Sex-Related Differences and Factors Associated with Peri-procedural and 1-year Mortality in Chronic Limb-Threatening Ischemia Patients from the CLIMATE Italian Registry.

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Abstract: Background: Identifying sex-related differences/variables associated with 30-day/1-year mortality in patients with chronic limb-threatening ischemia (CLTI). Methods: Multicenter/retrospective/observational study. Database sent to all-the-Italian vascular surgeries to collect all-the-patients operated for CLTI in 2019. Acute lower-limb ischemia and neuropathic-diabetic foot not included. Follow-up: 1-year. Data on demographics/comorbidities, treatments/outcome, and 30-day/1-year mortality investigated. Results: Information on 2399 cases (69.8% men) from 36/143 (25.2%) centers. Median (IQR) age: 73 (66-80) and 79 (71-85) yrs for men/women, respectively (p<.0001). Women more over-75 (63.2%vs40.1%, p=.0001). More men smokers (73.7%vs42.2%, p<.0001), on hemodialysis (10.1%vs6.7%, p=.006), affected by diabetes (61.9%vs52.8%, p<.0001), dyslipidemia (69.3%vs61.3%, p<.0001), hypertension (91.8%vs88.5%, p=.011), coronaropathy (43.9%vs29.4%, p<.0001), bronchopneumopathy (37.1%vs25.6%, p<.0001), underwent more open/hybrid surgeries (37.9%vs28.8%, p<.0001), and minor amputations (22%vs13.7%, p<.0001). More women underwent endovascular revascularizations (61.6%vs55.2%, p=.004), major amputations (9.6%vs6.9%, p=.024), and obtained limb-salvage if with limited gangrene (50.8%vs44.9%, p=.017). Age >75 (HR3.63, p=.003) associated with 30-day mortality. Age >75 (HR2.14, p<.0001), nephropathy (HR1.54, p<.0001), coronaropathy (HR1.26, p=.036), infection/necrosis of the foot (dry, HR1.42, p=.040; wet, HR2.04, p<.0001) associated with 1-year mortality. No sex-linked difference in mortality statistics. Conclusion: Women exhibit fewer comorbidities, but are struck by CLTI when over-75, a factor associated with short/mid-term mortality, explaining why mortality doesn't statistically differ between the sexes.

Keywords: chronic limb-threatening ischemia; outcome; sex; age; limb salvage

1. Introduction

Chronic limb-threatening ischemia (CLTI) affects 1% to 10% of patients with peripheral arterial disease (PAD), representing its advanced stages, and is characterized by rest pain or tissue necrosis in the foot. It generally results from involvement of at least two arterial segments (aorto-iliac, femoropopliteal, tibiopedal) or severe tibiopedal disease. The latter is particularly involved in patients with diabetes mellitus, end-stage renal disease, or very elderly. It represents a very broad range of severe malperfusion of the lower limb and associated limb threat. General and limb prognosis of these patients is adverse: they are at continuous risk of a major cardiovascular event, sudden death, and of course amputation [1].

Survival of female and male patients that underwent treatment for CLTI have been investigated with discordant results. For instance, some studies from Germany and the USA showed that 30-day mortality was significantly higher in females, while others from Japan and Sweeden respectively identified female sex as a

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significant positive predictor of 2-year survival, or reported that male sex was significantly associated with an increased risk of death [2-11].

Understanding the pathophysiological differences between the sexes is important to improve the quality of care. In this setting, it is reported that a lower rate of diagnostic angiograms and interventional procedures are performed in women compared with men [12]. This has raised the concern that the therapeutic approach to cardiovascular diseases should be sex-specific because of the existence of sex-related disparities in cardiovascular physiology [13-4]. Sex differences have been identified as additional determinants in diagnostic definitions and referral requirements for some diseases and sex-specific treatments are set including percutaneous coronary intervention, coronary artery bypass graft surgery, and PAD [15]. In particular, factors such as older age, late presentation, delayed diagnosis, smaller-size vessels, and other sex-related biases have been postulated to account, at least in part, for the portended less-favorable outcome in women with PAD. In addition, most studies on PAD have had low enrollment rates for women. Fortunately, the sex disparity in the management of PAD has been recognized, and more effort and resources have been dedicated to study this issue. Men and women have distinct and significant biological differences. Physiologically, women differ from men in many respects (eg, they have smaller blood vessels; their menopausal state and eventual estrogen replacement therapy can affect their cardiovascular risk; etc.) [16-18]. It is possible that these differences may contribute to the different presentations of the disease between the sexes and postoperative complications of major vascular procedures.

Related to the increased awareness of sex differences, the objective of the present study is to evaluate sex-related differences in the immediate post-surgery outcome and 1-year mortality in patients affected by CLTI. Secondary endpoints consist in the identification of any demographic, risk factor for atherosclerosis, comorbidity or treatment significantly associated with operative and 1-year mortality.

