Interstitial lung disease after COVID-19 and the effect of Remdesivir treatment on Long-COVID syndrome

PhD thesis

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1. Introduction

Several terms and definitions have been introduced to describe the long-term sequelae condition following the acute onset of coronavirus disease 19 (COVID-19) otherwise referred to as long-COVID or post-COVID syndrome. According to the most recent definition the term "long-COVID" is used to describe an "infection-associated chronic condition, that occurs after Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ system" (The National Academies of Sciences, Engineering, and Medicine, 2024). The most prevalent symptoms include fatigue, shortness of breath, impaired cognitive function, gastrointestinal problems and sleep disturbances, however more than 200 symptoms have been linked to the condition.

Respiratory infections, particularly those caused by viruses and intracellular pathogens, affect the alveolar epithelial cells and alter or delay alveolar regeneration. SARS-CoV2 infection might lead to reactive epithelial lesions, diffuse alveolar damage, as well as thrombotic events in the small pulmonary vasculature. In many cases these may heal without residual damage, however abnormal healing processes and regeneration may also result in post-infectious inflammatory and fibrotic changes in the lungs.

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases, characterized by structural changes in the lungs' interstitial space, with or without a known etiology. Patients affected by ILDs often report high symptom burden and impaired quality of life.

As part of long-COVID, persisting post-infectious abnormalities may be visible over time on radiological images, indicating the presence of post-infectious or fibrotic ILDs in either symptomatic or asymptomatic cases.

A wide range of therapeutic options is described in several studies and guidelines; however therapeutic approaches were changing over time according to the new variants and the presence of vaccination. In the following section, a summary of the 2024 recommendation of the National Institutes of Health and the 2024 Hungarian guideline for confirmed, hospitalized, adult COVID-19 patients will be presented on Figure 1.

