ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Long-Term Lung Sequelae of COVID-19

Baimakanova GE[1]*, Samsonova MV[1,2], Chernyaev AL[2,3,4], Kontorschikov AV[3] and Belevsky AS[4]

[1]State Budgetary Institution of Healthcare of the City of Moscow "Moscow Clinical Scientific and Practical Center Named After A.S. Loginov of the Moscow City Health Department", Moscow, Russia

[2]Federal State Budgetary Institution "Research Institute of Pulmonology" of the Federal Medical and Biological Agency of Russia, Moscow, Orekhovy Boulevard, Russia

[3]Federal State Budgetary Scientific Institution Research Institute of Human Morphology, Moscow, Russia

[4]Federal State Autonomous Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation, Moscow, Russia

***Corresponding Author:** Baimakanova GE, State Budgetary Institution of Healthcare of the City of Moscow "Moscow Clinical Scientific and Practical Center named after A.S. Loginov of the Moscow City Health Department", Moscow, Russia.

Received: July 21, 2025; **Published:** August 13, 2025

Abstract

Introduction: We studied the clinical and histological profile of lung tissue in patients with persistent pulmonary disease, respiratory symptoms and computed tomography (CT) findings after SARS-CoV-2 infection.

Materials and Methods: The study included 15 patients (7 females and 8 males) with a mean age of 57.7 years. All patients underwent laboratory tests, chest CT, echocardiography, and pulmonary function tests (PFT). Pulmonary tissue and bronchoalveolar lavage (BAL) samples were obtained by fibrobronchoscopy (FBS), transbronchial (TB) forceps (2 patients), and lung cryobiopsy (11 patients); open biopsy was performed in 2 patients. Cellular composition, DNA of herpesvirus, Mycobacterium tuberculosis complex and galactomannan optical density index, bacterial and fungal microflora growth were determined in BAL. SARS-CoV-2 was also identified in samples from the nasal mucosa, throat, BAL and feces using a polymerase chain reaction (PCR).

Results: The results showed no true pulmonary fibrosis in patients recovered from SARS-CoV-2 infection with persistent respiratory symptoms, functional impairment, and CT findings after SARS-CoV-2 infection.

Conclusion: Thus, no true pulmonary fibrosis was found in patients after SARS-CoV-2 infection with persistent respiratory symptoms, functional impairment, and CT findings. The observed changes comply with the current and/or resolving infection and inflammatory process.

Keywords: *SARS-COV2; Interstitial Pneumonia; Pulmonary Fibrosis*

Introduction

Long-term sequelae of COVID-19 presents a significant public health challenge with wide-ranging implications [1-3]. Approximately 31-69% of patients with COVID -19 suffer from sequelae of COVID -19 [4], which are defined as a series of new, recurrent, or ongoing health problems ≥ 4 weeks after the initial SARS - CoV-2 infection [5,6]. Symptoms may persist for months or even years in patients with COVID-19, which are defined as long COVID, post-COVID syndrome, or post-acute sequelae of COVID-19 (PASC) [2-4]. Long-term COVID-19 leads to damage to many organs, with predominant manifestations in the respiratory, cardiovascular, and gastrointestinal systems, and also affecting the nervous system and mental status of patients. Most studies report varying health consequences of COVID-19 within 1-2 years after acute infection based on the analysis of clinical, laboratory and functional data [5,7-12].

During the acute phase of COVID-19, viral pneumonia was the main reason for hospitalization due to the development of respiratory failure. The clinical manifestations and treatment of the acute phase of COVID -19 are now better understood, but data on the long-term consequences of COVID-19 are still insufficient. The prevalence of persistent lung tissue abnormalities on CT ranges from 7% to 94% one year after discharge and varies depending on the severity of the disease in patients included in the studies [5,7,13-19].

Pulmonary fibrosis in the recovery phase attracts special attention, its prevalence varies widely in different studies and ranges from 0 to 72% [18,20-22]. It remains unclear whether fibrosis-like lesions represent true fibrotic lung disease and what is the rate of its progression. Histopathological data have been studied in the acute period of the disease, mainly based on autopsy data, and autopsy and biopsy studies on long-term follow-up are few [23-25].

Objective of the Study

To study the clinical and histological profile of lung tissue in patients with persistent lung damage and respiratory symptoms and CT imaging after SARS-CoV-2 infection.

Materials and Research Methods

The study included 15 patients (7 women and 8 men) with a documented diagnosis of previous SARS-CoV-2 infection and lung damage according to CT data, with a lesion volume from 10 to 95%. The average age was 57.7 years (range 30 - 76 years).

All patients were analyzed for demographic parameters, smoking history, body mass index, information on comorbidities, previous therapy, number of hospitalizations after the first episode of SARS-CoV-2, as well as current symptoms and physical signs. All patients underwent chest CT, echocardiography, PFT, including spirometry, body plethysmography, measurements of the diffusion capacity of the lungs; general and biochemical blood tests, levels of total immunoglobulins M, G, A, E.

All patients underwent rheumatoid-immunological examination to determine autoantibodies to extractable nuclear antigens (Sm, SS-A, SS-B, PM-B, SSA/Ro-52), antibodies to histidine-tRNA synthetase (Jo-1), antibodies to proliferating cell nuclear antigen (PCNA), anticentromere antibodies (CENT-B), antibodies to double-stranded (native) DNA (dsDNA), Histones, Nucleosomes, and antibodies to ribosomal protein P (Rib.P-protein), antibodies to mitochondria (AMA-M2), antibodies to non-histone chromosomal protein Scl-70 (topoisomerase I enzyme with a molecular weight of 70 kDa).

Lung and BAL samples were obtained by FBS, TB cryobiopsy of the lungs (11 patients), using standardized methodology. Open biopsy was performed in 2 patients, TB forceps biopsy - in 2 patients. Cellular composition, cytomegalovirus (CMV) DNA, herpes viruses types 1,2,6, Epstein-Barr virus, P. jirovici, SARS Coronavirus RNA, M. tuberculosis complex, galactomannan optical density index, bacterial and fungal microflora growth in BAL were determined. SARS-CoV-2 was also determined in samples from the nasal mucosa, pharynx and feces.

