Impact of Nutritional State on Critical Limb Ischemia Early Outcomes (DENUCRITICC Study)

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Background: Despite current progress, the prognosis of critical limb ischemia (CLI) remains poor. The ageing of the population, the increasing prevalence of diabetes mellitus, and the stability of tobacco use will increase the prevalence of CLI. CLI patients have risk factors for malnutrition, and the impact of malnutrition on morbidity and mortality has been demonstrated in the general population. However, we have little information on the consequences of undernutrition in the CLI population. The aim of this study is to assess the impact of malnutrition on the early outcomes in CLI patients.

Methods: This is a double-center prospective study that included all consecutive hospitalized patients with CLI. All patients were screened for malnutrition and divided into 2 groups: severe malnourished patients (group A) and moderate malnourished and well-nourished (group B). This distribution was based on age-indexed clinical and biological data and the patient's general condition: the Nutritional Risk Index for patients younger than 75 years, the Mini Nutritional Assessment, or the Geriatric Nutritional Risk Index for those older than 75 years. The primary end point was defined as the rate of 30-day death. Outcomes were compared in a univariate analysis. Stepwise logistic regression was used for the multivariate analysis. Variables with a P value <0.2 in the univariate analysis were introduced in the multivariate model.

Results: We included 106 patients. The prevalence of malnutrition was 75.5%, divided into moderate malnutrition (51.9%) and severe malnutrition (23.6%). Six patients (24%) died in group A compared with 8 in group B (4.9%) ($P = 0.01$). By univariate analysis, severe malnutrition was the only factor associated with death at 30 days. By stepwise logistic regression, severe malnutrition (odds ratio 6.1, 95% confidence interval 1.6–23.7, $P = 0.006$) was found to be the significant risk factors for death at 30 days.

Conclusions: This study is the first to demonstrate prospectively the major importance of malnutrition in the early prognosis of CLI patients.

INTRODUCTION

Nowadays, endovascular therapies allow more and more procedural approaches to treat increasingly fragile populations, but the overall prognosis of critical limb ischemia (CLI) remains the same, with mortality similar to that of cancer.[1] With ageing population, increase in diabetes mellitus, and stable levels of tobacco use, the incidence of CLI is likely to increase dramatically,[2,3] and will force physicians to improve their current results in this field.

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Patients with CLI present several risk factors for malnutrition, such as old age, use of analgesics, renal insufficiency, and respiratory or heart failure.[4] It has been established that malnutrition is an independent risk factor for complications, increased length of hospital stay and mortality.[5] In surgery in particular, the role of malnutrition is significant in terms of wound healing, postoperative infections, morbidity, and mortality.[5–7] Malnutrition has been estimated to range from 20% to 50% in a general population of hospitalized patients.[8,9]

However, malnutrition in the context of CLI begins to be now investigated in the literature.[10] Vega de Céniga et al.[11] found a deficit in iron and vitamins in this population in a retrospective study, while another study[12] estimated the prevalence of malnutrition in CLI patients to be above 60%. The methods of evaluation of nutritional status are very different from one study to another, and include anthropomorphic tools, biological parameters, or nutritional indices. Published guidelines now recommend systematic screening in hospitalized populations using specific tools, such as the Mini Nutritional Assessment (MNA) and Nutritional Risk Index (NRI), but they are rarely applied in CLI populations.[13] Thus, more widespread systematic screening using these instruments in the CLI population could be of interest, to assess the clinical impact of malnutrition in these patients.

The aim of this study is to assess the impact of malnutrition, as assessed by MNA, NRI and Geriatric (G)-NRI tests, on mortality at 30 days in CLI patients. Secondary objectives were to assess risk factors for malnutrition, prevalence of malnutrition and its impact on mortality and/or major amputation, on major amputation at 30 days, and on the length of hospital stay.

MATERIALS AND METHODS

The DENUCRITICC study is a 2-center, prospective, observational study. Between February 2011 and April 2012, we included all consecutive patients hospitalized for CLI in the Vascular Surgery Unit of the University Hospital of Besancon (France), and between May and October 2012, in the Vascular Surgery Unit of the University Hospital of Dijon (France). Inclusion criteria were CLI diagnosed in accordance with current consensual definitions.[1] CLI was defined as ischemic rest pain, ulcer, or gangrene with objective evidence of ischemia according to the Trans-Atlantic Inter-Society Consensus II definition,[1] and was recorded. Nutritional status was evaluated during the 2 first days of hospitalization. Only patients hospitalized for the first time for CLI were included. All patients received information about the study, but the need for informed consent was waived. The study protocol was approved by the local ethics committee.

