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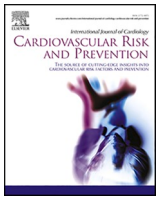

High prevalence of cardiac post-acute sequelae in patients recovered from Covid-19. Results from the ARCA post-COVID study

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ABSTRACT

Background: Many data were published about Long-Covid prevalence, very few about the findings of new cardiac alterations (NCA) in COVID-19-recovered people. *ARCA-post-COVID* is an observational study designed to investigate the prevalence of NCA in patients recovered from Covid-19.
Methods: from June 2020 to December 2022, we enrolled 502 patients with a positive nasopharyngeal swab for SARS-CoV2 and a subsequent negative one. We performed anamnesis, lab-test, and routine cardiological tests (ECG, Holter, TTE).
Results: The median age was 56 years (IQR 44–67); women were 52.19%; in the acute phase 24.1% of patients were treated in a medical department, 7.2% in the ICU and the others at home. At the visit, 389 patients (77.49%) complained of a broad range of symptoms. We reported patients' characteristics according to the course of the disease and the persistence of symptoms. NCA were found in 138 patients (27.49%): among them 60 cases (11.95%) of pericardial effusion. Patients with NCA were older (median 60y, IQR: 47–72, vs median 56y, IQR 42–65), had a higher prevalence of smokers (27% vs 17%; p0.014), CAD (11% vs 6%; p0.048) and stroke/TIA (3.6% vs 0.3%; p0.002) and a lower prevalence of hypercholesterolemia (18% vs 30%; p0.007). The prevalence of NCA seems constant with different subtypes of the virus.
Conclusion: the prevalence of NCA in patients who recovered from COVID-19 is high and constant since the beginning of the pandemic; it is predictable based on hospitalization and long-lasting symptoms (9.64%–42.52%). Patients with one of these characteristics should undergo cardiological screening.

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1. Introduction

The global pandemic coronavirus disease 2019 (COVID-19), has significantly affected healthcare systems worldwide with 682,909,796 recovered patients and 6,835,809 deaths reported until March 18, 2023 [1] and a fair part of survived patients still experimenting with the sequelae of the disease. According to Raman et al. [2], regardless of the severity of the infection or a previous hospitalization, in 1 out of 5 patients symptoms persist beyond 5 weeks, and in 1 patient out of 10, beyond 12 weeks.

The term PASC (Post Acute Sequelae of Covi- 19), otherwise known as long COVID, refers to the persistence of symptoms or sequelae beyond three weeks of SARS-CoV-2 infection onset [3]. The United Kingdom National Institute for Health and Care Excellence defined this post-acute phase as ***ongoing COVID-19*** when symptoms last >4 weeks after SARS-CoV-2 infection and ***chronic or post-COVID*-19 syndrome** when symptoms last >12 weeks [4]. Recently, the World Health Organization has defined post-COVID-19 as the condition where symptoms persist more than 3 months after infection and cannot be explained by an alternative diagnosis [5]. Long COVID (LC) includes both ongoing symptoms (4–12 weeks) and post-acute symptoms (more than 12 weeks). Although Long COVID pathogenesis is not entirely understood, immune response, molecular mimicry, and prothrombotic phenotypes rather than viral persistence may be involved, stimulating the production of cytokines and inflammatory mediators, leading to endothelial dysfunction and metabolic impairment [6]. The Long COVID syndrome includes a broad spectrum of local and systemic clinical manifestations. Among these, a large part of patients complain of cardiovascular symptoms such as fatigue, cough, shortness of breath, chest pain, palpitation [7,8]' and cardiovascular signs of autonomic dysfunction such as orthostatic hypotension, postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia [9].

A large number of cardiovascular and pulmonary complications with important prognostic value, such as peri-myocarditis, pulmonary embolism, arrhythmias (in particular atrial fibrillation), acute heart failure, acute coronary syndromes, Takotsubo syndrome, often associated with troponin increase, were described in the acute phase of COVID-19 [10–13]. Nevertheless, in the past three years of the pandemic, patients have often been discharged from the hospital without a comprehensive cardiological evaluation, because of wards overcrowding, in an attempt to limit the spread of infection. Furthermore, in Italy most patients, even if symptomatic, have been treated at home, where they could have experienced subclinical cardiovascular damage, evident only at subsequent follow-up visits. The first year of the pandemic occurred with a lack of medical knowledge about the disease evolution [14]. In addition, early studies lacked a prospective evaluation, and some have recalled only selected populations [15,16] so long-term COVID consequences and cardiovascular complications are very poorly known.

The purpose of our study was to collect information about the presence of new cardiovascular damage (NCA) after COVID-19 and to find possible predictive markers of cardiovascular complications in a post-COVID-19 population discharged from hospital or treated at home without any cardiological involvement diagnosed during the acute phase of the illness.

