DEMYSTIFYING LONG COVID

INTERNATIONAL CONFERENCE 2023

ABSTRACT BOOK

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INTERNATIONAL CONFERENCE 2023

7-9 DECEMBER 2023
HYBRID MEETING
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ABSTRACTS
ORAL PRESENTATIONS

O01

SARS-CoV-2 Viral Persistence in Lung Alveolar Macrophages Is Controlled By IFN- γ and NK Cells

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In this study, we delve into the dynamics of SARS-CoV-2 infection within the respiratory system, exploring the intricate interplay between viral replication and the host's immune responses. Our investigation, conducted in a cohort of 25 cynomolgus macaques 6-18 months after infection with the original or Omicron SARS-CoV-2 strains, aimed to unravel the mechanisms underpinning a long-term persistence of SARS-CoV-2 in the body.

Our findings illuminate the persistence of replication-competent virus in bronchioalveolar lavage (BAL) macrophages even six months post-infection. Notably, viral propagation within these macrophages was observed to occur through cell-to-cell transmission and was notably impeded by interferon-gamma (IFN-γ). Paradoxically, while IFN-γ hindered viral replication, it facilitated the survival of infected BAL macrophages by enhancing the resistance to natural killer (NK) cell-mediated killing. This effect was mediated by the up-regulation of MHC-E on the surface of BAL macrophages, a process crucial for the persistence of infected cells.

Our study delved further into the intricate immune responses elicited during SARS-CoV-2 infection. We observed robust IFN-γ production in specific subsets of BAL NKG2r+CD8+ T cells and NKG2Alo NK cells, especially following Spike protein stimulation. However, NK cells from macaques with persisting virus displayed impaired IFN-γ production. Remarkably, macaques with lower levels of persisting virus exhibited the emergence of adaptive NK cells capable of evading MHC-E-dependent inhibition, providing a potential avenue for controlling viral persistence.

In essence, our research uncovers a complex interplay between NK cells and macrophages, orchestrated by IFN-γ, which intricately regulates the persistence of SARS-CoV-2 in macrophages. These findings not only deepen our understanding of the virus-host dynamics but also shed light on potential therapeutic avenues for managing prolonged SARS-CoV-2 infections.

O02

Blood Transcriptomics Reveal Persistent SARS-CoV-2 RNA And Candidate Clinical Biomarkers in A Belgian Long COVID Cohort

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Background: With millions of people currently suffering from Long COVID (LC), validated therapeutic options and biomarkers are direly needed to guide clinical management. In this study, we propose whole blood transcriptomics to identify non-invasive candidate biomarkers for viral persistence, disease severity and clinical evolution in a general practice-based cohort.

Materials and Methods: A cohort of LC patients (diagnosis according to WHO criteria) was followed up for 1-30 months after acute COVID. Complete clinical history and follow-up was obtained at a single general practice (MJ, Charleroi, Belgium) using electronic health records and several established clinical scales (DUSOI Duke Severity Overall Index, COOP Dartmouth Coop chart initiative) were used to quantify patient evolution. Severe neurocognitive deficits were confirmed by brain scintigraphy (SPECT), with 25/48 patients (52%) displaying vascular defects. Whole blood samples were obtained from 48 LC patients and 12 controls (matched for age, sex, time since acute COVID-19, vaccination status and comorbidities) and analyzed by digital transcriptomic analysis (nCounter, Nanostring) to quantify a total of 800 RNAs (SARSCoV2 and innate/adaptive immunity), as previously established for critical COVID-19 (Menezes et al., Lancet Microbe 2021). Neutralizing antibodies against 10 different SARSCoV2 variants were quantified using a sensitive electrochemoluminescent assay (MSD). Statistical analysis included non-parametric Mann-Whitney test, Spearman correlation and multivariable logistic regression.

Results: Digital transcriptomic analysis revealed a total of 212 differentially expressed genes between LC patients and matched controls. Among 120 transcripts significantly increased in LC were several viral RNAs: Nucleocapsid, ORF7A, ORF3A, Mpro (target of Paxlovid) and antisense RNA, the latter suggesting ongoing viral replication, while Spike RNA was remarkably low/absent. In addition, several SARSCoV2-realted host genes were also increased in LC (ACE2/TMPRSS2 receptors and DPP4/FURIN proteases). Other upregulated RNAs were specific for memory B cells (CD27/IGHE/BMP8A), and platelets (CD99/PBX1/PDZK1IP1). Platelet transcripts were also positively corelated to viral load ($p<10^{-7}$), providing a mechanistic link to the hypercoagulative state previously demonstrated in LC. Summarizing these 800 transcripts into biological pathways, we found significantly decreased TLR signaling ($p=0.0039$), lymphocyte activation ($p=0.016$) and immunometabolism ($p=0.023$) in LC patients. Moreover, immunometabolism was negatively correlated with blood viral load ($R=-0.56$, $p<0.0001$), suggesting an “exhausted” immune status in LC due to ongoing viral replication.

Using multivariable regression, we found that age and sex were not associated with “low” vs. “high” viral RNA status, whereas the number of comorbidities (1.61 95% CI [1.14-2.49], $p=0.014$) and the number of COVID vaccine doses (0.36 95% CI [0.14-0.79], $p=0.018$) were independent predictors of “low” vs. “high” status, confirming a protective role of vaccination. SPECT-positive patients could be discriminated from SPECT-negative by increased RNA levels of insulin receptor (INSR) and platelet P-selectin (SELP), further incriminating perturbated (immuno)metabolism and platelet activation/coagulation in disease severity.

Conclusions: We used digital transcriptomics to identify non-invasive (blood) biomarkers for viral persistence, disease severity and clinical evolution, guided by SPECT imaging. Overall, increased platelet RNAs and decreased immunometabolism are significantly correlated to viral load, providing mechanistic links as well as therapeutic targets to tackle Long COVID.

O03

Cytokine Profile Associated with Post-COVID-19 Condition

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At least 10% of SARS-CoV-2 infected patients suffer from persistent symptoms for >12 weeks, known as post-COVID-19 condition (PCC). Reported symptomatology is diverse with >200 physical and neurological debilitating symptoms. The pathophysiology is poorly understood and is a barrier to accurate management and treatment. One proposed hypothesis is an altered immunoinflammatory response. In this study, we aim to analyze soluble markers to elucidate a potential cytokine profile underlying the persistent symptomatology.

We used clinical data and samples from the KING cohort extension, a 2-year prospective cohort including PCC (N=341), COVID-19 recovered and uninfected individuals. A hierarchical clustering analysis (Ward's minimum variance method) was used to identify different symptom patterns among PCC patients. Cytokine levels of randomly selected PCC (N=135), recovered (N=98) and uninfected subjects (N=78) were measured plasma samples collected at least >5 months after infection, using the 30-Plex Panel for Luminex (LifeTechnologies). Mann-Whitney and Kruskal-Wallis t-tests were used to compare groups. FDR correction was applied for statistical significance (p-adj).

PCC participants (N=341) were predominantly females (69.3%) with mean age of 46 (IQR 38-54) years. During acute SARS-CoV-2 infection, only 38.1% required hospitalization and 9% high flow oxygen. Hierarchical clustering of PCC identified 3 distinct clusters according to their symptomatology. Symptoms considered were those present in >40% of subjects, where PCC1 was enriched in fatigue and neurocognitive complaint, PCC2 additionally had dyspnea, headache, arthralgia, myalgia, chest pain, tachycardia, neurosensitive symptoms and cough and PCC3 had PCC2 symptoms plus low-grade fever, diarrhea, dysphagia, smell and dermatological alterations. We randomly selected 135 PCC (59 from PCC1, 57 from PCC2 and 19 from PCC3), 98 recovered and 78 uninfected participants for cytokine profiling. Seven soluble markers were significantly altered (IL-1RA, HGF, Eotaxin, MCP-1, IL-7, IP-10, and IL-8) in PCC and recovered groups compared to uninfected (all p-adj<0.04). PCC individuals showed higher levels of IL-1RA compared to recovered group (p-adj=0.0003). A random forest model with classes 'Uninfected', 'Recovered', and 'PCC' was built, obtaining a prediction accuracy of 55%. Importance analysis revealed IL1RA, HGF and Eotaxin as the most contributing variables to distinguish between groups.

The analysis of cytokine profile within PCC clusters revealed an elevation of IL1RA in PCC2 and PCC3 compared to PCC1 not reaching statistical significance (p-adj=0.057 and 0.054 respectively). IL1RA levels in PCC1 were similar to recovered group, but still higher than uninfected controls. HGF levels tended to be gradually elevated from PCC1 to PCC3 but not statistically significant.

In this large cohort, we identified some cytokines that remained altered in all SARS-CoV-2 infected individuals independently of persistent symptoms, being IL1RA, HGF and Eotaxin the most discriminatory markers between groups.

O04

Transfer of IgG of Long-COVID Patients Induces Subgroup-Specific Symptoms in Mice

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Background: The absence of objective diagnostic tests and approved Long-COVID treatments has impeded progress in treatment development. Several hypotheses have been proposed underlying Long-COVID symptoms, including viral latency, microvascular clots, and autoimmunity. Yet, it remains unclear whether these parameters are causal or consequential in the disease's progression. This study aims to investigate the causal link between autoimmunity and Long-COVID.

Materials and Methods: Long-COVID patients meeting the WHO Delphi Consensus definition were assessed 6-9 months post non-hospitalized SARS-CoV-2 infection. Patients were categorized into three groups based on primary symptoms and serum analysis. Total IgG was purified from patient blood samples, pooled by group, and intraperitoneally injected into mice.

Results: Serum proteomics revealed various differentially activated pathways in Long-COVID patients, such as a notable reduction in neuronal system activation. Further validation using a multiplex absolute quantification assay focusing on pro-inflammatory cytokines, interferons, and neural damage markers showed that tachycardia patients exhibited increased neuronal damage, astrogliosis markers, and pro-inflammatory cytokines. Post-exertional malaise (PEM) patients had elevated serum type-I IFN levels, while those with pain symptoms displayed no elevated markers. Strikingly, intraperitoneal injection of the pooled IgG of the three Long-COVID groups induced pronounced subgroup-specific behavioral symptoms in in mice compared to healthy control IgG injections. We assessed pain-like behavior by Von Frey method and found that mice injected with Long-COVID IgG exhibited pronounced pain behavior, while those injected with control IgG did not. We also observed differences in pain response between male and female mice injected with IgG from different Long-COVID subgroups. Additionally, human iPSC-derived cardiomyocyte spheroids displayed reduced contraction amplitude after exposure to pooled serum IgG from three Long-COVID patients with palpitation symptoms. Furthermore, skeletal muscle cells (C2C12) treated with recombinant antibodies targeting Long-COVID-specific autoantigen we identified showed mitochondrial hyper-polarization.

Conclusions: These findings provide compelling evidence for the causal role of IgG autoantibodies in Long-COVID. Subsequent tissue staining and 'autoantibodyome' analysis will identify key targeted tissues and autoantigens for the three Long-COVID groups. This data not only hold promise for developing an objective Long-COVID diagnostic tool but also demonstrates proof-of-concept for an in vivo Long-COVID model suitable for treatment testing.

O05

Improvement of Immune Dysregulation and Health-Related Quality of Life in Individuals with Long COVID at 24-Months Following SARS-COV-2 Infection

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This study investigated the humoral and cellular immune responses in individuals with long COVID (LC) compared to age and gender matched recovered COVID-19 controls (MC) over 24-months. LC participants showed elevated spike and nucleocapsid IgG levels, higher neutralizing capacity, and increased spike- and nucleocapsid-specific CD4+ T cells, PD-1, and TIM-3 expression on CD4+ and CD8+ T cells at 3- and 8-months, but these differences did not persist at 24-months. Some LC participants had detectable IFN-β and IFN-λ1 that was attributed to reinfection and antigen re-exposure. Single-cell RNA sequencing at 24-month timepoint revealed similar immune cell proportions and reconstitution of naïve T and B cell subsets in LC.

No significant differences in exhaustion scores or antigen-specific T cell clones were observed. These findings suggest resolution of immune activation in LC and return to comparable immune responses between LC and MC over time. Improvement in self-reported health-related quality of life at 24-months was also evident in the majority of LC (62%). PTX3, CRP levels and platelet count were associated with improvements in health-related quality of life.

