**Pharmacotherapy from pre-COVID to post-COVID: longitudinal trends and predictive indicators for long COVID symptoms**

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What is already known about this subject:

* COVID-19 increases medication usage to manage acute symptoms and complications.
* Long COVID, characterized by persistent symptoms beyond 3 months, requires a precision medicine approach due to its heterogeneity.
* While there are many known risk factors such as age and sex, the predictive value of pre-COVID pharmacotherapy as health status indicator remains underexplored.

What the study adds:

* Longitudinal insights into pharmacotherapy from pre-COVID through post-COVID phases, demonstrating peak usage of corticosteroids and antithrombotic agents during acute COVID-19 alongside consistent high use of alimentary tract medication.
* We identified pre-COVID pharmacotherapy associated with long COVID outcomes, demonstrating its potential as health status indicator in characterizing patients for disease management.

**Abstract**

Aim:

Approximately 10% of all COVID-19 cases experience persistent symptoms after the acute infection phase, a condition known as long COVID or post-acute sequelae of COVID-19. Approved prevention and treatment options for long COVID are currently lacking. Given the heterogeneous nature of long COVID, a personalized medicine approach is essential for effective disease management. This study aimed to describe trends in pharmacotherapy from pre-COVID to post-COVID phases to gain insights into COVID-19 treatment strategies and assess whether pre-COVID pharmacotherapy can predict long COVID symptoms as a health status indicator.

Methods:

In the Precision Medicine for more Oxygen (P4O2) – COVID-19 study, 95 long COVID patients were comprehensively evaluated through post-COVID outpatient clinics and study visits. The study focused on descriptive analysis of the pharmacotherapy patterns across different phases: pre-COVID-19, acute COVID, and post-COVID. Furthermore, associations between pre-COVID medication and long COVID outcomes were analyzed with regression analyses.

Results:

We observed peaks in the use of certain medications during the acute infection phase, including corticosteroids and antithrombotic agents, with a decrease in the use of renin-angiotensin inhibitors. Consistent high use of alimentary tract medications was noted across all phases. Notably, pre-COVID respiratory medications were associated with fatigue symptoms, while antiinfectives and cardiovascular drugs were linked to fewer persisting long COVID symptom categories.

Conclusion:

Our findings provide longitudinal descriptive pharmacotherapy insights and suggest that medication history can be a valuable health status indicator in characterizing patients for personalized disease management strategies, addressing the heterogeneous nature of long COVID.

Key words: precision medicine, long COVID, COVID-19, pharmacotherapy, longitudinal trends

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**Introduction**

The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly became a global pandemic. While many individuals recover from the acute phase, a significant number develops persistent symptoms, known as Long COVID (LC), post-acute sequelae of COVID-19, or post-COVID syndrome. The World Health Organization defines LC as the persistence of symptoms beyond three months(1). These symptoms can last for months to years, impacting quality of life and creates challenges to healthcare systems.

LC can include various symptoms, including fatigue, respiratory, cardiovascular, neurological, and gastrointestinal complaints, complicating diagnosis and management(2–4). Current treatment strategies lack effective, approved interventions. Hypotheses regarding its pathophysiology include viral persistence, immune dysregulation, microvascular injury, and autonomic dysfunction. Understanding these mechanisms is crucial for developing targeted interventions(5,6).

Precision medicine, which is meant to tailor treatments based on individual characteristics such as genetics, environment, and lifestyle, is needed for LC considering its heterogeneity. Risk factors identified by previous studies include severe initial COVID-19, age (particularly over 50), sex (with women more likely to experience persistent symptoms), smoking status and chronic conditions like hypertension, obesity, psychiatric disorders, and immunocompromised conditions(7,8).

Pre-existing medication history, or pharmacotherapy, is a relevant aspect of assessing a patient's health status and potential susceptibility to long COVID development. While pharmacotherapy is a known predictor of disease outcomes in other conditions, its impact on LC is less studied(9–11). Because longitudinal pharmacotherapy data may provide insights into COVID-19 management, this study aims to evaluate the pharmacotherapy of LC patients from pre-COVID to post-COVID phases, identifying potential predictors of LC symptoms. Furthermore, longitudinal pharmacotherapy data may provide insights into COVID-19 management. These findings can aid in identifying specific patient subsets and developing targeted treatment strategies, ultimately contributing to precision medicine approaches in LC with to improve patient outcomes.

