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EMJ Respiratory

Review of
ERS Congress 2022

Editor's Pick

Current Perspectives and Future Directions of Repeat Pulmonary Rehabilitation Programmes in People with Chronic Obstructive Pulmonary Disease: A Narrative Review of the Literature

Interviews

J. Brady Scott discusses his career in respiratory medicine as a therapist, educator, and researcher

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Welcome to the 2022 edition of *EMJ Respiratory*. It has been a year of great advances in respiratory medicine, and in this issue we bring you a plethora of articles alongside our coverage of the European Respiratory Society (ERS) International Congress 2022.

This year's congress took place in Barcelona, Spain, and featured highly engaging sessions, with its highlights including a randomised controlled trial comparing lung volume reduction surgery and bronchoscopic lung volume reduction for emphysema, as well as a study on the risks associated with obstructive sleep apnoea, both of which you can find summarised in our highlights section. We are also proud to present an interview with the Director of Clinical Education, Respiratory Care at Rush University, Illinois, USA, J. Brady Scott, who provides insights into his role as a respiratory therapist, researcher, and educator.

The journal also features our Editor's Pick, offering a perspective on repeat pulmonary rehabilitation programmes in people with chronic obstructive pulmonary disease, and an article outlining an observational study using high-resolution CT to study radiological findings on post-COVID-19 pulmonary fibrosis. Finally, the issue includes case reports, ranging from a paediatric case of eosinophilic pneumonia to acute pancreatitis and acute respiratory failure related to EBV infection in a female patient.

I would like to take this opportunity to thank our contributors, reviewers, and Editorial Board for their invaluable involvement in bringing this issue together. I look forward to the next European Respiratory Society Congress in 2023 in Milan, Italy. Until then, I hope you enjoy reading our journal, and I look forward to your contributions.

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Foreword

Dear Colleagues,

I would like to welcome you to the latest issue of *EMJ Respiratory*, which features content from the European Respiratory Society (ERS) International Congress 2022. Held in Barcelona, Spain, and online, this hybrid congress allowed respiratory experts from around the world to present findings and advances in the field of respiratory medicine.

This issue features a fascinating and timely article by Kant et al., which discusses the aetiology of parenchyma of the lungs, a condition that typically has a poor outcome, and how COVID-19 should be considered in the aetiology of fibrotic lung diseases. The authors highlight the most common complaints in post-COVID-19 pulmonary fibrosis, and how high resolution CT can be used to study different radiological findings.

Still a topic on many healthcare professionals' minds, this issue also contains other articles relating to COVID-19, including one that discusses the psychological effects that the disease has on doctors and non-doctors. Iftikhar et al. analysed data from the two cohorts to determine how COVID-19 has affected the mental health of these individuals in Pakistan.

Focusing on the impact pulmonary rehabilitation has on patients and resources, McNamara et al.'s narrative review considers the evidence around repeat pulmonary rehabilitation programmes and the areas that require questioning in the future, while Sandes et al. delve into human toxocariasis in a paediatric patient.

While I have mentioned only three of the articles that can be found in this issue of *EMJ Respiratory*, you can be assured that this journal is filled with invaluable information, as well as an interview with J. Brady Scott, Director of Clinical Education at Rush University, Chicago, Illinois, USA.

Finally, I would like to say a big thank you to all the authors, interviewees, Editorial Board members, and reviewers who have contributed to this issue.

Antonio Rossi

Senior Medical Director, Oncology Center of Excellence, Therapeutic Science & Strategy Unit, IQVIA, Milan, Italy

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ERS 2022

Review of the European Respiratory Society (ERS) International Congress 2022

Location: Barcelona, Spain
Date: 4th–6th September
Citation: EMJ Respir. 2022;10[1]:10-17. DOI/10.33590/emjrespir/10061176. https://doi.org/10.33590/emjrespir/10061176.

PRESENTED in a hybrid format for the first time, this year's European Respiratory Society (ERS) International Congress welcomed over 19,000 respiratory professionals, with over 10,000 attending in-person in Barcelona, Spain. Known for its stunning buildings, Barcelona is home to many unusual architectural wonders, including Antoni Gaudí's Casa Batlló, which was classified as a UNESCO World Heritage Site in 2005. For those who could not attend personally, a panoramic view of the city could be seen behind the presenters in the studio.

