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Impact of COVID-19 pandemic on patients affected by peripheral arterial disease: an Italian single-center study

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) has evolved into a global pandemic, affecting a wide range of medical and surgical specialties. During COVID-19, we assisted in the reallocation of medical resources and services, as well as social distancing measures, and many patients with chronic diseases and comorbidities may have experienced difficulties in obtaining the correct medical care. The aim of the study was to investigate the impact of the COVID-19 pandemic on major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in patients with peripheral arterial disease (PAD) and chronic limb-threatening ischemia (CLTI), compared to previous years.

PATIENTS AND METHODS: We evaluated 1,335 hospital admissions of 877 patients with PAD admitted to Policlinico A. Gemelli Hospital between January 2017 and February 2020 and 368 hospital admissions of 272 patients with PAD admitted to the Policlinico A. Gemelli Hospital between March 2020 and March 2021. Data on demographic characteristics, comorbidities, symptoms, physical and radiological findings, laboratory tests, and routine visits before or after discharge were collected from electronic medical records.

RESULTS: Emergency room (ER) admissions among PAD patients during COVID-19 were higher than before the pandemic [190 (51.63%) *vs.* 579 (43.37%), $p = 0.01$]. A MACE was found in 78 (5.84%) pre-pandemic hospitalizations and 126 (34.24%) pandemic hospitalizations ($p < 0.01$). A MALE was identified in 942 (70.56%) pre-pandemic hospitalizations and 331 (89.95%) pandemic hospitalizations ($p < 0.01$). Amputation rates during the pandemic were higher than before the pandemic [80 (21.74%) *vs.* 191 (14.31%), $p < 0.01$]. The number of in-hospital deaths did not differ between the pandemic and pre-pandemic periods [11 (2.99%) *vs.* 51 (3.82%), $p = 0.55$].

CONCLUSIONS: In patients with PAD and CLTI, the number of MACE, MALE, and amputations was higher during the COVID-19 period compared to the three years before the pandemic.

Key Words:
SARS-CoV-2, COVID-19, Peripheral artery disease (PAD), Amputations.

Abbreviations

Novel coronavirus (SARS-CoV-2); Coronavirus disease 2019 (COVID-19); severe acute respiratory distress syndrome (ARDS); chronic limb-threatening ischemia (CLTI); peripheral arterial disease (PAD); major adverse cardiovascular events (MACE); major adverse limb events (MALE); International Classification of Diseases (ICD); computed tomography (CT); Gemelli Generator Real World Data (G2 RWD); low-density lipoprotein cholesterol (LDL-C); cerebrovascular disease (CVD); coronary artery disease (CAD); emergency room (ER); Wound, Ischemia, and foot Infection (WIfI); acute coronary syndrome (ACS).

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Introduction

In December 2019, a cluster of novel pneumonia associated with a novel coronavirus (SARS-CoV-2) was reported in Wuhan, China[1]. Coronavirus disease 2019 (COVID-19) is characterized by multiple symptoms, including cough, sore throat, fever, fatigue, headache, myalgia, arthralgia, conjunctival and nasal congestion[2]. More severe cases develop interstitial pneumonia and severe acute respiratory distress syndrome (ARDS)[2].

Although SARS-CoV-2 is known to primarily affect the respiratory system, it has also been associated[2] with systemic effects, including complications in the cardiovascular, hematological, neurological, immune, and renal systems. Given its rapid spread around the world, COVID-19 has become a global pandemic affecting various medical and surgical specialties.

Due to the growing number of COVID-19 hospitals, healthcare has shifted from providing routine care to emergency care only[3]. Most outpatient visits and primary care physician visits have been reduced to the minimum[3]. In addition, the hospitals instituted priority levels for COVID-19 patients, postponing all planned surgery procedures for chronic conditions[3]. Consequently, patients with chronic diseases and comorbidities struggle to receive adequate care from conventional healthcare networks, even taking into account the limitations due to disease control measures[4].

In particular, a study[3] conducted in the Netherlands showed that the rate of amputations in 2020 (42%), was higher than in 2019 (18%) and 2018 (15%). Furthermore, patients with chronic limb-threatening ischemia (CLTI) who underwent surgery showed a higher Rutherford grade of ischemic injury. A study[4] conducted in Italy also showed higher amputation rates during the pandemic.

Lower extremity peripheral arterial disease (PAD) represents one of the manifestations of systemic atherosclerotic disease. It affects approximately 230 million people worldwide[5]. Nonetheless, it remains an underdiagnosed and undertreated entity[5]. Approximately 60% of patients with PAD are affected by coronary artery disease (CAD) and 30% are affected by cerebrovascular disease (CVD)[6]. PAD is also associated with a high risk of adverse outcomes, including major adverse cardiovascular events (MACE) and major adverse limb events (MALE)[5,6].

PAD can be asymptomatic, characterized by pain during walking (intermittent claudication), pain at rest, and tissue loss, in the case of CLTI. Specifically, CLTI represents the end stage of the disease, with an increasing prevalence and a high impact on healthcare worldwide[6,7].

The purpose of this study was to assess the impact of the COVID-19 pandemic on the development of MACE, MALE and amputations in patients with PAD and CLTI in a single Italian center, from March 2020 to March 2021, compared to previous years, from January 2017 to February 2020.

Patients and Methods

We evaluated 1,703 hospital admissions of 1,080 inpatients with PAD and CLTI who were consecutively admitted at Policlinico A. Gemelli Hospital between January 2017 and March 2021.