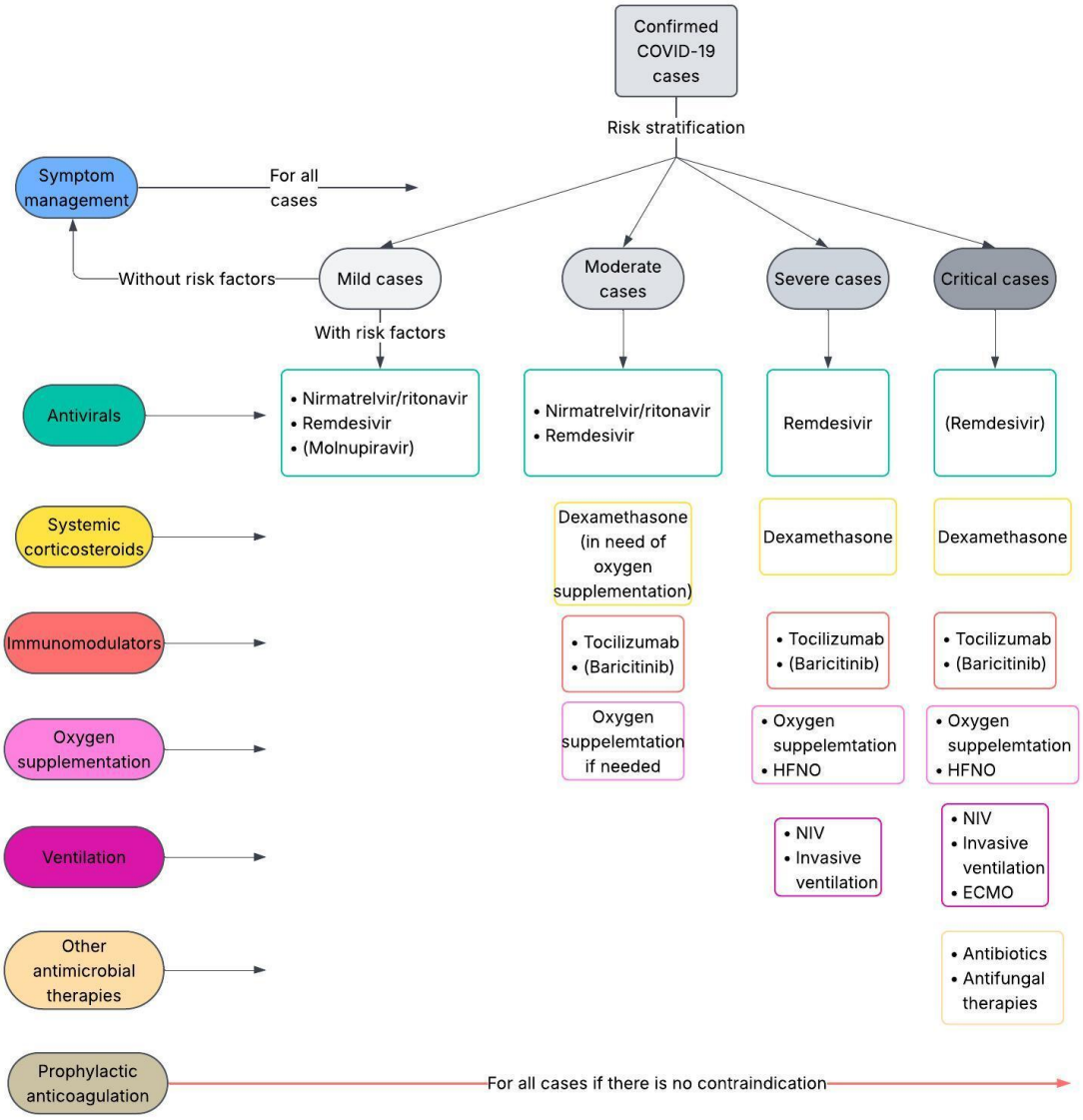

Figure 1: Therapies for COVID-19, unpublished figure based on: National Institutes of Health. Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) 2025;2019:1–243; and National Centre for Public Health and Pharmacy (NNGYK); Lakatos B. et al. Principles for the treatment of adults with confirmed SARS-CoV-2 infection March 2024. [Lakatos B et al. Igazolt SARS-CoV-2 fertőzött felnőttek kezelésének alapjai 2024. március. 2024;1–14.] ECMO: extracorporeal membrane oxygenation; NIV: non-invasive ventilation.

RDV received approval for the treatment of COVID-19 and has been extensively used in clinical practice for managing the disease. Evidence from previous studies suggests that early administration of RDV may mitigate disease progression, decrease mortality risk,

and shorten hospitalization duration. However, the long-term post-acute effects of RDV remain insufficiently characterized, with limited data available concerning its impact on post-COVID-19 condition symptomatology and quality of life.

The long-term consequences of acute severe COVID-19 pneumonia require further investigation. The objectives of the following studies were to assess long-COVID condition and potential long-lasting structural changes in the lungs (ILDs) in our patient population; as well as to evaluate the effects of timely administered RDV antiviral drug on the development of long-COVID, and on long-term symptom burden.

2. Objectives

2.1 General objectives of the studies

To build a well-structured database and collect data of patients presenting to post-COVID pulmonary care at the Department of Pulmonology, Semmelweis University.

To describe symptoms and patient characteristics of post-COVID patients.

2.2 Objectives of the post-COVID ILD study

To assess the prevalence of suspected structural lung parenchymal changes (ILDs) among post-COVID patients (ILD suspected subgroup).

To analyze and compare data of the ILD suspected and non-ILD subgroups.

2.3 Objectives of the post-COVID Remdesivir study

To evaluate the effects of RDV therapy received during the acute phase on patient centered and functional outcomes at long-COVID evaluation.

To further assess RDV therapy's impact on the resolution of symptom burden after the acute phase of COVID-19.

3. Methods

The studies discussed in the thesis were both based on retrospective evaluation and analysis of patients' data collected in a prospective registry at the post-COVID pulmonary care outpatient clinic of the Department of Pulmonology, Semmelweis University, between 01/02/2021 and 03/02/2023. The post-COVID pulmonary care facility aimed to diagnose long-COVID syndrome, and to follow and support affected patients.

The data analyzed in the first study (post-COVID ILD study) were sourced from the registry between February 2021 and February 2022. Furthermore, the post-COVID Remdesivir study (post-COVID RDV study) utilized a more extensive data set, drawn later from the post-COVID registry. Consequently, the data analyzed in that study were collected between 1 February 2021 and 3 February 2023.

