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The Immune Response in Post-Acute COVID-19 Syndrome

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Abstract

Hyper-inflammation caused by COVID-19 is related to worsening of symptoms and, probably, to development of Post-acute COVID-19 Syndrome, whose probable mechanisms contributing to the pathophysiology of post-acute COVID-19 include: Virus-specific pathophysiologic changes; immunologic aberrations and inflammatory damage in response to the acute infection; and sequelae of post-critical illness. A mini-review was carried out to elucidate what are the potential immunological determinants related to the clinical presentation of the post-acute COVID syndrome (PACS). This literature review sought to answer the question: what are the potential immunological determinants related to the post-acute COVID syndrome? Studies that evaluated immunological markers in PACS, published in English, Portuguese, or Spanish were included; and literature reviews, case reports and case series, animal studies, or *in vitro* studies, excluded. Performed searches on PubMed, Web of Science, Scopus databases; used the descriptors "immune markers" and "post-acute COVID-19 syndrome"; identified a total of 343 studies, of which 135 were duplicate records; of these, only 9 studies met the adopted eligibility criteria. Potential mechanisms contributing to the pathophysiology of PACS include virus-specific damage and inflammatory damage in response to the acute infection; and sequelae of post-critical illness. The Practice Community continues waiting for research to propose innate and specific immunity biomarkers that point out patients' profiles PASC susceptible.

Keywords

COVID-19, Post-acute Syndrome, Immune Response, Inflammatory damage

Background of Review

COVID-19 is a multiorgan disease caused by the SARS-CoV-2 virus, which infects cells through the interaction between the viral protein SPIKE and the angiotensin-2 converting enzyme (ACE2).When virus replication is no longer observed, some patients have new, recurring, or ongoing symptoms, called Post-acute COVID-19 syndrome (PACS) or long-COVID, defined as a multisystem disease, characterized by the development of sequelae or persistence of symptoms 4 weeks from the onset of acute COVID-19 [1]. It can be classified into two types: subacute, from 4 to 12 weeks after infection, and chronic, beyond this period. PACS can occur in patients who have had varying degrees of illness during acute infection, including those who had mild or asymptomatic infections [2].

At this moment, longitudinal surveillance data on PACS are lacking and the prevalence is challenging to estimate, ranging from 5% to 80%, because there is no unanimity in case definition for post-COVID conditions, or temporal criteria used, neither population included, and how conditions are researched [3].

PACS have been more commonly reported in female sex [4], as well as in patients who need admission to intensive care units (ICUs), with previous severe clinical status, with a high number of comorbidities or body mass index (BMI), older groups of age [5,6], health professionals [7] and black, Asian or ethnic minority populations, in Europe [8]. Evidence suggests that PACS occurs in children and adolescents as well as adults in good health, and despite the good prognosis, they present visits to the doctor, consumption of symptoms and absences from school and work, respectively [9].

