Clinical Microbiology and Infection 31 (2025) S44–S54

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

ORCHESTRA Delphi consensus: diagnostic and therapeutic management of post-COVID-19 condition in vulnerable populations

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ARTICLE INFO

Article history:
Received 10 January 2025
Received in revised form
3 April 2025
Accepted 7 April 2025
Available online 17 April 2025

Editor: L. Leibovici

Keywords:
Delphi
Haematological malignancies
HIV
Long COVID
Rheumatological diseases

ABSTRACT

Objectives: Post-COVID-19 condition (PCC) remains poorly understood, especially in clinically vulnerable groups. We applied the Delphi approach to drive recommendations for the diagnosis, management, and prevention of PCC in people living with HIV (PWH) and patients affected by rheumatological diseases (RD) and haematological malignancies.

Methods: On the basis of literature review, three areas of interest in PCC in PWH, haematological malignancies, and RD were identified: (a) features and risk factors; (b) diagnosis and management; and (c) prevention. A three-round Delphi anonymous survey consisting of 15 questions was conducted including 69 experts. Consensus was measured by the six-point Likert scale categorized into four tiers: strong disagreement, moderate disagreement, moderate agreement, and strong agreement. Statements were generated on questions achieving consensus.

Results: Eleven statements were generated: six on features and risk factors of PCC in clinically vulnerable populations, two on diagnosis and management, and three on prevention. Chronic fatigue was identified as the most frequent presentation of PCC in PWH and RD populations. A different case definition of PCC is required for RD population, as symptoms of PCC and autoimmune disorders may overlap. Risk factors for PCC include age >65, severity of COVID-19, and female sex; the latter is also associated with increased smell/taste impairment. A clinical assessment or a routine laboratory test performed 3 months after acute infection is not suggested to diagnose PCC in PWH. PWH and RD should be screened to exclude additional autoimmune disorders in case of chronic fatigue/arthralgia of new onset. Full-course vaccination and early treatment for COVID-19 should be promoted to prevent PCC, whereas corticosteroids during acute infection are not recommended.

Discussion: Diagnosis, management, and prevention of PCC are still under discussion. This Delphi offers valuable insights on PCC in selected clinically vulnerable populations and suggests a tailored approach in vulnerable populations. **Elisa Gentilotti, Clin Microbiol Infect 2025;31:S44**

This article was published as part of a supplement supported by the ORCHESTRA project. The ORCHESTRA project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016167. The views expressed in this article are the sole responsibility of the author and the Commission is not responsible for any use that may be made of the information it contains.

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https://doi.org/10.1016/j.cmi.2025.04.009
1198-743X/

Introduction

Post-COVID-19 condition (PCC) is defined by WHO as the presence of at least one symptom that lasts for at least 2 months after SARS-CoV-2 diagnosis and cannot be explained by an alternative diagnosis [1]. It affects approximately 10% of people after SARS-CoV-2 infection, with a different incidence depending on the viral variant, population, and vaccination status. It has an extremely heterogeneous presentation, including more than 200 symptoms persisting, relapsing or fluctuating over time [1,2]. In this complex scenario, risk factors and determinants of PCC remain unclear, and recommendations for diagnosis, treatment and prevention are lacking, which is especially concerning for individuals with underserved clinical conditions who may face disparities in care [2].

PCC affect both young and healthy individuals and those with chronic diseases, including immunocompromised patients. Nevertheless, it has been proposed that the immune system profoundly influences the pathogenesis of COVID-19 and PCC, suggesting that immunocompromised patients may be at increased risk of developing PCC. People with HIV (PWH) are reported to have a higher probability of developing PCC, the most common symptoms including cough, fatigue, and asthenia. Several demographic and clinical factors might increase PCC occurrence in PWH, including the severity of acute COVID-19. However, the biological drivers of PCC in this population remain poorly understood [3,4]. For patients with rheumatological diseases (RD), observational data report up to 25% of patients with RD having COVID-19 symptoms lasting 28 days or longer and nearly 10% for 90 days or longer [5]. PCC is likely to be underdiagnosed in patients with haematological diseases, as this population is at higher risk for COVID-19 infection and less likely to develop an adequate immune response to COVID-19 vaccines, with increased risk also for long-term consequences [6,7]. Similarly, it is reasonable to hypothesize that PCC could be more frequent in solid organ transplant (SOT) recipients because of the higher risk for severe COVID-19 and the effect of chronic immunosuppressive treatment [8–10].

Guidelines for managing PCC in the general population have been produced [11,12], summarizing the current recommended strategies. According to the type of PCC manifestation, the suggested diagnostic methods and management approaches usually refer to the general population and do not include a specific focus for selected clinically vulnerable groups [13]. Furthermore, evidence was reported as insufficient to provide any recommendation other than conditional guidance.