2. Materials and Methods

CLIMATE (Chronic Limb-threatening Ischemia Mortality At short-medium Term and sEx) is a multicenter and retrospective observational study.

The same ad hoc electronic questionnaire was sent by email to all the 143 Italian Divisions of Vascular Surgery, which consist of 20 (14%) academic and 123 (86%) non-academic centers. The questionnaire asked to anonymously collect data regarding all the patients treated in each Center from January 1 to December 31, 2019 for the first episode of CLTI on the target limb (by endovascular, surgical, hybrid revascularization, regenerative cellular therapy, or major amputation). Patients with acute lower limb ischemia or exclusively neuropathic diabetic foot (non-ischemic, i.e. with triphasic wave distal arterial blood-flow at duplex scan) were not object of this study, and were not considered in the database. Follow-up was limited to the first year after the operative treatment.

Data on demographics, risk factors for atherosclerosis, comorbidities, clinical presentation, treatment, technical and clinical success, post-operative medical therapy, limb salvage, 30-day and 1-year mortality, and cause of death were collected from clinical charts, operator reports, discharge letters, institutions' archives, and reported on the electronic database by each Division of Vascular Surgery. The result from each variable of the database was classified as reported in Table 1 (for instance: 0=no, 1=yes), that is, ready for statistical analysis. Each Center provided two surgeons for this study: the one deputed to data collection, and the Chief of the Division, who was responsible for the accuracy and integrity of it. All the 35 databases were checked for congruency, and summarized together in the original database from the first author (EM). Further supervision of all the data collected from all the Centers was performed by the co-first author (MZ), and by the statistician co-authors # 3, 4, and 7 (GS, LS, and MP). Data supporting the findings of this study are available from the corresponding author upon reasonable request. Weekly web meetings were held between the authors and the study group while drafting the protocol, and over the following two months of patient recruitment, to standardize data collection.

Here are some definitions we adopted, the remaining are reported in the tables. Hyperlipemia: low-density lipoprotein, or total cholesterol, or triglyceride severe elevation. Arterial hypertension: systolic and/or diastolic blood pressure ≥ 140 mmHg and ≥ 90 mmHg, respectively. Coronary artery disease (CAD): stable or unstable angina, ejection fraction < 30%, history of myocardial infarction or congestive heart failure. Chronic obstructive pulmonary disease (COPD): symptomatic, but even only radiological signs. Cerebrovascular disease (CVD): previous TIA or stroke. Minor amputation: toe or trans-metatarsal amputation. Limb salvage (LS): any treatment for CLTI which is successful in avoiding a major amputation. Use of antiplatelets, anticoagulants, and statins was classified as mono-therapy, two medications, and three or more medications.

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Institutional Review Board approval and patient informed consent were waived. The current Italian legislation on observational studies (our study falls under this category) does not request the above-mentioned documents when clinical data are anonymized (Official Gazette of the Italian Republic # 76, March 31, 2008).

2.1 Statistical analysis

Sample characteristics were collected in ad hoc dataset (supplementary file: dataset S1).

Qualitative variables were summarized with absolute and relative (percentages) frequencies, quantitative ones with median and interquartile range (IQR). Pearson or Fisher exact tests were used to evaluate differences of qualitative variables between males and females, whereas the Mann-Whitney test was performed to compare quantitative variables.

Survival analysis at 30-days and at 1-year was performed by Cox proportional hazard regression. Candidate variables for multivariate analysis were chosen if they were statistically significant at univariate analysis or clinically relevant.

Kaplan–Meier curve and Log-Rank test were performed to describe survival according to gender.

A p-value less than .05 was considered statistically significant. STATA13 statistical software was used for all statistical computations.

3. Results

Thirty-six (25.2%) of the 143 Divisions of Vascular Surgery from 17 of the 20 Italian Regions replied to the invitation and joined the study. The proportion between the typology of the adhering Centers, compared to the typology of the Italian Divisions of Vascular Surgery, was found to be constant: 5 (14.3%) academic vs 35 (85.6%) non-academic. Information on 2399 cases was collected. All the data requested from the database was obtained from each Vascular Surgery Center, and at follow-up no patient was lost at 30 days, while 20 (0.8%) were missing at 1 year.

Table 1 shows the sample characteristics stratified by sex.

Table 1. Sample characteristics.