2. Methods

The ARCA post-COVID (Assessing the Rate of CArdiovascular disease in post-COVID patients) is a non-profit, prospective, observational study designed and conducted by the A.R.C.A. (Associazioni Regionali Cardiologi Ambulatoriali) Scientific Society with the purpose to collect cardiovascular information on patients following a SARS-CoV2 infection (COVID-19). The A.R.C.A. Cardiologists participated in the study on a voluntary, non-profit basis. The investigators, representative of five Italian regions were encouraged to enroll consecutive nonacute outpatients meeting the inclusion criteria from their ambulatories.

Each investigator was requested to fill an electronic case report form (CRF) [17] with the following information: demographic data; clinical history; cardiovascular risk factors; comorbidities; information related to the eventual hospitalization for COVID-19; information related to the first and follow-up visits (symptoms, physical examination, blood pressure, laboratory data, electrocardiogram, Holter, transthoracic echocardiography, results of any additional examination prescribed during the first visit).

The CRFs, containing data from all enrolled patients, were collected in a web-based, central database, to form the ARCA post-COVID Registry.

All patients were verbally informed of the purpose and nature of the study and the anonymous management of individual data. To ensure patients' privacy, every CRF reported two matched numbers: the first number identified the investigator and the second one the patient. Only the referring investigator was aware of the match between the patient's number and his/her name. All patients were given only the tests they needed according to their clinical indication.

2.1. Inclusion and exclusion criteria

Every outpatient with a previous COVID-19, presenting to a participating A.R.C.A. cardiologist for an elective control visit, for persistent or recurrent symptoms, for work or sports fitness certification was considered eligible in the study. Both patients with or without hospitalization at the time of COVID-19 were considered enrollable. A positive nasopharyngeal swab was needed to confirm the SARS-CoV2 infection. In both cases, a subsequent negative swab was required before enrolling the patient.

Any cardiac damage attributable to COVID-19, already known and documented, before the first visit, and the lack of a negative nasopharyngeal swab were considered as exclusion criteria.

2.2. Design of the study

The investigators were encouraged to consecutively enrol at the first visit every patient fulfilling the inclusion criteria and without a non-eligibility reason. A second follow-up (FU) visit was planned after three months in symptomatic patients or if any cardiac abnormality was found at the first visit.

2.3. Study end-points

The primary end-point was the prevalence of any cardiac damage in patients following COVID-19, not known before the disease and at the hospital discharge.

Secondary end-points were the prevalence of symptoms following COVID-19 and the prevalence of cardiovascular risk factors (CVRF) and comorbidities in patients with symptoms or cardiac damage.

2.4. Statistical analysis

Continuous variables are expressed as mean ± SD (standard deviation). The normal distribution was assessed using the Shapiro–Wilk test. If the distribution is not normal, we reported data as median and Interquartile Range (IQR). Comparisons between groups were performed with the use of Student's t-test in the case of continuous variables with normal distribution or with the use of a Mann-Whitney's *U* test in the case of non-normal distribution. Categorical variables are expressed as numbers and percentages and were compared using the chi-square test and the Fisher's exact test. For all comparisons, a p-value <0.05 was considered statistically significant.

3. Results

From June 2020 to December 2022, 502 outpatients with previous

COVID-19 [mean age 54 ± 18 years; 262 females (52%) and 240 males (48%)], were enrolled in the Registry. Demographic and clinical characteristics, CVRF, and comorbidities in the whole population and compared in patients with and without hospitalization for COVID-19, are reported in Table 1. The first cardiological visit was performed after a median period of 76 days (IQR 24–158) from the first negative swab. The time between the first positive and the first negative test was 16 days (IQR 12–24).

3.1. Course of COVID-19

Three hundred and thirty-nine patients (67.5%) didn't require hospitalization; 121 (24.1%) were admitted to the medical department (6 receiving CPAP) and 36 (7.2%) were treated in the intensive care unit (ICU) (18 receiving CPAP and 15 endotracheal intubation); the investigators didn't report the information for 6 patients.

3.2. Hospitalization

Patients with previous COVID-19 who required hospitalization were mostly males and older, and more frequently had hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease, coronary artery disease, and atrial fibrillation. The prevalence of patients with heart failure, complex ventricular arrhythmias, with pace-maker and implantable cardioverter devices was very low in both groups so that any difference could not be estimated (Table 1)

3.3. Symptoms

At the inclusion visit, 389 patients (77.49%) reported a broad range of symptoms (Table 2). The most frequent symptoms were dyspnoea (46%), weakness (41%), palpitations (24%), fatigue (21%), and anxiety/depression (12%).

The rate of symptoms at the first visit was slightly, but not significantly higher in patients hospitalized at the time of COVID (127/157 patients; 80,89%), as compared with patients treated at home (256/339 patients; 74.2%) (p = 0.225).

Demographic and clinical characteristics of symptomatic and asymptomatic patients are shown in Table 3. Symptomatic patients were more frequently females (55% vs 47%; p 0.0104), older (median 58 years and IQR 47–67 vs median 48.5 years and IQR 32–65; p 0.0019), hypertensive (41% vs 34%; p 0.0338) and overweight (median BMI 26.27 and IQR 23.05 vs median 24.22 and IQR 23.05–29.38; p 0.0013), when compared with asymptomatic patients. The cumulative rate of CVRF and comorbidities was significantly higher in symptomatic patients.