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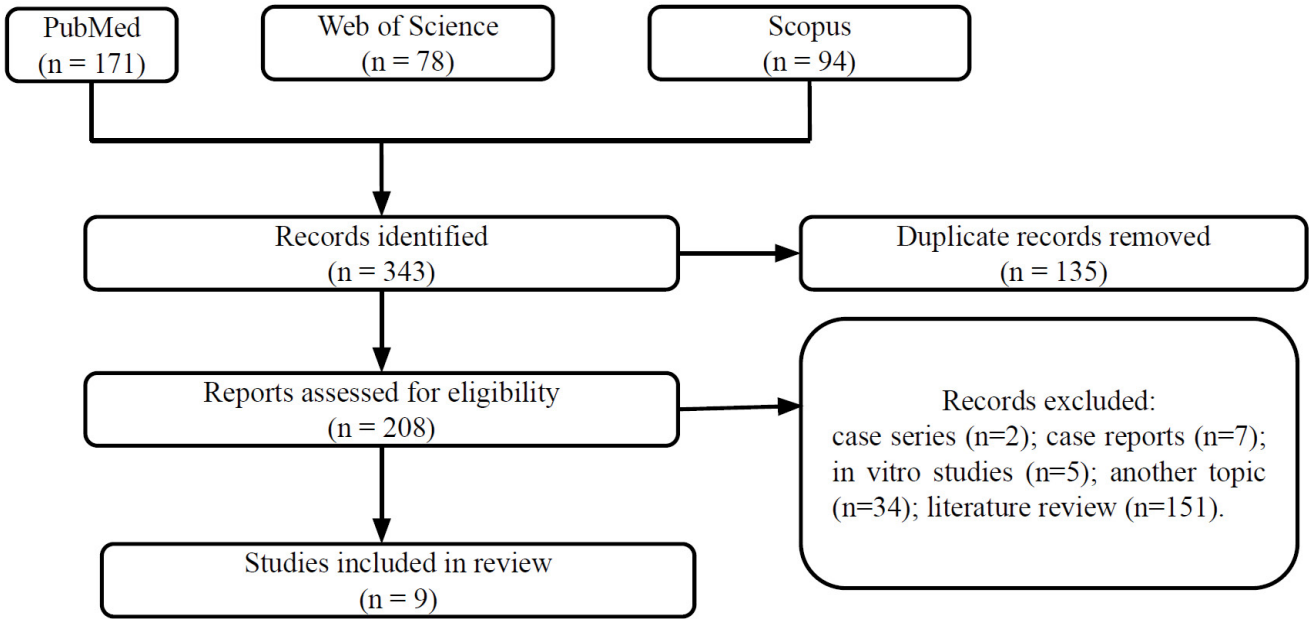

Figure 1: Flow diagram of literature search and selection of articles.

Large cohorts show that, like the acute COVID-19, clinical manifestations can affect several systems, being the most prevalent: Fatigue and post-exertional malaise and/or poor endurance, anosmia, ageusia and fever; alopecia and rash; arthralgia, myalgia and impaired daily function and mobility, followed by: Headache, depression, cognitive and sleep disorders, encephalitis and myelitis; dyspnea, cough, prolonged dependence on oxygen therapy; venous thromboembolic events, chest pain and palpitations; thyroiditis and diabetic ketoacidosis, acute kidney injury; abdominal pain and diarrhea [10,11].

The pathophysiology of PACS, although complex and not fully elucidated, potential determinants seems to be related to direct viral damage and immune system dysfunction, which triggers a state of hyper inflammation, with increased production of cytokines (such as interleukins 1, 2 and 6, TNF-α, TGF-β, IFN-γ), and consequently, hypercoagulation, tissue damage, emergence of new pathologies and worsening of previous diseases [1,12].

Therefore, given the important influence of immune changes in the generation of complications and persistent symptoms post-acute COVID syndrome, it was decided to review studies on the topic, which can enable the development of prophylaxis and therapeutics capable of improving the prognosis of affected patients.

Methods

This literature review sought to answer the question: what are the potential immunological determinants related to the post-COVID syndrome? Based on this question, the following inclusion criteria were adopted: Clinical trials (n = 0), cohort (n = 6) and transversal studies (n = 3) that evaluated immunological markers in post-COVID syndrome, published in English, Portuguese or Spanish. Were excluded: case series (n = 2), case reports (n = 7), *in vitro* studies (n = 5), another topic (n = 34) and literature review (n = 151).

We performed searches on November 1, 2021, in the following databases: PubMed, Web of Science, Scopus. We use the descriptors "Immune Markers" and "post-acute COVID-19 syndrome", and similar terms to construct the search strategy. More details about search strategies can be found in the Supplementary Table S1.

Regarding the study selection process, the searches identified a total of 343 studies, of which 135 were duplicate records. Therefore, 208 studies were evaluated in the selection process. Of these, only 9 studies met the adopted eligibility criteria (Figure 1).