O06

PBMC Immunophenotyping, Plasma Inflammatory Profile and Antibody Levels of Children with Long COVID

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Background: Long COVID can be developed by individuals after an infection with SARS-CoV-2 as described by the WHO. Although this condition is more commonly described in adults, it can occur in children and adolescents with a wide range of estimated prevalence of 1-25%. Little is known about the role of the immune system in long COVID. However, one of the main hypotheses about the underlying mechanism in long COVID is that there is an immune and inflammatory dysregulation that persists after the acute infection. The objective of this study is to compare immune cells populations, inflammatory biomarkers and antibody levels in paediatric populations with and without long COVID.

Materials and methods: We analyzed 131 blood samples from the pediaCOVID cohort (Hospital Germans Trias i Pujol), which includes 108 children diagnosed with long COVID and 23 controls. We measured different immune cell populations using spectral cytometry with a panel of 37 cellular markers, 42 inflammatory markers using Luminex or ELISA, and plasma IgG/IgA levels using ELISA. EdgeR was used for statistical analysis of the spectral data; p-values of inflammatory markers were calculated using the likelihood ratio test and they were corrected for multiple comparisons; p-values from antibody levels were calculated using Mann-Whitney Test.

Results: The study cohort had a median age of 14.3 (IQR, 12.5-15.2) and 69.1% female. Patients had at least 3 symptoms associated with long COVID (median [IQR]; 10 [7-16]). The most common symptom was asthenia/fatigue (98.2%). Compared to the control cohort, children with long COVID had increased numbers of CD4+CD8+ T cells, IgA+CD21+CD27- memory B cells, and IgA+CD21–CD27– memory B cells, while CD4+ TEMRA cells (CD45RA+, CCR7–), intermediate monocytes (CD14+, CD16+) and classical monocytes (CD14+, CD16–) were decreased (all $p<0.05$; q=n.s.). Eotaxin, IL-15 and PDGF-AB ($p=0.032$, $p=0.044$. $p=0.034$ respectively) were increased in children with long COVID while RANTES ($p=0.012$) was decreased. Moreover, children with long COVID had significant lower levels of RBD IgG and RBD IgA ($p<0.0001$; $p=0.0332$, respectively).

Conclusions: The results of this study suggest that specific populations of peripheral blood immune cells, inflammatory dysregulation and lower antibody levels might be involved in the mechanisms underlying long COVID in children and adolescents. The increase in both IgA+CD21–CD27– and IgA+CD21+CD27- memory B cells could be associated with the persistence of viral antigen in the gut and/or gut dysbiosis. Moreover, the decrease in CD4+ TEMRA cells could be related to autoantibodies against G-protein coupled receptors (GPCRs), since this cell population can express GPR56, and autoantibodies against GPCRs were previously reported to be elevated in adults with long COVID. Lower RBD IgG/IgA antibody levels in plasma of children with long COVID might be associated with a poor antibody response compared to those that do not develop the condition.

O07

The Relationship between Self-Reported Persistent Symptoms Post-COVID-19 and Employment among Adults in England, UK

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Background: The United Kingdom has witnessed an exodus of working-age adults from the labour market following the COVID-19 pandemic. There is limited research on the relationship between employment and persistent symptoms post-COVID-19 across different job categories. In this analysis, we explore the impact of employment sector, nature (full-time, part-time) and financial security on the risk of developing persistent symptoms following COVID-19, and further examine the impact of these symptoms on future employment.

Materials and methods: We used data from 274,800 adults (aged 18 and above) from the REACT (Real-time Assessment of Community Transmission) Study of SARS-CoV-2 prevalence in England (August 2020 – March 2022) plus data from a late-2022 follow-up survey of REACT participants (n=107,031). We identified people with self-reported persistent symptoms lasting 12 or more weeks following a confirmed SARS-CoV-2 infection. Logistic regression models adjusted for socio-demographic factors were used to examine the association between employment-related variables and persistent symptoms. Financial security was assessed by asking whether taking two weeks off work due to illness or isolation would have a significant impact on household finances. We report adjusted odds ratios (aOR) with 95% confidence intervals.

Results: Individuals working in healthcare and in logistics and security had an increased odds of developing persistent symptoms (aOR 1.47,1.28-1.68 and 1.28, 1.03-1.58 respectively) compared to people who did not work in public-facing roles. The nature of employment and formal access to sick pay was not associated with the risk of persistent symptoms. However, people who reported a serious financial impact of time off work were 29% more likely to report persistent symptoms compared to those who said the impact would not be serious (aOR 1.29, 1.09-1.52). In the follow-up study, individuals reporting persistent symptoms were 4 times more likely to have reduced their work hours due to their health than those who recovered from COVID-19 within 4 weeks (aOR 3.98, 3.52-4.49). Compared with those working full-time, part-time and self-employed workers were more likely to report reduced paid work hours due to persistent symptoms (aOR 1.41, 1.27-1.56 and 2.62, 2.36-2.90 respectively). Additionally, individuals in public-facing roles, including those in business and services (aOR 1.55, 1.33-1.79), care work (1.60, 1.16-2.16), healthcare (1.49, 1.33-1.68), logistics or security (1.36, 1.11-1.66), and other public-facing roles (1.51, 1.34-1.70) had higher odds of reducing paid work hours compared to those in non-public facing roles.

Conclusions: This study shows that healthcare workers and people who feared loss of income from time off work had an increased odds of developing persistent symptoms following COVID-19. In addition, we found that people with persistent symptoms were more likely to report having to reduce their hours of work because of their health, and that this was particularly true for those in part-time work and self-employment. These findings demonstrate the unequal long-term impact of COVID-19 on individuals working in different sectors and in those where taking time off work had a negative impact on household finances. This indicates the importance of long-term support to those working in sectors who have been disproportionately impacted.

O08

Vascular Inflammation in Neuropsychiatric Post-Acute Sequelae of COVID-19

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Neuropsychiatric post-acute sequelae of COVID-19 (N-PASC) include cognitive impairment, mood changes, headache, and neuropathy. Biomarkers of endothelial and platelet dysfunction are elevated in individuals with acute COVID-19, but it is unknown if this persists in individuals with N-PASC. We investigated for vascular inflammation in individuals with N-PASC versus post-COVID controls without N-PASC.

Individuals with N-PASC (ongoing neuropsychiatric symptoms >3 months after COVID-19) and controls underwent cross sectional clinical assessment and blood collection. Plasma samples were tested via multiplex bead-based ELISA for the following analytes: a-2 macroglobulin, α1-acid glycoprotein (AGP), C-reactive protein (CRP), Fetuin A36, haptoglobin, L-selectin, platelet factor 4 (PF4), and serum amyloid protein (SAP) A (Eve Technologies). Non-parametric multiple Mann-Whitney testing was used with False Discovery Rate adjustment made to address multiple comparisons.

The N-PASC (N; n=40) and control (C; n=16) groups were similar in age (N: 45 years, C: 40 years, p=0.15), gender (N: 73% female, C: 69% female, p=0.76), race (N: 20% non-white, C: 37% non-white, p=0.19) and cardiovascular risk factors (diabetes, smoking, hypertension, obesity, and cardiac disease, p>0.05). The groups had similar time from acute COVID-19 to study visit (N:325 days, C:418, p=0.95). N-PASC symptoms included cognitive issues (72%), new or worsening anxiety or depression (67%), and headache (61%). Five markers were elevated in N-PASC: a-2 macroglobulin (N: 994,143 ng/mL, C: 749,109, p=0.04), CRP (N: 8,851,400 pg/mL, C: 3,625,000, p=0.01), haptoglobin (N: 194,735 ng/mL, C: 99,319, p=0.046), L-selectin (N: 808,346 pg/mL, C: 670,940, p=0.01), and SAP (N: 6,252,000 pg/mL, C: 3,186,650, p=0.0003). Fetuin A36 was reduced (N: 132,476 ng/mL, C: 207,355, p=0.05). There were no differences in the other biomarkers tested.

We report key differences in vascular inflammatory plasma biomarkers in individuals with N-PASC, including elevations in plasma proteins that indicate ongoing systemic inflammation (CRP, haptoglobin, SAP), endothelial dysfunction (a-2 macroglobulin), and atherosclerosis (L-selectin, fetuin A36, SAP). These findings suggest the N-PASC population may be at risk of persistent vascular inflammation and/or atherosclerosis. Further studies should longitudinally investigate endothelial inflammation and atherosclerosis in individuals with N-PASC.

O09

Focal Cerebral Hypoperfusion in Individuals with Cognitive Impairment After COVID-19

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Cognitive impairment is a common symptom of neuropsychiatric post-acute sequelae of COVID-19 (N-PASC), characterized by neuropsychological deficits including impaired executive functioning, processing speed, motor speed, attention, recall, and verbal fluency. Little is known about the underlying mechanism of cognitive N-PASC. We report preliminary analyses of noninvasive MRI measurements of brain perfusion in individuals with and without N-PASC.

Individuals with cognitive N-PASC (self-reported symptoms of cognitive impairment >3 months after COVID-19) referred from a NeuroCOVID Clinic and controls with prior COVID without PASC underwent an MRI protocol, which included Arterial Spin Labeling (ASL) to assess perfusion (Cerebral Blood Flow; CBF). All imaging was performed on a Siemens 3T MRI scanner. A standard 3D ASL sequence was used (TA: 4:59, voxel: 1.5×1.5×3.0 mmRel, SNR: 1.00, TR: 4600ms, TE: 16.18ms). Post-processing was completed using MATLAB and the Harvard-Oxford atlas to generate CBF for 48 cortical and 21 subcortical regions of interest (ROI). Group comparisons used non-parametric statistics.

14 individuals with cognitive N-PASC (median age 43 [IQR 37 – 55], 79% female, median 450 days after COVID-19 symptom onset [IQR 354 – 694]) and 6 controls (median age 34 [30 – 40], 67% female) underwent MRI. The groups did not differ in age, gender, race, or cardiovascular risk factors, which were low in prevalence. CBF was lower in N-PASC compared to controls (C) in the right supplementary motor area (N-PASC: median of 22.5 mL/g/min and C: 27.7 mL/g/min; p = 0.025). a trend of hypoperfusion that did not reach significance was identified in three other ROIs in the right hemisphere: the frontal pole (N-PASC: 23.5 mL/g/min and C: 30.4 mL/g/min; p = 0.06), middle frontal gyrus (N-PASC: 24.8 mL/g/min and C: 31.3 mL/g/min; p = 0.06), and post-central gyrus (N-PASC: 22.5 mL/g/min and C: 27.7 mL/g/min; p = 0.06). There was no difference in CBF between groups in the remaining ROIs.

We report preliminary evidence of focal hypoperfusion in the right frontal lobe and a trend of hypoperfusion in the right parietal lobe in individuals with N-PASC. These findings suggest that altered perfusion in the non-dominant hemisphere may play a role in cognitive N-PASC symptoms, possibly by affecting motor speed and motor control of speech. We look forward to collecting additional data to investigate the mechanism of decreased cortical perfusion in cognitive N-PASC.

O10

Presentation and Factors Associated with Long COVID Among Individuals Presenting to Post Acute COVID-19 Clinics in Zambia

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Background: Long COVID (LC) is an emerging public health threat with an estimated 100 million people suffering from LC globally, yet there are few dedicated services to manage individuals suffering from this syndrome. This has further limited appropriate understanding, diagnosis and clinical care of LC especially in Africa. In Zambia, we therefore set up post-acute COVID-19 (PAC-19) clinics. We hereby describe the presentation, characteristics and factors associated with LC among individuals presenting to PAC-19 clinics.

Materials and Methods: Using a multidisciplinary team, we developed PAC-19 clinics operational and management guidelines following which we set up clinics to manage individuals presenting with symptoms post acute phase of COVID-19. Long COVID was defined as symptoms that persist ≥4 weeks after the initial SARS-CoV-2 infection. All the clinical and demographic information was entered into an electronic database (REDCap v11.0.3). We analysed the information from this electronic database for individuals who were attended to from August 2020 to January 2023. We developed logistic regression models for cross-sectional and longitudinal (patients with ≥2 visits) analysis. We reported odds ratios (OR) for factors associated with long COVID and statistical significance as at $p<0.05$.