Results

Patients underwent FBS with cryobiopsy and BAL on average 169.3 days after the acute episode of SARS-CoV-2 infection. At the time of biopsy, all patients had a negative SARS-CoV-2 PCR result for upper respiratory tract swab and stool. All patients were not vaccinated against SARS-CoV-2. The common complaint of all patients was shortness of breath and general weakness. Twelve patients had respiratory failure, 10 had 3-4 episodes of hospitalization for fever and development/worsening of respiratory failure. During those hospitalizations, CMV infection was confirmed in 2 patients, extrapulmonary herpes in 1 patient, and pulmonary bacterial infection, including Aspergillus spp. in 5 patients. During repeated hospitalizations, all patients received antibacterial therapy, additionally glucocorticosteroids - 2 patients and baricitinib - 2 patients. Some patients with proven viral and fungal infection had appropriate therapy.

Blood tests at the time of biopsy showed slight leukocytosis in one patient, lymphopenia in 2, and an increase in D -dimer levels in 2. The CRP level was elevated in 6 patients, significantly in 2 people.

Rheumatoidal immunological testing revealed no abnormalities. Gram-negative microflora growth in BAL was obtained in 1 patient, CMV PCR - in 1 patient. In 2 patients, SARS-CoV-2 persistence was detected as the background of secondary drug-induced immunodeficiency. According to PFT, all patients showed a decrease in volumetric indicators and diffusion capacity of the lungs. Grade 1 pulmonary hypertension was detected in 3 patients.

BAL cytology in all patients was characterized by an increase in lymphocytes and neutrophils; eosinophils of 1-3% were found in 3 patients. Histological examination of lung biopsy samples revealed different patterns (Table 1). The most common patterns were organizing pneumonia (OP) (Figure 1) and the cellular variant of nonspecific interstitial pneumonia (NSIP) (Figure 2) - in 5 patients, respectively, the fibrous variant of NSIP and fibroatelectasis - in 2 patients (Figure 3-5). Focal intraalveolar hemorrhages with focal edema and hyaline membranes were observed in 3 patients (20%), (Figure 5). Focal interstitial peribronchial fibrosis with slit-like structures was detected only in 2 patients (Figure 6 and 7).

Parameters	n
Organizing pneumonia	5
Nonspecific interstitial pneumonia (cellular)	5
Nonspecific interstitial pneumonia (fibrous) + fibroatelectasis	2
Focal intraalveolar hemorrhages with focal edema and hyaline membranes	3
Focal interstitial peribronchial fibrosis with slit-like structures	2

Table 1: *Histopathological data of patients.*

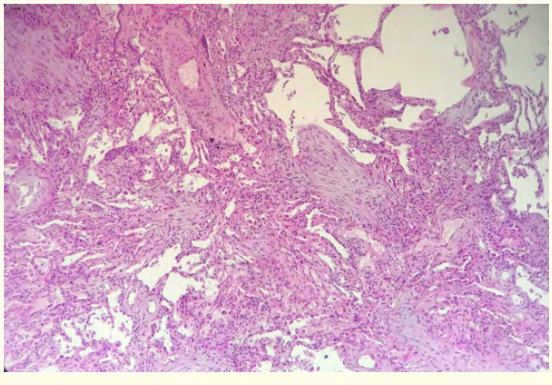

Figure 1: *Focal organizing pneumonia. Hematoxylin and eosin staining.*

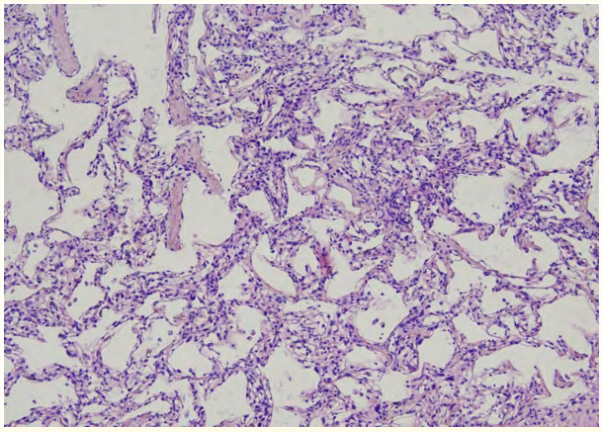

Figure 2: *Cellular variant of nonspecific interstitial pneumonia. Hematoxylin and eosin staining.*

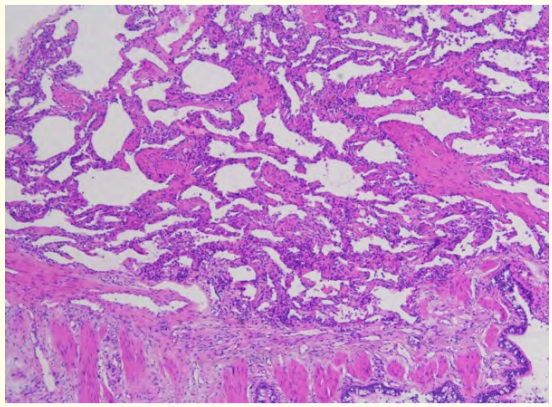

Figure 3: *Fibrous variant of nonspecific interstitial pneumonia. Hematoxylin and eosin staining.*

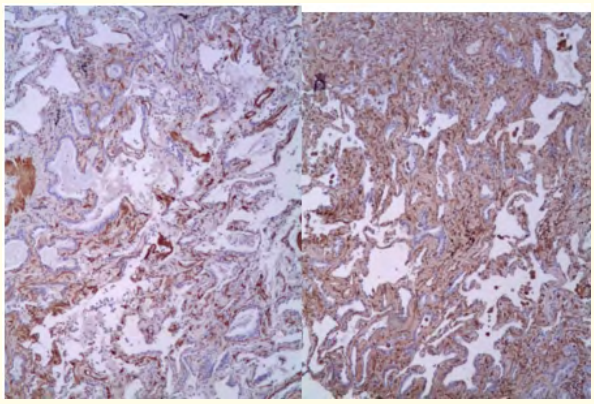

Figure 4: *Fibrous variant of nonspecific interstitial pneumonia: thickening of the interalveolar septa due to proliferation of myofibroblasts and fibroblasts. IHC: a: SMA, b: vimentin.*

