THE PATTERN OF RISK FACTORS IN PATIENTS WITH CRITICAL LIMB ISCHEMIA

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Abstract: *Our study aimed to identify the pattern of the risk factors in patients with critical link ischemia in a North-West Romanian population. A four-year-retrospective matched case-control study was conducted on subjects hospitalized at Second Surgical Clinic, Emergency County Hospital Cluj-Napoca. The medical charts of patients with critical limb ischemia (CLI) or varicose veins (VAR) as control patients were assessed. Six hundred and seventy-four patients were confirmed eligible and analyzed. The majority of subjects were males (M:F=227:110, P<0.0001). A significantly higher percentage of subjects in the CLI group were overweight, compared to the VAR group (P<0.0001), while a significantly higher percentage of subjects in the VAR group had normal weight (P<0.0001) or were obese (P=0.0218). As expected, a significantly higher percentage of subjects were smokers in the CLI group (P<0.0001). The multivariate analysis shows that type 2 diabetes mellitus (OR=7.4, 95%CI (4.2−13.0)), arterial blood hypertension (OR=2.5, 95%CI (1.6−4.0)), ischemic heart disease (OR=3.1, 95%CI (1.7−5.4)), smoking (OR=11.6, 95%CI (7.3−18.4)) and atherosclerosis (OR=9.3, 95%CI (1.2−72.4)) are significant risk factors for CLI. The patient with critical limb ischemia is an overweight smoker with type 2 diabetes mellitus, hypertriglyceridemia, arterial blood hypertension, ischemic heart disease and atherosclerosis.*

INTRODUCTION

Critical limb ischemia (CLI) is the last stage of peripheral arterial disease and a severe condition with a growing economic impact (1) on the medical care units, due to long-term hospitalization, recurrence of symptoms, advanced stage at the time of diagnosis and other comorbidities frequently encountered in these patients.(1) A consensus about the best assessment strategy of the CLI patients was published in 2007 (2) with the identification of the risk factor (such as race, gender, age, smoking, diabetes mellitus, hypertension, and dyslipidemia). However, the latest studies are focusing on the prophylactic approach to this pathology.(3)

Varicose veins affect approximately one-quarter of the adult population. These patients can serve as a control group in the assessment of CLI, owing to the different physiopathology of the two disorders.

About 50% of the patients are symptomatic, and orthostatic pain and engorged veins mark the earliest signs. Some persons may develop edema, fatigue, tension in legs, but the motor functions and the pulse are intact. The main symptoms of chronic venous insufficiency are cramps, woody, brawny, brown pigmentation of the legs' skin and ulcers (distal calf, irregular, pink, sizeable yellow drainage).(4) As a parallel, CLI patients have pain (worse at night or constant pain during the day), pallor, paraesthesia, modified pulse (diminished or absent), muscle rigidity (paralysis), hair loss over calf, ankle and foot, numbness, dry skin, claudication, ulcers (distal, concentric, pale) and, in the worse stages, gangrene which causes limb loss.(2,3)

PURPOSE

A matched case-control study of 337 patients with CLI (cases, CLI group) and 337 patients with hydrostatic varicose veins of the lower limbs (controls, VAR group) was conducted, aiming to assess the most critical risk factors, including comorbidities on a North-West Romanian population.

MATERIALS AND METHODS

A retrospective matched case-control study was conducted between January 2010 and December 2014 on subjects hospitalized for Critical Lower Limb Ischemia (CLI) at the Second Surgical Clinic, Emergency County Hospital Cluj-Napoca. 3 million citizens from the North-West of Romania are served with medical care at this University Clinic.

Selection of Participants

Subjects were matched by sex (for each female with critical limb ischemia a corresponding woman was included in the varicose vein group, the same being applied for male patients).

Subjects hospitalized for Critical Limb Ischemia (CLI group) or Varicose Veins (VAR group) as the primary diagnosis were included in the study. The CLI group comprised patients with peripheral artery disease grade II category 4 – ischemic rest pain (according to the Rutherford classification) while the VAR group included patients with varicose veins of the inferior limb. Subjects with incomplete charts or missing data, those with acute ischemia, peripheral vascular disorders of inflammatory or immune origin, venous ulcers, and neuropathic ulcers or Buerger's disease were excluded from the sample.

The patients' medical charts were reviewed and the following data were collected: demographics (such as gender, age, environment, smoking status and educational status) and co-morbidities (such as type 2 diabetes, arterial hypertension, ischemic heart disease, and heart rhythm disorders), and whenever available laboratory results (cholesterol, glucose and

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triglyceride levels).

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca (no. 475/22.10.2015).