Within the Horizon 2020 funded ORCHESTRA project ("Connecting European cohorts to increase common and effective response to SARS-CoV-2 pandemic") [14], Work Package 4 (Fragile population cohorts), we conducted a Delphi-based survey to leverage the collective expertise of specialists to address unresolved questions regarding PCC characteristics, risk factors, management, and prevention in clinically vulnerable populations, including PWH and patients affected by haematological and rheumatological diseases (RD). The ultimate goal is to achieve an expert consensus on key clinical issues related to PCC, develop shared statements on the best practices, and inform physicians and policymakers to improve PCC outcomes for these clinically vulnerable individuals.

Methods

Study design

The present cross-sectional study based on the Delphi method was conducted within the ORCHESTRA project. A three-round Delphi survey was applied to cover several areas of interest in the field of PCC and clinically vulnerable populations where the evidence from the literature showed nonconclusive or insufficient results. Four clinically vulnerable populations were selected based on the internal expertise of the ORCHESTRA consortium and the evidence from the literature showing an increased risk of severe COVID-19 and PCC [3–10]: SOT recipients, PWH, patients affected by RD, and patients with haematological malignancies (HM).

Identification and selection of a panel of experts

The experts were identified by the ORCHESTRA team based on their clinical and research experience on the specific topics covered by the survey within the ORCHESTRA investigators, also involving the Spanish Society of Rheumatology, the Icona Foundation Scientific Committee, the European Study Group of Infection in Immunocompromised Hosts of the European Society of Clinical Microbiology and Infectious Diseases, the International Immunocompromised Host Society, and the 'Infections in Hematology' group of the European Hematology Association. One hundred and three experts were invited, and 84 agreed to be part of the panel (15 for SOT, 34 for PWH, 15 for RD, and 20 for HM). Considering the gaps in the knowledge of PCC in these specific populations, the number of experts included was considered adequate for a Delphi consensus. The three rounds of Delphi were conducted anonymously. None of the researchers of the ORCHESTRA team who conceived and conducted the study participated as experts in the Delphi survey. The researchers were not aware of the identities of the experts while elaborating on the responses. Patient advisory groups were not involved in the study.

Questionnaire elaboration

A scoping review of the literature was performed by three researchers of the ORCHESTRA team based at the University of Verona, including infectious diseases and internal medicine specialists with different backgrounds and expertise in COVID-19, PCC, and clinically vulnerable populations. The review focused on providing an overview of the available evidence and highlighting gaps in the current knowledge on three specific areas of interest lacking conclusive results: (a) features and risk factors for PCC; (b) diagnosis and management of PCC; (c) prevention of PCC. The ORCHESTRA team formulated and discussed internally the question to be addressed within each of the three areas. Fifteen questions were finally developed and approved. To avoid bias, the experts were not provided with results from the literature review and were not involved in formulating the questions.

Data collection and analysis

This article presents the statements reached through the survey and is structured according to the ACcurate COnsensus Reporting Document (ACCORD) reporting checklist (Table S1) [15]. The study was not prospectively registered. The survey was electronically administered using the Research Electronic Data Capture (REDCap) capture tool of the ORCHESTRA project hosted at the CINECA Interuniversity Consortium, Italy [16]. The experts were asked to answer the questionnaire in three consecutive rounds using a six-point Likert scale ('strongly disagree'—SD, 'disagree'—D, 'somewhat disagree'—SWD, 'somewhat agree'—SWA, 'agree'—A, 'strongly agree'—SA). In addition, under each question, the experts were encouraged to comment using an open-text box. The consensus was a priori defined by obtaining a percentage agreement of 79% or more [17]. After the first round, the responses were assessed to determine the level of consensus among all participants using the six-point Likert scale. Cumulative agreement was defined as the sum of response percentages on items 1–2 (SD + D), 2–3 (D + SWD), 4–5 (SWA + A), or 5–6 (A + SA), distinguishing a strong degree of agreement (A + SA) or disagreement (SD + D) from a

moderate degree of agreement (SWA + A) or disagreement (D + SWD).

Any question achieving 79% or higher consensus was excluded from the questionnaire administered in the subsequent round. Questions were reformulated in case of suspected misinterpretation based on the comments received or if there were minimal differences, resulting in a lack of consensus. If a question showed little to no significant changes in responses (less than 5% difference) over the two rounds, the required cut-off for consensus was not reached [17]. Each expert was invited to re-evaluate their initial response in light of the other experts' anonymous responses and comments to avoid biases and ensure an independent opinion. The procedure was repeated for the second and the third round.

A final statement was formulated in case consensus was obtained, with a strength of recommendation (moderate or strong) based on the concordance of the responses across the cohorts. For one of the four selected populations (SOT recipients), a further round after the first one was not performed because of the unavailability of the experts. Hence, results for the SOT panel were not reported.

Ethical

The approval of an Institutional Review Board was not required as this Delphi study does not involve research and data on human subjects or animals. The study was based entirely on the feedback provided by the experts. Participants were asked for their willingness and authorization to participate and to process the data provided for scientific research.

