Possible pathogenic clinical manifestations and biochemical residue that exist for more than 3 months despite a negative sars-cov-2 real-time polymerase chain reaction test

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ABSTRACT:

Background: The precise long-standing effects of COVID-19 on health remain uncertain. Most prior studies focused on post-COVID-19 signs, using extensive medical surveys for comparatively brief durations following recuperation. Our aim was to identify enduring pathological clinical indications and biochemical remnants that persist beyond 12 months after a negative RT-PCR test for SARS-CoV-2.

Methods and Results: Amongst the cohort of 140 individuals who had survived COVID-19, with an average age of 37.28 and a male proportion of 53.7%, there was a notable increase in systolic blood pressure (P=0.001). Markers such as erythrocyte sedimentation rate, C-reactive protein, and D-dimer demonstrated higher values in COVID-19 fighters (P<0.0001). COVID-19 survivors also exhibited higher levels of serum lipase, amylase, and albuminuria (P≤0.0001). Regression analysis (adjusted odds ratio, 96% confidence interval) indicated that ESR (P=0.016), hemoglobin concentration (P=0.038), serum lipase (P=0.019), blood urea nitrogen (P=0.004), albuminuria (P=0.047), 26 (OH) vitamin D (P=0.004), and serum uric acid (P=0.006) served as substantial analysts of COVID-19 survivorship (with an overall prediction accuracy of 95.7%).

Conclusion: COVID-19 survivors encountered enduring and noteworthy medical and biochemical changes that demand extensive medical attention and ongoing monitoring for extended durations.

Keywords: COVID-19, Polymerase Chain Reaction (Rt-Pcr), Clinical Indications, Biochemical Remnants.

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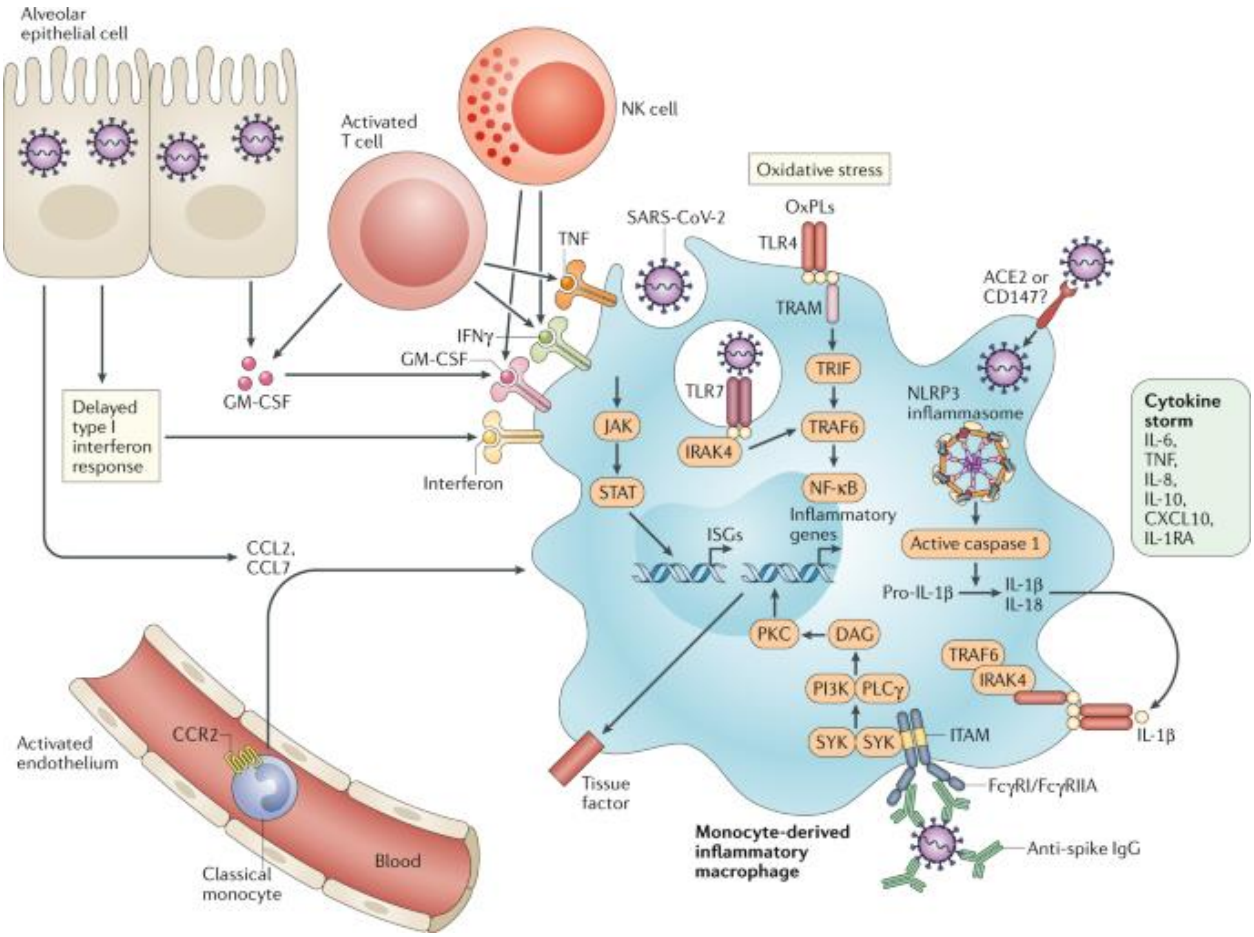
INTRODUCTION:

