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

PhD thesis

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List of Abbreviations

6MWT	6-minute walk test
ACE2	angiotensin-converting enzyme 2
ALAT	alanine transaminase
ATS	American Thoracic Society
BMI	body mass index
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CHF	chronic heart failure
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CTD	connective-tissue diseases
DAD	diffuse alveolar damage
D_{LCO}	diffusion capacity of the lung for carbon monoxide
ECMO	extracorporeal membrane oxygenation
EMA	European Medicines Agency
ERS	European Respiratory Society
ESSS	Epworth Sleepiness Scale Score
FDA	U.S. Food and Drug Administration
$FEF_{25\%}$	forced expiratory flow at 25% of FVC

FEF25-75%	average flow between 25% and 75% of exhaled FVC
$FEF_{50\%}$	forced expiratory flow at 50% of FVC
$FEF_{75\%}$	forced expiratory flow at 75% of FVC
FEV_1	forced expiratory volume in 1 s
FSS	Fatigue Severity Scale
FVC	forced vital capacity
GGO	ground glass opacity
HFNO	high-flow nasal oxygen
HIV	human immunodeficiency virus
HP	hypersensitivity pneumonitis
HR	hazard ratio
HRCT	high resolution chest CT
HT	hypertension
ICU	intensive care unit
IIP	idiopathic interstitial pneumonia
ILD-MDT	interstitial lung diseases multidisciplinary team
ILDs	interstitial lung diseases
IP	interstitial pneumonia
IPF	idiopathic pulmonary fibrosis
IQR	interquartile range
K_{LCO}	transfer coefficient of the lung for carbon monoxide
LAM	lymphangioleiomyomatosis

LCH	Langerhans cell histiocytosis
LDCT	low dose CT
LMWH	low-molecular-weight heparin
LTFU	lost-to-follow-up
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mRNA	messenger ribonucleic acid
NASEM	The National Academies of Sciences, Engineering, and Medicine
NIH	National Institutes of Health
NIV	non-invasive ventilation
NNGYK	National Centre for Public Health and Pharmacy (Hungarian)
PAD	peripheral artery disease
PCC	post-COVID-19 condition
PCPF	post-COVID pulmonary fibrosis
PEmax	maximal expiratory mouth pressure
PFTs	pulmonary function tests
PImax	maximal inspiratory mouth pressure
PPF	progressive pulmonary fibrosis
PSM	propensity score matching
PSQI	Pittsburgh Sleep Quality Index
QoL	quality of life
RDV	remdesivir
RNA	ribonucleotide acid

RV	residual volume
SARS- CoV-2	Acute Respiratory Syndrome Coronavirus 2
SD	standard deviation
SmPC	summaries of product characteristics
SOC	standard of care
TIA	transient ischemic attack
TLC	total lung capacity
TMPRSS2	transmembrane serine protease 2
UIP	usual interstitial pneumonia
VAS	visual analogue scale
VOCs	variants of concern
WHO	World Health Organization

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"(1,2). 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 (1–4).

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(5–7).

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 (8,9).

Respiratory infections, particularly those caused by viruses and intracellular pathogens, affect the alveolar epithelial cells and alter or delay alveolar regeneration (10). SARS-CoV2 infection might lead to reactive epithelial lesions, diffuse alveolar damage (DAD), as well as thrombotic events in the small pulmonary vasculature (11–13). 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 (9,11,14)

The long-term consequences of acute severe COVID-19 pneumonia are not completely well-defined and 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 remdesivir (RDV) antiviral drug on the development of long-COVID, and on long-term symptom burden.

1.1. SARS-CoV-2 virus

The SARS-CoV-2 virus was first detected in December 2019 in Wuhan, China (15). The rapid and global spread of the virus has led to a pandemic outbreak and a serious health emergency. On 11 March 2020, the World Health Organization (WHO) declared the globally spreading infection as pandemic (16). The disease caused by the virus (COVID-19), the complications that arise, and the long-term consequences posed a significant challenge to medical science.

SARS-CoV-2, a member of the coronavirus family, is an enveloped virus with a positive single-stranded ribonucleotide acid (RNA) genome that was initially transmitted through zoonotic transmission. The first coronavirus to cause human disease was identified in the 1960s. In 2002, the SARS-CoV virus and in 2018 the Middle East Respiratory Syndrome coronavirus (MERS-CoV) virus caused an epidemic. Whole-genome sequencing of the novel coronavirus has revealed that it belongs to the genus of Betacoronavirus but is distinct from SARS-CoV and MERS-CoV, which caused the previous outbreaks (17,18).

Inhaled virus particles initially infect the nasal mucosa, where they adhere, replicate, and then escape from the cells (19). This stage of infection may be asymptomatic or may be associated with local symptoms (20,21). The cell-surface receptor for the virus is angiotensin-converting enzyme 2 (ACE2), to which the surface S protein of the virus binds; while the transmembrane serine protease 2 (TMPRSS2) is a serine protease that cleaves the S protein to allow virus entry (22). The infected ciliated cells are damaged, which likely facilitates disease progression, and the disintegrating cells can enter the lungs via respiration (14,23). A distinctive feature of the disease is the loss of smell, or anosmia, which has been observed in many patients. This is likely due to the infection of the epithelial cells of the olfactory epithelium (24).

The signaling cascade leading to the release of cytokines (also known as cytokine storm) initiates with the recognition of the virus as foreign, followed by the activation of transcription and regulatory factors responsible for the production of interferons and various cytokines (25). The subsequent phase of the disease commences upon the virus's

penetration in the respiratory tract, likely through micro aspiration of pharyngeal secretions. This process is particularly straightforward in older individuals, who exhibit a diminished cough reflex and reduced capacity to clear mucous membranes (14). In the bronchi, infection causes epithelial cell damage, immune cell infiltration and marked epithelial transformation in some cases (23). At this stage the cells that are the target of infection are again ciliated epithelial cells that express ACE2. In cases of moderate to severe, the infection may spread to the lower airways, resulting in damage to the alveolar epithelium. In this context, the ACE2-expressing type II alveolar epithelial cells represent the primary target cells of the virus, while the type I alveolar epithelial cells being damaged later by inflammation (26). Infection-induced damage in this region results in progressive hypoxia and pulmonary infiltration of inflammatory cells. Within 48 hours of infection, a significant increase in cytokine levels can be detected, which can lead to an uncontrolled activation of the immune system, the so-called cytokine storm syndrome. This can result in life-threatening conditions and lead to intensive care unit (ICU) admission (23,26,27).

1.2. COVID-19 disease

Pathological changes observed in patients with COVID-19 include the presence of pulmonary oedema, diffuse alveolar damage with the formation of hyaline membranes, development of reactive type II pneumocyte hyperplasia, formation of protein aggregates and fibrinous exudate, appearance of monocytes and macrophages in the alveolar spaces, and development of inflammatory infiltration. These primary lesions are the result of direct cellular damage and inflammation caused by the virus, whereas later lesions may be exacerbated by uncontrolled activation of the immune system (13,23,28).

Since the beginning of the pandemic, several studies have investigated the risk factors and predisposing factors leading to the serious condition of COVID-19. A meta-analysis from 2021 (initial waves of pandemic) identified older age, male gender, smoking, obesity, diabetes, hypertension, chronic obstructive pulmonary disease (COPD), cancer and elevated D-dimer levels as risk factors for the development of severe COVID-19 or death. Mortality was associated with male sex, older age and active smoking status. The mortality rate ranged from 3.14% to 61.51% in the studies included in the meta-analysis

(29). Since the onset of the COVID-19 pandemic, new variants of concern (VOCs) have emerged, and the vaccination status of patients has evolved. These developments may have influenced the risk of severe illness and mortality associated with COVID-19. The Centers for Disease Control and Prevention (CDC) has recently published an updated list of risk factors associated with an increased likelihood of experiencing at least one severe outcome of COVID-19 (30). This list, derived from systematic reviews and meta-analyses, includes: advanced age, belonging to an ethnic minority group, current or former smoking, obesity, cancer, cerebrovascular disease, chronic kidney disease, asthma, COPD, bronchiectasis, ILD, pulmonary embolism, pulmonary hypertension, cirrhosis, alcoholic and non-alcoholic liver disease, diabetes, cystic fibrosis, cardiovascular disease, human immunodeficiency virus (HIV), neurological and mental health conditions, physical inactivity, pregnancy, primary immunodeficiencies, organ transplantation, and states of immunosuppression (30,31).

The most prevalent symptoms of the disease are cough, fever, fatigue, and loss of olfactory and gustatory sensation (32). The clinical picture is further complicated by the occurrence of less common symptoms, including muscle aches, headache, sore throat, red eye and/or itching of the eyes, and diarrhea. Several studies have investigated the asymptomatic onset of infection and the asymptomatic course of the disease, which posed a significant challenge for the control of the epidemic (21,33,34). Several studies aimed to compare different VOC regarding symptom profile: patients infected with earlier variants (Wuhan, Alpha) were more likely to experience fever, dyspnea and smell/taste disorders, while later variants (particularly Omicron) were associated with milder symptoms (cold-like symptoms) (35,36).

Diagnosis of the disease is based on the detection of viral particles in respiratory samples. Polymerase chain reaction can be used to identify the genetic material of the virus, while rapid antigen tests can detect viral proteins (37,38).

A wide range of therapeutic options is described in several studies and guidelines (12,38,39), 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 (NIH) and the Hungarian

guideline 2024 for confirmed, hospitalized, adult COVID-19 patients will be presented on Figure 1 (12,38).

Both NIH and Hungarian guidelines recommend prompt initiation of symptom relief for all confirmed cases. Symptoms management therapy includes antipyretics, analgesics, and hydration, tailored to clinical presentation.

Further treatment decisions are influenced by disease severity. According to the Hungarian guideline prior to initiating treatment for a patient with COVID-19, the severity of the disease should be assessed, and risk stratification should be performed, considering the following parameters: oxygen demand, laboratory parameters (e.g. markers of inflammation; white blood cell count), clinical picture (including the presence of dyspnea and respiratory rate) and radiological abnormalities (extent of infiltration). Patients are classified into four categories: mild, moderate, severe, and critical disease; and can receive antiviral and supportive therapies.

The use of antiviral therapies differs according the need for hospitalization. For non-hospitalized patients at risk for severe disease NIH recommends starting antivirals early in the course of illness. Options include oral nirmatrelvir/ritonavir within 5 days, RDV via intravenous route within 7 days, or molnupiravir if first-line agents are contraindicated. For hospitalized patients, RDV is recommended in cases with or without oxygen requirements. It is often combined with dexamethasone, and in more severe cases, with immunomodulators such as baricitinib or tocilizumab. For patients receiving high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV), dexamethasone and baricitinib are recommended. RDV may be used if active viral replication is suspected or if the patient is within 10 days of symptom onset or immunocompromised. In cases requiring invasive ventilation or extracorporeal membrane oxygenation (ECMO), dexamethasone and a second immunomodulator are advised. There is insufficient evidence to support or oppose RDV in these cases.

RDV received approval for the treatment of COVID-19 from both the U.S. Food and Drug Administration (FDA)(40) and the European Medicines Agency (EMA)(41) and has been extensively used in clinical practice for managing the disease. It is a nucleotide prodrug derived from an adenosine analog. It targets the viral RNA-dependent RNA

polymerase, disrupting viral replication by causing premature termination of RNA synthesis. Evidence from the ACTT-1 trial and related studies suggests that early administration of RDV may mitigate disease progression, decrease mortality risk, and shorten hospitalization duration (42–46). During the early phases of the SARS-CoV-2 pandemic, RDV was administered to patients requiring varying levels of oxygen support, ranging from low- to high-flow oxygen therapy, as well as non-invasive ventilation (42,47,48). Nonetheless, evidence regarding its short-term efficacy in patients undergoing invasive mechanical ventilation was inconsistent (43,44,49–51) As a result, in the initial waves of the pandemic, RDV was typically not prescribed to patients receiving invasive ventilation or those presenting with elevated liver enzymes (alanine transaminase (ALAT) level increased to >10 times the upper limit of normal) or pre-existing renal impairment (<30 mL/min estimated glomerular filtration rate), in accordance with the EMA and FDA summaries of product characteristics (SmPC) available at the time (39,40,48) Subsequently, emerging data supported the expansion of RDV use to include individuals with impaired renal function (38,52) However, the long-term post-acute effects of RDV remain insufficiently characterized, with limited data available concerning its impact on post-COVID-19 condition (PCC) symptomatology and quality of life (QoL) (11,53).

Supportive care remains important in COVID-19 management, especially in hospitalized or critically ill patients. Oxygen therapy is administered based on oxygen saturation levels and respiratory rate. HFNO and NIV are used due to increasing hypoxemia, while invasive mechanical ventilation or ECMO may be required for patients with severe respiratory failure. Prophylactic anticoagulation with low-molecular-weight heparin (LMWH) is generally recommended unless contraindicated. Therapeutic dosing may be considered in patients with elevated D-dimer or confirmed thrombosis. Antibiotic and antifungal therapies may also be given to prevent/treat secondary infections in critical conditions. The use of convalescent plasma therapy is no longer recommended (12,38).