Results

The rounds of the Delphi survey were conducted between February and September 2024. Results are provided for each question by topic and type of population. In the supplement, the list of questions included in the survey and the detailed report of the answers divided per round are reported (S1–S5). Eleven statements were developed (ten in PWH, eight in RD, and six in HM) and are summarized in Table 1.

Features and risk factors for PCC

Statement 1. Chronic fatigue, either of new onset or worsening after COVID-19, is the most frequent clinical presentation of PCC in PWH and RD. The impact of age and the progression of symptoms associated with comorbidities should be considered for characterizing PCC (moderately supported).

Chronic fatigue has been identified as the most common presentation of PCC in PWH and RD. PCC shares evident similarities and a wide range of symptoms with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [18,19]. Considering the correspondence between PCC and ME/CFS, some authors speculated that the two conditions may share the same biological drivers [20]. Several disability measurements have been suggested to assess and quantify exercise intolerance. Still, few studies have applied objective measures in addition to questionnaires to evaluate ME/CFS, integrating multiple modalities of assessment (i.e. physical functioning scale of the Short Form Health Survey 36 (SF-36) questionnaire, number of steps/d (in table) using an actometer, and %peak VO_2 of a cardiopulmonary stress test) [18]. Similarly to ME/CFS, PCC negatively impacts several organs and systems, including skeletal muscle, leading to fatigue, lower mobility, weakness, and poor physical performance [21–23]. In a cross-sectional study, patients with PCC had significantly lower absolute and relative muscle strength measurements than control participants, whereas a longitudinal study applying functional measurement commonly used for the assessment of sarcopenia and dynapenia observed that handgrip strength might be used as a proxy indicator of functional

Table 1
Summary of the statements and strength of recommendation

Features and risk factors for PCC		Level of support
Statement 1	Chronic fatigue, either of new onset or worsening after COVID-19, is the most frequent clinical presentation of PCC in PWH and RD. The impact of age and the progression of symptoms associated with comorbidities should be considered for characterizing PCC	Moderate
Statement 2	Female sex should be considered as the main risk factor for developing PCC in PWH, RD, and HM. In these populations, female patients should be prioritized for PCC assessment	Moderate
Statement 3	Age above 65 years should be considered as a risk factor for PCC in PWH and HM. In these populations, patients aged above 65 years should be prioritized for PCC assessment	Moderate
Statement 4	Chemosensory dysfunction is associated with both HIV and RD and may be a PCC-related symptom, especially among females. A dedicated screening should be suggested in women with HIV and RD	Moderate
Statement 5	The severity of COVID-19 increases the risk of developing PCC in PWH and HM population. To allow a better allocation of resources and to promote early diagnosis of PCC, an assessment of PCC risk factors should be prioritized at the end of SARS-CoV-2 acute infection, and a dedicated follow-up should be designed accordingly	Moderate
Statement 6	Symptoms presented by patients with RD may overlap with PCC most frequent presentations, i.e. chronic fatigue and arthralgia/myalgia. A different case definition of PCC should be formulated for patients with RD to account for rheumatological comorbidities and pre-existing symptoms	Moderate
Diagnosis and management of PCC		**Level of support**
Statement 7	There is no evidence that a laboratory assessment performed 3 months after acute infection (including urine test, full blood count, thyroid/liver/kidney function, glucose/haemoglobin A1c, coagulation profile, troponin, pro-BNP, and inflammatory biomarkers) could support early diagnosis of PCC in PWH. A clinical assessment of PCC symptoms 3 months after acute infection is also not recommended as part of the routine follow-up for PCC. Clinical and laboratory evaluation should be tailored to the single patient based on the evidence of PCC symptoms to rule out other conditions	Strong
Statement 8	PWH and RD population with a new complaint of arthralgia and chronic fatigue after SARS-CoV-2 infection should undergo an autoimmune screening to exclude a new autoimmune diseases, whether unrelated to or triggered by SARS-CoV-2	Moderate
Prevention of PCC		**Level of support**
Statement 9	Updated SARS-CoV-2 vaccination should be promoted in PWH, RD, and HM populations to reduce the risk of PCC	Strong
Statement 10	Early treatment for SARS-CoV-2 infection (i.e. nirmatrelvir/ritonavir, molnupinavir, remdesivir, effective anti-spike monoclonal antibodies) should be recommended to PWH, RD, and HM populations to prevent PCC	Moderate
Statement 11	Corticosteroid treatment should not be administered to asymptomatic PWH, RD, and HM populations during acute SARS-CoV-2 infection to reduce the risk of PCC	Moderate

BNP, Brain natriuretic peptide; HM, haematological malignancies; PCC, post-COVID-19 condition; PWH, PCC in people living with HIV; RD, rheumatological disease.

impairment also in PCC [23]. Despite the similarities between patients with sarcopenia/dynapenia and patients with PCC-related chronic fatigue, doubts arise on the reference values to consider when applying functional tests, as they have been mainly used and validated on a population aged above 65 years [23].