**Methods**

This study is based on data collected from LC patients who participated in the Precision Medicine for more Oxygen (P4O2) COVID-19 study, a longitudinal multi-center prospective observational cohort study. The study was approved by the medical ethical board of the Amsterdam University Medical Centers, reference number NL74701.018.20. Eligible LC patients were referred to a post-COVID outpatient clinic for persisting symptoms in one of the participating study hospitals. Written informed consent was obtained from all participants. An extensive study protocol description was published by elsewhere(4).

Study design and setting

During study visits longitudinal data was collected from pre-COVID, the acute infection phase, post-COVID and LC. The P4O2 COVID-19 dataset (n=95) includes post-COVID outpatient care reports, computed tomography (CT) scans, pulmonary function tests, laboratory measurements, physiotherapy records, questionnaires, and biological samples. Among these data, symptom data related to LC was categorized according to persistent fatigue, respiratory, neurological, gastrointestinal and cardiovascular complaints. During P4O2 COVID-19 study visits, self-reported medication data was collected from all LC patients. The electronic health records (EHRs) were screened to verify self-reported medication data based on physician contact letters, pharmacy notes, and medication administration records. While data on dosage, timing, and route of administration were collected, the current study is based on a relatively small patient group, therefore the medication data was analyzed qualitatively.

Classification of medication data

To answer the research questions, data from four time points was analyzed (see Figure 1) including:

* Pre-COVID
* Acute COVID-19: during the acute infection phase
* Post-COVID: referring to the immediate phase following recovery from acute infection
* Long COVID: at 3-6 months post-infection

The prescribed medications were classified according to the corresponding Anatomical Therapeutic Chemical (ATC) code. This system, that is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology, is used to categorize the active substances into groups according to organ or system they act upon, and their chemical, pharmaceutical and therapeutic properties. The first level of this code refers to the main anatomical group of medications and was used in regression analysis to gain insight into pharmacological categories. The second (therapeutic subgroup) was used for descriptive purposes.

The first level of ATC medication groups included:

* Alimentary tract (A)
* Blood and blood forming organs (B)
* Cardiovascular system (C)
* Dermatologicals (D)
* Genito urinary system and sex hormones (G)
* Systemic hormonal preparations, excluding sex hormones and insulins (H)
* Antiinfective for systemic use (J)
* Antineoplastic and immunomodulating agents (L)
* Musculo-skeletal system (M)
* Nervous system (N)
* Antiparasitic products, insecticides and repellents (P)
* Respiratory system (R)
* Sensory organs (S)
* Various (V)

Pre-COVID Acute COVID-19 Post-COVID Long COVID

Statistical analysis

Data analysis was performed using R software (version 4.2.1). Longitudinal data were analyzed descriptively. A logistic regression analysis was used to assess the association between the pre-COVID medication use and the dichotomous outcome pulmonary abnormalities and the presence of the most prevalent symptom categories amongst P4O2 COVID-19 study participants, including fatigue, respiratory and neurological complaints(4). Results were presented as odds ratios (OR) with the corresponding 95% confidence intervals (CI) and p-values and considered significant if p<0.05. Linear regression analyses were used to assess the association between pre-COVID pharmacotherapy and the number persisting symptom categories. For linear regression, results were presented as regression coefficients (β), 95% CIs and p-value were reported for each medication group. ATC groups were included in the regression analyses if >5 long COVID patients had prescribed medication in the respective class. Both logistic and linear regression models were explored with and without confounders that included age, sex, body mass index (BMI), smoking status and acute COVID-19 severity. The World Health Organization classification for acute COVID-19 was used to categorize patients into mild, moderate and severe disease severity groups for the acute COVID-19 severity confounding variable(4).

**Results**

Pharmacotherapy changes over time

The pharmacotherapy data, collected at multiple time points, revealed patterns in medication usage across the pre-COVID, acute COVID-19, post-COVID, and 3-6 months post-COVID (LC) periods. Figure 2 demonstrates an overview of these longitudinal pharmacotherapy courses, and Table A1 additionally shows the exact percentages of pharmacotherapy users over time per medication group.