Variables		Total cohort (n=2399)	Men (n=1677)	Women (n=722)	p-value
Median (IQR) age, yrs		75 (67-81)	73 (66-80)	79 (71-85)	<.0001
Age > 75 yrs		1128 (47.0)	672 (40.1)	456 (63.2)	.0001
Tobacco use:		1538 (64.2)	1234 (73.7)	304 (42.2)	<.0001
	never	857 (35.8)	441 (26.3)	416 (57.8)	<.0001
	former (stop > 10 yrs)	840 (35.1)	693 (41.4)	147 (20.4)	<.0001
	smoker	698 (29.1)	541 (32.3)	157 (21.8)	<.0001
Overt diabetes mellitus (yes vs no):		1418 (59.2)	1038 (61.9)	380 (52.8)	<.0001
	no	978 (40.8)	638 (38.1)	340 (47.2)	<.0001
	non-insulin dependent	717 (29.9)	529 (31.6)	188 (26.1)	.007
	insulin dependent	701 (29.3)	509 (30.4)	192 (26.7)	.068
Hyperlipemia:		1601(66.9)	1160 (69.3)	441 (61.3)	<.0001
	no	794 (33.1)	515 (30.8)	279 (38.6)	.001
	under therapy	1498 (62.6)	1089 (65.0)	409 (56.8)	.0001
	no therapy	103 (4.3)	71 (4.2)	32 (4.4)	.825
Arterial hypertension:		2176 (90.8)	1538 (91.8)	638 (88.5)	.011
	no	221 (9.2)	138 (8.2)	83 (11.5)	.011
	under therapy	2147 (89.6)	1515 (90.4)	632 (87.7)	.047
	no therapy	29 (1.2)	23 (1.4)	6 (0.8)	.245
Chronic renal insufficiency:		626 (26.1)	453 (27.0)	173 (24.0)	.123
	no	1769 (73.9)	1222 (73.0)	547 (76.0)	.125
	creatinine >2mg/dl	408 (17.0)	283 (16.9)	125 (17.4)	.765

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	hemodialysis treatment	218 (9.1)	170 (10.1)	48 (6.7)	.006
Coronary artery disease:		947 (39.6)	736 (43.9)	211 (29.4)	<.0001
	no	1447 (60.4)	939 (56.0)	508 (70.7)	<.0001
	revascularized	705 (29.5)	559 (33.4)	146 (20.3)	<.0001
	non-revascularized	242 (10.1)	177 (10.6)	65 (9.0)	.246
Chronic obstructive pulmonary disease:		806 (33.7)	622 (37.1)	184 (25.6)	<.0001
	no	1589 (66.3)	1054 (62.9)	535 (74.4)	<.0001
	only radiological signs	479 (20.0)	363 (21.7)	116 (16.1)	.002
	symptomatic	327 (13.7)	259 (15.4)	68 (9.5)	.0001
Cerebrovascular disease:		186 (7.8)	128 (7.6)	58 (8.0)	.736
	no	2213 (92.2)	1549 (92.4)	664 (92.0)	.918
	previous TIA	139 (5.8)	95 (5.7)	44 (6.1)	
	previous stroke	47 (2.0)	33 (2.0)	14 (1.9)	
Rutherford category:	4 (rest pain)	964 (40.2)	697 (41.6)	267 (37.0)	.107
	5 (minor tissue loss)	1078 (44.9)	738 (44.0)	340 (47.1)	
	6 (major tissue loss)	357 (14.9)	242 (14.4)	115 (15.9)	
Necrosis/infection of the foot:	no	1194 (49.9)	854 (51.0)	340 (47.4)	.202
	dry	603 (25.2)	407 (24.3)	196 (27.3)	
	wet	596 (24.9)	414 (24.7)	182 (25.4)	
First intervention:	endovascular only (rarely, regenerative cellular therapy)	1366 (57.1)	922 (55.2)	444(61.6)	.004
	any open revascularization surgery	840 (35.2)	632 (37.9)	208 (28.8)	<.0001
	any major amputation	184 (7.7)	115 (6.9)	69 (9.6)	.024
Any intervention below the knee		1287 (53.9)	912 (54.6)	375 (52.3)	.313
Technical success of CLTI revascularization:	no	211 (9.5)	152 (9.7)	59 (9.0)	.611
	yes	2004 (90.5)	1410 (90.3)	594 (91.0)	
Associated minor amputation		467 (19.5)	368 (22.0)	99 (13.7)	<.0001
Post-operative antiplatelets, anticoagulants, statins:	mono-therapy	561 (24.3)	373 (23.1)	188 (26.9)	.105
	two medications	1229 (53.2)	863 (53.6)	366 (52.4)	
	three or more medications	519 (22.5)	375 (23.3)	144 (20.6)	
Clinical success of CLTI revascularization:	worsen	157 (7.1)	109 (7.0)	48 (7.4)	.951
	no change	343 (15.5)	142 (15.5)	101 (15.5)	
	improved	1716 (77.4)	1212 (77.5)	504 (77.2)	
Limb salvage:		1965 (82.1)	1382 (82.6)	583 (80.9)	.307
	in Rutherford category 4	882 (44.9)	638 (46.2)	244 (41.9)	.080
	in Rutherford category 5	917 (46.7)	621 (44.9)	296 (50.8)	.017
	in Rutherford category 6	166 (8.5)	123 (8.9)	43 (7.4)	.275
30-day mortality		74 (3.1)	44 (2.6)	30 (4.2)	.047
1-year mortality		317 (13.5)	211 (12.8)	106 (14.9)	.167
Cause of death:	cardiac	141 (42.1)	91 (41.2)	50 (43.9)	.635
	neurologic	19 (5.7)	10 (4.5)	9 (7.9)	.202
	pulmonary	33 (9.9)	31 (14.0)	3 (2.6)	.001
	cancer	19 (5.7)	13 (5.9)	6 (5.3)	.822
	multi-organ failure	46 (13.7)	25 (11.3)	21 (12.4)	.074

