INFLUENCE OF RISK FACTORS AND COMORBIDITIES ON THE SUCCESSFUL THERAPY AND SURVIVAL OF PATIENTS WITH CRITICAL LIMB ISCHEMIA

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Abstract

Background. Critical limb ischemia (CLI) is associated with an increased risk of limb amputation, low quality of life and cardiovascular death.

The aim of this study is to identify the prognostic factors of mortality, revascularization failure and amputation failure, as part of risk factors for atherosclerotic and comorbidities.

Patients and methods. We examined 198 patients operated for CLI. Cox analysis was performed to discern the factors that were associated with failure of initial surgical therapy and death.

Results. For survival analysis, a significant model emerged with hypertension (p=0.00), cardiac comorbidities (p=0.00), renal comorbidities (p=0.04) and respiratory comorbidities (p=0.02) as significant predictors. Regarding the time to amputation failure, there was a significant model with insulin treated diabetes (p=0.00), coronary artery disease (p=0.02) and cerebrovascular disease (p=0.05) as significant predictors.

Conclusions. Significant predictors for mortality in CLI patients are high risk hypertension, severe coronary artery disease, renal failure requiring dialysis and chronic obstructive pulmonary disease. The association of these prognostic factors results in a proportional decrease of survival.

The predictors for amputation failure were, in addition to local factors, insulin treated diabetes, coronary artery disease and cerebrovascular disease.

The revascularization for limb salvage depends on the correct indication and accurate surgical technique.

Keywords: critical limb ischemia, risk factors, survival, mortality.

Introduction

Critical limb ischemia is the most advanced stage of peripheral artery disease and is associated with an increased rate of major amputations, cardiovascular death and low quality of life [1].

Surgical revascularization is one of the effective therapeutic options in critical limb ischemia. Failure of revascularization frequently leads to amputations, at a higher level compared to that of a possible primary amputation. Although the factors related to the operative technique are known to have the highest impact in successful revascularization, the influence of risk factors is insufficiently defined. The clinical presentation of critical limb ischemia (rest pain, ulceration, gangrene) seems to influence the prognosis of revascularization [2]. Due to the fact that severe ischemia reflects systemic atherosclerotic involvement, morbidity and mortality in critical limb ischemia are high. At the same time, the indication of revascularization in the case of these patients should be well documented. In order to improve the results of surgery for limb salvage, the factors that can have a favorable or unfavorable influence on its outcome should be recognized. The knowledge of these factors can allow to prevent or
correct the events that negatively influence this evolution, and potentiate those that positively influence it. Prognostic models can play an important role in therapeutic decision and the management of a patient or a group of patients with a certain disease. These models are built in order to estimate or anticipate the probability or the risk of a patient to develop some future clinical event, based on a number of patients and characteristics of the disease [3].

The aim of defining some prognostic factors in critical limb ischemia is to guide the surgeon regarding the prognosis of each case, following the analysis of factors that are easy to assess preoperatively.

The aim of this study is to identify the prognostic factors of revascularization failure, amputation failure and mortality, among risk factors for atherosclerosis and comorbidities.

**Material and method**

We performed a prospective study in 198 patients admitted at Surgical II Department, between February 2009 and November 2010 with the diagnosis of critical limb ischemia. Diagnosis was based on clinical data (rest pain, ulceration or necrosis), non-invasive investigations (peripheral pulses, segmental pressures, ankle-brachial index), and imaging data (Doppler ultrasound, angiography, CT angiography). Critical limb ischemia was defined as the presence of rest pain, ulceration or gangrene, with a segmental pressure in the ankle lower than 50-70 mm.

**Variables used:** We included in the study demographic data (age, sex), major risk factors for atherosclerosis (smoking, diabetes mellitus, arterial hypertension, dyslipidemia) and the presence of comorbidities (cardiac, pulmonary, neurovascular and renal disease). All patients received postoperative antiaggregant treatment. The patients were divided into 4 groups depending on the surgery performed and postoperative evolution: (1) revascularization; (2) revascularization failure; (3) primary amputation and (4) iterative amputation.