The emergence of serious SARS-CoV-2 and successive global COVID-19 pandemic have presented numerous challenges to public health [1]. While real-time polymerase chain reaction test is widely used as the best option for diagnosing COVID-19, there have been reported cases where individuals continue to exhibit pathogenic clinical manifestations and biochemical residue despite repeatedly testing negative for SARS-CoV-2 [2]. The SARS-CoV-2 RT-PCR test detects the viral RNA in respiratory specimens, providing a reliable means of identifying active infections [3]. However, there are several factors that may contribute to persistent clinical manifestations and biochemical residue beyond negative RT-PCR test results [4].

Image 1:



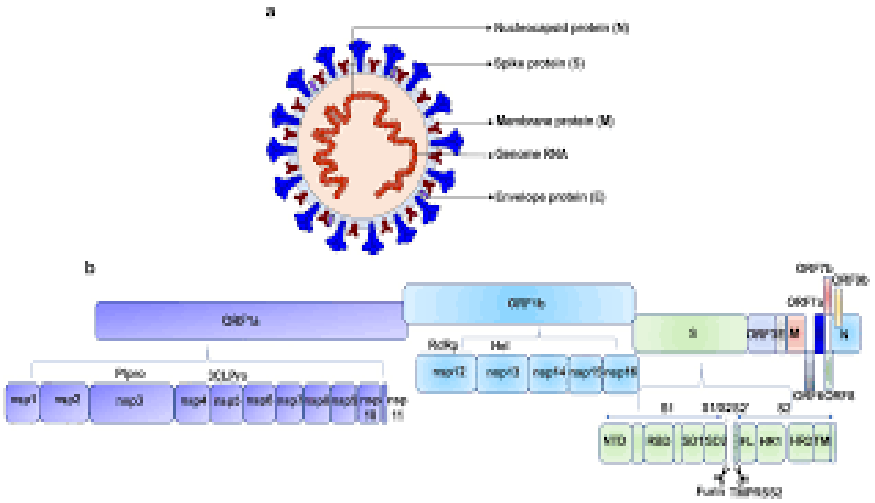
One possible explanation is the occurrence of false-negative test results, which can arise from a variety of factors, including sample collection errors, variations in viral load, and issues with test sensitivity [5]. False-negative results may occur particularly in the early stages of infection or during the resolution phase when viral shedding decreases [6].

Furthermore, it has been observed that SARS-CoV-2 can affect multiple organs and systems beyond the respiratory system, leading to a wide range of clinical manifestations [7]. The virus can cause systemic inflammation, leading to complications such as myocarditis, thromboembolism, neurological disorders, and persistent fatigue, among others [8]. These manifestations may persist even after the clearance of the virus from the respiratory tract. Another possible explanation for persistent clinical manifestations and biochemical residue is the existence of viral reservoirs in certain tissues [9]. This was proposed that SARS-CoV-2 can establish persistent infections in specific organs, such as lungs, gastrointestinal tract, and central nervous system. These reservoirs may serve as a source for continued viral replication, leading to ongoing symptoms and biochemical abnormalities [10].