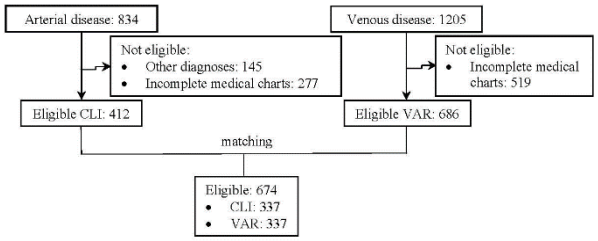
Statistical analysis

Data were described according to their type and distribution. Absolute or relative frequencies (and associated 95% confidence intervals calculated using an exact method (5)) were used to report categorical data. Metric data that proved not to follow the normal distribution were reported as medians and interquartile ranges (as (Q1−Q3), where Q1 = 25th percentile and Q3 = 75th percentile). Comparisons between groups were made with Z-test for proportions, while the association in contingency tables were tested with McNemar test. Comparisons between groups were made with Wilcoxon matched pairs test whenever metric data were compared. The conditional maximum likelihood method (6) was used to estimate the Odds Ratio (OR) in uni- and multivariate analysis. Statistical analysis was done with Statistica software (Stat. Soft, USA; v. 8.0) at a significance level of 5%.

RESULTS

Eight hundred and thirty four patients with arterial disease and 1205 patients with venous disorders were treated in our clinic during the investigated period, and 337 were included in each group (see figure no. 1). From 834 patients with arterial disease, 689 patients had critical limb ischemia and were eligible for the study, 119 had peripheral arterial disease stage 1 and 2 by the Rutherford classification, 20 had acute limb ischemia, and 6 had Buerger's disease (other diagnoses in figure no. 1).

Figure no. 1. Schematic view of the process of patient selection and matching (CLI = critical limb ischemia, VAS = varicose veins)



The matching of cases and controls was done by gender, in a 1 to 1 ratio. In the CLI group, most of the patients were men, and in the VAR group, most of the patients were women. The matching design leads to the inclusion of just a half of the eligible CLI patients.

As expected, a significantly higher percentage of patients were males (M:F = 227:110, P<0.0001). The age of subjects included in the study varied from 31 to 92 years old with significant differences between groups (table no. 1).

Table no. 1. Demographic and social characteristics by groups

Characteristic	CLI (n=337)	VAR (n=337)	Statistic (P-Value)
Age (years)[a]	68 (60−75)	63 (55−71)	4.9 (<0.0001)
Area, Urban[b]	49 (48−59)	54 (43−54)	1.5 (0.2162)
Education[b]			0.4 (0.5322)
Higher	39 (36−47)	42 (34−45)	
Secondary	61 (53−64)	59 (56−66)	
Class of body mass index (BMI)[b]			130.9 (<0.0001)
Underweight	3 (1.8−6.0)	0.3 (0.0−1.8)	
Normal	36 (31−41)	73 (68−78)	
Overweight	50 (45−56)	12 (9−16)	
Obese	11 (7.7−14.5)	15 (11−19)	
Smoking, Yes[b]	66 (60−71)	19 (15−24)	120.2 (<0.0001)

a: median (Q1−Q3), where Q1 = 25th percentile, Q3 = 75th percentile; Wilcoxon Matched Pairs Test;
b: % (95%CI), where CI = confidence interval;
McNemar (2×2 contingency) or Chi-Square test (for BMI class)

The VAR group (median=310 (48−687.5), n=304) had a significantly (P<0.0001) longer duration of disease compared with the CLI group (median=12 (4−48), n=331). A significantly higher percentage of investigated subjects had secondary education, compared with higher education, in both groups (P<0.0001). A significant association was identified between classes of body mass index and groups (see Table 1). While a significantly higher percentage of subjects in the CLI group were overweight when compared with the VAR group (P<0.0001), a significant percentage of subjects in VAR group had normal weight (P<0.0001) or were obese (P =0.0218), in comparison to the CLI group. As expected, a significantly higher percentage of subjects were smokers in the CLI group (P<0.0001), while a significantly higher percentage of subjects in control group were non-smokers (P<0.0001). Smoking proved a risk factor for critical limb ischemia - OR (odds-ratio) = 7.5 (95%CI (5.0-11.8)).

The frequency of diabetes mellitus type two was significantly higher in the CLI, compared with the VAR group (see table no. 2). The arterial blood hypertension was significantly more frequent among subjects in the case group compared with those in the control group (P-value<0.0001, table no. 2).