Results: In the thirteen PAC-19 clinics we established across Zambia 1,359 patients were followed up; 548 (40.3%) had ≥2 visits. Patients' median age was 53 (interquartile range [IQR]: 41-63) years, 919 (84.5%) were hospitalized for acute COVID-19, of whom 606 (74.5%) had severe illness.Long Covid patients, commonly reported cough (38.7%), fatigue (38.5%), shortness of breath (26.5%), chest pain (20.9%), headache (14.8%), muscles aches/pain (14.1%), palpitations (12.5%), joint aches/pain (11.9%), and forgetfulness or brain fog (8.0%). Overall, 232 (28.9%) patients had limitations in daily activities functional status since acute COVID-19. The functional status patients commonly reported difficulty in undertaking was walking long distances greater than 1km (22.6%), day-to-day work/school (cognitive) activities (19.4%), standing for ≥30 minutes (19.4%), taking care of household task (17.8%), and self-care (activities like bathing and dressing) – 15.1%. Fifty-nine (6.6%) patients were referred to specialist care, including cardiology (35.6%), endocrinology (33.9%), psychiatry (25.4%), pulmonology (18.6%) and nephrology (1.7%).

Patient with a hospital length of stay ≥15 days (adjusted [aOR]: 5.88; 95% confidence interval [95% CI]: 3.20-11.2), treatment with remdesivir and/or steroids (aOR: 1.68; 95% CI: 1.16-2.45), and comorbidities (aOR:1.59; 95% CI: 1.08-2.47) had significantly higher odds of long COVID. For an overall median follow up time of 7 (IQR: 4-12) weeks, prevalence of long COVID among individuals attending the PAC-19 clinics ranged from 82.9% (95% CI: 70.5-90.0%) at the second PAC-19 visit to 99.7% (95% CI: 98.4-100.0%) at the final visit.

Conclusion: Setting up services for LC patients is feasible in resource limited settings. Long COVID symptoms were common among persons presenting for care in specialized PAC-19 clinics in Zambia with features suggestive of severe disease (e.g longer hospital stay, steroid use and comorbidities) appearing to be risk factors for LC. Due to the persistence of LC even in these settings, scaling up PAC-19 services and integrating into routine clinical care could improve access by patients and is warranted.

DEMYSTIFYING LONG COVID
INTERNATIONAL CONFERENCE 2023

7-9 DECEMBER 2023
HYBRID MEETING
MADRID SPAIN

ABSTRACTS
POSTER PRESENTATIONS

P01

High Levels of IL-1β, TNF-α and MIP-1α One Month after the Onset of the Acute SARS-CoV-2 Infection, Predictors of Post COVID-19 in Hospitalized Patients

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Background: According to WHO "post COVID-19" is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months that cannot be explained by an alternative diagnosis. The pathophysiological mechanisms remain controversial; however, a link between a persistent inflammatory environment and these long-term sequelae has been suggested. Herein, we assessed the dynamic of up- and downstream molecules of the NLRP3 inflammasome's pathway, among other inflammatory cytokines.

Materials and Methods: A longitudinal study with individuals belonging to the Galicia Sur Health Research Institute COVID-19 Cohort was performed defining three groups: healthy blood donors (HC) and donors with a confirmed SARS-CoV-2 infection who had been hospitalized. The latter was divided into 2 groups: post COVID-19 (PC) and non-post COVID-19 (nPC) patients based on the presence or absence of symptomatology at month 6, respectively. Multiplex bead-based immunoassay was used to quantify the levels of plasma cytokines (IL-1β, IL-3, IL-6, IL-8, IL-18, IP-10, MIG, TNF-α, IFN-γ, MIP-1α, and MIP-1β). Reactive Oxygen Species (ROS) levels were quantified by measuring total peroxide (TPX) with a commercial colorimetric assay. Both quantifications were performed at baseline-time of SARS-CoV-2 diagnosis (M0), month 1 (M1) and 6 (M6) after the onset of the SARS-CoV-2 infection. Statistical analysis including Friedman's test, Mann-Whitney U test and Kruskal-Wallis' test were performed to identify differences between different time points and the study groups.

Results: A total of 68 individuals were included: 27 nPC, 27 PC and 14 healthy controls. Within COVID-19 patients, 37.0 % met obesity criteria (BMI ≥ 30), with a median hospitalization time of 7 days [IQR: 4-9.75] from March to December 2020, 20.4 % were admitted to the ICU and 29.6 % required invasive mechanical ventilation. The most frequent symptoms among people with post COVID-19 condition were thoracic 59.3 % (dyspnea, chest pain, cough), general 44.4 % (asthenia, hair loss), nervous 25.9 % (behavioral disorder, headache) and 25.9 % musculoskeletal (arthralgias, myalgias). No significant differences between nPC and PC groups were observed based on clinical data (age, gender, comorbidities, SARS-CoV-2 severity). At baseline, significant higher values of ROS and cytokines were recognized for nPC and PC compared with HC that subsequently decrease during the follow-up. Of note, only IL-1β (PC: 8.94 [5.63-12.81] vs nPC: 6.27 [2.21-8.80], p = 0.024), MIP-1α (PC: 25.45 [15.65-38.85] vs nPC: 18.99 [9.18-23.82], p = 0.020) and TNF-α (PC: 22.45 [15.65-31.69] vs nPC: 15.85 [12.35-22.34], p = 0.026) levels (in pg/ml) were significantly higher among PC than nPC at month 1 after the onset of SARS-CoV-2 infection. A ROC analysis established the best cut-offs for distinguishing PC and nPC at month 1 and to design a model which correctly identified all patients who experienced post COVID-19 symptomatology when the levels of IL-1β, MIP-1α, and TNF-α were above of these 3 cut-offs.

Conclusions: These findings suggest that a persistent inflammatory state one month after the onset of SARS-CoV-2 infection related to specific cytokines (IL-1β, MIP-1α, and TNF-α) may be useful to predict post COVID-19 symptomatology.

P02

Characterization of Long COVID in Mexico

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Background: Long COVID is defined as the persistence of symptoms after 4 weeks of an acute picture. There is talk of 65 million people affected in the world. In Mexico there are no statistics or studies that explore this entity in the population.

Materials and Methods: A descriptive, cross-sectional, and prospective study was carried out using an online survey, in adults who wish to participate and who are living in Mexico from January to March 2023, whose main objective is to characterize patients who present symptoms of Long COVID

Results: 336 participants with an average age of 41 years (range 18-79 years), the most affected gender is female (69%); Risk factors are Obesity 41%, Diabetes 16%, Hypertension 15.8%; 43.5% commented that they were healthy before COVID-19. Cases of acute COVID they have suffered, 42.3% comment that 2 previous infections, 29.5% had one and 28.3% 3 or more. 77% refer to mild COVID, 13% to severe COVID, and 10% both. Regarding vaccination, 45% have 3 or more vaccines, 36% 2 vaccines, 9% have one vaccine and 10% have not been vaccinated against COVID-19. The most prevalent symptoms are Neuropsychiatric 90%, Musculoskeletal 88%, Cardiovascular 82%, Gastrointestinal 78%, and Pulmonary 71%. The most frequent Neuropsychiatric symptoms: fatigue 76%, memory disorder 72%, anxiety 65%; Musculoskeletal symptoms are arthralgia 71.4%, myalgia 40%, arthritis 28%. Cardiovascular symptoms are palpitations 58%, tachycardia 38%, precordial pain 27%. Gastrointestinal symptoms are diarrhea 43%, abdominal pain 41%, Colitis 26%. Pulmonary symptoms are chronic cough 40%, persistent expectoration 29%, dyspnea 23%. Other symptoms are alopecia 53.3%, chronic dermatitis 38%, frequent infections after COVID-19 20%, menstrual disorders 17%, thyroid disease 12%, development of autoimmune diseases 9.5%, sexual dysfunction 9%, COVID tests persistently positive 6%, thrombotic events 3.6% (cerebral 0.9%, pulmonary thromboembolism 0.6%, myocardial infarction 0.3%), myocarditis 3.3%, chronic renal failure 2.4% and cancer 1.8%. Regarding diagnostic protocol attempts, the following studies have been used: electrocardiogram/holter 48%, lung CT scan 36%, echocardiogram 26%, coagulation profile 23%, brain MRI 21%, immunity profile 14%, concomitant viral/bacterial studies 14%, cranial CT 11%, autoimmune profile 10%, digestive endoscopy 9%, electromyography 6%, biopsy 4%, brain PET Scam 2%, bronchoscopy, lumbar puncture and audiometry 1%.
Regarding the most frequent treatment that has been prescribed, the following stands out: vitamins 39%, NSAIDs/analgesics 30%, antineuritics 20%, anticoagulants 17%, antidepressants/anxiety drugs 16%, probiotics 11%, steroids 10%, antivirals/antibiotics 7%, lipid-lowering agents 7%, antiarrhythmics 2%, naltrexone 1%, immunoglobulin 1%.

Conclusion: It is important to characterize this population since it has particularities that make it susceptible to this new entity and the creation of clinical guidelines in the country should be encouraged to begin limiting sequelae.

P03

Heart Rate Variability Biofeedback Intervention for Long Covid

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Background: Biofeedback is an established behavioral intervention for stress-related symptoms related to dysautonomia. This pilot study sought to examine the efficacy of a six-session heart rate variability and temperature biofeedback intervention for patients with varying long COVID symptoms.

Materials and Methods: Participants were asked to complete self-report questionnaires before the treatment, immediately after, and three months

after the intervention. Of the twenty adult participants initially recruited (aged 22-63; Mage = 44.1, SDage = 12.2), 16 completed all six sessions and 14 completed the final three-month post-treatment assessment.

Results: Post-intervention, participants reported significant improvements in depressive, anxiety, and somatic symptoms, sleep quality, quality of life, and number of "bad days," $p < .05$. These improvements were also sustained three months post-treatment, $p < .05$. We also observed a reduction in number of self-reported medical doctor visits and prescription drug use, as well as an increase in emotional wellbeing at the three-month time point only, $p < .05$. Effect sizes for the treatment effects ranged from 1.2 to 0.4 for significant changes.

Conclusion: Biofeedback presents as a potentially effective way to treat dysautonomic symptoms of long COVID. Future research should include inclusion of a control group.

P04

Long COVID Web: A National Research Network on Post-covid Condition (PCC) In Canada

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Canada has a diverse population with approximately 30% non-white across 13 provinces and territories. Recent data suggests that 1.4 million Canadians are suffering from post-COVID condition (PCC). The Long COVID Web is the pan-Canadian research network funded by the Canadian Institutes of Health Research in 2023 to increase our understanding and to improve our treatment of PCC.

Our network's vision is to have a Canada without PCC. Our mission is to: 1) Accelerate the discovery and validation of Canadian-led science in PCC; 2) Activate a learning health system that prioritizes the needs of individuals with PCC; 3) Identify the best therapeutics and practices, and accelerate equitable access to PCC care; and 4) Maintain rigorous surveillance of the impact of PCC.

We have more than 400 investigators and patient partners participating in the network. These are organized into the four pillars of science: basic and translational, clinical, health services research and population health. In addition, we have a patient advisory council, an equity/diversity/inclusion committee, an indigenous committee, a knowledge mobilization group, a steering committee, an operations committee, an executive committee, and an international advisory board.

Our key driving questions are centred around people with lived experience, which includes children, elderly, different sex and gender, different races/ethnic background, as well as family caregivers. These questions encompass: a) how we can diagnose and assess (through understanding disease mechanisms and identifying biomarkers); b) how we can manage and treat (through identifying therapeutic targets and scaling up pharmaceutical and rehabilitation trials); and c) how we can access health and social services (through establishing integrated care pathways across Canada and informing a harmonized response to personal, societal and economic impacts of PCC).

Over the past year, we have conducted a prioritization meeting, coordinated interdisciplinary research, funded four foundational projects, and led a national conference on PCC. In this presentation, we will share the lessons learned, and our early accomplishments and impact.

P05

Psychological Impact of Long COVID: Experience in a Long COVID Multidisciplinary Care Unit in Catalonia, Spain

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Background: At least 5-10% of people who have had Covid-19 develop a post-viral syndrome known as post-COVID-19 condition, post-acute COVID-19 sequelae or “Long Covid”. This syndrome includes a variety of long-lasting and debilitating symptoms that affect quality of life significantly and presents an enormous emotional challenge. Recently, it has been shown that recovery during the first two years is extremely rare.

Objective: To describe psychological health care needs of Long Covid patients in an Infectious Disease Service, with a Long Covid Multidisciplinary Care Unit.