In the post-COVD ILD study we enrolled 318 patients presenting to the post-COVID pulmonary care. The collected data was analyzed retrospectively, and the total patient population (N=318) was divided into 2 groups based on the low dose CT (LDCT) and other clinical findings (abnormal physical examination findings related to the respiratory system): ILD-suspected patients and non-ILD patients. The 2 groups were compared and analyzed for differences in anthropometric data, symptom burden, pulmonary function tests (PFTs) results, and additional therapy.

At the time of the post-COVID RDV study the prospective post-COVID registry included 470 patients. In our study we only enrolled the formerly hospitalized patients (N=293), dividing them into two groups by the applied treatment: patients who received additional antiviral RDV during the acute phase of COVID-19 (N=183) and the ones treated with only standard of care (SOC) (N=110). To control for potential confounders, in our statistical analysis we evaluated 2 comparable propensity score matched patient population based on the formerly received therapy (SOC+ RDV group if the patient received RDV and SOC, N=94; SOC group if the patient only received SOC treatment, N=94). We excluded individuals with chronic kidney disease, liver disease, those lost to follow-up, or cases with missing or inconsistent data related to hospitalization, patient history, or follow-up symptoms from this study. The 2 groups were compared for the primary endpoints of: asymptomatic status; at least 50% reduction of symptoms score at

post-COVID care; and for the secondary outcomes including quality of life (QoL) parameters, PFTs and 6-minute walk test (6MWT) results.

The prospective post-COVID registry was an online, well-structured platform which included all the collected data of patients presented at the post-COVID pulmonary care at the Dept. of Pulmonology. The registry included data on patients' previous health conditions and diseases; COVID-19 related history about hospitalization and received therapies; symptom burden at time of the acute phase and at time of the visit, during post-COVID condition. Furthermore, at the first post-COVID visit pulmonary function tests, 6-minute walk test and low-dose chest CT were assessed; and patients completed detailed questionnaires, which included the followings: Epworth Sleepiness Scale Score, visual analogue scale, Pittsburgh Sleep Quality Index, Fatigue Severity Scale and EQ-5D-3L questionnaire. Symptoms scores were determined by quantifying the number of symptom domains present in each patient during hospitalization and at time of post-COVID care visit, including fever/chills, cough, dyspnea, fatigue, sleepiness, insomnia, headache, palpitation, loss of smell/taste, upper respiratory symptoms, and gastrointestinal complaints, with a maximum score of 11.

In the post-COVID RDV study to address potential confounding factors in the analysis, propensity score matching (PSM) was employed. Given the significant difference in the use of ventilation therapy—a known predictor of post-COVID condition —between the two groups, PSM was stratified by ventilation status and conducted separately within each stratum to ensure an equal proportion of ventilated patients in both groups. Propensity scores were estimated using logistic regression based on 17 covariates. In both studies categorical variables were compared using either the chi-squared test or two-tailed Fisher's exact test, as appropriate; continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR); and were compared by Student's t-test or the Mann–Whitney U test. Kaplan–Meier survival curves were generated to illustrate the time to event outcomes with Cox proportional hazards tests used for group comparisons. To further account for confounding, multivariable Cox regression models were applied. IBM SPSS (IBM Corp., Armonk, NY, USA, version 28), Stata (StataCorp LLC, College Station, TX, USA, release 18) statistical software packages and Microsoft Excel were used for data analysis. In both studies P-value < 0.05 was defined as statistically significant.

4. Results

4.1 Results for the post-COVID ILD study

Our results mostly focused on patient reported and functional outcomes in this study. The prevalence of ILD suspected cases were 44 out of 318 total cases (13.8%). Patients suspected of having ILD were generally older and required hospitalization during their acute COVID-19 illness more frequently than the non-ILD group. While sex distribution did not differ significantly between groups, both cohorts had a higher proportion of male patients. Most individuals across both groups were overweight (BMI over 25). The time interval between hospitalization for acute COVID-19 and the post-COVID visit did not differ between groups.