Considering the first level ATC medication groups, for most medication groups, the self-reported drug administration peaked during acute COVID-19, see Figure 2. The largest absolute usage changes of drugs between time points according to therapeutic subgroups (ATC level 2) is shown in Table A2.

The overall usage of alimentary tract and metabolism medications, which treat digestive conditions referring to acid reflux, irritable bowel syndrome and peptic ulcers, remained relatively stable, while absolute changes in specific therapeutic subgroups were relatively large. Before COVID-19, 45 patients (47.9%) reported usage, increasing to 55 (57.9%) during acute COVID-19, then slightly decreased to 43 (45.3%) post-COVID. Notable increases during the acute phase were observed in subgroups A06 (drugs used for constipation), A07 (antidiarrheals and intestinal anti-inflammatory/anti-infective agents), A10 (drugs used in diabetes) and A12 (mineral supplements). Post-COVID, the usage of A07, A10 and A12 decreased, while A06 usage remained elevated reflecting a prolonged need or lack of discontinuation.

Blood and blood-forming organs medications, including anticoagulants, saw an increase during acute COVID-19, rising from 13 patients (13.8%) pre-COVID to 63 (66.3%), and then decreasing to 14 (14.7%) post-COVID. This change was primarily in subgroup B01 (antithrombotic agents), reflecting the treatment needs during the acute infection phase, with other changes also noted in B05 (blood substitutes and perfusion solutions).

Cardiovascular system medications for conditions including hypertension, heart failure and arrhythmias, remained relatively stable across time points. However, on level 2 ATC groups, notable increases were observed in subgroup C03 (diuretics), with an addition of 16 users during acute COVID-19. Increases were also seen in C01 (cardiac therapy) and C02 (antihypertensive drugs), while usage of C09 (agents acting on the renin-angiotensin system (RAS)) and C10 (lipid-modifying agents) declined from pre-COVID to acute COVID-19 followed by a subsequent increase to baseline post-infection.

The usage of dermatologic medications, applied to conditions like eczema and psoriasis, remained stable, with usage around 5% across all time points. Similarly, medications for the genito-urinary system and sex hormones, including treatments for urinary tract infections and hormonal therapies, were consistently low, fluctuating between 4% and 6.3%.

Systemic hormonal preparations, excluding sex hormones and insulins, saw a notable increase during acute COVID-19, with usage rising to 69 patients (72.6%) reflecting the role of corticosteroids in managing COVID-19 symptoms. Post-COVID, usage dropped to 7 patients (7.4%), with subgroup H02 (corticosteroids) showing the most distinct change between time points across all medication groups. Antiinfectives for systemic use, including antibiotics and antivirals, peaked at 35 patients (36.8%) during acute COVID-19 and then decreased to 3 patients (3.2%) post-COVID.

Antineoplastic and immunomodulating agents, used in cancer treatment and for autoimmune diseases, increased to 36 patients (37.9%) during acute COVID-19, then decreased to 5 (5.3%) post-COVID, driven primarily by subgroup L04 (immunosuppressants). Musculo-skeletal system medications remained consistent, with a slight increase to 16 patients (16.8%) during acute COVID-19 and stabilization

post-COVID, with notable changes in level 2 ATC group M03 (muscle relaxants).

Nervous system medications, including analgesics, antiepileptics and antidepressants, increased to 51 patients (53.7%) during acute COVID-19 and remained elevated at 34 (35.8%) post-COVID. The analgesics subgroup (N02) particularly peaked during the acute phase. The usage of respiratory system drugs, such as those for asthma and COPD, increased to 30 patients (31.6%) during acute COVID-19, with a slight decrease to 22 patients (23.2%) post-COVID. This was primarily due to increased use of cough and cold medications (R05).

For sensory organ medications, particularly ophthalmological drugs (S01), usage peaked at 14 patients (14.7%) during acute COVID-19, then decreased to 1 patient (1.1%) post-COVID. The various medications category, including general nutrients (V06) and contrast media (V08), peaked at 27 patients (28.4%) during acute COVID-19, followed by a decrease post-COVID.

