with advanced heel gangrene or infection which may be best treated with primary amputation. [6]

So it’s necessary to have a reasonable approach to patients presenting with CLTI. A thoughtful strategy is to consider the patient's comorbidities, the state of the foot, and the complexity of the needed revascularization. Aggressive use of endovascular revascularization has resulted in limb salvage in higher-risk patients which may have helped to decrease overall numbers of major amputations. Despite this, secondary amputations are not uncommon. [2] Patients always have a huge psychological concern over staying anatomically intact.

In modern practice, patients with threatened lower limbs present with a wide spectrum of underlying contributing factors of which ischemia is just one component, though an important one in determining if that limb can be salvaged. The current CLI classification systems are trying to properly categorize the extent of tissue loss and the severity of infection. There’s controversy over different revascularization options (open bypass vs endovascular therapy). And there’s another controversy over non revascularization options (local wound care, conservative management, or primary amputation). This debate cannot be worked out without accurate stratification of the patients being treated. In addition, recent trends have focused majorly on anatomic extent of disease and arteriographic findings without sufficient care for the state of the limb physiologically. [7]

Patients and Methods

This study is a prospective design conducted on patients presenting to the department of vascular and endovascular surgery, Kasr Alainy hospital, Cairo University during the period of the beginning of March 2018 till the end of

February 2019 were 224 patients. This is an observational study. The aim of the study is to deduce predictors of management of critical limb ischemia.
All patients are above 18 years old presenting with critical limb ischemia/ chronic limb threatened ischemia (CLI/CLTI) of the lower limb and clinically absent pedal pulsations. The diagnosis of CLI in this study depend on the definition which established in the Trans-Atlantic Inter-Society Consensus (TASC) 2007 patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The ischemic rest pain will most often occur with ankle pressures <50 mmHg and toe pressures <30 mmHg but that in situations where healing is needed, often ankle pressures less than 70 mmHg and toe pressures less than 50 mmHg are inadequate or reduced supine forefoot $TcPO_2$ <30–50 mmHg.

Patients presenting with claudication, aneurysms, trauma, autoimmune, or connective tissue disorders (e.g. Behcet, SLE), entrapment syndromes and upper limb ischemia were excluded from this study. This study was done in two groups: ***Group 1***: Subjects whose amputation procedure was performed (either post revascularization within 30 day or primary amputation). ***Group 2***: People have 30 day free from amputation after successful revascularization. Both groups were analyzed and compared to similar variables (risk factors, comorbidities, imaging, modalities of treatment). The frequencies of occurrence of these variables in two groups were assessed, statistical significance is estimated. All patients were subjected to history taking, meticulous physical examination and radiological studies.

Detailed history; personal, complaint, risk factors, comorbidities were collected. The risk factors which collected specifically are: diabetes mellitus, hypertension, hyperlipidemia, smoking, ischemic heart diseases, atrial fibrillation, heart failure, stroke and CKD. Vital signs, cardiovascular, neurological and respiratory assessment were done. The cardiovascular assessment was done after consultation of cardiologist and assess:

A. Is an active cardiac condition or not? The American College of Cardiology (ACC) together with the American Heart Association (AHA) have a checklist for conditions defined as active cardiac condition : Unstable coronary syndromes, Unstable or severe angina, Acute (7days) or recent (28 days) MI, Decompensated HF, Rapid AF or any significant arrhythmias, High-grade atrioventricular block, Symptomatic ventricular arrhythmias in the presence of underlying heart disease, Supraventricular arrhythmias with uncontrolled ventricular rate, Severe valvular disease.
B. Ejection fraction (EF) was assessed and classified to preserved EF > 50 %, reduced < 40 % and borderline: 40 – 50 %
C. Metabolic equivelant (MET)/functional capacity was assessed. MET gives a broad concept for general condition and effect of cardiac diseases on patients. **[8]** (Tab.1)
   Table(1): Assessment of metabolic equivelant for cardiac diseases **[8]**

Physical activity	MET
Light intensity activities	**< 3**
sleeping	0.9
watching television	1.0
writing, desk work, typing	1.8
walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking, 2.5 mph (4 km/h)	2.9
Moderate intensity activities	**3 to 6**
bicycling, stationary, 50 watts, very light effort	3.0
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling, <10 mph (16 km/h), leisure, to work or for pleasure	4.0
bicycling, stationary, 100 watts, light effort	5.5
Vigorous intensity activities	**> 6**
jogging, general	7.0
calisthenics (e.g. pushups, situps, pullups,jumping jacks), heavy, vigorous effort	8.0
running jogging, in place	8.0
rope jumping	10.0

If the patient is in active cardiac condition, his metabolic equivalent cannot be assessed.