Results: From January 2021 to September 2023, 142 people with Long Covid started a psychotherapeutic follow-up in the Unit after the evaluation of a clinical psychologist. Major depressive disorder and post-traumatic stress disorder were rare in this population. Instead, adjustment disorder with depressed, anxiety or mixed mood were frequent. During the same period, 736 consecutive psychotherapeutic visits were performed. The frequency of the visits depended on the seriousness of the emotional suffering. Main concerns of patients were uncertainty and fear of not recovering, or impairing, and the impact of the limitation caused by Long Covid symptoms on work/family/social activities. From the 142 patients, 40 (28%) have been discharged from psychological follow-up. However, the main reason for discharge in these patients was to continue psychological follow-up in their corresponding mental health care centre, and not because of an improvement in their emotional wellbeing.

Conclusions: Only a minority of patients present major psychiatric disorders. Emotional suffering exists in a great number of people with Long Covid and is largely attributed by patients to the presence of organic pathology. Therefore, the need for psychological care is considerable and resources to provide mental health care should be made available.

P06

SARS-CoV-2 Vaccination and Post COVID-19 Condition Symptoms

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Background: At least 5-10% of individuals who survive COVID-19 develop a condition known as post-COVID-19 (PCC) or 'Long COVID.' It is estimated that there are a total of 65 million cases with 17 million occurring in the European Region. The clinical presentation of PCC is heterogeneous, encompassing a variety of debilitating symptoms and long-term medical conditions that often lead to physical, social, and psychological disability, significantly impacting patients' quality of life. It is unknown whether PCC is a single entity or a heterogeneous syndrome with overlapping pathophysiological bases. Its pathogenesis is still being deciphered and long-term clinical implications of PCC, also the role of the vaccionation in this patients, remain unknown.

Materials and Methods: We described the vaccination Covid-19 status and the clinical situation pre and post vaccination (Worsening, improvement, or or without changes) in the PCC patients (fulfilling the WHO PCC definition) inside a 2-year prospective cohort study of subjects surviving COVID-19.

Results: 645 patients with PCC were included, 456 were women (70.7%) with a mean age of 50 years old. Among the total 645 PCC patients, 581 (90.1%) had received the first dose of the vaccine. Of those, 53/581 (9.1%) reported worsening of symptoms, 4/581 (0.7%) reported an improvement, and 425/581 (73.1%) did not report any changes. Additionally, 460 (71.3%) out of the total 645 PCC patients had received the second dose of the vaccine. Among them, 44/460 (9.6%) reported worsening of symptoms, 5/460 (1.1%) reported an improvement, and 331/460 (72%) did not report any changes. Furthermore, 212 (32.9%) had received the third dose of the vaccine. Out of this group, 32/212 (15.1%) reported worsening of symptoms, none reported improvement, and 147/212 (69.3%) did not report any changes

Conclusions: The impact of vaccination in PCC symptoms is controversial. In our cohort, most participants did not report symptom changes after SARS-CoV- 2 vaccine administration.

P07

Mental Disorders among Zambian Individuals with Long COVID

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Background: The syndrome of long COVID-19 (LC) remains an unclear area among health care workers and much more among individuals suffering from LC. New or worsening physical and nonphysical features associated with long COVID impact the quality of life. Among those features mental disease have been repeatedly reported.
Sadly, there is scanty data on post COVID-19 related mental health among sub-Saharan populations.
Yet, given the weaker health system, social stigma around mental health, and poor health seeking behavior, COVID-19 may cause similar or even worse post infection mental disorders in Africa. We thus sought to investigate the prevalence and distribution of COVID-19 related mental disorders among Zambian individuals at the University Teaching Hospital.

Materials and Methods: We retrospectively collected data from the electronic data base of the University Teaching Hospital's Post COVID clinic.Individuals with persistent complaints three or more weeks after discharge to acute care were reviewed at the post COVID-19 clinic. A simple self-assessment was performed on past mental health history, mood change, anxiety, alcohol abuse and post-traumatic stress disorder (PTSD). Subsequently, individuals were evaluated by an experienced mental health nurse using a detailed patient health questionnaire 9 item (PHQ-2), Generalized Anxiety Disorder Assessment (GAD-7), Trauma Screening Questionnaire (TSQ), and the Alcohol Use Disorders Identification Test (AUDIT) questionnaires.

Results: 242 were screened for mental disorders, with 5 of them reporting history of mental health disorder prior to acute COVID-19 infection. 30 individuals had developed a mental disorder during and post-acute phase of the infection. When classified according to various disorders, 21 (8.7%) had depression, 17 (7.0%) had anxiety, 10 (4.1%) had PTSD and 22 (9.1%) had alcohol misuse. Depression was more common among the female (52%), individuals above 45 years (52%), those who had being on oxygen (57%), not undergone ICU care (81%), and the unvaccinated against COVID-19 (81%). Anxiety was more prevalent among the female (59%), individuals above 45 years (76%), those who had not undergone ICU care (94%), and those not vaccinated against COVID-19 (82%). Post-Traumatic Stress Disorder was more prominent among the female (80%), those above 45 years (60%), those who had been admitted for less than 7 days (50%), those who required oxygen therapy (70%), those who had not undergone ICU care (90%), and those not vaccinated (70%).Alcohol misuse was more recorded among the male (62%), individuals

among 45 years (72%), those who were hospitalized for less than 7 days (38%), in non-ICU setting (78%), individuals who required oxygen therapy (59%), and those who are not vaccinated (62%).
However, using logistic regression, we did not find any statically significant association between the various mental disorders and age, gender, duration of stay in hospital and severity of disease.

Conclusion: We found a high prevalence of mental disorders among individuals with long COVID with majority presenting with depression and alcohol misuse especially among the females. Assessment and evaluation of mental disorders among individuals presenting with LC is warranted in order to optimize care and improve the quality lives of individuals with LC.

P08

The Experiences of Post-COVID Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) On Adults Living with Pre-existing Chronic Health Conditions: An Interpretive Phenomenological Analysis

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Background: Recent research have been investigating the relationships between long-covid, Myalgic Encephalomyelitis or chronic fatigue syndrome (ME/CFS), and one's pre-existing chronic health conditions. To date, no qualitative analysis on the lived experience of post-covid ME/CFS alongside one's pre-existing chronic health conditions has been conducted. The primary aim of this study was to qualitatively explore the personal experiences of individuals with post-covid ME/CFS who are living with pre-existing chronic health condition.

This study employed a qualitative methodology with data collected through semi-structured interviews and were analysed using interpretative phenomenological analysis (IPA).

Materials and Methods: A small and homogenous sample of six participants from Chest Heart Stroke Scotland's (CHSS) long-covid services were recruited via purposive sampling. The six participants selected purposively were individuals with chronic health conditions who have been experiencing long-covid ME/CFS for more than six months prior interview.

Results: Through IPA, five superordinate theme were emerged: "adjusting to sudden life changes", "revisiting loss of control", "re-learning to live with illness", "re-defining self-management", and "finding meaning to illness", with each containing several subthemes. The findings explored an in-depth lived experiences of post-covid ME/CFS alongside one's pre-existing chronic health condition(s) in aspects of illness impacts, management, and personal growth, and support.

Conclusions: This study highlighted the biopsychosocial impacts and risk factors of post-covid ME/CFS on people with pre-exiting chronic health conditions. It is recommended that more practical and organised support from the healthcare and psychological services should be provided according to the needs and demands of this population.

P09

Blood Biomarkers of Long COVID: A Systematic Review

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Background: Long COVID (LC) affects millions of people worldwide. The exact mechanisms which result in a broad, undulating, and detrimental

symptom phenotype remain unknown. Blood biomarkers associated with LC have been described; however, consensus on these remains elusive, in-part due to a lack of continuity between studies on a universally accepted definition of LC. This review aimed to consolidate current knowledge of blood biomarkers associated with the prevalence of LC based on the WHO clinical definition of this condition.

Materials and Methods: A systematic literature search of Cochrane, Embase, PubMed, and Web of Science databases was performed.

Results: Eighteen observational studies comprising 2,093 participants were included in this review which identified 139 blood biomarkers thought to be associated with LC. Three blood biomarker subtypes were associated with the development of LC: 1) Inflammation, 2) Vascular transformation, and 3) Immunity. Our data is consistent with previous findings; however, no single biomarker was sufficiently associated with LC prevalence and instead a profile of biomarkers across various physiological systems may be more clinically useful. Eighty studies were excluded due to a lack of healthy comparator groups and/or failure to meet the WHO LC definition. This demonstrates a need for further research incorporating a universal LC definition across all disease severity groups and phenotypes, and longitudinal data reflecting the relapsing and remitting nature of this condition.

Conclusions: Further investigation into blood biomarkers of LC, including healthy comparator groups and the investigation of acute and chronic biomarker changes, within the context of medical practice, may support the development of curative/restorative approaches.

P10

Polymerized Type I Collagen (Fibroquel) As a Therapeutic Option in Long COVID

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Background: Fibroquel is a drug used in Mexico with great success in severe COVID-19 cases that present with inflammatory pneumonia. Its potential in Long COVID is currently being studied. The downregulation of inflammatory mediators was related to better oxygen saturation and decreased dyspnea, chest pain, cough, and chronic fatigue syndrome in the acute phase of infection and the long term. Fibroquel is an agonist of LAIR-1 and down-regulates STAT-1 phosphorylation. Fibroquel could be relevant for treating STAT-1-mediated inflammatory diseases, including COVID-19 and long COVID.

Materials and methods: Descriptive and observational study, which enrolls adult patients with persistent symptoms of COVID-19, 4 weeks after the acute episode and who consent to participate in the study. Main chronic symptoms are questioned, as well as determination of acute phase reactants (C-reactive protein, ferritin, D-dimer) is performed.

Results: 25 patients with symptoms of Long COVID for more than 4 months are entered into studies; 80% women, average age 42 years; predominating neuropsychiatric symptoms (fatigue, headache, anxiety, depression and attention/cognition disorders) and osteomuscular (arthralgia, myalgia, sarcopenia). 80% presented elevated C-reactive protein (average 12mg/dl) and ferritin (average 450ng/dl). 60% presented elevation of D-dimer (average 550ng/dl). Fibroquel scheme was indicated for two weeks, 2 mls intramuscular every third day for 6 doses. At the end of the treatment, the symptoms resolved in 80% of the patients, the inflammation and coagulation markers became negative; surveillance was maintained for two weeks and there were no relapses.

Conclusion: Fibroquel could be a therapeutic option in patients with Long COVID who, in addition to persistent symptoms, present concomitant inflammation markers; RCTs are needed to assess these observations

P11

Long COVID in Latin America, Bibliometric Study

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Background: It is said that around the world there are 65 million people affected by Long COVID, with great morbidity and disability that has forced nations such as the United States of America or the United Kingdom to allocate large amounts to investigate treatments for this entity; In Latin America there is no such initiative.

Materials and Methods: We carried out a bibliometric search of Long COVID publications in Latin America, analyzing characteristics of the population studied in the various nations that make up Latin America, risk factors and the main symptoms reported.

Results: 16 studies were found, 1 that integrated 16 countries, 1 study from Argentina, 4 from Brazil, 1 from Colombia, 7 from Mexico and 2 from Peru. The total population included in this analysis was 41,637 patients, 61% predominantly female, with an average age of 43 years. The main risk factors in this Latin American population were: Diabetes, Hypertension, Obesity and associated Cardioparties. The main symptoms reported were: Fatigue (90%), Dyspnea (75%), Cough (70%), Headache (68%) and Arthralgia (55%).

Conclusions: The Latin American population faces pandemics such as diabetes and obesity that predispose the population to suffer more severe symptoms of COVID-19, which will subsequently condition a higher prevalence of Long COVID. The population with the greatest affectation is that of the female gender and of economically active age, which translates into greater risks of morbidity and mortality; stresses that fatigue is the main symptom to take into consideration, which in the same way translates into greater disability, and strategies must be created for its treatment in Latin America.

P12

Effects of Post- COVID-19 Vaccination on Circulating Cytokine Profile

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Background: The worldwide emergence of the COVID-19 pandemic led to the expeditious development and implementation of vaccinations to prevent infection and contain the spread of disease Understanding the dynamics of immune responses following vaccination is critical for optimizing vaccine strategies in future pandemics. In this retrospective longitudinal investigation we analyzed the effect of COVID19 vaccination on circulating cytokine profile in individuals living in Saudi Arabia.