Demographic and clinical characteristics were prospectively recorded, namely age, sex, symptoms,[14] presence of diabetes mellitus, hypertension, hyperlipidemia, and smoking status. Additional characteristics were history of revascularization, cerebrovascular disease, coronary artery disease, heart failure, arrhythmia, respiratory failure, and end-stage renal disease with hemodialysis. Serum albumin was recorded for all patients. Cerebrovascular disease was defined as documented stroke or transient ischemic attack. Coronary artery disease was defined as documented diagnostic intervention for angina or myocardial infarction.

Initial treatment was classified as surgical arterial reconstruction, endovascular treatment, hybrid revascularization (surgical arterial reconstruction combined with endovascular treatment), major amputation (above the ankle), minor amputation, or medical treatment with prostanoids and/or antibiotic therapy.

We recorded the preoperative risk factors of malnutrition for each patient.[4] Risk factors related to the patient such as age >70 years, cancer and hematologic malignancy, chronic disease digestive, organ failure (respiratory, cardiac, renal, intestinal, pancreatic, liver), neuromuscular disease and multiple disabilities, and diabetes mellitus were collected. Sepsis, inflammatory syndrome, HIV, major gastrointestinal surgery (short bowel syndrome, pancreatectomy, gastrectomy, bariatric surgery), depressive syndrome, cognitive disorders, and dementia were picked up. Risk factors related to treatment were informed: referred to oncological treatment (chemotherapy, radiotherapy), corticosteroid therapy more than 1 month and more than 5 oral treatment.

Nutritional status of the patients was assessed by the NRI for patients under 75 years[15] or by the MNA for patients older than 75 years.[16] The GNRI was used for patients older than 75 years who were unable to answer the questions of the MNA.[17] The NRI score was used to determine nutritional status according to the following formula: NRI = [1.519 × serum albumin (g/L)] + [41.7 × [present weight/usual weight]]. The GNRI score was calculated as follows: [1.489 × serum albumin (g/L)] + [41.7 × [present weight/ideal weight]].

Patients were divided into 3 groups: well-nourished (NRI > 97.5 or MNA > 23.5 or GNRI > 98), moderate malnutrition (defined as MNA between

Table I. Comparison of characteristics of group A (severe malnourished patients) and group B (moderately malnourished and well-nourished patients)

Characteristic	Overall (n = 106), n (%)	Group A (n = 25), n (%)	Group B (n = 81), n (%)	P value
Age >75 years	73 (68.9)	16 (64.0)	57 (70.4)	0.55
Male sex	71 (67.0)	15 (60.0)	56 (69.1)	0.39
Hypertension	84 (79.2)	20 (80.0)	64 (79.0)	0.89
Hyperlipidemia	55 (51.9)	13 (52.0)	42 (51.8)	0.73
Current smokers	24 (22.6)	4 (16.0)	20 (24.7)	0.36
Diabetes mellitus	45 (42.4)	7 (28.0)	38 (46.9)	0.09
BMI	25.0 (5.2)	22.5 (5.1)	25.8 (5.3)	0.01
Prior revascularization	51 (48.1)	11 (44.0)	40 (49.4)	0.60
Rutherford class 6	16 (15.1)	5 (20.0)	11 (13.6)	0.52
Primary major amputation	4 (3.8)	2 (9.5)	2 (2.5)	0.23
Medical treatment alone	10 (9.4)	1 (4)	9 (11.1)	0.44
Stroke	11 (10.4)	3 (12.0)	8 (9.9)	0.72
Coronary artery disease	34 (32.1)	7 (28.0)	27 (33.3)	0.59
Heart failure	27 (25.5)	4 (16.0)	23 (28.4)	0.21
Arrhythmia	35 (33.0)	10 (40.0)	25 (30.9)	0.44
Respiratory failure	33 (31.1)	10 (40.0)	23 (40.0)	0.27
Dialysis	9 (8.5)	2 (8.0)	7 (8.6)	1.0
Albuminemia[a]	31.6 (5.7)	26.5 ± 5.2	33.1 ± 4.9	$<10^{-3}$

[a]Presented as mean (standard deviation).

17 and 23.5, or NRI between 83.5 and 97.5, or GNRI between 82 and 98), and severely malnourished patients (NRI < 83.5, MNA < 17, and GNRI <82).

The primary end point was defined as the rate of 30-day death. Secondary end points were combined end points defined as the rate of 30-day death and/or 30-day major amputation, the 30-day major amputation (above the ankle), the duration of hospital stay, and the number of risk factors for pre- and postoperative malnutrition.