At the time of the post-COVID pulmonary assessment, the most frequently reported persistent symptoms were fatigue (34%), dyspnea (25.2%), and cough (22.6%), with no significant differences observed between the two groups. These were followed by sleep-related issues, including insomnia (13.2%) and excessive daytime sleepiness (8.25%). Newly developed symptoms reported after the acute phase of the illness included insomnia (5.3%), palpitation (4.4%), fatigue (3.8%), and dyspnea (3.8%). Notably, new-onset cough (11.4% vs. 2.2%) and sleepiness (9.1% vs. 2.6%) were significantly more common in the suspected ILD group than in non-ILD patients. Persistent and new-onset symptom profile is shown in Figure 2/A and 2/B.

Pulmonary function testing revealed that ILD suspected patients exhibited significantly lower values in key respiratory function parameters, such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV), diffusion capacity of the lung for carbon monoxide (D_{LCO}), correlating with the possible underlying interstitial changes of the lung parenchyma, however also suggesting mixed ventilatory abnormalities (Table 1). Moreover, these patients did a significantly shorter distance during the 6MWT and experienced oxygen desaturation (>3%) more frequently (40.9% vs. 17.9%).

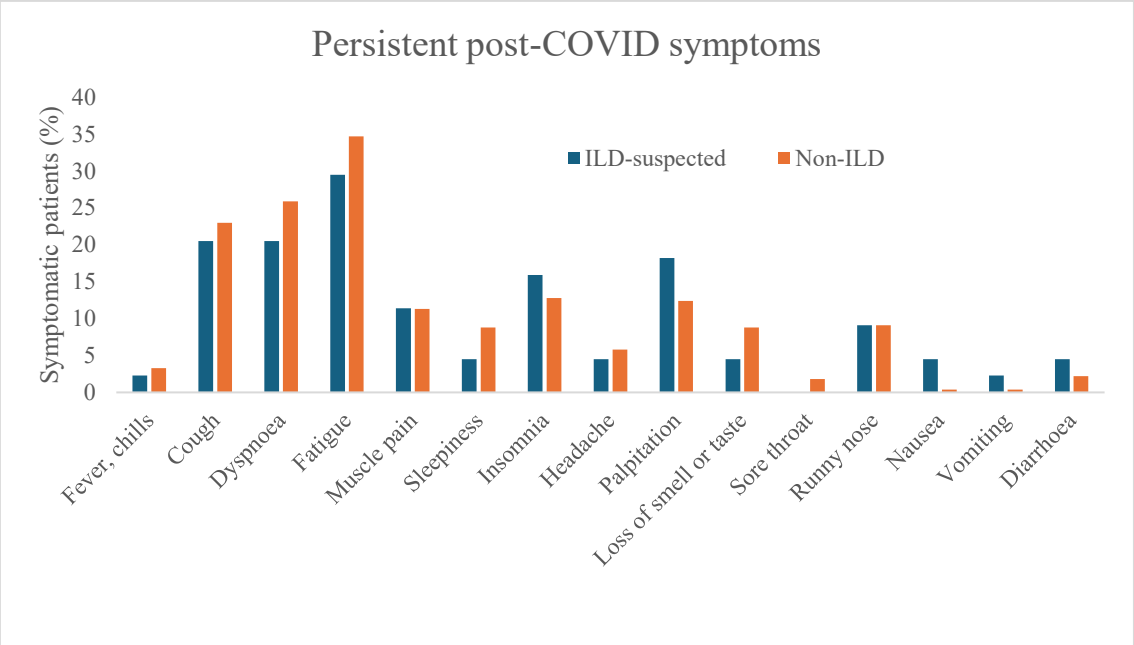

Figure 2/A: Proportion of patients with persistent post-COVID symptoms for each symptom domain. ILD: interstitial lung disease; unpublished figure.

