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Short and long-term trajectories of the post COVID-19 condition: Results from the EuCARE POSTCOVID study

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Abstract

Background Post COVID-19 condition (PCC) affects 10–40% of patients and is characterized by persisting symptoms at ≥ 4 weeks after SARS-CoV-2 infection. Symptoms can last 7 or even more months. How long PCC persists and any changes in its clinical phenotypes over time require further investigation. We investigated PCC trajectories and factors associated with PCC persistence.

Material and methods We included both hospitalized COVID-19 patients and outpatients from February 2020 to June 2023, who underwent at least one follow-up visit after acute infection at San Paolo Hospital, University of Milan. Follow-up visits were conducted at the post COVID-19 clinic or via telemedicine. During each follow-up examination, patients completed a short version of the World Health Organization (WHO) Case Report Form (CRF) for ongoing symptoms, the Hospital Anxiety and Depression Scale (HADS), and a screening tool for Post-Traumatic Stress Disorder (PTSD). Statistical analyses involved Chi-square, Mann–Whitney, Kruskal–Wallis tests, and logistic regression analysis.

Results We enrolled 853 patients (median age 62, IQR 52–73; 41% females). 551/853 (64.6%), 152/418 (36.4%) and 21/69 (30.4%) presented PCC at median follow up of 3 (IQR 2–3), 7 (IQR 6–10) and 26 (IQR 20–33) months, respectively ($p < 0.001$). The main clinical phenotypes were fatigue, respiratory sequelae, brain fog and chronic pain; anosmia/dysgeusia was observed mostly in the first post-acute period. Female sex, acute disease in 2020, a longer hospital stay and no COVID-19 vaccination were associated with persistence or resolution of PCC compared to never having had PCC. Anxiety, depression and PTSD were more common in PCC patients. By fitting a logistic regression analysis, acute infection in 2020 remained independently associated with persistent PCC, adjusting for age, sex, preexisting comorbidities and disease severity (AOR 0.479 for 2021 *vs* 2020, 95%CI 0.253–0.908, $p = 0.024$; AOR 0.771 for 2022 *vs* 2020, 95%CI 0.259–2.297, $p = 0.641$; AOR 0.086 for 2023 *vs* 2020, 95%CI 0.086–3.830, $p = 0.565$).

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Conclusions There was a reduction in the PCC burden 7 months following the acute phase; still, one third of patients experienced long-lasting symptoms. The main clinical presentations of PCC remain fatigue, respiratory symptoms, brain fog, and chronic pain. Having had SARS-CoV-2 infection during the first pandemic phases appears to be associated with persistent PCC.

Keywords SARS-CoV-2, Long COVID, Post Acute Sequelae of SARS-CoV-2, Post COVID-19 condition

Background

Long COVID, also referred to as Post-COVID-19 Condition (PCC), is defined by the Center for Disease Control and Prevention (CDC) as the presence of persisting symptoms four weeks after the acute SARS-CoV-2 infection [1, 2]. It is estimated that PCC affects a substantial proportion of patients, ranging from 10 to 40%, placing a heavy burden on already stressed health systems [3–6]. Symptoms can last for months, with many studies following patients for up to one year since the acute phase, and a few others suggesting symptoms may last even longer [7–9].

For the sake of simplicity, symptoms can be grouped in clusters in order to identify different PCC phenotypes [10, 11]. One study found shortness of breath and chronic fatigue as the most frequent long COVID manifestations, while female sex and severe COVID-19 infection during the acute phase were the main risk factors for developing PCC [12–14]. Evidence indicates a decline in PCC incidence following the surge of the Omicron variant compared to the wild-type virus, while incidence was higher with the Alpha and Delta variants [15–18]. A follow-up study on long-term outcomes in 242,712 COVID-19 patients showed patients infected with the Omicron variant were 88% less likely to experience lingering symptoms compared to the original viral strain [15]. Preliminary data suggest a reduction in the risk of developing long-term cardiorespiratory sequelae after Omicron infection compared to the wild-type virus, while neurological symptoms, such as depression and anxiety, continue to be prevalent [8, 15]. It is currently unclear how long this condition persists, and whether clinical phenotypes change over time.