Materials and Methods: A total of 318 Saudi subjects (59.7% females), comprising individuals of varying ages from 12-60 years, received COVID-19 vaccines as per the national vaccination program. Anthropometric data and fasting blood samples were collected at specific time points pre-and post-vaccination. Information on dates of vaccination, and whether or not infected with COVID during the study period were collected. For this study, the samples from 84 subjects were used for a comprehensive 18-parameter cytokine profiling analysis using state-of-the-art techniques. The participants were stratified into two groups based on the interval between the final vaccine dose and follow-up visits.

Results: Preliminary findings indicate that circulating cytokine profiles are importantly impacted by vaccination. Notably, when shorter (≤ 4 months) and longer (≥ 5 months) intervals between the final dose and follow-up were compared, significant differences in cytokine profiles were observed, as follows: interleukin-1β (6.5 (0.8 - 12.3) pg/ml vs. 0.0 (-1.3 - 4.3) pg/ml, p=0.024), interleukin-7 (6.2 (1.5 - 9.5) pg/ml vs 0.8 (-2.4 - 4.3) pg/ml, p=0.001), tumor necrosis factor-alpha (1.0 (-2.4 - 10.5) pg/ml vs. -0.8 (-5.7 - 4.5) pg/ml, p=0.028), and monocyte chemoattractant protein-1 (95.1 (-25.7 - 259.7) pg/ml vs. -6.5 (-83.8 - 84.1) pg/ml, p=0.019).

Conclusions: This longitudinal study sheds light on nature of the immunologic response induced by COVID-19 vaccination and indicates that vaccine-induced cytokine production wanes in-time after the last dose of vaccine Further research is required to investigate the stability of these cytokine profiles over time and to determine their relationship with vaccine efficacy and long-term immunity.

P13

Baricitinib, a Possible Therapeutic Option for Long COVID

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Background: Long COVID is a potentially disabling syndrome affecting at least 5-15% of subjects who survive COVID-19. There are several research studies describing the pathophysiology; dysregulation of the immune system may explain some of the long-lasting symptoms. Currently we only have symptomatic treatment for this condition. The use of immunomodulatory treatments could be a therapeutic target. Baricitinib, an inhibitor of JAK1 and JAK2, indicated for the treatment of rheumatoid arthritis, has also shown a benefit in severe acute SARS-CoV-2 infection.

Materials and Methods: We present two patients, women, aged 41 and 44, with no history of heart disease, who were infected by SARS-CoV-2 (RT-PCR) in March and August 2020 respectively. None of the patients required hospitalization. Both cases were diagnosed as Long COVID according to WHO criteria. Persistent symptoms such as fatigue, fever, arthralgia and chest pain were present in both cases; bradycardia, hypotension, syncope and diarrhea in case 1 and anosmia, ageusia, myalgia, headache and dry cough in case 2 respectively. Laboratory test, transthoracic echocardiography and coronary computerized tomography did not show alterations. Pulmonary thromboembolism was ruled out also. Decisively cardiac MRI with adenosine (140 ug/kg/min) was performed, which showed an inducible defect of circumferential subendocardial perfusion highly suggestive of microvascular dysfunction. Treatment for microvascular angina was started with mild improvement.

Only in case 1, prednisone at 1mg/kg was started to treat arthralgia, with initial improvement but with a recurrence of joint and chest pain with dose reduction. In both cases, for huge worsening and with the objective of saving corticoids, baricitinib 4mg per day was started as immunomodulatory treatment. Surprisingly, within 48 hours of starting, there was a significant improvement of functional status, with a noticeable reduction in join and chest pain, that allowed reduce corticosteroids in case 1 and cardiac treatment in both, as well as practice sports and return to work. The treatment was stopped after three and two months respectively with worsening symptoms at 48 hours after withdrawal, requiring the reintroduction of cardiac treatment. In one moth, baricitinib was started again in the two patients.

On this occasion the symptomatology improved 30 days after restarting and the cardiovascular drugs were decreased, but not fully withdrawn. The evolution of the cases was as follows: case 1 presented a worsening of chest pain and arthralgia, for what prednisone was prescribed. Finally, the chest pain occurred with minimal efforts and arthralgia and diarrhea persisted despite baricitinib treatment, so it stopped. In case 2, a reduction of baricitinb to 2 mg was performed but a reinfection by Sars-CoV-2 (treated with nirmatrelvir-ritonavir) required an increase in the dose, allowing a reduction of the dose up to the present time.

Discussion: Since one plausible causes of persistent symptoms in long COVID is immune dysregulation, immunomodulatory treatment with baricitinib may be a therapeutic option. Despite the clinical results of these two cases with significant improvement in functional status, randomized clinical trials are necessary to demonstrate the benefit of this treatment in long COVID patients.

P14

Semiotics and Imaging Manifestations of Internal Organs Involvement in Long COVID - Consideration for High Risk Patients Stratification

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Background: Long COVID is a condition characterized by persistent symptoms in individuals who have recovered from acute COVID-19 [1]. Choosing an appropriate imaging algorithm for evaluating various scenarios and settings in long COVID cases can be challenging [2-4].
This article aims to assess the effectiveness of different imaging modalities in evaluating multiorgan involvement in patients with long COVID, with a focus on high-risk patient stratification.

Materials and Methods: We conducted a retrospective analysis of 15 cases of patients diagnosed with long COVID, presenting with lung and extrapulmonary organ involvement. A multidisciplinary approach was employed, utilizing multimodality imaging techniques such as contrast-enhanced CT and multiparameter ultrasound (US). Specifically, we selected complicated cases for evaluation. All patients underwent initial lung ultrasound, followed by CT and bronchoscopy when necessary. Multiparameter ultrasound examinations were performed to assess the liver and bile ducts, including shear wave elastography (SWE), for evaluating liver size, structure, and bile duct diameters. Additionally, we assessed colon peristalsis, wall thickness, identified US signs of gastritis and nephropathy.

Results: CT scans revealed lesions in the liver, lungs, kidneys, and retroperitoneum. Focal lesions were rare and largely incidental, but effectively detected using both CT and expert-level ultrasound. However, ultrasound occasionally missed lymph nodes, whereas CT detected larger nodes without detection structure regardless of localization. Ultrasound proved effective in diagnosing abdominal organ involvement, including the kidneys and liver. It was also highly useful for evaluating peripheral nerves, muscles, and detecting lung changes such as consolidations, pneumonia, atelectasis, and hydrothorax with high accuracy.
CT did not provide specific information regarding diffuse changes in the kidneys, liver, kidney artery blood flow, mesenteric flow, etc. Furthermore, CT failed to detect brain changes, such as focal infarction likely associated with COVID-19 in two patients, in some cases that required MRI.

Discussion: The findings of this study contribute to understanding the manifestations of internal organ involvement in long COVID patients. Ultrasound proved valuable in functionally evaluating organs, monitoring lung involvement, and providing valuable information. The use of CT should be carefully considered based on specific indications, given its limitations in detecting certain changes and its inability to provide diffuse information in specific organs. In cases where CT falls short, MRI may play a complementary role.
Conclusion: In patients with long COVID, ultrasound can be effective in assessing organ involvement, monitoring lung changes, and providing valuable information. The use of CT should be carefully considered based on specific indications. These findings are particularly relevant for healthcare organizers, especially in settings with limited resources, as they provide insights into high-risk patient stratification and appropriate imaging modalities.

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P15

The Frequency and Pattern of Abnormal Liver Function Test among Hospitalized SARS-COV2 Infection in Sudanese Patients from April 2020 to May 2021

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Background: Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread rapidly across the world. Recent studies reported that patients with coronavirus disease-2019 (COVID-19) might have liver injury. Our aim is to study the frequency and pattern of abnormal liver function tests (LFTs) among hospitalized COVID-19 patients.

Materials and Methods: A multicentre retrospective study included 300 COVID-19 patients attended during the period from April 2020 to October 2021. Data regarding; demographics, comorbidities, managements, inflammatory markers, liver profile and outcomes were collected.

Results: Among 300 patients 197(65.7%) were males and 103(34.3%) were females, with mean age 66±13 years. The frequency of abnormal liver function tests was 15% (n= 45). The pattern of abnormal liver function tests is predominantly hepatocellular (32/45; 71.1%) and mixed (10/45; 22.3%). In liver profile; 45(15%) patients had hypoalbuminemia, 22(7.3%) had hyperbilirubinemia and 19(6.3%) had hypoproteinaemia. In enzymology, elevated AST, ALT, ALP and GGT found in 16.7%, 13.7%, 11% and 6.6%, respectively. The determinants of LFTs abnormalities were; severe COVID-19 infection (OR=10.6; 95%CI: 4.5-24.8; P= 0.000), hypertension (OR=2.8; 95%CI: 1.2-6.5; P= 0.017), DM (OR=2.2; 95%CI: 1.1-4.6; P= 0.021), CVD (OR=6.7; 95%CI: 3.2-14.0; P= 0.000) and renal diseases (OR=2.6; 95%CI: 1.2-5.7; P= 0.016). Also, LFTs abnormalities significantly increased the hazard of ICU admission (OR=11.7; 95%CI: 3.5-39.2; P. value= 0.000), intubation (OR=14.3; 95%CI: 6.1-33.6; P. value= 0.000), respiratory support (OR=6.6; 95%CI: 1.9-22.0; P. value= 0.001), length of hospital stays > 2 weeks (OR=4.4; 95%CI: 2.3-9.5; P. value= 0.001) and morality (OR=17.7; 95%CI: 8.2-38.5; P. value= 0.000).

Conclusion: The frequency of abnormal liver functions on admission was considerable and predominately as hepatocellular pattern. Patients with abnormal liver tests were at higher risk of progressing to severe disease, adverse in-hospital events, and worse outcomes (death).

P16

Long COVID: Three Philosophical Problems

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The National Research Action Plan on Long COVID and the Services and Supports for the Longer-term Impacts of COVID-19 propose the following working definition: “Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing– remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection. Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.”

This definition is broad and inclusive, but it is very unspecific too. I argue that this working definition of Long COVID is philosophically problematic, in three ways: 1) Signs, symptoms and conditions are, all of them, equally possible attributes for diagnosing Long COVID. This fact leads to the problem of mixing three very different scientific dimensions in medicine: disease, illness, and sickness. If we confusingly mix the elements of these orthogonal dimensions, constructing a scientific characterization of the entity will be extremely difficult. 2) Signs are indicators of diseases, but we cannot predicate of signs its

progression or worsening. We can only predicate of signs its sensibility and specificity. It is possible to describe progression or worsening of symptoms, but it relates to the narrative the patient constructs and does not directly depend on disease progression. The only referent on which we can predicate a worsening is that of 'condition', but the working definition does not specify which kind of conditions they are. We can term the first problem 'the ontological problem', which consists in the problematic definition of the Long COVID construct. The second problem can be explained as an 'epistemological problem', because changes in the disease cannot be validly evaluated. These two problems lead to a third, 'ethical problem', of taking public health decisions based on an ontological and epistemological problematic construct.

P17

Lessons Learnt during the Development of Nepalese Model of Care for Post-COVID-19 Conditions

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Like many resource–constrained settings with limited research of their own, the clinical management guidelines in Nepal are developed mostly based on guidelines elsewhere or based on data elsewhere. The limited number of publications on post-COVID-19 conditions (PCC) and the lack of a working definition at that time made our job of developing the protocol and model of care for Nepal quite challenging. We decided to overcome this limitation by collecting data from 12 thousand individuals who had recovered from acute COVID-19 and developing the protocol based on the major symptoms reported. Considering the limitations of daily activities reported from among the 6153 individuals' data we were able to collect, physiotherapy and rehabilitation formed the bulk of the care plan.

The Good

1. Acceptance - The collection of data from a large Nepalese population and the incorporation of physiotherapy and rehabilitation in the protocol made it more widely acceptable.
2. Cost-effectiveness and efficiency - The inclusion of limited laboratory-based tests and more bedside tests and assessment tools made the workup very cost-effective and the inclusion of existing telemedicine for consultations reduced the time and burden of travel for the patient.
3. Ease and uniformity of delivery – Grading of exercises by dyspnea grades and inclusion of pictures to teach exercises made the service delivery easy even by minimally trained staff.
4. Effortless referrals - The draft of a single-page questionnaire including red-flag signs made data collection and referrals easy.