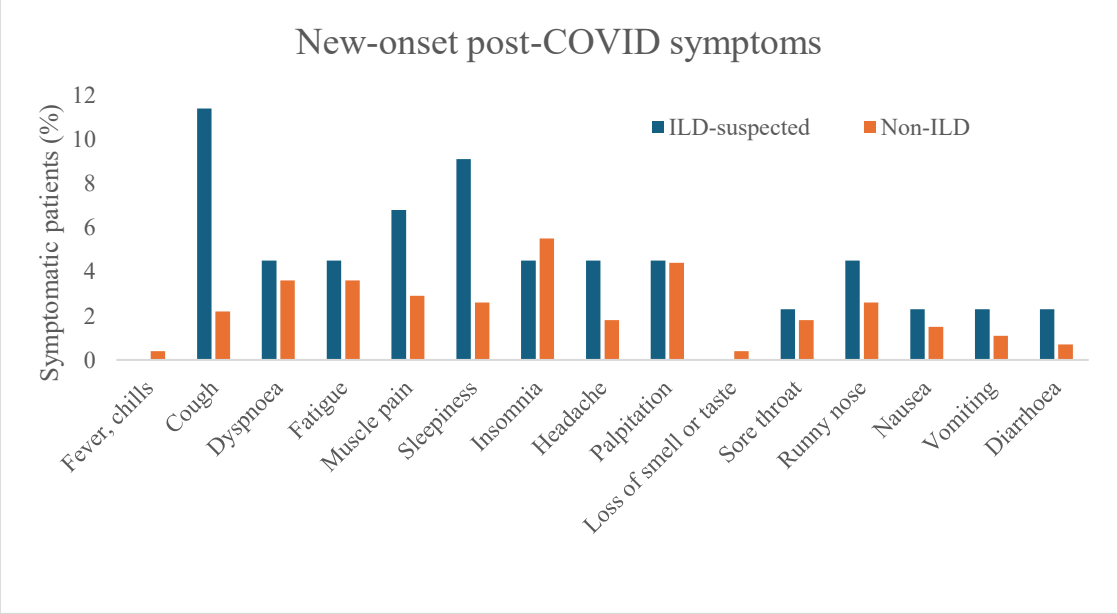

Figure 2/B: Proportion of patients with new-onset post-COVID symptoms for each symptom domain. ILD: interstitial lung disease; unpublished figure.

Table 2: Results of pulmonary function test from post-COVID ILD study. Significant p values highlighted in bold. Adapted from Fesu D et al: Post-COVID interstitial lung disease in symptomatic patients after COVID-19 disease. Inflammopharmacology. 2023 Apr;31(2):565-571. Under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Lung function test results	**All (N=318)**	**ILD suspected (N=44)**	**Non-ILD suspected (N=274)**	**P-value**
FVC (ref %)	82.7±16.3	76.7±18.1	83.8±15.7	**0.018**
FEV1 (ref. %)	87.3±17.7	83.5±19.1	87.9±17.4	0.171
FEV1/FVC (%)	77.4±23.3	66.7±33.4	79.3±20.5	**0.024**
TLC (ref. %)	94.3±24.6	85.6±28.1	95.8±23.7	**0.035**
RV (ref. %)	99.6±49.1	82.2±40.6	103.3±50.0	**0.014**
D_{LCO} (ref. %)	103.8±26.9	85.0±21.2	107.1±26.5	**<0.001**

D_{LCO}: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ref. %: reference %; RV: residual volume; TLC: total lung capacity

4.2. Results of the post-COVID Remdesivir study

There were no statistically significant differences between the two groups in terms of age, sex, BMI, pre-existing comorbidities, Charlson comorbidity index scores, or duration of hospital stay. The majority of patients were infected with pre-Delta VOCs, with similar distributions in both groups (SOC: 69.2% vs. SOC+RDV: 73.4%), and no significant differences were observed in variant type between the groups, and most of the patients exhibited pulmonary involvement of at least 10%. Oxygen therapy was required for a significant number of patients, and nearly all received antibiotics, corticosteroids, and anticoagulants as part of the standard treatment protocol during that period. Notably, oxygen supplementation (SOC: 80% vs. SOC+RDV: 94%, p=0.005) and corticosteroid administration (SOC: 88% vs. SOC+RDV: 97%, p=0.027) were significantly more prevalent in the SOC+RDV group. Patients managed with SOC alone presented for post-COVID pulmonary evaluation significantly later than those treated with RDV (median days: SOC: 97 vs. SOC+RDV: 68, p=0.003). At the time of post-COVID pulmonary follow-up, the majority of patients remained symptomatic, with no significant difference in symptom prevalence between the groups (SOC: 66% vs. SOC+RDV: 61%, p=0.449).