The study was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy. Patient consent was waived due to organizational issues.

Our cohort was divided into two groups based on the period of hospitalization: pre-pandemic hospitalizations (January 2017 to February 2020) and pandemic hospitalizations (March 2020 to March 2021).

All patients over 18 years of age with PAD category 4, 5 or 6, according to the Rutherford classification, and with CLTI, as previously defined[8-10], were included in the study.

Using machine learning techniques, data on demographic characteristics, comorbidities, as defined according to the International Classification of Diseases (ICD)-11codes, symptoms, physical and radiological findings [particularly lower extremity ultrasound evaluation, computed tomography (CT) angiography and angiography], and laboratory tests, were collected retrospectively. Routine data before or after hospital discharge were also collected.

Structured and unstructured clinical data were automatically extracted from electronic medical records using the hospital's data science facility Gemelli Generator Real World Data (G2 RWD)[11].

Variables for the pandemic period were extracted from the COVID-19 DataMart[12], an ontology-based data mart elaborated by an interdisciplinary team composed of vascular medicine experts and engineers. The same extraction procedures were applied to the pre-pandemic period using the corresponding data sources.

The outcomes of the analysis were MACE, defined as acute myocardial infarction, stroke and cardiovascular death, MALE, defined as acute limb ischemia, CLTI requiring revascularization, amputations, and in-hospital mortality.

Statistical Analysis

Traditional statistical methods were employed in order to assess the significance of observed differences. Continuous variables were compared with a *t*-test or Mann-Whitney U test, according to their distributions. The normality of distributions was tested by the Shapiro-Wilk test.

Categorical variables were compared using the Chi-squared test or Fisher's exact test. Fisher's exact test was used when the number of observations was lower than 100 or when 20% of the cells in the contingency table had a frequency lower than 5.

When comparing the populations across four years included in the study (2017, 2018, 2019, 2020), continuous variables were compared using ANOVA or non-parametric Kruskal-Wallis test, according to their distributions. A p-value < 0.05 was considered statistically significant. All analyses were performed by R software version 4.2.0 (CRAN®, R Core 2022, Vienna, Austria), and data were stored in SAS Viya V.03.05 and accessed through R with SWAT library version 1.5.0.

Results

Characteristics of the Study Population

In total, we evaluated 1,703 medical records of 1,080 patients affected by PAD for our study. We included 1,335 medical records of 877 patients admitted to the Policlinico A. Gemelli Hospital between January 2017 and February 2020 and 368 medical records of 272 patients admitted to the Policlinico A. Gemelli Hospital between March 2020 and March 2021.

The median age of the patients included in the study was 73 (IQR: 65-80). 1,191 (69.94%) hospitalizations referred to male patients. Regarding the Rutherford classification, 491 (24.72 %) hospitalizations were for PAD Rutherford category 4; 192 (11.27%) for PAD Rutherford category 5 and 1,090 (64%) for PAD Rutherford category 6.

Across all the medical records evaluated, median low-density lipoprotein cholesterol (LDL-C) level was 70 mg/dl (IQR: 53-90.75); median glycated hemoglobin level was 55 mmol/mol (IQR: 45-69); median C-reactive protein level was 94.45 mg/L (IQR: 33.77-153.50); median procalcitonin level was 0.26 ng/ml (IQR: 0.11-0.68); median NT-proBNP level was 3,393.00 pg/ml (IQR: 781.00-12,325.00); median neutrophil level was 5.99 $\times 10^9$/l (IQR: 4.36-8.44); median platelet level was 265.00 $\times 10^9$/l (IQR: 201.00-348.00).

Of the assessed medical records, 805 (47.27%) had a history of CAD; 237 (13.92%) had heart failure, 206 (12.10%) had CVD and 1,271 (74.63%) had a diabetes mellitus diagnosis. Smoking habits were found in 181 (10.63%) medical records, but 589 (34.59%) of them had no relevant data. The complete demographic and clinical characteristics of the population are shown in Table I.

Characteristics of the Study Population Before and During the Pandemic

The clinical characteristics of the population assessed in the pre-pandemic period and during the pandemic were similar (Table II). Emergency room (ER) admissions for PAD were higher during the pandemic than before the pandemic [190 (51.63%) *vs.* 579 (43.37%), $p = 0.01$].

Male sex was more represented than female sex, both in the pre-pandemic period and during the pandemic. Patients did not differ in total cholesterol levels ($p = 0.36$); creatinine levels ($p = 0.52$); glycated hemoglobin ($p = 0.95$); procalcitonin levels ($p = 0.84$), C-reactive protein levels ($p = 0.87$). LDL-C levels were higher in the pre-pandemic period than in the pandemic period ($p = 0.03$), and high-density lipoprotein cholesterol (HDL-C) levels were higher in the pre-pandemic period than in the pandemic period ($p < 0.01$).

The Rutherford category of disease was similar in the pre-pandemic and pandemic populations evaluated ($p = 0.07$).

A history of CAD was found in 612 (45.84%) pre-pandemic medical records and 193 (52.45%) pandemic medical records ($p < 0.02$); heart failure was found in 135 (10.11%) pre-pandemic and 102 (27.72%) pandemic medical records ($p < 0.01$); CVD was found in 153 (11.46%) pre-pandemic and 53 (14.40%) pandemic medical records ($p < 0.05$), and diabetes mellitus diagnosis was found in 1,008 (75.51%) pre-pandemic and 263 (71.47%) pandemic medical records ($p < 0.03$). Hypertension was found in 550 (41.20%) pre-pandemic and 277 (75.27%) pandemic hospitalizations ($p < 0.01$). Smoking habits were recorded in 105 (7.87%) pre-pandemic medical records and 76 (20.65%) pandemic medical records ($p < 0.01$).