Statistical Analysis

Quantitative variables were expressed as means and standard deviations when normally distributed. Qualitative variables were expressed as number (percentage). The Student *t*-test and chi-squared or Fisher's exact tests were used to compare the characteristics between the 2 groups as appropriate. We calculated the prevalence of malnutrition in our population. Patients were categorized into 2 groups according to nutritional status, and we compared severely malnourished patients (group A) with moderately malnourished and well-nourished patients (group B). Outcomes were compared in a univariate analysis. To identify factors significantly associated with the primary outcome at 30 days, stepwise logistic regression was used for the multivariate analysis. Variables with a P value <0.2 by univariate analysis were included in the multivariate model. In all cases, severe malnutrition and age were included. The significance threshold was set at 0.05. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

In total, 106 patients were included. The mean age was 77.3 ± 12.1 years. The majority were men (67%). Overall characteristics were presented in Table I. Initial presentation was ischemic rest pain in 15 patients (14.1%) and a majority of ischemic ulcers: 75 (70.8%) patients Rutherford 5 and 16 (15.1%) Rutherford 6. Initial treatment was presented in Table II.

Overall, 80 of 106 (75.5%) patients had malnutrition: with moderate malnutrition in 55 patients (51.9%) and severe malnutrition in 25 patients (23.6%). The majority of patients (79.2%) had 2 or more risk factors of malnutrition. Only 4 patients (3.8%) had no risk factor for malnutrition (Fig. 1).

We compared severely malnourished patients (group A, n = 25) with moderately malnourished and well-nourished patients (group B, n = 81). The comparison of demographics, risk factors, and comorbidities and treatment between groups is presented in Table I. Initial treatment was presented in Table II.

Six patients (24%) died in group A compared with 8 in group B (4.9%) (P = 0.01). Four patients were amputated in each group (group A 16%, group B 4.9%, P = 0.08). The combined death/major

Table II. Initial treatment

Initial treatment	Overall (n = 106), n (%)	Group A (n = 81), n (%)	Group B (n = 25), n (%)
Surgical treatment	36 (34.0)	24 (29.6)	12 (48.0)
Endovascular treatment	33 (31.1)	29 (35.8)	4 (16.0)
Hybrid treatment	15 (14.1)	13 (16.0)	2 (8.0)
Primary amputation	4 (3.8)	2 (2.5)	2 (8.0)
Medical treatment	18 (17.0)	13 (16.1)	5 (20.0)

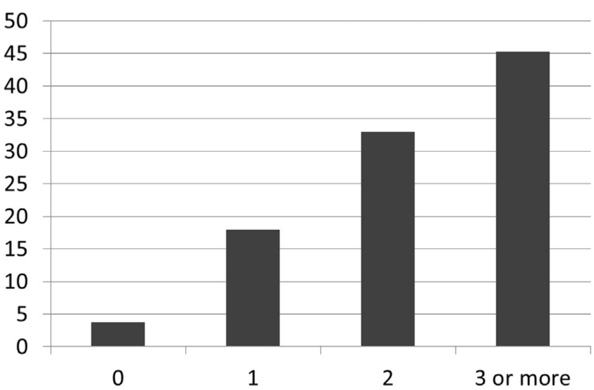

Fig. 1. Risk factors of malnutrition in the studied population. *Vertical*: percentage of the population.

amputation rate at 30 days was 16.0%. The rate of the combined end point at 30 days was higher in group A than in group B (36.0% vs. 9.9%, $P = 0.004$). We investigated the risk factors of death by univariate and multivariate analysis (Table III). By univariate analysis, severe malnutrition was the only factor associated with death at 30 days. By stepwise logistic regression, only severe malnutrition (odds ratio 6.1, 95% confidence interval 1.6–23.7, $P = 0.006$) was found to be the significant risk factor for death at 30 days.

The mean hospital stay was 19.9 days (±15.1) in group A versus 14.5 (±12.7) ($P = 0.08$).

DISCUSSION

This work represents a prospective study assessing the impact of malnutrition, defined by current nutritional recommendations, on the risk of death in a population hospitalized for CLI. Malnutrition has been associated with higher morbidity, mortality, and hospital length of stay in surgical patients.[18] Considering the numerous predictive factors of malnutrition observed in the CLI population, we expected a high prevalence, but not as high as that observed, of 75.5% for malnutrition and 23.6% for severe malnutrition. The impact of this malnutrition was significant, because severe malnutrition was found to be an independent risk factor for death at 30 days by multivariate analysis and a risk factor for death and/or major amputation at 30 days by univariate analysis.