Overall, during acute COVID-19, there was an increase in medication usage across most therapeutic groups, particularly in anticoagulants, corticosteroids, and respiratory medications, reflecting the intensive management required during the infection. Post-COVID, medication usage generally decreased, with most returning close to pre-COVID levels, although some, like drugs for constipation and nervous system medications, remained slightly elevated. Overall, the acute phase saw the most significant shifts in drug administration, with stabilization occurring afterwards.

Regression Analyses

The regression analyses explored associations between pre-COVID medication usage and LC outcomes, focusing on pulmonary abnormalities, fatigue, respiratory, and neurological symptoms, and the number of LC symptom categories. The most relevant results of the logistic regression analyses are summarized in Table 1. Supplementary tables A3-A7 show all identified associations. For the regression analyses, the following ATC groups were not included, because n<5: antiparasitic products, insecticides and repellents, sensory organs and various.

In the context of fatigue symptoms, LC patients with pre-COVID usage of respiratory system medications demonstrated significant higher odds for fatigue symptoms compared to those without pre-COVID respiratory system treatments (adjusted OR 5.74, 95% CI: 1.16 - 28.54, p = 0.03). The most prevalent pre-COVID category of respiratory medications was for obstructive airway disease (n=15). The cardiovascular system group users presented an adjusted OR of 0.35 (95% CI: 0.12 - 1.06, p = 0.06), suggesting a possible protective of such pre-COVID treatments effect against LC fatigue symptoms. On the contrary, the antiinfective for systemic usage group had a lower adjusted OR of 0.22 (95% CI: 0.04 - 1.23, p = 0.09), which, while not statistically significant, potentially demonstrates a reduced occurence of fatigue symptoms among users.

Regarding the persistence of pulmonary symptoms, none of the pre-COVID medication groups show strong associations based on the results in Table 1. The user group of respiratory system medication had higher odds for pulmonary symptoms compared to LC patients without pre-COVID respiratory medication (adjusted OR 2.67, 95% CI: 0.51 - 14.00, p = 0.25), reflecting a possible association with these symptoms.

For neurological symptoms, LC patients with pre-COVID cardiovascular system treatments had lower odds compared to those without (adjusted OR 0.39, 95% CI: 0.13 - 1.14, p = 0.09), suggesting less neurological symptoms. LC patients with pre-COVID antiinfectives for systemic use had significantly lower odds compared with LC patients without such treatments (adjusted OR 0.11, 95% CI: 0.02 - 0.66, p = 0.02), indicating a protective effect against neurological symptoms.

The linear regression analysis of the number of symptom categories, demonstrated some trends. Notably, the users of the pre-COVID cardiovascular system treatments had significant fewer persistent symptoms categories compared to those who did not use cardiovascular system drugs (adjusted β -0.76, 95% CI: -1.49 - -0.03, p = 0.04),

The most commonly used therapeutic subgroups were N09 (RAS agents) and N10 (lipid modifying therapies). The antiinfective for systemic user group also showed a significant adjusted β of -1.21 (95% CI: -2.40 - -0.03, p = 0.046), suggesting an association with fewer symptom categories.

The analysis of pulmonary radiological abnormalities shows varying odds ratios across medication groups, with the adjusted ORs generally aligning closely with the unadjusted ones. While not significant, the respiratory system group users exhibited higher odds (adjusted OR 5.04, 95% CI: 0.73 - 34.87, p = 0.10) for radiological abnormalities compared with LC patients that did not have pre-COVID respiratory medication. The nervous system group showed a lower adjusted OR of 0.29 (95% CI: 0.09 - 0.97, p = 0.045), suggesting a protective effect. The most frequently prescribed subgroups were N02 (analgesic drugs) and N05 (psycholeptics drugs).