Table 2
Symptoms and their prevalence. Other symptoms under 2% are not reported. Regr%: percent of patients with regression of symptoms at the follow-up visit.

	N pts	%	Regr%
Dyspnea	232	46.22	50.00
Weakness	204	40.64	20.33
Palpitations	118	23.51	70.11
Fatigue	105	20.92	100.00
Anxiety/depression	59	11.75	14.55
Sleep disorders	48	9.56	82.22
Digestive disorders	46	9.16	91.11
Chest pain	41	8.17	85.71
Chest tightness	38	7.57	36.00
Joint pains	33	6.57	62.50
Mood disorders	29	5.78	93.10
Dry cough	19	3.78	75.00
Dizziness	17	3.39	73.33
Memory loss	16	3.19	91.67
Anosmia	15	2.99	100.00
Ageusia	13	2.59	100.00
Headache	12	2.39	77.78

3.4. Cardiological lab findings

The prevalence of new ECG, 24-h ECG monitoring (Holter), and transthoracic echocardiography (TTE) abnormalities unknown before COVID-19 in hospitalized and non-hospitalized patients and in symptomatic and asymptomatic patients are respectively reported in Table 4 and Table 5. At the 1st visit, a significant number of new anomalies were found in 138 patients (27.49%): 54 patients by ECG, 30 patients with arrhythmias by Holter (8 Atrial fibrillation and 22 repetitive premature ventricular beats), and 101 by TTE. A high prevalence of pericardial effusion (PE) was observed (60 cases; 1.95%). Comparing the prevalence of instrumental parameters between patients not hospitalized and hospitalized for COVID-19 we found statistically significant differences for ECG anomalies (respectively 7.96% vs 17.20%; p 0.0021, OR 2.4), LVEF<50% (0.29% vs 5.73%; p 0.0001, OR 20.55), diastolic

Table 1
The table shows the characteristics (demographic and anthropometric data, FRCV, and comorbidities) of all the patients. The same parameters are shown for the hospitalized and not hospitalized patients with their statistical differences.

	All pts (n 502)		Hospitalized (n 157)		Not Hospitalized (n 339)			
	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	P	OR
Females	262 (52.19)		67 (42.68)		193 (56.93)		0.003	0.56
Age (yr)		56 (44–67)		64 (55.5–74)		51 (38–64)	<0.001	
Hypertension	194 (38.65)		92 (58.60)		100 (29.50)		0.000	2.55
Diabetes Mellitus	57 (11.35)		26 (16.56)		31 (9.14)		0.013	2.01
Hypercholesterolemia	136 (27.09)		61 (38.85)		74 (21.83)		<0.001	2.33
Smokers	99 (19.72)		34 (21.66)		63 (18.58)		0.370	
COPD	43 (8.57)		15 (9.55)		26 (7.67)		0.444	
CKD	17 (3.39)		13 (8.28)		4 (1.18)		<0.001	7.70
Immune diseases	28 (5.58)		8 (5.10)		19 (5.60)		0.981	
Cancer	9 (1.79)		3 (1.91)		6 (1.77)		0.857	
CAD	36 (7.17)		20 (12.74)		15 (4.42)		0.001	3.21
Stroke/TIA	6 (1.20)		3 (1.91)		3 (0.88)		0.320	
HF	3 (0.60)		2 (1.27)		1 (0.29)		0.483	
AF	31 (6.18)		18 (11.46)		13 (3.83)		0.001	3.31
CVA	2 (0.40)		0 (0.00)		2 (0.59)		Na	
PM	3 (0.60)		2 (1.27)		1 (0.29)		Na	
ICD	1 (0.20)		1 (0.64)		0 (0.00)		Na	
BMI		25.8 (22.86–29.07)		27.72 (25.28–31.23)		24.44 (22.22–27.89)	<0.001	

Abbreviations: AF: atrial fibrillation. BMI: Body Mass Index. CAD: coronary artery disease. CKD: chronic kidney disease. COPD: chronic pulmonary obstructive disease. CVA: complex ventricular arrhythmias. CVRF: cardiovascular risk factors. HF heart failure. ICD: Implantable cardioverter-defibrillator. IQR: Interquartile Range. n: number. na: not assessable. OR: Odds Ratio. p: p value. PM: pacemaker. pts patients. SD standard deviation. TIA: transient ischemic attack. yrs.: years.

Table 3
Characteristics (demographic and anthropometric data, FRCV, and comorbidities) of the symptomatic and asymptomatic patients with their statistic differences.