Depending on the definition used, the prevalence of hospital malnutrition reported in the literature is usually within a much lower range, namely between 20% and 50%. The discrepancy with our results could be explained by the characteristics of CLI patients, some of which are well-known risk factors for malnutrition. Theoretically, CLI necessarily induces malnutrition, because patients are elderly, with more associated comorbidities than other populations; they suffer from chronic pain and require high levels of analgesic consumption. All these characteristics are known to represent risk factors for malnutrition.[4] In our population, many of these factors were strongly represented: over 65% of our patients were aged over 75 years and 42.4% had diabetes with associated comorbidities (heart failure, respiratory failure, and dialysis). Furthermore, although we did not objectively assess pain in our study, the majority of our patients suffered pain causing insomnia. The majority had inflammatory syndrome due to infected tissue loss, and polymedication was also common. The distribution of risk factors for malnutrition in our population was noteworthy: <3% of our population did not have any risk factors, and almost 45% had 3 or more risk factors for malnutrition. These findings suggest that CLI is strongly associated with malnutrition.

Another possible explanation for the difference between our results and those of the literature is the heterogeneity in the methods of assessing nutrition. Several studies have been published about nutritional status in patients with peripheral artery disease, using various parameters. As early as 1997, Eneroth et al.[19] reported that nearly 90% of patients with transtibial amputation for vascular reasons were malnourished, based on clinical (arm muscle circumference, triceps skin fold thickness) and biological parameters (serum albumin and prealbumin, total lymphocyte count) of nutrition. Spark et al.[20] did not observe any difference in serum albumin

Table III. Risk factors for death at 30 days by univariate and multivariate analysis

Risk factor	Univariate *P*	OR	Multivariate 95% CI	*P* value
Age >75 years	0.73			0.37
Male	0.83			
Hypertension	0.93			
Hyperlipidemia	0.18			0.20
Current smoking	1.0			
Diabetes mellitus	0.52			
Rutherford 6	0.17			
Stroke	0.68			
Coronary artery disease	0.39			
Heart failure	0.71			
Arrhythmia	0.20			
Respiratory failure	0.49			
Dialysis	0.59			
Severe malnutrition	0.01	6.1	1.6−23.7	0.006
Albuminemia	0.21			
BMI	0.43			

CI, confidence interval; OR, odds ratio.

concentration or body mass index (BMI) between CLI patients and controls, but showed a significant reduction in other markers (maximum voluntary contractions, lean body mass) in vascular patients. Hassen et al.[21] assessed nutrition with MNA and X-ray absorptiometry, and demonstrated that fat-free mass and skeletal muscle mass were negatively associated with systemic inflammatory response syndrome following major vascular surgery. In a prospective cohort study, Owens et al.[22] showed that, in addition to renal impairment and inflammatory state, serum albumin <3.5 mg/dL is an excellent predictor of all-cause mortality. In a study purporting that BMI is not a good indicator of survival, Murata et al.[23] demonstrated that serum albumin <3.0 mg/dL was associated with poorer survival; in our population, albuminemia was not associated with death at 30 days. Overall, a meta-analysis showed that only serum albumin and weight were able to predict postoperative outcomes in elderly patients.[24] In our study, we did not analyze serum albumin separately because it is a component of the NRI and GNRI, which were already tested.

With the use of MNA and NRI in our work, we are in line with current recommendations for nutritional assessment.[13,15] MNA is known to be a very sensitive test and easy to use, while the GNRI is a more predictive tool for outcomes in the geriatric population.[17,25,26] Our experience demonstrates that both instruments are useful in the CLI population for the screening of malnourished patients. Moreover, we showed that, by multivariate analysis, nutritional status is an independent risk factor for death and/or major amputation. These results emphasize the need to improve overall management of our patients. A recent study published similar results in diabetic foot ulcers, and thus confirms our experience.[27] In a retrospective study, Shiraki et al.[28] showed that the GNRI on admission was independently associated with mortality and major amputation after endovascular therapy in patients with CLI. Renal impairment and inflammatory status have also been shown to be risk factors for mortality in peripheral arterial disease populations.[22] However, the nutritional status is probably easier to improve in real-life care, ranging from specific home nutrition programs to parenteral nutrition in hospital. In France, current recommendations[4] for malnourished patients are to have oral complement 10 days before surgery; the possibility to apply depends on the severity of CLI. The decision to wait for surgery must be decided case-by-case.

The major limitation of this study is that we did not take into account the precise vascular status (level of revascularization, ankle or toe brachial index), which is clearly significant in terms of limb salvage and survival. However, we wanted to get an overview of the nutritional status and its impact, and then demonstrate that nutritional tests are mandatory in a CLI population, whatever the limb treatment proposed.

CONCLUSION

This study prospectively demonstrates the major impact of malnutrition on early outcomes after hospitalization for CLI. Likewise, it emphasizes that the prevalence of malnutrition in this patient population is clearly underestimated. These results should prompt more effective treatment for CLI and contribute to improving prognosis. Malnutrition should be treated with validated therapeutic strategies, in parallel with the CLI treatment.

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