Findings

The articles selected in this review are summarized in Table 1, as well as their main findings. Of the nine selected articles, six were cohort trials and three were cross-sectional studies.

Theoretical reference

The link between innate immune activation and Post-acute COVID-19 Syndrome: Hyper-inflammation caused by COVID-19 is related to worsening of symptoms and, probably, to the development of PASC. In accordance with Nalbadian, et al., 2021, the potential mechanisms contributing to the pathophysiology of post-acute COVID-19 include virus-specific damage and inflammatory damage in response to the acute infection; and sequelae of post-critical illness [12]. SARS-CoV-2 appears to trigger a prolonged production of pro-inflammatory mediators like IL-6, IL-1β, TNF-α, and CXCL8 (IL-8) by macrophages and other innate immune cells, a fact that causes lung damage and thrombosis observed in later stages of acute COVID-19 [13]. In the pathogenesis of PACS,

Table 1: Summary of selected articles in this review.

Manuscrip ttitle	Study Group	Main Findings
Mast cell activation symptoms are prevalent in Long-COVID [15].	-136 PACS subjects; -136 health controls; -80 mast cell activation (MCA) patients.	-Pre-PACS subjects and controls had virtually identical MCA symptom and severity analysis; -PACS subjects and MCAS patients before treatment had identical MCA symptom and severity analyses.
Mild and Asymptomatic COVID-19 Convalescents Present Long-Term Endotype of Immunosuppression Associated With Neutrophil Subsets Possessing Regulatory Functions [19].	-13 convalescent patients who underwent a mild or asymptomatic infection; -13 healthy donors without SARS-CoV-2 infection in the past.	-Even 3 months after infection, an elevated level of LDNs/PMN-MDSCs in blood; -LDNs/PMN-MDSCs correlates negatively with CD8+ T cells; -Higher levels of GM-CSF in the convalescent serum.
Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning [21].	-29 controls, 26 Mild-Moderate COVID-19 individuals, 48 Severe COVID-19 individuals, and 121 with PASC symptoms.	-Increased of IFN-g, CCL5/RANTES, IL-2, IL-4, CCL3, IL-6,IL-10 and VEGF levels in PACS; -Reduced CCL4 and GM-CSF production; -Increased B cells and CD14+, CD16+, CCR5+ monocytic subset frequency; -Reduced % CD4 and CD8 PD-1+ T-cells and T-regulatory cells; -“PASC Score”: (IFN-g + IL-2)/CCL4-MIP-1b; -Threshold of “PASC score”= 0.5.
Markers of Immune Activation and Inflammation in Individuals With Post Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection [22].	-121 participants in a SARS-CoV-2 recovery cohort at early (< 90 days) and late (> 90 days) time points.	-Individuals who went on to develop PASC had higher levels of cytokine biomarkers: TNF-alpha (1.14 -fold higher) and IFN-gamma-induced protein 10 (1.28 -fold higher); - PASC patients there was higher IL-6 levels in late recovery (1.44-fold higher).
Long-term SARS-CoV-2 specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms [23].	-70 cohort patients between 14 and 90 days after onset of COVID-19 symptoms; -Monthly visits until 4 months after illness onset; they are then seen every 4 months thereafter.	-Patients with PACS have a lower frequency of CD8+CD107a+ (a marker of degranulation) and a more rapid decline in the frequency of N-specific IFN-gamma producing CD8+ T cells.
Longitudinal Analysis of COVID-19 Patients Shows Age-Associated T Cell Changes Independent of Ongoing Ill-Health [24].	-Paired immunophenotyping at initial SARS-CoV-2 infection and convalescence (n = 40); -Validated findings in 71 further convalescent patients; -40 pre-pandemiccontrols.	-Persistent expansion of intermediate monocytes (HLA-DR+CD14+CD16+), effector CD8+,activated CD4+ and CD8+ T cells at 68 days; -Reduced naïve CD4+ and CD8+ T cells at 68 days.
Alterations in T and B cell function persist in convalescent COVID-19 patients [25].	-Patients were examined during COVID-19 and at up to 6 months of convalescence; -Controls were sampled, frontline workers.	-B cell subsets in acute COVID-19 patients were recovered in convalescent patients; -The recovery of IL-10+ B cells was associated with the resolution of lung pathology; -T cells from convalescent patients have persistence of a cytotoxic program in CD8+ T cells and elevated production of type 1 cytokines andinterleukin-17 (IL-17).