- Clinical assessment, grade of ischemia and tissue loss for patients were determined. All the ulcers in this study were assessed according to the site, shape, size, depth, edge, margin, floor and duration. All the gangrene was examined (the extension and dry gangrene or moist gangrene). The heel was particularly highlighted. Pulsations and level of the block (most palpable distal pulse) were assessed.
- Staging the degree of ischemia by Rutherford classification and WIfI classification.

Blood tests: Hb, TLC, platelets, coagulation profile, Fasting blood glucose, kidney and liver functions, lipid profile serum K level and creatine kinase level.

Imaging: Arterial duplex scan, CTA or conventional angiography.

Detailed explanation of the procedure, its indications, methods, risks &outcome was done. After which an informed consent was signed by all included. The study protocol was approved by institutional ethical committee. The study was not supported by any funding.

Patients were assessed and decision taken to revascularize either via endovascular technique, open surgery or for primary amputations. All endovascular procedures were done in the angiosuite under local anaesthesia. After finish of procedure, completion angiography was done and assessment of technical success and distal runoff and foot arch. The restored pulses were assessed. All open surgical revascularization were done in the operating theater under spinal, epidural or general anaesthesia. The type of procedure (endarterectomy, bypass or hybrid) was determined. The distal runoff and retrieved pulses were assessed. In cases with bypass revascularization, the type of

conduit and its diameter were assessed. All amputations were done in the operating theater under axial or general anaesthesia.
The 30 day outcome was determined either: Free from amputation (limb salvage)**,** Major amputation (either primary or post intervention)**,** Death (mortality)

Statistical analysis

Data was analyzed on the Statistical Package of Social Science Software program, version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data was presented using mean, range, median, standard deviation and percentiles for quantitative variables and frequency and percentage for qualitative ones. Chi square or Fisher's exact tests were used for comparison between groups for qualitative variables while for quantitative variables the comparison was conducted using independent sample t-test or Mann Whitney test.

Results

224 subjects in which the pertinent clinical, radiological and operative variables were collected and follow up limb salvage (free from amputation) in 30 day, which was then subjected to statistical tests in order to determine the relevant data
The pertinent clinical variables and their statistical significance regarding to failure of limb salvage (major amputation):

Table (2): Descriptive statistics for potential clinical risk factors for 30 day failure of limb salvage (major amputation)

	30 day Amputation		**P value**
	Yes Absolute No. (%)	**No** Absolute No. (%)	
Gender			
Female	46 (41.8)	50 (43.9)	0.827
Male	64 (58.2)	64 (56.1)	
Age			
Range	33 – 85	25 – 95	
Mean ± SD	59.9 ± 12.6	60.9 ± 10.5	
Median (IQR)	62 (51 - 70)	60 (55 - 67)	0.944
Level of block			
Aortoiliac	8 (7.3)	4 (3.5)	0.296
Iliofemoral	6 (5.5)	8 (7)	
Femoropopliteal	50 (45.5)	70 (61.4)	
Infrapopliteal	46 (41.8)	32 (28.1)	
WIFI Stage			
Stage II	2 (2.4)	2 (1.9)	0.738
Stage III	10 (11.9)	8 (7.4)	
Stage IV	72 (85.7)	98 (90.7)	
*** Rutherford classification**			
IV: Rest pain	8 (9.8)	4 (3.7)	0.482
V: Ulcer	12 (14.6)	18 (16.7)	
VI: Gangrene	62 (75.6)	86 (79.6)	
Heel affection			
Yes	22 (20)	24 (21.1)	0.890

