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Rheumatology Meets Rehabilitation: Post-Acute COVID-19 Sequelae Clinical Phenotypes and Targeted Care in Patients with Immune-Mediated Inflammatory Rheumatic Diseases

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Abstract: Post-acute coronavirus disease sequelae (PACS/long COVID) variably affects patients with immune-mediated inflammatory rheumatic diseases (IMIRDs), complicating accurate diagnosis and longitudinal care. We conducted a retrospective observational study in a Romanian Teaching Hospital including adults with IMIRDs and confirmed infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 2020 and December 2024. PACS was defined as persistence of ⩾1 symptom, ⩾12 weeks post-infection. We defined every clinical phenotype (pulmonary, cardiovascular, musculoskeletal, gastrointestinal, neurological, systemic), anlysing also multisystem overlap.Demographical, clinical and paraclinical characteristics, including novel composite inflammatory indices were extracted; associations were explored with univariable tests. Of 211 IMIRD cases, 51 (24.2%) met PACS criteria. Pulmonary PACS were significantly associated with valvular heart diseases (p=0.045); cardiovascular PACS with: arrhythmias (p=0.004), obesity (p=0.018), hepatic steatosis (p=0.033), and chronic lung disease (p=0.037); musculoskeletal sequelae were significantly associated with pre-existing pulmonary fibrosis (p=0.014), gastrointestinal sequelae with current smoking (p<0.001) and pulmonary comorbidities (p=0.002), neurologic PACS with higher neutrophil-based indices and coexisting dual IMIRDs (p=0.001-0.03). Somehow unusual: systemic sequelae were associated only with the lack of corticosteroid administration (p=0.006). By January 2025, mortality was 11.8% (without having the possibility to find out the exact death cause), correlating amongst – vs. survivors – significantly with older age (p=0.015), acute-phase hypoxemia (p=0.027), and other paraclinical markers (mainly anemia). In IMIRDs, PACS is pulmonary-centered with frequent overlap and phenotype-specific clinical correlates. The findings, although objectively limited exploratory by design, guide more comprehensive diagnosis and rehabilitation-oriented follow-up, while avoiding excessive immunosuppression in the absence of objective inflammatory activity.

Keywords: long COVID; PACS; IMIRDs; sequelae; rehabilitation; rheumatology; inflammatory indices

1. Introduction

As the epidemiological demeanor of Coronavirus Disease 2019 (COVID-19) shifts towards endemicity, a clinically significant subset of convalescent patients develop persistent or de novo symptomatology after the acute illness – collectively referred to as the post-acute COVID-19 condition (PACS, also known as long COVID). A pragmatic and internationally accepted framework for this pathology defines PACS as a systemic and heterogeneous syndrome with features arising during or after the SARS-CoV-2 infection, persisting for ≥12 weeks (approximately 3 months) and up to 12 months, and not better explained by alternative diagnoses [1–5]. Variable nosology, detection, and follow-up methodology makes the overall PACS frequency to be remarkably different across population. Published estimates are inconsistent (10–80%), so that a robust analysis is momentarily unattainable without harmonized and coordinated definitions, as well as standardized outcome instruments [3]. Moreover, estimates of the global incidence are around 400 million patients with PACS, creating a significant economic burden [4].

Within rheumatology cohorts, specifically patients with IMIRDs, meta-analytic synthesis underscores a substantial burden: pooled prevalence of 56% (95% CI: 34–76) across 15 studies (n=2,995), with 69% among those hospitalized for acute COVID-19 versus 41% in non-hospitalized patients [2]. Some other studies report a frequency of 24.3% in IMIRDs cohorts [6–8]. From a broader perspective, registry-derived signals are emergent; however, they were architected mainly around hospitalization, mortality, and medication exposure rather than longitudinal PACS endpoints [9,10]. The Global Rheumatology Alliance Vaccine Survey [11] found that 10% of patients with IMIRDs developed long COVID, with hospitalization (aOR 6.49) and comorbidities (aOR 1.11 per condition) independently associated with higher risks [6]. On the other hand, reported results from the SAR-COVID Registry (Argentina) show a lower frequency of 2% [12]. These figures, however, are conditioned by very high in-between study heterogeneity (different disease thresholds, variable follow-up, and self-report vs. clinician verification), reinforcing the need for unified stratification and classification.

In the ReumaCoV Brasil cohort, 321 IMIRD patients with prior SARS-CoV-2 infection were compared with 280 IMIRD non-COVID controls at six months; the post-COVID group reported greater fatigue, anxiety, depression, and psychological distress, while mean disease-activity scores were comparable [13]. To our knowledge, as of August 31, 2025, dedicated, purpose-built rheumatology registries with PACS as the primary endpoint remain rare [6,12,13].

Pathophysiological mechanisms relevant to patients with IMIRDs

PACS is best conceived as a multisystem disorder anchored by a pulmonary-centric pathophysiology. Viral perturbation culminate with a "lethal triad" of inflammatory pulmonary edema, cardiovascular instability, and coagulopathy [14]. Considering that a comprehensive pathophysiologic review lies beyond the scope of this manuscript, we briefly outline the main mechanisms most frequently reported in patients with IMIRDs. For these individuals, immune dysregulation is central and even more pronounced in the context of PACS; it is characterized by persistent type I/III interferon signatures, increased tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6, IL-8, IL-13), activation of myeloid and CD4+/CD8+ T-cell compartments, perturbations of naïve B cells, fibroblast proliferation, oxidative stress, and gastrointestinal dysbiosis [2,3,14–18].

Moreover, molecular mimicry, neutrophil extracellular traps (NET)-mediated endotheliopathy, viral persistence that sustains a chronic low-grade persistent inflammation, and autoantibody production (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-SSA/Ro, lupus anticoagulant) plausibly link to musculoskel-

etal-dominant PACS [2,3,14–18]. Within skeletal muscle, a shift from anti-inflammatory myokine signaling to a pro-inflammatory milieu, accompanied by the upregulation of angiotensin-converting enzyme 2 and transmembrane serine protease 2, promotes tissue invasion and catabolism, resulting in weakness, fatigue, and deconditioning [14]. Beyond these immune and muscle-intrinsic processes, evolving fibrotic lung disease in convalescent patients reflects a marker of fibroblast priming and sustained profibrotic cytokine exposure, which can co-occur with myokine dysregulation and heightened pain sensitivity. In parallel, chronic ventilatory limitation and high-dose corticosteroids that both activate osteoclasts and thus increase bone resorption, together with long hospitalization duration and malnutrition of such patients, foster systemic deconditioning/sarcopenia - lower anaerobic threshold, faster lactate accumulation, and delayed recovery - experienced by patients as diffuse myalgia disproportionate to workload [19–22].

