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SARS-COV-2 pandemic for patients with chronic obstructive peripheral arterial disease: impact of interruption to access according to gender in a single center experience

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1 **manuscript**

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35 Abstract

36 SARS-COV-2 pandemic for patients with chronic obstructive peripheral arterial disease: impact
37 of interruption to access according to gender in a single center experience.

38

39 This retrospective study aims to evaluate the impact of interrupted services for peripheral artery
40 disease (PAD) patients and especially women in a single north-eastern Italian center over a period
41 of 3 months prior to the pandemic, during the first (2020) and during the second (2021) wave of
42 contagion in northern Italy.

43 Materials and methods

44 Patients with PAD at Rutherford stages 3 to 6 that required revascularization between March 2019
45 and March 2021 were classified into three groups, according to the period of treatment: Pre-pandemic
46 period, pandemic20 period, pandemic21 period.

47 Results

48 28 patients were treated in the Pre-pandemic period, 21 in the pandemic-20 and 39 in the pandemic-
49 21. It was observed that in the both pandemic periods patients presented with more severe stages of
50 limb ischemia, Rutherford 5 and 6 stages. During the Pandemic-20, patients underwent mostly open
51 surgery, followed by hybrid procedures. No differences were observed between the three groups in
52 major amputations, length of hospital stay, type of discharge, limb salvage and mortality. During
53 long-term follow up limb salvage appeared to be significantly better in the pandemic-21 group. The
54 gender analysis revealed a significantly reduced female proportion of overall treated patients in 2020
55 and 2021 compared to the pre-pandemic period. In the pandemic-20 this difference appears even
56 more evident since treatments on females represented 19% of the total while in the same period of
57 the previous year the male / female percentage was comparable (54% vs 46%). The women admitted
58 presented higher stages of disease and tended to have a longer hospital stay than men. At 12-month
59 follow up limb salvage was similar between the two genders but slightly worse in women.

60 CONCLUSIONS

61 An efficient reorganization of the vascular surgery services during the pandemic period guaranteed
62 the quality and standard of treatment offered in the preceding periods. Among patients suffering
63 from PAD the impact of the pandemic was greater for the female gender. It is therefore important
64 that in addition to a reorganization of hospital services to provide adequate care for patients with
65 ACOP in the pandemic period, greater information and awareness of women.

66

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68 Manuscript**69 SARS-COV-2 pandemic for patients with chronic obstructive peripheral arterial disease: impact
70 of interruption to access according to gender in a single center experience.**

71 Keywords: SARS-COV-2 pandemic, peripheral arterial disease gender differences

72 Introduction

73 The SARS-CoV-2 pandemic changed world-wide health service management organization, causing
74 interruptions to diagnosis and treatment for all patients, including cancellation and delay of chronic
75 illness surveillance¹. As authors report, following the first wave of contagion (2020), patients with
76 chronic peripheral arterial disease (PAD) presented with more severe stages of disease due to a
77 delayed or absent health access². Moreover as health services decline a significant rise also in lower
78 limb amputations was observed³⁻⁴. Data regarding the effects of interrupted services during the initial
79 and second waves of the pandemic are continuously emerging however little is known about gender
80 differences in PAD patients during pandemic. Generally, gender-specific data on PAD are lacking
81 and for women the disease is still under-recognized⁵.

82 This retrospective study aims to assess the impact of interrupted services for chronic PAD patients
83 and especially in women, according to access type (elective vs. urgent) and outcome (limb salvage
84 vs. amputation) in a single north-eastern Italian center over a period of 3 months prior to the
85 pandemic, during the first (2020) and during the second (2021) wave of contagion in northern Italy.

86 Materials and methods

87 This single-center retrospective observational study was conducted at Unit of Vascular and
88 Endovascular Surgery at University Hospital of Ferrara. The observational study was approved by
89 the local Ethics Committee (Approval number 277/19) and patients provided informed consent to
90 data collection. Patients were included in the analysis if they presented peripheral artery disease
91 (PAD) at Rutherford stages 3 to 6 that required revascularization between March 2019 and March
92 2021. Patients diagnosed with acute ischemia of the lower limbs from distal embolization of cardiac

93 origin were excluded. Then patients were classified into three groups, according to the period of
94 treatment:

- 95 - Pre-pandemic period from March 2019 to May 2019
- 96 - Pandemic-20 period from March 2020 to May 2020
- 97 - Pandemic-21 period from March 2021 to May 2021

98 The demographics characteristics, risk factors, comorbidities, previous revascularizations and all the
99 factors related to the PAD revascularization, including type of intervention, major and minor
100 amputation and length of hospital stay, were collected. In addition, for each patient a follow up period
101 of 12 months was scheduled, when re-interventions, mortality and other issues were monitored. For
102 the stratification of the state of PAD the Rutherford classification was utilized ⁶.