Many factors have been associated with PCC development, most notably older age, female sex, the severity of acute infection, and prior comorbidities. In contrast, vaccination appears to offer protective benefits, and while evidence remains limited, emerging data suggests that antiviral and anti-inflammatory agents during the acute phase may have a preventive effect, with stronger support for oral nirmatrelvir/ritonavir in particular. No treatment for PCC is currently available. [17–25]. Several authors have suggested a possible role of psychological factors in the development of PCC, especially during the initial waves of the pandemic (2020–2021) due to isolation during lockdowns and fear of a new, previously unknown disease [26, 27]. One study measured depression and anxiety levels during lockdowns, which resulted to be at quasi-clinical levels [21]. Evidence for a possible reduction in psychological symptoms with later variants is currently limited.

Since the onset of the ongoing COVID-19 pandemic, healthcare professionals have encountered unprecedented challenges in the management and follow-up of patients. The implementation of lockdown measures, coupled with the surge in patient numbers and the resulting strain on health systems, necessitated novel approaches to follow-up care and the optimization of hospital resources. Additionally, the prevalence of old age and comorbidities, common characteristics in COVID-19 patients, heightened the risk of loss to follow-up. In response to these challenges, new methods of patient re-evaluation, such as telemedicine, have been introduced, benefiting both patients and healthcare providers [20]. Telemedicine employs audio and/or visual devices to facilitate communication between patients and healthcare professionals.

This study presents the outcomes of a follow-up program designed for COVID-19 patients from the EuCARE POSTCOVID cohort [28], conducted from January 2020 to June 2023, employing in person evaluations and telemedicine. Our aim was to examine the trajectories of PCC and clinical outcomes over time, as well as to identify potential factors associated with PCC persistence in a cohort of both hospitalized and non-hospitalized patients.

Materials and methods

Study design and population

The EuCARE POSTCOVID study is a retrospective cohort study including patients with at least one follow-up examination at 2–3, 6–10 and ≥ 12 months after an acute SARS-CoV-2 infection. It includes 6 centers in over 3 continents and aims to investigate the long-term outcome of SARS-CoV-2 infection; the study protocol has already been described elsewhere [28]. Patients included in this study have been evaluated at the post COVID service of the Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, Milan, Italy

or by telemedicine from February 2020 to June 2023. We included both hospitalized COVID-19 patients and outpatients with milder disease who were not hospitalized during the acute phase. The study flow chart is depicted in Fig. 1.

Study procedures

At each visit, patients underwent blood exams and completed a condensed version of the post-COVID-19 WHO Case Report Form (CRF) to document symptoms. Following the acute phase and/or hospital discharge, we gathered data on persistent symptoms not previously experienced before COVID-19 infection. If any symptoms were reported, we investigated whether they persisted, their frequency, or if they had already resolved. Additionally, patients completed the Hospital Anxiety and Depression Scale (HADS-A/D) to assess symptoms of anxiety and depression and a screening tool for Post-Traumatic Stress Disorder (PTSD).

The HADS-A/D includes 7 questions each for anxiety and depression. A total HADS score between 8 and 10 indicates "possible" cases, while scores of 11 or more denote "probable" cases for both anxiety and depression. Scores higher than 10 were utilized to identify symptoms of anxiety and depression. The Post-traumatic Stress Disorder Checklist-5 (PCL-5) is a 20-item self-report measure assessing the 20 DSM-5 symptoms of PTSD, with a 5-point scale for each symptom. A total symptom severity score ranging from 0 to 80 can be obtained, and a cut-off of 33 was considered indicative of PTSD [29–31].

The primary outcome was the proportion of participants who were diagnosed with PCC, as defined by the CDC definition: the presence of ≥ 1 symptom 4 or more weeks after the acute infection, either at entry in the cohort (2–3 months after the acute infection) or at any of the follow-up visits. We also focused on the main symptoms clusters of PCC as previously identified [11, 32]: fatigue, respiratory symptoms, brain fog/central nervous symptoms, chronic pain and anosmia/dysgeusia. A list of symptoms included in each PCC phenotype is provided in Supplementary Table 1.

This study has been approved by the Ethics Committee Milano Area 1 (n 1869, 01/08/2022) and all patients have signed an informed consent.