Ageing, patients' comorbidities and concomitant therapies received to treat underlying chronic diseases may impact the specificity of the PCC diagnosis, particularly concerning fatigue, for which an alternative explanation might be present based on the patient's medical history. The WHO and other institutions agree on considering PCC in the absence of an alternative diagnosis, but it remains unclear how to assess the worsening of a pre-existing chronic symptom or underlying disease [1,2,11]. On the other hand, recent literature reveals the utility of considering the dynamic evolution of previous symptoms and clinical conditions [24]. The presence of chronic fatigue can be used to diagnose PCC when the timing of the symptom is compatible, even in patients with pre-existing conditions.

Statement 2. Female sex should be considered as the main risk factor for developing PCC in PWH, RD, and HM. In these populations, female patients should be prioritized for PCC assessment (moderately supported).

Female sex is a well-recognized risk factor for PCC in the general population [25]. Females elicit a more robust humoral and cellular immune response than men, possibly because of sex hormones and genetic factors [26]; this enhances the risk for local inflammation that could be involved in the mechanisms leading to PCC. A recent systematic review and meta-analysis, including transcriptomic studies about PCC, revealed several differences in molecular dynamics between males and females [27]. The impact of the female sex on the development of PCC may differ for each clinical presentation of PCC [24]. Respiratory symptoms seem independent of sex, whereas a clear association was detected in the case of PCC-related fatigue, pain, chemosensory dysfunction, brain fog and depression [24,28,29]. The association of PCC and sex in specific populations, such as PWH, RD, and HM, has not been extensively explored so far. Nevertheless, given the increasing evidence of the association between women's higher vulnerability to PCC and biological and hormonal factors, it seems probable that the association between PCC and female sex may not depend on underlying chronic diseases, including HIV, RD, and HM.

Statement 3. Age above 65 years should be considered as a risk factor for PCC in PWH and HM. In these populations, patients aged above 65 years should be prioritized for PCC assessment (moderately supported).

The role of age as a risk factor for PCC is unclear, and whether the risk is independent of other aspects, including underlying chronic diseases. PCC may be underreported in the elderly population for several reasons, including lower attention to PCC symptoms by older patients or even difficulties in accessing online surveys [30]. Age influences the probability of onset and resolution of PCC because of age-related physiological changes, immune system alterations, and comorbidities [31]. In a retrospective cohort study, which included 133 366 individuals, an increased risk of PCC was observed in patients older than 65 years, compared with two historical comparison groups [32]. The relationship between ageing and PCC appears to be bidirectional, as it has been reported that chronic conditions commonly observed in the elderly, such as cardiovascular and respiratory diseases, neurodegenerative diseases, and functional decline, are exacerbated after COVID-19 [33].

More than 50% of PCC prevalence was observed among patients with HM, but no age differences were found between patients with and without PCC [3,34]. Most data on PCC in PWH and RD come from cohorts enrolling middle-aged individuals [35], thus suggesting that the available PCC prevalence may be less representative of fragile populations, including PWH, RD, and HM. Nevertheless, similar risk factors for PCC among individuals aged above 65 years should probably recognized also for patients affected by HM and in PWH, thus recommending a prioritization of diagnostic efforts in these groups.

Statement 4. Chemosensory dysfunction is associated with both HIV and RD and may be a PCC-related symptom, especially among females. A dedicated screening should be suggested in women with HIV and RD (moderately supported).

Olfactory and gustatory dysfunction are reported in more than half of the patients with SARS-CoV-2 infection, often as the first and sometimes as the sole presentation of acute COVID-19 [36]. Evidence from a meta-analysis shows that PCC-related anosmia and ageusia each account for about 15% of PCC manifestation [37]. Chemosensory dysfunction may persist for more than 1 year after the onset [38] and significantly impact social relations and activities [38]. Females have up to 2.5 times higher risk of long-term chemosensory dysfunction after COVID-19 [39]. Furthermore, studies on the risk and determinants of PCC-related chemosensory dysfunction in selected clinically vulnerable populations are lacking. The correlation between HIV and chemosensory dysfunctions has been extensively described: neuroinflammation, HIV-related brain atrophy, and HIV-associated dementia have been suggested [40]. A retrospective study on a large multi-hospital network database, including hospitalized patients with COVID-19, observed that PWH presented a higher proportion of smell and taste dysfunction [41]. More recently, pre-pandemic studies revealed that smell and taste dysfunction were more common in women with HIV compared with control, with a possible pathogenic role of both opportunistic infection of the upper respiratory tract and the neurotropic effect of HIV on the olfactory nerve [42]. Several autoimmune conditions have been associated with olfactory dysfunction, including systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and fibromyalgia [43,44], sharing some similarities with COVID-19-related chemosensory impairment [45,46].