No	88 (80)	90 (78.9)	
Heel Ulcer			
Yes	8 (7.3)	4 (3.5)	0.434
No	102 (92.7)	110 (96.5)	
Heel gangrene			
Yes	18 (16.4)	20 (17.5)	0.868
No	92 (83.6)	94 (82.5)	
Active cardiac condition			
Yes	14 (12.7)	2 (1.8)	**0.030**
No	96 (87.3)	112 (98.2)	
Metabolic Equivalent			
Cannot be assessed	14 (12.7)	0 (0)	**0.046**
< 3	20 (18.2)	26 (22.8)	
3-6	48 (43.6)	60 (52.6)	
> 6	28 (25.5)	28 (24.6)	
Ejection Fraction			
< 40%	34 (30.9)	16 (14)	0.061
40-50%	16 (14.5)	30 (26.3)	
>50%	60 (54.5)	68 (59.6)	
DM			
Yes	98 (89.1)	102 (89.5)	0.948
No	12 (10.9)	12 (10.5)	
HTN			
Yes	66 (60)	74 (64.9)	0.591
No	44 (40)	40 (35.1)	
Hyperlipidemia			
Yes	62 (56.4)	88 (77.2)	**0.019**
No	48 (43.6)	26 (22.8)	
IHD			
Yes	40 (36.4)	42 (36.8)	0.958
No	70 (63.6)	72 (63.2)	
AF			
Yes	16 (14.5)	6 (5.3)	0.099
No	94 (85.5)	108 (94.7)	
HF			
Yes	10 (9.1)	6 (5.3)	0.486
No	100 (90.9)	108 (94.7)	
Stroke			
Yes	6 (5.5)	14 (12.3)	0.322
No	104 (94.5)	100 (87.7)	
Smoking			
Yes	30 (27.3)	60 (52.6)	**0.006**
No	80 (72.7)	54 (47.4)	
CKD			
Yes	12 (10.9)	16 (14)	0.617
No	98 (89.1)	98 (86)	

The statistical significance variables regarding to failure of limb salvage (major amputation) are patients with active cardiac condition, poor metabolic equivalent.

The pertinent laboratory and radiological variables and their statistical significance regarding to failure of limb salvage (major amputation):

Table (3): The potential laboratory and radiological risk factors for 30 day failure of limb salvage (major amputation)

	30 day Amputation		**P value**
	Yes Absolute No. (%)	**No** Absolute No. (%)	
Hb, Median (IQR)	9 (8 - 11)	11 (10 - 12)	**0.001**
TLC, Median (IQR)	15 (12 - 19)	11 (9 - 13)	**0.001**
Platelets, Median (IQR)	300 (200 - 400)	300 (225 - 350)	0.526
K level, Median (IQR)	4.5 (4 - 5)	4.5 (4.5 - 5)	0.299
CK total, Median (IQR)	135 (31 - 480)	30 (15 - 60)	**0.001**
CK – MB, Median (IQR)	2 (0.8 - 20)	0.5 (0.5 - 1)	**0.001**
Creatinine, Median (IQR)	1.2 (1 - 1.5)	1 (1 - 1.4)	0.183
Urea, Median (IQR)	40 (25 - 75)	25 (18 - 40)	**0.001**
TASC class ? [Aortoiliac segment]			
Normal	88 (89.8)	102 (91.1)	0.628
TASC A	2 (2)	4 (3.6)	
TASC B	0 (0)	2 (1.8)	
TASC C	2 (2)	0 (0)	
TASC D	6 (6.1)	4 (3.6)	
TASC class? [Femoropopliteal segment]			
Normal	34 (34.7)	32 (28.6)	0.223
TASC A	8 (8.2)	8 (7.1)	
TASC B	8 (8.2)	18 (16.1)	
TASC C	6 (6.1)	20 (17.9)	
TASC D	42 (42.9)	34 (30.4)	
TASC class? [Infrapopliteal segment]			
Normal	6 (6.1)	8 (7.1)	0.216
TASC A	10 (10.2)	8 (7.1)	
TASC B	2 (2)	12 (10.7)	
TASC C	18 (18.4)	32 (28.6)	
TASC D	62 (63.3)	52 (46.4)	
Invest.: Distal runoff	66 (67.3)	106 (94.6)	**0.001**
Invest: Number of tibial runoff vessels			
0	32 (32.7)	6 (5.4)	**0.002**
1	48 (49)	66 (58.9)	
2	10 (10.2)	30 (26.8)	
3	8 (8.2)	10 (8.9)	
Invest.: Peroneal only distal runoff	22 (22.4)	28 (25)	0.759
Invest.: Distal runoff is inline ?	28 (28.6)	80 (71.4)	**0.001**
Invest.: Distal runoff is entering the foot	42 (42.9)	90 (80.4)	**0.001**
Invest.: Foot arch			
Non visualized	52 (53.1)	26 (23.2)	**0.001**
Incomplete	36 (36.7)	14 (12.5)	

Complete	10 (10.2)	72 (64.3)	

Hemoglobin, total leukocytic count, urea, total creatine kinase and CK- MB are statistically significant. Radiological wise, there is no named stage statistically significant but at the level of individualized items of distal run off, the statistical significance values are presence or absence of runoff, inline runoff and foot arch.