Statistical analyses

Categorical variables are presented as absolute numbers and percentages, quantitative variables as median and interquartile range (IQR). The proportion of patients diagnosed with PCC and the main PCC phenotypes at each time point have been compared by Chi-square test. Among patients with at least two follow up examinations, we compared those who had never experienced PCC, those who resolved PCC, and those with persistent PCC at the last available follow-up using Chi-square test and non-parametric Kruskal–Wallis test. For patients diagnosed with PCC at the first follow-up (2–3 months post-acute phase), we examined factors associated with the persistence of PCC *versus* its resolution using Chi-square test and non-parametric Mann–Whitney test. Finally, by fitting a multivariable logistic regression analysis adjusted for possible confounders (age, sex, comorbidities, and calendar time of infection) we explored factors associated with ongoing PCC at the last available follow-up in comparison to those who had never experienced PCC or had recovered from it. Age and sex influence both susceptibility to and recovery from PCC, comorbidities may independently affect both the risk of exposure and the outcome, and calendar time of infection accounts for new viral variants and treatment options that could impact the

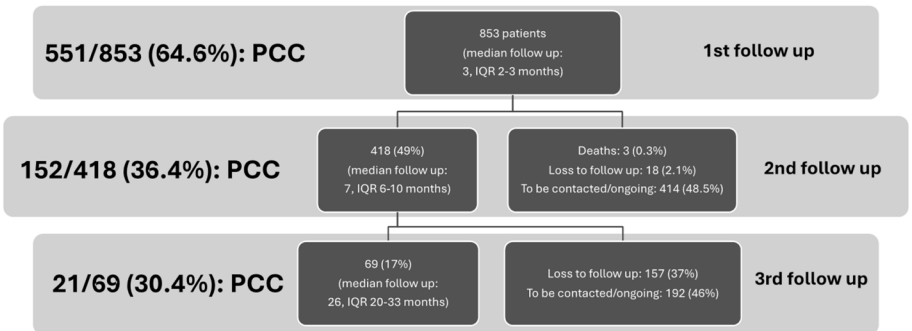

Fig. 1 Study flow chart. Legend: 853 patients were followed up at 3, 2–3 months after acute COVID-19 disease. Of these, 418 patients were followed up also at 7, IQR 6–10 months and 69 patients also at 26, IQR 20–33 months. Loss to follow up: patients that didn't keep an appointment or didn't answer to phone call to schedule next appointments; to be contacted/ongoing: patients with a next scheduled appointment or patients still to be phone contacted. PCC, post COVID-19 condition

outcome. Statistical analyses were performed by SPSS (version 29) and STATA software (version 14).

Results

Study population

Three medical evaluations were conducted in total (Fig. 1). Patients were evaluated at 2–3 months after the acute phase and then followed up at 6–10 months and more than 12 months. Initially, 853 patients underwent a first follow-up assessment at 3 months post-acute phase (IQR 2–3), and thus were included in our study. The median age was 62 years (IQR 52–73), with the majority being men (59% males, 41% females). Most patients were evaluated in 2020 and 2021 (66.7% and 19.3% respectively). Accordingly, only 12.5% of the cohort had received at least two doses of the vaccine prior to SARS-CoV-2 infection, as the majority of patients were enrolled before vaccination became widely available. All enrolled patients had a primary SARS-CoV-2 infection, with no documented cases of reinfection.

The cohort includes 766 hospitalized COVID-19 patients (89.8%) and a smaller subset of individuals (87, 10.2%) who experienced a mild acute illness and were not hospitalized. Regarding disease severity during the acute phase, approximately one third of patients received treatment with a reservoir mask (RM), high-flow nasal cannula (HFNC), or continuous positive airway pressure (CPAP), while 8% of patients required admission to the intensive care unit (ICU) (Table 1).

Of 853 patients, 418 individuals (49%) also completed follow-up evaluations at 7 months (IQR 6–10); 69 patients (17%) were followed up at a median of 26 months (IQR 20–33). 26/853 (3%), 218/418 (52%) and 58/59 (98%) evaluations were performed by telemedicine. The missing patients included those lost to follow-up (18 at the second follow-up visit, 157 at the third), those with ongoing scheduled appointments who were in the process of completing their long-term follow-up, and those yet to be contacted to arrange subsequent evaluations. Challenges in maintaining follow-up included patients not responding to phone calls, refusing further evaluations, logistical difficulties such as travel constraints for older patients, and others who dropped out of the study. Additionally, 3 patients (0.35%) died after the first evaluation.