Table I. Demographic characteristics and clinical data of the study population.

	Hospitalizations, n = 1,703
Age, median (IQR)	73.00 (65.00 - 80.00)
Albumin, g/L, median (IQR)	34.00 (28.00 - 39.00)
Urea nitrogen, mg/dL, median (IQR)	24.00 (17.00 - 38.00)
Total cholesterol, mg/dL, median (IQR)	129.00 (106.00 - 157.50)
HDL cholesterol, mg/dL, median (IQR)	35.00 (27.00 - 43.00)
LDL cholesterol, mg/dL, median (IQR)	70.00 (53.00 - 90.75)
Triglycerides, mg/dL, median (IQR)	112.50 (84.00 - 149.00)
Creatinine, mg/dL, median (IQR)	1.09 (0.82 - 1.87)
D-dimer, ng/mL, median (IQR)	1,173.00 (667.50 – 2,335.00)
Hb1Ac, mmol/mol, median (IQR)	55.00 (45.00 - 69.00)
Hemoglobin, g/dL, median (IQR)	11.50 (10.10 - 13.20)
Fibrinogen, mg/dL, median (IQR)	459.00 (363.00 - 614.00)
Fasting bood glucose, mg/dL, median (IQR)	121.00 (93.00 - 169.00)
Neutrophil count, $\times 10^9$/L, median (IQR)	5.99 (4.36 - 8.44)
Lymphocytes count, $\times 10^9$/L, median (IQR)	1.65 (1.23 - 2.19)
MCV, fL, median (IQR)	88.60 (84.30 - 93.27)
NT-ProBNP, pg/mL, median (IQR)	3,393.00 (781.00 - 12,325.00)
Platelets, $\times 10^9$/L, median (IQR)	265.00 (201.00 - 348.00)
Procalcitonin, ng/mL, median (IQR)	0.26 (0.11 - 0.68)
C-reactive protein, mg/L, median (IQR)	94.45 (33.77 - 153.50)
ALT, UI/L, median (IQR)	13.00 (9.00 - 20.00)
AST, UI/L, median (IQR)	17.00 (13.00 - 22.00)
Pre-pandemic hospitalizations, n (%)	1,335.00 (78.39)
Pandemic hospitalizations, n (%)	368.00 (21.61)
Male, n (%)	1191.00 (69.94)
Rutherford II-4, n (%)	421.00 (24.72)
Rutherford III-5, n (%)	192.00 (11.27)
Rutherford III-6, n (%)	1,090.00 (64.00)
ER visits, n (%)	769.00 (45.16)
Amputations, n (%)	271.00 (15.91)
MACE, n (%)	204.00 (11.98)
MALE, n (%)	1,273.00 (74.75)
CVD, n (%)	206.00 (12.10)
Heart failure, n (%)	237.00 (13.92)
CAD, n (%)	805.00 (47.27)
Atrial fibrillation, n (%)	280.00 (16.44)
COPD, n (%)	270.00 (15.85)
Obesity, n (%)	31.00 (1.82)
Hypercholesterolemia, n (%)	420.00 (24.66)
Hypertension, n (%)	827.00 (48.56)
Diabetes, n (%)	1,271.00 (74.63)
Cancer, n (%)	187.00 (10.98)
Sepsis, n (%)	242.00 (14.21)
Smoking, n (%)	181.00 (10.63)
Cognitive impairment, n (%)	316.00 (18.56)
Autoimmune disease, n (%)	48.00 (2.82)
Chronic kidney disease, n (%)	758.00 (44.51)
Death, n (%)	62.00 (3.64)

ER, emergency room; MACE, major adverse cardiovascular events; MALE, major adverse limb events; CVD, cerebrovascular disease; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease.

Incidence of MACE, MALE and Death Before and During the Pandemic

Of the total hospitalizations analyzed, 204 (11.98%) were associated with a MACE, 1,273 (74.75%) were associated with a MALE, and 271 (15.91%) were associated with amputation procedures. 62 (3.64%) of the hospitalized patients died (Table I). Comparing the pandemic and pre-pandemic periods, a MACE was observed in 78 (5.84%) pre-pandemic hospitalizations and 126 (34.24%) pandemic hospitalizations. The increase in MACE during the pandemic was significant compared to the pre-pandemic period ($p < 0.01$) (Table II).

Table II. Demographic characteristics and clinical data of the study population before and during pandemic.