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	other	77 (23.0)	51 (23.1)	25 (21.9)	.804

Quantitative variables are expressed with median and interquartile range (IQR), qualitative ones as absolute and relative (percentages) frequencies, n (%). TIA, transient ischemic attack. CLTI, chronic limb-threatening ischemia.

Among 2399 patients, 1677 (69.9%) were males, median (IQR) age in the sample was 75 (67-81) yo with significant difference between men and women [73 (66-80) yrs vs 79 (71-85) yrs, p<.0001, respectively]. Women were more over-75 yo compared to men (63.2% vs 40.1%, p=.0001). The age 75 cut-off (≦ 75 or > 75) was chosen on the basis of the median value.

The most common cardiovascular risk factor and comorbidity in the total cohort are, respectively, arterial hypertension and CAD, followed by hyperlipemia, tobacco use, diabetes mellitus, and COPD, chronic renal insufficiency, CVD.

A significantly greater proportion of men were smokers, affected by diabetes, dyslipidemia, end-stage renal disease on hemodialysis treatment, arterial hypertension, CAD, COPD, have undergone significantly more open or hybrid surgeries for CLTI revascularization, and amputations of the toes or the forefoot as a complementary treatment for LS. On the contrary, a significantly greater proportion of women underwent less-invasive direct or indirect revascularizations for CLTI, mainly endovascular (cellular therapy only in 18, 2.5% of women, 27, 1.6% of men), and major amputations.

CVD, clinical presentation according to the Rutherford's classification, infection/necrosis of the foot, above the knee vs below the knee revascularization, technical and clinical success of revascularization for CLTI, postoperative medical therapy, 1-year mortality, cardiac, neurologic, malignant and multi-organ failure causes of death do not statistically differ between the sexes, as well as 30-day mortality which, despite being close to being so, is not statistically significant (p=.047, which with approximation is p=.05). Instead, significantly more women with limited tissue loss (Rutherford category 5) obtain LS, and significantly more males die for pulmonary causes.

Table 2 reports the Cox regression analysis to assess relationship between demographic, epidemiological, clinical characteristics, and 30-day mortality.

Table 2. Cox regression analysis to assess risk factors for 30-day mortality.

Variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age > 75 yrs		3.42 (1.93-6.01)	<.0001	3.63 (1.53-8.62)	.003
Men		0.62 (0.38-1.03)	.063	0.71 (0.34-1.48)	.359
Tobacco use		1.20 (0.71-2.04)	.501	-	-
Overt diabetes mellitus		0.80 (0.49-1.32)	.386	-	-
Hyperlipemia:	no	Ref.	Ref.	Ref.	Ref.
	under therapy	0.60 (0.36-0.98)	.042	0.86 (0.39-1.86)	.693
	no therapy	0.26 (0.04-1.92)	.187	-	-
Arterial hypertension		1.19 (0.48-2.97)	.705	-	-
Chronic renal insufficiency:		2.01 (1.22-3.32)	.006	1.37 (0.82-2.27)	.227
	no	Ref.	Ref.	Ref.	Ref.
	creatinine >2	1.78 (0.97-3.23)	.061	0.96 (0.39-2.39)	.937
	hemodialysis treatment	2.45 (1.25-4.81)	.009	-	-
Coronary artery disease:		1.69 (1.03-2.78)	.037	0.69 (0.25-1.92)	.479
	no	Ref.	Ref.	Ref.	Ref.
	revascularized	1.79 (1.06-3.03)	.029	2.88 (0.90-9.17)	.074
	non-revascularized	1.40 (0.62-3.19)	.424	-	-
Chronic obstructive pulmonary disease		1.14 (0.68-1.90)	.624	-	-
Cerebrovascular disease		2.89 (1.54-5.41)	.001	2.02 (0.80-5.06)	.136
Necrosis/infection of the foot:	no	Ref.	Ref.	Ref.	Ref.
	dry	1.37 (0.64-2.95)	.424	0.88 (0.34-2.24)	.783

