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Critical Limb Ischemia in Nonagenarians: A Challenge of our Times

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The study was conducted with the approval of the Institutional Human Research Ethics Committee (CEIC/PSMAR).

ABSTRACT

Background

As a result of the increasing life expectancy of the western population, the number of elderly patients with chronic limb-threatening ischemia (CLTI) seeking medical care is growing. Our objective was to describe the characteristics of a consecutive series of nonagenarian patients with CLTI and evaluate the outcomes of their management.

Materials and Methods

Retrospective analysis of a consecutive series of nonagenarian patients with CLTI attended at our institution between 2005 and 2019. The primary endpoint was the amputation-free survival (AFS).

Results

A total of 171 patients were included (mean age 92.7, 51.5% women), of which in 59 (34.5%) primary major amputation (n=10) or palliative care (n=49) were indicated due to advanced dementia (n=30, 50.8%), knee retraction (n=17, 28.8%), terminal condition (n=13, 22%) or a non-salvageable foot (n=28, 47.4%). In the remaining 112 (65.5%) the need for a revascularization was further assessed finally performing A)conservative treatment/minor amputation (n=57, 50.9%), B)revascularization (n=50, 44.6%) or C)direct major amputation (n=15, 4.4%). Predictive factors for AFS included a hemoglobin level <10.5mg/dL (HR=2.06, CI=1.13-3.39), non-advanced dementia (HR=2.11, CI=1.12-4.02) and regular mobility with wheelchair (HR=2.67, CI=1.49-4.77). Excluding patients requiring a primary major amputation or palliative care, the 1-year AFS of revascularization vs conservative treatment/minor amputation was 70% vs. 48.7% (p<0.001).

Conclusion

Nearly one-third of nonagenarian patients with CLTI have a direct indication for amputation or palliative care at presentation. In the remaining, revascularization treatment is associated with

better rates of AFS. The absence of anemia, dementia, and wheelchair dependence may help to identify those patients who may benefit most from revascularization.

INTRODUCTION

The average age in Western countries is increasing and has raised 5 years since 2,000 [1]. Age-dependent diseases such as peripheral artery disease (PAD) are thus expected to grow. Despite tobacco consumption decreasing worldwide there has been a mean growth of 23.5% of patients with PAD in several countries in the last two decades [2]. This rise has been attributed to the increase of life expectancy and diabetes mellitus [3]. Chronic limb threatening ischemia (CLTI), the most severe form of PAD, represents approximately 11% of newly diagnosed PAD patients in Europe [4] and, among them, up to 31.6% are patients over 75 years [5].

Nonagenarians represent currently the 0.9% of the western population and are expected to grow to 1.2% and 4.4% in 2,050 and 2,100, respectively, according to data derived from a report of the United Nations [6]. Nonagenarians with CLTI are also becoming a clinical problem on the rise in vascular departments due to the aging of the population and the increasing prevalence of PAD [7].

Patients with CLTI at these extreme ages frequently share certain characteristics, including advanced frailty, dependency, low life expectancy, cognitive impairment or permanent institutionalization [8]. These features, make the decision-making process more complex. In addition, because a conservative trial has been frequently indicated for some time, some patients may present with extensive ischemic lesions. Unfortunately, their occlusive disease is in no case easier to treat than that seen in their younger counterparts.

In this setting, the decision to revascularize, amputate or keep the nonagenarian patient with CLTI under a conservative (frequently palliative) approach is therefore difficult to make. While it is generally accepted that a successful revascularization is associated with a better quality of life and longer survival when compared with primary major amputation or conservative treatment [9], this approach may be hampered by an advanced dementia, a non-functional or partially retracted limb or an unacceptable surgical risk for medical reasons. The majority of current decisions about these patients are based more in common sense rather

than in evidence. To date very little is known about the full picture of CLTI at these ages and factors related to a poor outcome [10].

The objective of this study was to describe the characteristics of a consecutive series of nonagenarian patients with CLTI and to determine risk factors related to amputation free survival (AFS).