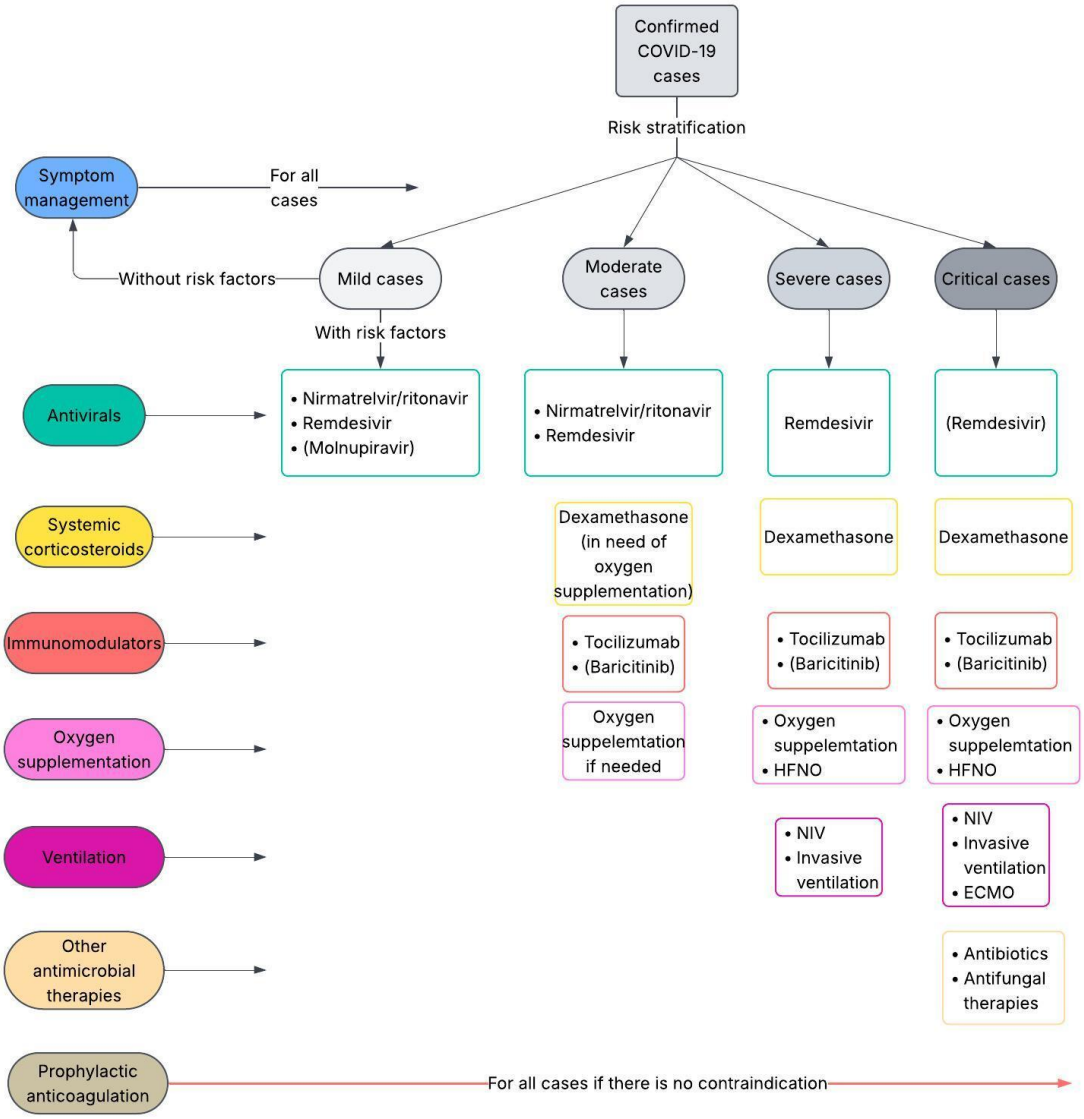

Figure 1: Therapies for COVID-19, unpublished figure based on: National Institutes of Health. Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) 2025;2019:1–243; and National Centre for Public Health and Pharmacy (NNGYK); Lakatos B. et al. Principles for the treatment of adults with confirmed 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.

Vaccination against the virus is widely considered as the most effective method of preventing severe infection (severe illness, hospitalization and death). It is recommended that booster doses of updated vaccine types are administered on an annual basis, due to the rapid mutation and heterogeneity of the strains (54). Currently, there are 5 types of vaccines approved by EMA for COVID-19 2024/25 campaign (these vaccines include both messenger ribonucleic acid (mRNA) and protein-based formulations) (54,55). Moreover, a number of studies have evaluated the long-term impact of vaccination, particularly in relation to long-COVID, and evidence has indicated that vaccination against SARS-CoV-2 prior to the manifestation of long-term symptoms is associated with a reduced risk of developing long-COVID (56,57). However, it has been observed that receiving vaccination during the course of long-term symptoms does not result in a substantial reduction of the symptom burden (57–59).

1.3. Long-COVID

Most individuals affected by COVID-19 recover from the acute disease without long term damage or residual symptoms, with an average recovery time of approximately four weeks after infection (1,4). However a proportion of patients report long-term symptoms and complications after the acute phase, present to healthcare facilities and experience an impaired quality of life (3,4,60). This complex chronic condition with various symptom clusters (persisting or emerging after infection) can be referred to as long-COVID-19 disease (long-COVID) or post-COVID-19 disease/condition (post-COVID). The most recent definition (The National Academies of Sciences, Engineering, and Medicine; NASEM) uses the term “long-COVID” and describes the condition as “Long COVID is an infection-associated chronic condition that occurs after 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 systems” (1,2) The underlying pathophysiological mechanisms are not completely well-known, and it may be difficult to distinguish long-COVID condition from other infection-related chronic conditions and/or the consequences of treatment or hospitalization, however long-COVID is not an exclusion diagnosis (2). The possible etiologies include aberrant inflammatory or antibody response for the acute phase, microvascular dysfunction, autoimmunity or direct organ damage by the acute disease (1,3,4,11,61). Currently no specific laboratory test or

indicator biomarkers are available for diagnosing long-COVID, and a positive rapid antigen test or serological test are no longer required to establish the diagnosis (1). Therefore, the diagnosis is based on clinical findings. The affected patients reported more than 200 symptoms of long-COVID, however the most common symptoms are fatigue, cough, shortness of breath, sleep disturbances and different forms of cognitive dysfunction (3,60,62). Patients can experience single or multiple symptoms or diagnosable conditions; and long-COVID can affect several organ systems (Figure 2) (1–3,61,63,64).

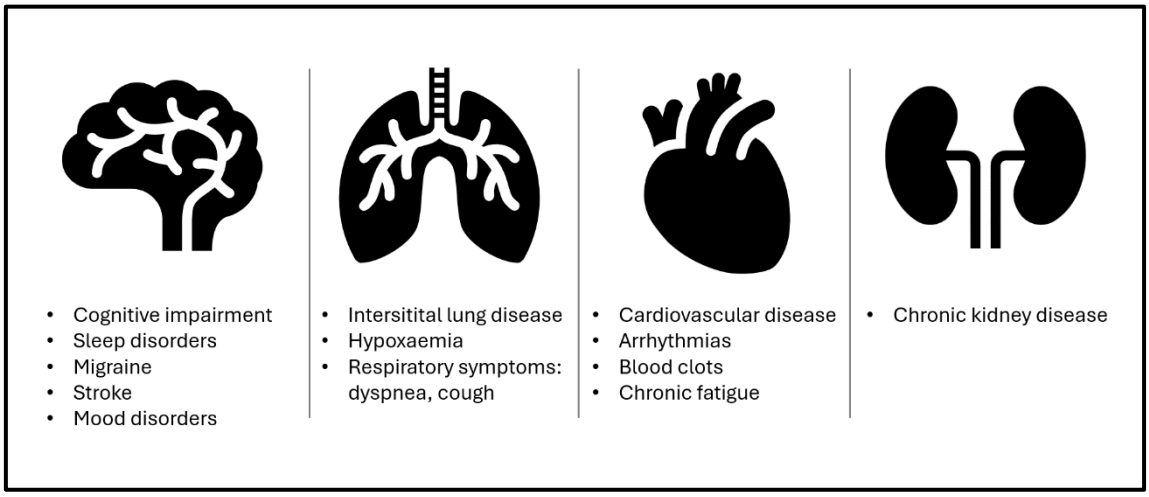

Figure 2: Long-COVID symptoms and involved organ systems (Modified; Reproduced with permission, from Ely EW, Brown LM, Fineberg H V. Long Covid Defined. N Engl J Med. 2024 Nov;391(18):1746–53., Copyright Massachusetts Medical Society)

Symptoms may be new onset, following initial recovery from an acute episode of COVID-19, may persist after the initial illness and fluctuate or regress/resolve by time, or may even develop after an asymptomatic acute phase (1,65). The severity (mild to severe) and duration (days to months) vary between individuals, and it can also accelerate pre-existing medical conditions and impair the patients' quality of life. The precise prevalence of long-COVID is difficult to determine due to heterogeneity in research methodologies, variations in post-COVID care settings, and inconsistent definitions of the condition (1,2,61). Nevertheless, recent meta-analyses and systematic reviews estimate that approximately 6–7% of adults previously infected with SARS-CoV-2 are affected by long COVID (4,61,66), and can develop in any person following COVID-19 disease, regardless of the variant of virus that caused the infection, sex, gender, age and

severity of the initial COVID-19 infection, or even in asymptomatic cases (3). Throughout the course of the pandemic, the risk of developing long-COVID decreased, influenced by the availability of vaccines and the emergence of various VOCs. Although individuals infected during the Omicron-dominant period had a lower likelihood of experiencing long-COVID compared to earlier phases, the risk remained substantial even within this group (67,68). The potential risk factors include female sex, older age, obesity, patients with more severe COVID-19 disease course and/or underlying medical conditions (69). The duration of recovery from long-COVID is typically between 4-9 months, however it can be longer in some cases (4,66), and it can be associated with the severity of the initial COVID-19 infection (70). Treatment options are mainly focused on personalized and holistic help and support, symptomatic relief and rehabilitation programs, since there is no approved long-COVID specific therapy or cure (1,3,4). However, clinicians must treat any emerging newly diagnosed, well-defined medical conditions, which may occur as part of long-COVID (4). The most effective way to prevent long-COVID is to prevent COVID-19 infection itself, or to reduce the chance of more severe COVID-19 disease, therefore personal hygiene; masks; and especially vaccination and adequate COVID-19 treatment (like potentially RDV) are considered as prevention methods for long-COVID (3,4,58,69,71).

1.4. Interstitial lung diseases

According to the definition of the Ministry of Human Resources, State Secretariat for Health, ILDs form a heterogeneous group of diseases with a common feature of cellular infiltration and/or extracellular matrix deposition in the distal (acinar) lung areas (5). The lesions originate in the endothelial membrane or alveolar epithelium and subsequently result in interstitial remodeling (5). In related diseases, diffuse inflammation and consequent fibrotic change of the interstitial space are characteristic features. The lesions that develop (fibrosis) are often irreversible and the course of the disease are usually chronic or subacute, however ILDs can manifest in acute forms as well, and acute exacerbations may happen over time (72). The exact prevalence of ILDs in Hungary is unknown, estimated at 10-20/100000 in men and 7-13/100000 in women (5), while in the USA the crude prevalence in 2019 was estimated at 179.7/100000 in males, and 218.9/100000 in female (6). The latest ATS/ERS/JRS/ALAT Clinical Practice Guideline

in 2022 established the definition of progressive pulmonary fibrosis (PPF) to describe and define the progressive fibrotic manifestation of any ILDs other than idiopathic pulmonary fibrosis (IPF) (7). Definition criteria of PFF is fulfilled if 2 of the followings apply for the patients in the past 1 year (with no other explanation): worsening respiratory symptoms; physiological evidence of disease progression (decline in forced vital capacity (FVC) >5%, or in diffusion capacity of the lung for carbon monoxide (D_{LCO}) >10%); radiological evidence of disease progression (confirmed on chest CT) (7). Various types of ILDs can manifest as PPF (e.g. IIPs; autoimmune-ILDs; exposure related ILDs; sarcoidosis) (7).

Diagnosis and treatment of patients with ILD is recommended in experienced centers, with close collaboration between different specialties. An ILD-multidisciplinary team (ILD-MDT) decision is essential for an accurate diagnosis. The Hungarian and international guidelines recommend that the ILD-MDT should include pulmonologists, radiologists and pathologists, with the added benefit of involving other specialists and disciplines (5,72,73).

The 2020 Hungarian guideline distinguishes between interstitial lung diseases of known etiology/associated with a known disease; and between diseases of unknown etiology, defining granulomatous ILD; rare ILD with well-defined clinicopathological lesions; and idiopathic interstitial pneumonia (IIP) subgroups (Figure 3) (5,74).