**Discussion**

The objectives of this study were to assess longitudinal pharmacotherapy patterns during different phases related to COVID-19 and to investigate the role of pre-COVID pharmacotherapy as a potential health status predictor for LC outcomes. This study showed an increase in overall medication usage during the acute COVID-19 phase, notably in corticosteroids and antithrombotics, followed by an overall decrease to pre-COVID pharmacotherapy usage. Additionally, a decrease in the use of RAS inhibitors was observed during acute COVID-19, while the usage of alimentary tract medications remained relatively high across all time points. These specific therapeutic subgroups provide insights into COVID-19 treatment strategies and suggest that pre-existing health conditions, as indicated by medication usage, are potentially linked to LC

Key Pharmacotherapy Trends

The marked increase in blood and blood-forming organ medications, particularly anticoagulants, during the acute phase aligns with known COVID-19 complications, such as coagulopathies(5). It was found that anticoagulation therapy can lead to improved patient outcomes in hospitalized COVID-19 patients(12). Moreover, anticoagulation therapy before and during the acute infection led to reduced mortality and severe COVID-19 patients(13). The use of anti-coagulants, particularly heparins, have been crucial in reducing the risk of systemic thrombosis in severe COVID-19(14). The identified relations between the chronic use of anticoagulants and COVID-19 outcomes are inconsistent(15). As patients recover from COVID-19, there is a noticeable decrease in the use of blood and blood-forming organ medications, indicating a reduction in thrombotic risks post-recovery. Although studies have shown that patients with COVID-19 who had superficial vein thrombosis (VTE) and stopped anticoagulation therapy after at least three months had a low incidence of recurrent VTE, it is still essential to maintain ongoing vigilance and manage thrombotic risks to prevent potential complications even after the acute phase of recovery(16).

The use of systemic hormonal preparations, notably corticosteroids, peaked during the acute COVID-19 phase, reflecting their role in controlling severe inflammatory responses. The significant reduction in usage post-COVID indicates that these medications were predominantly used for short-term management during the height of the infection. A meta-analysis has shown that corticosteroids are effective in reducing mortality in critically ill COVID-19 patients compared with usual care or placebo(17). Furthermore, corticosteroids are frequently prescribed as adjuvant therapy for acute respiratory distress syndrome in general, because of their anti-inflammatory properties(18). However, prolonged use (>10 days) of corticosteroids therapy was associated with higher mortality(19).

Cardiovascular medications, including diuretics and antihypertensives, saw a slight increase during acute COVID-19, which is consistent with managing conditions like myocarditis and thromboembolic events. The subsequent decrease in usage suggests a resolution of acute issues for many patients, though chronic conditions likely require ongoing management. A Swedish cohort study, demonstrated that the initiation of all antihypertensive medicines increased during acute COVID-19. It was proposed that this increase is associated with COVID-19-related hypertension or more frequent hypertension diagnosis due to increased health care consultancy, which could contribute to the findings of our study(20). The usage of agents acting on the renin-angiotensin system (RAS), among other declined during the acute infection phase. In a study that assessed whether discontinuation of chronic RAS inhibition treatment influences COVID-19, based on the rationale that SARS-CoV-2 cell entry depends on angiotensin-converting enzyme 2 that can be upregulated by these drugs, found that discontinuation of RAS-inhibition in COVID-19 had no significant effect on the maximum severity of COVID-19 but may lead to a faster and better recovery and suggested that decisions on treatment continuation or discontinuation should be made on an individual level(21). Furthermore, a protective effect of RAS inhibition on COVID-19 hospitalization and mortality was found among patients with pharmaceutically treated hypertension(22).

The analysis revealed consistent high usage of alimentary tract medications throughout the COVID-19 timeline, suggesting a stable need for managing gastrointestinal-related conditions. This could reflect both pre-existing disorders and new issues arising during or after COVID-19. The manifestation of alimentary symptoms, such as poor appetite, diarrhea, nausea, and abdominal pain, in COVID-19 patients underscores the importance of understanding and managing gastrointestinal issues in the context of the disease(23). While in the P4O2 COVID-19 cohort gastrointestinal complaints were not among the most frequently mentioned persistent symptoms, this can indicate that these complaints were managed or that such conditions potentially remain a concern even after acute recovery.

Associations with LC Symptoms

The regression analysis revealed several key associations between medication groups and LC symptoms. However, while these associations are noteworthy, the study's observational nature limits causal inference, and potential confounding factors must be considered.