In the univariable analysis, patients in the SOC+RDV group achieved asymptomatic status and/or experienced at least a 50% reduction in symptom score significantly earlier following infection compared to those in the SOC group (unadjusted hazard ratio [HR] = 1.89, 95% confidence interval [CI]: 1.14–3.13, $p = 0.014$; and HR = 2.05, 95% CI: 1.44–2.94, $p < 0.001$, respectively) (Figure 3/A and 3/B). After adjusting for relevant covariates, including the use of oxygen therapy and corticosteroids, RDV treatment remained significantly associated with a more rapid achievement of asymptomatic status (adjusted HR = 2.28, 95% CI: 1.33–3.92, $p = 0.003$) and with ≥50% reduction in symptom burden (adjusted HR = 2.08, 95% CI: 1.43–3.02, $p < 0.001$). Additionally, infection with a later VOC and having a lower initial symptom burden were both independently associated with a faster complete resolution of symptoms. The proportional hazards assumption was satisfied for both multivariable models ($p = 0.320$ for the first model and $p = 0.761$ for the second model).

A detailed summary of patient-reported symptoms during the acute phase of COVID-19 and the post-COVID period is presented in Figure 4. The prevalence of sleep disturbances

during the post-COVID period was significantly lower in the RDV group compared to the SOC group (14% vs. 27%, $p = 0.029$), and a significantly greater proportion of patients in the RDV group experienced resolution of sleep disturbances following acute infection (48% vs. 31%, $p = 0.017$).

With respect to QoL parameters, scores on the PSQI questionnaires indicated significantly better sleep quality among patients treated with RDV (mean score: SOC: 7.66 vs. SOC+RDV: 5.90, $p = 0.025$). No statistically significant differences were observed between the two groups for PFTs results. Both FVC and the FEV_1/FVC ratio were below 80% in both cohorts, indicating the presence of generally mild, mixed ventilatory impairment. The 6MWT results were within normal limits for the majority of participants; however, oxygen desaturation exceeding 3% was observed in 21.5% of patients in the SOC group and 28% in the SOC+RDV group (non-significant difference).

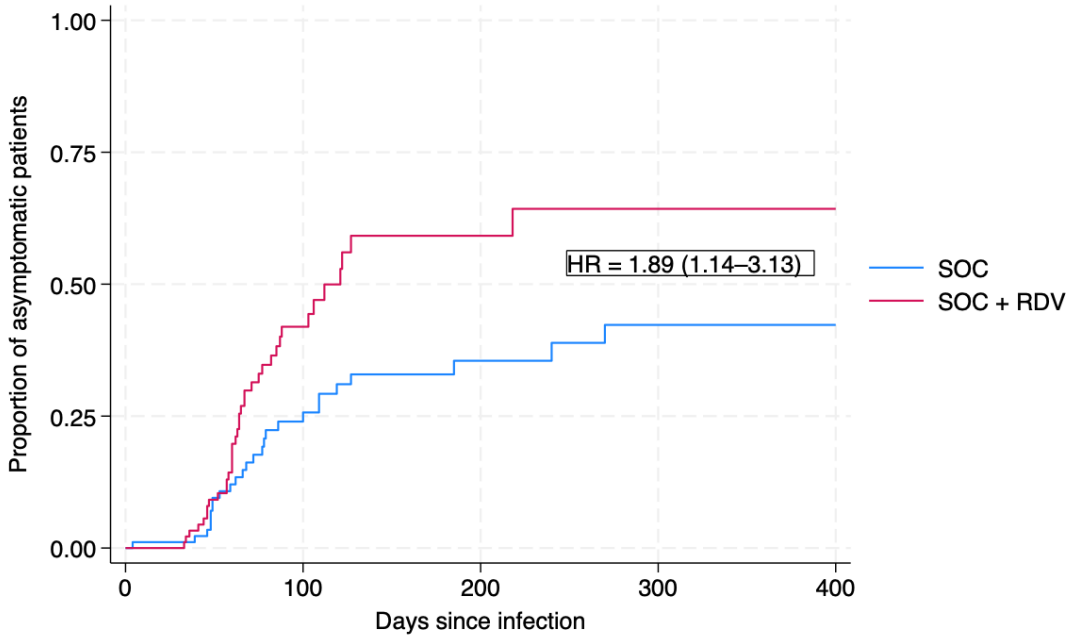

Figure 3/A: Kaplan-Meier curve of the proportion of asymptomatic patients over time since hospital admission (days); HR: hazard ratio; RDV: remdesivir; SOC: standard of care. Reproduced from Fésü D et al: Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

