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Gender related Long-term Differences after Open Infrainguinal Surgery for Critical Limb Ischemia

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WHAT THIS PAPER ADDS

The gender related disparity in critical limb ischemia outcomes has been clearly emphasized, highlighting the need for further and longer follow-up investigations, and justifying the recent call to action concerning women and peripheral arterial disease by the American Heart Association, which is why critical limb ischemia and open infrainguinal surgery in women have been focused on. The results show worse immediate and long-term outcomes in women, justifying intensive care in pre-operative period, but also better follow up.

Objective: The role of gender on long-term infrainguinal open surgery outcomes still remains uncertain in critical limb ischemia patients. The aim of this study is to evaluate the gender-specific differences in patient characteristics and long-term clinical outcomes in terms of survival, primary patency and limb salvage among patients undergoing infrainguinal open surgery for CLI.

Material and methods: All consecutive patients undergoing infrainguinal open surgery for critical limb ischemia between 2003 and 2012 were included. Survival, limb salvage and primary patency rates were assessed. Independent outcome determinants were identified by the Cox proportional hazard ratio using age and gender as adjustment factors.

Results: 584 patients (269 women and 315 men, mean age 76 and 71 years respectively) underwent 658 infrainguinal open surgery (313 in women and 345 in men). Survival rate at 6 years was lower among women compared to men with 53.5% vs 70.9% ($p < 0.001$). The same applied to primary patency (35.9% vs 52.4%, $p < 0.001$) and limb salvage (54.3% vs 81.1%, $p < 0.001$) at 6 years. Female-gender was an independent factor predicting death (hazard ratio 1.50), thrombosis (hazard ratio 2.37) and limb loss (hazard ratio 7.05) in age and gender-adjusted analysis.

Conclusion: Gender-related disparity in critical limb ischemia open surgical revascularization outcomes still remains.

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INTRODUCTION

Within the last decade, there has been an increased awareness of peripheral arterial occlusive disease (PAOD) in women, especially critical limb ischemia (CLI). Moreover, women have experienced a steady increase in cardiovascular mortality, despite improved diagnostic approaches and continuing advances in medical therapy.[1–4] It has also been demonstrated that female gender may be an independent predictor for severe and diffuse atherosclerotic disease, particularly of the femorocrural axis.[1] The common multi-level disease associated with more occlusions in women with CLI also means that lesions often require open surgery.[1]

Gender related differences in coronary artery disease or stroke have largely been studied. Evidence based gender specific treatment guidelines have already been released for coronary artery disease and cerebrovascular disease, but there are actually no guidelines concerning gender specific treatment for CLI.[2–8] Previous studies showed that women with PAOD disease had higher amputation rates and lower graft or stent patency rates after revascularization than men.[9–12] Other reports however showed similar outcomes between women and men, when adjustment for age and

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severity of disease were taken into consideration.[13–16] Unfortunately, literature analysis is difficult because of a multitude of factors that might affect outcomes, such as surgical indication (claudication, CLI), location of the disease (aorto-iliac of infrainguinal), type of intervention performed (endovascular or open surgery), type and quality of the conduit if a bypass is performed, and gender differences in patients specifically presenting with CLI remain relatively poorly studied. Nevertheless, the gender related disparity in long-term CLI outcomes has been mentioned, highlighting the need for further and longer follow up studies, and justifying the recent call to action for studies concerning women and peripheral arterial disease by the American Heart Association.[17]

In such a context, because of the diffuse and preferentially femoro-crural lesions in women, often requiring open surgery, the aim of the present study was to evaluate gender specific differences in patient characteristics and long-term clinical outcomes in terms of survival, primary patency and limb salvage among patients undergoing infrainguinal open surgery for CLI.

MATERIALS AND METHODS

Design of the study

A consecutive study of all patients who underwent infrainguinal open procedures for CLI between January 2003 and December 2012 was performed. CLI was defined as chronic ischemic rest pain or ischemic skin lesions (either ulcers or gangrene) evolving over 2 weeks, and confirmed by ankle brachial index (ABI), or transcutaneous oxygen pressure ($TcPO_2$), according to TASC II guidelines.[18] Patients presenting with infrainguinal lesions associated with supra-inguinal lesions were excluded.

Patients were retrospectively divided into two groups: men and women. Both groups were compared in terms of pre-operative, peri-operative, and post-operative parameters.

Pre-operative parameters

The following pre-operative parameters were recorded: demographics data, cardiovascular risk factors, comorbidities, surgical risk, clinical CLI status, hemodynamic measures, and number of run off arteries. Data concerning these parameters were prospectively collected in a dedicated institutional database using a data collection form specifically dedicated to CLI patients, and retrospectively analyzed.

Cardiac comorbidity was defined as congestive heart failure with ejection fraction $< 40\%$, or coronary artery occlusive disease defined as history of myocardial infarction or history of any revascularization of the coronary arteries. Renal comorbidity was defined as a creatinine clearance below 30 mL/min, and a history of stroke corresponded to cerebral comorbidity.

Surgical risk was recorded on the pre-operative anesthesia report, and defined according to the guidelines for the peri-operative cardiac management in non-cardiac surgery of the European Society of Anesthesiology.[19] High risk status patients were thus defined as patients with three or more serious comorbidities, including chronic obstructive pulmonary disease (FEV1 $< 80\%$ theoretical value), congestive heart failure (left ventricular ejection fraction $< 40\%$), coronary artery occlusive disease (defined as history of any revascularization of the coronary arteries), or chronic renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2).

Clinical CLI status was systematically noted pre-operatively in the data collection form, and included symptoms (rest pain or wound), wound location, wound depth, and infection. Wound depth was defined according to the Armstrong classification (grade 1, superficial ulcer; grade 2, penetrating ulcer; grade 3, ulcer penetrating to muscle, tendon, or joint articulation; grade 4, ulcer penetrating to bone).[20] Infection was defined as typical inflammatory clinical signs of infection (including foot erythema, rubor, or cellulitis) associated with a C reactive protein level > 6 mg/L, and positive local bacterial analysis.

Hemodynamic measures included ABI measurement and/or $TcPO_2$ values, and duplex ultrasound imaging.

All patients had pre-operative arteriography or computed tomography scans, and all pre-operative images were retrospectively reviewed to access the length of the lesions (according to TASC II classification) and the number of run off arteries.[1]

Surgical procedures

Types of bypasses done and types of conduits used were recorded. The policy was to carry out venous bypasses whenever possible; the suitability and quality of the vein were systematically verified pre-operatively by Duplex ultrasound imaging. The patency of all bypasses was immediately confirmed by intra-operative angiography.

Post-operative parameters

The following post-operative parameters were recorded: 30 day mortality (death within 30 days of operation), 30 day morbidity (morbidity within 30 days of operation), and post-operative length of hospital stay. Morbidity was defined as surgery related morbidity (graft thrombosis, hemorrhagic complication, operative site infection) or systemic morbidity (renal, pulmonary, cardiac or neurological failures).

The long-term follow up program consisted of clinical and hemodynamic examination with ABI or $TcPO_2$ measurements and duplex scan within 6 weeks post-operatively, at 6 and 12 months, and then annually. Patients were reviewed face to face at 6 weeks and at 6 months, and subsequently remained under angiologist supervision. Ultrasound monitoring was performed at the first check up, and then on an annual basis or even more frequently. Follow up results were analyzed in terms of survival, primary patency and limb salvage rates.

Chosen outcomes

The primary chosen outcome was long-term survival. Secondary chosen outcomes were 30 day mortality and morbidity, primary patency, and limb salvage rates.