**Inclusion criteria:** patients aged at least 50 years (the minimum age at which atherosclerotic critical limb ischemia can develop) [1], diagnosed with atherosclerotic critical limb ischemia following vascular surgery examination, who underwent at least one surgical intervention in our service.

**Patient follow-up:** The patients were clinically followed up by postoperative control at 1, 3, 6 months and subsequently once a year.

**Data collection:** The data of the patients were introduced in a database, which was periodically updated according to postoperative control, rehospitalization or death.

**Statistical analysis:** We analyzed the influence of the risk factors of atherosclerosis and comorbidities on survival using Cox proportional regression. We used as covariables demographic factors (1, 2), risk factors (3-6) and comorbidities in atherosclerotic disease, plus pulmonary involvement (7-10):

1. **age** - continuous covariable, with a mean of 66.51;
2. **sex** - (1=men, 2=women);
3. **dyslipidemia** (0=normal total cholesterol, LDL-cholesterol, triglycerides; 1=normal cholesterol, LDL, triglycerides after dieting, 2=normal cholesterol, LDL, triglycerides after drug treatment) [4,5,6];
4. **hypertension** (0=normal BP values, 1=BP controllable with single drug, 2=BP controllable with 2 drugs) [4,5,6];
5. **diabetes mellitus** (0=no DM, 1=insulin treated DM, 2=non-insulin treated DM);
6. **smoking** (0=non-smoker, 1=ex-smoker, 2=active smoker) [4,5,6];
7. **coronary artery disease** (0=asymptomatic patient, 1=occult AMI on ECG, AMI older than 6 months, stable angina, silent ischemia on Holter monitoring, compensated congestive heart failure (CHF), drug compensated arrhythmia, EF between 25% and 50%, 2=unstable angina, AMI more recent than 6 months, decompensated CHF, arrhythmia not controlled by drugs, EF<25%) [4,5,6];
8. **renal involvement** (0=normal renal function, 1=creatinine between 1.5 and 5.9, 2=creatinine higher than 6 or dialysis) [4,5,6];
9. **chronic lung disease** (0=no respiratory dysfunction, 1=mild/moderate respiratory dysfunction – mild dyspnea, minimal RX changes, 20-35% functional alteration, 2=severe respiratory dysfunction, vital capacity (VC) <1.85 L, FEV1 <1.2 L (forced expiratory volume in 1 second), pCO₂ >45 mmHg, pulmonary hypertension, O₂ requirements, maximum expiratory volume per second VEMS <50%) [4,5,6];
10. **cerebrovascular disease** (0=asymptomatic, carotid stenosis <70%, 1=asymptomatic, carotid stenosis >70%, transient ischemic attack (TIA), non-specific symptomatology, 2=specific symptomatology, carotid stenosis >70%, sequelar CVA) (according to a model developed in our service [4,5,6]).

**Results**

The characteristics of the patients, depending on the surgery performed (primary amputation vs repeat amputation vs revascularization vs secondary amputation for failed revascularization) are detailed in Table I.

Table II shows the Cox survival coefficient for each factor included in the study. Hypertension, coronary artery disease (CAD), renal failure and pulmonary dysfunction were predictors of mortality with statistical significance ($\chi^2 [21]=59.52$, $p=0.00$). Patients with mild and severe hypertension (controlled by one drug, controlled by 2 drugs or uncontrolled) [4,5,6] had a lower survival rate compared to those with normal blood pressure values.
Table I. Characteristics of N = 198 patients with critical limb ischemia, stratified by surgical intervention.