Respiratory system medications were linked to an increased risk of persistent fatigue, demonstrating the complexity of LC symptoms. This association may be influenced by underlying respiratory conditions, as indicated by pre-COVID medication use for obstructive airway disease that is particularly used in patients with chronic obstructive pulmonary disease (COPD). While the prescription of this medication category can lead to decreased fatigue in COPD patients, these patients may have a higher level of pre-existing fatigue compared to healthy individuals, possibly explaining this association(24,25).

Antiinfective medications showed significant protective effects against neurological symptoms and reduced the number of symptom categories. This could potentially result from the early management of infections, preventing extensive inflammation and immune responses contributing to LC. The protective effects of antineoplastic and immunomodulating agents against neurological symptoms may suggest that immune modulation can influence also impact specific LC outcomes. While these associations should be interpreted with caution due to unclear underlying mechanisms, supporting evidence indicates that conditions with pre-existing inflammation, such as seasonal allergies and autoimmune diseases, are indeed linked to an increased risk of long COVID (LC) when adjusted for the severity of acute COVID-19(26).

Cardiovascular medications were associated with a reduction in the number of LC symptom categories. While it was demonstrated that pre-existing cardiovascular disease can lead to poor COVID-19 outcomes, a study that focused on the effect of diuretics prior to COVID, found no effect on the prognosis of COVID-19(27,28). A population-based case-control study in the UK showed that antihypertensive therapy including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, thiazide diuretics and other antihypertensive drugs is not associated with increased risk of COVID-19 diagnosis or mortality, most antihypertensive classes showed negative associations with COVID-19 diagnosis(29). While acute COVID-19 severity is linked LC development(30), studies in concerning cardiovascular LC outcomes are still lacking.

Nervous system medications were associated with less pulmonary radiological abnormalities. Among the most prescribed nervous system drugs were analgesics and psycholeptics drugs including anxiolytics. The relation between anxiety and LC in general has been established. While there is no evidence of associations between pre-existing neurological drug therapies and LC outcomes, it is known that pre-existing psychiatric disorders are associated with LC development(26,31).

Limitations and Future Directions

The study has several strengths, including its longitudinal design, comprehensive data collection, and the use of standardized ATC codes for medication classification. However, the reliance on self-reported medication usage introduces the possibility of recall bias that is influenced by a variety of factors, although efforts were made to validate this data with EHRs(32). In another study, it was found that self-reported medication and prescribing data agreed with each other across a wide variety of medication groups(33). Furthermore, the observational design limits the ability to identify causality, and residual confounding cannot be ruled out despite adjustments for known confounders. Additionally, the sample size, may have limited the power to detect smaller effects and interactions.

Future research should focus on validating these findings in larger, more diverse populations and exploring the biological mechanisms underlying these associations. Incorporating pharmacogenomics could provide deeper insights into how genetic profiles interact with medication use, further refining personalized treatment strategies. Additionally, it was shown that COVID-19 severity was associated with significant differential gene expression for several genes involved drug metabolizing enzymes and membrane transporters, including upregulation in *CYP2C19* and *CYP2C19*(34). Longitudinal studies are also essential to understand the persistence of symptoms and the long-term effects of COVID-19, offering a pathway to improved management and care for affected individuals.

Concluding, this study demonstrated that from pre-to post-COVID, medication usage peaked during the acute infection based on self-reported medication data. The most notable increases were in ATC therapeutic subgroups of corticosteroids and antithrombotics. Furthermore, a decrease in the use of RAS inhibitors was observed during acute COVID-19, and alimentary tract medication remained relatively high across all time points while most groups declined back to pre-COVID usage percentages. The study revealed associations between pre-COVID medication use and LC outcomes. While these associations need to be interpreted with caution, they suggest that medication history can potentially be a valuable health status tool to identify subsets LC patients. By integrating precision medicine approaches, ultimately healthcare providers can develop more effective treatment plans tailored to individual patient histories, potentially improving outcomes for those suffering from LC.

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**Author contributions**

Study design: KG, NB, AHM, CD, acquisition: KG, NB, DVE, PJ, MEBC, SV analysis: KG, DVE, NB interpretation of data: KG, NB, DVE, AHM; drafting the manuscript: KG, NB; critical review of the manuscript: all authors.