MATERIALS AND METHODS

This is the retrospective analysis of a consecutive series of patients aged 90 years or more with CLTI attended at the Vascular Surgery Department of the Hospital del Mar (Barcelona, Spain) between January 2,005 and December 2,019. This institution has a referral population of 330,000 inhabitants of which 1.2% are 90 years or older [11]. All vascular surgical consultations and procedures from this area of referral are done exclusively by our vascular team. All patients with CLTI attended at the emergency department, during any hospital admission or in the outpatient clinic were included. CLTI was defined as the presence of peripheral artery disease in combination with rest pain, gangrene, or a lower limb ulceration >2 weeks duration. The study was conducted with the approval of the Institutional Human Research Ethics Committee (CEIC/PSMAR).

Baseline characteristics:

Data collected at baseline included demographical data, cardiovascular diseases and risk factors, as well as other comorbidities. Patients were categorized into smokers (current or former) or never smokers. Hypertension, diabetes and dyslipidemia were considered if previously diagnosed by a physician or under treatment. Chronic obstructive pulmonary disease (COPD) was considered if the patient was under drug treatment or had required a hospital admission. History of cardiac disease, cerebrovascular events and cancer were also obtained through the electronic hospital and primary care records.

Specific features of nonagenarians were collected as follows. Dementia was considered if physician-diagnosed and categorized as advanced if required specialized care at home or institutionalization. Knee retraction (defined as the inability to fully extend the knee

joint) or a non-salvageable foot (defined as extensive, deep or bone-affected trophic lesions that impeded the salvage of the foot) were determined by the vascular surgeon at the baseline evaluation. Functional data included living (home, nursing/sheltered home, healthcare center or hospital), ambulatory (walking with or without aid, wheelchair, bedridden) and dependence status for managing one's basic physical needs (independent, partially dependent or fully dependent). Functional information was obtained from medical and nurse records at the baseline evaluation.

All cases had CLTI and were treated according to the following general indications. Whenever possible, patients with a potentially salvageable limb were managed conservatively or with a minor amputation followed by a close supervision of the vascular team. Patients in whom this conservative approach failed, were revascularized according to an endovascular first basis. Secondary minor amputation was considered if necessary. Patients with advanced dementia, chronically bedridden, or those with a knee retraction or a non-salvageable foot were managed with a direct major amputation (if needed) or palliative care.

The primary outcome was the amputation free survival (AFS), which was defined as the composite end-point of major amputation and/or death for any cause.

Statistical analysis:

Categorical variables were expressed as frequencies and percent values. Continuous variables were expressed as mean $\pm$ standard deviation. Cumulative AFS rates were estimated according to the Kaplan-Meier method. Cox bivariate models were used to determine the relationship between variables with AFS. For practical purposes all continuous variables significantly related to AFS were categorized according to the best cutoff value in a ROC curve (best Youden index). Variables related to AFS with $p < 0.1$ on bivariate analyses were included in a Cox multivariate regression model. The discrimination capacity of the resulting multivariate model was assessed by means of the C statistic. Statistical analysis was performed using SPSS 25.0 software (SPSS Inc. Chicago, IL, USA).

RESULTS:

One-hundred eighty nonagenarians with CLTI were consecutively attended at our institution during the period of study. Of these, 9 (5%) patients were excluded because of missing information. Among the remaining 171 patients, 88 (51.5%) were female and the mean age was 92.7 years. The number of patients increased in the second half of the period of study (2,013-2,020) when compared with the time lapse between 2,005 and 2,012 (54 vs 117 cases). A similar ratio (28 vs 54 cases) was observed when only hospitalized patients considered. Hypertension was the most prevalent vascular risk factor (91.8%). Up to 71 (41.5%) patients showed some degree of dementia, of which in 30 (17.5%) it was advanced. Regarding functional characteristics, 97 (56.7%) patients required a wheelchair for mobilization, 72 (42.1%) were totally dependents for managing basic physical needs and up to 44 (25.7%) cases were institutionalized. Baseline characteristics of patients are shown in Table 1.