Refining "Long-COVID" by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection [26].	-30 patients with persistent symptoms (> 30 days) attributed to COVID-19; -17 convalescent COVID-19 individuals without persistent symptoms as control.	-Multiplex cytokines and ultra-sensitive interferon-a2 measurements were similar between both groups; -Only 50% of patients had cellular and/or humoral signs of a past SARS-CoV-2.
Establishing the prevalence of common tissue-specific autoantibodies following SARS CoV-2 infection [27].	-84 individuals previously infected with SARS-CoV-2, with acute or convalescent COVID-19. -32 individuals were in the intensive therapy unit for non-COVID reasons.	-Higher frequency of autoantibodies in the COVID-19 group; -The autoantibodies were found in the serum 3-5 months post COVID-19 infection.

we found articles evaluating the role of neutrophils and mast cells.

Mast cells: Mast cells are innate immune cells that play pathogenic roles in COVID-19 [14] and evidence points to its relationship with the PACS [15]. Pulmonary fibrosis occurs in patients with PACS and the activity of fibroblasts is stimulated by cytokine storm mediated by immune cells, including mast cells [16]. According to Afrin, et al., the prevalence of severe COVID-19 is similar to that of mast cell activation syndrome (MCAS) and the mast cell alterations of MCAS may underlie chronic Covid-19 illness [17]. In a study conducted by Weinstock, et al. [15], of 136 patients with long-COVID-19 symptoms, 80 subjects have had MCAS. Both groups before treatment had identical MCA symptom and severity analyses. Moreover, MCA symptoms were increased in post-COVID-19 patients. Potential limitations of this study are gender recruitment imbalance since sex could influence the immune response of both groups. Together, these facts suggest the involvement of mast cells in the pathogenesis of PACS. No study has directly assessed the activity and production of cytokines by mast cells in PACS, which suggests that further studies are needed.

Neutrophils: Neutrophils are involved in the immunology of COVID-19 and disease severity. Besides the antiviral roles, an unbalanced neutrophil immune response may contribute to lung tissue damage and thrombosis observed in COVID-19 patients [18]. According to Sieminska, et al. [19], post COVID-19 convalescents patients, even 3 months after infection, have an elevated number of granulocytic myeloid-derived suppressor cells, including neutrophils, in the blood, which correlates negatively with the number of CD8+ cells. Moreover, low-density neutrophils and normal density neutrophils may interfere directly with the production of anti-SARS-CoV-2 neutralizing antibodies. These neutrophils also showed a suppressive anti-CD3-induced proliferation of autologous T cells associated with a high expression of immunosuppressive PD-L1. In conclusion, these results suggest important alterations in the neutrophil activity that can help the study of the pathophysiology of PACS. However, the small number of patients and controls included in the study [13] makes it necessary that further research be carried out.

Alterations in cytokine levels and Post-acute COVID-19 Syndrome: The cytokine storm is an important proven mechanism related to the severity of COVID-19. The sequelae attributed to this disease and observed in the PACS can be partly caused by the intense production of proinflammatory cytokines [20]. Patterson, et al. [21] evaluating 29 control subjects, 26 patients with moderate COVID-19, 48 patients with severe COVID-19, and 121 subjects with PACS, and related that CCL5/RANTES, IL-2, IL-4, CCL3, IL-6, IL-10, IFN-γ, and VEGF were elevated when compared to controls, while the levels of CCL4 and GM-CSF were reduced. The authors established a binary model for separating cases of PASC and non-PASC according to the evaluated markers. "PASC Score" was defined as (IFN-g + IL-2)/CCL4-MIP-1b and the threshold of "PASC score" was 0.5. This cut-off has 97.5% of sensibility and specificity of 100% for healthy control and mild-moderate cases and 85% for severe cases. The authors hypothesize that, in PASC, the IFN-g and IL-2 cytokines would create a favorable microenvironment to Th1 polarization, however, the low levels of CCL4 can affect the recruitment of these cells impairing the antiviral response and leading to inflammatory myeloid cell activation, as evidenced by the augmented frequency of inflammatory CD14+, CD16+, CCR5+ monocytes in the PASC group compared to healthy donors [21].