| Variable                        | Revascularization (N = 59) | Primary amputation (N = 98) | Secondary amputation (N = 13) | Iterative amputation (N = 28) |
|---------------------------------|---------------------------|-----------------------------|-------------------------------|-----------------------------|
| Sex                             |                           |                             |                               |                             |
| males                           | 51 (86.4%)                | 73 (74.4%)                  | 12 (92.3%)                    | 22 (78.5%)                  |
| females                         | 8 (13.5%)                 | 25 (25.5%)                  | 1 (7.6%)                      | 6 (21.4%)                   |
| Age                             | 62.21 ± 5.96              | 69.21 ± 5.96                | 63.92 ± 8.52                  | 67.22 ± 8.67                |
| Smoking                         |                           |                             |                               |                             |
| Non-smoker                      | 17 (28.8%)                | 37 (37.7%)                  | 3 (23%)                       | 9 (32.1%)                   |
| Ex-smoker                       | 17 (28.8%)                | 33 (33.6%)                  | 4 (30.7%)                     | 11 (39.2%)                  |
| Active smoker                   | 25 (42.3%)                | 28 (28.5%)                  | 6 (46.1%)                     | 8 (28.5%)                   |
| Diabetes mellitus               |                           |                             |                               |                             |
| No DM                           | 51 (86.4%)                | 41 (41.8%)                  | 11 (84.6%)                    | 13 (46.4%)                  |
| Non-insulin treated DM          | 6 (10.1%)                 | 23 (33.6%)                  | 0                             | 5 (17.8%)                   |
| Insulin treated DM              | 2 (3.3%)                  | 34 (34.6%)                  | 2 (15.3%)                     | 10 (35.7%)                  |
| Hypertension                    |                           |                             |                               |                             |
| Normal values                   | 11 (18.6%)                | 23 (23.4%)                  | 9 (69.2%)                     | 8 (28.5%)                   |
| BP ctrl by 1 drug               | 31 (52.5%)                | 41 (41.8%)                  | 2 (15.3%)                     | 10 (35.7%)                  |
| BP ctrl by 2 drugs              | 17 (28.8%)                | 34 (34.6%)                  | 2 (15.3%)                     | 10 (35.7%)                  |
| Dyslipidemia                    |                           |                             |                               |                             |
| Normal cholest, LDL, TG values  | 24 (40.6%)                | 44 (44.8%)                  | 6 (46.1%)                     | 1 (3.5%)                    |
| Normal values with dieting      | 16 (27.1%)                | 24 (24.4%)                  | 1 (7.6%)                      | 9 (32.1%)                   |
| Drug treatment                  | 19 (32.2%)                | 29 (29.5%)                  | 6 (46.1%)                     | 8 (28.5%)                   |
| Cardiac comorbidities           |                           |                             |                               |                             |
| Asymptomatic                    | 34 (57.6%)                | 34 (34.6%)                  | 8 (61.5%)                     | 7 (25%)                     |
| Occult AMI on ECG               | 21 (35.5%)                | 52 (53.3%)                  | 4 (30.7%)                     | 21 (75%)                    |
| Unstable angina                 | 4 (6.7%)                  | 12 (12.2%)                  | 1 (7.6%)                      | 0                          |
| Renal comorbidities             |                           |                             |                               |                             |
| Normal renal function           | 56 (94.9%)                | 81 (82.6%)                  | 13 (100%)                     | 24 (85.7%)                  |
| Creatinine between 1.5-5.9      | 2 (3.3%)                  | 11 (11.2%)                  | 0                             | 4 (14.2%)                   |
| Severely altered renal function | 1 (1.6%)                  | 5 (5.1%)                    | 0                             | 0                          |
| Respiratory comorbidities       |                           |                             |                               |                             |
| No resp dysfunction             | 46 (77.9%)                | 70 (73.4%)                  | 13 (33.3%)                    | 21 (75%)                    |
| Mild resp dysfunction           | 13 (22%)                  | 21 (21.4%)                  | 0                             | 6 (21.4%)                   |
| Severe resp dysfunction         | 0                        | 6 (6.1%)                    | 0                             | 1 (3.5%)                    |
| Neurovascular comorbidities     |                           |                             |                               |                             |
| Asymptomatic, carotid stenosis <70% | 48 (81.3%)           | 79 (80.6%)                  | 12 (92.3%)                    | 25 (89.2%)                  |
| Asymptomatic, carotid stenosis >70%, TIA | 5 (8.4%)                 | 6 (6.1%)                    | 0                             | 0                          |
| Spec symptoms                   | 6 (10.1%)                 | 13 (13.2%)                  | 1 (7.6%)                      | 3 (10.7%)                   |

*The mean and standard deviation are reported for this continuous variable.

b One missing value.