	Asymptomatic (n 113)		Symptomatic (n 389)			
	n (%)	Median (IQR)	n (%)	Median (IQR)	p	OR
Females	47 (41.59)		215 (55.27)		0.0104	1.74
Age (yr)		48.5 (32–65)		58 (47–67)	0.0019	
Hypertension	34 (30.09)		160.00 (41.13)		0.0338	1.62
Diabetes Mellitus	10 (8.85)		47 (12.08)		0.3403	
Hypercholesterolemia	30 (26.55)		106 (27.25)		0.8830	
Smokers	16 (21.34)		83 (14.16)		0.0910	
COPD	7 (6.19)		36 (9.25)		0.3060	
CKD	1 (0.88)		16 (4.11)		0.0950	
Immune diseases	2 (2.00)		26 (7.00)		0.0770	
Cancer	1 (1.00)		8 (2.00)		0.4090	
CAD	5 (4.00)		3 (8.00)		0.1990	
Stroke/TIA	0 (0.00)		6 (1.53)		0.4030	
HF	0 (0.00)		3 (0.77)		0.8080	
AF	5 (4.42)		26 (6.68)		0.3800	
CVA	1 (0.88)		1 (0.26)		0.9330	
PM	1 (0.88)		2 (0.51)		0.8080	
ICD	0 (0.00))		1 (0.26)		0.5100	
BMI		24.22 (22.31–27.89)		26.27 (23.05–29.38)	0.0050	
n. CVRF & Comorbidities		0 (0–2)		1 (0–2)	0.0013	

Abbreviations: see Table 1.

Table 4
ECG. Holter and TTE abnormalities that were undiagnosed before the first visit in hospitalized and not hospitalized patients.

	All pts (n 502)		Not Hospitalized (n 339)		Hospitalized (n 157)		p	OR
	n pts	%	n pts	%	n pts	%		
ECG	54	10.76	27	7.96	27	17.20	0.0021	2.4
AF	13		1	0.29	12	7.64		
BB	19		10	2.95	9	5.73		
PVC	19		13	3.83	6	3.82		
LVS	1		1	0.29	0	0.00		
Ischemia	2		2	0.59	0	0.00		
Holter	30	5.98	17	5.01	13	8.28	0.1559	
TTE	101	20.12	57		44			
LVEF (<50%)	10	1.99	1	0.29	9	5.73	0.0001	20.55
TAPSE (<16 mm)	6	1.20	6	1.77	0	0.00	0.0935	
PAPs (>40 mmHg)	10	1.99	6	1.77	4	2.55	0.5664	
Ddisf (>1st dgr)	13	2.59	3	0.88	10	6.37	0.0004	7.62
E/e' (>15)	3	0.60	0	0.00	3	1.91	na	
Wall Motion Abn.	14	2.79	6	1.77	8	5.10	0.0375	2.98
Pericardial Effusion	60	11.95	41	12.09	19	12.10	0.9981	
Pts with injuries	138	27.49	79	23.30	59	37.58	0.0010	1.98

Abbreviations: Abn Abnormalities. AF atrial fibrillation. BB bundle block. BMI body mass index. Ddisf Diastolic disfunction. HF heart failure. EKG electrocardiogram. LVEF left ventricular ejection fraction. LVS left ventricular strain. n number. na not assessable. Or Odds Ratio. Pts patients. PVC premature ventricular complex. TAPSE Tricuspid annular plane systolic excursion. TTE transthoracic echocardiography.

dysfunction ≥2nd degree (0.88% vs 6.36%; p 0.0004, OR 7.62), wall motion abnormalities (1.77% vs 5.10%; p 0.0375, OR 2.98) and all the instrumental abnormalities (23.30% vs 37.58%; p 0.001, OR 1.98) (Table 4).

The comparison of the same instrumental parameters between asymptomatic and symptomatic patients showed statistically significant differences for ECG anomalies (respectively 1.77% vs 13.37%; p0.0005, OR 8.56), Holter anomalies (0.88% vs 8.23%; p 0.0095, OR 9.02), pericardial effusion (4.42% vs 14.14%; p 0.0051, OR 3.56) and all the instrumental abnormalities (13.27% vs 31.62%; p 0.0001, OR 3.02). No significant difference was found for all the other parameters (**Table 5**). In particular, we looked for whether, in patients with specific symptoms such as dyspnoea and fatigue, alterations such as FE<50% or E/e'>15 were more frequent or if arrhythmias were found more frequently in patients with palpitations, dizziness, and syncope: we did not find any statistical significance for these parameters.

Clinical characteristics and comorbidities of patients with and without previously unknown instrumental anomalies are reported in Table 6. Patients with new cardiovascular alterations were older (median 60 vs 56 years and 95%CI 54.21–60.21 vs 51.09–54.87; p = 0.0143), with a higher prevalence of smokers (26.81% vs 17.03%; p0.014, OR 1.78), of CAD (10.87% vs 5.77%; p 0.048, OR 1.99) and stroke or TIA (3.62% vs 0.27%; p 0.0021, OR 13.65) and a lower prevalence of hypercholesterolemia (18.12% vs 29.95%; p 0.0075, OR 0.52). Other parameters were not statically different, or their differences were not assessable.