Neurobiologically, cytokine-driven coagulopathy, persistent neuroinflammation, disruption in neurotransmitter metabolism, and the documented neurotropism of the Spike protein – which can break the blood-brain barrier – provide a coherent substrate for anosmia, ageusia, cognitive complaints, and stroke [14,23,24].

Diagnosis

Clinically, PACS manifests as multisystem clusters, with more than 200 different such symptoms being cited in the literature. In IMIRD-focused cohorts, the dominant features include: fatigue (33%), arthralgia (31%), chemosensory disturbance (27%), headaches (15%), dyspnea (21%), and nasal congestion (12%), with frequent polysymptomatic presentations [2,5,16,25]. For analytic coherence and clinical relevance, this manuscript focuses on six main clinical phenotypes, addressed in the sections that follow, and are selected for either vital prognostic significance and/or high frequency and functional impact.

Pulmonary sequelae comprise: persistent dyspnea, cough, chest pain and restrictive ventilatory defects. As the lungs are the principal viral target with major prognostic weight, the current guidelines underline that individuals who recover from COVID-19 and have residual pulmonary injury should be followed for at least 36 months with structured visits that include functional testing, such as: 6-minute walk test (6MWT), quality-of-life (QoL) instruments, blood tests, and – if abnormalities were present in the initial computer tomography (CT) investigation - non-contrast high-resolution chest CT every 6 months [3,14,16,17,26].

The cardiovascular spectrum of PACS is diverse, including myocarditis, pericarditis, cardiomyopathies, myocardial infarction, heart failure, postural orthostatic tachycardia syndrome, arterial hypertension, arrhythmias and thromboembolic events [3,14,16,27,28], raising legitimate concerns about the medium- and long-term survival in affected patients. Literature data indicate that cardiovascular PACS is underpinned by a convergent triad of endotheliopathy, autonomic dysregulation, and subtle myocardial dysfunction. Convalescent cohorts without overt heart disease demonstrate persistent abnormalities in left-ventricular systolic and/or diastolic indices and myocardial strain on follow-up imaging, while cardiopulmonary exercise testing frequently reveals chronotropic incompetence or dysautonomia despite modest subjective limitation —findings that can magnify the impact of borderline valve disease on symptoms. In parallel, long-COVID cohorts frequently demonstrate exertional dyspnea with mixed contributors – ventilatory inefficiency, autonomic load, and sometimes circulatory limitations – underscoring the need to re-interrogate cardiac as well as pulmonary drivers. Finally, observational series in severe valvular heart diseases patients infected with SARS-CoV-2 describe poorer short-term outcomes, suggesting a vulnerable substrate in which even modest residual lung injury may tip patients into chronic dyspnea [29–31]. In addition, incident atrial arrhythmias have been reported months after infection—especially among individuals with pre-existing susceptibility—involving inflammation and fibrosis-related remodeling as

plausible triggers [27,32,33]. Given the increased thromboembolic risk observed in COVID-19 survivors, particularly in those with atrial fibrillation or heart failure, prior clinical experience with anticoagulant management in these populations [34] may inform therapeutic strategies for PACS patients with overlapping cardiovascular comorbidities.

Musculoskeletal sequelae include: myalgia, weakness, fatigue, muscular atrophy, not attributable to the underlying IMIRD; this type of PACS can inflate patient-reported indices despite stable objective inflammation. A thorough examination is mandatory. Epidemiological and experimental data indicate that SARS-CoV-2, like SARS-CoV (2002–2004), causes: muscle atrophy, necrosis, immune cell infiltration, demyelination, and deconditioning, ultimately contributing to long-term weakness, fatigue, and impaired endurance [1,3,14,16,18,22].

Gastrointestinal PACS (diarrhea, anorexia, nausea, vomiting, abdominal pain, constipation) are nontrivial; gut dysbiosis, inflammation along the lung–intestine–brain axis, and immune-metabolic derangements likely form the gastrointestinal phenotype [14,16].

Neurological involvement, affecting roughly one-third of patients, include: anosmia, ageusia, headache, dizziness, seizures, encephalopathy, "brain fog" phenomena, visual impairment, ataxia, neuropathic pain, and thromboembolic stroke phenotypes [3,14,16,35], with a profound impact on functionality and QoL.

Systemic symptoms – mainly fatigue – a manifestation long recognized including in Rheumatology, are both the most dominant and difficult symptoms to assess and treat in long COVID. In IMIRDs and in the general population, fatigue is typically multifactorial (pain, depression, sleep disturbance, reduced physical activity), but in its more severe or chronic forms, a defining feature is post-exertional exacerbation, whereby even modest physical, cognitive, emotional, or orthostatic stressors, trigger a delayed and disproportionate symptom flare. Patients frequently describe profound, role-limiting fatigue that impairs work, home and social life, making it an important problem worth studying further [3,16,36].

Regarding biochemical abnormalities, acute SARS-CoV-2 infection is associated more commonly with anemia, neutrophilia and relative lymphopenia. Acute-phase anemia synergizes with hypoxemia to depress systemic oxygen delivery, driving higher cardiac output, supply-demand ischemia, and escalating respiratory support needs in COVID-19 pneumonia—thereby seeding multi-organ hypoxic injury. Beyond serving as a severity marker, persistent iron-restricted erythropoiesis and endothelial sequelae sustain low functional capacity, sarcopenia, and deconditioning. Hypoxia itself is a major driver of vascular and tissue remodeling, as it stabilizes hypoxia-inducible factor-1α and thereby induces vascular endothelial growth factor overexpression and messenger ribonucleic acid (mRNA) stabilization [37–40]. Such hypoxia-mediated mechanisms have also been reported in neuraxis injuries, where oxygen deprivation shapes both tissue damage and recovery potential [41].

Composite inflammatory indices— the neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), aggregate inflammatory score (AISI), and systemic immune-inflammation (SII) —have repeatedly stratified in-hospital severity and mortality, as reported in the literature [39,42–44]. Whether these markers forecast post-acute trajectories remains less certain [45,46] and robust prospective validation in PACS is still needed.