Christopher E. Brightling, ERS Science Council Chair, who opened the congress with Richard Costello, ERS Education Chair, commented on the in-person registration for the congress: "There was an incredible buzz, a real crowd of people, and that showed me what we had been missing." However, he also stated that it was fantastic that so many people could join online.

This year, the ERS International Congress saw 3,500 poster sessions, over 500 presentations, and over 300 industry sessions on a variety of topics, including acute and chronic respiratory failure and patient quality of life. Some of the sessions that Brightling was most looking forward to, however, were the four ALERT sessions, which focused on randomised clinical trials that are most likely to have an impact on practice. Another highlight was the Lungs on Fire session, which is now a regular at the ERS International Congress. This innovative, interactive session explored real-life clinical cases where a panel of experts were put to the test against the audience.

A number of awards were presented, including the ERS Presidential Award to Gérald Simonneau, Faculté Médecine, Université Paris Saclay, Le Kremlin-Bicêtre, France, and Centre de Référence de l'Hypertension Pulmonaire, Hopital Marie-Lannelongue, Le Plessis-Robinson, France, for his contribution to strengthening respiratory medicine worldwide. The ERS Congress Chair Award went to Hans Henri P. Kluge, World Health Organization (WHO) Region Office for Europe, Copenhagen, Denmark, for his contribution to research and training.

The ERS Mid-Career Gold Medals were awarded for various specialities, including Asthma, which was presented to Hamida Hammad, Laboratory of Mucosal Immunology and Immunoregulation, VIB-UGent Center for Inflammation Research, Belgium, and Department of Internal Medicine and Pediatrics, Ghent University, Belgium. Francesca

Polverino, Asthma and Airway Disease Research Center, University of Arizona, Tucson, USA, was awarded the Gold Medal in Chronic Pulmonary Disease, while Anne Holland, Central Clinical School, Monash University, Melbourne, Australia; Department of Physiotherapy, Alfred Health, Melbourne, Australia; and Institute for Breathing and Sleep, Melbourne, Australia, received the one for Allied Health Professionals. The Non-tuberculous Mycobacteria gold medal was awarded to Andres Floto, Molecular Immunity Unit, University of Cambridge Department of Medicine, MRC Laboratory of Molecular Biology, UK; Cambridge Centre for AI in Medicine, UK; and Cambridge Centre for Lung Infection, Royal Papworth Hospital, UK, and the ERS Mid-Career Gold Medal in Clinical Technique, Imaging, and Endoscopy was awarded to Daniel Steinfort, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Australia, and Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Parkville, Australia. Gold Medals in Epidemiology and Environment, Cystic Fibrosis, and Pulmonary Arterial Hypertension were awarded to Zorana Jovanovic Andersen, Department of Public Health, University of Copenhagen, Denmark; Pierre-Régis Burgel, Université Paris Cité, L'Institut national de la santé et de la recherche médicale (Inserm) U1016, Institut Cochin, Paris, France; and Christophe Guignabert, L'Institut national de la santé et de la recherche médicale (Inserm) UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France, and School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France, respectively.

"Costello rounded up the ERS International Congress by introducing Monika Gappa as the new ERS President for 2023–2024."

After a fantastic couple of days, Costello rounded up the ERS International Congress by introducing Monika Gappa as the new ERS President for 2023–2024. She stated that she was looking forward to her role and that it was great to be back. Also referring to the COVID-19 pandemic, ERS Science Council Chair Elect Nicolas Roche commented on the "extraordinary" output from ERS and that we are now seeing a return of more "normal" scientific activities.

Next year's congress will take place in Milan, Italy, from 9th–13th September 2023. Until then, please enjoy our key insights and reviews from this year's ERS International Congress.

Invasive Versus Bronchoscopic Lung Volume Reduction: Which Is Best?

PIONEERING randomised controlled trial data comparing lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR) as surgical management options for emphysema was presented at ERS International Congress 2022 on 6th September. The overall study findings revealed that both surgeries assessed resulted in similar improvements in lung volume reduction, exercise capacity, and breathlessness.

LVRS involves resection of areas with significant alveolar damage and is therefore more invasive than BLVR, in which a fibreoptic camera is introduced into the lungs to deploy one-way endobronchial valves, which cause partial collapse of the lung adjacent to it. Whilst both interventions have previously documented positive impact on symptoms and lung function, no trials have compared the two to determine which is best.