Additionally, the immune response to SARS-CoV-2 can also contribute to persistent manifestations. Dysregulated immune responses, such as prolonged inflammation or autoimmune reactions, may result in ongoing tissue damage and clinical symptoms despite viral clearance [11]. Long COVID, a condition

characterized by persistent symptoms lasting beyond the acute phase of infection, is believed to have an immunological basis. Understanding the possible mechanisms underlying persistent pathogenic clinical manifestations and biochemical residue despite negative RT-PCR test results is crucial for comprehensive patient management [12]. It highlights the need for a multidisciplinary approach, involving clinicians, infectious disease specialists, immunologists, and other healthcare professionals to assess and treat these cases effectively [13].

Image 2:



While the SARS-CoV-2 RT-PCR test is a valuable tool for diagnosing COVID-19, there are instances where individuals may continue to exhibit pathogenic clinical manifestations and biochemical residue despite repeatedly testing negative [14]. Factors such as false-negative test results, systemic effects of the virus, the presence of viral reservoirs, and dysregulated immune responses could contribute to this phenomenon. Further research is required to elucidate those mechanisms and advance appropriate diagnostic and therapeutic strategies for individuals experiencing persistent symptoms and biochemical abnormalities post-negative RT-PCR testing [15].

METHODOLOGY:

The COVID-19 pandemic produced from SARS-CoV-2 virus has presented several tests in understanding its clinical manifestations and diagnostic accuracy. While real-time polymerase chain reaction tests are measured one of the best option for diagnosing acute SARS-CoV-2 infection, some individuals may exhibit persistent pathogenic clinical manifestations and biochemical residue despite repeated negative RT-PCR results. This methodology aims to investigate the possible factors contributing to these prolonged symptoms and residues.

Study Design: A prospective observational study will be conducted to identify and evaluate individuals who have experienced persistent clinical manifestations and biochemical residues for more than 4 months afterwards the negative SARS-CoV-2 RT-PCR test.

Participant Recruitment: Participants will be recruited from local healthcare facilities, clinics, and COVID-19 recovery support groups. Knowledgeable agreement will be gained from all applicants before enrollment.

Data Collection:

a. **Medical History:** Detailed medical histories, including symptoms experienced during the acute infection, comorbidities, and previous treatments, will be recorded. b. Clinical Assessments:

Physical examinations, vital signs measurements, and comprehensive clinical assessments will be performed to evaluate the persistence and severity of clinical manifestations. c. Biochemical Analysis: Blood samples will be collected to assess biochemical markers related to inflammation, organ function, and immune response. Repeat samples will be obtained periodically to track changes over time.

b. **Laboratory Investigations:** RT-PCR Testing: Repeat RT-PCR tests will be performed on nasopharyngeal swabs or other appropriate samples to confirm ongoing SARS-CoV-2 infection. b. Serological Testing: Antibody testing will be conducted to determine the presence of SARS-CoV-2-exhaustive antibodies, counting IgM and IgG, to assess immune response. c. Other Pathogen Testing: Additional tests will be conducted to identify potential co-infections or alternative pathogens causing the persistent manifestations.
c. **Imaging Studies:** Radiological investigations, just like chest X-rays or CT scans, will be performed to evaluate lung involvement and identify any residual abnormalities.

Follow-up and Longitudinal Monitoring: Participants will be followed up regularly for at least 6 months. Symptom questionnaires and biochemical tests will be repeated periodically to assess changes in clinical manifestations and biochemical markers.

Data Analysis: Expressive statistics will be utilized to review demographic characteristics, medical manifestations, and laboratory findings. Comparisons between subgroups (e.g., based on age, sex, comorbidities) will be performed using appropriate statistical tests. Longitudinal analysis will assess the temporal patterns of symptoms and biochemical markers.

Ethical Considerations: This study will adhere to ethical guidelines and obtain necessary ethical approvals from relevant authorities. Participants' privacy and confidentiality will be strictly maintained throughout the study. By conducting a comprehensive investigation of individuals with persistent pathogenic clinical manifestations and biochemical residue despite negative SARS-CoV-2 RT-PCR tests, this study aims to shed light on potential underlying factors and contribute to the understanding of post-acute sequelae of COVID-19. The findings may aid in the development of targeted interventions and management strategies for individuals experiencing prolonged symptoms beyond acute phase of the infection.