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	wet	4.61 (2.56-8.31)	<.0001	1.71 (0.73-4.02)	.217
First intervention:	endovascular only (rarely, regenerative cellular therapy)	Ref.	Ref.	Ref.	Ref.
	any open revascularization	1.26 (0.67-2.37)	.474	1.02 (0.48-2.17)	.962
	any major amputation	8.96 (5.05-15.90)	<.0001	-	-
Any intervention below the knee		0.77 (0.47-1.27)	.309	-	-
Associated minor amputation		1.31 (0.64-2.69)	.460	-	-
Technical success of CLTI revascularization		0.41 (0.19-0.88)	.023	0.60 (2.25-1.47)	.262
Post-operative antiplatelets, anticoagulants, statins:	mono therapy	Ref.	Ref.	Ref.	Ref.
	two medications	0.45 (0.27-0.77)	.003	0.73 (0.33-1.61)	.440
	three or more medications	0.24 (0.10-0.57)	.001	0.39 (0.12-1.27)	.118
Clinical success of CLTI revascularization:	worsen	Ref.	Ref.	Ref.	Ref.
	no change	0.34 (0.13-0.91)	.032	0.50 (0.16-1.55)	.230
	improved	0.22 (0.10-0.47)	<.0001	0.53 (0.18-1.56)	.248
Limb salvage		0.15 (0.09-0.25)	<.0001	0.51 (0.19-1.36)	.180

CLTI, chronic limb-threatening ischemia.

Results from multivariate analysis shows that age >75 yrs was the only variable associated with the 30-day mortality (HR=3.69, 95%CI: 1.53-8.62; p=.003).

Table 3 reports the Cox regression analysis to assess relationship between demographic, epidemiological, clinical characteristics, and 1-year mortality.

Table 3. Cox regression analysis to assess risk factors for 1-year mortality.

Variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age > 75 yrs		2.50 (1.96-3.18)	<.0001	2.14 (1.60-2.87)	<.0001
Men		0.83 (0.65-1.06)	.134	0.99 (0.72-1.34)	.928
Tobacco use		0.70 (0.55-0.88)	.002	0.89 (0.66-1.20)	.447
Overt diabetes mellitus		0.90 (0.72-1.14)	.395	-	-
Hyperlipemia:	no	Ref.	Ref.	Ref.	Ref.
	under therapy	0.64 (0.51-0.81)	<.0001	0.69 (0.51-0.93)	.015
	no therapy	0.86 (0.50-1.50)	.602	0.97 (0.51-1.86)	.937
Arterial hypertension		1.04 (0.69-1.55)	.865	-	-
Chronic renal insufficiency:		1.92 (1.52-2.43)	<.0001	1.54 (1.28-1.84)	<.0001
	no	Ref.	Ref.	Ref.	Ref.
	creatinine >2	1.42 (1.06-1.92)	.021	0.84 (0.59-1.21)	.354
	hemodialysis treatment	2.89 (2.15-3.88)	<.0001	-	-
Coronary artery disease:		1.51 (1.20-1.90)	<.0001	1.26 (1.02-1.57)	.036
	no	Ref.	Ref.	Ref.	Ref.
	revascularized	1.47 (1.14-1.89)	.003	1.20 (0.88-1.65)	.255
	non-revascularized	1.64 (1.16-2.32)	.005	-	-
Chronic obstructive pulmonary disease		1.02 (0.80-1.29)	.902	-	-
Cerebrovascular disease:		1.48 (1.01-2.17)	.046	-	-
	No	Ref.	Ref.	Ref.	Ref.
	previous TIA	1.86 (1.25-2.76)	.002	1.53 (0.95-2.46)	.084

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	previous stroke	0.39 (0.10-1.57)	.19	0.38 (0.1-1.55)	.177
Necrosis/infection of the foot:	no	Ref.	Ref.	Ref.	Ref.
	dry	1.83 (1.35-2.48)	<.0001	1.42 (1.02-1.98)	.040
	wet	3.15 (2.39-4.13)	<.0001	2.04 (1.46-2.85)	<.0001
First intervention:	endovascular only (rarely, regenerative cellular therapy)	Ref.	Ref.	Ref.	Ref.
	any open revascularization	0.81 (0.62-1.06)	.122	0.86 (0.64-1.15)	.310
	any major amputation	3.05 (2.25-4.13)	<.0001	-	-
Any intervention below the knee		1.06 (0.84-1.33)	.624	-	-
Associated minor amputation		1.29 (0.96-1.73)	.091	-	-
Technical success of CLTI revascularization		0.83 (0.55-1.25)	.37	-	-
Post-operative antiplatelets, anticoagulants, statins:	mono-therapy	Ref.	Ref.	Ref.	Ref.
	two medications	0.63 (0.48-0.82)	.001	0.93 (0.67-1.29)	.678
	three or more medications	0.52 (0.37-0.73)	<.0001	0.78 (0.52-1.18)	.242
Clinical success of CLTI revascularization:	worsen	Ref.	Ref.	Ref.	Ref.
	no change	0.81 (0.50-1.34)	.415	1.02 (0.59-1.77)	.949
	improved	0.58 (0.38-0.88)	.011	0.89 (0.52-1.51)	.666
Limb salvage		0.41 (0.32-0.52)	<.0001	0.71 (0.47-1.06)	.092

TIA, transient ischemic attack. CLTI, chronic limb-threatening ischemia.