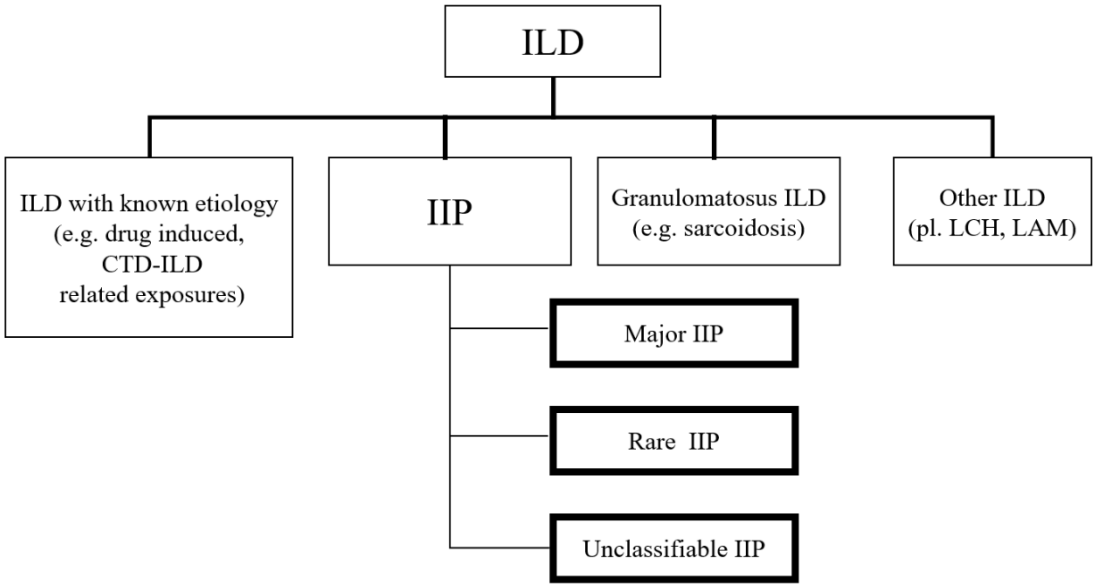

Figure 3: Classification of ILD according to the Hungarian guideline. Adapted from: Ministry of Human Resources – State Secretariat for Health. Health Care Guideline – Diagnosis of interstitial lung diseases (ILD) and treatment of idiopathic pulmonary fibrosis (IPF) in adults. 2020 *[Emberi Erőforrások Minisztériuma – Egészségügyért Felelős Államtitkárság. Egészségügyi szakmai irányelv - Az interstitialis tüdőbetegségek (ILD) diagnosztizálásáról és az idiopathiás tüdőfibrosis (IPF) kezeléséről felnőttekben. 2020,]* translated from Hungarian, CTD: connective-tissue diseases, IIP: idiopathic interstitial pneumonia; ILD: interstitial lung diseases; LAM: lymphangioleiomyomatosis; LCH: Langerhans cell histiocytosis.

Among the diseases of unknown etiology, the most common are IIPs, which group is divided into 3 main groups: major IIPs; rare IIPs and unclassifiable IIPs. Major IIPs are idiopathic pulmonary fibrosis (IPF); idiopathic nonspecific interstitial pneumonia; smoking related interstitial pneumonias; acute interstitial pneumonia; and cryptogenic organizing pneumonia (5). The group of rare IIPs include idiopathic lymphoid interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis (5,75). In addition to IIP,

ILDs of unknown etiology include two additional groups: granulomatous diseases (e.g. sarcoidosis); and pathologies with characteristic clinicopathological changes (e.g. Boeck's sarcoidosis, eosinophilic pneumonia, granulomatous polyangiitis) (5,76).

Among the ILDs with known etiology factors, several infectious agents (bacteria, viruses and fungi) can cause interstitial changes in the lungs (5). Another significant subset is associated with connective tissue diseases (CTD), including rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, and systemic lupus erythematosus. Additionally, systemic vasculitis—such as giant cell arteritis, Takayasu's arteritis, and microscopic polyangiitis—may involve pulmonary manifestations, leading to the development of ILDs. Fibrotic changes are also observed in the context of vascular pathologies, including antiphospholipid syndrome, various coagulopathies, and primary pulmonary hypertension. Moreover, ILDs may result from environmental or iatrogenic exposures, including pneumoconiosis due to inorganic dust, hypersensitivity pneumonitis (HP) triggered by organic antigens (e.g. feather), and pulmonary fibrosis induced by certain pharmacological agents or radiation therapy (e.g. bleomycin) (5,76).

The symptoms and the clinical picture of the patient may be the first findings to lead clinicians to the diagnosis of ILD. The most typical symptom is dyspnea on exertion and dry cough (72). Dyspnea is due to a thickened alveolo-capillary membrane caused by inflammation and scarring, which increases the diffusion pathway for gas exchange. Exercise-induced accelerated capillary blood flow shortens the contact time available for red blood cells to exchange gas, resulting in a significant reduction in oxygen uptake during physical activity (5,72,76). The diffusion and ventilation disturbance, which initially appears only as effort dyspnea, can later cause respiratory distress even at rest. Non-specific symptoms include chest pain and general weakness. Symptoms usually develop slowly (over a period of years) and the course of the disease itself can be slow (5). On physical examination, bilateral fibrotic crepitations (Velcro-like crepitations) are heard over the base on both sides, and finger clubbing can be noted (5).

Once ILD is suspected, it is important to take a detailed history, which should include exposure (dust, feathers, fungi, asbestos), occupational, smoking, lifestyle and medication history (5,72).

This should be followed by general pulmonary investigations: chest X-ray, pulmonary function test (PFT), measurement of diffusion capacity indicators. Respiratory function parameters typically show a restrictive ventilatory dysfunction (reduced lung expandability due to fibrosis). A restrictive pattern may be associated with reduced total lung capacity (TLC), reduced forced vital capacity (FVC); reduced residual volume (RV), reduced or normal forced expiratory volume in 1 s (FEV_1) and normal or occasionally elevated FEV_1/FVC ratios. In terms of diffusion parameters D_{LCO} and transfer coefficient of the lung for carbon monoxide (K_{LCO}) may be reduced as well (5,72,75–77).

Other tests to be performed are the 6-minute walk test (6MWT), blood gas analysis, and various laboratory tests (e.g. immuno-serological panel) (5,78).

For diagnosing ILDs chest imaging tests are recommended. The most sensitive way to detect abnormal lesions and patterns is high resolution chest CT (HRCT). Individual radio morphological patterns are characteristic of an ILD entity to varying degrees. In addition, the localization of the patterns is essential for the diagnosis, as it is also specific in some pathologies (5,7,72,77).

Regular follow-up examinations are recommended to monitor the patients' status. This should include respiratory function tests, 6MWT, blood gas analysis and HRCT scan in addition to physical examination (5,7,72)

If the HRCT pattern; the clinical picture and other investigations suggest the possibility of ILD, the patient should be referred for an ILD-MDT discussion, where experts of different disciplines (e.g. pulmonologist, rheumatologist, radiologist) will jointly review the case and formulate opinion and recommendations for further investigations and therapy (5,79).

Once an ILD is diagnosed and linked to a known etiology, subsequent evaluation and treatment should be guided by the established recommendations and clinical guidelines specific to the underlying disease or condition, with appropriate pharmacological therapy initiated accordingly. In cases of IPF, antifibrotic agents such as nintedanib or pirfenidone should be started promptly, as these medications have been shown to slow disease progression (5,7,72,80,81). Nintedanib may also be considered for patients with PPF.

Additionally, clinicians are encouraged to refer patients for participation in clinical trials enrolling individuals with progressive fibrotic ILDs (7,82).

1.5. Long-term lung specific effects of COVID-19 and post-COVID ILD

The lungs are the most frequently affected organs in COVID-19, with respiratory symptoms commonly reported by patients even during long-COVID period. These symptoms constitute one of the three principal symptom clusters associated with long-COVID—namely, respiratory and cardiac, cognitive, and general symptoms (60). In addition to respiratory complaints, individuals with long-COVID may develop structural abnormalities of the lung parenchyma, such as post-COVID ILD, which is often referred to in the literature as post-COVID pulmonary fibrosis (PCPF) (11,83). The reported prevalence of PCPF varies across studies, likely due to the absence of standardized outcome definitions and the heterogeneity of research methodologies employed (61). A recent meta-analysis estimated the prevalence of PCPF to be 44.9% among individuals after 6 months following hospitalization for COVID-19 (83). Other studies have identified chest CT abnormalities indicative of ILDs in approximately 23% of patients six months post-infection (8). Furthermore, inflammatory sequelae have been estimated to affect 50% of patients, while fibrotic sequelae were observed in 29% at a three-month follow-up (84). However, robust longitudinal data are still required to better characterize the trajectory and precise prevalence of PCPF over time. Potential risk factors for developing PCPF include former ICU admission, more severe COVID-19, comorbidity of hypertension and chronic lung diseases, excessive dyspnea in the acute phase, older age and higher inflammatory blood marker levels (9,11,83). A recent review estimated that the prevalence of persistent PCPF after 15 years will be approximately 9.2%, based on long-term data from SARS-CoV infection and current evidence on post-COVID and PCPF (9).

Several studies have investigated the underlying pathological mechanism of fibrosis that may arise as an adverse consequence of COVID-19 infection. The infection damages the alveolar epithelium, inducing the release of inflammatory and immune cytokines from the epithelium and macrophages, which leads to lung tissue damage (11,14) Activated inflammatory cells and damaged epithelial cells collectively contribute to basal

membrane injury, which then facilitates the migration and proliferation of interstitial fibroblasts within the alveolar space (9,28). The uncontrolled activation of fibroblasts may result in the fibrotic transformation of lung tissue. Other potential etiological factors that may contribute to the fibrosis and post-COVID ILD include acute respiratory distress syndrome in critically ill patients; direct barotrauma during invasive ventilatory support; and thromboembolism (61,85,86).

Pulmonary function tests in individuals with long-COVID frequently demonstrate abnormalities consistent with restrictive ventilatory impairment, accompanied by a reduced diffusing capacity (8,84,87,88) Although recent studies have indicated that pulmonary function may improve over time, even in severe cases (89), persistent functional impairment has been documented in some patients at 12 months post-infection (87) and, in certain cases, up to two years following the acute illness (8,89). These functional abnormalities may be associated with respiratory symptoms and structural lung changes; however, clinical symptoms often resolve earlier than measurable improvements in pulmonary function, and functional recovery may precede the resolution of chest CT abnormalities (8).

CT scans of patients who have recovered from COVID-19 show that most of them have post-acute lesions (typically ground glass opacity (GGO)(11) and reticulation (90–94). Some of these lesions may regress over time (14,95), while in others the abnormalities may persist long-term and result in occasionally fibrosis (8,96). Studies have shown that regression of CT abnormalities is more likely in younger patients and in those with less initial lung involvement (14). A 2-year follow-up study evaluated changes in CT abnormalities, reporting a decreased incidence of overall abnormalities and GGO, but an increased event rate of honeycombing and reticulation. No significant change was observed in the incidence of fibrotic patterns, which remained the most frequent abnormalities both in the short and long term. The study concluded that chest CT abnormalities may persist for up to two years in patients who experienced severe COVID-19 (96). Another study evaluating chest CTs at 6 and 24 months post-infection found that, in some cases, abnormalities may even progress over time (8). A meta-analysis investigating short-term post-COVID CT findings found that inflammatory-like

abnormalities tend to have a lower rate over time, whereas fibrotic changes did not demonstrate a similar time-related association. (84). In case of SARS-CoV infection—which shares certain pathophysiological similarities with COVID-19—more than half of the affected patients exhibited CT lesions in the short term, which gradually regressed over time. However, in approximately 5% of patients, interstitial abnormalities persisted even after 15 years (11,97).

Antifibrotics used for treating IPF and PPF may represent a potential therapeutic option for post-COVID fibrosis as well. A study has investigated whether pirfenidone has a beneficial effect on the improvement of FVC and HRCT scores during the long-COVID phase (98). Based on their findings, there was no significant difference between the placebo-treated and pirfenidone-treated groups in FVC, HRCT scores, or QoL improvement (98). Another study is currently ongoing to evaluate the effect of nintedanib on the progression of post-COVID fibrosis and on FVC changes over time (99). COVID-19 vaccination policies and guidelines do not currently include considerations for reducing the risk of long-COVID (61), however, emerging data suggest that vaccination may also lower the risk of PCPF (9,100).

2. Objectives

2.1 General objectives of the studies

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

2.2 Objectives of the post-COVID ILD study

1. To assess the prevalence of suspected structural lung parenchymal changes (ILDs) among post-COVID patients (ILD suspected subgroup).
2. To analyze and compare data of the ILD suspected and non-ILD subgroups.

2.3 Objectives of the post-COVID Remdesivir study

1. To evaluate the effects of RDV therapy received during the acute phase on patient centered and functional outcomes at long-COVID evaluation.
2. To further assess RDV therapy's impact on the resolution of symptom burden after the acute phase of COVID-19.

3. Methods

3.1 Study population

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. At the time of the initial VOCs patients infected in pre-Delta era (before 1st of Sept. 2021) or Delta era (1st Sept. 2021- 1st Jan. 2022), with persisting symptoms were referred for post-COVID care, mostly 4-12 weeks after the acute phase of the infection. Following Delta VOC (Omicron era from the 1st of Jan. 2022), the policy has been changed, and evaluation was offered for all patients. During their acute phase of COVID-19, evaluated patients were treated at our department, any other Hungarian hospital, or at home if hospitalization was not needed. Patients presented for post-COVID evaluation to our facility were mainly affected by COVID-19 with significant respiratory involvement.

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 (Figure 4).