Patients were managed as follows (see flowchart in Figure 1). A first group of 59 (34.5%) patients were not deemed to have an indication for limb salvage at baseline evaluation because of an advanced dementia (n=30, 50.8%), terminal condition (n=13, 22%), a non-salvageable foot (n=28, 47.4%) or knee retraction (n=17, 28.8%). Among these patients, 10 primary major amputations were done and a conservative palliative treatment was indicated in the remaining cases. The 1-year AFS in this group of patients was 14.7%.

A second group of 112 subjects were considered to have a potentially salvageable limb at baseline and were further evaluated. To avoid an unnecessary major procedure a trial of conservative management or a minor amputation was indicated when clinically possible. This approach did not go further in 57 of these patients (50.9%) of which only one case required a major amputation during follow-up. The remaining 56 patients healed the wounds or at least kept their lesions stable during follow-up, tagged by many short or mid-term deaths (29 cases). The 1-year AFS of this group of patients managed conservatively or with a minor amputation was 48.7%.

The remaining 55 (32.1%) patients had a potentially salvageable limb that could not be managed conservatively or with a minor amputation, or in whom this approach failed during the first hospital admission. They were treated with a major amputation (5 cases, 9%) or a revascularization technique (50 cases, 91%), of which 34 were endovascular and 16 open surgical (68% vs 32%). Characteristics of revascularization procedures are shown in Table 2. The most frequent endovascular technique was the angioplasty with stenting of superficial femoral and/or popliteal arteries (22 cases, 64.7%) and in the surgical group the vein bypass to a below-the-knee artery (7 cases, 43.7%). During follow-up, 2 revascularized patients required a major limb amputation and 33 patients died. The 1-year AFS of revascularized patients was 70% and no differences were found between endovascular and surgical revascularization groups.

Considering the whole group of 112 patients with a potentially salvageable limb at baseline evaluation, regardless they were finally revascularized or not, 8 (7.1%) required a major amputation and 88 (78.6%) died during a mean follow-up of 13.32 months. Variables associated with lower AFS rates in the bivariate analysis included a hemoglobin level <10.5 mg/dl (HR 2.05, $p=0.011$), atrial fibrillation (HR 1.69, $p=0.073$), partial dementia (HR 2.43, $p=0.005$), wheelchair mobility (HR 3.11, $p<0.001$) and dependence for managing one's physical needs (HR 2.11, $p=0.014$). In the multivariate analysis a hemoglobin level <10.5 (HR 2.06, 95% CI 1.13-3.39, $p=0.013$), partial dementia (HR 2.11, 95% CI 1.12-4.02, $p=0.021$) and wheelchair mobility (HR 2.67, 95% CI 1.49-4.77, $p=0.01$) at baseline were independently associated with lower AFS rates (Table 3). The multivariable score resulting from these three variables showed a good discrimination for predicting AFS with a C-statistic of 0.73. One-year AFS rates among patients with 0, 1, 2 and 3 of these risk factors were 80.6%, 51.7%, 23.7% and 0%, respectively.

Irrespective of the treatment group (salvageable limb at baseline evaluation or not) and the time of intervention (at baseline or during follow-up), the survival of nonagenarians with CLTI submitted to a major amputation (18 cases as a whole) at 1 and 12 months after the procedure was 44.4% and 27.8%, respectively.

DISCUSSION:

Over the last decades there has been an increase in the life expectancy of the Western population [1]. This may have led to an increase of nonagenarian patients seeking attention for CLTI, a trend that is consistent with our results. To date, however, few studies have analyzed CLTI at these extreme ages [9, 10, 12, 13]. In addition, most of them have failed to present a full picture of the problem since only revascularized patients were included. To avoid this limitation, we included all consecutive nonagenarians with CLTI attended at our institution over a period of 15 years, including from those arriving at the emergency department to those referred to the outpatient clinic or admitted in the hospital for this or other reason, and from those most palliative cases to those candidates to a revascularization procedure. We think that only under this perspective it is possible to manage clinical decisions dodging both catastrophism and over-optimism.