Table 1 Study population characteristics

Characteristics	Study population N 853
Age, median (IQR)	62 (52–73)
Females, n (%)	346 (40.6%)
Comorbidities, n (%)	323 (37.9%)
Obesity, n (%)	151/545 (17.7%)
COVID-19 vaccination before infection, n (%)	107 (12.5%)
Calendar period, n (%):	
2020	569 (66.7%)
2021	165 (19.3%)
2022	97 (11.4%)
2023	22 (2.6%)
Setting, n (%):	
Outpatients	87 (10.2%)
Hospital admission	766 (89.8%)
Antiviral treatment, n (%):	N 166
NMV/r	20 (12%)
RDV	112 (67.5%)
mAb	34 (20.5%)
Steroid therapy, n (%)	284/375 (75.7%)
Interstitial pneumonia, n (%)	565/643 (87.9%)
Oxygen therapy, n (%):	
None	215 (25.2%)
NC/VM	285 (33.4%)
RM/HFNC/cPAP	285 (33.4%)
NIV/OTI	68 (8%)

Quantitative variables are presented as median and Interquartile Range, categorical variables as absolute numbers and percentages.

All patients were enrolled at the post-COVID service of the Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, Milan.

Comorbidities included in the analysis: asthma, cancer, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes mellitus, HIV/AIDS, heart disease, arterial hypertension, mental health disorders, and neurological disorders.

Comorbidities, at least one comorbidity; obesity, Body Mass Index >30; NMV/r: Nirmatrelvir/ritonavir; *RDV* Remdesivir, *mAB* anti SARS CoV-2 monoclonal antibodies, *NC* nasal cannula, *MV* Venturi mask, *RM* reservoir mask, *HFNC* high flows nasal cannula, *cPAP* continuous positive airway pressure, *NIV* Non invasive ventilation, *OTI* orotracheal intubation.

PCC and main phenotypes over time

Interestingly, we observed a reduction in the proportion of symptomatic patients over time: PCC was present in 551 out of 853 patients (64.6%) at the first medical evaluation; at the second visit, 152 out of 418 patients (36.4%) still had PCC symptoms, and finally, PCC persisted in 21 out of 69 patients (30.4%) at the third medical evaluation ($p < 0.001$).

In our cohort of patients, we identified five main clinical phenotypes of PCC: fatigue, respiratory sequelae, brain fog, chronic pain, and anosmia/dysgeusia (Table 2). The clinical presentation of PCC varied through time: while anosmia/dysgeusia was the most prominent symptom at the first follow-up (211/853 patients, 24.7%; 211/551 PCC patients, 38.3%), it became less common at the second evaluation and was only reported once at the third follow up (1/69 patients, 1.4%; 1/21 PCC patients,

Table 2 PCC phenotypes over time

	PCC 1st follow up N 551	PCC 2nd follow up N 152	PCC 3rd follow up N 21	p values
PCC phenotypes:				
Fatigue	123 (22.3%)	62 (40.7%)	13 (61.9%)	< 0.001
Respiratory sequelae	143 (25.9%)	75 (49.3%)	11(52.4%)	< 0.001
Brain fog	29 (5.3%)	48 (31.6%)	5 (23.8%)	< 0.001
Chronic pain	49 (8.9%)	49 (32.3%)	10 (47.6%)	< 0.001
Anosmia/Dysgeusia	211 (38.3%)	24 (15.8%)	1 (4.8%)	< 0.001

Phenotypes of Post COVID-19 condition: fatigue (fatigue, post exertional malaise; respiratory sequelae: dyspnea, cough, shortness of breath, chest pain; brain fog: headache, cognitive deficits; chronic pain: joint, muscle and bone pain; anosmia/dysgeusia)

PCC Post COVID-19 condition

4.8%), making it the less represented symptom cluster in the long term.

Fatigue and respiratory symptoms were present in approximately 1 in 4 PCC patients at the first follow-up visit (123/853, 14.4%; 123/551 PCC patients, 22.3% for fatigue, and 143/853, 16.8%; 143/551 PCC patients, 25.9% for respiratory symptoms). The frequency of these symptoms increased with each subsequent evaluation in PCC patients. For fatigue, it was present in 62/418 total patients (14.8%; 62/152 PCC patients, 40.7%) at the second visit and in 13/69 total patients (18.8%; 13/21 PCC patients, 61.9%) at the third visit. Similarly, respiratory sequelae were found in 75/418 total patients (17.9%; 75/152 PCC patients, 49.3%) at the second visit and in 11/69 total patients (15.9%; 11/21 PCC patients, 52.4%) at the third visit, making them the most common manifestations of PCC after long-term follow-up.