Results from multivariate analysis shows that factors associated with 1-year mortality were: age >75 yrs (HR=2.14, 95% CI: 1.60-2.87; p< .0001); therapy for hyperlipemia (HR=0.69, 95% CI: 0.51-0.93; p=.015); chronic renal insufficiency (CRI) (HR=1.54, 95% CI: 1.28-1.84; p< .0001); CAD (HR=1.26, 95% CI: 1.02-1.57; p=.036); dry necrosis (HR=1.42, 95% CI: 1.02-1.98; p=.040) and wet necrosis (HR=2.04, 95% CI: 1.46-2.85; p< .0001) of the foot.

Figures 1 and 2 show the Kaplan-Meier survival curves (overall distribution and for men/women) at 30 days and 1 year, respectively. Again, no statistically significant difference is noted between the sexes.

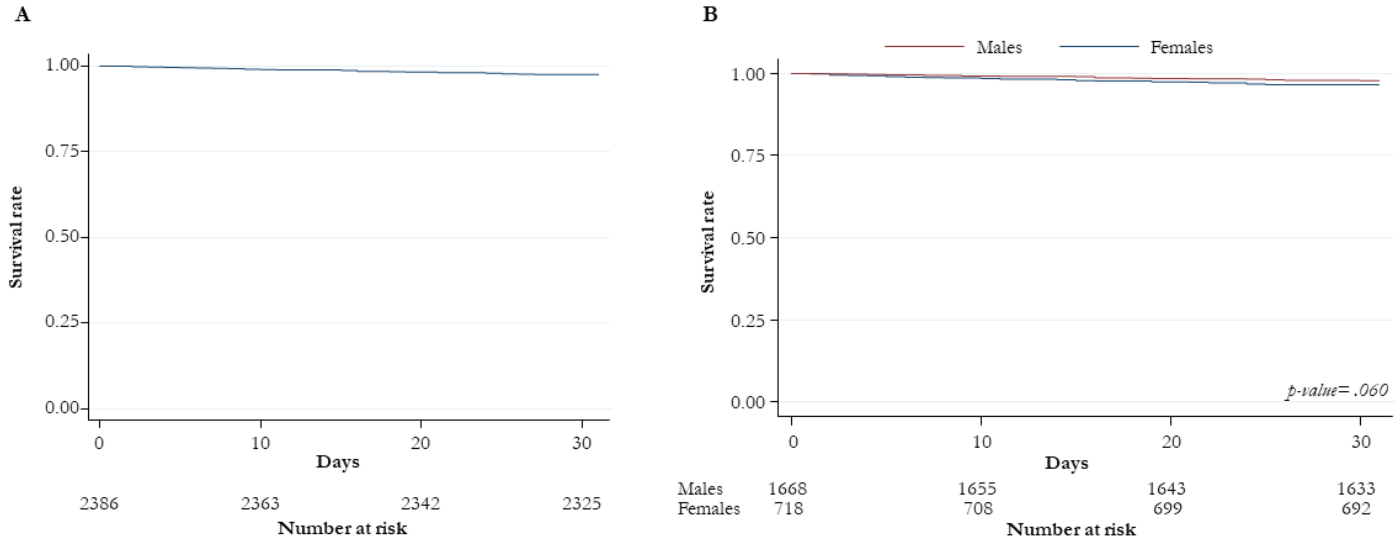

Figure 1. Kaplan–Meier curves for overall survival at 30 days. (A) distribution of overall survival (B) overall survival for males and females.