Our study reveals that one third of patients directly did not have a salvageable limb at the first vascular clinical evaluation, either because the patient condition was very poor or a viable and functional limb could not be restored. Fortunately, these cases are infrequent at younger ages. The best therapeutic approach is usually conservative, often involving palliative regimens. A major amputation can be a solution in selected patients when the surgical indication is only for local (limb) reasons. The mid-term survival prognosis after amputation at these ages, however, is poor [14, 15], as we also observed among our patients.

One additional third of our patients could be managed conservatively or with a minor amputation. Some of these cases did not always heal their lesions during follow-up but at least did not progress enough to require a major amputation. The survival prognosis of these patients is poor, and this is probably the reason why the conservative approach was successful. With similar results, Thomas et al [16] reported that the conservative management was associated with acceptable limb salvage (84%) and wound healing rates (58%), although the mortality was high (42% at 12 months)(58). However, Klaphake et al [17] did not found differences in mortality rates between conservative and non-conservative approaches and recommended the first as the treatment of choice in elder comorbid patients. The conservative

management appears thus to be a reasonable option in the less functional and independent nonagenarians but who, otherwise, are not candidates for a palliative treatment.

Finally, one third of our patients were submitted to a revascularization procedure. They were without doubt the most functional and independent patients. The 1-year AFS in these cases was high thus reflecting that there is a subset of nonagenarians that no matter their age merit a revascularization procedure. Brosi et al [9] and Sarineen et al [10] reported acceptable rates of wound healing, limb salvage and survival after revascularization among nonagenarians when compared with conservative approaches. The best revascularization technique, however, is not so clear. Yan et al [19] and Trestman et al [20] compared surgical and endovascular techniques and found better AFS results within the endovascular group despite a higher rate of early redo-procedures. Our results however do not appear to support this beneficial effect.

One relevant issue when managing CLTI in nonagenarians is to recognize which factors at baseline may be related to a low AFS rate. This is especially important among patients who have a potentially salvageable limb at baseline, which, in our experience, occurs in two thirds of nonagenarians. Our multivariate analysis identified as risk factors for a low AFS an hemoglobin level <10.5, partial dementia and wheelchair mobility, which are consistent with previous studies. Saarinen et al [10] described a high mortality among patients with cognitive impairment (1-year AFS 25%), suggesting that their best treatment would be the conservative management. Functional status is another determining factor. Vogel et al [21] found the highest morbidity and mortality rates among patients' dependent on basic physical needs or residents in nursing homes.

The present study has several limitations that are worth to disclose. First, its retrospective design which inherently entails the possibility that some information registered in clinical records contains imprecise data and restrict the inclusion of certain variables. Second, despite the adjusted factors found seemed clinically reasonable, these variables were subjectively selected and therefore there is a possibility that another potential risk factors were

not described. And finally, as this study is a single institution report, its external validation and applicability in other populations should be determined in future research.

The indication of a revascularization procedure in a nonagenarian with CLTI should be done judiciously to avoid maleficence. Our study shows that at present it is reasonable to consider that about one third of these patients can be managed satisfactorily with revascularization techniques. A proper selection of cases is, however, very important. Nonagenarians with a potentially salvageable limb but with risk factors such as anemia, partial dementia or a limited functional status, which are not obvious for directly recommending a palliative care, have a poor AFS and a conservative approach should be considered. Further research is needed to better clarify the best treatment in this growing subset of patients with CLTI.

Table 1: Clinical and functional characteristics of nonagenarian patients with chronic limb threatening ischemia according to the baseline vascular evaluation.