	Pre-pandemic	Pandemic	
	Hospitalizations, n = 1,335	Hospitalizations, n = 368	*p*-value
Age, median (IQR)	73.00 (65.00 - 80.00)	73.00 (64.00 - 80.00)	0.79
Albumin, g/L, median (IQR)	33.00 (28.00 - 38.00)	34.00 (28.00 - 39.00)	0.09
Urea nitrogen, mg/dL, median (IQR)	24.00 (17.00 - 37.00)	26.00 (17.00 - 42.00)	0.05
Total cholesterol, mg/dL, median (IQR)	129.00 (107.00 - 159.00)	127.00 (105.00 - 155.00)	0.36
HDL cholesterol, mg/dL, median (IQR)	35.00 (28.00 - 44.00)	32.00 (25.00 - 39.00)	< 0.01
LDL cholesterol, mg/dL, median (IQR)	71.00 (53.00 - 93.00)	67.00 (51.00 - 84.00)	0.03
Triglycerides, mg/dL, median (IQR)	113.00 (84.00 - 149.00)	112.00 (85.00 - 155.00)	0.53
Creatinine, mg/dL, median (IQR)	1.10 (0.82 - 1.85)	1.06 (0.78 - 2.00)	0.52
D-dimer, ng/mL, median (IQR)	1,347.00 (741.50 - 2,374.50)	926.00 (559.00 - 1,902.25)	0.02
Hb1Ac, mmol/mol, median (IQR)	54.00 (45.00 - 68.00)	55.00 (44.00 - 69.00)	0.95
Hemoglobin, g/dL, median (IQR)	11.40 (10.00 - 13.10)	11.70 (10.20 - 13.40)	0.05
Fibrinogen, mg/dL, median (IQR)	458.00 (360.00 - 615.00)	465.00 (380.00 - 613.00)	0.29
Fasting bood glucose, mg/dL, median (IQR)	119.00 (91.00 - 165.00)	127.00 (96.00 - 177.50)	0.01
Neutrophil count, $\times 10^9$/L, median (IQR)	5.93 (4.30 - 8.28)	6.22 (4.45 - 9.32)	0.01
Lymphocytes count, $\times 10^9$/L, median (IQR)	1.66 (1.24 - 2.21)	1.59 (1.22 - 2.12)	0.09
MCV, fL, median (IQR)	88.90 (84.50 - 93.50)	88.00 (83.00 - 92.10)	0.01
NT-ProBNP, pg/mL, median (IQR)	3,208.00 (670.50 - 12,330.50)	3579.00 (1,104.00 - 12,267.00)	0.4
Platelets, $\times 10^9$/L, median (IQR)	267.00 (203.00 - 349.00)	258.00 (199.00 - 337.00)	0.36
Procalcitonin, ng/mL, median (IQR)	0.25 (0.11 - 0.63)	0.26 (0.11 - 0.80)	0.84
C-reactive protein, mg/L, median (IQR)	94.95 (36.62 - 152.27)	93.55 (18.68 - 176.18)	0.87
ALT, UI/L, median (IQR)	13.00 (9.00 - 20.00)	13.00 (9.00 - 19.00)	0.73
AST, UI/L, median (IQR)	17.00 (13.00 - 22.00)	17.00 (13.00 - 22.00)	0.63
Male, n (%)	925.00 (69.29)	266.00 (72.28)	0.3
Rutherford II-4, n (%)	346.00 (25.92)	75.00 (20.38)	
Rutherford III-5, n (%)	152.00 (11.39)	40.00 (10.87)	0.07
Rutherford III-6, n (%)	837.00 (62.70)	253.00 (68.75)	
ER visits, n (%)	579.00 (43.37)	190.00 (51.63)	0.01
Amputations, n (%)	191.00 (14.31)	80.00 (21.74)	< 0.01
Below-knee amputations, n (%)	46.00 (3.45)	30.00 (8.15)	
Foot amputations, n (%)	49.00 (3.67)	10.00 (2.72)	
Above the knee amputations, n (%)	66.00 (4.94)	23.00 (6.25)	0.03
Toe amputations, n (%)	18.00 (1.35)	7.00 (1.90)	
Revision amputation surgery, n (%)	9.00 (0.67)	8.00 (2.17)	
MACE, n (%)	78.00 (5.84)	126.00 (34.24)	< 0.01
MALE, n (%)	942.00 (70.56)	331.00 (89.95)	< 0.01
CVD, n (%)	153.00 (11.46)	53.00 (14.40)	0.05
Heart failure, n (%)	135.00 (10.11)	102.00 (27.72)	< 0.01
CAD, n (%)	612.00 (45.84)	193.00 (52.45)	< 0.02
Atrial fibrillation, n (%)	208.00 (15.58)	72.00 (19.57)	0.04
COPD, n (%)	200.00 (14.98)	70.00 (19.02)	0.05
Obesity, n (%)	12.00 (0.90)	19.00 (5.16)	< 0.01
Hypercholesterolemia, n (%)	271.00 (20.30)	149.00 (40.49)	0.09
Hypertension, n (%)	550.00 (41.20)	277.00 (75.27)	< 0.01
Diabetes, n (%)	1,008.00 (75.51)	263.00 (71.47)	< 0.03
Cancer, n (%)	116.00 (8.69)	71.00 (19.29)	0.12
Sepsis, n (%)	160.00 (11.99)	82.00 (22.28)	0.49
Smoking, n (%)	105.00 (7.87)	76.00 (20.65)	0.01
Cognitive impairment, n (%)	211.00 (15.81)	105.00 (28.53)	0.35
Autoimmune disease, n (%)	37.00 (2.77)	11.00 (2.99)	0.2
Chronic kidney disease, n (%)	595.00 (44.57)	163.00 (44.29)	< 0.02
Death, n (%)	51.00 (3.82)	11.00 (2.99)	0.55

ER, emergency room; MACE, major adverse cardiovascular events; MALE, major adverse limb events; CVD, cerebrovascular disease; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease.

A MALE was identified in 942 (70.56%) pre-pandemic hospitalizations and 331 (89.95%) pandemic hospitalizations. Also, in this case, the difference in MALE between the two groups was significant ($p < 0.01$) (Table II).