The Bad

1. Obscurity – Prior to the development of the WHO definition by Delphi Consensus, it was not clear who to include and what to consider as eligible for PCC.
2. Indecisiveness – Because of the lack of a pathognomonic finding for PCC and the government's prior commitment to treat all COVID-related patients free of cost, and considering the possibility of any healthcare consumer to claim the services free of charge because of the myriad of possible presentations of PCC, it was difficult to decide what to keep and what to omit – inclusion would mean financial burden to the state and exclusion would deprive a needy of accessible healthcare.
3. Playing God – As the services were not classified as life-saving or Quality-of-Life upgrading or mere assistance and there were no quantifiable measures of costs included, the onus of deciding what to keep in the protocol and what not to was like playing god.

The lessons

1. Share the burden – When creating a guiding document, it's always better to share the burden with all relevant stakeholders like the patients, other healthcare providers, and the sponsors/insurers or the state.
2. Frangible data - All data collections, especially of undefined conditions, should have more data on the variables that have the confusion (e.g. If the duration of PCC was in debate, collection of data should have been clear on the time aspect - duration of symptoms, when it started, how long was it present, etc.): When in doubt, fill it out.

P18

Modeling COVID in Seiqrin Using the RK4 Method

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SEIQRIN (Susceptible-Exposed-Infectious-Quarantined-Recovered-Immunized-Not susceptible) in which several compartments representing different stages of COVID disease will be considered. The governing SEIQRIN equations with the assumptions made describing the flow between the compartments will be analyzed. These equations will be transformed to the numerical Runge-Kutta 4th order (RK4) and solved explicitly by the finite difference method. The requisite governing equations are non-dimensionalized using the time and space domains and the Agent-Based Modeling (ABM) techniques where heterogeneity and complex social dynamics will be considered as the system variables of concern and evaluated sets of equations relating to variables. By iterating the RK4 method for the desired number of time steps, the simulation of the COVID disease dynamics over time will be established. The SEIQRIN model will enable in tracking the changes in different compartments representing the stages of the disease (susceptible, exposed, infectious, quarantined, recovered, immunized, and not susceptible) over time and thus will help handle infection dynamics. This will be able to describe cases such as COVID disease spread, timing and magnitude of peaks, impacts of interventions, disease outcomes as well as sensitivity analysis. This will be graphically represented by using MATLAB software.

P19

The Necessity for Education to Aid Long COVID Recovery

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Long Covid is a complex, heterogenous condition that requires a multi-pronged approach to aid recovery. The universal experience from patients with Long Covid identifies three collective areas of difficulty: the patients perception that their condition is disbelieved by health services and the general public, colloquially called ‘gas lighting’, symptom burden and a massively impaired quality of life.

In order to tackle these areas of difficulty, an educational program and resources that provides clear understanding and insight into the condition, both for patients and health professionals is needed.

An educational program for patients with Long Covid will enable them to have an understanding of their condition, the underlying pathophysiology and to have their symptomatology explained. In order to accept their condition, they need to expect a protracted time course, the possible degrees of recovery and eventual prognosis. To aid their recovery, they need to understand self-help through measures that include pacing, energy management, as well as nutrition, sleep optimisation and mind-body strategies.

Along with these direct needs, patients with Long Covid require reliable and trustworthy support from their GP in primary care and a resilient, functional secondary care Post Covid Service, composed of allied health professionals. To achieve this, these professionals also need an educational provision in order to be informed, accepting of the condition and willing to work in unison for the optimal patient experience and outcome.

Without educational input, patients with Long Covid are uninformed and vulnerable. Out of desperation they are at risk of following self-guided treatment pathways and options, often delivered by unregulated practitioners whose intentions may be honourable, but could be misguided, unsafe and costly.

Ideally, education of patients with Long Covid, allied health professionals in Post Covid Services, primary care and secondary care should be delivered by trusted, statutorily regulated medically trained practitioners, informed in current ‘up to date’ research and understanding of Long Covid, backed up by medical training and standards.

Education of patients and health professionals with those criteria can be delivered on many platforms and formats: webinars, seminars, conferences, interactive question and answer sessions on live audio-visual platforms, podcast and YouTube postings, professional social media groups, internet sites acting as a resource and knowledge bank. Educational activity delivered remotely using digital services has become the accepted and preferred format for practical reasons.

As an educator of patients and health services (primary care, secondary care and allied health professional services) during and post-pandemic, the methods best received have been remote digital webcasts, podcasts and medic only WhatsApp groups for peer support, the exchange of expertise, advice and experience.

Looking to the future, trusted, reliable, current education is an essential part of the recovery from Long Covid. Educational programs and resources to achieve this must be introduced, to ensure that all those involved in Long Covid patient care are informed and upskilled to a standard that should be expected by all responsible health professionals.

P21

Randomized Controlled Trials for Post-COVID-19 conditions: A Systematic Review

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Background: With the global burden of COVID19, interventions for the post-COVID19 condition (PCS) symptoms are urgently needed. This study aims to examine all PCS interventions tested in randomized controlled trials (RCTs), evaluate their quality, and summarize their findings.

Materials and Methods: A systematic review of databases such as PubMed, Google scholar, and ClinicalTrials.gov was conducted between January 2020 and April 2023. Included were RCTs focusing on PCS as defined by the World Health Organization. The PRISMA checklist was used to guide this review with appraisal of trial quality using the latest version 2.0 of Cochrane's risk of bias tool. This review was registered on PROSPERO (CRD42023415835).

Results: Twenty-three trials from 10 countries, representing 1,916 subjects (mean age 44.9, 25.8% male) were included. Mean time from COVID19 infection to receipt of intervention was 256.6 days. Trials targeted long COVID symptoms (35%), fatigue (30%), breathlessness (17%), olfactory dysfunction (17%), and brain function (9%). Trials were double-blinded (44%), single-blinded (26%), or unblinded (30%). Most trials (74%) had a high risk of bias with some concerns in 13% and low risk in 13%. Interventions included physical therapies, dietary treatments, regenerative injections, electrical stimulation and digital wellness programs.

Conclusions
Several PCS interventions have been studied, but high bias levels in these trials preclude recommending the tested treatments. Trials focusing on populations with mental health disorders and musculoskeletal complaints were scarce. Further, well-designed RCTs are needed to establish more definitive interventions for PCS. Adherence to rigorous trial standards to minimize biases is crucial for future studies.

P22

Single-Photon Emission Computed Tomography Facilitates the Diagnosis of Vascular Encephalitis in Cases of Severe Long COVID and Correlates with Transcriptomic Studies

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Since July 2021, a cohort exceeding 100 Long Covid patients has been identified during family

medicine consultations in Charleroi, Belgium. The diagnosis of Long Covid, characterized by a constellation of medically unexplained symptoms, is predominantly reliant on clinical assessment. Conventional biological examinations and imaging studies yield no fruitful findings. In instances of severe presentation, cognitive dysfunction has prompted the utilization of single-photon emission computed tomography (SPECT CT), a modality capable of detecting anomalies in cerebral blood perfusion. Furthermore, through collaboration with the Covid Human Genetic Effort network, comprehensive multi-omics investigations involving 80 patients have been conducted

During clinical encounters and through the comprehensive review of medical histories, a constellation of medically unexplained symptoms has become evident. These symptoms encompass cognitive impairments, profound fatigue, exertional exhaustion, and procedural memory disturbances, among numerous others, occurring in individuals who were previously in good health or exhibited stable health conditions. To assess the severity of cases as perceived by healthcare providers, the Wonca Duke Overall Severity Index (DUSOI) has been employed, graded on a scale ranging from 0 to 5. Simultaneously, to gauge the functional status from the patients' perspective, the COOP Wonca Charts have been utilized, featuring scores ranging from 6 (representing a state of health) to 30 (indicating severe functional impairment). In instances where cases are deemed very severe (DUSOI exceeding 3) and where there is a pronounced alteration in global health status (exceeding 20), it has been opted to request single-photon emission computed tomography (SPECT-CT) scans for further evaluation. Notably, the majority of patients have consented to participate in multiomics research by providing blood samples.

A total of 53 patients with severe long-standing long covid agreed to undergo SPECT-CT. Cerebral flow disorders were detected in 45 of them. This kind of protocol is usual in such cases ;The tracer fixation exhibits marked heterogeneity, with more pronounced hypo-fixations observed in the right parieto-occipital, left parietal, right fronto-parietal, and bilateral posterior parietal regions. There exists a robust correlation between SARS-CoV-2 viral RNA levels and the outcomes observed in SPECT-CT scans.

The discussion will be conducted as part of the presentation.

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P23

Improvement of Depressive Symptoms in People Living with Post-COVID Condition after Following an Immersive Virtual Reality-Based Rehabilitation Program

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Background: People living with post-COVID-19 condition (PCC) suffer cognitive and mental health issues. Immersive Virtual Reality (IVR) is the representation of scenes or images of items generated by a computer program that offers the appearance of realism despite being a simulation of an artificial world. Using these interactive simulations, IVR technology facilitates the transfer of abilities learned in a virtual environment to the real world. It has been helpful in the rehabilitation of cognitive and emotional problems. Our objective was to assess the effect of a multimodal IVR program on mental health in a sample of people with PCC and cognitive and emotional complaints.

Materials and Methods: 24 individuals with PCC were assigned to an experimental (n= 13; 9 females, mean age= 49.85; SD= 7.55 years) or waiting list (n= 11; 10 females, mean age= 49.91; SD= 4.55) group. The experimental group received a 60-minute, twice-weekly, 8-week IVR-based multimodal rehabilitation program to stimulate cognition, emotion, and physical condition. Before and after the intervention, each participant's mental health was tested using validated Spanish versions of the Patient Health Questionnaire 9 and General Anxiety Disorder 7 scales, which assess the severity of depressive and anxiety symptoms in the previous two weeks. Mixed between-group (group) and within-group (pre-post assessments) ANOVAs with Bonferroni corrections were

performed. The alpha level was set at p=0.05. All analyses were performed using SPSS 27.

Results: Mixed ANOVA analyses revealed a statistically significant interaction between group and assessment time, measured by the PHQ-9, with a large effect size (F(1, 23) = 5975, P =.03, partial 2 =.206). Follow-up analyses of the PHQ-9 revealed a statistically significant improvement (mean difference = -6.00, standard error = 1.66, P =.002) in the experimental group from baseline to post-assessment (mean difference = -6.00, standard error = 1.66, P =.002). Compared to the experimental group, the control group did not report significant changes in depressive symptoms before and after intervention.

Conclusion: The IVR multimodal rehabilitation approach resulted in notable enhancements in depressive symptomatology among participants with PCC in the experimental group. The observed amelioration of depression symptoms can be ascribed to the synergistic impact of physical and cognitive training.

P24

Long COVID: Less than 10% Remission Rate at 12 Months and Major Impact on Daily Life

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Background: Understanding the evolution of Long COVID symptoms and their impact on daily life is critical for both patients and healthcare providers. This study investigates the 12-month follow-up outcomes of Long COVID from initial COVID-19 episode, including self-assessment scores, symptom remission rates, and the effects on participants' daily activities.

Materials and Methods: A cross-sectional survey was conducted among outpatients conforming to the WHO's clinical case definition for post-COVID-19 condition, who were under the care of a reference center for Long COVID. Participants had their initial COVID-19 episode between January 15, 2020, and May 21, 2021. Data regarding demographics, daily life activities, and remission status were collected through a comprehensive questionnaire and a post-COVID remission scale. Symptom severity was quantified on a self-assessment scale, ranging from 1 (symptoms worsening) to 10 (complete symptom remission).

Results: Among the 231 participants, with a median age of 45 years (IQR: 38-53), and 77.5% being female, notable demographic characteristics were identified: 26.0% were healthcare workers, 57.6% had a history of atopy, allergies, or asthma, and 24.7% had a history of depression or anxiety predating the Long COVID phase. The mean self-assessment score for Long COVID symptoms was 6.6 (median; interquartile range: 7.0; 6.0 to 8.0).
At the 12-month assessment, only 8.7% of participants reported complete symptom remission, with an additional 28.6% experiencing significant improvement. Concerningly, 22.1% of participants (scoring 0-5) continued to endure symptoms with varying degrees of dependency on daily activities or substantial limitations in their daily life.

The impact on daily life was profound. During the Long COVID phase, 62.2% of participants (120/193) who had been employed before their COVID-19 infection had to discontinue their work. Among those who stopped working, only 66.7% (80/120) resumed their professional activities. Notably, a little more than half of those who had ceased working were back to full-time employment at one year (47/80).

Regarding routine domestic activities, only 24.7% of participants were able to resume them after 12 months. For sports activities, just 29% could engage without any difficulty. A worrying picture also emerged regarding driving without difficulties (64.5%) and reading (59.7%), with over 50% of participants experiencing difficulties in these activities.