3.5. Pericardial effusion

In the ARCA post-COVID Registry, a consistent rate of patients with pericardial effusion was found (60/502 patients: 11.95%; 43.48% of all instrumental anomalies). The great majority of patients with PE were symptomatic (91.67%; p 0.0051). No pericardiocentesis was needed and all the effusion were mild. Only a minority of patients with PE were hypercholesterolemic or diabetics (8.33% and 3.33% respectively), as compared with 29.64% and 12.44% of patients without PE (p 0.001 and OR 0.22; p 0.037 and OR 0.24 respectively). No significant differences regarding sex, age, BMI, comorbidities, and other CVRF were found between patients with and without PE.

Table 5
ECG. Holter and TTE abnormalities undiagnosed before COVID-19 in symptomatic and asymptomatic patients with their statistical differences.

	Asymptomatic (n 113)		Symptomatic (n 389)		P	OR
	n pts	%	n pts	%		
ECG	2	1.77	52	13.37	0.0005	8.56
AF	1	0.88	12	3.08		
BB	1	0.88	18	4.63		
PVC	0	0.00	19	4.88		
LVS	0	0.00	1	0.26		
Ischemia	0	0.00	2	0.51		
Holter	1	0.88	29	8.23	0.0095	9.02
TTE	14		87			
LVEF (<50%)	2	1.77	8	2.06	0.8478	
TAPSE (<16 mm)	3	2.65	3	0.77	0.1048	
PAPs (>40 mmHg)	1	0.88	9	2.31	0.3387	
Ddisf (>1st dgr)	1	0.88	12	3.08	0.1949	
E/e' (>15)	2	1.77	1	0.26	na	
Wall Motion Abn.	2	1.77	12	3.08	0.4785	
Pericardial Effusion	5	4.42	55	14.14	0.0051	3.56
Pts with injuries	15	13.27	123	31.62	0.0001	3.02

Abbreviations: see Table 4.

3.6. Period of COVID-19 and consequences

Fig. 1 describes the trends of hospitalizations for COVID-19, symptoms post-COVID-19, and instrumental anomalies found during cardiological visits according to the period of SARS-CoV2 infection. We selected the periods according to the prevalent variant of SARS-CoV-2 circulating in Italy. It was not possible to know the virus variant until January 2021. From February '21 till June '21 variant Alpha, from June to December '21 Delta variant, and from December '21 to December '22 Omicron variant was largely prevalent. Hospitalizations progressively decreased from the first to the last period with statistically significant differences. In the first period, we found a significantly higher proportion of symptomatic patients. There are no differences in the prevalence of instrumental anomalies found in patients infected in different periods.

3.7. Follow-up visit

Not all the patients came back for the follow-up control: 239 patients (59.16%) out of 404 with symptoms or cardiac damage at the 1st control were visited for the second time a median value of 96 days (IQR 84–110) after the 1st visit and of 169 days (IQR 122–292.5) after the 1st negative test for SARS-CoV 2 infection. Two hundred and three out of 233 patients (87.12%) with symptoms at the 1st visit were still symptomatic at the follow-up visit. 104 patients (75.36%) with instrumental anomalies at the 1st visit came back for a follow-up visit; 63 of them (60.58%) continued to show instrumental anomalies. Thirty-one patients without symptoms or new cardiac damage came back for a second visit for personal reasons.

Symptoms at the FU visit are shown in Table 2. Dyspnoea regression occurred in 50% of patients. Other symptoms like weakness, anxiety or depression, and chest tightness frequently were still lasting at the time of the control visit.

4. Discussion

The ARCA post-COVID Registry is a prospective, observational study performed on a non-selected population with previous COVID-19. The patients, characterized by a broad range of age and comorbidities and infected by different SARS-CoV2 variants from 2020 until 2022, were mainly (67%), but not exclusively, treated at home at the time of the

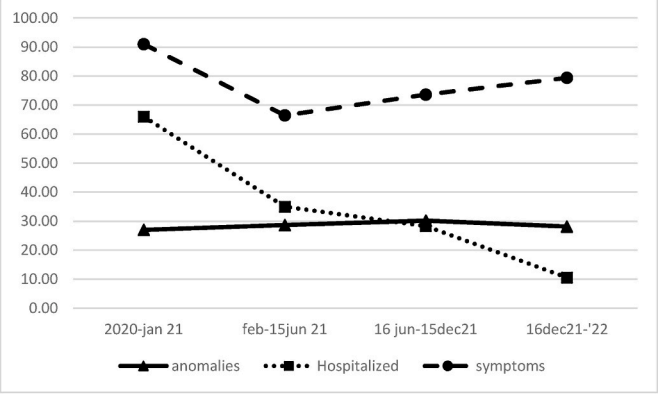

Fig. 1. Hospitalization. persistence of symptoms and CV sequelae in different periods. Squares represent the percentage of hospitalization in the acute phase of COVID-19; circles represent the percentage of symptomatic patients at the time of the visit; triangles represent the percentage of patients with instrumental anomalies detected at the 1st visit.