Fig. 1. (A). Relation between survival and hypertension: the continuous line represents normal BP values; the interrupted line represents BP controllable with one drug; the dotted line represents BP controllable with 2 drugs; (B). Relation between survival and cardiac comorbidity: the continuous line represents the asymptomatic profile; the interrupted line represents occult AMI on ECG, AMI older than 6 months, stable angina, silent ischemia on Holter monitoring, compensated CHF, drug compensated arrhythmia, EF between 25% and 50%; the dotted line represents unstable angina, AMI more recent than 6 months, decompensated CHF, arrhythmia difficult to control by drugs, EF <25%; (C). Relation between survival and renal comorbidity: the continuous line represents normal renal function; the interrupted line represents creatinine between 1.5 and 5.9 and the dotted line represents creatinine higher than 6 or dialysis; (D). Relation between survival and pulmonary disease: the continuous line represents no respiratory dysfunction; the interrupted line represents mild/moderate respiratory dysfunction – mild dyspnea, minimal RX changes, 20-35% functional alteration; the dotted line represents severe respiratory dysfunction, VC <1.85 L, VEF1 <1.2 L, pCO2 >45 mmHg, PAH, O2 requirements, MEVS <50%.
A recent history of unstable angina, myocardial infarction, the presence of congestive heart failure or arrhythmia difficult to control by drugs decreased the survival of these patients compared to asymptomatic patients or those with occult acute myocardial infarction (AMI) on Holter monitoring, myocardial infarction older than 6 months, stable angina, compensated congestive heart failure (CHF), drug compensated arrhythmia, EF between 25% and 50% (Fig. 1B).

Survival was also lower in the case of patients with severely altered renal function compared to those with normal or slightly altered renal function (creatinine values between 1.5 and 5.9 mg%) (Fig. 1C), as well as in the case of patients with severe respiratory dysfunction compared to those without respiratory dysfunction or with mild/moderate respiratory dysfunction.