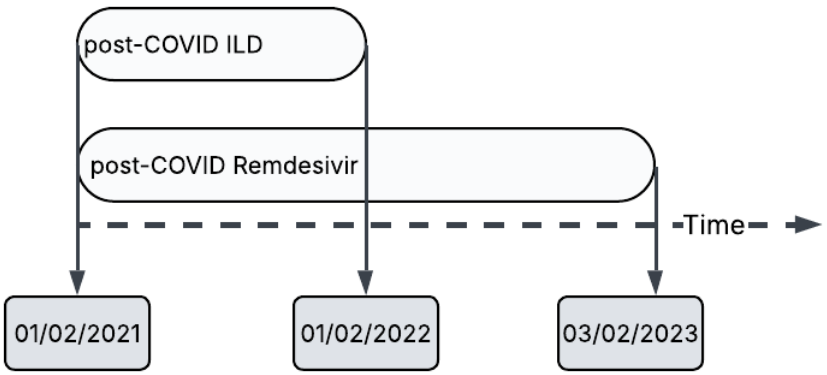

Figure 4: Timeline of the studies included in the thesis; unpublished figure; ILD: interstitial lung disease.

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 (Figure 5). The 2 groups were compared and analyzed for differences in anthropometric data, symptom burden, PFTs results, and additional therapy. All patients exhibiting persistent ILD-like changes on LDCT (ILD-suspected group) were referred to ILD-MDT meetings. The ILD-MDT oversaw the diagnostic process and provided recommendations regarding further investigations and treatment. The results of the consecutive ILD-MDT meetings, including the definitive diagnosis of ILDs, were not available at the time of study and the publication; however, had been included in a subsequent evaluation. Among the ILD-suspected cases there were no cases with known history of previously diagnosed ILD.

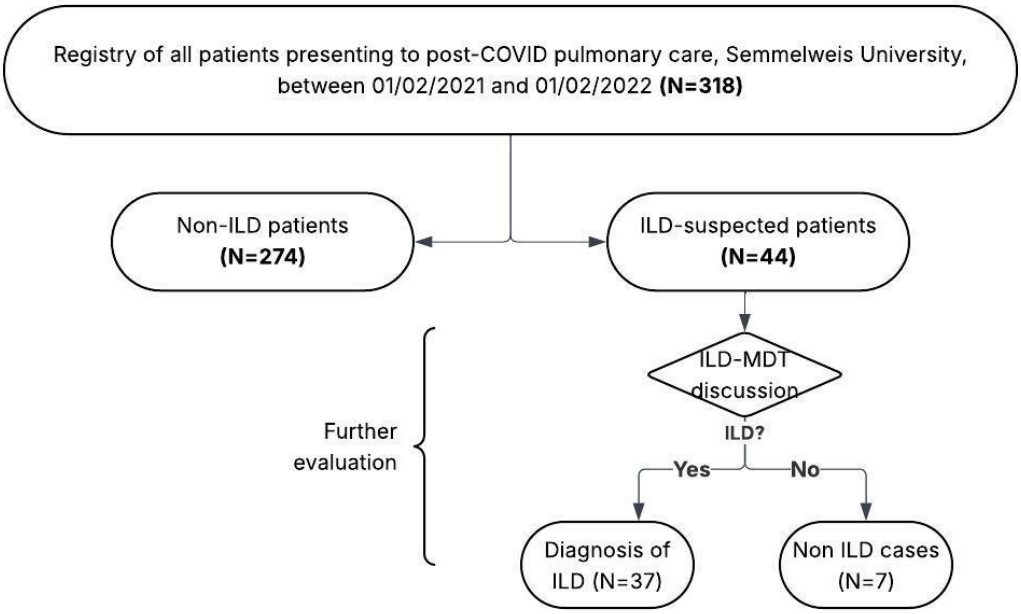

Figure 5: Flowchart of patient selection for the post-COVID ILD study; unpublished figure; ILD: interstitial lung disease; ILD-MDT: interstitial lung disease multidisciplinary team discussion.

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) (Figure 6). Regarding SOC therapy, almost all patients received antibiotics, corticosteroids, and anticoagulants as part of the standard treatment protocol during that period (101). RDV was used in all suitable cases according to the actual SmPC of the drug, where the patient has agreed to the therapy, needed oxygen supplementation and the drug was available at the hospital. 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 QoL parameters, PFTs and 6MWT results (described in details in the next section) (78,102–108).

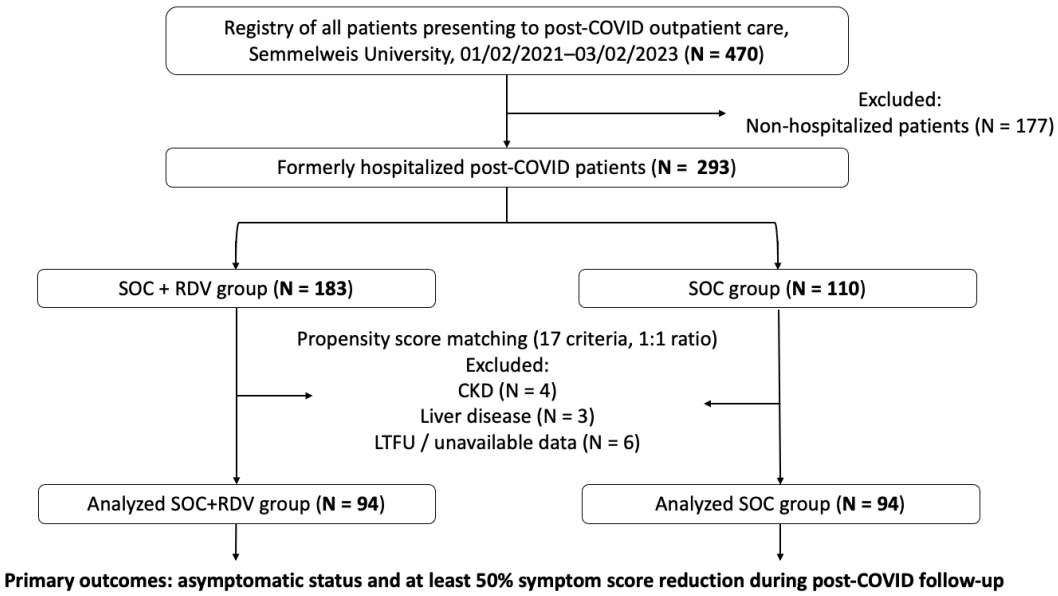

Figure 6: Study flow-chart showing the attainment of the analyzed comparison groups. Reproduced from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) CKD: chronic kidney disease, LTFU: lost-to-follow-up, RDV: remdesivir, SOC: standard of care.

3.2 Data collection

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. (Figure 7). 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 PFTs, 6MWT and LDCT were assessed (109); and patients completed detailed QoL questionnaires, which included the followings: Epworth Sleepiness Scale Score (ESSS), visual analogue scale (VAS), Pittsburgh Sleep Quality Index (PSQI), Fatigue Severity Scale (FSS) and EQ-5D-3L questionnaire (78,104–107). PFTs were conducted in accordance with the

guidelines established by the American Thoracic Society and European Respiratory Society (ATS/ERS) (103), measuring FVC, FEV_1, TLC, and RV. The D_{LCO} was measured by using the single-breath carbon monoxide uptake method, and the K_{LCO} was subsequently calculated (102). Respiratory muscle strength was evaluated by recording maximal inspiratory mouth pressure (PImax) and maximal expiratory mouth pressure (PEmax) (108). All pulmonary function measurements were pre-bronchodilator and were performed using the PDD-301/s device (Piston, Budapest, Hungary). The patients did the 6MWT following the ATS/ERS guidelines (78); outcomes as 6-minute walk distance, dyspnea on scale (BORG) (110), heart rate and oxygen saturation at start and at end were reported. Regarding COVID-19 related history, in most of the cases chest CT scan performed at the beginning of hospitalization for COVID-19 was available, and for our analysis we defined 5 groups according to lung involvement: <10%; 10-24%, 25-49%, 50-74% and ≥75% for the total lungs. When collecting symptom burden data, the registry categorized symptoms into three main groups—those experienced during the acute phase of COVID-19 (COVID-19 symptoms), those that persisted for an extended period after the acute infection (persistent symptoms), and those that either newly emerged or reappeared after initially resolving (new-onset symptoms)—with post-COVID symptoms including both persistent and new-onset symptoms. 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. These symptom domains were predefined at the initiation of the registry, in alignment with institutional protocols for assessing COVID-19 and post-COVID related symptoms and were registered by questionnaires completed at post-COVID care visit.

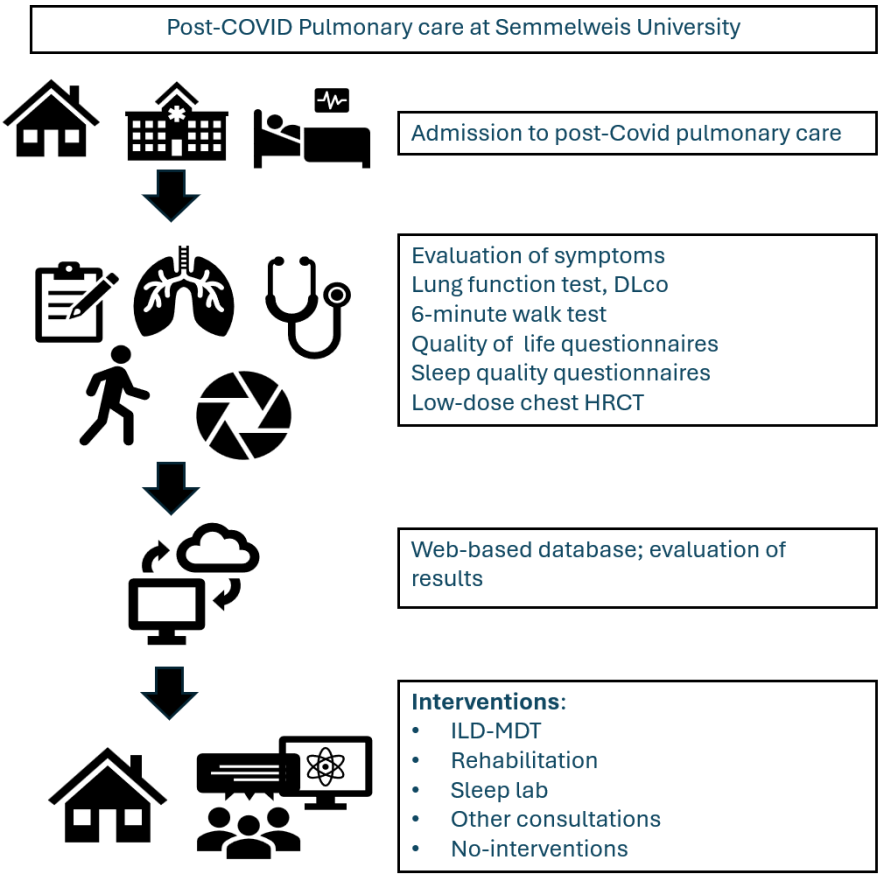

Figure 7: Post-COVID pulmonary care at Semmelweis University, Department of Pulmonology, unpublished figure; D_{LCO}: diffusion capacity of the lung for carbon monoxide, ILD-MDT interstitial lung disease multidisciplinary team discussion.

In both studies data about vaccination status was not available because its collection was not required when the registry was first established, which occurred before vaccines became accessible. In Hungary, the vaccination campaign initially focused on high-risk groups, such as healthcare professionals, and was only extended to the general public toward the end of the pre-Delta period. As a result, the majority of patients included in the analysis were likely to be not fully vaccinated at the time they contracted the infection.

The studies were designed in accordance with the 1964 Helsinki declaration and its later amendments (111), and the retrospective protocol was approved by the ethical committee of the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE RKEB 145/2022 and 147/2022).

3.3 Statistical analysis

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 (112)—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: age, sex, body mass index (BMI), VOC, COPD, asthma, diabetes mellitus, coronary artery disease (CAD), chronic heart failure (CHF), peripheral artery disease (PAD), history of stroke or transient ischemic attack (TIA), Charlson Comorbidity Index (a scoring system predicting 10-year survival in patients with multiple comorbidities) (113), use of antibiotics, corticosteroids, anticoagulants, oxygen supplementation, and favipiravir. A 1:1 nearest-neighbor matching algorithm without replacement was applied to construct comparable groups. In both studies categorical variables were compared using either the chi-squared test or two-tailed Fisher's exact test, as appropriate. In both studies continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. Comparisons of continuous variables were conducted using Student's t-test or the Mann–Whitney U test. Additionally, in the post-COVID RDV study Kaplan–Meier survival curves were generated to illustrate the time to event outcomes (asymptomatic state and ≥50% reduction in symptom score), with Cox proportional hazards tests used for group comparisons. To further account for confounding, multivariable Cox regression models were applied. Covariates included in these models were selected based on their association with the variable of interest (RDV use) and predefined endpoints. Variables demonstrating a trend toward association in univariable regression analyses, and those deemed clinically relevant were incorporated. Variables with more than 5% missing data, including the extent of lung involvement, were excluded from the regression analysis. For variables with less than 5% missing data, simple imputation using the median or mode was applied (e.g., BMI: median =29.6; VOC: mode =1, pre-Delta variant). Proportional hazard assumptions were evaluated using the Schoenfeld residuals test. 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 Post-COVID ILD study

Our results mostly focused on patient reported and functional outcomes in this study. Key data on patient demographics, lung function, 6MWT outcomes, symptom profiles and therapies used are presented in Table 1, 2, 3, 4 and 5. 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 8/A and 8/B.

Pulmonary function testing revealed that ILD suspected patients exhibited significantly lower values in key respiratory function parameters, such as FVC, FEV_1, FEV_1/FVC ratio, TLC, RV, D_{LCO}, and K_{LCO}, correlating with the possible underlying interstitial changes of the lung parenchyma, however also suggesting mixed ventilatory abnormalities. Moreover, these patients did a significantly shorter distance during the 6MWT and experienced oxygen desaturation (>3%) more frequently (40.9% vs. 17.9%).