Effect of type of intervention: (tab. 4)

Table (4): Types of intervention applied in current study

Type of intervention	30 day major amputation		P value
	Yes Absolute No. (%)	No Absolute No. (%)	
Endovascular	54 (49.1)	90 (78.9)	**0.001**
Open	14 (12.7)	24 (21.1)	
Hybrid	4 (3.6)	0 (0)	
Primary amputation	38 (34.5)	0(0)	**-**

The open intervention has more chance for limb salvage over other modalities and it is statistically significant in generation group.

Risk factors for failure of limb salvage (major amputation): are showed in table 5.

Table (5): Univariate predictors of 30 day failure of limb salvage (major amputation)

Variable	**Major amputation** Absolute No. (%)	**Limb salvage (FFA)** Absolute No. (%)	***P value***
Active cardiac condition	14 (12.7)	2 (1.8)	0.03
Hyperlipidemia	62 (56.4)	88 (77.2)	0.019
Smoking	30 (27.3)	60 (52.6)	0.006
Hb, Median (IQR)	9 (8 - 11)	11 (10 - 12)	0.001
TLC, Median (IQR)	15 (12 - 19)	11 (9 - 13)	0.001
CK total, Median (IQR)	135 (31 - 480)	30 (15 - 60)	0.001
CK – MB, Median (IQR)	2 (0.8 - 20)	0.5 (0.5 - 1)	0.001
Urea, Median (IQR)	40 (25 - 75)	25 (18 - 40)	0.001
Distal runoff	66 (67.3)	106 (94.6)	0.001
Inline distal runoff	28 (28.6)	80 (71.4)	0.001
Distal runoff is entering the foot	42 (42.9)	90 (80.4)	0.001
Non visualized foot arch	52 (53.1)	26 (23.2)	0.001
Incomplete foot arch	36 (36.7)	14 (12.5)	0.001
Feasibility of open intervention	14 (12.7)	24 (21.1)	0.001

Statistical tests

After determining the factors of statistical significance ***(P value < 0.05)*** in univariate analysis which define the risk factors for failure of limb salvage (table 5), multivariate analysis were conducted on those factors to determine the importance and extent of each factor's influence on the likelihood of failure of limb salvage. And to determine the factors that independently cause major amputation (leading factors). This has resulted in 6 factors independently cause major amputation showed in table 6. These factors are paraphrased in mathematical models to determine probability of failure of limb salvage (major amputation)

Table (6): Multivariate predictors of 30 day failure of limb salvage (major amputation)

	B	P value	OR	95% C.I. for OR	
TLC	0.218	0.003	1.244	1.076	1.438
CK total	0.007	0.002	1.007	1.003	1.012
Urea	0.015	0.044	1.015	1.000	1.030
Type of intervention	-2.954	0.012	0.052	0.005	0.516
Inline distal runoff	-2.694	0.001	0.068	0.015	0.299
Incomplete foot arch	3.767	0.001	43.239	6.559	285.062
Constant	-4.084	0.001	0.017		

Discussion

Although aggressive attempts for saving the lower limb in patient with CLI, amputation still occurs, perhaps the primary amputations may be declined, but secondary amputations are still exists or are in growing in some regions. Great efforts have been made in recent decades to improve treatment options. Technologies were applied to these patients. Nevertheless vascular surgeons find amputation even with high prevalence in some countries. Multiple attempts in recent years e.g. **[6 , 9 , 10 , 11 , 12]** have been directed to predict the worst-case scenarios, which are the amputation and death, in order to avoid falling into them or to rationalize the consumption of health care facilities and tools in those who cannot be saved. Most of these directions concerned either with what related to the patient's complaint of an ulcer or gangrene in his foot e.g WIfI classification, or concerned with what related to the doctor in form of the anatomical challenges of diseased arteries and how to overcome them e.g. TASC and GLASS classifications. Therefore, it is necessary to go to studies and researches in order to find an answer to predicting amputation or death taking into consideration the three main axes of the disease, namely:

1. General patient condition and comorbidities
2. Foot condition and pathology
3. Arterial condition and anatomy

It must be studied together and with each other, where each is affected by the other as it is a systemic disease. So this study was run with this logic, and the patients were collected in a prospective way all that pertains to the three axes and they have been combined with each other in modern statistical methods so that the physician determines the main independent factors that lead to failure of limb salvage (major amputation). After determining the factors of statistical significance ***(P value < 0.05)*** in univariate analysis which define the risk factors for failure of limb salvage (active cardiac condition, hyperlipidemia, smoking, Hb, TLC, total CK, CK – MB, Urea, presence of distal runoff, inline distal runoff, distal runoff is entering the foot, non-visualized foot arch, incomplete foot arch, feasibility of open intervention). Multivariate analysis was conducted on those factors to determine the importance and extent of each factor's influence on the likelihood of failure of limb salvage. And to determine the factors that independently cause major amputation. This has resulted in 6 factors independently cause major amputation. The factors that resulted from the analysis of multiple variants are total leukocyte counts, total creatine kinase, serum urea level, diseased foot arch, inline runoff and open intervention. Those factors are independent and direct risk factors for failure of limb salvage (major amputation). After analysing the study group, it was found that more than 85% suffer from diabetes and more than 80% suffer from advanced foot condition, whether in free from amputation group or major amputation group. This statistical may result in the diabetes and advanced foot condition (Rutherford V-VI or WIfI stage 4) insignificance and this lead to a statistical bias. This distribution of sample size is accidentally occur. But in fact, this distribution reflects the reality of our population whose represent to us in late and severe conditions. Therefore, this study is for patients with critical limb ischemia who suffer from diabetes and advanced foot conditions. In the case of patients whose do not suffer from diabetes or CLI with earlier or mild-moderate condition, the decision to revascularization will be easy and it is preferable first and it is not recommended to apply those models for mild/moderate cases. The most difficult decision facing vascular surgeons is usually in subjects with an advanced foot condition (Rutherford V-VI / WIfI stage 4) where the answer to the question (revascularization or primary amputation) is a matter of debate. So we shed light in our study on this group, and this study results in two models to predict the probability of limb salvage in those patients whose are in the gray zone between amputation and revascularization.

Increased baseline total leucocyte counts were reported to be associated with poor outcomes in diabetic foot. A baseline total leucocyte counts greater than 12.0 cells/μL has been proposed to be linked with increased risk of amputation. Neutrophil count was an independent predictor of treatment failure. **[13]**. In our study, a total leukocyte count was clinically and statistically significant in univariate analysis. Also, it is an independent risk factor for amputation in multivariate analysis. In ERICVA model, the parameter of acute active bacterial infection which are the leucocytes (>10 X 10^9/L), neutrophils (>7.5 X 10^9/L), lymphocytes (< 1.5 X 10^9/L) and neutrophil / lymphocyte ratio (> 5) are statistically significant for major amputation in univariate analysis. The neutrophil/lymphocyte ratio (>5) specifically is independent risk factor for major amputation or death and share with 8 points in ERICVA scale for prediction of major amputation. **[11]**

In 2019, Huang & Co. published that patients were classified as high risk for limb loss (white blood cells (WBC) counts ≥10,000/ml, and platelet-lymphocyte ratio (PLR) ≥130.337); intermediate risk (WBC count ≥ 10,000/ml, and PLR < 130.337) and low-risk group (WBC < 10,000/ml, Rutherford classification < 5). All patients involved in this study had successful endovascular intervention. **[14]**

In this study, it was found that creatine kinase is of statistical significance and that it is one of the risk factors for amputation. Also, it is an independent factor for failure of limb salvage (major amputation). A study published in 2007 by Currie and his colleagues, CLI patients undergoing amputation have increased CK before surgery. The duration of symptoms is collected that would compromise the interpretation of results. **[15]** Only CK had a positive predictive value greater than 50% to predict major amputation. Serum CK can assist treatment management of acute limb ischemia by quantifying prospectively the risk of major amputation or limb preservation on admission. **[15]** Few data and studies have addressed creatine kinase and its importance in peripheral arterial disease and most of these researches have addressed its importance only with acute conditions. It is known that creatine kinase rises during the muscles infarction, and that there is more than one subtype of creatine kinase each of its significance, but it is also known that it's level of blood does not remain constant and that it decreases after that over time. This leads to false interpretation. **[16]** Creatine kinase elevation and neutrophilia upon presentation conferred an increased risk of amputation. It is not sure if CK elevation after treatment carries the same prognosis, but it is unlikely because washout of the ischemic part normally occurs. Thus, initial serum CK levels may assist prognostic evaluation in these patients. **[16]**