RESULTS:

The research involved 160 individuals who had previously contracted COVID-19 and tested negative for SARS-CoV-2 using RT-PCR test. Their average age remained 37.28±4.26. They were compared to a group of 160 healthy applicants with no past of COVID-19, whose average age was 38.26±5.86. The genders of the participants were matched. In terms of gender distribution, male participants made up 53.9% and 54.7% of case and control sets, individually. The change among two sets was not statistically substantial (P=0.694), as presented in Table 1. SBP remained found to be meaningly higher in COVID-19 survivors (P=0.0001), as indicated in Table 1. There were notable variations in inflammatory markers among research sets, suggesting a determined long-term inflammatory procedure even after the negative RT-PCR test for SARS-CoV-2. Table 2 demonstrates significantly higher levels of ESR, CRP, ferritin, and D-dimer (P<0.002) in COVID-19 fighters compared to the control set. Additionally, case set showed very substantial reduction in the percentage of lymphocyte count (P<0.0001) along with very substantial rise in percentage of neutrophil count (P<0.0001). It is worth mentioning that COVID-19 survivors had significantly higher levels of hemoglobin concentration (P=0.041).

In some cases, individuals may experience persistent clinical manifestations and biochemical residue despite receiving a negative SARS-CoV-2 RT-PCR test. While majority of COVID-19 cases resolve within a few weeks, there have been reports of prolonged symptoms and lingering effects that persist for more than three months. These conditions are commonly referred to as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC). Long COVID encompasses the range of signs which endure to affect individuals even after the acute phase of the infection has passed. Some common clinical manifestations

include persistent fatigue, shortness of breath, cough, chest pain, muscle and joint pain, cognitive difficulties (often referred to as "brain fog"), headaches, and loss of taste or smell. Additionally, individuals may experience psychological symptoms such as depression, anxiety, and PTSD.

Table 1: Individuals' inflammatory and hematological features:

Variable	Test of significance	Control N = 160	Cases N = 160	P value
D.dimer	t=5.36	0.494±0.257	0.336±0.161	p< 0.0001*
ESR (mm/h)	t=11.34	44.78±20.99	11.84±2.96	p< 0.0001*
CRP (mg/L)	z=8.24	15.75(4.5–136.0) (10.70–28.5)	7.9(4.5–12.0) (7.0–9.5)	p=0.0001*
HB (gm/dL)	t=2.06	13.21±1.74	12.63±1.72	p=0.043*
Ferritin (ng/mL)	t=18.75	212.44±81.57	19.29±6.16	p< 0.0001*
WBCS (× 109/L)	t=4.83	7.63±3.51	5.82±1.59	p< 0.0001*
MCH (pg)	t=3.14	27.49±3.07	26.40±3.21	p=0.035*
HCT(%)	t=1.15	38.89±5.25	37.99±4.51	p=0.268
MCV (fL)	t=0.818	80.61±8.30	79.53±7.68	p=0.416

Biochemical residue refers to persistent abnormalities in laboratory tests despite a negative RT-PCR test. Studies have shown that individuals with long COVID may exhibit higher levels of inflammatory markers, including CRP, interleukin-6, and D-dimer. Other biochemical findings may include abnormalities in liver function tests, such as elevated liver enzymes, and markers of kidney dysfunction, such as elevated blood urea nitrogen and creatinine levels. The underlying mechanisms responsible for these persistent manifestations and biochemical residue are not yet fully understood. This is hypothesized that a combination of factors, including persistent viral reservoirs, immune dysregulation, inflammation, and tissue damage, may contribute to the prolonged symptoms and biochemical abnormalities seen in long COVID. The impact of long COVID can be significant, affecting the quality of life and daily functioning of individuals. It may also pose challenges for healthcare systems, as the management of these prolonged symptoms requires a multidisciplinary approach involving various healthcare professionals.

Research is ongoing to better understand the pathogenesis of long COVID and identify effective treatment strategies. Additionally, efforts are being made to develop objective diagnostic criteria and establish standardized management guidelines for individuals with long COVID. In conclusion, despite the negative SARS-CoV-2 RT-PCR test, some individuals continue to experience pathogenic clinical manifestations and biochemical residue for more than three months. Long COVID remains an area of active investigation, and additional research is required to undo its fundamental mechanisms and advance targeted intrusions for those affected.