### Table II. Coefficients from Cox proportional hazards regression in which survival was regressed on risk factors.

| Variable                                                                 | Regression coefficient (b) | Standard error (SE(b)) | p-value | exp(b) hazard ratio | 95% confidence interval for hazard ratio |
|--------------------------------------------------------------------------|----------------------------|------------------------|---------|---------------------|----------------------------------------|
| Sex (1=male; 2=female)                                                   | 0.12                       | 0.21                   | 0.57    | 1.13                | 0.74 - 1.71                             |
| Smoking (0=non-smoker; 1=ex-smoker; 2=current smoker)                     | 0.11                       | 0.21                   | 0.59    | 1.12                | 0.75 - 1.68                             |
| Diabetes (0=no DM, 1=insulin treated DM, 2=non-insulin treated DM)       | 0.42                       | 0.25                   | 0.08    | 1.53                | 0.94 - 2.48                             |
| Hypertension (0=normal BP values, 1=BP controllable with one drug, 2=BP controllable with 2 drugs) | -0.68                      | 0.24                   | 0.00    | 0.51                | 0.32 - 0.81                             |
| Dyslipidemia (0=normal total cholesterol, LDL-cholesterol, triglycerides; 1=normal cholesterol, LDL, triglycerides after dieting, 2=normal cholesterol, LDL, triglycerides after drug treatment) | -0.23                      | 0.19                   | 0.22    | 0.8                 | 0.55 - 1.15                             |
| Cardiac comorbidities (0=asymptomatic patient, 1=occult AMI on ECG, AMI older than 6 months, stable angina, silent ischemia, compensated CHF, drug compensated arrhythmia, EF between 25% and 50%, 2=unstable angina, AMI more recent than 6 months, decompensated CHF, arrhythmia difficult to control by drugs, EF <25%) | -1.13                      | 0.31                   | 0.00    | 0.32                | 0.18 - 0.59                             |
| Renal comorbidities (0=normal renal function, 1=creatinine between 1.5 and 5.9, 2=creatinine higher than 6 or dialysis) | -0.98                      | 0.48                   | 0.04    | 0.38                | 0.15 - 0.96                             |
| Respiratory comorbidities (0=no respiratory dysfunction, 1=mild/moderate respiratory dysfunction – mild dyspnea, 2=severe respiratory dysfunction) | -0.99                      | 0.44                   | 0.02    | 0.37                | 0.16 - 0.89                             |
| Neurovascular comorbidities (0=asymptomatic, carotid stenosis <70%, 1=asymptomatic, carotid stenosis ≥70%, TIA, 2=specific symptomatology, carotid stenosis ≥70%, sequelar CVA) | 0.2                        | 0.26                   | 0.46    | 1.22                | 0.73 - 2.03                             |

* A negative sign means that the hazard (survival) is lower, and thus the prognosis worse, for subjects with higher values of that variable (if p-value is ≤0.05). A positive sign means that the hazard (survival) is lower, and thus the prognosis worse, for subjects with lower values of that variable (if p-value is ≥0.05).
A similar analysis was performed for the identification of the prognostic factors of amputation failure. The presence of diabetes mellitus, cardiac and neurovascular involvement were found to significantly influence prognosis. The prognosis of patients without diabetes mellitus or with diabetes controlled by oral antidiabetics was better regarding the success of primary amputation compared to patients with insulin treated diabetes mellitus (Fig. 2A). Likewise, patients with asymptomatic coronary artery disease or occult AMI on ECG (Fig. 2B), as well as patients with asymptomatic neurovascular involvement, carotid stenosis less than 70% or TIA, had a better prognosis compared to patients with carotid stenosis more than 70% or specific symptomatology (Fig. 2C).

A third statistical analysis was carried out in order to detect prognostic factors for revascularization failure, but no statistically significant factors were identified ($\chi^2$ [17] = 22.3, $p=0.17$).

**Discussion**

The major aim of the study was to analyze survival in the first place, then, depending on the group, the success of amputation or revascularization. Regarding survival, the factors that proved to be predictive were difficult-to-control arterial hypertension, advanced coronary artery disease (defined as unstable angina, AMI more recent than 6 months, decompensated CHF, arrhythmia difficult to control by drugs, EF <25%), dialysis dependent renal failure, and severe respiratory dysfunction. The predictive factors of amputation failure included insulin treated diabetes mellitus, coronary artery disease defined like in the case of survival analysis, and neurovascular involvement with specific symptomatology.

Depending on the final goal of the study, different risk factors can be highly predictive or, in the case of a different final goal, they can have no predictive capacity [7]. In our study, only coronary artery disease maintained its predictive capacity regardless of the endpoint.

The first predictive factor found by us was **arterial hypertension**. The fact that this is not found to be a significant risk factor in other studies [8,9] can be explained by the division of the patients into three degrees of severity. Only patients with difficult-to-control arterial hypertension (N=63) had a poorer survival rate, which was significantly lower compared to patients with normal blood pressure values or BP controlled by one drug. However, there are studies that support antihypertensive therapy as a protective factor against cardiac events [12,13].

The impact of **respiratory dysfunction** on the evolution of patients with critical limb ischemia is investigated in the majority of the studies [7,8,11,12]. While in multicenter studies survival does not seem to be influenced [8,10], there are studies that find severe respiratory dysfunction to be a risk factor for the
development of cardiac events [12,13].