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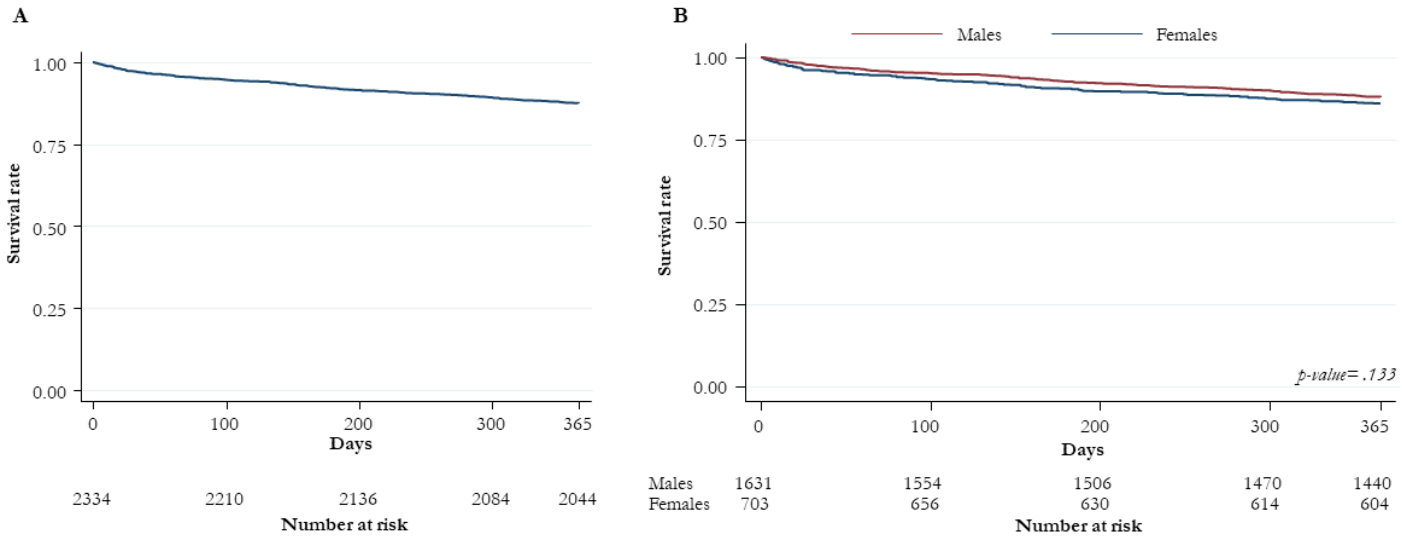

Figure 2. Kaplan–Meier curves for overall survival at 1 year. (A) distribution of overall survival (B) overall survival for males and females.

4. Discussion

The aim of the study was to evaluate the differences between men and women in 30-days and 1-year mortality. Our findings showed that no differences were observed between the sexes.

In this study on 2399 patients treated for CLTI, 30-day mortality is overall 3.1%. One-year mortality is 13.5%, which is much lower than 23.1–28.7% reported in the COPART French registry on 411 patients treated for CLTI [19]. Differences in risk factors and comorbidities of the French and Italian populations may explain the difference in 1-year-mortality between these two studies.

Notwithstanding our male patients were significantly more smokers, affected by diabetes, end-stage renal disease on hemodialysis treatment, arterial hypertension, CAD, COPD, revascularized for CLTI by open surgery, however they were also significantly younger, more on statin therapy and more revascularized for CAD, potentially inducing more protection from cardiovascular risk.

Also the male patients of the Medicare population affected by CLTI and analyzed from 2015 to 2017 received significantly more statin therapy compared to females [4].

The current clinical practice guidelines from the European Society for Vascular Surgery strongly recommend the use of moderate or high-intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI [20].

Cardiologists from the University of Minnesota found that patients with unprotected left main coronary artery disease benefit with preoperative coronary artery revascularization before vascular surgery [21].

Our findings that some vascular beds are more affected than others when comparing men and women (ie. the coronary district vs the peripheral arterial district), and that some risk factors are so disparate between the groups, suggests a potentially different phenotypic expression of the disease process. However, it is due to notice that this result might merely be a function of which men and women were selected for the treatment.

Anesthesiologists from Melbourne, Toronto and Auckland have recently evaluated the effects of randomized interventions by sex in large international perioperative trials, and concluded that women were healthier than men but outcomes were similar. These authors encouraged further research to understand the reason for this discrepancy [22].

Colleagues from Auckland and Hamilton analyzed 1773 patients with CLTI in the midland region of New Zealand over a 12-year period. They found a worse long-term survival rate for women with CLTI, despite 30-day mortality not differing depending on sex [23].

A recent German study from the cardiologists of the University of Muenster on almost 200000 unselected patients treated for CLTI over an 8-year-period showed that 30-day-mortality is significantly higher in women [3]. Same results were obtained from the US National Inpatient Sample database [7,10].

Other French colleagues from the University of Strasbourg demonstrated a significantly lower survival rate at 6 years, but not at 30 days, among women compared to men undergoing infra-inguinal open surgery for CLTI: they concluded that female sex was an independent factor predicting death [24].

A possible explanation of this worse long-term survival in women treated for CLTI is that they are associated with more severe disease at presentation (although in our study Rutherford categories were similar in both sexes), develop arteriosclerotic changes later in life, and require treatment in older age [16].
On the contrary, a recent multicenter study, from Japan, has identified female sex as a significant positive predictor of 2-year overall survival in patients treated for CLTI [11].
Another Swedish population based study conducted between 2008 and 2013 on over 10000 patients undergone revascularization for CLTI and followed up for a median 2.7 yrs. reported that male sex was significantly associated with an increased risk of amputation or death at multivariate analysis [6].
This dichotomy could open a reflection on the genetic, environmental, and dietary factors implied on the outcome of CLTI. The Atherosclerosis Risk in Communities (ARIC) study has already focused the attention on the association of race ("Blacks vs Whites" in the ARIC study) with incident CLTI related hospitalizations that leads to differences in clinical disease risk and presentation [25].