Table 6
Characteristics of patients with and without instrumental alterations at 1st visit and statistical differences.

	No Instrumental anomalies (n = 364)		Instrumental anomalies (n = 138)		p	OR
	N. pts (%)	Median (IQR)	N. pts (%)	Median (IQR)		
Age (years)		56 (42–65)		60 (47–72)	0.0143	
BMI		25.28 (22.66–29.30)		26.44 23.53–28.73	0.101	
Females	192 (52.75)		69 (50.00)		0.5823	
Hypertension	137 (37.95)		56 (40.58)		0.5452	
Diabetes Mellitus	41 (11.36)		16 (11.59)		0.9170	
Hypercholesterolemia	108 (29.92)		25 (18.12)		0.0028	0.48
Smoker	62 (17.17)		37 (26.81)		0.0140	1.78
COPD	27 (7.48)		16 (11.59)		0.1355	
CKD	7 (1.94)		10 (7.25)		0.1985	
Immune diseases	17 (4.71)		11 (7.97)		0.1502	
Cancer	8 (2.22)		1 (0.72)		0.2668	
CAD	19 (5.26)		15 (10.87)		0.0245	2.21
Stroke/TIA	1 (0.28)		5 (3.62)		0.0021	13.65
HF	0 (0.00)		3 (2.17)		na	
AF	16 (4.43)		12 (8.70)		0.0609	
CVA	2 (0.55)		0 (0.00)		na	
PM	2 (0.55)		1 (0.72)		na	
ICD	0 (0)		1 (0.72)		na	

Abbreviations: see Table 1.

acute disease. The investigators of the Registry, representative of five regions in northern, central, and southern Italy, enrolled patients from their elective activity, to select a population as representative as possible of current practice, allowing to investigation of clinical data and routine non-invasive cardiological findings from ECG, Holter, TTE. Other studies with a larger number of patients followed for a longer time, reporting hard outcomes such as mortality, hospitalizations for CV diseases, and other major events, were based on data from archives [18]; some other research evaluating even minor cardiac injuries by a visit or cardiological tests considered selected populations: athletes [16,19,20], only symptomatic patients [9], only patients without comorbidities [21]; finally, in other studies the authors didn't perform the standard cardiological tests [22].

4.1. Symptoms

In the present study, involving 502 patients with previous COVID-19, most of whom (67.5%) were not hospitalized, we found that 77.49% of patients continued to present symptoms at a median value of 96 days (IQR 84–110) after the first negative swab, independently from the setting of care (hospital or home) of the acute disease. Moreover, 67.51% of them were still symptomatic 169 days (IQR 122–292.5) after the 1st negative test, at the time of the follow-up visit. The patients very often reported cardiological symptoms. In the literature, data concerning the persistence of the symptoms over 12 weeks (Long COVID) are very heterogeneous: from 2.3% to 76% [23–36]. The persistence of symptoms in the ARCA post-COVID Registry is slightly higher than that reported by Blomberg et al. [37] in a similar population (mostly home-isolated) of 312 patients, during the first pandemic wave in Norway. In the Blomberg study, at 6 months, 61% of all patients had persistent symptoms, which were independently associated with the severity of the initial illness.

The rate of Long COVID, as emerging from our study, is a secondary endpoint, because the spontaneous request of a cardiological visit represents a selection bias. It is however remarkable that many patients reported symptoms from 5 to 8 months after the first negative swab. Another secondary endpoint of our study was to identify risk conditions predictive of symptom persistence. In agreement with many other authors, we found that women are more exposed to LC than men (55% vs 47%); symptomatic patients were older (median 58 years and IQR 47–67, vs median 48.5 and IQR 32–65), more frequently hypertensive (41% vs 34%) and overweight (median BMI 26.27 and IQR 23.05–29.38, vs median BMI 24.22 and IQR 22.31–27.89), when compared with asymptomatic patients. Cumulative rate of CVRF and comorbidities were significantly higher in symptomatic patients. Sudre et al. [38] reported similar findings about the relationship between the persistence of symptoms, sex, and age, showing that LC was prevalent in women and older patients, but they found that also the severity (hospitalization), the length of disease and the number of symptoms during the acute period were predictive of persistent symptoms. Chudzik et al. [39] reported that in a young and healthy population, BMI, number of risk factors, the severity of the disease (but not the hospitalization), and arthralgias are factors related to the long persistence of symptoms. In conclusion, different authors found different risk factors for the persistence of symptoms, and our findings are only partially aligned with previous research.

4.2. Cardiac injury following COVID-19

The primary endpoint of the present study was the prevalence of cardiac injury following COVID-19, not present before the disease and unknown at the hospital discharge for hospitalized patients. We found little data in the literature about this issue, especially considering patients who experienced COVID-19 at home.