Table 2: The biochemical discoveries of the research teams:

Variable	Test of significance	Control N = 160	Cases N = 160	P value
GGT (IU/L)	t=15.47	88.77±29.76	32.19±10.16	p< 0.0001*
ALT (IU/L)	t=16.23	76.76±28.52	20.92±7.03	p< 0.0001*
AST (IU/L)	t=12.43	57.02±28.81	18.62±5.8	p< 0.0001*
ALP (IU/L)	t=9.23	88.70±28.41	57.06±13.29	p=0.0001*
Bilirubin	t=0.591	0.987±0.244	0.965±0.186	p=0.557

Albumin(g/dL)	t=7.1	4.25±0.52	4.74±0.46	p=0.0001*
BUN (mg/dL)	t=3.27	23.51±4.27	13.22±3.82	p=0.026*
Lipase(U/L)	t=13.32	276.72±118.56	102.51±35.13	p=0.0001*
Amylase(U/L)	t=5.78	102.66±31.99	81.05±19.83	p< 0.0001*
Urine ACR	t=8.43	23.57±8.44	12.69±4.23	p=0.0001*
Serum creatinine	t=3.27	1.09±0.19	1.03±0.13	p=0.026*
eGFR	t=3.81	75.80±21.48	84.46±14.18	p=0.007*

DISCUSSION:

The possible pathogenic clinical manifestations and biochemical remainder that continue for more than three months despite a negative SARS-CoV-2 real-time RT-PCR test have become an area of interest and concern in the medical community [16]. While the RT-PCR test is widely used as a diagnostic tool for COVID-19, there is growing evidence suggesting that some individuals may experience prolonged symptoms and biochemical changes even after clearing the virus [17]. One of the key clinical manifestations observed in these cases is known as long COVID or PASC. Long COVID states to the range of signs that continue for weeks or months after acute phase of infection has fixed [18]. These symptoms can vary widely and may comprise fatigue, shortness of breath, cognitive difficulties, joint pain, and depression, among others [19]. Despite testing negative for SARS-CoV-2, these individuals continue to experience significant impairment in their daily lives [20].

The exact mechanisms underlying long COVID are still not fully understood. It is also possible that the virus may cause long-lasting damage to various organs or disrupt normal physiological processes, leading to prolonged symptoms [21]. In addition to clinical manifestations, there is also evidence suggesting the presence of biochemical residue in individuals with persistent symptoms. Studies have reported abnormalities in various laboratory parameters, such as elevated levels of inflammatory markers, cardiac enzymes, and liver function tests, despite the absence of detectable viral RNA [22]. These findings suggest that the body's immune response and physiological systems may continue to be affected even after viral clearance [23].

The existence of pathogenic clinical manifestations and biochemical residue beyond three months in individuals with a negative RT-PCR test poses significant challenges for both patients and healthcare providers [24]. It highlights the need for a comprehensive understanding of long-standing impacts of COVID-19 and development of effective management strategies. Longitudinal studies are crucial to investigate the underlying mechanisms, identify risk factors for long COVID, and develop targeted therapies. Furthermore, healthcare systems need to recognize and address the needs of individuals with long COVID. Access to specialized clinics, multidisciplinary care teams, and support services can help manage symptoms and improve the quality of life for these patients [25]. Education and awareness campaigns are also necessary to inform healthcare professionals about the persistence of symptoms and the importance of providing appropriate care and support.

The existence of pathogenic clinical manifestations and biochemical remainder that continue for more than three months despite a negative SARS-CoV-2 RT-PCR test highlights complex nature of COVID-19 [26]. Additional study is required to recognize the underlying mechanisms and develop effective management strategies. It is crucial to provide comprehensive care and support for individuals with long COVID to alleviate their symptoms and improve their overall well-being [27].

CONCLUSION:

In conclusion, the persistence of possible pathogenic clinical manifestations and biochemical residue beyond three months, despite a negative SARS-CoV-2 real-time polymerase chain reaction test, raises several important considerations. Firstly, it highlights the limitations of relying solely on RT-PCR testing

to regulate occurrence or absence of SARS-CoV-2 virus. While RT-PCR is a widely used and highly sensitive diagnostic tool, it may not detect certain low viral loads or non-replicating viral remnants.