Beyond clinical and laboratory follow-up, medical imaging plays a central role in the evaluation of PACS. Recent advances in artificial intelligence have introduced deep learning–based segmentation models, such as U-Net and ensemble learning strategies, which allow highly precise and automated quantification of imaging findings. These methods, initially validated in gastrointestinal and other imaging datasets, could be adapted for long COVID to provide objective assessment of residual lung fibrosis, cardiac remodeling, or neuroimaging abnormalities. Integration of such

approaches may enhance reproducibility, enable large-scale image analysis, and ultimately support personalized rehabilitation and monitoring strategies in PACS [47,48].

Risk factors and potential modifiers

Overall, IMIRD cohorts appear to experience greater long-COVID burden than the general population, with a musculoskeletal-dominant phenotype aligned with underlying pain susceptibility in these patients. Across mixed and IMIRD-specific cohorts, acute-phase severity—particularly the length of hospitalization and the intensive care unit stay—emerges as the most consistent predictor of PACS. Additional risk markers include: advanced age (>60 years), females, white ethnicity, smoking, greater comorbidity burden (and specific: cardiovascular diseases, diabetes, obesity, asthma, hyperthyroidism), poor pre-pandemic general and mental health and laboratory correlates such as lymphopenia. Medication exposures, especially to chronic systemic glucocorticoids and hydroxychloroquine have also been signaled in some analyses [2,3,5,16,25,35].

Age brings cumulative alveolar and microvascular vulnerability, diminished repair capacity, a higher background burden of subclinical interstitial change and together with immunosenesce, a basal pro-inflammatory profile, higher comorbidity burden and metabolic imbalances (e.g., vitamin D deficiency) contribute to greater COVID-19 severity and thus the higher probability of pulmonary PACS [49–54].

Importantly, PACS can follow mild infections. Observational data suggest that prior vaccination and timely antivirals may mitigate the risk or attenuate the burden, while the risk varies by epidemic variant, being higher in earlier waves [3,16].

Recent host-genetic data further strengthen biological plausibility: a large-scale Genome-Wide Association Study (GWAS) implicates a Forkhead box protein P4 (FOXP4) lung-regulatory locus whose effect persists after adjustment for acute severity and is accentuated in pre-vaccine/early-variant strains; Mendelian-randomization analyses support acute hospitalization as a causal determinant, indicating convergent severity-driven and genetic-susceptibility pathways [55].

Why this matters for health professionals and what this study adds

Prospective data in inflammatory arthritis – rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondylarthritis (axSpA), and juvenile idiopathic arthritis (JIA) – corroborate a measurable functional toll based on internationally accepted questionnaires: relative to infected individuals without PACS and to never-infected comparators, patients with long COVID report greater disability and disease impact, lower physical and mental health, and higher fatigue and pain, impaired QoL, with broad economic and social impact [5,36].

Accurate diagnosis and classification are the main challenges. In IMIRDs, fatigue, dyspnea, and diffuse pain frequently overlap with PACS and can mimic inflammatory flares, prompting unwarranted disease-modifying anti-rheumatic drugs (DMARDs) escalation and missed opportunities to treat the actual drivers (post-exertional symptom exacerbation, autonomic dysfunction, deconditioning, and pulmonary impairment). PACS is a newly recognized disease, where Rheumatology and Rehabilitation meet: meticulous examination and rigorous diagnosis define the pathway towards mechanism-targeted rehabilitation rather than unnecessary disease-modifying therapy.

This manuscript follows a harmonized ≥12-week case definition of PACS tailored to IMIRDs and operationalizes a six clinical phenotype, non-exclusive taxonomy that clinicians can apply at the bedside. The assessment captures clinical symptoms, comorbidities and novel inflammatory indices, creating a pragmatic template for risk-informed follow-up without inffering causality.

2. Materials and Methods

2.1. Study design and setting

We conducted a retrospective observational study including patients with IMIRDs: RA, axSpA, systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) treated at a Teaching Hospital in Bucharest, Romania, who also had a confirmed SARS-CoV-2 infection, from March 1, 2020 to December 31, 2024. Confirmation of COVID-19 was based on the National Protocol [56] and involved either a rapid antigen or reverse transcription polymerase chain reaction (RT-PCR) test.

Long COVID was defined as persistence of ≥1 symptom beyond 12 weeks (approximately 3 months) after the acute infection. Six predefined categories of PACS were used, each cluster including one of the minimal clinical criteria (described in the Introduction) and objective measurements were incorporated where available. Phenotypes were non-mutually exclusive and overlap was recorded.

A total of 211 IMIRD patients formed the source cohort; PACS was identified in 51 patients (24.2%), who were included in the present analyses. Vital status and clinical outcomes were prospectively ascertained through January 2025.

2.2. Ethical Considerations

The study complied with the Declaration of Helsinki, Good Clinical Practice (GCP) standards and was approved by the Scientific Research Ethics Committee of the "Sfânta Maria" Clinical Hospital (No. 6655/21.03.2022). Written informed consent, including authorization under the General Data Protection Regulation (GDPR), was obtained from all enrolled patients before the study procedures. Patients' personal data were coded.

2.3. Participants: eligibility criteria

Inclusion criteria

We included individuals aged 18 years or older, with a documented IMIRD diagnosis (RA, axSpA, SSc, SLE), laboratory-confirmed SARS-CoV-2 infection (antigen or RT-PCR), who provided the Informed Consent. Patients were required to have sufficient clinical and laboratory records to allow PACS classification.

Exclusion criteria

Patients were excluded if they lacked adequate medical documentation, were unable to provide informed consent, or had an alternative diagnosis that could fully explain their persistent symptoms. We also excluded individuals with critical missing data (e.g., key laboratory or clinical follow-up information) and those lost to follow-up before 90 days after acute infection.

2.4. Outcomes

Primary outcome

To determine patient- and disease-related determinants of PACS clinical phenotypes (pulmonary, cardiovascular, musculoskeletal, neurological, gastrointestinal, systemic) and multisystem overlap (≥2 categories), using demographic, clinical, and paraclinical data.

The **secondary outcome** was identifying possible predictors of all-cause mortality until January 2025.

2.5. Data sources

Data were collected directly by face-to-face consultations or indirectly, from electronic medical records and institutional databases, in both cases using a standardized case-report form. Where applicable, follow-up status was updated from subsequent visits and records through January 2025.