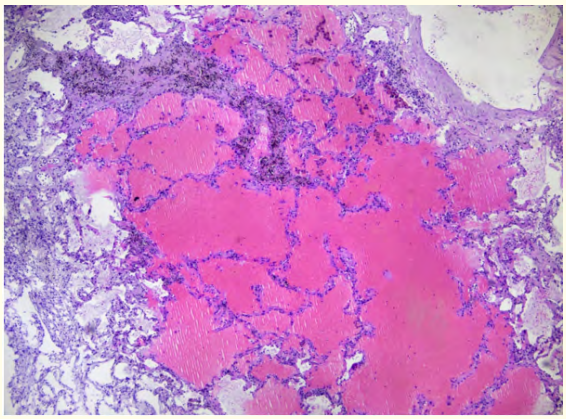

Figure 5: *Focal intraalveolar hemorrhage, edema. Hematoxylin and eosin staining.*

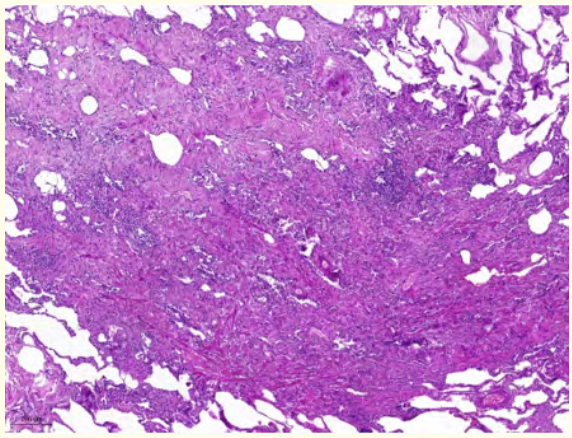

Figure 6: *Focal fibroatelectasis. Hematoxylin and eosin staining.*

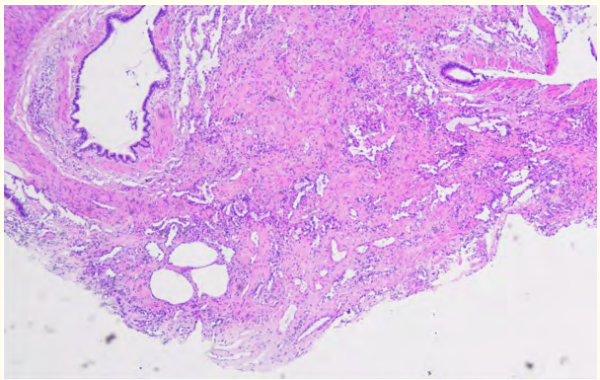

Figure 7: *Focal peribronchial fibrosis, represented by fibroatelectasis with the presence of slit-like structures. Hematoxylin and eosin staining.*

Discussion

The long-term consequences of COVID-19 remain a pressing and important public health issue. Several hypotheses have been proposed for its pathogenesis, including persistent tissue reservoirs of SARS-CoV-2 [26,27]; immune dysregulation [27,28] with or without reactivation of herpes viruses and others [27-29]; the impact of SARS-CoV-2 on the microbiota [27,30,31], autoimmunity [27,32-34] and alteration of the immune system due to molecular mimicry [27]; microvascular coagulopathy with endothelial dysfunction [27,35,36] and dysfunction of brainstem and/or nervus vagus signaling [27,37]. In our study, we attempted to find associations of some of these and others with the histopathological lung changes profile. The first published papers based on the autopsies results in the acute phase of COVID-19 corresponded to such variants as diffuse alveolar damage (DAD), acute fibrinous pneumonia, OP, lymphocytic pneumonia (LP), thrombotic microangiopathy, pulmonary embolism [23-25]. Previous single publications based on the results of TB cryobiopsies during the first month of the disease showed the presence of LP [38], DAD in combination with endotheliitis without necrosis and thrombosis [39], DAD without hyaline membranes with hyperplasia of type II alveolocytes, absence or rare myofibroblasts, hyperplasia of alveolar capillaries with their dilation, dilation and tortuosity of venules [40]. Barisione., *et al*. studied cryobiopsy samples from 8 deceased patients, 39 lung tissue samples taken from all lung lobes after 30 minutes death, and compared them with the CT picture. In 2 deceased patients with a disease duration of <14 days, DAD was found in the early exudative phase, with positive PCR for SARS-CoV-2, which corresponded to the "ground-glass opacity" phenomenon on chest CT. The 6 cases with a median disease duration of 32 days demonstrated "crazy paving" CT symptom with an average/proliferative phase of DAD (n = 3) and with a late phase of DAD (n = 3) - consolidation, one of the them with "honeycombs" [41]. In our study, lung biopsy was performed at a late stage after SARS-CoV-2 infection, in most patients - by TB cryobiopsy.

The changes which we identified are likely to be the result of several factors. In 10 patients, a wave-like course with episodes of fever and hospitalizations was noted. Such a course of post-COVID syndrome may correspond to the following theory. Y Su., *et al.* performed a multiomic analysis of data from 309 patients from the initial diagnosis of COVID-19 to recovery (after 2-3 months). The authors identified 3 consistent profiles of patients: 1) acute period with the presence of the virus and reduced cortisol levels in the blood; 2) hyperinflammation and the presence of autoantibodies in the blood; 3) the convalescent period, characterized by an increase in the population of CD8+ and CD4+ T cells, including SARS-CoV-2-specific clonotypes, which are not activated during the acute period, but during convalescence [42]. We were interested in the 2nd and 3rd profiles of patients. Autoantibodies, which can neutralize interferons type I (IFNs), associated with immune dysfunction and mortality in COVID-19 [43,44], as well as with long-term COVID-19 [27]. Systemic lupus erythematosus-associated autoantibodies have been detected in patients with acute COVID-19 infection [45]. We investigated the possibility of such a relationship by measuring routine autoantibodies, but rheumatoid immunological testing did not reveal any abnormalities. Y Su., *et al*. compared a panel of autoantibodies, including anti-IFN-α2 and 5 antinuclear autoantibodies (Ro/SS-A, La/SS-B, U1-snRNP, Jo-1 and P1) with different isotypes of antibodies against SARS-CoV-2, which made it possible to identify the abovementioned profile of "hyperinflammation with the presence of autoantibodies". However, mature types of autoantibodies were also detected, which suggests their synthesis before the acute period of COVID-19 and a reflection of the subclinical state [42]. Despite the fact that we did not identify obvious autoimmune disorders in our patients, we can assume a relationship between relapses, fever, severe general weakness with a hyperinflammation profile.