To address this, a research team, led by Sara Buttery, National Heart and Lung Institute, Imperial College London, UK, conducted a trial which randomised 88 patients to either LVRS (n=41) or BLVR (n=47) to directly compare the procedures to help "inform decision-making when a person seems to be suitable for either." The mean age of participants was 64 years and patients were followed up for 1 year. Response to the procedure was measured by assessing the percentage change in residual volume in combination with the composite disease severity index score, iBODE, which accounts for BMI, airflow obstruction, dyspnoea, and exercise capacity.

> **"These promising results provide important information to encourage larger trials with higher power, so that patients and clinicians can have informed conversations and decision-making discussions."**

The authors found that both procedures resulted in similar improvements in iBODE scores, reduction in gas trapping, and were equally safe, with one death in each arm of the trial during the 1-year follow-up period.

These promising results provide important information to encourage larger trials with higher power, so that patients and clinicians can have informed conversations and decision making discussions. For the future, Buttery commented that further research to identify patient factors that indicate whether a person would respond better to one procedure or the other and analysis into the cost–benefit of both procedures is required. ●

Risk of Cancer, Mental Decline, and Blood Clots All Linked to Obstructive Sleep Apnoea

STUDY data presented as ERS International Congress 2022 has indicated that individuals who suffer from obstructive sleep apnoea (OSA) are at an increased risk of cancer. This data was presented alongside a second study which indicated OSA was also linked to a decline in processing powers in the elderly. Finally, a third study found patients with severe OSA were at a greater risk of developing blood clots in their veins.

OSA causes individuals to experience partial or complete obstruction in their airways during sleep and can stop breathing several times throughout the night. The disorder is thought to affect approximately 7–13% of the population. Risk factors include obesity, smoking, and high alcohol consumption.

The first study investigating correlation with cancer examined data from 62,811 patients, 5 years prior to the commencement of OSA treatment. These patients were treated with continuous positive airway pressure and data was collected from the Swedish National Cancer Registry and Statistics Sweden. The researchers identified 2,093 patients with OSA who also had a cancer diagnosis up to 5 years before OSA diagnosis. They found that patients with cancer tended to have more severe OSA and that the O_2 desaturation index (ODI) of patients tended to be lower in those with lung cancer.

Looking to the future, the researchers described the need for larger studies with more patients to investigate the potential influence of continuous positive airway pressure treatment on cancer incidence and survival.

The second study presented at ERS International Congress linked OSA with greater mental decline. Individuals aged 65 years and older between 2003 and 2008 were examined with sleep tests to define presence of OSA. This was subsequently followed up with cognitive assessments assessing global cognitive function. The researchers found that low O_2 levels during sleep due to OSA were associated with a greater decline in global cognitive function. They further identified that males and those aged over 74 years were at higher risk of cognitive decline related to OSA.

The third OSA study demonstrated a link between severe OSA and venous thromboembolism (VTE) by following 7,355 patients over the course of 6 years. Overall, 104 developed VTEs. The researchers found that individuals who spent more than 6% of sleep with O_2 levels below 90% of normal ranges had an almost two-fold increase in the risk of developing VTE compared to patients without nocturnal O_2 deprivation.

“These three studies show worrying associations between obstructive sleep apnoea and important diseases that affect survival and quality of life,” explained Winfried Randerath, Bethanien Hospital, University of Cologne, Germany, and Head of the ERS specialist group on sleep disordered breathing. “The data support the relevance of sleep apnoea on cancer, VTE, and mental health. While they cannot prove that OSA causes any of these health problems, people should be made aware of these links and should try to make lifestyle changes to reduce their risk of OSA, for instance, by maintaining a healthy weight. However, if OSA is suspected, definite diagnosis and treatment should be initiated. We look forward to further research that may help to clarify whether OSA may be causing some of the health problems seen in these studies.”

Preventing Croup Before Birth

CHILDREN whose mothers took fish oil and vitamin D supplements during pregnancy are less likely to develop croup, according to Nicklas Brustad, Copenhagen University Hospital, Denmark, who presented the findings of Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) at the ERS International Congress 2022.