2.6. Exposures and covariates

We extracted:

- Demographics: age, sex, residence (urban/rural), smoking status.
- Background IMIRD data: disease type, extra-musculoskeletal involvement, antibodies [rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)], Human Leukocyte Antigen (HLA)-B27 status and IMIRD flare within 3 months post-COVID.
- Comorbidities: cardiovascular (hypertension, valvular disease, venous insufficiency, heart failure, ischemic heart disease, arrhythmias); metabolic (dyslipidemia, thyroid disease, diabetes, obesity, hepatic steatosis); pulmonary [pulmonary fibrosis, interstitial lung disease (ILD), asthma, chronic obstructive pulmonary disease (COPD)]; psychiatric (mainly anxiety and depression), musculoskeletal (osteoarthritis, osteoporosis, fractures), neurologic (stroke, epilepsy, Parkinson's Disease), thrombophilia and malignancy.
- Features of acute COVID-19: diagnostic test (antigen/RT-PCR), symptoms, severity according to the World Health Organization (WHO) criteria (mild/moderate/severe) [57], setting (community-acquired vs. known contact), hospitalization, respiratory support (oxygen, non-invasive ventilation), and therapies (antivirals, immunomodulators, antibiotics, systemic corticosteroids, anticoagulation).
- Laboratory parameters: routine hematology and chemistry markers, including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, hepatic and renal function, coagulation markers; composite inflammatory indices (NLR, dNLR, AISI, SII) calculated from standard counts according to established formulas in the literature [58].

2.7. Statistical analysis

The initial dataset was compiled in Microsoft Excel 2010 and analyzed using International Business Machines Corporation Statistical Package for the Social Sciences version 29 (IBM SPSS Statistics for Windows, Version 29.0.2.0) [59,60].

PACS was coded as present/absent and further stratified into six non-mutually exclusive clinical phenotypes (pulmonary, cardiovascular, musculoskeletal, neurological, gastrointestinal, systemic). Multisystem overlap was defined as the number of clinical PACS phenotypes per patient (1, 2, 3, or ≥4). Mortality was assessed through January 2025.

Descriptives. Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as n (%).

Continuous variables: Independent-samples t-tests were used. Homogeneity of variances was examined using Levene's test. When this test indicated unequal variances ($p<0.05$), we reported the Welch t-test.

Categorical variables: Between-group differences were tested with Pearson's χ^2. When any expected cell count <5, we used Fisher's exact test and report the exact p-value.

Analytic plan. For each clinical PACS phenotype, we screened for associations with demographics, comorbidity domains, acute-phase features, therapies, and laboratory indices using the tests above. We applied the same approach to compare survivors vs. non-survivors through January 2025.

All tests were two-sided with $\alpha=0.05$. We label 0.05–0.10 as a trend/marginal significance and report exact p-values. No adjustment for multiple comparisons was performed and we did not adjust for potential confounders, given the exploratory nature of the study, thus findings should be interpreted with caution.

3. Results

A total of 211 patients with IMIRDs (RA, axSpA, SSc, and SLE) and confirmed SARS-CoV-2 infection were included in this retrospective analysis. According to the National Protocol [56], COVID-19 was diagnosed using Rapid Antigen testing or RT-PCR. PACS was defined as the persistence of one or more symptoms beyond 12 weeks (approximately 3 months) after the acute infection. Based on this definition, 51 patients (24.2%) fulfilled the criteria and were included in the following analyses.

Within the PACS group, women predominated (n = 39; 76.5%), while men represented a smaller proportion (n = 12; 23.5%). The mean age at the time of COVID-19 diagnosis in the overall group was 56.14 ± 13.30 years; men tended to be older (60.17 ± 14.90 years) compared to women (54.90 ± 12.72 years), although the difference did not reach statistical significance (Welch's t = -1.11, p = 0.28).

Regarding patients' residence, the majority originated from urban areas (n = 39; 76.5%), while a smaller subset lived in rural areas (n = 12; 23.5%). The distribution was relatively similar across sexes, with 74.4% of women and 83.3% of men living in urban areas. The Chi-square test confirmed that there was no significant difference in residence distribution according to sex ($\chi^2 = 0.06$, p = 0.80).

Smoking status was also assessed within the PACS group. Overall, six patients (11.8%) reported active smoking, while the majority (n = 45; 88.2%) were non-smokers. Stratification by sex demonstrated that smoking occurred more frequently among women (12.8%) compared to men (8.3%). The difference in smoking status between sexes was not statistically significant ($\chi^2 = 0$, p = 1.00).

Taken together, these findings indicate that the PACS group consisted predominantly of middle-aged women from urban areas, with very few active smokers, and no significant demographic differences between men and women. These demographic characteristics are summarized in Table 1.

Characteristic	Total (n=51)	Women (n=39)	Men (n=12)	p-value
Age (years)	56.14 ± 13.30	54.90 ± 12.72	60.17 ± 14.90	0.28[1]
Residence (n, %)				
Urban	39 (76.5%)	29 (74.4%)	10 (83.3%)	0.80[2]
Rural	12 (23.5%)	10 (25.6%)	2 (16.7%)	
Smoking status (n, %)				
Smoker	6 (11.8%)	5 (12.8%)	1 (8.3%)	1.00[2]
Non-smoker	45 (88.2%)	34 (87.2%)	11 (91.7%)	

Table 1 – Demographic characteristics of the study group; 1 - Welch's t-test, 2 - Chi-square test

The comorbidity burden in the PACS group was considerable, reflecting the complex clinical profile of these patients. Cardiovascular comorbidities were the most prevalent, affecting nearly three-quarters of the cohort (72.5%), underscoring their central role in vulnerability to severe outcomes. Within this category, hypertension was the leading condition (52.9%), followed by valvular heart disease (27.5%), chronic venous insufficiency (23.5%), chronic heart failure (19.6%), ischemic heart disease (15.7%), and arrhythmias (9.8%).

Metabolic comorbidities were also highly represented in 60.8% of patients. The most frequent were dyslipidemia (25.5%) and thyroid disease (23.5%), while diabetes mellitus (17.6%) and obesity (19.6%) contributed additional risk factors that may aggravate both systemic inflammation and long-term outcomes.

Pulmonary comorbidities added a further layer of complexity, with pre-existing pulmonary fibrosis in 21.6%, ILD in 7.8%, asthma in 5.9%, and COPD in 2% of patients. These underlying respiratory conditions may predispose to more severe or prolonged pulmonary sequelae after SARS-CoV-2 infection.