Accompanying COVID-19 immunological disorders are associated with infection activation. S Parasa., *et al.* found a relationship between the presence of SARS-CoV-2 in the gastrointestinal tract and post-COVID syndrome [46,47]. Y Su., *et al.* showed spontaneous activation of CMV-specific T cells [42]. In our study, we did not detect SARS-CoV-2 in feces and throat swabs. During previous hospitalizations, herpes virus infection was confirmed in 3 patients, bacterial infection - in 5 patients, and fungal infection - in 1 patient. At our stage, growth of gram-negative microflora in BAL was obtained in 1 patient, CMV PCR - in 1 patient, and persistence of SARS-CoV-2 was detected in 2 patients. There is systemic inflammatory response syndrome (SIRS) during COVID-19. On other hand, there is Compensatory Anti-inflammatory

Response Syndrome (CARS), leading to post-infectious/post-injury immunosuppression [48]. The goal of the CARS response, mirroring the SIRS, is to attenuate the pro-inflammatory cascade, prevent inappropriate multi-organ dysfunction [45], and regulate the return to immunological homeostasis [49]. This process involves multiple factors simultaneously interacting and counteracting to orchestrate the balance of these syndromes, which ultimately determines COVID-19 outcomes. The excessive inflammatory response depends on the viral exposure, comorbidities and immunocompetence and is characterized by excessive release of inflammatory cytokines such as interleukins 1, 6, 8, 17 and 1β, monocyte chemoattractant protein-1 and tumor necrosis factor-α [50]. This process leads to the development of acute lung injury, acute respiratory distress syndrome, coagulopathy, hypotension, hypoperfusion, multiple organ failure and death [51]. If the inflammatory response is excessively suppressed towards GARS, the patient, having managed to "survive" the initial hyperinflammatory cytokine storm and progression to acute lung injury, may enter a stage of prolonged immunosuppression [52,53], known as persistent inflammation, immunosuppression and catabolism syndrome (PICS), which is observed after sepsis and is one of the putative causes of persistent postseptic syndrome. Post-septic patients are prone to latent viral reactivation, including SARS-CoV-2, in recovered COVID-19 patients [54]. Similar to sepsis, COVID-19 patients are at risk of developing secondary bacterial and fungal infections [55], implying immunosuppression and dysregulation. Overt immunosuppression and positive BAL PCR for SARS-CoV-2 were observed in 2 patients with Hodgkin lymphoma and multiple sclerosis treated with rituximab and ocrelizumab, respectively. These patients had low levels of immunoglobulins M and G, as well as lymphopenia. Immunophenotyping of peripheral blood mononuclear cells revealed depletion of B lymphocytes due to anti-B cell therapy, as well as a slight absolute and relative decrease in NK cells in the context of SARS-CoV-2 viral pneumonia. No antibodies to SARS-CoV-2 were detected. The COVID-19 pandemic affected patients with various immunosuppressive disorders and therapies, who had an increased risk of developing a severe course of the disease [56,57]. At the same time, the inability to eliminate the virus, leading to disease progression [58]. Recent studies have shown that such persistent infection may harbor multiple mutations and deletions in SARS-CoV-2 genomes that evolved into new variants in immunocompromised patients [59,60]. Impaired anti-SARS-CoV-2 specific antibody responses during SARS-CoV-2 infection and/or vaccination in patients with solid organ transplantation, autoimmune diseases, and hematological malignancies contributed to increased morbidity and mortality due to COVID-19 [61,62]. Antibody levels in SARS-CoV-2 seropositive immunocompromised patients have been shown to decline faster than in immunocompetent individuals [63-65], although the survival time and function of antibodies are not fully known. Cellular responses play an important role in preventing infection and the development of severe disease [65]. Interestingly, despite different antibody levels, the rate of SARS-CoV-2-specific T cell response after vaccination was similar in immunocompromised and immunocompetent individuals [65]. However, due to their functional heterogeneity in different immunodeficiency states, the short- and long-term protective role of T cells in COVID-19 is still not fully understood. The presence of specific memory CD4 and CD8 T cells with the ability to proliferate for 10 months after recovery from COVID-19 has been reported [66-68]. A protective effect against SARS-CoV-2 has been described for tumor necrosis factor inhibitors, which is associated with a strong CD4 and CD8 T cell response and a decrease in tumor necrosis factor receptor-mediated T cell apoptosis [69]. The use of TNF inhibitors is associated with a reduced risk of severe COVID-19 and an enhanced cellular response to the vaccine [69]. Previous studies have shown that a significant proportion of patients experienced functional impairment for 1–2 years, especially a decrease in lung diffusion capacity [5,7], which was also observed in our patients.

The prevalence of persistent CT abnormalities ranged from 7 to 94% one year after discharge and varied depending on the severity of the disease [5,7,14-19]. In this regard, some authors believe that in addition to the loss of immune competence, patients after COVID-19 are susceptible to the development of pulmonary fibrosis [20-23]. However, the true extent of pulmonary fibrosis after COVID-19 has not been determined. The prevalence of pulmonary fibrosis or fibrosis-like changes varies widely across studies and ranges from 0 to 72% [18,20-23]. Histological changes in the lungs of patients with COVID-19 demonstrate fibroblast proliferation and interstitial fibrosis, which is possibly associated with the participation of transforming growth factor β [70]. Other predisposing factors for the development of pulmonary fibrosis include older age, male gender, smoking and diabetes, concomitant pulmonary and cardiovascular diseases [71-73], severe inflammatory response during the acute period [70], lymphopenia [74], decreased plasma levels of IFN-γ [75], mechanical

ventilation, oxygen therapy, and other infections [70]. In our study, the results of the histological examination did not reveal pronounced fibrosis with the formation of "honeycombs" in any observation.