Table 1: Patients characteristics for the post-COVID ILD study. Significant p values highlighted in bold. Adapted from 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 . under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Patient characteristics	**ALL**	**ILD suspected**	**Non-ILD suspected**	**p-value**
N (%)	318	44 (13.8)	274 (86.2)	-
Age (years)	53.1±15.2	64.0±12.3	51.3± 14.9	**<0.001**
Sex (female:male; N)	133:185	14:30	119:155	0.147
Time between hospital discharge and post-COVID visit (months)	2.6±2.3	2.4±2.3	2.7±2.3	0.501
Not-hospitalized patients, N (%)	100 (31.4)	7 (15.9)	93 (33.9)	**0.017**
BMI (kg/m2)	30.2±7.1	29.1±4.2	30.0±6.8	0.168

BMI: body mass index; ILD: interstitial lung disease.

Table 2: Results of pulmonary function test from post-COVID ILD study. Significant p values highlighted in bold. Adapted from 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 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 (L)	3.4±1.0	3.0±1.0	3.5±1.0	**0.009**
FVC (ref. %)	82.7±16.3	76.7±18.1	83.8±15.7	**0.018**
FEV_1 (L)	2.9±0.9	2.5±0.8	2.9±0.9	**0.004**
FEV_1 (ref. %)	87.3±17.7	83.5±19.1	87.9±17.4	0.171
FEV_1/FVC (%)	77.4±23.3	66.7±33.4	79.3±20.5	**0.024**
TLC (L)	5.7±4.0	6.5±9.6	5.6±1.6	0.528
TLC (ref. %)	94.3±24.6	85.6±28.1	95.8±23.7	**0.035**
RV (L)	2.15±1.6	2.1±0.9	2.2±1.6	0.604
RV (ref. %)	99.6±49.1	82.2±40.6	103.3±50.0	**0.014**
$FEF_{25\%}$ (L/sec)	6.2±2.04	6.0±1.9	6.3±2.1	0.324
$FEF_{25\%}$ (ref. %)	92.9±5.3	88.8±24.2	93.8±25.6	0.294
$FEF_{50\%}$ (L/sec)	3.6±1.3	3.2±1.0	3.7±1.3	**0.007**
$FEF_{50\%}$ (ref. %)	81.4±28.9	75.1±25.5	82.7±29.5	0.136
$FEF_{75\%}$ (L/sec)	1.2±0.6	0.9±0.4	1.2±0.6	**<0.001**
$FEF_{75\%}$ (ref. %)	120.4±62.7	133.5±75.7	118.1±60.0	0.223

FEF25-75% (L/sec)	3.5±2.6	2.9±1.0	3.6±2.8	**0.002**
FEF25-75% (ref. %)	113.3±37.1	118.7±39.7	112.3±36.7	0.347
Raw (kPa*s/L)	0.4±2.7	0.2±0.1	0.5±2.9	0.231
D_{LCO} (mmol/min/kPa)	9.3±5.3	7.2±2.3	9.7±5.6	**<0.001**
D_{LCO} (ref. r%)	103.8±26.9	85.0±21.2	107.1±26.5	**<0.001**
K_{LCO} (mmol/min/kPa/L)	2.1±8.1	4.6±20.7	1.7±0.4	0.375
K_{LCO} (ref. %)	105.5±26.8	89.5±24.7	108.4±26.2	**<0.001**
PImax (kPa)	7.8±3.4	7.9±3.5	7.8±3.4	0.914
PEmax (kPa)	9.2±3.4	9.1±3.8	9.2±3.3	0.794

D_{LCO}: diffusion capacity of the lung for carbon monoxide, $FEF_{25\%}$: forced expiratory flow at 25% of FVC; FEF25-75%: average flow between 25% and 75% of exhaled FVC; $FEF_{50\%}$: forced expiratory flow at 50% of FVC; $FEF_{75\%}$: forced expiratory flow at 75% of FVC; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; K_{LCO}: transfer coefficient of the lung for carbon monoxide; PEmax: maximal expiratory mouth pressure; PImax: maximal inspiratory mouth pressure; ref. %: reference %; RV: residual volume; TLC: total lung capacity

Table 3: Result from the 6-minute walk test from the post-COVID ILD study. Significant p values highlighted in bold. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

6MWT results:	**ALL (N=318)**	**ILD suspected (N=44)**	**Non-ILD suspected (N=274)**	**p - value**
6MW distance (m)	455.1±113	395.6±159.6	464.9±101	**0.0110**
Heart rate at start (1/min)	85.67±13.9	85.8±13.3	85.7±14.0	0.9660
Heart rate at end (1/min)	199.1±22.4	118.5±24.3	119.2±22.1	0.8490
Oxygen saturation at start (%)	96.3±1.9	95.9±1.5	96.4±2.1	0.3400
Oxygen saturation at end (%)	89.5±6.7	88.0±7.9	90.1±6.2	0.3200
Patients with desaturation (>3%) N (%)	67 (21.1%)	18 (40.9%)	49 (17.9%)	**0.0005**

6MW: 6-minute walk; 6MWT: 6-minute walk test

Table 4: Applied therapies during the acute phase of COVID-19 in case of patients analyzed in the post-COVID ILD study. Significant p values highlighted in bold. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

COVID-19 therapy N (%)	**ALL (N=318)**	**ILD suspected (N=44)**	**Non-ILD suspected (N=274)**	**p-value**
Antibiotics	219 (69.9%)	35 (79.5%)	184 (67.2%)	0.099
Favipiravir	46 (14.5%)	8 (18.2%)	38 (13.9%)	0.450
Remdesivir	145 (45.6%)	25 (56.8%)	120 (43.8%)	0.107
Reconvalescent plasma	17 (5.3%)	3 (6.8%)	14 (5.1%)	0.640
Systemic corticosteroids	221 (69.5%)	37 (84.1%)	184 (67.2%)	**0.024**
Anticoagulants	218 (68.6%)	36 (81.8%)	182 (66.4%)	**0.041**
Oxygen supplementation	208 (65.4%)	36 (81.8%)	172 (62.8%)	**0.014**
Non-invasive ventilatory support	57 (17.9%)	9 (20.5%)	48 (17.5%)	0.637
Invasive ventilatory support	15 (4.7%)	1 (2.3%)	14 (5.1%)	0.410

Table 5: Symptom burden of patients analyzed in the post-COVID ILD study. Significant p values highlighted in bold. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Patients with persisting symptoms since hospital discharge: N (%)	**ALL (N=318)**	**ILD suspected (N=44)**	**Non-ILD suspected (N=274)**	**p-value**
Fever, chills	10 (3.1%)	1 (2.3%)	9 (3.3%)	0.721
Cough	72 (22.6%)	9 (20.5%)	63 (23.0%)	0.709
Dyspnea	80 (25.2%)	9 (20.5%)	71 (25.9%)	0.439
Fatigue	108 (34%)	13 (29.5%)	95 (34.7%)	0.505
Muscle pain	36 (11.3%)	5 (11.4%)	31 (11.3%)	0.992
Sleepiness	26 (8.2%)	2 (4.5%)	24 (8.8%)	0.344
Insomnia	42 (13.2%)	7 (15.9%)	35 (12.8%)	0.569
Headache	18 (5.7%)	2 (4.5%)	16 (5.8%)	0.730
Palpitation	42 (13.2%)	8 (18.2%)	34 (12.4%)	0.294
Loss of smell or taste	26 (8.2%)	2 (4.5%)	24 (8.8%)	0.344
Sore throat	5 (1.6%)	0 (0%)	5 (1.8%)	0.366
Runny nose	29 (9.1%)	4 (9.1%)	25 (9.1%)	0.994
Nausea	3 (0.9%)	2 (4.5%)	1 (0.4%)	**0.008**
Vomiting	2 (0.6%)	1 (2.3%)	1 (0.4%)	0.137
Diarrhea	8 (2.5%)	2 (4.5%)	6 (2.2%)	0.354

Patients with new symptoms since hospital discharge: N (%)	**ALL (N=318)**	**ILD suspected (N=44)**	**Non-ILD suspected (N=274)**	**p-value**
Fever, chills	1 (0.3%)	0 (0%)	1 (0.4%)	0.688
Cough	11 (3.5%)	5 (11.4%)	6 (2.2%)	**0.002**
Dyspnea	12 (3.8%)	2 (4.5%)	10 (3.6%)	0.772
Fatigue	12 (3.8%)	2 (4.5%)	10 (3.6%)	0.772
Muscle pain	11 (3.5%)	3 (6.8%)	8 (2.9%)	0.189
Sleepiness	11 (3.5%)	4 (9.1%)	7 (2.6%)	**0.028**
Insomnia	17 (5.3%)	2 (4.5%)	15 (5.5%)	0.800
Headache	7 (2.2%)	2 (4.5%)	5 (1.8%)	0.254
Palpitation	14 (4.4%)	2 (4.5%)	12 (4.4%)	0.960
Loss of smell or taste	1 (0.3%)	0 (0%)	1 (0.4%)	0.689
Sore throat	6 (1.9%)	1 (2.3%)	5 (1.8%)	0.839
Runny nose	9 (2.8%)	2 (4.5%)	7 (2.6%)	0.460
Nausea	5 (1.6%)	1 (2.3%)	4 (1.5%)	0.162
Vomiting	4 (1.3%)	1 (2.3%)	3 (1.1%)	0.515
Diarrhea	3 (0.9%)	1 (2.3%)	2 (0.7%)	0.326

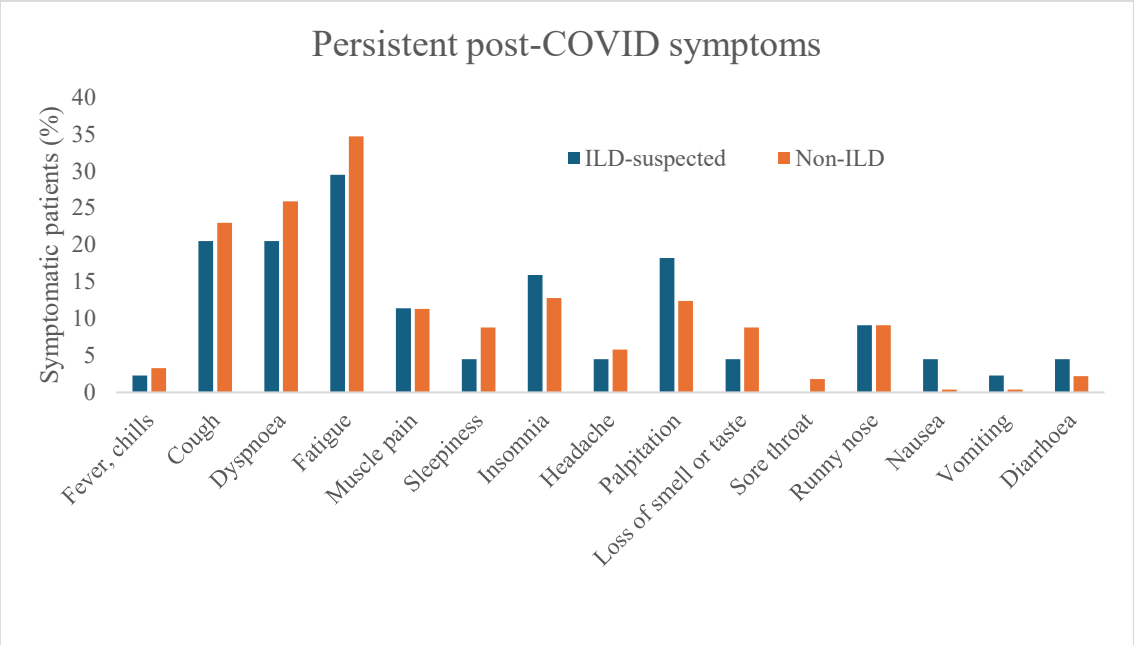

Figure 8/A: Proportion of patients with persistent post-COVID symptoms for each symptom domain. ILD: interstitial lung disease; unpublished figure.

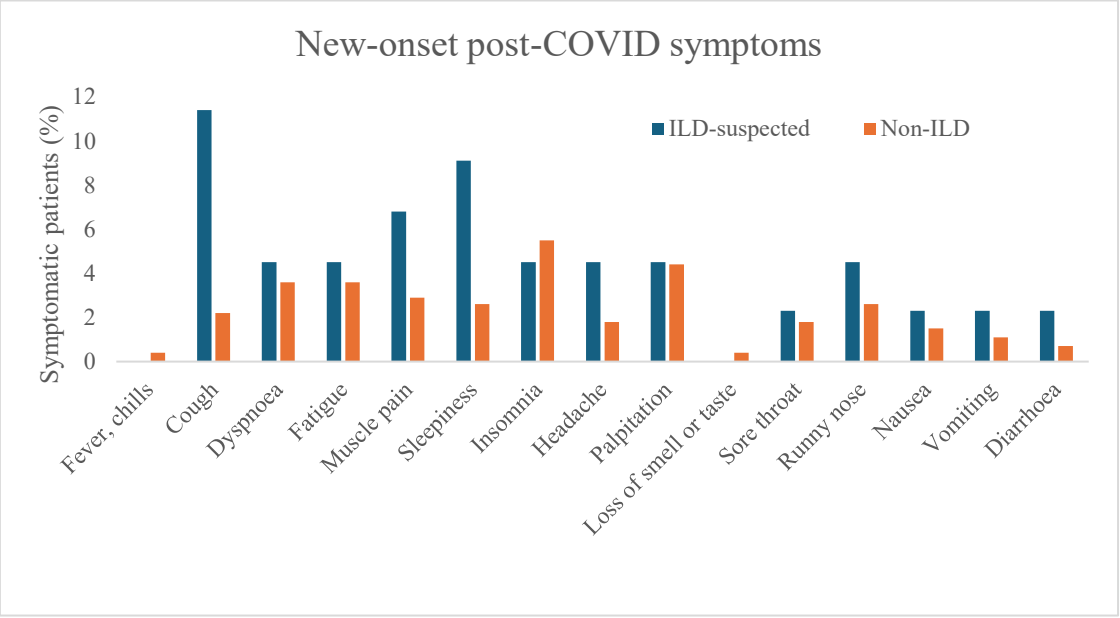

Figure 8/B: Proportion of patients with new-onset post-COVID symptoms for each symptom domain. ILD: interstitial lung disease; unpublished figure.