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**Conflicts of interest**

KG: received funding from STIMAG, GSK ISS, ZonMw. Payments made to institution by GSK and ALK. AHM: She is the PI of a public private consortium (P4O2 (Precision Medicine for More Oxygen)) sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (AbbVie. Boehringer Ingelheim, Breathomix, Clear, Fluidda, Ortec Logiqcare, Olive, Philips, Quantib-U, Smartfish, Clear, SODAQ, Thirona, Roche, TopMD, Novartis, RespiQ). Received unrestricted research grant from GSK and Boehringer Ingelheim. Received Vertex Innovation Award Grant. Honoraria paid to Institution from Boehringer Ingelheim, Astra Zeneca and GSK. She is Chair of DSMB of a study on BPD in neonates. NB, MEBC, JMB: received salary from the PPP Allowance made available by Health Holland, Top Sector Life Sciences & Health (LSHM20104; LSHM20068), to stimulate public-private partnerships. JMB: honorarium paid to institution from Vitakruid. STV, HJB, VCB, JT: nothing to declare.

**Data availability statement**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**Tables**

Table 1. Pre-COVID medication associations with persisting LC symptoms, the number of LC symptoms and pulmonary radiological abnormalities.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Fatigue symptoms** | | | | | | |
|  |  | **Unadjusted** |  |  | **Adjusted\*** |  |
| **Medication Group** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| Cardiovascular system | 0.56 | 0.23 - 1.36 | 0.20 | 0.35 | 0.12 - 1.06 | 0.06 |
| Antiinfective for systemic use | 0.20 | 0.05 - 0.85 | 0.03 | 0.22 | 0.04 - 1.23 | 0.09 |
| Respiratory system | 5.48 | 1.18 - 25.41 | 0.03 | 5.74 | 1.16 - 28.54 | 0.03 |
| **Pulmonary symptoms** | | | | | | |
|  |  | **Unadjusted** |  |  | **Adjusted\*** |  |
| **Medication Group** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| Respiratory system | 2.89 | 0.61 - 13.69 | 0.18 | 2.67 | 0.51 - 14.00 | 0.25 |
| **Neurological symptoms** | | | | | | |
|  |  | **Unadjusted** |  |  | **Adjusted\*** |  |
| **Medication Group** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| Cardiovascular system | 0.51 | 0.21 - 1.25 | 0.14 | 0.39 | 0.13 - 1.14 | 0.09 |
| Antiinfective for systemic use | 0.10 | 0.02 - 0.52 | 0.01 | 0.11 | 0.02 - 0.66 | 0.02 |
| **Number of symptom categories** | | | | | | |
|  |  | **Unadjusted** |  |  | **Adjusted\*** |  |
| **Medication Group** | **β** | **95% CI** | **p-value** | **β** | **95% CI** | **p-value** |
| Cardiovascular system | -0.50 | -1.18 - 0.19 | 0.15 | -0.76 | -1.49 - -0.03 | 0.04 |
| Antiinfective for systemic use | -1.59 | -2.68 - -0.50 | 0.01 | -1.21 | -2.40 - -0.03 | 0.046 |
| **Pulmonary radiological abnormalities** | | | | | | |
|  |  | **Unadjusted** |  |  | **Adjusted\*** |  |
| **Medication Group** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| Nervous system | 0.50 | 0.18 - 1.39 | 0.18 | 0.29 | 0.09 - 0.97 | 0.045 |
| Respiratory system | 2.79 | 0.58 - 13.39 | 0.20 | 5.04 | 0.73 - 34.87 | 0.10 |

**\***Adjusted for confounders including age, sex, BMI, smoking status, acute COVID-19 severity (WHO score).

**Figure Legends**

**Figure 1. Methods visualization.** Data was collected from 95 P4O2 COVID-19 study participants at 3-6 months post-infection.Pharmacotherapy was reported at four time points (pre-COVID-19, acute COVID-19, post-COVID and at 3-6 months post-infection or long COVID). Self-reported symptom data at 3-6 months data was categorized into fatigue, respiratory, neurological, cardiovascular, gastrointestinal and other complaints.

**Figure 2. Pharmacotherapy from pre-COVID to LC.** A longitudinal visualization of the percentages of pharmacotherapy use among P4O2 COVID-19 study participants, categorized according to the first level ATC medication groups.