Conclusion

Thus, true pulmonary fibrosis was not detected in patients after SARS-CoV-2 infection with persistent respiratory symptoms, functional impairment, and CT imaging after SARS-CoV-2 infection. The identified changes correspond to an ongoing and/or resolving infection and inflammatory process.

Disclosure of Interest

The authors declare that they have no competing interests.

Authors' Contribution

The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding Source

The authors declare that there is no external funding for the exploration and analysis work.

Bibliography

1. WHO. WHO coronavirus disease (COVID-19) dashboard (2023).
2. Soriano JB., *et al*. "WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus". *Lancet Infectious Diseases* 22.4 (2022): e102-e107.
3. Chuchalin AG. "COVID-19 and human safety". *Terapevticheskii Arkhiv* 93.3 (2021): 253-254.
4. Lizinfeld IA., *et al*. "Assessing factors influencing the likelihood of hospitalization of COVID-19 patients with concomitant pathologies and developing a prognostic model based on them". *Terapevticheskii Arkhiv* 94.1 (2022): 57-63.
5. Chuchalin AG. "Pulmonary fibrosis in patients who have had COVID-19". *Terapevticheskii Arkhiv* 94.11 (2022): 1333-1339.
6. Avdeev SN., *et al*. "Profilaktika, diagnostika i lecheniie novoi koronavirusnoi infektsii (COVID-19): vremennyie metodicheskiie rekomendatsii". Versiia 15, Moscow (2022).
7. Mannanova IV., *et al*. "Clinical and laboratory characteristics of COVID-19". *RMJ* 4 (2021): 22-25.
8. Maleev VV., *et al*. "Modern concepts of cerebral dysfunction at COVID-19". *Infectious Diseases* 19.3 (2021): 109-115.
9. Seeßle J., *et al*. "Persistent symptoms in adult patients 1 year after coronavirus disease 2019 (COVID-19): A prospective cohort study". *Clinical Infectious Diseases* 74.7 (2022): 1191-1198.
10. Rivera-Izquierdo M., *et al*. "Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes - a multicentre cohort study". *BMC Medicine* 20.1 (2022): 92.

11. Liu T., *et al*. "Twelve-month systemic consequences of coronavirus disease 2019 (COVID-19) in patients discharged from hospital: A prospective cohort study in Wuhan, China". *Clinical Infectious Diseases* 74.11 (2022): 1953-1965.

12. Huang L., *et al*. "Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study". *Lancet Respiratory Medicine* 10.9 (2022): 863-876.

13. Chen Y., *et al*. "One-year follow-up of chest CT findings in patients after SARS-CoV-2 infection". *BMC Medicine* 19.1 (2021): 191.

14. Han X., *et al*. "Fibrotic interstitial lung abnormalities at 1-year follow-up CT after severe COVID-19". *Radiology* 301.3 (2021): E438-E440.

15. Pan F., *et al*. "Chest CT patterns from diagnosis to 1 year of follow-up in patients with COVID-19". *Radiology* 302.3 (2022): 709-719.

16. Luger AK., *et al*. "Chest CT of lung injury 1 year after covid-19 pneumonia: The CovILD study". *Radiology* 304.2 (2022): 462-470.

17. Eberst G., *et al*. "Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia". *Annals of Intensive Care* 12.1 (2022): 23.

18. Vijayakumar B., *et al*. "CT lung abnormalities after COVID-19 at 3 months and 1 year after hospital discharge". *Radiology* 303.2 (2022): 444-454.

19. Bocchino M., *et al*. "Chest CT-based assessment of 1-year outcomes after moderate COVID-19 pneumonia". *Radiology* 305.2 (2022): 479-485.

20. Guler SA., *et al*. "Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study". *European Respiratory Journal* 57.4 (2021): 2003690.

21. van Gassel RJJ., *et al*. "High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19". *American Journal of Respiratory and Critical Care Medicine* 203.3 (2021): 371-374.

22. Caruso D., *et al*. "Post-acute sequelae of COVID-19 pneumonia: six-month chest CT follow-up". *Radiology* 301.2 (2021): E396-E405.

23. Ravaglia C., *et al*. "Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection". *European Respiratory Journal* 60.4 (2022): 2102411.

24. Aesif SW., *et al*. "Pulmonary pathology of covid-19 following 8 weeks to 4 months of severe disease: a report of three cases, including one with bilateral lung transplantation". *American Journal of Clinical Pathology* 155.4 (2021): 506-514.

25. Konopka KE Perry., *et al*. "Usual interstitial pneumonia is the most common finding in surgical lung biopsies from patients with persistent interstitial lung disease following infection with SARS-CoV-2". *EClinicalMedicine* 42 (2021): 101209.

26. Swank Z., *et al*. "Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae". *Clinical Infectious Diseases* 76.3 (2023): e487-e490.

27. Proal AD and VanElzakker MB. "Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms". *Frontiers in Microbiology* 12 (2021): 698169.

28. Phetsouphanh C., *et al*. "Immunological dysfunction persists for 8 months following initial mild-to moderate SARS-CoV-2 infection". *Nature Immunology* 23.2 (2022): 210-216.

29. Zubchenko S., *et al*. "Herpesvirus infections and postCOVID-19 manifestations: a pilot observational study". *Rheumatology International* 42.9 (2022): 1523-1530.

30. Liu Q., *et al*. "Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome". *Gut* 71.3 (2022): 544-552.

31. Yeoh YK., *et al*. "Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19". *Gut* 70.4 (2021): 698-706.

32. Wallukat G., *et al*. "Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms". *Journal of Translational Autoimmunity* 4 (2021): 100100.

33. Su Y., *et al*. "Multiple early factors anticipate post-acute COVID-19 sequelae". *Cell* 185.5 (2022): 881-895.e20.

34. Arthur JM., *et al*. "Development of ACE2 autoantibodies after SARS-CoV-2 infection". *PLoS One* 16.9 (2021): e0257016.