In particular, amputation rates during the pandemic were higher than before the pandemic [80 (21.74%) *vs.* 191 (14.31%), $p < 0.01$].

Instead, the number of in-hospital deaths did not differ between the pandemic and pre-pandemic periods [11 (2.99%) *vs.* 51 (3.82%), $p = 0.55$] (Table II).

In particular, hospitalized patients who underwent amputation had a higher incidence of MACE during the pandemic than before the pandemic [33 (41.25%) *vs.* 12 (6.28%), $p = 0.02$] and a higher incidence of heart failure [27 (33.75%) *vs.* 14 (7.33%), $p = 0.01$] (Table III).

Hospitalized patients who underwent amputation before and during the pandemic did not differ for the history of CAD [48 (60%) *vs.* 88 (46.7%), $p = 0.36$], and CVD [12 (15%) *vs.* 14 (7.33%), $p = 1$]. Instead, a history of diabetes was higher in pre-pandemic inpatients compared to pandemic inpatients [158 (82.72%) *vs.* 59 (73.75%), $p = 0.01$] (Table III).

In terms of amputation type, there were 30 (37.50%) below-knee amputations during the pandemic, compared to 46 (24.08%) before the pandemic ($p < 0.03$); 10 (12.50%) foot amputations during the pandemic and 49 (25.65%) in the pre-pandemic period ($p < 0.03$); 23 (28.75%) above the knee amputations during the pandemic and 66 (34.55%) during the pre-pandemic period ($p < 0.03$) and 7 (8.75%) toe amputations during the pandemic and 18 (9.42%) during the pre-pandemic period ($p < 0.03$). In-hospital deaths were similar in the pandemic and pre-pandemic periods among amputated inpatients [7 (8.75%) *vs.* 15 (7.85%), $p = 1$] (Table III).

Similarly, non-amputee patients had a higher incidence of MACE during the pandemic than before the pandemic [93 (32.29%) *vs.* 66.00 (5.77%), $p < 0.02$] (Table IV). Non-amputee patients had a higher incidence of MALE during the pandemic than before the pandemic [251.00 (87.15%) *vs.* 751.00 (65.65%), $p < 0.03$] (Table IV). Moreover, they had a higher incidence of CAD [145 (50.35%) *vs.* 524 (45.80%), $p < 0.01$], CVD [41 (14.24 %) *vs.* 139 (12.15%), $p < 0.04$] and heart failure [121 (10.58%) *vs.* 75 (26.04%), $p < 0.01$] during the pandemic than before the pandemic (Table IV).

Mortality was similar in non-amputee patients during the pandemic and before the pandemic [4 (1.39%) *vs.* 36 (3.15%), $p = 0.16$] (Table IV).

Discussion

The main findings of this study were that during COVID-19 pandemic, hospitalized PAD patients experienced more MACE, MALE and amputations, than PAD patients admitted before the pandemic. Instead, the number of in-hospital deaths was similar in the two periods evaluated.

Previous evidence[3,4,13,14] showed that amputation rates were higher before the pandemic than during the pandemic. Interestingly, in a cohort of 885 Dutch patients, Exelmans et al[13] showed a higher amputation rate for PAD Fontaine stage 4 in 2020 compared to 2018 and 2019, with a significant increase in surgeries performed in 2020 compared to 2018. They showed, conversely, a significant reduction of femoro-popliteal bypass in 2020 compared to 2018[13]. Another study by Lancaster et al[14] showed that PAD patients at hospital admission had a more severe condition during the pandemic, compared with the six months before the pandemic; in particular, patients with CLTI had a significantly increased infectious component according to the Wound, Ischemia, and foot Infection (WIfI) score[14]. Our cohort experienced an increase in the number of Rutherford category 6 hospitalizations during the pandemic compared to pre-pandemic. However, this increase was not significant. We observed even an increase in the number of PAD patients admitted to emergency departments during the pandemic compared to before the pandemic. This phenomenon may be associated with more severe PAD requiring ER visits, even accounting for higher amputation rates during the pandemic. However, an increase in emergency department admissions due to a decrease in elective surgery program admissions cannot be completely ruled out.

Among the cohorts analyzed, males were most prevalent among amputees and non-amputees during the two periods evaluated.

Interestingly, a retrospective analysis by Traina et al[15], aimed at assessing the impact of interruption in medical services for PAD patients during the pandemic, showed that vascular surgeries on female patients were markedly reduced during the pandemic compared to the pre-pandemic period[15].

Although the prevalence of PAD appears to be similar in people over the age of 70 years[16], a study by Egorova et al[17] showed that, regardless of age, women had lower rates of PAD-related hospitalizations compared to men[17], which is consistent with our finding. Specifically, Egorova et al[17] showed that women were more likely to be hos-

Table III. Demographic characteristics and clinical data of amputee patients before and during pandemic.