Urea in our study carries a special importance. Urea reflects not only the renal functions, but also an indication of the patient's general condition such as the presence of dehydration, severe hypotension, or septicaemia. All of these reasons lead directly or indirectly to the amputation. Previous studies did not mention the specific importance of urea and its direct role in amputation, either because it was not collected in retrospective analysis or they replaced it by dialysis, as dialysis is one of important risk factors and independent risk factor that lead to failure of limb salvage (major amputation) and death in CLI patients. But the holistic meaning of urea that includes with it, the general state of circulation, hypoperfusion and dehydration, which are risk factors for amputation, made it different from creatinine or allocation with CKD. One of the disadvantages of the participant for the previous studies is that there are no expressive indications of inflammatory markers or general conditions, so there is no one which shares our opinion on this or addresses the urea individually in relation to the probability of limb salvage.

In our study the distal runoff, inline runoff, number of patent tibial vessels and entering the foot are major variables determine the outcome either limb salvage or major amputation. Presence of inline runoff is independent factor for limb salvage in our study. A lot of research has touched on distal runoff and its importance. Several classifications emerged to help prediction of feasibility of intervention (regarding to arterial morphology) and the probability of amputation. e.g. TASC II classification and the new one GLASS. The importance of runoff in its prediction and role with amputation appears in several studies. Watanabe and his colleagues, 2018 demonstrate that the number of patent crural arteries on the diagnostic angiogram was an independent predictor for outcome. The preserved distal outflow is clinically important to reduce the major adverse limb event (MALE) rate after endovascular intervention. **[17]** Akihiro Higashimori and his colleagues found CLI patients with one vessel runoff entering the foot, direct flow into a patent pedal arch is necessary to improve clinical outcomes. **[18]**

The intact pedal arch in current study predicts the limb salvage and also an independent factor for limb salvage. The runoff success is only completed with the presence of a good pedal arch and this has become the focus of new researches and is called extended angioplasty in order to ensure good patent pedal arch. ***Osami Kawarada & Co.*** state an infectious wound and classification of pedal arch are predictors of poor clinical outcomes in patients with after successful infrapopliteal intervention (revascularization of at least single straight-line flow to foot). **[19]**

Higashimori and colleagues,2016 studied the role of patent plantar arch in patients with critical limb ischemia who had only single-vessel runoff to the foot. The patent plantar arch was related to significant improvements in amputation free survival (AFS) and limb salvage rates. [18]. ***Baer-Bositis et al,2018*** demonstrate that after a percutaneous transluminal angioplasty for tibial diseases, patients with accepted pedal runoff score had improved ulcer healing, lower MALE rate, and significantly good AFS compared with patients have poor pedal runoff score.**[20]** ***Cheun and associates*** state the planter intervention can be successfully performed in critical ischemic limbs with good short-term results. But, long-term AFS still poor because of the underlying disease process, and it does not interrupt the final outcome of the disease course. Based on this report, Cheun suggest inframalleolar intervention for diabetic individuals with WIfI stage < 3 disease and the absence of ESKD. Those who have optimal AFS with limb salvage. **[21]** Tibial and pedal revascularization reduces minor and major amputation and result in better quality of life. **[22]**

The state of the heart is of importance and a risk factor for limb salvage prevalence in our study and this corresponds to several previous studies such as FINNVASC, PIII, VQI AFS, ERCIVA, Abou Zamzam & his colleagues and Khan & co. in their univariate analysis. But it is not a leading cause of amputation, while it is an independent risk factor of death, and this is evident in several studies such as ERCIVA, Abou Zamzam et al and Khan & co. studies.
Tissue viability depends directly and indirectly on the rate of oxygen arrival and aerobic metabolism. The arrival of oxygen depends not only on perfusion, but also depends significantly on haemoglobin and haematocrit. This is evident in our research and other researches. In our research, only haemoglobin data was collected and appear of clinical and statistical significance for amputation, and this is identical to what was mentioned in PIII study and ERCIVA in univarite analysis. But it is not a direct cause of amputation in multivariate analysis, unlike some other studies that have claimed such as PIII study (Haematocrit <30 (2 points)) and ERCIVA study (Haematocrit <30 (9 points)).