103 *Interventions*

104 The strategy of revascularization was based on symptoms, disease extension, anatomic complexity
105 and patients' comorbidities and included endovascular procedures (PTA, stenting) and/or open
106 surgery (endarterectomy, bypass surgery, minor or major amputation). The type of amputation was
107 defined as the highest level of amputation performed for each patient. Minor amputation was defined
108 as an amputation at the level of ankle joint and below. Amputations above this level were defined as
109 major amputations.

110 The endpoints of the study included: successful revascularization defined as arterial or graft patency
111 verified by ultrasound evaluation before discharge and at 30 days, reintervention at 30 days, major
112 amputation at 30 days and 12 months, limb salvage and mortality at 30 days and 12 months.

113 *The pandemic period and the surgical reorganization*

114 Nationally, all elective surgical activities were suspended at the beginning of the SARS-COV-2
115 pandemic, with interventions reserved for urgent cases only⁷. Outpatient clinics were also suspended
116 and follow-up controls interrupted. For patients with acute and critical limb requiring treatment,
117 hospital admission and rapid revascularization were undertaken (depending upon hospital bed,
118 disease severity and operating theatre availability).

119 At our center, a single weekly operating session and outpatient clinics were reintroduced in May
120 2020, with 3 operating sessions and 100% ward capacity reestablished by September 2020. As per
121 hospital protocol, COVID patients requiring urgent vascular interventions were hospitalized in
122 dedicated COVID wards and surgery was performed in dedicated COVID operating theaters. From
123 September 2020, chronic PAD patients' clinical pathway included follow up controls at the outpatient
124 clinics with imaging investigations (DUS, CTA and peripheral angiography).

125 *Statistical analysis*

126 Data are presented as mean \pm standard deviations or median (interquartile range) or number
127 (percentage) according to data nature and distribution. Data distribution was verified with the
128 Shapiro-Wilk test. The between-period comparison was carried out by means of chi-squared tests for
129 categorical variables and by One-way analysis of variance or Kruskal-Wallis test for continuous
130 variables. A p-value < 0.05 was considered as statistically significant. Statistical analysis has been
131 performed with MedCalc® Statistical Software version 20.014 (MedCalc Software Ltd, Ostend,
132 Belgium).

133 **Results**

134 The analyses included 28 patients in the Pre-pandemic period, 21 in the pandemic-20 and 39 in the
135 pandemic-21. During the First period, as expected, a reduced number of patients with chronic PAD
136 was admitted, compared to pre-pandemic activity. However, it was observed that in the both
137 pandemic periods patients presented with more severe stages of limb ischemia, Rutherford 5 and 6
138 stages (table 1). The mean age of patients was similar in the three periods but gender analysis revealed
139 a significantly reduced female proportion of overall treated patients in 2020 and 2021 compared to
140 the pre-pandemic period ($p=0.047$; Table 1).

141 Differences were also found between the three periods in terms of hospital access. In the pandemic-
142 20 the majority of patients presented to emergency department as scheduled admissions were
143 cancelled (table 2).

144 As reported in table (2) in the pre-pandemic period and in the pandemic-21 period endovascular
145 treatment was more frequently performed followed by open surgery and hybrid treatment.
146 Interestingly during the Pandemic-20, patients underwent mostly open surgery, followed by hybrid
147 procedures. No differences were observed between the three groups regarding major amputations.
148 Nevertheless the rate of patients who underwent revascularization together with a minor amputation
149 was higher in the pandemic-20 period. Length of hospital stay, type of discharge and in-hospital
150 mortality were similar in all groups. Early outcomes were also comparable including successful
151 revascularization although it was higher in the pre-pandemic group. No differences were observed in
152 mortality, as described in table 2. In the pandemic-21 group it was observed a higher rate of
153 reinterventions within 30 days but it did not include any minor or major amputation. In addition, the
154 rate of limb salvage was higher in the latter group although not statistically significant. During long-
155 term follow up, rates of limb salvage was observed to be significantly higher in the pandemic-21
156 group. Data regarding the female sex are reported in tables II and III. Besides the low rates of hospital
157 admissions in both pandemic periods, women were admitted in a higher stage of disease. No statistical
158 differences were observed in length of hospital stay although appeared slightly greater in women. At
159 12-month follow up limb salvage was similar between the two genders but slightly worse in women.