35. Charfeddine S., *et al*. "Long COVID-19 syndrome: is it related to microcirculation and endothelial dysfunction? insights from TUN-EndCOV Study". *Frontiers in Cardiovascular Medicine* 8 (2021): 745758.

36. Pretorius E., *et al*. "Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/Post-Acute Sequelae of COVID-19 (PASC)". *Cardiovascular Diabetology* 21.1 (2022): 148.

37. Spudich S and Nath A. "Nervous system consequences of COVID-19". *Science* 375.6578 (2022): 267-269.

38. Ehab A., *et al*. "Transbronchial lung cryobiopsy performed in acute COVID-19 pneumonia: first report". *Advances in Respiratory Medicine* 89.1 (2021): 72-74.

39. De Gopegui Miguelena PR., *et al*. "Afectación endotelial por Covid-19 en criobiopsia pulmonar". *Archivos de Bronconeumología* 57 (2020): 65.

40. Doglioni C., *et al*. "Acute Lung injury evolution in Covid-19". MedRxiv (2020).

41. Barisione E., *et al*. "Fibrotic progression and radiologic correlation in matched lung samples from COVID-19 post-mortems". *Virchows Archiv* 478.3 (2021): 471-485.

42. Su Y., *et al*. "Multiple early factors anticipate post-acute COVID-19 sequelae". *Cell* 185.5 (2022): 881-895.e20.

43. Bastard P., *et al*. "Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths". *Science Immunology* 6.62 (2021): eabl4340.

44. Wang C., *et al*. "COVID-19 in early 2021: current status and looking forward". *Signal Transduction and Targeted Therapy* 6.1 (2021): 114.

45. Bone RC. "Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation". *Critical Care Medicine* 24.1 (1996): 163-172.

46. Chang S., *et al*. "Mobility network models of COVID-19 explain inequities and inform reopening". *Nature* 589.7840 (2021): 82-87.

47. Parasa S., *et al*. "Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis". *JAMA Network Open* 3.6 (2020): e2011335.

48. Hotchkiss RS., *et al*. "Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach". *Lancet Infectious Diseases* 13.3 (2013): 260-268.

49. Sugimoto MA., *et al*. "Resolution of inflammation: what controls its onset?" *Frontiers in Immunology* 7 (2016): 160.

50. Bozza FA., *et al*. "Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis". *Critical Care* 11.2 (2007): R49.

51. Pretorius L., *et al*. "Iron dysregulation and dormant microbes as causative agents for impaired blood rheology and pathological clotting in Alzheimer's type dementia". *Frontiers in Neuroscience* 12 (2018): 851.

52. Fitridge R and Thompson M. "Mechanisms of vascular disease: A reference book for vascular specialists". Adelaide (AU): University of Adelaide Press (2011).

53. Hamers L., *et al*. "Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options". *Minerva Anestesiologica* 81.4 (2015): 426-439.

54. Walton AH., *et al*. "Reactivation of multiple viruses in patients with sepsis". *PLoS One* 9.2 (2014): e98819.

55. Xu K., *et al*. "Management of COVID-19: the Zhejiang experience". *Zhejiang Da Xue Xue Bao Yi Xue Ban* 49.2 (2020): 147-157.

56. Baek MS., *et al*. "Clinical and radiological findings of adult hospitalized patients with community-acquired pneumonia from SARS-CoV-2 and endemic human coronaviruses". *PLoS One* 16.1 (2021): e0245547.

57. Di Felice G., *et al*. "Effect of cancer on outcome of COVID-19 patients: a systematic review and meta-analysis of studies of unvaccinated patients". *Elife* 11 (2022): e74634.

58. Wei J., *et al*. "Genome-wide CRISPR screens reveal host factors critical for SARS-CoV-2 infection". *Cell* 184.1 (2021): 76-91.e13.

59. Truong TT J., *et al*. "Increased viral variants in children and young adults with impaired humoral immunity and persistent SARS-CoV-2 infection: A consecutive case series". *EBioMedicine* 67 (2021): 103355.

60. Choi B., *et al*. "Persistence and evolution of SARS-CoV-2 in an immunocompromised host". *New England Journal of Medicine* 383.23 (2020): 2291-2293.

61. Obeid M., *et al*. "Humoral responses against variants of concern by COVID-19 mRNA vaccines in immunocompromised patients". *JAMA Oncology* 8.5 (2022): e220446.

62. Sjöwall J., *et al*. "SARS-CoV-2 antibody isotypes in systemic lupus erythematosus patients prior to vaccination: associations with disease activity, antinuclear antibodies, and immunomodulatory drugs during the first year of the pandemic". *Frontiers in Immunology* 12 (2021): 724047.

63. Huang L., *et al*. "Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study". *Lancet Respiratory Medicine* 10.9 (2022): 863-876.

64. Moss P. "The T cell immune response against SARS-CoV-2". *Nature Immunology* 23.2 (2022): 186-193.

65. Mohanraj D., *et al*. "Antibody responses to SARSCoV-2 infection-comparative determination of seroprevalence in two high-throughput assays versus a sensitive spike protein ELISA". *Vaccines (Basel)* 9.11 (2021): 1310.

66. Sherina N., *et al*. "Persistence of SARS-CoV-2-specific B and T cell responses in convalescent COVID-19 patients 6-8 months after the infection". *Medicine* 2.3 (2021): 281-295.e4.

67. Jung JH., *et al*. "SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells". *Nature Communications* 12.1 (2021): 4043.

68. Zuo J., *et al*. "Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection". *Nature Immunology* 22.5 (2021): 620-626.

69. Izadi Z., *et al*. "Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19". *JAMA Network Open* 4.10 (2021): e2129639.

70. Ahmed H., *et al*. "Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis". *Journal of Rehabilitation Medicine* 52.5 (2020): jrm00063.

71. Marvisi M., *et al*. "First report on clinical and radiological features of COVID-19 pneumonitis in a Caucasian population: Factors predicting fibrotic evolution". *International Journal of Infectious Diseases* 99 (2020): 485-488.

72. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

73. Ojo AS., *et al*. "Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies". *BMC Pulmonary Medicine* (2020): 6175964.