	Patients (n=171) n (%)	Non-salvageable limb (n= 59, 34.5%) n (%)	Potentially salvageable limb (n=112, 65.5%) n (%)	p-value
Age*	92.72	93.58	92.27	ns
Sex, female	88 (51.5)	25 (42.4)	63 (56.3)	ns
Current or previous smoking	58 (33.9)	11 (18.6)	47 (42)	ns
Hypertension	157 (91.8)	50 (84.7)	107 (95.5)	ns
Diabetes	77 (45)	24 (40.7)	53 (47.3)	ns
Dyslipidemia	89 (52)	30 (50.8)	59 (52.7)	ns
Coronary artery disease	29 (17)	6 (10.2)	23 (20.5)	ns
Congestive heart failure	42 (24.6)	13 (22)	29 (25.9)	ns
Atrial fibrillation	56 (32.7)	26 (44.1)	30 (26.8)	0.016
Cerebrovascular disease	32 (18.7)	16 (27.1)	16 (14.3)	ns
Dementia - Partial - Advanced	41 (24) 30 (17.5)	21 (35.6) 30 (50.8)	20 (17.9) 0	<0.001
Dialysis	6 (8.6)	4 (6.8)	2 (1.8)	ns
Hemoglobin*	11.21	10.88	11.39	ns
Ambulatory status - Independent - Mobility with assistance - Wheelchair/Bedridden	47 (27.4) 27 (15.7) 97 (56.7)	6 (10.1) 3 (5) 50 (80.7)	41 (36.6) 24 (21.4) 47 (41.9)	0.01
Dependence for managing basic physical needs - Partial or independent - Total	99 (57.9) 72 (42.1)	11 (18.6) 48 (81.4)	88 (78.6) 24 (21.4)	<0.001
Living status - Home - Nursing/Sheltered home - Health center	22 (12.9) 105 (61.4) 44 (25.7)	2 (3.4) 27 (45.8) 30 (50.8)	20 (17.9) 78 (69.6) 14 (12.5)	0.012

* mean (standard deviation)

Table 2: Revascularization procedures done in selected nonagenarian patients (n= 50, 29.2%).

Surgical revascularization:	16 (32%)
- Femoro-femoral bypass	6
- Femoro-Popliteal Bypass	3
- Femoro-distal Bypass	7
Endovascular revascularization:	34 (68%)
- Iliac stenting	7
- Superficial femoral-Popliteal stenting	22
- Infrapopliteal angioplasty	5