160

161 **Discussion**

162 The SARS-CoV-2 pandemic has led to a singular modification and reorganization of all hospital
163 services worldwide. Being in one of the regions most affected by the pandemic in Italy, also in our
164 hospital it was necessary to limit the flow of patients (for example, the reduction of surgical activities
165 and the suspension of outpatient activities) and enhance the assistance to patients with SARS-CoV-
166 2⁸. Therefore, the bed capacity of intensive care unit was firstly increased, consequently reducing the
167 number of ordinary hospital beds for all other pathologies and all outpatient checks were suspended.
168 This reorganization made the care pathways insufficient both in terms of diagnosis, follow up and
169 treatment for all clinical conditions other than SARS-CoV-2 infection.

170 In the field of vascular surgery, vascular surgical societies published guidelines regarding the
171 management of patients with vascular disease during the pandemic, indicating as a priority the aortic
172 aneurysmal pathology in the rupture phase or symptomatic carotid stenosis⁹⁻¹⁰. As reported in
173 literature also in our study we observed a reversal of hospitalizations in the COVID period with a
174 decrease in those in election and an increase in urgent ones^{11 12}. This inversion was linked to the
175 suspension of the scheduled operating sessions in the first pandemic period, which in turn prolonged
176 the waiting list for treatment, even if not in a statistically significant manner.

177 Lancaster et al² report that in the pandemic period, patients with PAD came to medical attention in
178 more serious conditions than in the pre-COVID period, with the need to choose treatments already
179 aimed at controlling complications and perioperative mortality. In our experience, a significant
180 increase in the most advanced stages, 4 and 6, has been highlighted in the whole pandemic period,
181 with a reduction of cases to stage 3. This reduction is probably also linked to the known fear of
182 patients with controllable symptoms of going to hospital due to the risk of contagion and also due to
183 the absence of outpatient activities that would have allowed them to be taken in charge for any
184 treatment.

185 In the COVER study, a covid-19 vascular service study¹³, it is described how in the pandemic period
186 it was necessary to change the therapeutic indications for patients with PAD with greater indication
187 for amputation or palliative treatments compared to revascularization procedures for those with
188 severe chronic ischemia and greater use of endovascular procedures such as first therapeutic option
189 in cases of critical ischemia. In our experience, no significant changes in the indications for treatment
190 have been observed thanks to an optimal organization of the surgical and anesthesia department which
191 has allowed us to offer the best treatment for each case. However, endovascular treatments were less
192 frequently performed due to the more severe stages of disease presentation but also due to the lack of
193 personnel occupied for the pandemic emergencies. The lower rates of successful revascularization
194 in both pandemic-20 and 21 groups together with the need of reintervention were predictable due to
195 the more severe stage of disease at presentation. As reported in literature also in our study was found

196 a higher rate of minor and major amputations during the pandemic¹⁴. Such finding was due to the
197 higher number of patients with more severe disease in this period rather to more stringent surgical
198 indications. During the pandemic-21 after a better organization of all vascular surgery services,
199 although patients presented still with advanced disease, management turned to be minimally
200 influenced by the pandemic with an increase in elective treatments and a higher rate of limb salvage
201 in the 12-month follow up.

202 An unexpected finding from this study is the significant reduction in female patients throughout the
203 pandemic period (pandemic-20 and pandemic-21 groups) compared to the previous year when there
204 were no differences between the two sexes. In the pandemic-20 this difference appears even more
205 evident since treatments on females represented 19% of the total while in the same period of the
206 previous year the male / female percentage was comparable (54% vs 46%). The reason for this
207 difference could be attributed to several socio-cultural factors. Galasso et al¹⁵, argue that women have
208 shown a greater perception of the severity of the pandemic and greater compliance with the restrictive
209 measures. Furthermore the arrival of the pandemic has resulted in an increase in family and domestic
210 organization activities for the female population, giving priority to these activities and with a greater
211 tendency to neglect their health¹⁶. Additionally, although the prevalence of PAD does not vary by
212 gender¹⁷, women present a higher prevalence of asymptomatic and atypical PAD¹⁸. As a result of
213 that, PAD, like cardiovascular diseases, remains underdiagnosed and undertreated. Taking into
214 account the restricted population of this study, women were characterized by more severe stages of
215 disease, required a longer hospital stay and had lower rates of limb salvage.

216 The main limitations of this study are inherent in its single centre, retrospective design. However, this
217 small study highlights the increased incidence of more severe comorbidities and disease, which have
218 important implications for the allocation of vascular resources for chronic PAD patients. Greater
219 efforts in atherosclerotic disease and the risk of limb loss information and awareness, especially for
220 women, are necessary.