Psychophysical tests to assess chemosensory function, i.e. the Sniffin' Sticks Extended Test (Burghart, Germany) to evaluate smell impairment and the Taste Strips Test (Burghart, Germany), for taste dysfunction, are relatively easy to be performed and offer a more exhaustive picture of chemosensory alterations compared with self-reported symptoms in the context of PCC [28]. Because of its simplicity and safety, olfactory training should probably be suggested for all patients experiencing PCC-related anosmia/hyposmia, as highlighted by the European Society of Clinical Microbiology and Infectious Diseases rapid guidelines for assessment and management of long COVID [12]. Overall, given the higher probability of developing COVID-19-related chemosensory dysfunction reported in women and considering the higher COVID-19-independent risk of smell/taste alteration observed in PWH and RD, the experts concluded that a dedicated chemosensory screening in women with HIV and RD should be recommended.

Statement 5. The severity of COVID-19 increases the risk of developing PCC in PWH and HM population. To allow a better allocation of resources and to promote early diagnosis of PCC, an assessment of PCC risk factors should be prioritized at the end of SARS-CoV-2 acute infection, and a dedicated follow-up should be designed accordingly (moderately supported).

Evidence suggests that the factors more frequently associated with PCC include severe COVID-19 and extended hospital stay [47]. Vulnerable populations, such as patients with HM and immunosuppressed individuals, are at higher risk of experiencing severe COVID-19 and higher risk of complications [48], as reported by a meta-analysis of 38 studies, including 3377 patients with haematologic malignancy hospitalized for acute COVID-19, showing a

pooled risk of death of 39%, approaching 50% in patients 60 years or older. As per the PWH cohort, the UK International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) study found an increased risk of mortality from COVID-19 for PWH compared with HIV-uninfected patients [49], and a large prospective cohort study from South Africa, including 22 308 patients observed an independent association between HIV infection and mortality because of COVID-19, regardless of HIV RNA level or CD4 cell count [50]. Considering the higher risk of severe COVID-19 observed in PWH and HM, these two populations are also expected to be at increased risk of PCC [51]. Furthermore, patients with HM may develop persisting COVID-19, a chronic protracted illness marked by fluctuating or progressive respiratory symptoms and prolonged viral shedding [52]. Loss of humoral immune responses, as observed in patients receiving B-cell-targeted therapies, appears to be associated with prolonged or recurrent COVID-19 infection [53], whereas PCC may be more common in patients with HM [7], possibly because of immune system dysregulation.

A meta-analysis of 17 studies (39 405 PWH and COVID-19) suggests an increased risk of PCC in PWH, with an association with COVID-19 severity [3]. Conversely, PCC does not seem to be more frequent among patients with RD, as suggested by a prospective cohort study reporting that PCC was numerically but not statistically increased in patients with inflammatory RD compared with healthy controls [54]. Nevertheless, in a meta-analysis exploring risk factors for PCC in patients with RD, COVID-19 severity was associated with an increased risk for PCC [35].

A detailed medical history appears to be relevant to better guide further PCC management and follow-up for PWH and patients with HM, including COVID-19 severity. The COVID-19 pandemic has forced physicians to allocate scarce resources [55], underlining the need for a rational use of the available services. A screening performed at the end of SARS-CoV-2 infection prioritizing patients who experienced a more severe COVID-19 and selected populations at increased risk of PCC may be critical to avoid the overload of national health systems.

Statement 6. Symptoms presented by patients with RD may overlap with PCC most frequent presentations, i.e. chronic fatigue and arthralgia/myalgia. A different case definition of PCC should be formulated for patients with RD to account for rheumatological comorbidities and pre-existing symptoms (moderately supported).

Even if multiple attempts to define PCC have been proposed so far, the definition of PCC is still lacking specificity [56]. In particular, the absence of a pre-pandemic control group limits the possibility of understanding the impact of age and the natural progression of pre-existing chronic illnesses on the onset and evolution of PCC [2]. The experts encourage the process of better defining PCC, especially in selected populations with specific characteristics that may impact the recognition of PCC and require a dedicated diagnostic approach. For example, PCC may mimic symptoms usually observed in fibromyalgia, a well-known entity that involves almost 5% of the general population, especially women [57,58]. Indeed, some authors speculated on the opportunity to reconsider some aspects of PCC, such as the chronic fatigue manifestation, suggesting replacing the term PCC or 'long COVID' with 'fibromyalgia-like post-COVID syndrome'. The strong similarities between fibromyalgia and PCC complicate the differential diagnosis between the two clinical conditions, affecting also the possibility of defining whether COVID-19 may trigger fibromyalgia. This considered, the panel suggests a population-based approach for the diagnosis and management of PCC to improve the discrimination power of the case definition of PCC and reduce diagnostic ambiguity. Pre-existing conditions should be considered in the diagnostic process to exclude that the self-reported symptoms could be driven by the natural progression of already diagnosed RDs and establish their direct association with PCC.