Conclusions: This study underscores the significant number of individuals still grappling with Long COVID symptoms at the 12-month mark, with a

persistent and profound impact on daily life, particularly in terms of work and daily activities. These findings underscore the pressing need for continuing research and support to enhance the quality of life and facilitate the reintegration of individuals with Long COVID into their professional lives.

P25

Links between Endothelial Glycocalyx Changes and Ocular Manifestations in Long-COVID-19 Patients

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Background: The aim of the study is to report on the indocyanine green angiography (ICGA), OCT and adaptive optic (AO) findings, evaluate the endothelial glycocalyx layer (EGL) injury, and correlate to ocular findings in patients with long COVID.

Materials and Methods: In this prospective monocentric cohort study, we included patients with long COVID.

Results: A total of 44 patients with a mean age of 47.5 ± 11.5 years and a female predominance (36 patients; 81.8%) were included. Main ICGA findings included hyperreflective dots in 32 eyes (36.4%), and hemangioma-like lesions in 7 eyes (8.0%). On OCT-A, capillary non-perfusion in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) was found in 42 eyes (47.7%) and 21eyes (23.9%) respectively. Eyes with hyperreflective dots and and those with superficial punctate keratitis were found have higher perfused boundary region (p= 0.02 and 0.002 respectively). Eyes with capillary non perfusion in the SCP had a lower density of capillaries less than 4µm (p=0.01) while eyes with hemangioma-like lesions had a lower density of capillaries less than 6µm (p = 0.001). No correlation was found between EGL injury and AO findings.

Conclusions: Patients with long COVID have EGL injury and both retinal and choroidal vasculature anomalies. Ocular pathology was associated with EGL injury. These anomalies seemed to be related to the chronic injury afflicted by the SARS-CoV2 virus on the glycolyx of both endothelial and epithealial cells.

P26

Variation in Long COVID Experiences in the Population

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Background: Long COVID (also known as Post-COVID-19 condition or Post-COVID-19 syndrome) is a significant public health challenge but remains poorly understood. Descriptive studies of symptoms and experiences are often based on samples drawn from online Long Covid support groups or patients accessing specialist clinical services. While these studies have produced key contributions to the body of knowledge on Long COVID, there is a need to understand the perspectives of a more diverse group of participants.

Materials and Methods:
The REACT programme is one of the world's largest coronavirus monitoring studies and is based on a random sample of adults in England. Here we use data from 1) a follow-up health and wellbeing survey sent to REACT participants (n= 276,840); and 2) interviews with a sample of participants reporting persistent symptoms for 12 or more weeks following COVID-19 (n=60). Interview participants were purposively sampled from the survey respondents to ensure diversity by oversampling underrepresented groups. The survey included questions on current health and wellbeing, symptoms and quality of life, and details of past COVID-19. We use descriptive statistics to describe the profile and duration of symptoms. Interviews were analysed using thematic analysis to understand symptom experiences and the effect of Long Covid on people's lives.
Results: In our survey, one in 13 people with symptomatic SARS-CoV-2 infection reported

symptoms for more than 12 weeks (meeting the WHO definition for "post COVID-19 condition (Long COVID)"); 69% of those with persistent symptoms at 12 weeks still had symptoms at 52 weeks, while 31% recovered within a year. The most common symptoms in people with Long COVID were mild fatigue (66·9%), difficulty thinking or concentrating (54·9%) and joint pains (54·6%); 52% reported their health status as "good", 36% as "fair" and 12% as "bad", compared to 76%, 20% and 4% respectively for people who had never had COVID-19.

The people we interviewed reported a wide variation in symptoms which were often fluctuating or unpredictable in nature. Some participants did not always link their persistent symptoms to COVID-19, and only a third were confident that the term Long COVID applied to them. Most had not accessed clinical services or joined Long Covid support groups and many reported barriers to engaging with treatment and support. Reasons for not seeking help included feeling they could manage without treatment, that their symptoms were not severe enough compared to others with Long COVID, and because there was a lack of knowledge, 'there is nothing anyone can do'. Participants from ethnic minority groups indicated structural barriers to accessing health care, with a lack of trust and fears of not being taken seriously.

Conclusions: The findings from a diverse population survey and interview study suggest a wide range of experiences of prolonged symptoms following COVID-19. The majority of those affected had not sought help through healthcare or Long COVID support groups, meaning that their experiences may be missed in much research and their needs not met in the development of approaches to treatment and care.

P27

ABO Blood Group as a Determinant of COVID-19 and Long COVID: An Observational, Longitudinal, Large Study

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Background: An association of ABO blood group and COVID-19 remains controversial.

Materials and Methods:
Following STROBE guidance for observational research, we explored the distribution of ABO blood group in patients hospitalized for acute COVID-19 and in those with Long COVID. Contingency tables were made and risk factors were explored using crude and adjusted Mantle-Haentzel odds ratios (OR and 95% CI).

Results: Up to September 2022, there were a total of 5,832 acute COVID-19 hospitalizations in our hospital, corresponding to 5,503 individual patients, of whom blood group determination was available for 1,513 (27.5%). Their distribution by ABO was: 653 (43.2%) group 0, 690 (45.6%) A, 113 (7.5%) B, and 57 (3.8%) AB, which corresponds to the expected frequencies in the general population. In parallel, of 676 patients with Long COVID, blood group determination was available for 135 (20.0%). Their distribution was: 60 (44.4%) from group 0, 61 (45.2%) A, 9 (6.7%) B, and 5 (3.7%) AB. The distribution of the ABO system of Long COVID patients did not show significant differences with respect to that of the total group ($p \geq 0.843$). In a multivariate analysis adjusting for age, sex, ethnicity, and severity of acute COVID-19 infection, subgroups A, AB, and B were not significantly associated with developing Long COVID with an OR of 1.015 [0.669-1.541], 1.327 [0.490-3.594] and 0.965 [0.453-2.058], respectively. The effect of the Rh+ factor was also not significant 1,423 [0.772-2,622] regarding Long COVID.

Conclusions: No association of any ABO blood subgroup with COVID-19 or developing Long COVID was identified.

P28

Persistence of SARS-CoV-2 in Platelets and Megakaryocytes in Long COVID

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Background: We have shown that acute COVID-19 pathogenesis is profoundly altered by infection of lung megakaryocytes (MKs) and platelets by SARS-CoV-2 (Zhu et al, 2022). A significant proportion of COVID-19 patients have symptoms persisting for > 3 months after initial infection with SARS-CoV-2, referred to as Long COVID or Post-acute Sequelae of SARS-CoV-2 (PASC) patients. Persistent or re-emerging symptoms are varied, with a predominance of asthenia, neuro-cognitive impairment and cardio-vascular symptoms. The pathophysiology underlying long-onset COVID remains poorly understood.

Materials and Methods: Blood was collected from patients with Long COVID (LC) (n=30), or previously infected by SARS-CoV-2 but without persistent symptoms (resolved COVID-19 (CR), n=20). MK frequency in blood was quantified by flow cytometry. Platelets and blood MKs were analysed for the presence of Spike and SARS-CoV-2 RNA by in situ hybridization and immunodetection visualized by confocal microscopy. Spike and serotonin were quantified in plasma.

Results: The frequency of CD41+ MKs in peripheral blood mononucleated cells (PBMCs) was significantly higher than healthy donors (0.28±0.05 versus 0.03±0.02) as a sign of MK infection, as we previously shown in acutely infected individuals with SARS-CoV-2 in platelets. Accordingly, in all samples analyzed, circulating MK in Long COVID sheltered both Spike and SARS-CoV-2 ssRNA, but also dsRNA suggestive of viral replication. These infected MKs produced blood platelets that contain also P Spike and SARS-CoV-2 ssRNA. Platelets microclots were detected in all tested COVID patients. Spike protein was detected at the pg level in 30 % of analyzed plasma from Long COVID but not CR individuals. Finally, the level of serotonin in platelet and of tryptophan hydroxylase-1 (TPH-1), the enzyme that regulates serotonin synthesis decreased in blood of Long COVID patients compared to COVID recovered individuals.

Conclusions: In patients developing Long COVID, SARS-CoV-2 persist and replicate in MKs that in turn produce platelets containing virus. The presence of circulating spike might be an additional sign of viral persistence that could be used as a Long COVID biomarker. The presence of the virus could lead to abnormal platelet activation and the formation of microclots, which would contribute to the various symptoms observed in long-onset COVID and to deregulation of serotonin uptake, contributing to the neurocognitive symptoms observed in long-onset COVID.

P29

Identifying Novel Genetic Biomarkers to Predict Long COVID Susceptibility

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Long COVID is a multisystemic condition defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. Common symptoms include fatigue, pulmonary dysfunction, muscle and chest pain, dysautonomia, and cognitive disturbances.

To date, several clinical risk factors have already been identified; however, the role of the host genetic factors remains unclear. To better understand the underlying genetic causes of long COVID and identify novel susceptibility genes, we have conducted a genome-wide association study (GWAS) including a total of 1,445 Spanish COVID-19 patients, 538 diagnosed with long COVID after three months of COVID-19 infection and 907 COVID-19 recovered individuals. Patients included came from the Scourge initiative (www.scourge-covid.org/), a project that was launched in Spain to investigate the role of genetics in acute COVID-19 severity, and from REiCOP (www.reicop.org/), the Spanish Research Network in Long COVID focused on the promotion and dissemination of scientific knowledge about long COVID and improving clinical care for patients affected by this disease.

A clinical questionnaire including more than 300 variables was completed at least three months after acute infection to record all persistent symptoms. Patients' DNA samples were analyzed using an array which interrogates more than 700,000 genetic variants (Illumina Global Screening Array). Our analysis has allowed us to identify novel candidate variants related with risk of developing long COVID to be validated in further studies.

P30

Impact of Osteopathic Medicine Treatment (OMT) On Thoracic Symptoms of PASC (Post Acute Sequelae of COVID): The COVOSTEO Observational Study.

A Monocentric, Longitudinal Observational Study Based on Data from a Common Management Approach.

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Background: Post acute sequelae of COVID-19 (PASC), occurring within 3 months following an acute infection, has been identified and evaluated through numerous studies. Findings reveal a large spectrum of symptoms, throughout several systems (vascular, neurological, respiratory, digestive….). More than 50 % of the patients suffering from PASC experience thoracic symptoms, such as dyspnea, thoracic pain, or tightness, cough. There is no experimental study about benefits of osteopathic medicine on PASC. Osteopathic Medicine Treatment (OMT), in its holistic approach, may have a beneficial impact on those symptoms.

Objective: This preliminary study evaluated the benefit of OMT on the thoracic symptoms of PASC patients.

Materials and Methods: We performed a mono-centric prospective study in patients with PASC thoracic symptoms. After an initial osteopathic check-up, a management adapted to each patient was conducted over 5 sessions spaced by 15 days (+/-7). In order to standardize the OMT diagnosis, a Subjective Objective Assessment Plan (SOAP) was elaborated based on the diagnosis of somatic dysfunctions aiming on TART: Tenderness, Asymmetry, Restriction in motion, or Tissue-texture changes. All usual associated treatments, including physiotherapy, were authorized. The main end points were: (1) decrease in the NIJMEGEN score, (2) improvement in quality of life through SSD-12 and HAD scores. Statistics analysis were conducted Per Protocol using the Wilcoxon Test.

Results: 38 patients (mean age=47, 84% women) were included among which 30 followed through the 5 osteopathic sessions. Between inclusion (J1) and the end of the 5 sessions, 27/30 (90%) saw their NIJMEGEN score improve with a mean decrease of 38% (from 34 to 21) [p<0.001], 18/30 patients (60%) saw their SSD-12 score improve with a mean decrease of 19% (from 26 to 21) [p=0.033], 21/33 (70%) saw their HAD score improve with a mean decrease of 24% (from 17 to 13) [p=<0.001].

A benefit was also observed on other symptoms notably various digestive disorders, pain and asthenia. The initial osteopathic whole body assessment revealed that all patients had various clinical symptoms such as allodynia, asymmetry, restriction of mobility or modification of tissue texture mainly in the regions of the chest, abdomen and cervical: hypertonia of the accessory inspirator muscles (n=30/30), hypomobility of the sternum (n=19/30), hypomobility of ribs and diaphragm and occipitomastoid suture (n=30/30), loss of elasticity and flexibility of the abdomen, of the epigastrium, right hypochondrium and umbilical region (n=30/30), with global abdominal defense (n=22/30).