Beyond the cardiometabolic and respiratory spectrum, other relevant conditions were documented, including psychiatric disorders (anxiety and depression) in 25.5%, musculoskeletal diseases in 49% (osteoporosis in 23.5% and osteoarthritis in nearly half of patients, 49.0%), thrombophilia in 15.7%, and malignancy in 5.9%. This diversity highlights the multisystemic challenges in post-COVID care.

Finally, 2 overlapping IMIRDs were recorded in eight patients (15.7%), comprising seven cases of Sjögren's disease and one of Adult Still's disease, further emphasizing the overlap between PACS and pre-existing autoimmune pathology.

Comprehensive data on each included IMIRD subtype and their specific characteristics are available in the Supplementary Material.

Figure 1 summarizes the existing comorbidities in the study group.

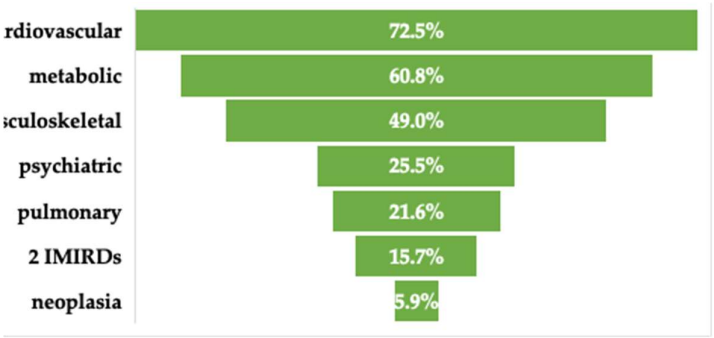

Figure 1 – The frequency of comorbidities in the PACS group

3.2. Acute SARS-CoV-2 infection characteristics

Regarding the method of diagnosis, 24 cases (47%) were diagnosed by RT-PCR and remaining 27 cases (53%) via Rapid Antigen tests.

With respect to the severity of COVID-19 at presentation, 21 cases (41.3%) were classified as mild, 16 (31.3%) as moderate, and 14 (27.4%) as severe, according to the WHO classification criteria [57]. No asymptomatic, nor critical cases were identified in the study group. Most infections were community-acquired (n = 44; 86.3%), while the remainder occurred following a confirmed infectious contact. More than half of the patients with PACS (n = 27; 52.9%) required hospitalization during the acute phase of COVID-19, reflecting the considerable disease burden in this population.

Among the 51 patients with PACS, the clinical spectrum of acute SARS-CoV-2 infection was heterogeneous, with frequent involvement of multiple systems. As anticipated for a disease that is respiratory from inception through transmission, respiratory manifestations predominated, being documented in 45 patients (88.2%). Systemic symptoms, such as fever, fatigue, and malaise, were reported in 41 patients (80.4%). Neurological symptoms were present in 22 patients (43.1%), while musculoskeletal manifestations (mainly myalgia and arthralgia) were described in 15 patients (29.4%). Digestive symptoms were less common, each occurring in 8 patients (15.7%).

Notably, a substantial proportion of patients presented with multisystem involvement. Almost half of the cohort (n = 25; 49%) experienced concurrent manifestations across three or more systems simultaneously, consistent with the polysymptomatic expression described across large observational datasets [2,7,8,12,15,61,62].

Regarding therapeutic interventions, symptomatic treatment was universally administered to all patients. Antiviral therapy was prescribed in 14 cases (27.5%), while immunomodulatory agents – such as hydroxychloroquine, anti-IL-1, or anti-IL-6 therapies – were used for 7 patients (13.7%). Antibiotic treatment was indicated in 29 patients (56.9%), systemic corticosteroids in 21 patients (41.2%), and anticoagulation in 20 patients (39.2%). With respect to respiratory support, 19 patients (37.3%) required supplemental oxygen delivered through a nasal cannula or simple mask,

and 2 patients (3.9%) necessitated non-invasive ventilation or high-flow oxygen devices. No patient required invasive mechanical ventilation or extracorporeal membrane oxygenation. Conversely, 30 patients (58.8%) did not require any form of oxygen supplementation.

Acute complications such as acute respiratory distress syndrome occurred in 14 individuals (27.4%).

Moreover, IMIRDs flares were frequent: 41.2% of patients experienced a flare of their underlying disease in the first three months post-COVID.

3.3. PACS

In the attempt to give added value to the very hard – and still evolving – endeavor of better systematizing the very complex, heterogeneous area of long COVID, we have focused on six phenotypes – as described in the first part of this manuscript.

3.3.1. Pulmonary PACS

The residual respiratory constellation of findings in the study group included persistent dyspnea, requiring at-home oxygen therapy, or radiological evidence of pulmonary fibrosis. This type of PACS was the most frequent, affecting 33 patients (64.7%). The mean age at the time of COVID-19 diagnosis was 58.7 ± 12.4 years, with women representing 72.7% of cases. Most lived in urban areas (84.8%) and 12.1% were active smokers. The majority had experienced moderate-to-severe acute SARS-CoV-2 infection, with 12 cases (36.3%) classified as mild, 11 cases (33.3%) as moderate and 10 (30.3%) as severe.

Of note, 19 individuals (57.5%) required hospitalization during the acute phase of the infection. Antiviral therapy was administered in 30.3% of cases, immunomodulators in 15.2%, antibiotics in 60.6%, systemic corticosteroids in 39.4%, and anticoagulation in 39.4%. Almost 40% of patients required oxygen supplementation during the acute episode, and two cases (6.1%) progressed to non-invasive mechanical ventilation.

Statistical analysis revealed that pulmonary sequelae were significantly linked to valvular heart disease ($p=0.045$), indicating an overlap between pre-existing cardiovascular pathology and post-infectious pulmonary outcomes. Moreover, this type of long COVID was marginally associated with older age ($p=0.065$) and higher AISI levels ($p=0.075$), suggesting that cumulative systemic inflammation and aging may predispose to persistent respiratory complications.

3.3.2. Cardiovascular PACS

The sequelae involving the cardiovascular system are of utmost importance, given the potentially fatal outcome. In the study group, this type of PACS – manifesting as persistent chest pain, palpitations, new-onset arrhythmias, or thromboembolic events – was documented in 8 patients (15.7%). The mean age at COVID-19 diagnosis in this subgroup was 61.8 ± 7.5 years, higher than the mean age of the overall PACS cohort. Women represented 62.5% of cases, and the majority resided in urban areas (87.5%). Only one patient (12.5%) was an active smoker.