Diagnosis and management of PCC

Statement 7. There is no evidence that a laboratory assessment performed 3 months after acute infection (including urine test, full blood count, thyroid/liver/kidney function, glucose/haemoglobin A1c, coagulation profile, troponin, pro-BNP, and inflammatory biomarkers) could support early diagnosis of PCC in PWH. A clinical assessment of PCC symptoms 3 months after acute infection is also not recommended as part of the routine follow-up for PCC. Clinical and laboratory evaluation should be tailored to the single patient based on the evidence of PCC symptoms to rule out other conditions (strongly supported).

Choosing the proper tests to follow-up on patients with previous SARS-CoV-2 infection and suspected PCC is challenging. No biochemical marker is available for PCC, so far [2,59]. No evidence of the clinical utility of routine laboratory testing to diagnose and follow-up PCC was found yet, and despite their relevance from a scientific perspective, cytokines, chemokines, vascular and neurological markers, and acute-phase proteins are not easy to introduce into clinical practice [60–62]. A recent cohort study using a propensity score-weighted linear regression model to evaluate differences in mean laboratory measures by prior infection and PCC revealed that none of the 25 routine clinical laboratory values assessed could serve as a clinically useful biomarker of PCC [61]. On the basis of these evidences, current guidelines on the diagnosis and management of PCC suggest that blood tests should be performed according to symptoms as part of an investigation to rule out other conditions [12]. Hence, a clinical and laboratory assessment should be proposed based on the presence of symptoms compatible with PCC, while the type of testing should be tailored to the single patient.

Statement 8. PWH are considered at higher risk for autoimmune diseases compared with the general population, whereas patients with RD have an increased probability of being diagnosed with new autoimmune diseases. PWH and RD population with a new complaint of arthralgia and chronic fatigue after SARS-CoV-2 infection should undergo an autoimmune screening to exclude a new autoimmune disorder, whether unrelated to or triggered by SARS-CoV-2 (moderately supported).

The diagnostic process for PCC is still poorly defined [2]. For patients with relevant comorbidities (such as RD and PWH), the onset of nonspecific symptoms such as arthralgia and fatigue may be a diagnostic challenge.

A higher risk of autoimmune diseases is observed in both PWH and patients with RD. HIV is responsible for immune dysregulation depending on the $CD4^+$ and $CD8^+$ levels, which facilitates the overall pathogenic process and can lead to the development of autoimmune and systemic diseases [63,64]. The highly active antiretroviral therapy, by inducing a restoration of immune competence, also contributes to the emergence of autoimmune diseases [63,65]. Despite the documented association between HIV and autoimmunity, the frequency of autoimmune diseases among PWH with a restored immune system is difficult to estimate as most of the reports refer to the pre-highly active antiretroviral therapy era, attesting to a highly variable prevalence between less than 1% and 60% [66].

New onset of symptoms in patients with RD may prompt a new diagnostic workup for RD [67]. The relationship between COVID-19 and RD is bilateral: on the one hand, there seems to be an increased

risk of COVID-19 progression in subjects with autoimmune diseases [68,69], whereas on the other hand, COVID-19 itself may trigger autoimmunity and result in a new autoimmune diagnosis [69].

The immune system plays a critical role in the pathogenesis of COVID-19 and PCC [20]. Mechanisms contributing to autoimmunity in PCC involve persistent virus or antigen reservoirs, changes in inflammatory activation, systemic immunity, immune subsets and their transcriptional profiles, mast cells activation, the induced extreme neutrophil extracellular traps formation, and the interaction between SARS-CoV-2 and host self-components through cross-reaction [70].

According to the available knowledge, a screening for RD should be indicated in the context of PCC based on the clinician's evaluation of the symptoms and the patient's medical history, with particular attention for PWH and RD populations, because of their higher risk of developing a new RD.

Prevention of PCC

Statement 9. Updated SARS-CoV-2 vaccination should be promoted in PWH, RD, and HM populations to reduce the risk of PCC (strongly supported).

Growing attention is paid to vaccination with respect to PCC [71,72], as vaccination may contrast viral replication and establishment of reservoirs and reduce the chance of nonspecific autoimmune reactions [73]. Current literature agrees on considering SARS-CoV-2 vaccination the most effective preventive measure against PCC, as demonstrated by several studies reporting a decreased prevalence of PCC among vaccinated patients [12,24,74,75]. A full two-dose regimen of vaccination (compared with no vaccination) was associated with reduced odds of long duration ($\geq$28 days) of symptoms in a prospective, community-based, nested, case-control study including more than 1.2 million participants [74]. A systematic review and meta-analysis involving 536 291 unvaccinated and 84 603 vaccinated (before SARS-CoV-2 infection) patients from six observational studies observed that two-dose vaccination was associated with a lower risk of PCC compared with no vaccination and one-dose vaccination [75]. This evidence was confirmed by other systematic reviews and meta-analyses detecting a significant reduction in PCC among patients receiving a complete COVID-19 vaccination before contracting the virus, also during the Omicron era [72,76,77]. A meta-analysis showed that the prevalence of PCC was lower in vaccinated individuals compared with unvaccinated (9.5% vs. 14.6%), with a decrease in activity-limiting symptoms and a quicker recovery and return to work [78]. Currently, the impact of SARS-CoV-2 vaccination on PCC in immunocompromised patients is not known. Data suggest that vaccine effectiveness and immunogenicity are lower in immunocompromised patients, including those with active cancer, transplant recipients, and PWH, than those without immunocompromising conditions [79]. Providing an additional vaccination dose may enhance the immune responses to SARS-CoV-2 in some immunocompromised patients, as demonstrated by the available literature [14,80]. According to the most recent recommendations affirming the importance of revaccination for groups at higher risk of severe disease and death (including immunocompromised individuals) [79], the experts suggest updating the vaccination schedule in PWH, HM, and RD by adhering to seasonal recommendations.