The percentage of PCC patients suffering from chronic pain and brain fog, which were relatively uncommon manifestations 3 months after the acute phase (49/853, 5.7%; 49/551 PCC patients, 8.9% for chronic pain, and 29/853, 3.4%; 29/551 PCC patients, 5.3% for brain fog), increased significantly at the last evaluation (10/69 total patients, 14.5%; 10/21 PCC patients, 47.6% for chronic pain, and 5/69 total patients, 7.2%; 5/21 PCC patients, 23.8% for brain fog).

Comparison among patients who had never had PCC, patients who had recovered from PCC and patients with ongoing PCC

A total of 418 patients, representing 49% of the initial 853-patient cohort, underwent a second medical evaluation. Subsequently, we proceeded to compare patients who had never developed PCC, patients who had recovered from PCC symptoms, and patients with persistent PCC at the last available follow-up (Table 3).

Female sex, having had the acute infection in 2020, a longer hospital stay, and lack of COVID-19 vaccination were positively associated with PCC (either persistent or resolved) when compared to patients who never developed PCC. Additionally, psychological symptoms such as anxiety, depression, and PTSD were more common among patients with PCC, with PTSD reaching statistical significance.

Notably, no statistically significant association was found between PCC and other commonly cited risk factors in current literature, such as obesity, the number of preexisting comorbidities and the maximum grade of oxygen therapy during the acute phase.

Comparison between patients with resolved PCC and ongoing PCC

We also analyzed a total of 308 patients who were diagnosed with PCC at the entry in the cohort and had at least two follow-up visits. Among these, 198/308 (64.3%) no longer had PCC symptoms at subsequent evaluations, while 110/308 (35.7%) had persistent PCC at a median follow up of 8 months (IQR 6–15) (Table 4). We compared these two groups to identify factors associated with PCC persistence over time. We observed that female sex and lack of COVID-19 vaccination were positively associated with PCC persistence. Additionally, while not reaching statistical significance, psychological symptoms such as anxiety, depression, and PTSD were also observed more frequently in patients with persistent PCC.

Factors associated with PCC persistence over time

Finally, we examined factors associated with ongoing PCC (compared to those who never had PCC or had resolved symptoms at the last available follow-up) using logistic regression analysis. Having had acute SARS-CoV-2 infection in 2020 remained independently associated with persistent PCC, even after adjusting for age, sex, preexisting comorbidities, and the severity of acute

Table 3 Comparison among patients who had never had PCC, patients with resolved and patients with persistent PCC

Characteristics	Study population N 418	Never PCC N 82 (19.6%)	Resolved PCC N 133 (31.8%)	Persistent PCC N 203 (48.6%)	p value
Age, median (IQR)	59 (52–71)	64 (51–73)	59 (50–68)	60 (53–72)	0.174
Females, n (%)	164 (39.2%)	36 (43.9%)	62 (46.6%)	66 (32.5%)	**0.022**
Comorbidities, n (%)	146 (34.9%)	27 (32.9%)	48 (36.1%)	71 (35%)	0.894
Obesity, n (%)	92/314 (29%)	10/44 (23%)	27/86 (31%)	55/184 (30%)	0.885
COVID-19 vaccination before infection, n (%)	37/366 (10.1%)	12 (19.7%)	15 (14.2%)	10 (5%)	**0.001**
Calendar period, n (%):					
2020	287 (69%)	32 (39.5%)	73 (55.3%)	182 (89.7%)	**< 0.001**
2021	98 (23.6%)	39 (48.1%)	44 (33.3%)	15 (7.4%)	
2022	24 (5.8%)	8 (9.9%)	12 (9.1%)	4 (2%)	
2023	7 (1.7%)	2 (2.3%)	3 (2.3%)	2 (1%)	
Setting, n (%):					
Outpatients	27 (6.5%)	10 (12.2%)	5 (3.7%)	12 (5.9%)	**0.004**
Hospital admission	391 (93.5%)	72 (87.8%)	128 (96.3%)	191 (94.1%)	
Lenght of hospital stay, days, median (IQR)	27 (22–36)	18 (7.7–24)	29 (23–35)	28 (21–39)	**< 0.001**
Interstitial pneumonia, n (%)	286/324 (88%)	44/53 (83%)	91/101 (90%)	151/170 (89%)	0.409
Oxygen therapy, n (%):					
None	96 (23%)	24 (29.3%)	30 (22.6%)	42 (20.7%)	0.444
NC/VM	143 (34.2%)	25 (30.5%)	43 (32.3%)	75 (36.9%)	
RM/HFNC/cPAP	151 (36.1%)	31 (37.8%)	49 (36.8%)	71 (35%)	
NIV/OTI	28 (6.7%)	2 (2.4%)	11 (8.3%)	15 (7.4%)	
Months from the acute phase, median (IQR)	8 (6–15)	8 (6–16)	10 (6–21)	7 (6–11)	**0.015**
HADS/A, n (%)	41/295 (13.9%)	1/28 (3.6%)	20/88 (22.7%)	20/179 (11.2%)	**0.009**
HADS/D, n (%)	25/293 (8.5%)	1/28 (3.6%)	13/86 (15.1%)	11/179 (6.1%)	**0.031**
PSTD, n (%)	68/216 (31.5%)	0/18 (0%)	30/66 (45.5%)	38/132 (28.8%)	**< 0.001**