Figure 1: Flowchart of patients according to each treatment group

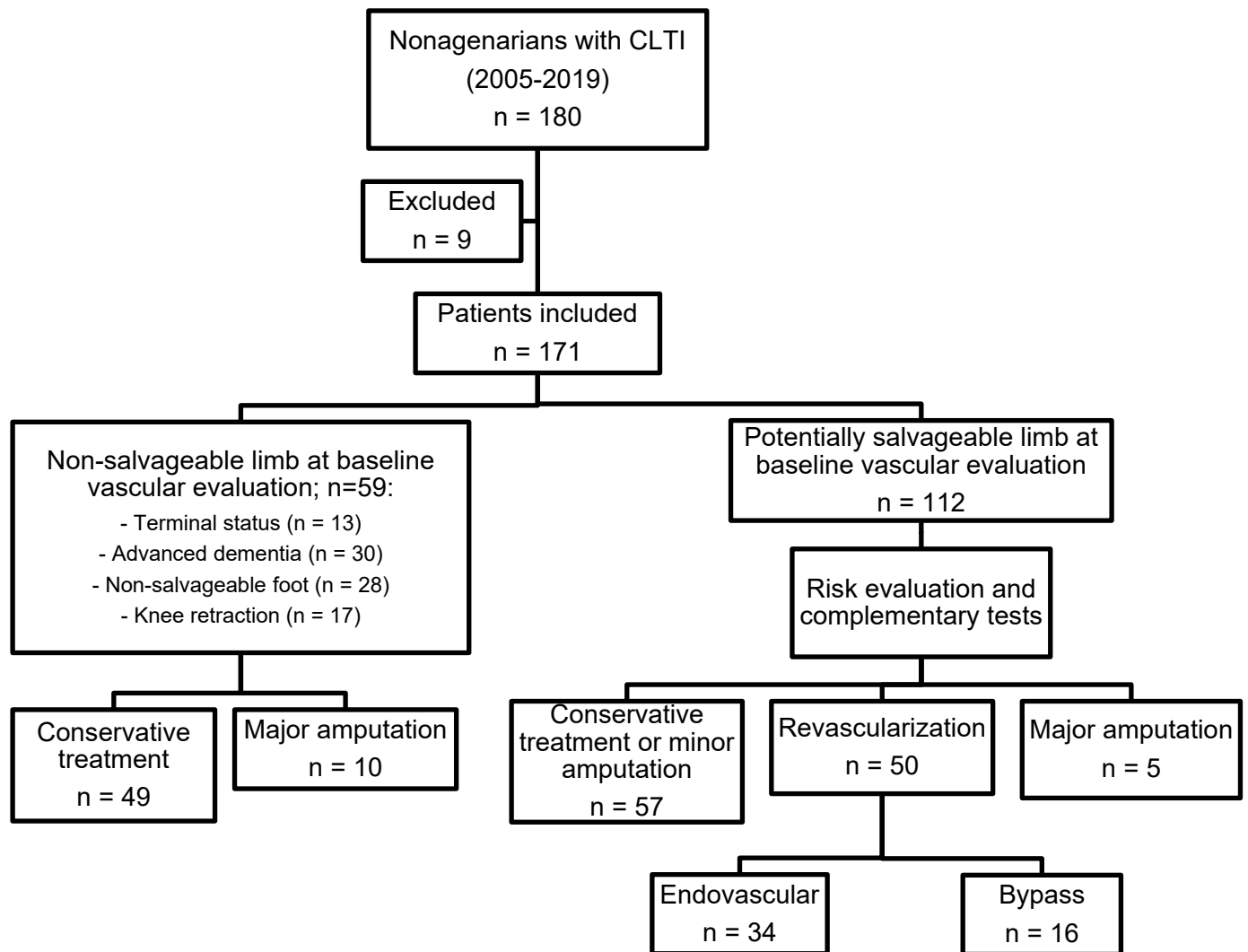


Table 3: Risk factors for amputation free survival among patients with a potentially salvageable limb at baseline evaluation.

	Patients	Bivariate Analysis	Multivariate Analysis
	n (%)	HR, p-value	HR, p-value
Categorized age <92.5	74 (66.1)	ns	ns
Sex, female	63 (56.3)	ns	ns
Current or previous smoking	47 (42)	ns	ns
Hypertension	107 (95.5)	ns	ns
Diabetes	53 (47.3)	ns	ns
Dyslipidemia	59 (52.7)	ns	ns
Coronary artery disease	23 (20.5)	ns	ns
Congestive heart failure	29 (25.9)	ns	ns
Atrial fibrillation	30 (26.8)	HR 1.69, p=0.073	ns
Cerebrovascular disease	16 (14.3)	ns	ns
Partial dementia	20 (17.9)	HR 2.43, p=0.005	HR 2.11, p=0.021
Dialysis	2 (1.8)	ns	ns
Hemoglobin < 10.5 mg/dL	44 (39)	HR 2.05, p=0.011	HR 2.06, p=0.013
Ambulatory status			HR 2.67, p=0.01
- No wheelchair/Bedridden	65 (58)	HR 3.11, p<0.001	
- Wheelchair/Bedridden	47 (42)		
Dependence for managing basic physical needs		HR 2.11, p=0.014	ns
- Non or partial	88 (78.6)		
- Total	24 (21.4)		
Living status		ns	ns
- Home	20 (17.9)		
- Nursing/Sheltered home	78 (69.6)		
- Health center	14 (12.5)		

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