	Pre-pandemic	Pandemic	
	Amputations, n = 191	Amputations, n = 80	*p*-value
Age, median (IQR)	69.00 (60.00 - 76.50)	69.00 (58.75 - 77.25)	0.93
Albumin, g/L, median (IQR)	26.00 (23.00 - 31.00)	28.00 (23.00 - 31.00)	0.36
Urea nitrogen, mg/dL, median (IQR)	27.00 (17.00 - 41.00)	25.00 (15.00 - 49.00)	0.98
Total cholesterol, mg/dL, median (IQR)	113.00 (93.00 - 133.00)	113.00 (93.50 - 140.00)	0.46
HDL cholesterol, mg/dL, median (IQR)	25.00 (21.00 - 32.50)	25.00 (21.25 - 29.75)	0.68
LDL cholesterol, mg/dL, median (IQR)	61.00 (48.00 - 77.00)	66.00 (53.00 - 87.00)	0.26
Triglycerides, mg/dL, median (IQR)	117.00 (84.00 - 153.00)	122.00 (88.75 - 162.25)	0.41
Creatinine, mg/dL, median (IQR)	1.23 (0.82 - 2.62)	1.08 (0.78 - 2.17)	0.69
D-dimer, ng/mL, median (IQR)	1,794.00 (1,076.50 - 3,028.75)	1,759.00 (993.00 - 3,319.50)	0.9
Hb1Ac, mmol/mol, median (IQR)	59.00 (50.00 - 75.00)	67.00 (52.75 - 78.50)	0.33
Hemoglobin, g/dL, median (IQR)	9.90 (8.70 - 11.00)	10.30 (9.40 - 11.95)	0.02
Fibrinogen, mg/dL, median (IQR)	597.00 (451.00 - 768.00)	623.00 (474.50 - 865.50)	0.22
Fasting bood glucose, mg/dL, median (IQR)	132.00 (90.00 - 194.50)	149.00 (110.50 - 207.00)	0.06
Neutrophil count, $\times 10^9$/L, median (IQR)	8.06 (5.86 - 10.68)	8.60 (5.90 - 12.54)	0.35
Lymphocytes count, $\times 10^9$/L, median (IQR)	1.43 (1.11 - 1.90)	1.31 (1.06 - 1.61)	0.04
MCV, fL, median (IQR)	87.10 (82.70 - 91.90)	87.80 (83.28 - 91.30)	0.9
NT-ProBNP, pg/mL, median (IQR)	6,659.50 (2,005.75 - 14,000.00)	4,198.00 (1,219.75 - 16,251.00)	0.44
Platelets, $\times 10^9$/L, median (IQR)	351.00 (267.50 - 445.50)	282.50 (222.75 - 426.25)	0.03
Procalcitonin, ng/mL, median (IQR)	0.24 (0.12 - 0.67)	0.40 (0.13 - 1.12)	0.34
C-reactive protein, mg/L, median (IQR)	126.40 (67.25 - 175.57)	180.55 (110.47 - 204.27)	0.08
ALT, UI/L, median (IQR)	13.00 (9.00 - 23.25)	12.50 (8.25 - 19.00)	0.51
AST, UI/L, median (IQR)	16.00 (12.00 - 24.75)	18.00 (13.00 - 26.50)	0.48
Male, n (%)	145.00 (75.92)	61.00 (76.25)	1
Rutherford II-4, n (%)	1.00 (0.52)	0.00 (0.00)	
Rutherford III-5, n (%)	3.00 (1.57)	0.00 (0.00)	0.43
Rutherford III-6, n (%)	187.00 (97.91)	80.00 (100.00)	
ER visits, n (%)	141.00 (73.82)	67.00 (83.75)	0.11
Below-knee amputations, n (%)	46.00 (24.08)	30.00 (37.50)	
Foot amputations, n (%)	49.00 (25.65)	10.00 (12.50)	0.03
Above the knee amputations, n (%)	66.00 (34.55)	23.00 (28.75)	
Toe amputations, n (%)	18.00 (9.42)	7.00 (8.75)	
Revision amputation surgery, n (%)	9.00 (4.71)	8.00 (10.00)	
MACE, n (%)	12.00 (6.28)	33.00 (41.25)	< 0.02
CVD, n (%)	14.00 (7.33)	12.00 (15.00)	1
Heart failure, n (%)	14.00 (7.33)	27.00 (33.75)	< 0.01
CAD, n (%)	88.00 (46.07)	48.00 (60.00)	0.36
Atrial fibrillation, n (%)	27.00 (14.14)	14.00 (17.50)	0.32
COPD, n (%)	11.00 (5.76)	13.00 (16.25)	0.42
Obesity, n (%)	2.00 (1.05)	4.00 (5.00)	0.41
Hypercholesterolemia, n (%)	29.00 (15.18)	32.00 (40.00)	0.18
Hypertension, n (%)	72.00 (37.70)	59.00 (73.75)	0.25
Diabetes, n (%)	158.00 (82.72)	59.00 (73.75)	0.01
Cancer, n (%)	9.00 (4.71)	24.00 (30.00)	< 0.01
Sepsis, n (%)	46.00 (24.08)	38.00 (47.50)	0.37
Smoking, n (%)	12.00 (6.28)	18.00 (22.50)	0.11
Cognitive impairment, n (%)	24.00 (12.57)	26.00 (32.50)	0.24
Autoimmune disease, n (%)	4.00 (2.09)	2.00 (2.50)	0.69
Chronic kidney disease, n (%)	98.00 (51.31)	40.00 (50.00)	0.01
Death, n (%)	15.00 (7.85)	7.00 (8.75)	1

ER, emergency room; MACE, major adverse cardiovascular events; MALE, major adverse limb events; CVD, cerebrovascular disease; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease.

Table IV. Demographic characteristics and clinical data of non-amputee patients before and during pandemic.