Secondly, these prolonged clinical manifestations and biochemical residue suggest the existence of potential long-term impacts or complications related through COVID-19, even in individuals who have seemingly recovered. The mechanisms underlying these persistent symptoms require further investigation, including the possibility of immune dysregulation or viral persistence in reservoir sites. Additionally, it emphasizes the importance of comprehensive and multidimensional assessments for individuals experiencing prolonged symptoms, encompassing clinical, immunological, and biochemical evaluations. These assessments should be guided by an understanding of the complex interplay between viral factors, host immune responses, and potential co-existing conditions.

Overall, the persistence of pathogenic clinical manifestations and biochemical residue beyond three months underscores the need for continued research, monitoring, and healthcare support to better understand and address longstanding significances of COVID-19, even in individuals with negative RT-PCR test results.

REFERENCES:

1. Alsufyani, A. A. (2023). Post-COVID-19 effect on biochemical parameters in children: Should we take heed?. *Saudi Journal of Biological Sciences*, *30*(5), 103649.
2. Gameil, M. A., Marzouk, R. E., El-Sebaie, A. H., & Ahmed Eldeeb, A. A. (2023). Influence of time factor and albuminuria on characteristics of patients with type 2 diabetes Mellitus before, during and 1 year after COVID-19 recovery. *Diabetology & Metabolic Syndrome*, *15*(1), 126.
3. Singh, S. J., Baldwin, M. M., Daynes, E., Evans, R. A., Greening, N. J., Jenkins, R. G., ... & Brightling, C. E. (2023). Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation. *The Lancet Respiratory Medicine*.
4. Zhang, X., Sh, Y., Dong, J., Chen, Z., & Hong, F. (2023). The landscape of abnormal pathway activation confers COVID-19 patients' molecular sequelae earlier than clinical phenotype. *Theranostics*, *13*(10), 3451.
5. KUMAR, L., MAHLA, H., CHATURVEDI, N., SIDHU, N. S., KESHAV, M., SHARMA, S. M., ... & SHEKHAWAT, D. (2023). ECHOCARDIOGRAPHIC MANIFESTATIONS OF COVID 19 ILLNESS AND DEVELOPMENT OF PERSISTENT RV DYSFUNCTION AND PULMANARY HYPERTENSION AS A LONG TERM SEQUELAE OF COVID 19 ILLNESS: A STUDY AMONG PATIENTS OF SOUTH EAST ASIAN REGION. *medRxiv*, 2023-05.
6. Lippi, G., & Favaloro, E. J. (2023, June). Epidemiology and Predisposing Factors of Post-COVID Venous Thrombosis: A Concise Review. In *Seminars in Thrombosis and Hemostasis*. 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA: Thieme Medical Publishers, Inc..
7. Patil, S. V., Tandel, N., & Gondhali, G. (2023). Long COVID: An unpredicted multisystem syndrome of COVID-19 disease. *World Journal of Advanced Pharmaceutical and Life Sciences*, *4*(01), 00
8. López-Hernández, Y., Oropeza-Valdez, J. J., García Lopez, D. A., Borrego, J. C., Murgu, M., Valdez, J., ... & Monárrez-Espino, J. (2023). Untargeted analysis in post-COVID-19 patients reveals dysregulated lipid pathways two years after recovery. *Frontiers in molecular biosciences*, *10*.
9. Mondal, S., DasGupta, R., Lodh, M., & Ganguly, A. (2023). Subacute thyroiditis following recovery from COVID-19 infection: novel clinical findings from an Eastern Indian cohort. *Postgraduate medical journal*, *99*(1172), 558-565.
10. Mohamed, I., de Broucker, V., Duhamel, A., Giordano, J., Ego, A., Fonne, N., ... & Remy-Jardin, M. (2023). Pulmonary circulation abnormalities in post-acute COVID-19 syndrome: dual-energy CT angiographic findings in 79 patients. *European Radiology*, 1-13.