Table no. 2. Frequency of associated co-morbidities and differences between groups

Variable (n)	CLI (n=337) % (95%CI)	VAR (n=337) % (95%CI)	McNemar (P-Value)
Type 2 diabetes mellitus, Yes	40 (34−45)	7 (5−10)	86.4 (<0.0001)
Arterial blood hypertension, Yes	79 (75−83)	37 (32−43)	20.1 (<0.0001)
Ischemic heart disease, Yes	49 (44−54)	11 (8−15)	101 (<0.0001)
Heart rhythm disturbances, Yes	19 (15−23)	3 (2−6)	38.6 (<0.0001)
Atherosclerosis, Yes	9 (6−12)	0.3 (0.0−1.8)	25.0 (<0.0001)
Positive familial history, Yes	12 (9−16)	12 (9−17)	0.1 (0.7218)
Total cholesterol >200 mg/dL	58 (51−64)	54 (43−64)	0.6 (0.4497)
Triglycerides >150 mg/dL	53 (46−59)	30 (22−40)	9.8 (0.0018)
Blood glucose level >100 mg/dL	59 (53−6.5)	36 (30−42)	28.8 (<0.0001)

95%CI = 95% confidence interval

Risk quantification analysis identified that diabetes mellitus type 2, ischemic heart disease, heart rhythm disturbances, triglycerides higher than 150 mg/dL and blood glucose level higher than 100 mg/dL were significant risk factors for CLI (table no. 3).

Table no. 3. Results on univariate unadjusted analysis

Risk factor	OR (95%CI)
Diabetes Mellitus type 2	8.3 (5.0−14.7)
Arterial blood hypertension	0.5 (0.3−0.7)
Ischemic heart disease	8.2 (5.1−13.7)
Heart rhythm disturbances	6.8 (3.5−14.5)
Positive Familial History	0.9 (0.67−1.5)
Total cholesterol>200 mg/dL (62)	1.3 (0.6−2.9)
Triglycerides >150 mg/dL (35)	3.1 (1.5−7.0)
Blood glucose level >100 mg/dL (93)	2.8 (1.9−4.2)

OR = odds ratio; 95%CI = 95% confidence interval

Multivariate regression analysis identified the following as significant risk factors for CLI: type 2 diabetes mellitus, high blood pressure, ischemic heart disease, smoking and atherosclerosis (table no. 4).

Table no. 4. Multivariate regression analysis: results

Variable	Coefficient	SE	p-value	OR (95%CI)
Age	0.0	0.0	0.0030	1.0 (1.0−1.1)
Type 2 diabetes mellitus	2.0	0.3	<0.0001	7.4 (4.2−13.0)
Arterial blood hypertension	0.9	0.2	0.0002	2.5 (1.6−4.0)
Ischemic heart disease	1.1	0.3	0.0001	3.1 (1.7−5.4)
Cardiac rhythm disturbance	0.8	0.4	0.0627	2.2 (1.0−4.9)
Smoking	2.4	0.2	<0.0001	11.6 (7.3−18.4)
Atherosclerosis	2.2	1.1	0.0325	9.3 (1.2−72.4)
Constant	-4.5	0.7	<0.0001	

OR = odds ratio; 95%CI = 95% confidence interval

As expected, complications were more frequent among CLI patients: haemorrhage (2 cases with CLI, 1 case with VAR), myocardial infarction (2 CLI subjects), 9 CLI subjects had bypass thrombosis (2.7% (1.2-5.0)), 22 CLI cases had sepsis (6.5% (4.2-9.8)), and 32 CLI subjects required repetitive surgical interventions (9.5% (6.5-13.3)).

DISCUSSIONS

The pattern of risk factors for CLI was successfully assessed. A greater preponderance of men over women (P<0.0001) was, as expected, observed.(7) The age of the subjects varied in the range from 31 to 92, a significant difference appearing between the two groups (table no. 1), which can be explained by the fact that CLI subjects are mainly older patients (8), in opposition to VAR patients, who are younger.(9) The time frame from the disease onset, until the first medical appointment, has been assessed and a more extended period in VAR patients in comparison with CLI subjects was reported (P<0.0001). This demonstrates that the arterial disease evolves more rapidly (10) than the venous disease (11) and also affects the patients' quality of life at an earlier stage, making them seek medical care a lot sooner.

When analyzing the two groups from the educational level point of view, a higher percentage of patients with medium education level was observed in both groups (see table no. 1). Our result is in agreement with that described in a previous study by Joseph et al., in which 59.4% of the subjects were unqualified workers.(9)

A statistically significant difference was seen between the two groups regarding BMI (table no. 1). If in the CLI group, more than half of the patients were overweight (50.15%), in the VAR group most of them had normal weight (73%) or were obese (14.54%). A similar percentage of overweight patients in the ischemic pathology of lower limbs has been detailed in the study realized by Chen et al..(12) They also demonstrated that overweight suppresses angiogenesis.