Comparison among patients who had never had PCC, patients with resolved and patients with persistent PCC at the last available follow up.

Quantitative data are expressed as median, interquartile range, categorical data as absolute numbers, percentages (p values by Chi-square and Kruskal-Wallis test).

PCC Post COVID-19 condition.

Comorbidities, at least one comorbidity; obesity, Body Mass Index >30; NMV/r: Nirmatrelvir/ritonavir; *RDV* Remdesivir, *mAB* anti SARS CoV-2 monoclonal antibodies, *NC* nasal cannula, *MV* Venturi mask, *RM* reservoir mask, *HFNC* high flows nasal cannula, *cPAP* continuous positive airway pressure, *NIV* Non invasive ventilation, *OTI* orotracheal intubation, *HADS/A-D* Hospital Anxiety and Depression scale; a score above 11 was considered pathological. PSTD, screening tool for post-traumatic stress disorders (PCL-5, a score above 33 was considered pathological).

disease (AOR 0.479 for 2021 *vs* 2020, 95%CI 0.253–0.908, $p=0.024$; AOR 0.771 for 2022 *vs* 2020, 95%CI 0.259–2.297, $p=0.641$; AOR 0.086 for 2023 *vs* 2020, 95%CI 0.086–3.830, $p=0.565$).

Discussion

This study stands out as one of the first comprehensive, ongoing, large-scale investigations to extend follow-up for PCC patients beyond the first year post-diagnosis, offering insights into both short- and long-term changes in the overall burden of PCC and the evolution of clinical phenotypes.

In our cohort, primarily consisting of unvaccinated hospitalized patients and a smaller sample of outpatients during the early stages of the pandemic, we observed a preliminary reduction in the percentage of PCC over the follow-up period. However, the significant proportion of missing outcomes at the second and third follow-up visits prevents us from drawing definitive conclusions regarding the initial cohort and limits the generalizability of these findings. According to the CDC definition [1], over two-thirds of patients in our cohort exhibited PCC symptoms at the initial 2–3-month follow-up, a proportion that decreased progressively with subsequent visits, with one-third of patients still experiencing PCC at a long follow-up of 2 years or more.

While anosmia/dysgeusia is prevalent in the first post-acute period, fatigue, respiratory sequelae, and to a lesser extent, brain fog emerged as the predominant long-term PCC phenotypes, in accordance with what described in other cohorts [33–36]. Similar data have already been published showing a reduction of ear, nose and throat (ENT) symptoms over time but a possible long-term