In the ARCA post-COVID Registry, we investigated the cardiovascular health status by non-invasive cardiological tests (ECG, Holter, and TTE) in a population of non-selected patients, more than 5 months after COVID-19, mostly not severe (67% with home cared disease) and we found new unknown cardiac alterations in 27.49% of them. This figure seems to be higher than the prevalence of cardiovascular alterations reported by other authors. Moulson et al. [16] investigated cardiac involvement in 3018 athletes (mean age 20 $\pm$ 1 years; 32% females) immediately after a SARS-CoV2 infection: in the arm of patients who first carried out standard test (2820 performing HS Troponin, ECG, and TTE), 4.2% were positive or probably positive and then underwent cardiac nuclear magnetic resonance (CMR): CMR was positive only in 0.5%; in the arm of patients who underwent CMR independently from standard test results, 3% of patients were positive or probably positive. Xie et al. [18] in a study based on the US Department of Veterans Affairs national healthcare databases assessed the burden and the risk for several categories of CV diseases in people with previous COVID-19 versus controls without COVID-19: every cardiovascular outcome resulted significantly higher in people with previous COVID-19 [9]. Hira et al. tested autonomic function in 70 patients (80% women, 87% non-hospitalized) with post-acute sequelae of SARS-CoV-2 infection (PASC) and found cardiovascular autonomic alterations in 73% of them.

It's remarkable the high prevalence (12%) of pericardial effusion in our data. Dini et al. [40] analyzed 180 patients with previous COVID-19 and found 22% of acute pericarditis in symptomatic patients, with a relationship with allergic or immune disorders; in the present paper, we were unable to demonstrate a relationship between pericardial effusion and immune comorbidity on an anamnestic basis. Xie et al. [18] found an incidence of pericarditis of 1.48 per 1000 persons in one year, significantly higher than the incidence observed in a no-COVID-19 control group.

Petersen et al. [41] performed a cardiac assessment by ECG, TTE, CMR, and lab tests in 443 SARS-CoV2 patients vs 1328 controls without infection in The Hamburg City Health Study COVID program. TTE revealed slightly lower left and right ventricular function and the lab tests an increased concentration of cardiac biomarkers (high-sensitivity troponin, and N-terminal pro-B-type natriuretic peptide) in post-SARS-CoV-2 patients compared with matched controls. However, the authors didn't find any significant difference in CMR imaging.

In our study, we found that new cardiovascular alterations were significantly more frequent in hospitalized and symptomatic patients, as compared to non-hospitalized and asymptomatic patients (38% vs 23% and 32% vs 13% respectively). Xie et al. [18] found that the risk increased according to the severity and the setting of care of COVID-19 but it was substantial also in not hospitalized patients. According to Hira et al., the rate of new cardiovascular alterations was independent of prior hospitalization. Van der Sluijs et al. [22] compared cardiovascular risk factors, arterial stiffness, and physical functioning in 101 patients with COVID-19, at a median of 6 months after infection: all the patients had been non-hospitalized and the authors were unable to relate the symptoms to cardiovascular risk factors, arterial stiffness, or physical dysfunction. Finally, Luchian et al. [21] investigated by clinical examination, spirometry, chest computed tomography, and TTE, 66 COVID-19 patients without a known cardiopulmonary disease. At one year of follow-up, 23 patients (34.8%) reported dyspnoea. The authors didn't find a left ventricular ejection fraction significantly different between patients with or without dyspnoea, while global longitudinal strain (GLS), global constructive work (GCW), and global work index (GWI) were lower in symptomatic compared to asymptomatic patients.

It is interesting that in the ARCA post-COVID registry the combination of the two anamnestic data of symptom persistence and setting of care was able to stratify groups of patients at different prevalences of cardiac alterations (Fig. 2). About 42% of patients hospitalized and with persistent symptoms exhibited new cardiac damage, probably due to COVID-19. The prevalence of cardiac damage in patients asymptomatic and with a less severe SARS-CoV2 infection is, however, not negligible (9%).

In this study, cardiac pathologic findings were more frequent in older

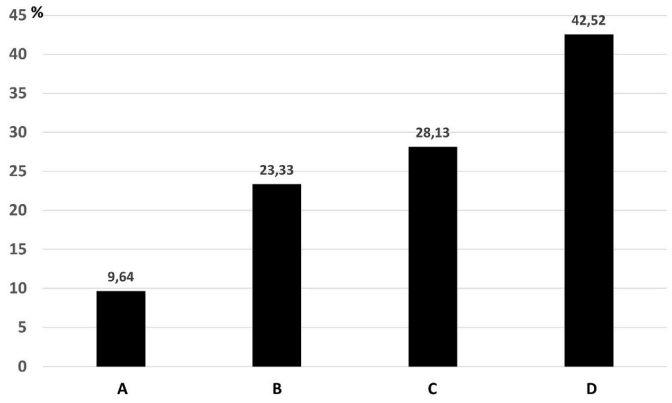

Fig. 2. Prevalence of cardiac anomalies based on symptoms and hospitalization. A: Patients without symptoms and hospitalization. B: patients with symptoms and without hospitalization. C: patients with hospitalization and without symptoms. D: patients with hospitalization and symptoms.

and hypertensive patients and those with a history of coronary or cerebrovascular disease. Unlike older age, which remains a risk factor for all groups compared, BMI and female sex, which affects symptoms and hospitalizations, do not seem to change the prevalence of NCAs. We have not been able to explain this point. It was surprising that hypercholesterolemic patients seemed less exposed to cardiac damage. We explored the hypothesis of a protective role of statins but our data did not confirm this possibility. Xie et al. [18] showed tables that compared the risk for CV disease among different subgroups: statistical significance wasn't indicated but hyperlipidemia seems to give some protection for any CV outcomes. The authors didn't report any comment about this topic.