Regarding COVID-19 severity, 2 patients (25.0%) had mild forms, 3 (37.5%) had moderate disease, and 3 (37.5%) had severe disease; 5 patients (62.5%) required hospitalization. Therapeutically, 2 patients (25.0%) received antiviral agents, 6 (75.0%) received antibiotics, and 3 (37.5%) were treated with systemic corticosteroids and anticoagulation. Four patients (50.0%) required oxygen therapy through a nasal cannula.

When further analyzed, cardiovascular sequelae showed multiple associations. Patients developing these complications had a significantly higher mean corpuscular hemoglobin concentration (MCHC, $p=0.019$) and comorbidities such as: arrhythmias ($p=0.004$), obesity ($p=0.018$), hepatic steatosis ($p=0.033$), and chronic pulmonary diseases ($p=0.037$). These findings underscore the interplay between metabolic, hepatic, and pulmonary dysfunction in shaping cardiovascular vulnerability after SARS-CoV-2 infection.

3.3.3. Musculoskeletal PACS

The sequelae that involved the locomotor apparatus – manifesting as new-onset or persistent arthralgia or myalgia not attributable to the underlying IMIRD – were identified in 7 patients (13.7%), all of whom were women, with a mean age at COVID-19 diagnosis of 51.4 ± 9.7 years. Most patients resided in urban areas (57.1%), and none were active smokers.

Only 2 patients necessitated hospitalization. The acute episode was predominantly mild to moderate, with 4 patients (57.1%) classified as mild and 3 (42.9%) as moderate; none experienced severe disease.

Therapeutically, this subgroup had limited exposure to specific anti-COVID regimens: one patient (14.3%) received antivirals, two (28.6%) antibiotics, two (28.6%) systemic corticosteroids, and one (14.3%) anticoagulation. Two individuals (28.6%) received oxygen supplementation through nasal cannula. Since the majority of patients had mild to moderate infection, that did not require advanced treatments, this treatment profile likely reflects the initial clinical impression. The subsequent development of musculoskeletal sequelae in such cases highlights that long-term musculoskeletal impairment may emerge independently of the severity of the acute disease or the intensity of therapeutic strategies.

Musculoskeletal PACS were significantly associated with pre-existing pulmonary fibrosis ($p=0.014$), raising the possibility of shared inflammatory or fibrotic pathways contributing to long-term musculoskeletal manifestations.

3.3.4 Gastrointestinal PACS

This last group of analyzed sequelae, consisting of persistent anorexia, weight loss, or dyspeptic symptoms, were identified in 6 patients (11.8%). All individuals were women, with a mean age of 55.3 ± 14.9 years and half of them were active smokers.

The severity of the acute infection was classified as mild in 3 patients (50.0%) and moderate in 3 (50.0%). Regarding treatment, none of the individuals received antiviral agents, immunomodulators, or anticoagulation; one patient (16.7%) was treated with antibiotics and two (33.3%) with systemic corticosteroids. None of the patients in this subgroup required oxygen supplementation.

Gastrointestinal sequelae were most strongly predicted by current smoking ($p<0.001$), but were also associated with IMIRD flare during acute infection ($p=0.017$), pre-existing pulmonary fibrosis ($p=0.028$), and COPD ($p=0.002$). There was also a trend toward association with psychiatric comorbidities ($p=0.062$), suggesting a multifactorial background where immune activation, lung pathology, and behavioral factors converge.

3.3.5. Neurological PACS

The residual neurological spectrum of findings – including dizziness, cognitive impairment (“brain fog”), persistent headaches, and in one case new-onset epilepsy – were documented in 4 patients (7.8%). This subgroup was older than the overall PACS cohort, with a mean age of 64.8 ± 5.1 years, and was predominantly female (75.0%). Most patients resided in urban areas (75.0%), and none were active smokers.

Three patients (75.0%) required hospitalization during the acute infection. With respect to COVID-19 severity, 1 case (25.0%) was mild and 3 (75.0%) were moderate. Regarding therapy, two patients (50.0%) received antivirals, one (25.0%) immunomodulatory treatment, two (50.0%) antibiotics, two (50.0%) systemic corticosteroids, and two (50.0%) anticoagulants. One patient (25.0%) required supplemental oxygen via nasal cannula.

Neurological sequelae stood out due to their strong correlation with systemic inflammation. They were associated with elevated neutrophil counts ($p=0.027$), increased NLR ($p=0.006$), higher SII ($p=0.015$), elevated dNLR ($p=0.011$), and increased

aspartate-aminotransferase (AST) levels (p=0.030). Furthermore, they were highly associated with the coexistence of two concurrent IMIRDs (p=0.001), emphasizing the impact of immune dysregulation on neurological PACS.

3.3.6. Systemic PACS

The sequelae in this group were primarily fatigue and reduced effort tolerance, representing the second most frequent category and being documented in 14 patients (27.5%). The mean age of this cluster was 56.4 ± 13.9 years, with a predominance of women (71.4%). More than half (57.1%) resided in urban environments, and 14.3% were active smokers.

Regarding COVID-19 severity, 4 patients (28.6%) had mild disease, 7 (50.0%) moderate, and 3 (21.4%) severe forms. Seven patients (50.0%) required hospitalization during the acute episode. Concerning therapy during acute COVID-19, 3 patients (21.4%) received antivirals, 1 (7.1%) immunomodulatory therapy, 7 (50.0%) antibiotics, 3 (21.4%) systemic corticosteroids, and 3 (21.4%) anticoagulants. Five patients (35.7%) received oxygen via nasal cannula, and one patient (7.1%) required non-invasive ventilation.

Rather unusual, systemic sequelae were more common among patients who did not receive corticosteroid therapy during their acute COVID-19 infection (p=0.006), suggesting a potential protective role of this treatment against long-term systemic symptoms, a connection further discussed below.

Detailed descriptive data are summarized in the following tables.