Renal failure and coronary artery disease are risk factors in another multicenter study [10], having as an endpoint the survival without amputation of patients with critical limb ischemia who underwent femoral-popliteal bypass with a venous graft.

Dialysis-dependent renal failure was a prognostic factor both in our study and in other studies [8,10,14]. Although the rate of permeability of infrainguinal bypass is acceptable in patients with dialysis dependent renal failure [15], there is clear evidence that terminal renal failure is associated with early secondary amputation [16,17] and very poor survival [18,19]. Thus, in our study, dialysis dependent renal failure proved to be a strong predictive factor of survival. Moreover, Owens et al. [14] evidenced a linear relationship between the alteration of renal function and the reduction of survival in patients undergoing revascularization of the lower limbs, starting even before the dialysis dependent stage.

Coronary artery disease, symptomatic or not, was present in more than 50% of the patients. It is well known that systemic atherosclerotic disease present in patients with peripheral artery disease not only affects immediate morbidity and mortality, but also increases the risk of death of cardiac cause [20,21,22].

Primary amputation is aimed at improving pain, healing the stump per primam, and ensuring a functional stump. Major amputation is not always associated with negative prognosis, and many patients succeed in maintaining their ambulatory status in spite of their disability [23]. Although extensive, the literature focuses on determining the prognostic factors of survival without amputation or of maintaining a functional limb or stump. As far as we are concerned, we considered that the choice of an adequate amputation level contributes to the improvement of the quality of life of these patients. The decision regarding the amputation level was made by weighing the probability of the per primam healing of the stump and the perspective of maintaining the ambulatory status of the patient.

Insulin treated diabetes mellitus was the main factor that influenced the quality of the amputation stump. Insulin requirements are associated with an increase in morbidity and mortality of cardiovascular cause [24,25], although some studies consider insulin requirements as a marker of the severity of diabetes mellitus [26,27]. Insulin treated diabetic patients with critical limb ischemia have a low survival rate and an increased rate of amputations. At the same time, survival and the limb salvage rate in patients treated with diet or oral antidiabetics are identical to those of non-diabetic patients [28]. In our study, insulin treated diabetic patients with critical limb ischemia have an increased risk of repeat amputations. Yip et al. [29] have studied the factors that influence the failure of amputation, which are mainly local: absence of popliteal pulse, amputation stump trauma, wound infection, distal trophic disorders. These local conditions can also be influenced by the presence of diabetes.

The comorbidities that can influence the evolution of an amputation or can determine the choice of an incorrect amputation level have been less studied.

Coronary artery disease is maintained as a predictive factor in the case of amputation failure. Patients with unstable angina, difficult-to-control arrhythmia, decompensated CHF seem to be more exposed to an unfavorable evolution of a minor or major amputation performed below the knee level. This can be due to more severe atherosclerotic involvement, which is why minor amputation can be insufficient. Severe cardiac involvement can also cause low cardiac output, with insufficient blood supply of the lower limbs, or can favor acute ischemia on an atherosclerotic terrain through an embolicogenic mechanism.

Cerebrovascular disease can influence the evolution of patients with minor amputation for critical limb ischemia in the context of extensive atherosclerotic involvement. In the case of the presence of associated motor deficit or cerebrovascular accident, the homolateral ischemic limb also has a clear indication of amputation above the knee. In this case, patients with reduced mobility are very unlikely to wear a prosthesis. Thus, palliative amputation above the knee is preferable to amputation below the knee, where there is an increased risk of decubitus lesions and delay/absence of healing [23]. The choice of an amputation level below the knee in patients with advanced cerebrovascular disease is incorrect and non-beneficial. These patients have a limited functional rehabilitation capacity, which is why thigh amputation is more risk free.

The analysis performed for the identification of risk factors for revascularization failure found no risk factor with statistical significance of the analyzed ones. When successful revascularization is considered, this is defined as graft permeability and limb salvage. This is supposed to result in an adequate ambulatory capacity of the patients, their independence and survival [30].