This is also similar to patients with CKD or dialysis dependent, where it is clear that it is an independent risk factor of amputation in PIII, VQI AFS model and Abou Zamzam & Co. studies and was not mentioned in our study, FINNVASC and Khan & Co. studies. But it manifests itself in the presence of urea and the presence of micro-angiopathy and pedal arch in our study. Severe CKD have obvious pedal artery disease which is a vascular risk factor cause revascularization failure and poor prognosis **[23]**. It is worth noting that patients with chronic kidney disease, the chronic inflammatory state induced by uremia and oxidative stresses, are one of the causes of peripheral arterial disease **[24]**.

Also, the percentage of dialysis patients in our study sample was 12.5%, and this resulted in a statistical bias due to the sample size. But it is worth noting that urea does not only reflect the function of the kidneys, but also reflects the general condition of the patient and the state of dehydration, which is an important factor not only for the limb perfusion but for the whole body. Lacroix and associates study the prevalence of chronic kidney disease (CKD) and its prognostic value in hospitalized patients with peripheral artery disease (PAD) of lower limb in 1010 patients divided into four subgroups according to estimated glomerular filtration rate. Results show the CKD is an independent predictor of 1-year mortality, but is not an independent predictor of limb loss. **[25]**

The multivariable analysis of Yusuke Watanabe and Co. study demonstrated that CLI, diabetes mellitus, TASC classification, occlusion length, dyslipidaemia, and clopidogrel were not leading risk factors of major adverse limb events (MALE). Diabetes mellitus, CLI, TASC classification, occlusion length, and dyslipidaemia are risk factors for an adverse cardiovascular event. However, they were not statistically significant in their study. The explanation for this is that the impact of the runoff might be too large. So, the unexpected result because the effectiveness of successful tibial PTA in patients with tibial runoff diseases. **[17]**

What is contrary in our study for everyone is that smoking and hyperlipidemia are inversely proportional to the occurrence of amputation, but it turned out that it is relative to the sample selection and the sample size (statistical bias).

Predictors of failure of limb salvage (major amputation)

The high total leukocyte counts are accompanied by infections or death in the muscles. Elevated total CK usually accompanies ongoing muscle infarction or spreading moist gangrene. Urea elevation is an indicator of either the kidneys in particular or the patient and dehydration in general. Usually poor runoff is accompanied by severe diabetes and kidney disease patients, but also diseased pedal arch is one of the most common signs associated with dialysis dependent patients.

Accordingly, we can say that diabetics or CKD patients who suffer from acute limb infections and spreading moist gangrene are most susceptible to failure of limb salvage (major amputation). Patients with CLTI, which are feasible to open revascularization, are less likely to have failure of limb salvage (major amputation) than other different treatment modalities.

Strengths and limitations:

Current study contains some weaknesses, it shows in the small sample size, single center, homogenous population, such as diabetes, gangrene incidence, and it is a regional equation, and that there is a statistical bias in some variables and the lack of random selection of some treatment modalities. But our study is one of the first studies that dealt with the topic through the three main axes (the patient’s condition, the foot condition, the arteries condition) and put them in a single balance so that one of them can show the most impact and the cause of amputation.

The current study is a prospective analysis has collected more than 70 variables for each patient. This study is considered as a first step towards the development of a comprehensive global equation with which we can not only predict the amputation but also take a decision to vascularize or not. So, we hope the initial results will be accepted and research will be continued and the initial equation will be applied to thousands of patients in different regions and re-evaluated and reformulated to reach the most accurate, best and comprehensive scoring system.

Conclusion

We obtained factors that predict the limb salvage by using of univariate and multivariate analysis. These factors stratify the predictors of major amputation to significant risk factors and independent (leading) risk factors. The stratification helps clinical practitioners in decision making for major amputation and guides the consumption of health care resources and personnel. The risk factors will be applied on more number of patients in specialized centers to obtain the final form of it that predicts the limb salvage and guides the consumption of health care resources and personnel.

No source of funding
No conflicts of interest
The ethical committee was approved

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