Table 4 Factors associated with PCC persistence

Characteristics	Study population N 308	Non PCC N 198 (64.3%)	PCC N 110 (35.7%)	p value
Age, median (IQR)	60 (51–72)	58 (50–68)	61 (53–72)	0.103
Females, n (%)	117 (38%)	62 (31.3%)	55 (50%)	**0.001**
Comorbidities, n (%)	112 (36.4%)	70 (35.4%)	42 (38.2%)	0.621
Obesity, n (%)	76/255 (29.8%)	53 (29.1%)	23 (31.5%)	0.968
COVID-19 vaccination before infection, n (%)	23/287 (8%)	9/195 (4.6%)	14/92 (15.2%)	**0.004**
Calendar period, n (%):				
2020	251 (81.8%)	181 (91.4%)	70 (64.2%)	**< 0.001**
2021	39 (12.7%)	12 (6.1%)	27 (24.8%)	
2022	13 (4.2%)	3 (1.5%)	10 (9.2%)	
2023	5 (1.3%)	3 (1%)	2 (1.8%)	
Setting, n (%):				
Outpatients	12 (3.9%)	3 (1.5%)	9 (8.2%)	**0.004**
Hospital admission	296 (96.1%)	195 (98.5%)	101 (91.8%)	
Interstitial pneumonia, n (%)	226/254 (89%)	148/167 (88.6%)	78/87 (89.7%)	0.803
Oxygen therapy, n (%):				
None	64 (20.8%)	40 (20.2%)	24 (21.8%)	0.836
NC/VM	111 (36%)	74 (37.4%)	37 (33.6%)	
RM/HFNC/cPAP	107 (34.7%)	69 (34.8%)	38 (34.5%)	
NIV/OTI	26 (8.4%)	15 (7.6%)	11 (10%)	
Months from the acute phase, median (IQR)	8 (6–15)	10 (6–19)	7 (6–11)	0.098
HADS/A, n (%)	39/263 (14.8%)	20/178 (11.2%)	19/85 (22.4%)	**0.018**
HADS/D, n (%)	23/261 (8.8%)	11 (6.2%)	12 (14.5%)	**0.035**
PSTD, n (%)	67/195 (34.4%)	38/131 (29%)	29/64 (45.3%)	**0.024**

Among patients diagnosed with PCC at entry in the cohort (at the first follow up examination after the acute phase), comparison between patients who resolved PCC and patients with persistent PCC.

Quantitative data are expressed as median, interquartile range, categorical data as absolute numbers, percentages (p values by Chi-square and Kruskal-Wallis test).

PCC Post COVID-19 condition.

Comorbidities, at least one comorbidity; obesity, Body Mass Index >30; NMV/r: Nirmatrelvir/ritonavir; *RDV* Remdesivir, *mAB* anti SARS CoV-2 monoclonal antibodies, *NC* nasal cannula, *MV* Venturi mask, *RM* reservoir mask, *HFNC* high flows nasal cannula; cPAP: continuous positive airway pressure; NIV: Non invasive ventilation; OTI: orotracheal intubation. HADS/A-D, Hospital Anxiety and Depression scale; a score above 11 was considered pathological. PSTD, screening tool for post-traumatic stress disorders (PCL-5, a score above 33 was considered pathological).

persistence of chronic fatigue [3, 37, 38]. Fatigue, observed in half of our patients, shares several similarities with myalgic encephalomyelitis [39], a condition that follows several infections, defined by chronic fatigue that lasts at least six months and is associated with brain fog, sleep disorders, post-exertional malaise and orthostatic intolerance [40, 41].

Similar to PCC, the diagnosis of myalgic encephalomyelitis is primarily clinical and requires the exclusion of differential diagnoses. Thus far, the pathogenetic mechanisms of myalgic encephalomyelitis remain poorly understood, and there is no specific treatment available apart from cognitive and motor rehabilitation therapies, which have been extensively studied [42]. Due to the overlap in symptoms and therapeutic approaches, myalgic encephalomyelitis is now acknowledged as one of the potential manifestations of PCC. Accurate identification and management of these patients could significantly improve their quality of life [43].

While these findings underscore the ongoing significance of PCC, with potentially millions of people still suffering from it, delineating whether these symptoms are exclusively attributable to long COVID remains complex [23, 44]. While certain manifestations may have a clear correlation with acute SARS-CoV-2 infection in the early post-acute phase, numerous confounding factors may emerge over time. For example, factors such as fatigue, cognitive difficulties, and anxiety tend to increase with age, as do comorbidities. This complicates the attribution of PCC outcomes solely to the viral infection rather than to other ensuing concomitant factors. Moreover, many PCC symptoms closely resemble those of other post-viral syndromes and poorly defined conditions like chronic fatigue syndrome, underscoring the imperative

for a more precise and concise definition of long-term PCC [45].