The factors that influence the success of revascularization are rather related to technique: the type of prosthesis used, the level of distal anastomosis and runoff [2].

Our results are in agreement with other studies that found no independent prognostic factors for survival without amputation [8]. However, the association of coronary artery disease and renal failure seems to influence survival without amputation [8]. Even PREVENT III, a randomized multicenter study that elaborated a prognostic score, proved to be less useful in evaluating the prognosis of successful revascularization than regarding survival [7], due precisely to the focus on systemic risk factors, not on factors relating to technique (graft type, vein diameter etc.).

The identification of risk factors will allow to
estimate prognosis at the time of presentation of the patient. This will finally serve to guide therapeutic decision and adjust treatment.

The limits of the study are related in the first place to the small number of patients and to the fact that the study was carried out in one center. Also, the diagnosis of comorbidities and the evaluation of risk factors were based on anamnesis and previous examinations, without being always accompanied by a multidisciplinary evaluation performed by the same team.

Another limit of the study was the absence of the cause of death. These patients may have an increased mortality rate of non-cardiovascular cause (neoplasms, diabetes mellitus, lung diseases). However, it should be noted that the absence of the control of risk factors associated with a poorer prognosis due to comorbidities results in a higher mortality rate of patients with critical limb ischemia.

Conclusions

Following the analysis of the major risk factors of atherosclerosis and comorbidities, we identified as prognostic factors of survival with statistical significance difficult-to-control arterial hypertension, severe coronary artery disease, dialysis dependent renal failure, and severe respiratory dysfunction. The association of these prognostic factors leads to a proportional decrease in survival.

The failure of a primary amputation is determined, in addition to local factors, by some predictive systemic factors: insulin treated diabetes mellitus, severe coronary artery disease, and cerebrovascular disease.

The success of revascularization depends in the first place on the correct indication and technique.

Further studies are required for the validation of the prognostic model proposed by us.