A common viral chest infection, croup affects young children who present with a barking cough, hoarse voice, and breathing difficulties. While most cases are mild, some children need breathing support. Brustad noted that there is no vaccine at the moment to prevent the disease; therefore, "other preventative strategies are needed."

This double-blind study consisted of 736 females who were cared for by COPSAC during their pregnancy. They were divided into four groups, where one group was given a high dose of vitamin D (2,800 IU/day) and fish oil (2.4 g), containing long-chain n-3-polyunsaturated fatty acids. Another group received a high-dose vitamin D and olive oil, while a third were given a standard dose (400 IU/day) of vitamin D and fish oil. The final group were given a standard dose of vitamin D and olive oil.

The supplements were taken daily from the patients' 24th week of pregnancy until 1 week after delivery.

The children were monitored until the age of 3 years and there were 97 cases of croup, diagnosed either by a doctor or through medical records. Children born to mothers who had taken high-dose vitamin D during pregnancy had an 11% risk of croup; however, those whose mother had the standard dose had an 18% risk. There were similar findings when comparing children of mothers who had taken fish oil and olive oil (11% and 17% risk, respectively).

> **"Brustad noted that there is no vaccine at the moment to prevent the disease."**

While unsure of the exact mechanisms, Brustad stated: "Our findings suggest that vitamin D and fish oil could be beneficial against childhood croup in sufficiently high doses." The COPSAC research team will continue looking vitamin D and fish oil to determine if there are any other benefits. ●

Artificial Intelligence Can Be Used to Detect COVID-19 Infection

COVID-19 can be detected using artificial intelligence (AI) that identifies the infection through people's voices, using recordings through a mobile app. This research was presented at ERS International Congress 2022 in Barcelona, Spain.

The app could be used in low-income countries, as the test is cheap, quick, easy to use, and more accurate than rapid antigen tests. While rapid antigen tests' accuracy can vary depending on the brand and is less accurate in asymptomatic people, the AI was accurate 89% of the time.

Since COVID-19 affects the upper respiratory tract and vocal chords, a person's voice can change, which is why researcher Wafaa Aljbawi, Institute of Data Science, Maastricht University, the Netherlands, and supervisors, investigated whether it was possible to analyse people's voices to detect the infection through AI. The app first collects basic information, then asks the user to record respiratory sounds, including reading a short sentence on the screen three times, coughing three times, and breathing deeply through their mouth three to five times.

The team used data from the University of Cambridge's crowd-sourcing COVID-19 Sounds App, including audio samples from 4,352 participants, of whom 308 had tested positive for COVID-19. A voice analysis technique called mel-spectrogram analysis then decomposed the properties of the voice. Different AI models were built in order to distinguish people affected by COVID-19 from those who weren't.

The app's sensitivity was of 89%, and its specificity was 83%. Aljbawi said: "They enable remote, virtual testing and have a turnaround time of less than a minute. They could be used, for example, at the entry points for large gatherings, enabling rapid screening of the population."

Henry Glyde, a PhD student at the University of Bristol, UK, then showed that AI could also be used in patients with chronic obstructive pulmonary disease (COPD) to predict acute exacerbations. The AI could be harnessed via the app myCOPD, which is already used by 15,000 patients with COPD to help manage their disease. Sensitivity for the most recent AI model was 32% and specificity was 95%, meaning that while the app is not as accurate in predicting when a patient will experience an exacerbation, it is very good at predicting when they will not, thereby preventing unnecessary treatment. Improving the sensitivity will be the next phase of the research.

Project lead James Dodd said: "It would empower patients to have more autonomy and control over their health. This is also a significant benefit for their doctors as such a system would likely reduce patient reliance on primary care."

E-cigarettes: A Route to Nicotine Addiction

TEENAGERS are more likely to try e-cigarettes if their parents are smokers, according to research presented by Luke Clancy, Director General of the TobaccoFree Research Institute Ireland (TFRI), Dublin, Ireland, at this year's ERS International Congress 2022.

TFRI analysed data from 6,216 teenagers aged 17–18 years, which included information on if their parents were smokers and whether they were also smokers or used e-cigarettes. The researchers combined this information with other Irish datasets, which included 10,000 Irish teenagers aged 16–17 years, to provide a more comprehensive analysis of e-cigarette usage in Ireland.