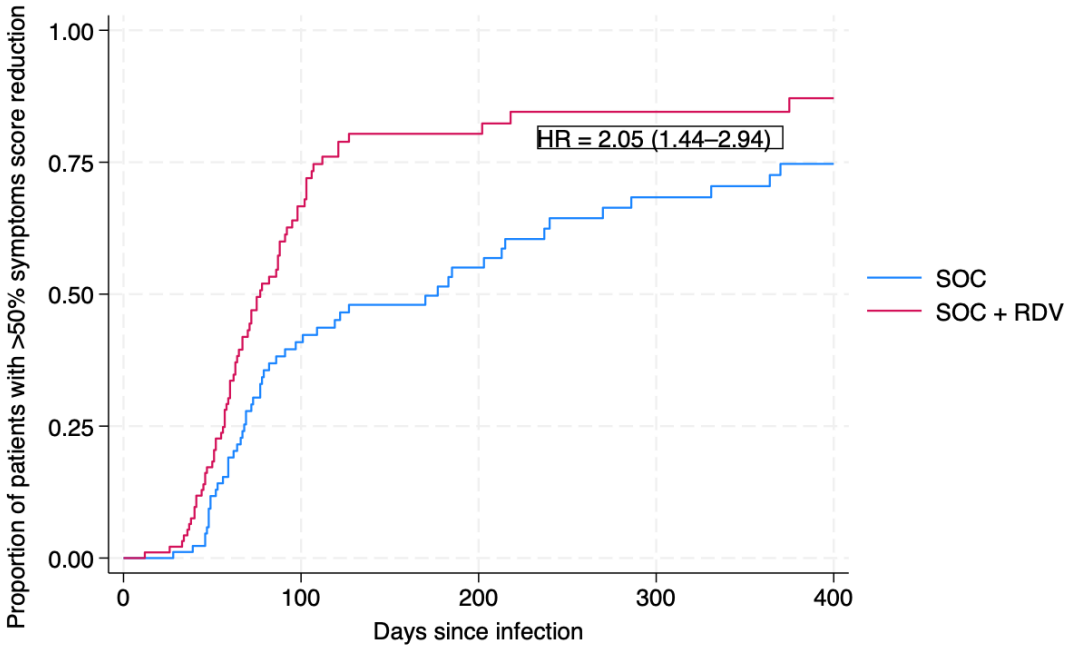

Figure 3/B. Kaplan-Meier curve of the proportion of patients ≥50% symptom score reduction over time since hospital admission (days). HR: hazard ratio; RDV: remdesivir; SOC: standard of care. Reproduced from Fésü D. et al: Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