74. Gao YD., *et al*. "Risk factors for severe and critically ill COVID-19 patients: A review". *Allergy* 76.2 (2021): 428-455.

75. Hu ZJ., *et al*. "Lower circulating interferon-gamma is a risk factor for lung fibrosis in COVID-19 patients". *Frontiers in Immunology* 11 (2020): 585647.

Bibliography

1. WHO. WHO coronavirus disease (COVID-19) dashboard (2025).

2. Soriano JB., *et al*. "WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus". *Lancet Infectious Diseases* 22.4 (2022): e102-e107.

3. Chuchalin AG. "COVID-19 and human safety". *Terapevticheskii Arkhiv* 93.3 (2021): 253-254.

4. Lizinfeld IA., *et al*. "Assessing factors influencing the likelihood of hospitalization of COVID-19 patients with concomitant pathologies and developing a prognostic model based on them". *Terapevticheskii Arkhiv* 94.1 (2022): 57-63.

5. Chuchalin AG. "Pulmonary fibrosis in patients who have had COVID-19". *Terapevticheskii Arkhiv* 94.11 (2022): 1333-1339.

6. Avdeev SN., *et al*. "Profilaktika, diagnostika i lecheniie novoi koronavirusnoi infektsii (COVID-19): vremennyie metodicheskiie rekomendatsii". Versiia 15, Moscow (2022).

7. Mannanova IV., *et al*. "Clinical and laboratory characteristics of COVID-19". *RMJ* 4 (2021): 22-25.

8. Maleev VV., *et al*. "Modern concepts of cerebral dysfunction at COVID-19". *Infectious Diseases* 19.3 (2021): 109-115.

9. Seeßle J., *et al*. "Persistent symptoms in adult patients 1 year after coronavirus disease 2019 (COVID-19): A prospective cohort study". *Clinical Infectious Diseases* 74.7 (2022): 1191-1198.

10. Rivera-Izquierdo M., *et al*. "Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes - a multicentre cohort study". *BMC Medicine* 20.1 (2022): 92.

11. Liu T., *et al*. "Twelve-month systemic consequences of coronavirus disease 2019 (COVID-19) in patients discharged from hospital: A prospective cohort study in Wuhan, China". *Clinical Infectious Diseases* 74.11 (2022): 1953-1965.

12. Huang L., *et al*. "Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study". *Lancet Respiratory Medicine* 10.9 (2022): 863-876.

13. Chen Y., *et al*. "One-year follow-up of chest CT findings in patients after SARS-CoV-2 infection". *BMC Medicine* 19.1 (2021): 191.

14. Han X., *et al*. "Fibrotic interstitial lung abnormalities at 1-year follow-up CT after severe COVID-19". *Radiology* 301.3 (2021): E438-E440.

15. Pan F., *et al*. "Chest CT patterns from diagnosis to 1 year of follow-up in patients with COVID-19". *Radiology* 302.3 (2022): 709-719.

16. Luger AK., *et al*. "Chest CT of lung injury 1 year after covid-19 pneumonia: The CovILD study". *Radiology* 304.2 (2022): 462-470.

17. Eberst G., *et al*. "Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia". *Annals of Intensive Care* 12.1 (2022): 23.

18. Vijayakumar B., *et al*. "CT lung abnormalities after COVID-19 at 3 months and 1 year after hospital discharge". *Radiology* 303.2 (2022): 444-454.

19. Bocchino M., *et al*. "Chest CT-based assessment of 1-year outcomes after moderate COVID-19 pneumonia". *Radiology* 305.2 (2022): 479-485.

20. Guler SA., *et al*. "Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study". *European Respiratory Journal* 57.4 (2021): 2003690.

21. van Gassel RJJ., *et al*. "High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19". *American Journal of Respiratory and Critical Care Medicine* 203.3 (2021): 371-374.

22. Caruso D., *et al*. "Post-acute sequelae of COVID-19 pneumonia: six-month chest CT follow-up". *Radiology* 301.2 (2021): E396-E405.

23. Ravaglia C., *et al*. "Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection". *European Respiratory Journal* 60.4 (2022): 2102411.

24. Aesif SW., *et al*. "Pulmonary pathology of covid-19 following 8 weeks to 4 months of severe disease: a report of three cases, including one with bilateral lung transplantation". *American Journal of Clinical Pathology* 155.4 (2021): 506-514.

25. Konopka KE Perry., *et al*. "Usual interstitial pneumonia is the most common finding in surgical lung biopsies from patients with persistent interstitial lung disease following infection with SARS-CoV-2". *EClinicalMedicine* 42 (2021): 101209.

26. Swank Z., *et al*. "Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae". *Clinical Infectious Diseases* 76.3 (2023): e487-e490.

27. Proal AD and VanElzakker MB. "Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms". *Frontiers in Microbiology* 12 (2021): 698169.

28. Phetsouphanh C., *et al*. "Immunological dysfunction persists for 8 months following initial mild-to moderate SARS-CoV-2 infection". *Nature Immunology* 23.2 (2022): 210-216.

29. Zubchenko S., *et al*. "Herpesvirus infections and postCOVID-19 manifestations: a pilot observational study". *Rheumatology International* 42.9 (2022): 1523-1530.

30. Liu Q., *et al*. "Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome". *Gut* 71.3 (2022): 544-552.

31. Yeoh YK., *et al*. "Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19". *Gut* 70.4 (2021): 698-706.

32. Wallukat G., *et al*. "Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms". *Journal of Translational Autoimmunity* 4 (2021): 100100.

33. Su Y., *et al*. "Multiple early factors anticipate post-acute COVID-19 sequelae". *Cell* 185.5 (2022): 881-895.e20.

34. Arthur JM., *et al*. "Development of ACE2 autoantibodies after SARS-CoV-2 infection". *PLoS One* 16.9 (2021): e0257016.

35. Charfeddine S., *et al*. "Long COVID-19 syndrome: is it related to microcirculation and endothelial dysfunction? insights from TUN-EndCOV Study". *Frontiers in Cardiovascular Medicine* 8 (2021): 745758.

36. Pretorius E., *et al*. "Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/Post-Acute Sequelae of COVID-19 (PASC)". *Cardiovascular Diabetology* 21.1 (2022): 148.