Peluso, et al. [22] evaluated the levels of inflammation soluble in a SARS-CoV-2 cohort at early (< 90 days) and late (> 90 days) time points. The patients who developed PACS had higher levels of TNF-alpha (1.28 -fold higher) and IP-10 (IFN-gamma-induced protein 10, 1.28 -fold higher). Among those with post COVID symptoms, there were higher IL-6 levels in late recovery. However, in another study of the same group, the authors did not observe alterations in IL-6, IL-10, IP-10 and IFN-α levels in post-COVID patients [23].

Adaptative Immune response and Post-acute COVID-19 Syndrome

T cells: T cells play an important role in the response against the SARS-CoV-2, and evidence shows that it may also be part of the dynamics of PACS. According to Patterson, et al. [21], there is a significant decrease in regulatory T-cells frequency on PACS in comparison to healthy patients, which may exacerbate the hyper immunity on PACS. On top of that, there is evidence that even convalescent patients may present immune abnormalities. The reduction of the frequency of exhausted T cells (CD4+PD1+/CD8+PD1+) was observed in PACS patients when compared with health and acute COVID-19

individuals. A possible limitation of this study was the use of refrigerated samples for immunophenotyping analysis, which can influence the expression of cell markers depending on the cryopreservation protocol used, and the imbalance between the number of participants in each sample group. In a study by Townsend, et al. [24], the convalescent patient may even present T cell abnormalities up to 3 months after the SARS-CoV-2 infection, as lymphocyte count reduction. In a similar case, another source suggests that T-cell response against SARS-CoV-2 may be stable during the 8 months following the infection onset [23]. In addition, Shuwa, et al. showed that the Infection with SARS-CoV-2 presented alteration in the functional potential of the T CD8+ cells up to 6 months after the hospital discharge, outlining a continuous expression of the cytotoxic activity. It was observed a great response of T CD8+ cells, with high expression of perforin and granzyme. This high cytotoxic activity was also present in convalescent patients, although the CD8+ cells in these patients weren't actively degranulating or proliferating. Additionally, it was also observed a reduced expression of CXCR3 and CXCR5 on patients with acute COVID-19, which may reflect the reduction of the direction of the lymphocytes to the lymphatic nodules and follicles, which is described as contributing to the immune dysfunction in other diseases such as advanced HIV [25]. Although this does not make the study unfeasible, the control group consisted of front-line workers at COVID-19. The differences could have been more dramatic if healthy people who were not on the front lines had been included.

B cells and antibodies: B lymphocytes and antibodies appear to play a notable role in PACS. One study verified the expansion of B lymphocytes negative for IgD and CD27 expression in critically ill and convalescent patients and worse clinical outcomes in convalescent patients with lower production of interleukin-10 by B lymphocytes [25]. Regarding the influence of antibodies during the post-acute period, a study with 70 individuals previously infected by the coronavirus showed that the level of neutralization exerted by IgG against the virus molecules N, S and RBD (receptor binding domain) decreased four months after the onset of symptoms [23]. Furthermore, in a study that enrolled 34 patients with persistent symptoms of COVID-19, all 15 people who tested positive for the interferon-gamma ELISPOT test had at least one positive serologic test: 14 (93.3%) for anti-RBD, 11 (73.3%) total for IgG/IgM anti-RBD, 12 (80%) for IgG anti-S and 11 for (73.3%) IgG anti-N [26]. It is also worth mentioning that one study revealed the development, greater than in other acute diseases, of autoantibodies against a limited repertoire of antigens (such as skeletal, epidermal and muscle) during and after COVID-19. In the post-acute period, this repertoire can increase. In addition, the study revealed that severe cases of COVID-19, when compared with cases that did not require hospitalization, generate a greater increase in the development of autoantibodies [27].