	Pre-pandemic	Pandemic	
	No amputations, n = 144	No amputations, n = 288	*p*-value
Age, median (IQR)	74.00 (65.00 - 81.00)	73.50 (66.00 - 80.00)	0.84
Albumin, g/L, median (IQR)	35.00 (30.00 - 39.00)	37.00 (31.00 - 40.00)	0.01
Urea nitrogen, mg/dL, median (IQR)	24.00 (17.00 - 36.00)	26.00 (18.00 - 41.00)	0.03
Total cholesterol, mg/dL, median (IQR)	133.00 (109.00 - 162.00)	131.00 (109.00 - 158.75)	0.39
HDL cholesterol, mg/dL, median (IQR)	36.00 (29.00 - 45.00)	34.00 (27.00 - 40.00)	< 0.01
LDL cholesterol, mg/dL, median (IQR)	72.00 (54.00 - 94.00)	67.00 (51.00 - 84.00)	0.01
Triglycerides, mg/dL, median (IQR)	112.00 (84.00 - 147.00)	110.00 (85.00 - 149.00)	0.84
Creatinine, mg/dL, median (IQR)	1.08 (0.82 - 1.76)	1.03 (0.78 - 1.88)	0.51
D-dimer, ng/mL, median (IQR)	1,109.00 (643.50 – 2,244.00)	792.00 (513.00 - 1,173.00)	0.01
Hb1Ac, mmol/mol, median (IQR)	53.00 (44.00 - 68.00)	53.00 (43.00 - 64.00)	0.49
Hemoglobin, g/dL, median (IQR)	11.70 (10.40 - 13.30)	12.00 (10.80 - 13.70)	0.03
Fibrinogen, mg/dL, median (IQR)	440.00 (352.25 - 581.75)	437.00 (362.00 - 572.00)	0.89
Fasting bood glucose, mg/dL, median (IQR)	117.00 (91.00 - 162.00)	120.50 (95.00 - 172.25)	0.12
Neutrophil count, $\times 10^9$/L, median (IQR)	5.70 (4.15 - 7.79)	5.80 (4.36 - 8.16)	0.09
Lymphocytes count, $\times 10^9$/L, median (IQR)	1.72 (1.28 - 2.24)	1.68 (1.29 - 2.23)	0.8
MCV, fL, median (IQR)	89.10 (84.80 - 93.70)	88.10 (83.00 - 92.20)	0.01
NT-ProBNP, pg/mL, median (IQR)	2,464.00 (549.50 - 12,195.50)	3579.00 (1,064.50 - 10,820.00)	0.32
Platelets, $\times 10^9$/L, median (IQR)	257.00 (197.00 - 326.50)	251.00 (194.00 - 325.00)	0.5
Procalcitonin, ng/mL, median (IQR)	0.28 (0.11 - 0.60)	0.22 (0.10 - 0.66)	0.55
C-reactive protein, mg/L, median (IQR)	77.55 (25.80 - 143.88)	57.90 (16.27 - 137.65)	0.3
ALT, UI/L, median (IQR)	13.00 (9.00 - 19.00)	13.00 (9.00 - 19.00)	1
AST, UI/L, median (IQR)	17.00 (13.00 - 22.00)	17.00 (13.00 - 22.00)	0.87
Male, n (%)	780.00 (68.18)	205.00 (71.18)	0.36
Rutherford II-4, n (%)	345.00 (30.16)	75.00 (26.04)	
Rutherford III-5, n (%)	149.00 (13.02)	40.00 (13.89)	0.39
Rutherford III-6, n (%)	650.00 (56.82)	173.00 (60.07)	
ER visits, n (%)	438.00 (38.29)	123.00 (42.71)	0.19
MACE, n (%)	66.00 (5.77)	93.00 (32.29)	< 0.02
MALE, n (%)	751.00 (65.65)	251.00 (87.15)	< 0.03
CVD, n (%)	139.00 (12.15)	41.00 (14.24)	0.04
Heart failure, n (%)	121.00 (10.58)	75.00 (26.04)	0.01
CAD, n (%)	524.00 (45.80)	145.00 (50.35)	< 0.01
Atrial fibrillation, n (%)	181.00 (15.82)	58.00 (20.14)	0.09
COPD, n (%)	189.00 (16.52)	57.00 (19.79)	0.04
Obesity, n (%)	10.00 (0.87)	15.00 (5.21)	< 0.01
Hypercholesterolemia, n (%)	242.00 (21.15)	117.00 (40.62)	0.19
Hypertension, n (%)	478.00 (41.78)	218.00 (75.69)	< 0.01
Diabetes, n (%)	850.00 (74.30)	204.00 (70.83)	< 0.02
Cancer, n (%)	107.00 (9.35)	47.00 (16.32)	1
Sepsis, n (%)	114.00 (9.97)	44.00 (15.28)	0.59
Smoking, n (%)	93.00 (8.13)	58.00 (20.14)	0.03
Cognitive impairment, n (%)	187.00 (16.35)	79.00 (27.43)	0.71
Autoimmune disease, n (%)	33.00 (2.88)	9.00 (3.12)	0.28
Chronic kidney disease, n (%)	497.00 (43.44)	123.00 (42.71)	< 0.02
Death, n (%)	36.00 (3.15)	4.00 (1.39)	0.16

ER, emergency room; MACE, major adverse cardiovascular events; MALE, major adverse limb events; CVD, cerebrovascular disease; CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease.

pitalized in emergency situations than men, suggesting that female patients may be hospitalized with more advanced PAD, as Vouyouka et al[18] later confirmed in their study. There are several hypotheses that could justify this sex difference in hospitalization rates. In particular, it has been hypothesized[17-19] that PAD symptoms in women are not recognized because they are atypical or masked by other conditions and pathologies. In fact, Bakılan et al[20], in an interesting study aimed

at evaluating musculoskeletal symptoms and their related factors of COVID-19 patients, showed that 65% of patients admitted to physical medicine and rehabilitation clinics for musculoskeletal problems were females[20].