Sequelae type	N (%)	Mean age ± SD	Women (n, %)	Urban (n, %)	Smokers (n, %)
Pulmonary	33 (64.7)	58.7 ± 12.4	24 (72.7%)	28 (84.8%)	4 (12.1%)
Cardiovascular	8 (15.7)	61.8 ± 7.5	5 (62.5%)	7 (87.5%)	1 (12.5%)
Musculoskeletal	7 (13.7)	51.4 ± 9.7	7 (100%)	4 (57.1%)	0 (0%)
Gastrointestinal	6 (11.8)	55.3 ± 14.9	6 (100%)	3 (50.0%)	3 (50.0%)
Neurological	4 (7.8)	64.8 ± 5.1	3 (75.0%)	3 (75.0%)	0 (0%)
Systemic	14 (27.5)	56.4 ± 13.9	10 (71.4%)	8 (57.1%)	2 (14.3%)

Table 2 - Demographic characteristics divided by clinical PACS phenotype

Sequelae type	N (%)	COVID-19 severity (n, %)			Hospitalized n (%)
		Mild	Moderate	Severe	
Pulmonary	33 (64.7)	12 (36.3)	11 (33.3)	10 (30.3)	19 (57.6)
Cardiovascular	8 (15.7)	2 (25.0)	3 (37.5)	3 (37.5)	5 (62.5)
Musculoskeletal	7 (13.7)	4 (57.1)	3 (42.9)	0 (0)	2 (28.6)
Gastrointestinal	6 (11.8)	3 (50.0)	3 (50.0)	0 (0)	1 (16.7)
Neurological	4 (7.8)	1 (25.0)	3 (75.0)	0 (0)	3 (75.0)
Systemic	14 (27.5)	4 (28.6)	7 (50.0)	3 (21.4)	7 (50.0)

Table 3 – SARS-CoV-2 severity divided by clinical PACS phenotype

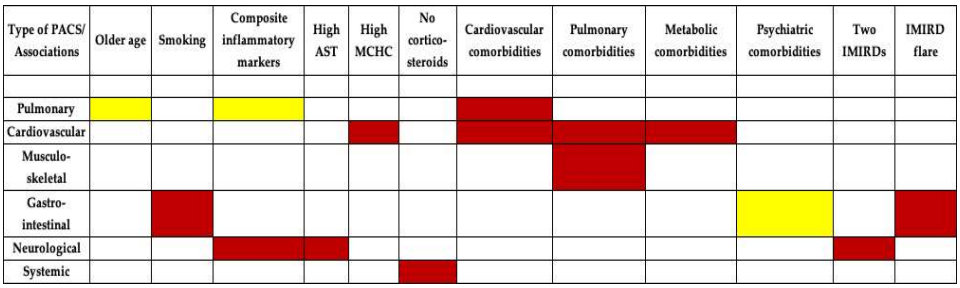

Figure 2. Associations between clinical PACS phenotypes (rows) and grouped predictors (columns). Colors reflect the level of statistical association: white = no association, yellow = marginal association ($0.05 < p < 0.10$), dark red = statistically significant ($p < 0.05$). Grouped predictors include: composite inflammatory markers (AISI, NLR, dNLR, SII), cardiovascular comorbidities (valvular heart disease, arrhythmias), pulmonary comorbidities (chronic lung disease, pulmonary fibrosis), and metabolic comorbidities (obesity, hepatic steatosis).

3.4. Multisystem Involvement and Possible Mortality Predictors

Beyond organ-specific sequelae, the analysis highlighted patterns of overlap and prognostic indicators that further delineate the systemic nature of PACS. More than half of the patients (n = 29; 56.9%) presented with a single sequela type, 11 patients (21.6%) had two sequela types, 4 patients (7.8%) had three types, and 2 patients (3.9%) presented with four or more sequela categories. Pulmonary sequelae were often the central component in multisystem involvement, most frequently co-occurring with systemic symptoms (n = 7), cardiovascular PACS (n = 5), or gastrointestinal sequelae (n = 4).

Prospective follow-up revealed that by January 2025, six patients (11.8%) with PACS had died (three with RA and the other three with SSc) although we couldn't find the death cause objectively. Mortality was significantly associated with older age (mean 68.3 vs. 57.3 years, p=0.015), lower oxygen saturation during the acute phase (p=0.027), higher ESR (p=0.043), and several hematologic abnormalities: lower hemoglobin (p=0.041), reduced erythrocyte counts (p=0.025), and lower hematocrit (p=0.039). In addition, higher AST levels (p=0.029) and a trend toward more pronounced lymphopenia (p=0.062) were observed, indicating systemic inflammation, hepatic stress, and hematological impairment as potential contributors to a poorer prognosis.

4. Discussion and Conclusions

This manuscript systematically characterizes the spectrum of long COVID/PACS clinical phenotypes in a subset of "at-risk" immunosuppressed population – patients with IMIRDs, and highlights clinical and biological associations in order to guide accurate and comprehensive diagnosis and management.

The severity gradient observed across clinical phenotypes – quantified by a higher frequency of hospitalization and WHO severity classification – shows that patients with pulmonary, cardiovascular, or systemic PACS fit a dose–response model, in which greater acute inflammatory and hypoxic loads culminate with more residual organ dysfunction.

Within the pulmonary cluster, the association with pre-existing valvular heart diseases (p=0.045) and the marginal associations with older age (p=0.065), and higher AISI (p=0.075) are clinically coherent. To summarize, aging biology and increased inflammatory tone sustaining dyspnea, restrictive physiology, as well as a cardiopulmonary interaction whereby limited hemodynamic reserve magnifies respiratory symptoms at follow-up, are possible explanations, mechanistic rationale being outlined in the Introduction [30, 31, 42, 48, 52].

Comorbidities such as: arrhythmias (p=0.004), obesity (p=0.018), hepatic steatosis (p=0.033), and chronic lung disease (p=0.037), and paraclinically: MCHC (p=0.019) show a significant association with cardiovascular PACS. Each of these diseases plau-

sibly amplifies neurohumoral stress, autonomic instability, and endothelial dysfunction following SARS-CoV-2 infection, as mentioned in the Introduction. Notably, obesity represents not only a global but also a particularly relevant burden in the Romanian population, where excess adiposity and overweight prevalence remain high [63], thus reinforcing its role as a critical modifier of PACS expression Therefore, these patients should benefit from an integrated cardio-pulmonary–metabolic assessment, with judicious use of ambulatory rhythm monitoring, echocardiography, and personalized rehabilitation rather than reflex immunomodulator escalation.

The musculoskeletal clinical phenotype (13.7%) was linked with pre-existing pulmonary fibrosis (p=0.014), despite low rates of acute hospitalization, association plausible on both biological and behavioral grounds, as developed in the first part of this manuscript [20-22]. The practical implication is to screen for ventilatory or diffusion limitations in IMIRDs with new or persistent post-COVID musculoskeletal pain and to privilege pulmonary rehabilitation over purely analgesic or immunosuppressive solutions.