The results showed that more teenagers tried e-cigarettes in 2019 than 2014 (39% and 23%, respectively). It also highlighted that teenagers were 55% more likely to have tried e-cigarettes and 51% more likely to have tried smoking. However, 29% stated that it was because their friends were vaping, while most teenagers (66%) said that they tried e-cigarettes out of curiosity. Only 3% said they tried e-cigarettes to quit smoking.

Clancy noted: "There's a perception that vaping is a better alternative to smoking, but our research shows that this doesn't apply to teenagers who usually haven't tried cigarettes prior to e-cigarettes. This indicates that, for teens, vaping is a route into nicotine addiction, rather than out of it."

Looking in more detail at the data from 3,421 teenagers aged 16 years, the researchers found that males are more likely to try e-cigarettes than females; however, they also discovered that the rates are increasing more rapidly amongst females, with 39% saying that they had tried e-cigarettes in 2019 compared with 23% in 2015.

> **"For teens, vaping is a route into nicotine addiction, rather than out of it."**

Joan Hanafin, Lead Researcher at TFRI, said: "We can see that the number of teenagers using e-cigarettes is changing fast, so we need to keep monitoring the situation in Ireland and around the world. We also plan to study social media to understand how this influences girls' and boys' vaping behaviour." ●

The Impact of Crisis on Healthcare

Author: Natasha Meunier-McVey, Editorial Assistant

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IN THIS pertinent session, which took place on the second day of the European Respiratory Society (ERS) International Congress 2022, in Barcelona, Spain, experts discussed the impact of crisis on both healthcare providers and patients. Chaired by Anita Simonds, Emeritus Professor of Respiratory and Sleep Medicine, Imperial College London, UK, and Arzu Yorgancıoğlu, Professor and Head of the Department of Pulmonology at Celal Bayar University, Turkey, the session saw experts and patient representatives share their experiences following the crisis of the Ukraine war.

ERS 2022

PERSPECTIVES FROM THE WORLD HEALTH ORGANIZATION

Hans Henri P Kluge, the World Health Organization (WHO) Regional Director for Europe, opened the session by explaining how the Russia–Ukraine war has seen the world's fastest displacement of people in recent history, with over 7 million people displaced with limited access to healthcare, and 7 million refugees having to rely on the healthcare systems of other countries. This growing humanitarian crisis may lead to the spread of contagious diseases including COVID-19 and polio, with people having limited means of self-protection or isolation.

Prior to the outbreak of the Ukraine war, the country was reforming its healthcare system, a challenge already impacted by the strain of the COVID-19 pandemic. Ukraine's leading cause of mortality is non-communicable diseases, with the five major non-communicable diseases, including chronic respiratory disease, responsible for 84% of all deaths. Kluge explained how the country already experiences severe and long-lasting impacts of disease outbreaks. With only one in three people in the Ukrainian population having their full course of severe acute respiratory syndrome coronavirus 2 vaccinations, there is both continued circulation and increased susceptibility to both COVID-19 and seasonal influenza, which place strain on healthcare systems.

Kluge went on to highlight Ukraine's fantastic work in the control and management of tuberculosis (TB), leading the country to be recognised as a pioneer in response to TB and its resistant forms. These efforts included the implementation of a drug force, and a patient-centred approach to improve services for the screening, diagnosis, and management of the disease. These actions saw a 20% decrease in TB cases; however, due to the ongoing active hostilities, Ukraine is faced with challenges for successful drug delivery and the overall safety of its citizens.

Kluge explained how the WHO has ensured that all medical responders are properly equipped for crisis response in Ukraine, also providing sufficient resources for ongoing management of respiratory disease, which included training over 9,000 healthcare workers. The WHO has extended its help to countries welcoming refugees, whilst also setting up 80 emergency medical teams in Ukraine, Poland, and the

"Ukraine's leading cause of mortality is non-communicable diseases, with the five major non-communicable diseases, including chronic respiratory disease, responsible for 84% of all deaths."

Republic of Moldova, as well as urgent care hubs in western Ukraine. An effective supply chain has facilitated the distribution of over 1,300 tonnes of critical medical supplies throughout the country in co-ordination with the Ministry of Health.

Kluge concluded his eye-opening session with the reminder that this winter may be challenging for Ukraine, with ongoing displacement and overcrowding coupled with cold weather. However, with the solidarity of surrounding countries and the European Union (EU), we can carry on greatly impacting the population in the midst of this crisis. Kluge stated the guiding principle of the WHO's European Programme of Work, "leave no one behind," leading him to emphasise: "The more collaboration, the better [...] let's not break the dialogue and technical link with specialists in any 53 member states of the European Union."