In addition, women with PAD are more likely to be older, live isolated, and have lower incomes. For all these reasons, they can ignore their symptoms, without referring to specialized centers[17-19].

However, gender differences in PAD diagnosis, treatment, and access to healthcare require further investigation.

By analyzing differences in clinical characteristics between the pre-pandemic and the pandemic periods, we found no differences in total cholesterol levels, glycated hemoglobin levels, C-reactive protein and creatinine levels in our population. Moreover, LDL-C levels were higher in the pre-pandemic period compared to the pandemic period. Before the pandemic, we also observed a large number of diabetic patients, while smoking habits and history of hypertension were higher during the pandemic than before the pandemic. An interesting study by Kıral et al[21], aimed at assessing the impact of smoking during the pandemic, showed that smoking behavior did not change in 63.4% of the analyzed population. Among patients who changed their smoking behavior, stress was the leading cause for patients to increase and start smoking again, while for those who reduced their number of cigarettes and quit smoking, health concerns related to the pandemic were the leading cause[21].

It is well known that the most important cardiovascular risk factors are dyslipidemia, diabetes, smoking habit, chronic kidney disease, and inflammation[22-26]. Moreover, it was shown that COVID-19 pandemic acted on the cardiovascular risk profile. In fact, the pandemic period has been associated with an increase in sedentary time, smoking habits, depression and negative dietary behavior leading to a worse control of cardiovascular risk factors[27]. However, as already discussed, there were no significant differences in the control of some of these major cardiovascular risk factors in our population.

This finding suggests that the greater number of MACE and MALE observed during the pandemic period, compared to pre-pandemic, may be related to social distancing measures and reallocation of health resources during the pandemic, rather than a worse control of cardiovascular risk factors in the same period. Furthermore, a worsening of cardiovascular outcomes due to a poorer control of risk factors, cannot be evaluated in the short term and should be analyzed in a prospective study.

Interestingly, data from a nationwide retrospective survey[28] conducted in Austria showed a lower rate of hospitalization and treatment of acute coronary syndrome (ACS) during March 2020 than before the pandemic. A retrospective analysis[29] of 15 hospitals in northern Italy confirmed these results and showed a lower rate of ACS admissions during the early Italian lockdown. Another report by Solomon et al[30] found a 48% reduction in hospitalizations for ACS during the COVID-19 period, compared to the previous year. They[30] also showed that among the patients admitted during COVID-19, the prevalence of previous CAD, previous acute myocardial infarction, and previous percutaneous coronary intervention was lower than among those admitted during the pre-pandemic period. Contrary results were found in our population, where pre-existent CAD was higher among patients hospitalized during the pandemic.

In addition, there is evidence[31,32] of reduced ER visits for heart failure during the pandemic. In particular, patients presenting to the ER with heart failure were in a more severe clinical condition[31,32]. In particular, Colivicchi et al[31] showed higher in-hospital mortality among patients admitted for heart failure during the pandemic compared to the year before the pandemic. In our population, we observed a higher incidence of heart failure among patients admitted during the pandemic compared to pre-COVID-19. However, differences in NT-ProBNP values were not significant between the two periods.

Although the previously discussed evidence is apparently contrary to our observations, it could support the main finding of our study. In fact, it confirmed a general trend of avoiding hospitalization in people with milder illnesses and postponing ER visits until they became more severe. Moreover, the reallocation of health services and social distancing measures during the COVID-19 pandemic have led to fewer outpatient visits, slowing the detection of chronic disease complications.

Limitations

This study has several limitations. First, the retrospective nature of the analysis may have introduced selection bias, thereby affecting the overall results. In addition, there are missing data related to the study design. Furthermore, the sample evaluated was based on a single-center population, which was relatively small and restricted

to hospitalized patients. Therefore, the impact of the pandemic on outpatients with PAD could not be assessed. However, the use of machine learning techniques and the construction of an ontology-based DataMart by an interdisciplinary team could represent an interesting approach to elaborate big data analysis and to guide clinical decision-making.

Conclusions

In conclusion, during COVID-19, we observed a higher number of MACE, MALE, and amputations in the PAD population compared to the three years prior to the pandemic. Although these results need to be confirmed in a larger population, they may be related to changes in the distribution of health resources and services observed in Italy during the pandemic, other than the way patients themselves manage their health problems. These experiences can help us develop new strategies to support and sensitize patients to treatment plans and improve primary and secondary prevention strategies through the use of new technologies and telemedicine.

Conflict of Interest
The authors declare that they have no conflict of interests.

Authors' Contributions
Conceptualization, M.M.R. and F.B.; methodology, M.M.R, F.B., C.M., M.S.; formal analysis, C.M. and M.S.; resources, M.M., A.G., A.F.; data curation, A.F.; writing-original draft preparation, M.M.R.; writing-review and editing, M.M.R., F.B., A.F., M.A.N., E.N., A.L.C., E.R, supervision, M.M., A.G., A.F. All authors have read and agreed to the published version of the manuscript.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy (protocol code 4915; date of approval: May 5th 2022).

Informed Consent
Not applicable.

Availability of Data and Materials
the datasets generated and analyzed during the current study are not publicly available as the data also forms part of an ongoing study but are available from the corresponding author on reasonable request.

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