4.2 Post-COVID Remdesivir study

Patient demographics, clinical characteristics during COVID-19 hospitalization, and therapeutic interventions are presented in Table 6. 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. Among the 136 patients who underwent chest CT, most exhibited pulmonary involvement of at least 10%. A substantial proportion of patients demonstrated severe COVID-19 pneumonia, defined as ≥50% lung involvement, with comparable rates in both cohorts (SOC: 55.6% vs. SOC+RDV: 53.4%). 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 (101). 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. No statistically significant differences were detected between the two groups concerning the requirement for either non-invasive or invasive ventilatory support. 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).

Table 6. Patient characteristics for the post-COVID RDV study. Significant p values highlighted in bold. Reproduced from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Baseline characteristics of study population	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Age (year), mean±SD	58 ± 15	60 ± 13	0.293
Sex, N (%)	34 (36.2)	34 (36.2)	1
BMI (kg/m²), mean±SD	29.2 ± 5.3	30.6 ± 7.6	0.442
HT, N (%)	47 (50.0)	49 (52.1)	0.770
COPD, N (%)	8 (8.5)	8 (8.5)	1
Asthma, N (%)	10 (10.6)	9 (9.6)	0.809
Diabetes, N (%)	6 (6.4)	8 (8.5)	0.578
CAD, N (%)	8 (8.5)	10 (10.6)	0.620
CHF, N (%)	1 (1.1)	1 (1.1)	1
PAD, N (%)	1 (1.1)	2 (2.1)	0.561
Stroke / TIA, N (%)	5 (5.3)	3 (3.2)	0.470
Charlson comorbidity score, mean±SD	1.87 ± 1.77	1.96 ± 1.56	0.483
Variants of concern, N (%)	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
pre-Delta era	65 (69.2)	69 (73.4)	0.789
Delta era	20 (21.3)	18 (19.2)	
Omicron era	9 (9.6)	7 (7.5)	
Lung involvement during COVID-19, N (%)	**SOC N = 63**	**SOC + RDV N = 73**	**p-value**
< 10%	3 (4.8)	1 (1.4)	0.503
10–24%	10 (15.9)	8 (10.1)	
25 –49%	15 (23.8)	19 (26)	

50 – 74%	15 (23.8)	19 (26)	
75% <	20 (31.8)	20 (27.4)	

Treatment during COVID-19, N (%)	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Remdesivir	0 (0.0%)	94 (100.0%)	–
Antibiotics	84 (89.4%)	86 (91.5%)	0.620
Favipiravir	29 (30.9%)	21 (22.3%)	0.187
Reconvalescent plasma	4 (4.3%)	9 (9.6%)	0.151
Systemic corticosteroids	83 (88.3%)	91 (96.8%)	**0.026**
Anticoagulants	86 (91.5%)	90 (95.7%)	0.233
Oxygen supplementation	75 (79.8%)	88 (93.6%)	**0.005**
Non-invasive ventilation	29 (30.9%)	29 (30.9%)	1
Invasive ventilation	14 (14.9%)	9 (9.6%)	0.266
Length of hospital stay, days (mean±SD)	18 ± 18	17± 14	0.664
Post-COVID care	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Days between infection and first visit, median (IQR)	97 [59–215]	68 [56–103]	**0.003**
Symptomatic patients at first visit N (%)	62 (66)	57 (61)	0.449
Asymptomatic patients at 6 month following infection N (%)	23 (24.5)	36 (38.3)	**0.041**
At least 50% symptom score reduction at 6 month N (%)	40 (42.6)	67 (71.3)	**<0.001**

BMI: body-mass index, CAD: coronary artery disease, CHF: chronic heart failure, COPD: chronic obstructive pulmonary disease, CT: computed tomography, HT: hypertension, PAD: peripheral artery disease, RDV: remdesivir, SD: standard-deviation, SOC: standard of care, TIA: transient ischemic attack.

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) (Table 7, Figure 9/A and 9/B). The results of the multivariable Cox regression analyses for the two primary endpoints (asymptomatic status and at least 50% reduction in symptom burden) are presented in Table 8, Figure 10/A and Figure 10/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).

Table 7: Univariable Cox regression results for symptom resolution endpoints in the post-COVID RDV study. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Univariable Cox regression models	**Endpoint of asymptomatic status**		**Endpoint of >50% symptom score reduction**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99 (0.98 - 1.02)	0.944	1.00 (0.99–1.01)	0.930
Female sex	0.4 (0.22 - 0.72)	**0.002**	0.61 (0.42–0.89)	**0.011**
BMI	0.96 (0.92 - 1.004)	0.072	1.00 (0.98–1.03)	0.960
Charlson comorbidity score, mean±SD	0.95 (0.82 - 1.11)	0.522	0.96 (0.86–1.07)	0.428
VOC	2.18 (1.54 - 3.07)	**<0.001**	1.77 (1.36–2.32)	**<0.001**
Symptom-score during COVID-19	0.86 (0.80 - 0.94)	**<0.001**	1.05 (0.99–1.12)	0.102
Remdesivir	1.89 (1.14 - 3.13)	**0.014**	2.05 (1.44–2.94)	**<0.001**
Antibiotics	0.43 (0.20 - 0.91)	**0.028**	0.54 (0.30–0.99)	**0.046**
Favipiravir	0.647 (0.36 - 1.17)	0.15	1.03 (0.70–1.50)	0.893
Reconvalescent plasma	1.94 (0.83 - 4.54)	0.127	1.74 (0.91–3.35)	0.096

Corticosteroids	3.06 (0.74 - 12.57)	0.122	1.79 (0.83–3.85)	0.139
Anticoagulants	2.06 (0.50 - 8.47)	0.317	1.10 (0.51–2.37)	0.800
Oxygen supplementation	1.99 (0.85 - 4.69)	0.115	1.80 (1.04–3.14)	**0.037**
Non-invasive ventilation	1.36 (0.82 - 2.26)	0.235	1.07 (0.73–1.56)	0.734
Invasive ventilation	0.92 (0.47 - 1.82)	0.817	0.63 (0.36–1.09)	0.100

BMI: body mass index, CI: confidence-interval, HR: hazard ratio, VOC: variant of concern.

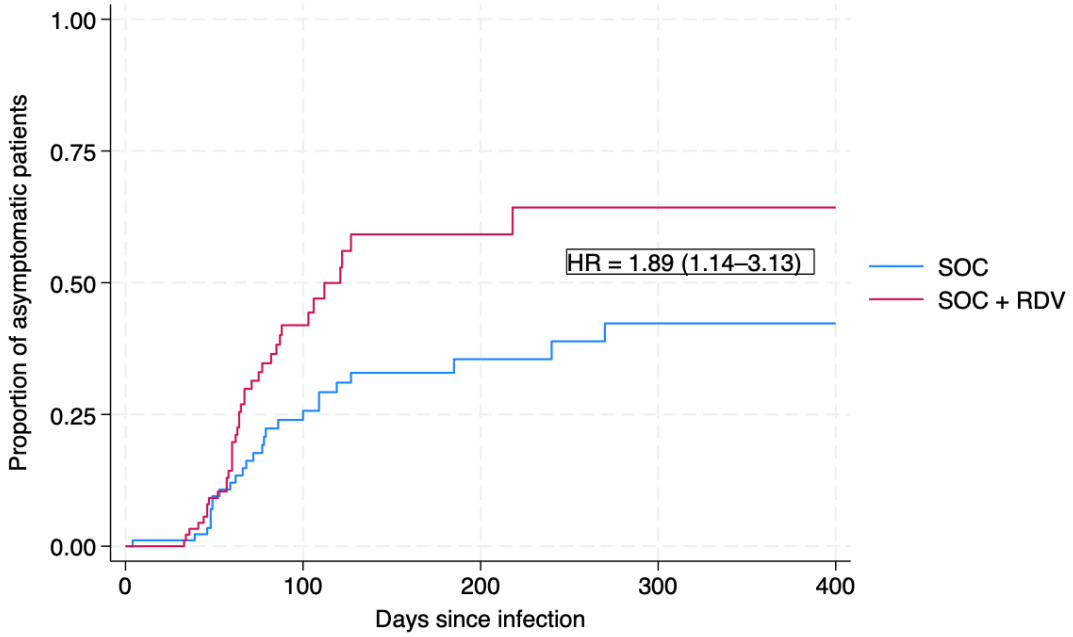

Figure 9/A: Kaplan-Meier curve of the proportion of asymptomatic patients over time since hospital admission (days); HR: hazard ratio; RDV: remdesivir; SOC: standard of care. Reproduced from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

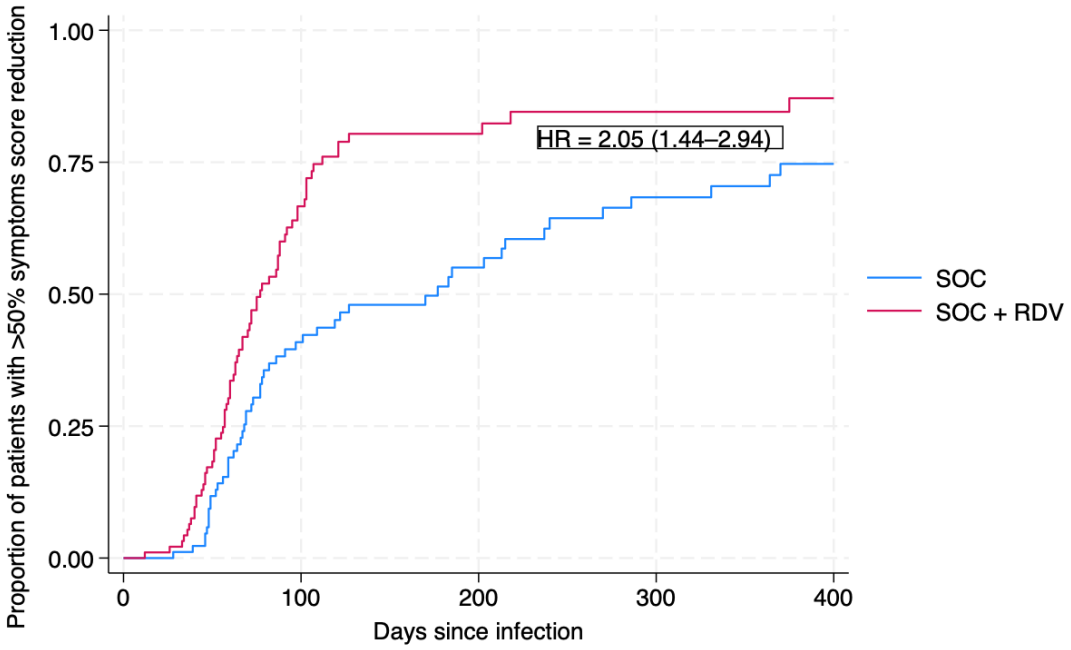

Figure 9/B. Kaplan-Meier curve of the proportion of patients ≥50% symptom score reduction over time since hospital admission (days). HR: hazard ratio; RDV: remdesivir; SOC: standard of care. Reproduced from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Table 8: Multivariable Cox regression models for symptom resolution endpoints in the post-COVID RDV study. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Multivariable Cox regression models	**Endpoint of asymptomatic status**		**Endpoint of >50% symptom score reduction**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Remdesivir	2.28 (1.33–3.92)	**0.003**	2.08 (1.43–3.02)	**<0.001**
Female sex	0.52 (0.28–0.98)	**0.043**	0.69 (0.46–1.03)	0.069
BMI	0.96 (0.92–1.01)	0.139	1.00 (0.97–1.02)	0.881
Later VOC	1.98 (1.34–2.94)	**0.001**	1.92 (1.43–2.57)	**<0.001**
Symptom score during COVID-19	0.89 (0.82–0.97)	**0.009**	1.07 (1.00–1.14)	0.051
Antibiotics	0.35 (0.15–0.79)	**0.012**	0.39 (0.20–0.75)	**0.005**
Favipiravir	1.20 (0.62–2.32)	0.581	1.37 (0.91–2.07)	0.127
Reconvalescent plasma	2.13 (0.88–5.17)	0.093	1.97 (1.00–3.88)	0.051
Steroid	3.08 (0.63–15.14)	0.166	1.75 0.70–4.38)	0.229
Oxygen	1.33	0.571	1.17	0.644

	(0.49–3.59)		(0.61–2.25)	

BMI: body mass index, CI: confidence-interval, HR: hazard ratio, VOC: variant of concern.