The gut microbiota is central to immune homeostasis and systemic crosstalk: a substantial proportion (~70–80%) of immune cells reside within the gut, where microbial signals educate and regulate host responses, balancing tolerance and immunity and preventing excessive inflammation. Disruption of this ecosystem (dysbiosis)—as observed after SARS-CoV-2 infection and in smokers—can perturb mucosal immunity and microvascular tone and reverberate into systemic immune dysregulation, plausibly amplifying post-infectious dyspepsia, bowel habit change, and abdominal discomfort in gastrointestinal PACS [64–67]. In IMIRDs, where gut–immune interactions are already pertinent (notably in spondyloarthritis), such dysbiosis may also help explain the association with flares and the observed lung–intestine axis signals, without requiring severe acute disease [66,68,69].

Although less frequent, the neurologic cluster was associated with a consistent inflammatory and immune signature, indicating a diminished systemic innate response that has been linked to microvascular dysfunction, prolonged viral clearance, and to severity and mortality in acute SARS-CoV-2 infection [39,44,70,71].

Rather unusual, the systemic clinical phenotype, was more frequent in individuals who did not receive systemic corticosteroids during acute COVID-19 (p=0.006). Timely anti-inflammatory therapy in selected acute cases may blunt the amplitude and duration of cytokine signaling that otherwise sustains post-viral fatigue. Because the analyses are univariable, the findings should be framed as hypothesis-generating; however, they are directionally plausible and clinically important. This suggests caution against equating post-acute fatigue with uncontrolled inflammatory rheumatic disease, and it indicates that rehabilitation-first strategies are often the appropriate frontline approach.

Finally, the identified mortality predictors converge into a coherent vulnerability profile. Age captures frailty and multimorbidity, as previously discussed [49–53,72,73]; high hypoxemia favors primary lung injury severity; elevated ESR marks persistent inflammatory phenotype that is associated with disease severity and mortality [74,75]. Beyond a severity marker, persistent iron-restricted erythropoiesis and endothelial sequelae sustain low functional capacity, sarcopenia/deconditioning, plausibly mediating the excess 12-month mortality observed after severe COVID-19, mechanisms already discussed in the Introduction [38,40,76].

Taken together, these parameters identify an at-risk stratum that deserves closer surveillance, intensive management of cardiopulmonary and metabolic comorbidities, and early referral to cardiopulmonary and musculoskeletal rehabilitation, while exercising therapeutic precaution with immunosuppression unless objective disease activity mandates escalation. Although rehabilitation outcomes were not measured here, the clinical phenotype map supports integrating these strategies in IMIRD follow-up.

Limitations. Methodological constraints should temper over-interpretation. The study design (single-center, retrospective study, lack of a control group, possible overrepresentation of more severe or health-seeking patients, potential confounding from concomitant treatments also could not be excluded) is susceptible to selection and information bias; some clinical phenotypes have small samples, limiting precision and univariable analyses can have residual confounding. PACS phenotypes are highly heterogeneous and our data could not fully stratify or capture all subtypes, limiting generalizability. Nonetheless, it is important to note that this manuscript focuses on a specific subset of individuals: patients with IMIRDs.

Future work should harmonize definitions of more than 3-months, embed standardized phenotyping, capture background IMIRD symptom burden (e.g., chronic pain/fatigue) and integrate patient-reported measures with objective functional evaluation (e.g., 6MWT, spirometry, orthostatic testing, cognitive assessments, functional scales).

Romanian neurorehabilitation research has long emphasized standardized functional outcome measures that have been consistently applied in cohorts of patients with traumatic brain injury and stroke, including clinical studies [77,78]. However, in the context of long COVID-19, recent findings suggest that Romanian patients continue to face limited access to rehabilitation services [79], highlighting the urgent need to improve availability and equity of care. This represents both a call for awareness and a policy-level priority to strengthen rehabilitation pathways for PACS patients.

Insights from other domains may inform future PACS research: for instance, experience with robot-assisted and electrostimulation-based rehabilitation in cerebral palsy [80] suggests potential avenues for adapting advanced motor recovery strategies to PACS phenotypes with neuromuscular impairment, while the regulatory qualification of a digital efficacy endpoint in neuromuscular disorders [81] points to the possible role of validated digital biomarkers in enhancing standardized monitoring within PACS registries.

Looking ahead, PACS surveillance should be embedded within rehabilitation pathways: Romania's newly reported National Electronic Register for Cardiovascular Rehabilitation (NERCVR) – a REDCap-based, proof-of-concept module within the planned National Electronic Register for Cardiovascular Diseases (NERCVD) – demonstrates the feasibility of rehabilitation-focused, outcomes-rich registries [82]; a parallel PACS module tailored to IMIRDs (but not necessarily exclusive) would enable standardized clasiffication and longitudinal benchmarking nationally.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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Abbreviations

The following abbreviations are used in this manuscript:

6MWT = 6-minute walk test
ACPA = anti-citrullinated protein antibodies
AISI = Aggregate Index of Systemic Inflammation
aOR = adjusted odds ratio
AST = aspartate aminotransferase
axSpA = axial spondyloarthritis
COPD = chronic obstructive pulmonary disease
COVID-19 = Coronavirus Disease 2019
CT = computed tomography
CV = cardiovascular
DMARDs = disease-modifying anti-rheumatic drugs
dNLR = derived neutrophil-to-lymphocyte ratio
ESR = erythrocyte sedimentation rate
FOXP4 = Forkhead box protein P4
GCP = Good Clinical Practice
GDPR = General Data Protection Regulation
GWAS = Genome-Wide Association Study
HLA = human leukocyte antigen
IBM SPSS = International Business Machines Corporation Statistical Package for the Social Sciences;
IL = interleukin(s)
ILD = interstitial lung disease
IMIRDs = immune-mediated inflammatory rheumatic diseases
JIA = juvenile idiopathic arthritis
MCHC = mean corpuscular hemoglobin concentration
mRNA = messenger ribonucleic acid
NERCVD = National Electronic Register for Cardiovascular Diseases
NERCVR = National Electronic Register for Cardiovascular Rehabilitation
NET = neutrophil extracellular traps
NLR = neutrophil-to-lymphocyte ratio
PACS = post-acute coronavirus disease sequelae
PsA = psoriatic arthritis
QoL = quality of life
RA = rheumatoid arthritis
RF = rheumatoid factor
RT-PCR = reverse transcription polymerase chain reaction
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SD = standard deviation
SII = systemic immune-inflammation index
SLE = systemic lupus erythematosus
SSc = systemic sclerosis
TNF-α = tumor necrosis factor-alpha
WHO = World Health Organization

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