Statement 10. Early treatment for SARS-CoV-2 infection (i.e. nirmatrelvir/ritonavir, molnupinavir, remdesivir, effective anti-spike monoclonal antibodies) should be recommended to PWH, RD, and HM populations to prevent PCC (moderately supported).

Early treatment for SARS-CoV-2 has proven effective and safe in reducing COVID-19 severity in high-risk patients, defined as having at least a relevant comorbidity including hypertension or obesity or over 50 years of age [81–84]. There is an increased interest in the possibility that early treatment of SARS-CoV-2, by reducing the risk of COVID-19 disease progression, may be useful also in preventing PCC [85]. In a large cohort study including patients at high risk for severe COVID-19 who received early treatment with monoclonal antibodies, a lower probability of developing PCC 12 months after acute infection was observed [24]. Nirmatrelvir–ritonavir is currently the only approved oral therapy recommended for treating mild-to-moderate COVID-19 among high-risk patients. Because this drug was approved in May 2023 based on clinical trials conducted on unvaccinated people infected with the SARS-CoV-2 Delta variant, its effectiveness in vaccinated individuals or patients infected with sub-variants of Omicron has been questioned. However, recent observational studies reassured of the current efficacy of nirmatrelvir–ritonavir, demonstrating a faster decrease in viral load in patients treated with this oral antiviral compared with the controls and a reduced mortality risk and in-hospital disease progression [86,87]. The effects of early treatment with nirmatrelvir–ritonavir could be protective also against the risk of developing PCC, as suggested by several reports [88]. Results from the Researching COVID to Enhance Recovery initiative funded by the U.S. National Institutes of Health report a 12% lower risk of developing PCC within 180 days of infection in patients treated with nirmatrelvir–ritonavir ($n = 165\,000$) compared with patients untreated who tested positive for SARS-CoV-2 between March 2022 and February 2023 [89]. Overall, given the indication to treat patients at high risk for disease progression and based on the evidence available, the experts agree on considering early treatment as a valid resource also to improve long-term outcomes in COVID-19 survivors.

Statement 11. Corticosteroid treatment should not be administered to asymptomatic PWH, RD, and HM populations during acute SARS-CoV-2 infection to reduce the risk of PCC (moderately supported).

Despite the consolidated knowledge regarding the safety and efficacy of corticosteroids for treating moderate-to-severe COVID-19, little is known about their impact on the development of PCC [90]. Evidence on the clinical utility of administering corticosteroids during COVID-19 to reduce the risk of PCC is lacking. Patients who received corticosteroids during acute infection have shown reduced the prevalence of PCC-related chemosensory dysfunction, but no differences were detected for PCC in general or for other PCC-related clinical presentations [24]. Another single-centre retrospective study in hospitalized patients with severe COVID-19 showed that a 10-day course of dexamethasone was associated with a lower probability of PCC. However, the study included a small sample size, and no detailed characterization of PCC symptoms was provided [90]. Furthermore, evidence on the protective role against PCC of corticosteroid administration among asymptomatic patients is currently lacking. The experts, in agreement with the available evidence, do not consider the use of corticosteroid treatment during asymptomatic acute infection for the prevention of PCC in clinically vulnerable groups.

Discussion

Adopting the Delphi approach for this survey allowed a valuable synthesis of expert opinion, yet several methodological limitations can be found. The questions were formulated based on a review of the available evidence by clinicians from a single country, potentially introducing a geographical bias. One of the panels (SOT cohort) could not perform a subsequent round after the first one. Thus, the conclusions that can be derived for his sub-population are partial and were not reported in this paper. PCC is a relatively novel

clinical condition whose pathophysiological underlying mechanisms are yet to be clarified. Therefore, the experts invited to the present survey, despite having a consolidated experience in the diagnosis, management and treatment of fragile patients, could not rely on a consolidated and agreed burden of evidence on specific topics related to PCC in vulnerable populations, as also emerged by the comments to the questions. However, the results of this survey add significant information to this poorly known condition, as the available literature itself needs robust and generalizable evidence on PCC in clinically vulnerable populations, and examples of follow-up programmes specifically designed to study PCC in a specific group of patients are rare.