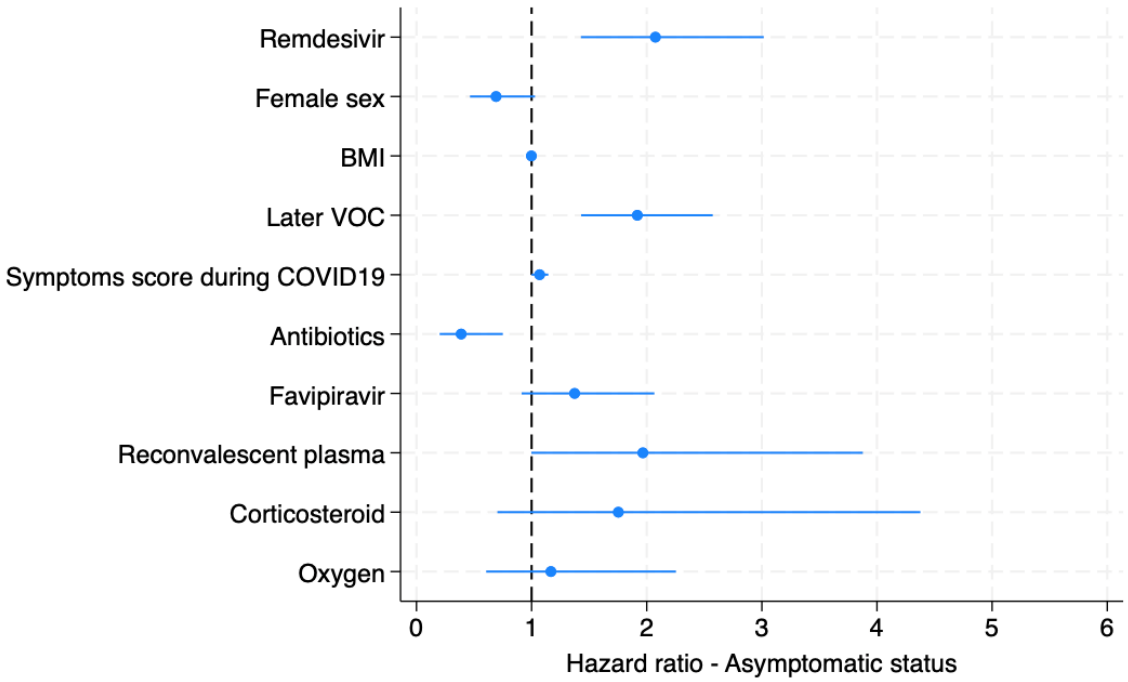

Figure 10/A. Factors influencing asymptomatic status analyzed by Cox regression model with hazard ratios and 95% confidence interval. BMI: body mass index, VOC: variant of concern. Reproduced from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

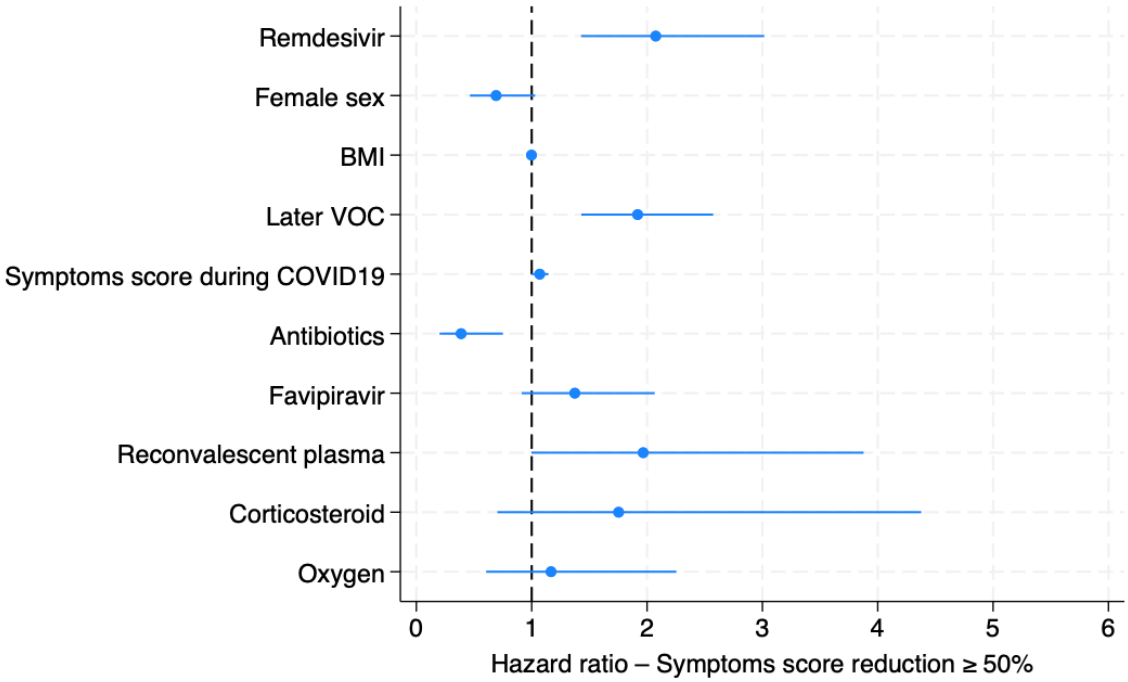

Figure 10/B. Factors influencing ≥50% symptom score reduction analyzed by Cox regression model with hazard ratios and 95% confidence interval. BMI: body mass index, VOC: variant of concern. Reproduced from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, Müller V. Real-world evidence of remdesivir in formerly hospitalized COVID-19 patients: patient-reported and functional outcomes. BMC Infect Dis. 2025 Jan 9;25(1):43 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

A detailed summary of patient-reported symptoms during the acute phase of COVID-19 and the post-COVID period is presented in Table 9 and Figure 11. During the acute infection, the most frequently reported symptoms included fatigue, respiratory complaints (such as cough and dyspnea), fever, and chills. In the post-COVID phase, a considerable number of patients continued to experience fatigue, sleep disturbances, palpitation, and respiratory symptoms. Notably, 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%, $p = 0.017$; Table 9).

Table 9: Patient reported symptom burden during COVID-19 and at post-COVID period. Significant p values highlighted in bold. Reproduced from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Symptoms during COVID-19, N (%)	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Fever, chills	67 (71.3%)	74 (78.7%)	0.238
Cough	66 (70.2%)	71 (75.5%)	0.412
Dyspnea	74 (78.7%)	69 (73.4%)	0.393
Fatigue	70 (74.5%)	76 (80.9%)	0.293
Sleep disturbance (sleepiness and /or insomnia)	35 (37.2%)	42 (44.7%)	0.299
Headache	28 (29.8%)	34 (36.2%)	0.352
Palpitation	36 (38.3%)	40 (42.6%)	0.552
Smell and taste loss	36 (38.3%)	30 (31.9%)	0.359
Upper respiratory	41 (43.6%)	44 (46.8%)	0.66
Gastrointestinal	35 (37.2%)	37 (39.4%)	0.764
Post-COVID symptoms, N (%)	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Fever, chills	3 (3.2%)	3 (3.2%)	1
Cough	25 (26.6%)	18 (19.1%)	0.224
Dyspnea	26 (27.7%)	24 (25.5%)	0.741
Fatigue	43 (45.7%)	43 (45.7%)	1
Sleep disturbance (sleepiness and /or insomnia)	25 (26.6%)	13 (13.8%)	**0.029**
Headache	11 (11.7%)	4 (4.3%)	0.060
Palpitation	18 (19.1%)	16 (17.0%)	0.705

Smell and taste loss	7 (7.4%)	3 (3.2%)	0.194
Upper respiratory	15 (16.0%)	9 (9.6%)	0.190
Gastrointestinal	5 (5.3%)	5 (5.3%)	1
Resolution of symptoms, N (%)	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Fever, chills	64 (68.1%)	71 (75.5%)	0.257
Cough	44 (46.8%)	54 (57.4%)	0.144
Dyspnea	49 (52.1%)	47 (50.0%)	0.770
Fatigue	32 (34.0%)	37 (39.4%)	0.449
Sleep disturbance (sleepiness and /or insomnia)	29 (30.9%)	45 (47.9%)	**0.017**
Headache	21 (22.3%)	30 (31.9%)	0.140
Palpitation	23 (24.5%)	28 (29.8%)	0.412
Smell and taste loss	29 (30.9%)	27 (28.7%)	0.750
Upper respiratory	30 (31.9%)	36 (38.3%)	0.359
Gastrointestinal	32 (34)	32 (34)	1

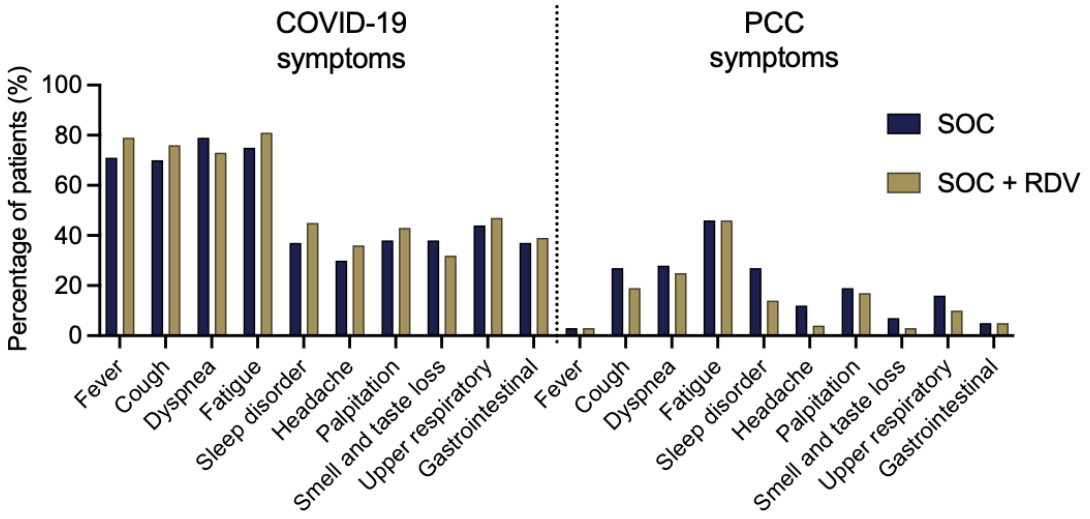

Figure 11. Proportion of symptomatic patients for each symptom domain experienced during COVID-19 infection and at the first post-COVID visit. PCC: post-COVID condition**,** RDV: remdesivir, SOC: standard of care. Adapted from Fésü D, Bárczi E, Csoma B, Polivka L, Boga M, Horváth G, Varga JT, Sebők S, 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

The results of PFTs, 6MWTs and QoL are presented in Table 10. 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). Although no significant differences were observed between groups in ESS, sleep disturbances—manifesting as either excessive daytime sleepiness or insomnia—remained prevalent symptoms in the evaluated population. 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). The only parameter showing a statistically significant difference between groups was heart rate, which was higher among patients in the SOC+RDV group.

Table 10: Pulmonary function test, 6MWT and quality of life results from the post-COVID RDV study. Adapted from 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 under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/)

Lung function tests at first visit	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
FVC, L	3.26 ± 0.89	3.17 ± 1.02	0.181
FVC, ref. %	79.59 ± 15.92	78.98 ± 16.97	0.647
FEV_1, L	2.73 ± 0.81	2.68 ± 0.88	0.278
FEV_1, ref. %	84.52 ± 19.44	85.25 ± 18.72	0.998
FEV_1 / FVC, %	73.38 ± 28.06	77.08 ± 24.17	0.339
TLC, L	5.56 ± 1.45	5.31 ± 1.45	0.209
TLC, ref. r%	95.65 ± 27.92	91.40 ± 24.95	0.666
RV, L	2.19 ± 1.13	2.14 ± 0.97	0.871
RV, ref. %	101.33 ± 52.05	102.35 ± 43.69	0.534
D_{LCO}, mmol/min/kPa	8.82 ± 2.62	8.39 ± 2.80	0.099
D_{LCO}, ref. %	100.70 ± 25.48	98.98 ± 23.84	0.526
K_{LCO} mmol/min/kPa/L	1.60 ± 0.40	1.53 ± 0.38	0.144
K_{LCO}, ref. %	106.32 ± 28.44	101.14 ± 24.83	0.115
PImax, kPa	7.81 ± 3.30	7.98 ± 3.39	0.857
PEmax, kPa	9.10 ± 3.13	9.30 ± 3.32	0.897
6MWT at first visit	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Distance, m	436.25 ± 130.71	429.35 ± 106.24	0.242
Saturation at start (%)	97.05 ± 1.54	96.50 ± 1.30	0.066

Saturation at end (%)	92.24 ± 7.21	91.42 ± 4.73	0.088
Patients with >3% desaturation, N (%)	20 (21.5)	26 (28.0)	0.308
Heart rate at start (1/min)	80.76 ± 14.17	86.73 ± 14.28	**0.008**
Heart rate at end (1/min)	111.65 ± 21.90	117.54 ± 21.15	0.015
BORG at start (0-10) (median) [range]	3.47 ± 8.35	3.10 ± 8.78	0.379
BORG at end (0-10) (median) [range]	15.06 ± 17.26	14.35 ± 15.58	0.938
Quality of life at first visit	**SOC N = 94**	**SOC + RDV N = 94**	**p-value**
Visual analog scale	70.51 ± 20.26	74.90 ± 15.16	0.108
PSQI score	7.66 ± 5.27	5.90 ± 4.12	**0.025**
FSS score	39.47 ± 17.92	35.69 ± 17.84	0.161
ESS score	6.53 ± 4.41	6.35 ± 4.53	0.794

6MWT: 6-minute walk test; D_{LCO}: diffusion capacity of the lung for carbon monoxide; ESS: Epworth Sleepiness Scale; FEV_1: forced expiratory volume in 1 s; FSS: Fatigue Severity Scale; FVC: forced vital capacity; K_{LCO}: transfer coefficient of the lung for carbon monoxide; PEmax: maximal expiratory mouth pressure; PImax: maximal inspiratory mouth pressure; PSQI: Pittsburg Sleep Quality Index; ref. %: reference %; RDV: remdesivir; RV: residual volume; SOC: standard of care; TLC: total lung capacity.