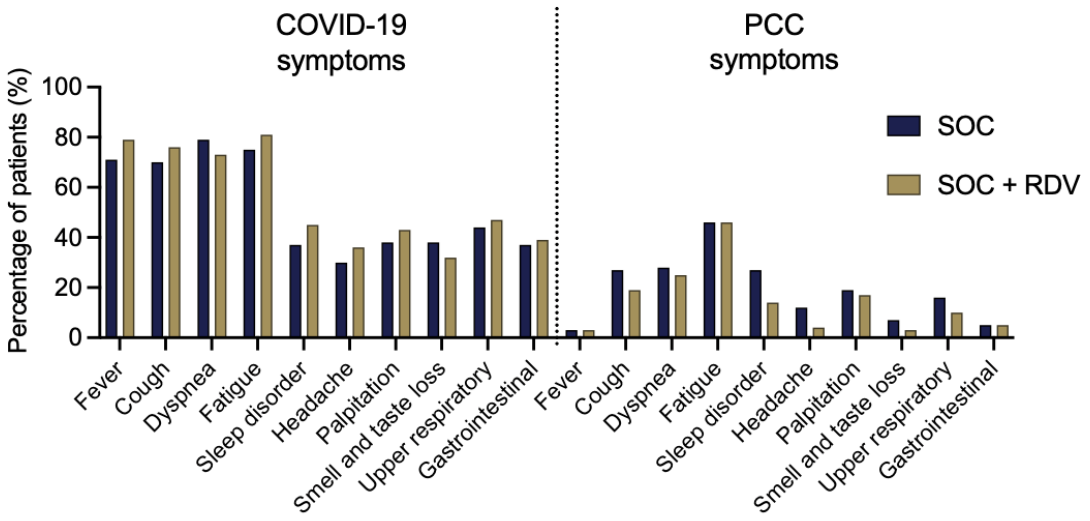

Figure 4. Proportion of symptomatic patients for each symptom domain experienced during COVID-19 infection and at the first post-COVID visit. PCC: post-COVID condition**,** RDV: remdesivir, SOC: standard of care. Adapted from Fésü D. et al: Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

5. Conclusions

The Department of Pulmonology at Semmelweis University has established a comprehensive registry system that is organized to facilitate the collection of patient data in the context of post-COVID pulmonary care. The data set includes results and findings derived from a range of sources, including general and COVD-19 history, symptoms, physical examination findings, radiological findings, functional status parameters and QoL-related questionnaires.

Two studies were conducted with different aims and approaches to assess post-COVID ILD and antiviral therapy's effect on long-COVID. In both studies, patients' characteristics were described. In the post-COVID ILD study, the ILD subgroup was found to be older and exhibited a similar sex distribution. In the post-COVID RDV study, two matched, comparable groups were established and analyzed, with no observed differences in patient characteristics. The symptom profile for both studies reflected the international data concerning long-COVID syndrome; patients most often reported respiratory symptoms, fatigue and sleep disturbances as persisting abnormalities after the acute infection.

The post-COVID ILD study revealed that in our patient population 13.8% of patients had ILD-suspected abnormalities based on LDCT and were subsequently referred for ILD-MDT. ILD-suspected patients were older, had been more often hospitalized during the acute infection and exhibited new-onset cough and sleepiness symptoms at a higher rate. ILD-suspected subgroup showed functional impairment based on 6MWT and PFT results, compared to the controls.

The post-COVID RDV study investigated the effect of previously used add-on to SOC RDV therapy on long-COVID outcomes in formerly hospitalized patients. In our matched cohort, the use of RDV was found to be associated with the earlier attainment of complete or at least 50% symptom resolution. Although there were no notable differences in functional outcomes including 6MWT and PFTs, RDV treated patients reported less sleep disturbances and better sleep quality. Our results indicated a possible beneficial effect of RDV in terms of symptom resolution after COVID19 infection.

6. Bibliography of the candidate's publications

6.1 Publications related to the thesis

- Fesu D, Polivka L, Barczi E, Foldesi M, Horvath G, Hidvegi E, Bohacs A, Muller V. Post-COVID interstitial lung disease in symptomatic patients after COVID-19 disease. Inflammopharmacology. 2023 Apr;31(2):565-571. doi: 10.1007/s10787-023-01191-3. Epub 2023 Mar 24. PMID: 36961666; PMCID: PMC10037361.
- Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43. doi: 10.1186/s12879-024-10398-w. PMID: 39789448; PMCID: PMC11715443.

6.2 Other publications

- Fesu D, Bohacs A, Hidvegi E, Matics Z, Polivka L, Horvath P, Czaller I, Sutto Z, Eszes N, Vincze K, Muller V. Remdesivir in Solid Organ Recipients for COVID-19 Pneumonia. Transplant Proc. 2022 Nov;54(9):2567-2569. doi: 10.1016/j.transproceed.2022.10.043. Epub 2022 Nov 2. PMID: 36400587; PMCID: PMC9626440.
- Fésü Dorottya, Bohács Anikó, Eszes Noémi, Vincze Krisztina, Fejér Bence, Maurovich-Horvát Pál, Müller Veronika: Interstitiális tüdőbetegségek multidiszciplináris megközelítése; 2021; Medicina Thoracalis, 74 évf. 4.