This ORCHESTRA Delphi consensus offers a deep insight into PCC diagnosis, management, and prevention in selected clinically vulnerable populations, exploring some of the most relevant issues that still represent a grey zone in the knowledge of PCC characteristics and dynamics. By examining the controversial topic of the available options for the diagnosis, prevention, and management of PCC, the survey also contributes to lighting the path to future investigations through sustained multidisciplinary approaches to fill the existing gaps in PCC research.

One of the most debated issues related to PCC is its case definition. To date, defining and diagnosing PCC remain challenging because of the lack of a reliable diagnostic framework and the difficulties in gathering data from non-COVID-19 populations for comparison [2,56,91]. The experts involved in this survey agreed on the need for more specific case definitions according to the populations involved, as in the case of PWH and RD. Not only could PCC present differently in these patient groups, but also its prevalence and associated risk factors may vary, thus suggesting that the screening and management for PCC should be tailored. As an example, the experts were concordant on identifying the female sex as the main risk factor for developing PCC in all the cohorts included in the survey, but age above 65 was considered as a risk factor only for PWH and HM, whereas chronic fatigue was referred to as the most frequent clinical presentation of PCC in PWH and RD, but not in HM. These population-based differences may depend on the underlying chronic conditions and highlight the need to account for patients' baseline characteristics to better define PCC and narrow the criteria included in the diagnostic framework. This is also confirmed by the evidence that when directly asked about needing a different case definition for PCC, the experts involved in the RD survey expressed an agreement. Indeed, patients with RD are at higher risk of presenting pre-existing clinical conditions characterized by symptoms that are frequently reported also in PCC, such as chronic fatigue and chronic pain, potentially enhancing diagnostic ambiguity. Furthermore, autoimmune diseases are more frequently diagnosed in patients with pre-existing autoimmune diseases and may be also triggered by infectious diseases, including COVID-19. These observations underscore the need for a personalized and multidisciplinary diagnostic approach and follow-up for PCC.

The severity of COVID-19 has been reported as a risk factor for developing PCC [47]. The experts involved in PWH and HM surveys agreed on the need to consider this clinical feature to assess the risk for PCC soon after the end of the acute phase, whereas a clinical evaluation 3 months after acute infection, also including a basic biochemical assessment (i.e. full blood picture, kidney and liver function, coagulation, and acute-phase proteins), was not suggested. This recommendation highlights once again the need to tailor PCC risk assessment and follow-up and reflects the gaps in current research on the clinical utility of blood testing with respect to PCC. Evidence coming from large cohort studies including different populations and with a robust longitudinal design may reveal specific biochemical signals that could be used to guide the diagnosis and follow-up of PCC [14]. Furthermore, diagnostic tests validated for different populations and clinical conditions, such as psychophysical tests for smell/taste impairment or functional tests for characterizing sarcopenia/dynapenia in the elderly, may be useful also in the diagnosis and management of PCC patients. However, robust evidence of their diagnostic accuracy in the context of PCC is needed, as well as a correct definition of the procedures and metrics to be applied to this population.

As per the prevention of PCC, the evidence from the literature generally agrees on the utility of promoting revaccination and early treatment, especially in vulnerable patients, to reduce the risk of a more clinically severe acute infection [80]. To conclude, this survey reveals the need for a more specific and patient-centred case definition and diagnostic pathway for PCC to guide the clinical management of patients living with post-COVID-19 lingering symptoms. A diagnostic algorithm for PCC diagnosis and management may take advantage of the analysis of data coming from large prospective PCC cohorts, would need to include the evidence available on the diagnostic tools currently suggested to assess PCC symptoms, and should utilize advanced computational methodologies to overcome the limits of current research. Among the methodologies that could be applied, latent transition analysis has been proposed as a promising tool to capture the temporal dynamics of symptoms, while addressing fluctuations often overlooked in cross-sectional studies and incorporating patient characteristics such as age, sex, quality of life metrics, and treatment details. By accounting for all the existing information on PCC prevalence in specific sub-groups, diagnostic alternatives, and management options, LTA may effectively model symptom progression and achieve a reliable prediction performance. The resulting information may be essential to increase our knowledge of PCC recovery trajectories and support the development of more effective management strategies.

Author contributions

The authors confirm their contribution to the paper as follows: E.G., L.M.C., J.R.-B., and E.T. were responsible for study conception and design. E.G. was responsible for systematic review of evidence. L.M.C., B.T., A.A. and M.G.C. were responsible for data collection. E.G. and L.M.C. were responsible for analysis and interpretation of results. E.G., L.M.C., and E.T. were responsible for draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

This work was supported by the European Union's Horizon 2020 Research and Innovation Program, grant agreement 101016167, within the ORCHESTRA project (EU H2020 ORCHESTRA).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.04.009.

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