We have found advanced age over 75 years old to be a negative prognostic factor, both for 30-day and 1-year mortality. Recently, our same result for 1-year mortality in advanced age was reported by a Dutch study, and a similar result by a study from the Yale School of Medicine [26-7].
The older population is increasing, and this knowledge of worse CLTI outcomes for the elderly population is important for clinical decision making.
Our female patients treated for CLTI are significantly older compared to males, and this is in contrast with the exception of the Italian data (females 0.9 year younger than males) reported in the VASCUNET and International Consortium of Vascular Registries [28].
Our analysis demonstrates that females are struck by CLTI at an age >75 yrs, a pivotal factor associated with short- and mid-term mortality. This fact may explain why the mortality rate does not significantly differ between the two sexes, although females have less risk factors and comorbidities associated with this condition.

Our study confirms other independent predictive factors for mortality at 1 year, that is CRI, CAD and tissue loss.
CLTI is a terminal manifestation of systemic atherosclerosis. Therefore, it is often accompanied by clinically significant CAD, resulting in high mortality. The goal of treating patients with CLTI is not only to save a still functional limb, but also to improve cardiovascular outcome. While some risk factors (age, sex) are immutable, others are (cigarette smoking, dyslipidemia, diabetes mellitus, a sedentary lifestyle, and treatable hypertension). In the absence of efficient cardiovascular work-up and aggressive treatment of risk factors and associated comorbidities, the prognosis of CLTI is generally poor [29-31].
End-stage renal disease and tissue loss are established critical factors for mid-term mortality in patients undergoing revascularization for CLTI [32-35].

Interestingly in our study, although significantly more women underwent major amputations, LS is achieved significantly more in women with minor tissue loss. Perhaps, the reason stands in the different CLTI treatment sort out between the sexes, that is significantly more less-invasive therapies in women and significantly more open surgery in men.
Also the US National Inpatient Sample database shows that women are more likely to undergo endovascular surgery for CLTI than men, and this is associated with a higher incidence of major amputation [10,36]. Therefore, in our series it seems that endovascular treatment has been more successful than open or hybrid treatment in terms of LS in women with CLTI at the Rutherford category 5.
In parallel, men had significantly undergone more open or hybrid surgeries for CLTI revascularization together with minor amputations, and significantly achieved less LS in Rutherford category 5: it seems that in men, minor amputation as a complementary act of an open or hybrid revascularization for CLTI does not give benefits in terms of LS.

Our study has limitations. First, data were retrospectively collected, and some key clinical information might be missing or might not be recorded appropriately in the clinical records. The selection criteria for offering CLTI interventions are based on real-world data, not systematic. For instance, we could not collect data on hormonal replacement/supplementation therapy for the two groups. Furthermore, we did not collect data on the extent of CLTI (for instance, below-the-knee vs multi-level disease). Finally, the role played by unknown confounders can be relevant in an observational design. In order to mitigate potential documentation errors, patients' data was collected from multiple hospital records, and several web meetings and phone calls were performed between the first author and the other authors during the writing of the study protocol and the patients recruitment period to standardize data collection.

Second, the time of patient recruitment does not coincide with actual appearance of disease. This may cause an artificial extension, as the atherosclerosis and symptomology may have developed earlier.
Third, we evaluated only one year of patients treated for CLTI; as such, inter-annual variability cannot be excluded.
Fourth, the staging of CLTI has not been performed using the current WIfI classification system: we have preferred to adopt the standard Rutherford classification, together with the presence/absence of necrosis/infection of the foot and excluding patients with only neuropathic (non-ischemic) diabetic foot, to make data collection easier and more realistic for the participating centers which are mostly non-academic [37]. For the same reason, the current international suggested standards for reports dealing with risk factors and comorbidities have been adjusted or synthetized (for instance, asymptomatic carotid stenosis has not been included in CVD since in the real-world not all patients treated for CLTI undergo carotid duplex scan) [38].

5. Conclusions

Our observational evaluation on patients operated for CLTI demonstrates that women are less represented, and have fewer risk factors and comorbidities, compared to men. However, women are struck by CLTI at an age >75 yrs, a pivotal factor associated with short- and mid-term mortality, explaining why the mortality rate does not differ between the two sexes. Also CRI, CAD, and tissue loss are independent negative prognostic factors for 1-year survival.
Endovascular techniques for limited gangrene are more likely to be successful in women.
Statin therapy is an independent positive prognostic factors for 1-year survival: once more, its aggressive use in CLTI patients appears justified.

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