11. Postolache, P. A., Nechifor, A., Buculei, I., Soare, I., Mocanu, H., & Petrariu, F. D. (2023). Clinical Features and Paraclinical Findings in Patients with SARS CoV-2 Pneumonia and the Impact of Pulmonary Rehabilitation on the Instrumental Activities of Daily Living in POST-COVID-19 Patients. *Journal of Personalized Medicine*, *13*(2), 182.
12. Sorokina, E., Pautova, A., Fatuev, O., Zakharchenko, V., Onufrievich, A., Grechko, A., ... & Chernevskaya, E. (2023). Promising Markers of Inflammatory and Gut Dysbiosis in Patients with Post-COVID-19 Syndrome. *Journal of Personalized Medicine*, *13*(6), 971.
13. Veerankutty, F. H., Sengupta, K., Vij, M., Rammohan, A., Jothimani, D., Murali, A., & Rela, M. (2023). Post-COVID-19 cholangiopathy: Current understanding and management options. *World Journal of Gastrointestinal Surgery*, *15*(5), 788.
14. Zainiddinovich, A. F. (2023). POSTCOVID SYNDROME: RISK FACTORS, PATHOGENESIS, DIAGNOSIS AND TREATMENT OF PATIENTS WITH RESPIRATORY DAMAGE AFTER COVID-19 (RESEARCH REVIEW). *Asian journal of pharmaceutical and biological research*, *12*(2).
15. Tiew, H. W., Tan, J. W. P., & Teo, C. H. Y. (2023). Delayed organising pneumonia in an immunocompromised host after a mild COVID-19 infection. *BMJ Case Reports CP*, *16*(5), e254737.
16. Park, J., Dean, L. S., Jiyarom, B., Gangcuangco, L. M., Shah, P., Awamura, T., ... & Devendra, G. (2023). Elevated circulating monocytes and monocyte activation in COVID-19 convalescent individuals. *Frontiers in Immunology*, *14*, 1151780.
17. Ceruti, S., Glotta, A., Biggiogero, M., Marzano, M., Bona, G., Previsdomini, M., ... & Capdevila, X. (2023, February). Long-Term Evolution of Activities of Daily Life (ADLs) in Critically Ill COVID-19 Patients, a Case Series. In *Healthcare* (Vol. 11, No. 5, p. 650). MDPI.
18. Raghuwanshi, P., Parashar, R., Mukherjee, S., Joshi, A., Joshi, R., & Singh, H. (2023). Inflammation status in COVID-19 survivors in the recovery phase. *Indian Journal of Inflammation Research*, *7*(1).
19. di Filippo, L., Frara, S., Nannipieri, F., Cotellessa, A., Locatelli, M., Rovere Querini, P., & Giustina, A. (2023). Low vitamin D levels are associated with Long COVID syndrome in COVID-19 survivors. *The Journal of clinical endocrinology and metabolism*.
20. Feng, B., Zheng, D., Yang, L., Su, Z., Tang, L., Zhu, Y., ... & Liu, Y. (2023). Post-hospitalization rehabilitation alleviates long-term immune repertoire alteration in COVID-19 convalescent patients. *Cell Proliferation*, e13450.
21. Lopez-Hernandez, Y., Monarrez-Aquino, J., Garcia-Lopez, D. A., Zheng, J., Borrego, J. C., Torres-Calzada, C., ... & Wishart, D. S. (2023). The plasma metabolome of long COVID-19 patients two years after infe
22. Shinfuku, K., Takasaka, N., Fukuda, T., Chida, K., Suzuki, Y., Shibata, S., ... & Kuwano, K. (2023). Association between serum ferritin level and decreased diffusion capacity 3 months after the onset of COVID-19 pneumonia. *PLoS One*, *18*(2), e0281249.
23. Harapan, B. N., & Harapan, T. (2023). The role of ozone therapy in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19): a review. *Medical Gas Research*, *13*(4), 165.
24. Lozano-Rodríguez, R., Avendaño-Ortíz, J., Terrón, V., Montalbán-Hernández, K., Casalvilla-Dueñas, J., Bergón-Gutiérrez, M., ... & Del Fresno, C. (2023). mRNA-1273 boost after BNT162b2 vaccination generates comparable SARS-CoV-2-specific functional responses in naïve and COVID-19-recovered individuals. *Frontiers in Immunology*, *14*, 1136029.
25. Gujral Jr, H. S., Sahasrabudhe, T. R., Nirmala, M. A., Singh Jr, H., Sahasrabudhe, T., & Nirmala, M. A. (2023). A Systematic Evaluation of Risk Predictors for COVID-19 Sequelae. *Cureus*, *15*(6).

26. Cho, H. N., de Souza, L. C., Johnson, C., Klein, J. R., Kirkpatrick, T. C., Silva, R., & Letra, A. (2023). Differentially expressed genes in dental pulp tissues of individuals with symptomatic irreversible pulpitis with and without history of COVID-19. Journal of Endodontics.