221

222 **CONCLUSIONS**

223 In conclusion, despite the restrictions imposed by the pandemic, the good reorganization of the local
 224 vascular surgery service ensured as much as possible the quality and standard of treatment offered in
 225 the preceding periods. Our experience, albeit limited, has also shown that among patients suffering
 226 from PAD the impact of the pandemic was greater for the female gender. It is therefore important
 227 that in addition to a reorganization of hospital services to provide adequate care for patients with PAD
 228 in the pandemic period, greater information and awareness of women about atherosclerotic disease
 229 and the risk of limb loss.

230

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	Pre-pandemic	Pandemic 20	Pandemic 21	P value
Patients	28	21	39	
Age - y	77±10	76±8	73±10	0.14
Female sex	13 (46)	4 (19)	10 (25)	0.047
Comorbidities				
Hypertension	23 (82)	20 (95)	34 (87)	0.39
Ischemic heart disease	15 (54)	12 (57)	21 (54)	0.96
Diabetes	11 (39)	11 (52)	21 (54)	0.47
CKD	6 (21)	7 (33)	8 (21)	0.50
COPD	2 (7)	0 (0)	10 (27) *	0.011
Obesity	0 (0)	2 (11)	8 (21) ‡	0.035
COVID-19 +	N/A	0 (0)	1 (3)	0.87
ASA class				
3	23 (82)	13 (62)	25 (64)	0.44
4	5 (17)	8 (38)	14 (36)	
Peripheral artery disease severity				
Rutherford stage 3/4	16 (57)	7 (33) †	14 (36) ‡	<0.001
-Female patients	7 (54)	1(25)	2 (20)	
Rutherford stage 5/6	12 (43)	14 (67) †	25 (74) ‡	<0.001
-Female patients	6 (46)	3 (75)	8(80)	
Previous vascular surgery				
Lower limb^	12 (86)	11 (84)	11 (100)	0.41
Aorta	0 (0)	1 (8)	0 (0)	
Carotid	2 (14)	0 (0)	0 (0)	
Other	0 (0)	1 (8)	0 (0)	

Table 1: patients risk factors and comorbidities. CKD: chronic kidney disease COPD chronic obstructive pulmonary disease.

	Pre-pandemic 28	Pandemic 2020 21	Pandemic 2021 39	P value
Hospital access type:				
Emergent/Urgent	12 (43)	15 (71) †	16 (41) *	0.049
- <i>In Females (N°in tot)</i>	6/13	3/4	4/10	
Elective	16 (57)	6 (29) †	23 (59) *	
Type of intervention:				
Open surgery	8 (29)	11 (50)	10 (25)	0.76
- <i>In Females</i>	3(25)	3(75)	3 (38)	
Major amputation	1(f)	1(m)	3 (1 f 2 m)	
Endovascular	15 (53)	4 (18)	21(52)	0.41
Hybrid	5 (18)	6 (27)	9 (23)	
Revascularization+ minor amputation	2 (7)	4 (20)	5 (14)	
Length of hospital stay – d	13±15	15±12	11±10	0.41
- <i>In females</i>	14.1 ±14.39	11 ±5.23	12.20 ±8.12	
Type of discharge				
Ordinary	23 (82)	18 (86)	35 (88)	0.51
Support structure	2 (7)	2 (10)	0 (0)	
In-hospital mortality	3 (11)	1 (5)	4 (10)	
Outcomes				
30 Days follow up				
Successful revascularization	25(93)	16(80)	30 (83)	0.31
Re-intervention	3 (11)	4 (15)	6 (17)	0.09
Revascularization	1(3)	1(5)	6(17)	
- <i>In females</i>	0	0	4/10	
Minor amputation	0(0)	1(5)	0 (0)	0.031
Major amputation	2(7)	2(10)	0 (0) * ‡	
Limb salvage	26 (93)	18 (90)	36 (100)	0.11
- <i>In females</i>	12(92)	4(100)	9(90)	
12 months follow up				
Major amputation	1 (f)	2(1f)	0	0.56
Limb salvage	25 (89)	16 (80)	36 (100)	0.07
- <i>In females</i>	11 (85)	3(75)	9(90)	
Time to first reintervention, <i>months (range)</i>	6 ± 5	3 ± 1	4 ± 2	0.47
Follow-up, months	10±5	10±5	10±4	0.99

Table II

Table III

	Pre-pandemic	Pandemic 20	Pandemic 21	P value
Patients	28	21	39	
MORTALITY				
30 days	2 (7)	1 (5)	3 (8)	0.32
- In Females (N°in tot)	0	1/4	2/10	
				0.32
12 months	8 (29)	4 (20)	7 (18)	
- In Females (N°in tot)	6/13	1/4	0/10	

Table III: Data regarding early and late mortality in males and females in the three periods.