Conclusions: This exploratory study suggests a benefit of OMT, verified by a Wilcoxon Test, on the respiratory symptoms of PASC and on quality of life during osteopathic management. The initial osteopathic assessment was evocative for some symptoms of an autonomic dysfunction. A randomized study is required to confirm the benefit of this management.

P31

Nicotine Patch Therapy in People with Long COVID Shows Significant Improvement in Baseline and a Quarter Report Remission Events: A Patient-Led Observational Survey

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Background: Since the onset of the COVID-19 pandemic, people have been suffering with Long Covid. Despite advancements in acute SARS-CoV-2 research, people living with Long Covid for more than three years have turned to self-experimentation. Nicotine patches emerged as a promising treatment option following Dr Leitzke's hypothesis, which was published in the Spring of 2023. With the aim of harm reduction and treatment research, we collected data from the early adopters (testers) through an online survey, a Twitter hashtag, and a private Facebook group in the summer of 2023.

Materials and Methods: Data is collected through a Google Forms survey with 60 questions after the testers (n=148) consent to anonymous sharing of the data for research purposes. This cohort is representative of the Long Covid community (sex, age, and gender). The primary measure is the testers' perceived quantitative change in their Bells' Score Percentage after completing at least a round of nicotine patches and a break period.

Results: Over two-thirds of the testers reported an improvement in baseline, with approximately one in five experiencing remission events (levels 1, 1+, and 2), either while using or shortly after discontinuing the use of the nicotine patch. Surprisingly, testers who used name-brand nicotine patches were less likely to benefit than testers who used generic/store-brand patches. Testers reporting symptoms of muscle/joint pain, SOB, Anxiety, MCAS, smell/taste issues, and cold sores in the mouth were more likely to report a higher improvement in baseline than those with symptoms of POTS, digestive issues, nocturia, low BP, headaches and migraines, skin issues or high RHR. However, no individual symptom can predict if a tester would be one of the 1 in 20 who had a drop in baseline while on the nicotine patch.
Similarly, thyroid, nattokinase, and blood thinner medication users had higher baseline increases, on average, than users of POTS, Benzodiazepines, SSRIs medications. About one-third of the participants were on LDN, this cohort had slightly below-average benefits, and five of the seven non-responders.

Conclusions: This data suggests that the nicotine patch treatment is beneficial for most people with Long Covid who try it and that there is minimal risk of a general drop in the baseline. Moreover, the patient-led, symptom-led approach and the short half-life of nicotine make the easily removable nicotine patch a relatively safe and very promising treatment for people with Long Covid. The length of treatment and dose naturally varies from person to person so there is no clear protocol or endpoint, but longer treatments correlate with better outcomes. It is unclear which subgroup would benefit the most and what adjunct medication might be beneficial/harmful. More research with biomarkers and full-body scans is needed to precisely illustrate changes.

P32

The poster for abstract number 32 has merged with that of abstract number 24, as both share similar results

Factors Associated with Significant Improvement of Long COVID Symptoms at 12 Months

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Background: Understanding the evolution of Long COVID symptoms and their impact on daily life is critical for both patients and healthcare providers. This study investigates the 12-month follow-up outcomes of Long COVID from initial COVID-19 episode, including self-assessment scores, symptom remission rates, and the effects on participants' daily activities.

Materials and Methods: A cross-sectional survey was conducted among outpatients conforming to the WHO's clinical case definition for post-COVID-19 condition, who were under the care of a reference center for Long COVID. Participants had their initial COVID-19 episode between January 15, 2020, and May 21, 2021. Data regarding demographics, daily life activities, and remission status were collected through a comprehensive questionnaire and a post-COVID remission scale. Symptom severity was quantified on a self-assessment scale, ranging from 1 (symptoms worsening) to 10 (complete symptom remission).

Results: Among the 231 participants, with a median age of 45 years (IQR: 38-53), and 77.5% being female, notable demographic characteristics were identified: 26.0% were healthcare workers, 57.6% had a history of atopy, allergies, or asthma, and 24.7% had a history of depression or anxiety predating the Long COVID phase. The mean self-assessment score for Long COVID symptoms was 6.6 (median; interquartile range: 7.0; 6.0 to 8.0).
At the 12-month assessment, only 8.7% of participants reported complete symptom remission, with an additional 28.6% experiencing significant improvement. Concerningly, 22.1% of participants (scoring 0-5) continued to endure symptoms with varying degrees of dependency on daily activities or substantial limitations in their daily life.

The impact on daily life was profound. During the Long COVID phase, 62.2% of participants (120/193) who had been employed before their COVID-19 infection had to discontinue their work. Among those who stopped working, only 66.7% (80/120) resumed their professional activities. Notably, a little more than half of those who had ceased working were back to full-time employment at one year (47/80).

Regarding routine domestic activities, only 24.7% of participants were able to resume them after 12 months. For sports activities, just 29% could engage without any difficulty. A worrying picture also emerged regarding driving without difficulties (64.5%) and reading (59.7%), with over 50% of participants experiencing difficulties in these activities.

Conclusions: This study underscores the significant number of individuals still grappling with Long COVID symptoms at the 12-month mark, with a persistent and profound impact on daily life, particularly in terms of work and daily activities. These findings underscore the pressing need for continuing research and support to enhance the quality of life and facilitate the reintegration of individuals with Long COVID into their professional lives.

P33

Post-COVID-19 Vaccination Syndrome (PCVS) Triggered by mRNA Vaccines in Patients with No Previous Long COVID

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Background: Although vaccines against SARS-CoV-2 have saved many human lives and the cost benefit ratio of RNA vaccines is unquestionably very positive, their side effects are not negligible and are still poorly known. Emergent nomenclature suggests to the term post-COVID-19 vaccination syndrome (PCVS) to describe such long lasting symptoms triggered by SARS-CoV2 mRNA vaccines (1).

Materials and Methods: We describe a series of 24 patients, all of them free of long COVID before vaccination. These 24 patients consulted a long COVID center in Paris, presenting long COVID-like symptoms following a SARS-coV-2 mRNA vaccination

Results: This population consisted of 24 patients (18 women, 6 men) with a mean age of 41.5 years CI95% [34-53]. 9/21 (42.9%) had an history of allergy and 11 /21(52.4%) of autoimmune disease (either personal n=6 and/or familial n=7).15 have

had no symptomatic COVID infection (could have had symptomatic one) before vaccination, while 9 have had a resolutive COVID infection for several months.
The first symptoms appeared a few days or weeks after Pfizer (n=20) or Moderna vaccinations (n=4), most of times after the 2nd or the 3rd injections. One patient had received a Sinovac vaccine and one a Spoutnik vaccine before mRNA vaccines.
Main symptoms were: musculo-squelettal disorders (n=20), fatigue (n=19), cognitive disorders (n=17), other neurological disorders (n=18), ENT disorders(n=15), thoracic symptoms (n=8), postural tachycardia (n=8), cutaneous and vascular (n=11), ophthalmologic disorders (n=8), headaches (n=8).

Out of 4 who performed a cerebral TEP scanner, 3 have areas of hypometabolism in the brain stem and adjacent areas. A hyperventilation syndrome was detected in 12 out of 16 patients who performed the Nijmegen score. A POTS confirmed for 6 patients.

17 out of 24 (70.8%) had to stop working and 10 (41,7%) could not resume work even partially at the last follow-up.

Conclusion: Same Long Covid symptoms can be observed after mRNA vaccines, than after Covid infection. In both cases, these symptoms suggest severe dysfunction of the autonomic nervous system. The fact that mRNA vaccines triggers long Covid-like symptoms in these patients raises at least two hypothesis:
- mRNA vaccines may have cause relapse of a previous symptomatic resolved infection or of an asymptomatic one.
- mRNA vaccines can directly cause these symptoms: any step between mRNA injection and Spike manufacturing by human cells could drive symptoms. In this case, we can hypothesize that Spike protein itself may cause problems.

Further immunological, biochemical and virological investigation are in progress to understand the underlying causes of this syndrome that will allow to consider therapeutic perspectives

Reference:

1. Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497.

P34

Unraveling the Enigma of Long COVID: A Journey from Clinical Uncertainty to Multi-Omics Research. July 2021-Sept 2023

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In family medicine, it's confronting the uncertainties posed by a new syndrome that has driven translational research forward, as this poster illustrates. Readers are invited to follow the arrows that trace the evolution of our research initiated in July 2021.

Several months after the acute phase of a Covid-19 infection, previously healthy or stable individuals present with a range of medically unexplained symptoms. These include cognitive impairment, profound fatigue, exertional exhaustion, procedural memory impairment and anomia. Despite rigorous efforts, traditional biological examinations and imaging studies fail to yield conclusive results.

In response to this puzzling clinical scenario, a classified bibliography freely accessible on Zotero was developed. An exhaustive analysis of the literature ultimately led to the diagnosis of Long Covid, which is the most plausible explanation for these enigmatic symptoms.

Guedj's exploration of 18 FDG PET scan hypometabolism in patients with Long Covid then stimulated the use of single-photon emission computed tomography (SPECT CT). This imaging modality, available in primary care in Belgium, has shown to be effective in detecting abnormalities in cerebral blood perfusion. In addition, collaborative efforts with the Covid Human Genetic Effort network have led to in-depth multi-omics investigations of over 80 patients in our cohort (104 patients to date).

At the clinical level, patients are given the opportunity to express their concerns and undergo symptom severity assessments. Their clinical profiles, pre-covid problems identified by International Classification of Primary Care codes, vaccination history, medical history and disease course are documented. Testimonies are collected

through interviews and written reports, enabling us to support, understand and defend their rights.

With the informed consent of patients and the approval of the University of Liège Ethics Committee, blood samples have been taken and a database created. This serves as a resource for research at various levels, including qualitative studies conducted by students from various Belgian universities, as well as transcriptomic, proteomic and genomic analyses carried out in collaboration with institutions such as the Rega Institute (KUL), the Brodin laboratory (Stockholm), Pharmacogenomics (UGent), and Necker (Paris). The neurobiology laboratory at the University of Namur is interested in exploring neuronal antibodies. Finally, the textual data collected can be used to develop an automated terminology and ontology tool, in collaboration with Macquarie (Australia) and the University of Rouen (France), capable of extracting relevant textual features from electronic medical records. Bibliography is central to the whole process.

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Self-Perceived Barriers to Healthcare Access for Patients with Post COVID-19 Condition

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Background: Many patients with post COVID-19 condition (PCC) require healthcare services. However, qualitative studies indicate that patients with PCC encounter many barriers to healthcare access. This cross-sectional study aimed to determine how many PCC patients report barriers to healthcare access and which barriers are reported, and to explore differences between subgroups.

Materials and Methods: Data were collected via an online survey from 10,462 adult patients with a confirmed or suspected COVID-19 infection in the Netherlands, who experienced persisting symptoms ≥3 months after the initial infection. To study self-perceived barriers, a list of eleven possible barriers was used, covering multiple aspects of healthcare access. Differences between subgroups based on sociodemographic characteristics, medical characteristics, PCC symptoms (fatigue, dyspnoea, cognitive problems, anxiety and depression), and healthcare use (general practitioner, paramedical professional, medical specialist, occupational physician and mental health professional) were studied through multivariable multinomial (0 vs. 1 vs. >1 barrier) and binomial regression analyses (for each individual barrier).

Results: A total of 83.2% of respondents reported at least one barrier to healthcare access. Respondents reported a median of 2.0 (IQR=3.0) barriers. The barriers "I didn't know who to turn to for help" (50.9%) and "No one with the right knowledge/skills was available" (36.8%) were most frequently reported. Respondents with younger age, higher educational level, not hospitalized during acute COVID-19 infection, longer disease duration, who had more severe PCC symptoms, and who did not consult an occupational physician or paramedical professional, were more likely to report barriers. Analyses per barrier showed that women were more likely to report financial and help-seeking barriers, while men had more likely to report barriers related to availability of care. Hospitalized respondents were less likely to report barriers related to availability of care, but not to report financial or help-seeking barriers.

Conclusions: This study shows that the majority of patients with PCC experiences barriers to healthcare access. Particular attention should be paid to younger, non-hospitalized patients with a long disease duration and severe PCC symptoms. Efforts to remove barriers should focus not only on improving availability of care, but also on helping patients navigate care pathways.