37. Spudich S and Nath A. "Nervous system consequences of COVID-19". *Science* 375.6578 (2022): 267-269.

38. Ehab A., *et al*. "Transbronchial lung cryobiopsy performed in acute COVID-19 pneumonia: first report". *Advances in Respiratory Medicine* 89.1 (2021): 72-74.

39. De Gopegui Miguelena PR., *et al*. "Afectación endotelial por Covid-19 en criobiopsia pulmonar". *Archivos de Bronconeumología* 57 (2020): 65.

40. Doglioni C., *et al*. "Acute Lung injury evolution in Covid-19". MedRxiv (2020).

41. Barisione E., *et al*. "Fibrotic progression and radiologic correlation in matched lung samples from COVID-19 post-mortems". *Virchows Archiv* 478.3 (2021): 471-485.

42. Su Y., *et al*. "Multiple early factors anticipate post-acute COVID-19 sequelae". *Cell* 185.5 (2022): 881-895.e20.

43. Bastard P., *et al*. "Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths". *Science Immunology* 6.62 (2021): eabl4340.

44. Wang C., *et al*. "COVID-19 in early 2021: current status and looking forward". *Signal Transduction and Targeted Therapy* 6.1 (2021): 114.

45. Bone RC. "Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation". *Critical Care Medicine* 24.1 (1996): 163-172.

46. Chang S., *et al*. "Mobility network models of COVID-19 explain inequities and inform reopening". *Nature* 589.7840 (2021): 82-87.

47. Parasa S., *et al*. "Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis". *JAMA Network Open* 3.6 (2020): e2011335.

48. Hotchkiss RS., *et al*. "Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach". *Lancet Infectious Diseases* 13.3 (2013): 260-268.

49. Sugimoto MA., *et al*. "Resolution of inflammation: what controls its onset?" *Frontiers in Immunology* 7 (2016): 160.

50. Bozza FA., *et al*. "Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis". *Critical Care* 11.2 (2007): R49.

51. Pretorius L., *et al*. "Iron dysregulation and dormant microbes as causative agents for impaired blood rheology and pathological clotting in Alzheimer's type dementia". *Frontiers in Neuroscience* 12 (2018): 851.

52. Fitridge R and Thompson M. "Mechanisms of vascular disease: A reference book for vascular specialists". Adelaide (AU): University of Adelaide Press (2011).

53. Hamers L., *et al*. "Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options". *Minerva Anestesiologica* 81.4 (2015): 426-439.

54. Walton AH., *et al*. "Reactivation of multiple viruses in patients with sepsis". *PLoS One* 9.2 (2014): e98819.

55. Xu K., *et al*. "Management of COVID-19: the Zhejiang experience". *Zhejiang Da Xue Xue Bao Yi Xue Ban* 49.2 (2020): 147-157.

56. Baek MS., *et al*. "Clinical and radiological findings of adult hospitalized patients with community-acquired pneumonia from SARS-CoV-2 and endemic human coronaviruses". *PLoS One* 16.1 (2021): e0245547.

57. Di Felice G., *et al*. "Effect of cancer on outcome of COVID-19 patients: a systematic review and meta-analysis of studies of unvaccinated patients". *Elife* 11 (2022): e74634.

58. Wei J., *et al*. "Genome-wide CRISPR screens reveal host factors critical for SARS-CoV-2 infection". *Cell* 184.1 (2021): 76-91.e13.

59. Truong TT J., *et al*. "Increased viral variants in children and young adults with impaired humoral immunity and persistent SARS-CoV-2 infection: A consecutive case series". *EBioMedicine* 67 (2021): 103355.

60. Choi B., *et al*. "Persistence and evolution of SARS-CoV-2 in an immunocompromised host". *New England Journal of Medicine* 383.23 (2020): 2291-2293.

61. Obeid M., *et al*. "Humoral responses against variants of concern by COVID-19 mRNA vaccines in immunocompromised patients". *JAMA Oncology* 8.5 (2022): e220446.

62. Sjöwall J., *et al*. "SARS-CoV-2 antibody isotypes in systemic lupus erythematosus patients prior to vaccination: associations with disease activity, antinuclear antibodies, and immunomodulatory drugs during the first year of the pandemic". *Frontiers in Immunology* 12 (2021): 724047.

63. Huang L., *et al*. "Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study". *Lancet Respiratory Medicine* 10.9 (2022): 863-876.

64. Moss P. "The T cell immune response against SARS-CoV-2". *Nature Immunology* 23.2 (2022): 186-193.

65. Mohanraj D., *et al*. "Antibody responses to SARSCoV-2 infection-comparative determination of seroprevalence in two high-throughput assays versus a sensitive spike protein ELISA". *Vaccines (Basel)* 9.11 (2021): 1310.

66. Sherina N., *et al*. "Persistence of SARS-CoV-2-specific B and T cell responses in convalescent COVID-19 patients 6-8 months after the infection". *Medicine* 2.3 (2021): 281-295.e4.

67. Jung JH., *et al*. "SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells". *Nature Communications* 12.1 (2021): 4043.

68. Zuo J., *et al*. "Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection". *Nature Immunology* 22.5 (2021): 620-626.

69. Izadi Z., *et al*. "Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19". *JAMA Network Open* 4.10 (2021): e2129639.

70. Ahmed H., *et al*. "Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis". *Journal of Rehabilitation Medicine* 52.5 (2020): jrm00063.

71. Marvisi M., *et al*. "First report on clinical and radiological features of COVID-19 pneumonitis in a Caucasian population: Factors predicting fibrotic evolution". *International Journal of Infectious Diseases* 99 (2020): 485-488.

72. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

73. Ojo AS., *et al*. "Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies". *BMC Pulmonary Medicine* (2020): 6175964.

74. Gao YD., *et al*. "Risk factors for severe and critically ill COVID-19 patients: A review". *Allergy* 76.2 (2021): 428-455.

75. Hu ZJ., *et al*. "Lower circulating interferon-gamma is a risk factor for lung fibrosis in COVID-19 patients". *Frontiers in Immunology* 11 (2020): 585647.

Volume 14 Issue 9 September 2025