Consistent with existing literature, female sex, prolonged hospitalization, and lack of COVID-19 vaccination were positively associated with PCC among patients with at least two follow-up visits [13, 14, 19–21, 46–48]. In our unadjusted analysis and in almost all previous studies investigating long COVID, females were characterized by a higher risk of PCC, possibly due to a higher prevalence of psychological issues and/or hormonal factors yet to be understood [46, 49, 50]. A recent study investigated the impact of sex and gender on PCC and found that socio-economic factors, as well as stress levels, income, being females and living alone and lower education, were predictors of PCC and may partially explain the higher incidence of PCC in women [12].

Even though few of the patients in our cohort had been vaccinated before infection, unvaccinated patients were found to be at higher risk of PCC, as well documented by various observational studies and meta-analyses [19, 20, 48].

We also observed that PCC persists over time, particularly among patients infected in the first waves of the pandemic. The reduction in PCC persistence was displayed only for the comparison between the two first calendar period (2021 vs 2020), while we didn't observe any reduction in most recent years (2022 and 2023) compared to 2020; this could be due to different reasons, including the small sample size mainly in the last years, the possible protective effect of COVID-19 vaccination in reducing the burden of PCC symptoms [51, 52], but also the reduction in PCC incidence following the infection with most recent variants. In fact, a reduction of PCC after Omicron infection compared to the Wuhan strain has also been reported by other authors and by other analyses in the EuCARE POSTCOVID study [15, 16, 53].

This study has some limitations. Our study design may introduce a possible selection bias that precludes definitive conclusions regarding PCC incidence rates, as patients returning for follow-up visits inherently have a higher risk of exhibiting PCC symptoms, while many others, who were lost to follow-up, were likely asymptomatic or followed up in other long COVID centers. Similarly, our study is unable to definitively ascertain the potential protective effects of vaccines and antiviral therapies, as they were introduced after the majority of our patients were enrolled, and the small sample of patients receiving specific treatments limits our ability to draw definitive conclusions. Given that most of our patients were unvaccinated, hospitalized during the acute phase and with mild to moderate symptoms, the generalizability of our findings might be limited. Finally, we haven't a control group of patients without COVID-19 to be followed up over time to ascertain the incidence of symptoms associated with PCC; this will be the focus of our future.

Despite the limitations due to incomplete follow-up data, which warrant caution in the generalizability of our results, our findings suggest a trend toward a potential decrease in the burden of PCC over time, with an evolving clinical phenotype characterized by prominent fatigue and respiratory sequelae, alongside, to a lesser extent, anxiety and depression-related symptoms. This underscores the potential role of psychological support in managing these patients and highlights the necessity for further long-term investigations.

Abbreviations

PCC	Post-COVID-19 Condition
CDC	Center for Disease Control and Prevention
WHO	World Health Organization
CRF	Case Report Form
HADS	Hospital Anxiety and Depression Scale
PTSD	Post Traumatic Stress Disorder
PCL-5	Post-traumatic Stress Disorder Checklist-5
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
IQR	Interquartile Range
RM	Reservoir mask
HFNC	High-flow nasal cannula
CPAP	Continuous positive airway pressure
ICU	Intensive care unit
ENT	Ear, nose and throat

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10805-w.

Additional file 1

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Authors' contributions

GM and FB developed the question research and the study protocol. AS, FB and MS helped with patients' recruitment. JFM, CCM, ASL, MMS, FCS, MI, DJ, ES, AA, CT, JARQ, CM, IF and FI participated in EuCARE POSTCOVID study. LB, KP, EV helped in psychological tests and interpretation. AS, FB, MG, RR and GM helped in analyzing and interpreting the data. AS, FB, and GM contributed to the final data interpretation and the writing of the manuscript. All authors contributed to the editing of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study will be conducted in accordance with the Declaration of Helsinki, ICH-GCP, and relevant national legal and regulatory requirements. The Ethics Committee Area A Milan and the Ethics Committee at each clinical research site have approved the study protocol, informed consent forms, and participant information materials before the beginning of the study commences (version 1.1; 08/02/2022). Each enrolled subjects sign an informed consent for study participation and personal data handling before enrollment. The confidentiality of all study participants will be protected, and all data will be kept confidential and stored in accordance with regulatory laws. Data dissemination will only occur in anonymous form, and personal information will not be released without the patient's written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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