5. Discussion

Our research is the first in Hungary to evaluate the post-COVID pandemic outcome in patients with severe lung involvement during their acute SARS-CoV-2 disease. The focus was on long-term structural lung damage by assessing late ILD development, and mainly functional and QoL outcomes assessed by post-COVID examinations.

Hungary's largest academic pulmonary center, Department of Pulmonology Semmelweis University, collected data of patients affected by long-COVID for 2 years (N=470). We established a well-structured database with separate modules for medical history, symptoms, physical examination findings, pulmonary function and 6MWT results, in addition to radiological findings and patient-reported QoL results. Our aim was to retrospectively analyze post-COVID patients data focusing on post-COVID ILD and the effect of RDV antiviral therapy (received during hospitalization for acute COVID-19) on the development and burden of long-COVID syndrome.

Our results from post-COVID ILD study have shown that the prevalence of suspected post-COVID ILD was 13.8% in our population with ILD-suspected patients being significantly older. The most common complaints and symptoms were fatigue, dyspnea and cough in both; the ILD suspected and in the control group. As new onset symptoms 11.4% and 9.1% of ILD suspected patients reported cough and insomnia respectively, which were more frequent in this group compared to controls. Besides symptom burden, functional status was analyzed with 6MWT and PFTs. Those results have revealed that ILD suspected patients had respiratory dysfunction consistent with restrictive ventilatory pattern, and decreased CO diffusion capacity. On the 6MWT patients with possible post-COVID ILD walked reduced distance and experienced more frequently desaturation, which might be associated to the persisting structural lung abnormalities.

To evaluate the effect of RDV antiviral treatment on long-COVID we conducted our second analysis, the post-COVID RDV study, using the same database collected at our post-COVID pulmonary care. We evaluated data from previously hospitalized patients, and assessed timely administered add-on RDV's effect on long-COVID outcomes by comparing only SOC treated patients with RDV+SOC treatment.

Our research focused on patient centered outcomes including symptom burden, PFTs, QoL questionnaires and 6MWT results. Our findings indicate that, within our study population (comprising two comparable matched groups without statistically significant differences in baseline characteristics), patients who had previously received add-on RDV on top of SOC achieved symptom resolution significantly earlier following infection compared to those treated with SOC alone. Moreover, the RDV-treated group presented earlier for post-COVID pulmonary assessment, reported resolution of sleep disturbances more frequently than controls, and demonstrated better sleep-related QoL outcomes. No significant differences were observed between groups in PFTs or 6MWT results.

The long-term consequences of COVID-19 remain insufficiently defined and may continue to evolve over time. Nevertheless, given the vast number of individuals affected by COVID-19 worldwide, even a relatively low prevalence of persistent post-COVID complications could impose a considerable burden on healthcare systems, underlying the need for ongoing research in the field. Our project was among the first in Hungary to establish a comprehensive and systematically organized database, collecting longitudinal data on patients with long-COVID over a two-year period. The analysis focused on patients with significant respiratory involvement and mainly pulmonary long standing complaints, assessing two primary aspects of long-COVID. The prevalence of post-COVID ILD and clinical characteristics of the affected patients; and the potential long-term impact of RDV antiviral therapy on long-COVID syndrome, symptom burden, and health-related QoL.

The prevalence of long-COVID syndrome and definitive PCPF still varies between studies. A meta-analysis found that 44.9% of hospitalized COVID-19 survivors develop PCPF on the short-term (83), however other meta-analyses and systematic reviews investigating the prevalence of long-COVID syndrome itself estimated that approximately 6–7% of adults previously infected with SARS-CoV-2 are affected by long COVID (4,61,66). In our post-COVID ILD study 13.8% of the included population had ILD-suspected CT abnormalities and were referred for ILD-MDT discussion, which is lower than the prevalence found in a UK study including early VOC COVID-19 patients,

where 24% of patients appeared to be ILD-suspected after the acute phase (94). In that study ILD-MDT established the diagnosis of definitive ILD in 76.6% of the ILD-suspected patients (4% of the total population). A few studies followed post-COVID patients for longer time frame, suggesting that most of the CT abnormalities and lung function parameters improved over time, however in some formerly hospitalized patients residual chest CT abnormalities (most likely fibrotic changes) and burden of health loss, or even increased risk of mortality are still detectable after 2-3 years (8,9,70,96). Prediction based on the previous outbreaks of SARS-CoV suggest that PCPF's longer-term prevalence is going to be around 9.2% among post-COVID patients, given that approx. 12.7% of former SARS-CoV patients had pulmonary fibrosis after 10-15 years. (97,114) Therefore further investigations about longer-term (even up to 10-20 years) follow-up of patients with long-COVID and PCPF are required (115).

Possible therapeutic options and prevention methods for long-COVID syndrome and PCPF are major concerns of ongoing investigations. Vaccination against COVID-19 can prevent severe infection, which is a main predisposing factor for developing long-COVID and PCPF as well; furthermore studies have found association with previous COVID-19 vaccination and a lower risk of PCPF and long-COVID syndrome (56,57,100). In our registry data about vaccination status was not recorded, as data collection about this was not mandated when the registry was started, most included patients' acute infection period predated the general availability of vaccines. Research about re-purposing available antifibrotics (nintedanib and pirfenidone) are ongoing. A phase 2 randomized clinical trial evaluating the efficacy and safety of pirfenidone in patients with fibrotic interstitial lung changes after recovery from severe COVID-19 pneumonia found no significant difference in lung improvement (lung function parameters) between pirfenidone and placebo groups (98). An ongoing randomized, placebo-controlled trial aims to evaluate the effectiveness of nintedanib antifibrotic medication in attenuating the advancement of PCPF (99).

Randomized clinical trials showed that the timely administration of RDV during the acute phase reduces the risk of mortality and shortens the duration of hospital stay (42). Mozaffari et al found that this beneficial effect of RDV on mortality of hospitalized

patients is detectable in vulnerable patient populations and most importantly the benefits were also observed during the Omicron era (45). Berry at al. investigated the risk of long-COVID in hospitalized individuals (more than 52.000 patients) treated with RDV during the acute COVID-19, and found that the use of RDV was associated with a reduced risk of any pre-defined long-COVID outcomes and composite long-COVID outcomes, concluding that the exposure to RDV was associated with lower risk of long-COVID (116). Boglione et al. evaluated the risk factors of long-COVID and the impact of RDV in developing long-COVID (53). In their population, severity of COVID-19 pneumonia, need of ICU-care and longer hospital stay were independent predictors for long-COVID; while RDV was found to have a protective effect on the development of long-COVID; and was associated with better functional status and QoL (53). Our post-COVID RDV study focused on symptom burden (pre-established domains of symptoms have been recorded) and other patients reported outcomes, and found that the use of RDV was associated with earlier complete or at least 50% symptom resolution, suggesting a beneficial effect of RDV on long-COVID in terms of symptom burden.

A large real-world data analysis evaluating the effect of nirmatrelvir-ritonavir on post-COVID outcomes demonstrated that timely administration of this antiviral treatment was associated with a reduced risk of developing post-COVID conditions, as well as lower rates of post-acute mortality and hospitalization (117).

Consistent with our findings, prior research has identified the most commonly reported persistent post-COVID symptoms as fatigue, sleep disturbances, respiratory complaints (such as cough and dyspnea), anxiety and depression, as well taste or smell disorders (92,118). Our post-COVID ILD study further compared the symptoms of patients with suspected ILD to those of control individuals (non-ILD patients) who had experienced COVID-19. A significant difference was observed between the two groups regarding new-onset symptoms, with cough and sleepiness occurring more frequently among patients with suspected ILD. These findings suggest that the persistence of these symptoms, in the context of a prior COVID-19 infection, should raise clinicians' attention to consider the possibility of underlying pulmonary abnormalities, including post-COVID ILD.

With respect to PFTs findings, the existing literature consistently reports a pattern of restrictive ventilatory impairment (characterized by reduced TLC, FVC, and RV) alongside with diminished diffusion capacity (D_{LCO}, K_{LCO} (8,84,87,90,93). In the studies under discussion, pulmonary function impairment and decreased diffusion capacity were likewise observed in the group with suspected ILD (post-COVID ILD study), showing a significant difference compared to the control group, where reductions in these parameters were not that significant. By contrast, in the post-COVID RDV study, the cohort did not demonstrate a restrictive ventilatory pattern and exhibited only slight parameter reductions. 6MWT parameters can also reflect the patients functional status, and previous studies, mainly from the early post-COVID period, reported reduced 6MW distance and desaturation during the testing in concordance with our results from the post-COVID ILD study (93,119).

A Finnish study assessing long-COVID parameters one year after hospitalization found no differences in QoL outcomes between patients treated with RDV and those in the control group (120). Our findings demonstrated a significant difference in sleep-related QoL as reflected by PSQI scores; however, the follow-up period in our study was shorter and lacked standardization. Moreover, the assessment of sleep disturbances using the ESS did not reveal any significant differences between the groups.

Treatment of post-COVID is a challenge especially the management of ill-defined symptoms, including fatigue. Post-acute deconditioning is a well-known complication of severe viral and bacterial infections (121). Interventions for these patients include participation in respiratory rehabilitation programs (also implemented in our department), which has led to significant improvements in post-COVID functional status (122,123).

General limitations of studies evaluating post-COVID conditions include the lack of a standardized definition of post-COVID condition and the absence of unified post-COVID pulmonary care systems (61). Furthermore, the studies under discussion, are based on registry data that include only patients who were able to self-present to outpatient post-COVID care; consequently, individuals with more severe disabilities were not represented in our analysis. The retrospective design of both studies presents certain limitations, such as potential recall bias in symptom reporting, confounding by indication

regarding RDV use, and the absence of data on vaccination status. Nevertheless, we assume that most of the patients analyzed were likely not fully vaccinated at the time of infection, given the timeline of the public vaccination campaign in Hungary. Additionally, in the post-COVID RDV study, the groups differed in the time interval between infection and the first post-COVID visit, while the ILD-focused study was limited to a single short-term follow-up involving a small patient cohort, which led to a low number of cases reporting certain symptom domains, and did not include re-evaluation of LDCT scans or functional status. In the RDV-focused study, we performed a multivariable regression analysis to account for potential confounders (e.g. differences in additional therapies) when evaluating the effects of RDV. The results showed that the use of RDV was associated with significantly faster patient-reported symptom resolution, independent of other analyzed treatments (45), and as SARS-CoV-2 viruses are still circulating in the population, effective antiviral treatment is important to reduce the post-infection burden.

6. 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 main 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 PF tests, 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.

7. Summary

After acute COVID-19, some patients develop post-COVID or long-COVID syndrome, characterized by persistent or new-onset symptoms, altered QoL and impaired functional status; posing challenges for both patients and healthcare systems. Although many SARS-CoV-2–related lung injuries resolve, impaired repair processes can result in chronic inflammatory or fibrotic changes, therefore long-COVID may present with persistent radiological abnormalities consistent with post-infectious or fibrotic ILDs.

At the Department of Pulmonology, a comprehensive registry collected post-COVID pulmonary care data between February 2021 and February 2023, including medical history, physical and radiological examinations' results, QoL assessments, and functional tests' results. Two retrospective studies were conducted: one evaluating the prevalence and characteristics of post-COVID ILD; and another assessing the impact of RDV antiviral therapy received during the acute phase on long-COVID symptom burden, and patient-reported outcomes.

The most frequently reported long-COVID symptoms were fatigue, respiratory complaints, and sleep disturbances. The post-COVID ILD study identified suspected ILD in 13.8% of patients, who were typically older, more often hospitalized for acute COVID-19, and more likely to develop new-onset cough and sleepiness. These patients also demonstrated reduced walking distance, oxygen desaturation during 6MWT, and a mild restrictive ventilatory pattern on PFTs. The post-COVID RDV study, which analyzed two matched patient groups without significant baseline differences, found earlier symptom resolution (complete or ≥50%) in the RDV-treated group compared to controls. RDV recipients also reported fewer long-term sleep disturbances and significantly better sleep quality.

In conclusion, severe acute SARS-CoV-2 lung infection requires appropriate antiviral therapy, which was associated with earlier symptom resolution in the post-COVID period. Although no differences in functional status or general QoL outcomes were observed, results suggest a potential benefit of RDV in accelerating recovery. Structural changes consistent with suspected post-COVID ILD were present in over 10% of patients and were associated with mild functional impairment.

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9. Bibliography of the candidate's publications

9.1 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.

9.2 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.

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