References

1. Consensus TI. Management of peripheral arterial disease: epidemiology, natural history, risk factors. J Vasc Surg, 2000; 31(1 part 2):S5–S34.
2. Nasr MK, McCarthy RJ, Budd JS, Horrocks M. Infragenual bypass graft patency and limb salvage rates in critical limb ischemia: influence of the mode of the presentation. Ann Vasc Surg, 2003; 17:192-197.
3. Collins G, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ, 2009; 339; b2584;doi10.1136
4. Mironiu IA (sub red). Ischemia cronică aterosclerotică a membrelor inferioare. Protocolle de evaluare. Casa Cărţii de Știință, Cluj Napoca, 2010; 34-37.
5. Rutherford RB, et al. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg, 1986; 4:80-94.
6. Rutherford RB, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg, 1997; 26:517-538.
7. Schanzer A. Impact of comorbidities on Decision-Making in Chronic Critical Limb Ischemia. Semin Vasc Surg, 2009; 22:209-215.
8. Engelhardt M, Boos J, Bruijnjen H, et al. Critical Limb Ischemia: Initial Treatment and Predictors of Amputation-free Survival. European Journal of Vascular and Endovascular Surgery, 2012; 43:55-61.
9. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Namini H, Seely L. Risk Factors, Medical Therapies and Perioperative Events in Limb Salvage Surgery: Observations from the PREVENT III Multicenter Trial. J Vasc Surg, 2005; 42(3):456-465.
10. Schanzer A, Mega J, Meadows J, Samson RH, Ban DF, Conte SM. Risk Stratification in Critical Limb Ischemia: Derivation and Validation of a Model to Predict Amputation Free Survival Using Multicenter Surgical Outcomes Data. J Vasc Surg, 2008; 48(6):1464-1471.
11. Monreal M, Alvarez L, Vilaseca B, et al. Clinical Outcome in Patients with Peripheral Artery Disease. Results from a Prospective Registry (FRENA). European Journal of Internal Medicine, 2008; 19:192-197.
12. Flu HC, Ploeg AJ, Marang van der Mheen P, et al. Patient and Procedure-Related Risk Factors for Adverse Events After Infragenual Bypass. J Vasc Surg, 2010; 51:622-627.
13. Flu HC, Laardenoye JVHP, Veen EJ, Aquarius AE, Henegouwen DP van Berge, Hamming JF. Morbidity and Mortality Caused by Cardiac Adverse Events after Revascularization for Critical Limb Ischemia. Ann Vasc Surg, 2009; 23:583-597.
14. Owens CD, Ho CJ, Kim S, et al. Refinement of survival prediction in patients undergoing lower extremity bypass surgery: stratification by chronic kidney disease classification. J Vasc Surg, 2007; 45:944-952.
15. Albers M, Romiti M, Braganca Pereira CA, Fonseca RLA, da Silva Junior M. A metaanalysis of Infragenual Arterial reconstruction in patients with end-stage renal disease. Eur J Vasc Endovasc Surg, 2001; 22:294-300.
16. Kalra M, Gloviczki P, Bower TC, et al. Limb salvage after successful pedal bypass grafting is associated with with improved long term survival. J Vasc Surg, 2001; 33:6-16.
17. Taylor LM, Hamre D, Dalman RL, Porter JM. Limb salvage vs amputation for critical ischemia. The role of vascular surgery. Arch Surg, 1991; 126:1251S8.
18. Albers M, Romiti M, Braganca Pereira CA, Fonseca RLA, da Silva Júnior M. A meta-analysis of Infragenual Arterial reconstruction in patients with endstage renal disease. Eur J Vasc Endovasc Surg, 2001; 22:294e300
19. Engelhardt M, Bruijnjen H, Schal J, Wölfle KD. Risk factors for survival in patients with end-stage renal disease undergoing infragenual bypass surgery. VASA, 2005; 34:250-254.
20. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med, 1992; 326:131-138.
21. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis, 1991; 87:119-128.
22. Howell MA, Colgan MP, Seeger RW, Ramsey DE, Summer DS. Relationship of severity of lower limb peripheral vascular disease to mortality and morbidity: a six-year follow-up study. J Vasc Surg, 1989; 9:691-696, discussion 6-7.
23. Taylor SM, Kalbaugh AC, Blackhurst DW, et al. Preoperative clinical factors predict postoperative functional outcomes after
major lower limb amputation: An analysis of 553 consecutive patients. J Vasc Surg, 2005; 42:227-235.
24. Boyne MS, Saudek CD. Effect of insulin therapy on macrovascular risk factors in type 2 diabetes. Diabetes Care, 1999; 22(Suppl 3):C45-C53.
25. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Arch Intern Med, 1999; 157:181-188.
26. Fontbonne A, Charles MA, Thibult N, et al. Hyperinsulinemia as a predictor of coronary artery disease mortality in a healthy population. Diabetologia, 1991; 34:356-361.
27. Liu QZ, Knowler WC, Nelson RG, et al. Insulin treatment, endogenous insulin concentration, and ECG abnormalities in diabetic Pima Indians. Cross-sectional and prospective analyses. Diabetes, 1992; 41:1141-1150.
28. Dosluglu HH, Lall P, Nader DN, Harris LM, Dryjski ML. Insulin use is associated with poor limb salvage and survival in diabetic patients with chronic limb ischemia. J Vasc Surg, 2010; 51:1178-1189.
29. Yip VSK, Teo NB, Johnstone R, et al. An analysis of risk factors associated with failure of below knee amputation. World J Surg, 2006; 30:1081-1087.
30. Taylor SM, Kalbaugh AC, Blackhurst DW, et al. Determinants of functional outcome after revascularization for critical limb ischemia: An analysis of 1,000 consecutive vascular interventions. J Vasc Surg, 2006; 44:747-756.