Smoking is incriminated as a significant risk factor for critical limb ischemia (OR (odds-ratio) = 7.54 (95%CI (5.00-11.78)). In antithesis, the VAR group consists mostly of non-smoking subjects (table no. 1). Many studies confirm this finding, and in fact Davies et al. demonstrated that giving up on smoking improves the quality of lives of ischemic patients and also induces a better response to treatment.(13)

Comparing CLI with VAR patients, a higher frequency of diabetes mellitus type 2 was observed in the case group (39%), than in the control group (7%, table no. 2). Patients with ischemic arterial disease and diabetes mellitus as co-morbidities have a lower rate of response to treatment and are prone to disease progression towards critical limb ischemia.(14) The pathogenic mechanism is not entirely known, but later theories suggest that oxidative stress and mitochondrial malfunction may play an essential role in this process.(14) Regarding varicose veins disease, no direct relationship with diabetes mellitus has been demonstrated, which is in agreement with the results of our study, in which very few patients with diabetes belonged to the VAR group.(15)

Arterial hypertension was present in 79.23% of CLI subjects, while it was associated with 37.4% of VAR patients (P<0.0001, table no. 2). Chace et al. proved in their study that patients with the peripheral arterial disease, including CLI, presented themselves with a high number of cardiovascular disorders, including arterial hypertension, ischemic heart disease and heart rhythm disturbances, which was not the case in the control group.(16) Our study provided statistically significant results, comparing the cases with the controls (table no. 2) with respect to arterial hypertension (CLI:VAR 79.2%:37.4%), ischemic heart disease (CLI:VAR 49%:11%) and heart rhythm disturbances (CLI:VAR 19%:3%). Moreover, atherosclerosis affected more patients in the case group than in control one (CLI:VAR 9%:0%, Table 2). This difference can be explained by the fact that the central event in the pathogenesis of critical limb ischemia is the formation of atheromatous plaques in the walls of peripheral arteries, in contrast with varicose veins.(17,18)

High blood triglyceride level (>150 mg/dL) was noticed, with a higher predominance in the case group (52.5%), compared with the control group (35.6%), with a statistical significance of P<0.0018. Similarly, high glycemia levels (>100 mg/dL) were seen in the CLI (59%) compared with VAS group (35.56%). In the scientific literature (19), dyslipidemia is recognized as a major risk factor for CLI, and the evidence of our study sustains this relationship. Jensen et al. demonstrated the link between the prevalence of CLI and high blood glucose levels, in agreement with our results.(20) The relationship between varicose veins and dyslipidemia was also investigated, but with no edifying results. Ashrani et al. designed a study in which they analyzed the antilipidic therapy in venous thromboembolism, leading to the conclusion that lipid-lowering therapy is associated with decreased risk for venous thromboembolism, after adjusting for known risk factors.(21) The results of studies analyzing how high blood glucose levels interfere with varicose veins pathogenesis were inconclusive.

In our study, type 2 diabetes mellitus, ischemic heart disease, arrhythmias, hypertriglyceridemia (levels above 150 mg/dL) and hyperglycemia (levels above 100 mg/dL) were identified as significant risk factors for CLI by both uni- and multivariate analysis (tables no. 3 and 4). Similar results were found in numerous other scientific studies.(22,23)

Both groups presented post-operatory complications, but a higher percentage was noticed in the CLI group. For CLI patients, revascularization remains the first therapeutic intention, although depending on the stage and speed of disease progression, it may finally prove unsuccessful and other therapeutic measures, such as amputation, must be taken into consideration.(24)

This study was rigorously designed to overcome possible errors. It had several limitations nonetheless. Because it is a retrospective study, data was collected from the medical charts, which may be influenced by the subjectivity of different physicians, while missing or incomplete data may have unfortunately modified our results. The factors that potentially affect the disease prognosis and the quality of life in these patients may have been insufficiently evaluated in some medical recordings.

CONCLUSIONS

As expected from the study of CLI pathogenic mechanisms, this matched case-control study involved a higher percentage of male subjects. Nonetheless, the level of education seems to play an essential role in the development and evolution of critical limb ischemia, most probably due to higher

addressability and accessibility of medical care and to the impact of associated risk factors.

Both risk quantification analysis and multivariate regression analysis identified smoking, type 2 diabetes mellitus, ischemic heart disease, heart rhythm disturbances, and dyslipidemia as significant risk factors for CLI. Moreover, complications were more frequently observed among CLI group subjects as expected, with direct influence on the length of their hospitalization and disease prognosis.

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