In a recent review, Parhizgar et al. [42] highlighted the evolving evidence on the potential cardiovascular complications after recovery from acute COVID-19, proposing possible underlying mechanisms. Cardiovascular outcomes included ischemic and non-ischemic myocardial injury, cardiac dysfunction, arrhythmias, and dysautonomia: these conditions were observed also in low-risk patients emphasizing the need for vigilance even in young and healthy populations.

In the literature, data on persistent CV alterations in patients recovered from COVID-19 with or without persisting symptoms are very heterogeneous in the methodology of collection, population characteristics, and the observed parameters. We believe that our research is more adherent to the common cardiological practice and can help clinicians decide how to address their examinations. We found a large prevalence of new cardiac damage after SARS-CoV2 infection also in people with a not severe course of the illness. Hospitalization and persistence of symptoms are positive predictive factors for CV alteration especially in older patients and in patients with hypertension or previous cardiac or cerebrovascular disease.

It is very interesting that, differently from the hospitalizations, that have been declining since the start of the pandemic, probably due to the change of virus variants, the prevalence of post-COVID-19 cardiac damages seems to remain constant.

4.3. Strengths and limitations of the study

ARCA post-COVID study has some strengths: a large number of patients with a complete cardiologic examination (not only by data from archives); not selected and consecutive patients (extended range of age, balanced for sex, different health state before COVID-19); most patients without a severe course of illness: (only one third hospitalized); the multicentric research collecting patients from different Italian region; the visit performed long time after the acute disease; the long period of observation (Jun 2020–Dec 2022) including all the main variant of SARS-CoV2. On the other hand, the study has some important limitations: the lack of a control group of people without a SARS-CoV2 infection; the data on the patient's health status before COVID-19 only based on the anamnesis; very few cardiac magnetic resonances (CMR) performed: CMR could confirm cardiac damage often explaining etiopathogenesis; the lack of a follow-up period long enough to understand the evolution of NCA evidenced.

5. Conclusions

The ARCA post-COVID Registry is a prospective, observational study that investigated the persistence of symptoms and the occurrence of new cardiological alterations in a non-selected population with previous COVID-19, mainly treated at home in the acute phase of the illness. More than 6 months after the SARS-CoV2 infection, 77% of patients were still symptomatic, regardless of hospitalization or home treatment. The most frequent symptoms were dyspnoea, weakness, palpitations, fatigue, and anxiety/depression, with a prevalence greater than 10%. Females, older patients, hypertensives, overweight patients, and those with multiple comorbidities, were more likely to present with long-COVID symptoms. A significant number of new cardiac alterations were found in 27% of patients by a routine cardiological examination including ECG, Holter, and TTE. Among these, pericardial effusion was particularly frequent (12% of patients). New cardiac alterations were more frequent in patients hospitalized for COVID-19 and still symptomatic 6 months later (42%), as compared to patients asymptomatic and with less severe infection (9%). The results of this study should inform the planning of the follow-up of patients after COVID-19, particularly if a comprehensive cardiologic evaluation was not performed in the acute phase.

CRediT authorship contribution statement

Valeria Antoncecchi: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ettore Antoncecchi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Enrico Orsini:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Giuseppe D'Ascenzo:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Ugo Oliviero:** Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ketty Savino:** Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Angelo Aloisio:** Supervision, Methodology, Investigation, Formal analysis. **Laura Casalino:** Supervision, Methodology, Investigation. **Adele Lillo:** Supervision, Methodology, Investigation, Conceptualization. **Emilia Chiuini:** Supervision, Methodology, Investigation. **Giosuè Santoro:** Methodology, Investigation. **Vincenzo Manfrè:** Methodology, Investigation. **Valeria Rizzo:** Methodology, Investigation. **Giovanni Battista Zito:** Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix B

ARCA Post-COVID Steering Committee

Angelo Aloisio, Ettore Antoncecchi, Valeria Antoncecchi, Laura Casalino, Giuseppe D'Ascenzo, Adele Lillo, Ugo Oliviero, Enrico Orsini, Ketty Savino, Giovanni Battista Zito, ARCA Post-COVID investigators, Angelo Aloisio, Ettore Antoncecchi, Valeria Antoncecchi, Laura Casalino, Emilia Chiuini, Giuseppe D'Ascenzo, Adele Lillo, Vincenzo Manfrè, Ugo Oliviero, Valeria Rizzo, Giosuè Santoro, Ketty Savino.

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