Conclusion

The spectrum of patients discharged from the hospital ranges from sequelae to new and persistent manifestations linked to COVID-19. On the other hand, any patient can develop numerous conditions related to Post-acute COVID syndrome. Despite the research groups' efforts to point out clinical-epidemiological and etiopathological determinants, the most appropriate guidance yet is to register patients and provide clinical-immunological follow-up, approached by a multidisciplinary primary care team, for those patients who need it. Meanwhile, the Practice Community continues waiting for research to propose innate and specific immunity biomarkers that point out patients' profiles PACS susceptible.

Author Contribution Statement

The authors confirm contribution to the paper as follows: Study conception and design: GFA; CF; SMAF; SGF. Data collection: CF; SMAF; SGF. Analysis and interpretation of results: GFA; ACMT; CF; GRFG; NRCR; PVTF; SMAF; SGF; TPRB. Draft manuscript preparation: GFA; ACMT; CF; GRFG; NRCR; PVTF; SMAF; SGF, TPRB. All authors reviewed the results and approved the final version of the manuscript.

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Table S1: Search strategies used in databases.

Databases	Search strategy
PubMed	(“Immune Markers” OR “Immunologic Markers” OR “Immune Marker” OR “Immunologic Marker” OR “immunology” OR “Inflammation”[Mesh] OR “Inflammation” OR “Cytokines”[Mesh] OR “Cytokines” OR “Cytokine” OR “Chemokines”[Mesh] OR “Chemokines” OR “Chemokine” OR “Interleukins”[Mesh] OR “Interleukins” OR “Interleukin”) AND (“post-acute COVID-19 syndrome” [Supplementary Concept] OR “post-acute COVID-19 syndrome” OR “long-COVID” OR “long-haul COVID” OR “chronic COVID syndrome” OR “post-acute COVID19 syndrome” OR “long COVID” OR “post-acute COVID syndrome” OR “post-COVID syndrome” OR “post COVID syndrome” OR “post COVID-19 syndrome” OR “post-COVID-19 syndrome”)
Web of Science	#1 TS = (“Immune Markers” OR “Immunologic Markers” OR “Immune Marker” OR “Immunologic Marker” OR “immunology” OR “Inflammation” OR “Cytokines” OR “Cytokine” OR “Chemokines” OR “Chemokine” OR “Interleukins” OR “Interleukin”) #2 TS = (“post-acute COVID-19 syndrome” OR “long-COVID” OR “long-haul COVID” OR “chronic COVID syndrome” OR “post-acute COVID19 syndrome” OR “long COVID” OR “post-acute COVID syndrome” OR “post-COVID syndrome” OR “post COVID syndrome” OR “post COVID-19 syndrome” OR “post-COVID-19 syndrome”)#1 AND #2
Scopus	TITLE-ABS-KEY ("Immune Markers" OR "Immunologic Markers" OR "Immune Marker" OR "Immunologic Marker" OR "immunology" OR "Inflammation" OR "Cytokines" OR "Cytokine" OR "Chemokines" OR "Chemokine" OR "Interleukins" OR "Interleukin") AND TITLE-ABS-KEY ("post-acute COVID-19 syndrome" OR "long-COVID" OR "long-haul COVID" OR "chronic COVID syndrome" OR "post-acute COVID19 syndrome" OR "long COVID" OR "post-acute COVID syndrome" OR "post-COVID syndrome" OR "post COVID syndrome" OR "post COVID-19 syndrome" OR "post-COVID-19 syndrome")

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