PATIENT PERSPECTIVES

Olena Yurchenko, a 34-year-old female Ukrainian patient who was diagnosed with pulmonary hypertension at birth, shared a patient's perspective on the impact of war on healthcare in the context of a chronic respiratory condition. Yurchenko began by explaining the stress factors and hostile circumstances associated with the current crisis. Patients have experienced deterioration in their health due to increased stress, respiratory triggers, and the limited knowledge as to where doctors are located, as many doctors have fled to other countries. In turn, medication has become less accessible due to scarcity and price increases, exacerbating health conditions, especially in patients who are unable to work. Yurchenko rounded off her talk by explaining how the population is staying positive despite the ongoing hostilities in Ukraine, with the thought of the end of war being at the forefront of their minds.

THE IMPACT OF RECENT CRISIS ON THE HEALTHCARE SYSTEM

Yurii Feshchenko, President of the Ukrainian Respiratory Society, Kyiv, Ukraine, discussed the impacts of the events of the last 3 years on the

European healthcare system, focusing on the outbreak of the Russia–Ukraine war. Feshchenko explained how these aggressive circumstances have multiplied the risk of exacerbated respiratory disease for the population, with there currently being no safe areas in Ukraine for protection.

Echoing the issues presented in Kluge's introduction, Feshchenko highlighted the importance of patient education and self-management for chronic respiratory conditions including asthma, to reduce disease exacerbation given the lack of medical personnel since the breakout of war. The mobilisation of healthcare workers would also allow those in need to receive appropriate care and assistance, explained Feshchenko, whilst the education of all doctors on respiratory disease management would facilitate optimal patient care in the current conditions.

PERSPECTIVES FROM THE EUROPEAN RESPIRATORY SOCIETY

Joanna Chorostowska, ERS Secretary General from the National Institute of Tuberculosis and Lung Diseases, Poland, led the final presentation of the session. Chorostowska shared perspectives from the ERS in their immediate support of frontline respiratory teams during the Ukraine crisis.

Only 5 days after the outbreak of war, the ERS published a statement of solidarity and support to those affected by the invasion of Ukraine, and weeks later urged members of the society to support humanitarian aid and initiatives subsidising frontline doctors, also taking steps to halt collaborations with Russian and Belarusian societies. For the ongoing education of Ukrainian healthcare providers, the ERS provided free registration to the congress and extended memberships with no charge, a similar initiative that was offered to Syrian and Afghan members during their respective times of crisis.

With the lack of resources and accessible healthcare in Ukraine, the ERS published disaster medicine resources, which were translated into Ukrainian. Chorostowska highlighted the actions taken to offer support on a patient-level, which involved a collaboration with the European Lung Foundation (ELF). The ERS published a combined support statement with the ELF, and an article in the ELF newsletter offering direct advice to patients with lung conditions, and uniting European initiatives by patient organisations. The ERS also maintained close communication with Oksana Kulish Skaara, a Ukrainian patient with pulmonary hypertension on the ELF council, also promoting their fundraising campaign, which offers support to people with the condition forced to flee the country. A special session statement was submitted by the ERS to the WHO Regional Committee, along with a financial donation of 90,000 EUR to support the WHO's ongoing work in respiratory and emergency medicine in Ukraine.

CONCLUSION

Highlighting both patient experience and the actions taken by European organisations, this session provided an impactful overview of the effect of crisis on a population. The overwhelming support given by the ERS, EFL, WHO, and other organisations, as well as individual contributions, reflects the solidarity offered in times of need, and reflects similar COVID-19 initiatives just a few years earlier. The importance of accessible education and information was emphasised throughout this session, demonstrating the range of support that can help a population during a time of crisis.

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Re-IMAGinING the Pathway for Clinical Decision Making in Rare Lung Diseases: Moving Towards a United Vision

This industry symposium took place on 4th September 2022 as part of the European Respiratory Society (ERS) International Congress

Speakers: Daiana Stolz,[1] Charlie Strange,[2] Marlies S. Wijsenbeek,[3] Elizabeth Estes,[4] Gerry McElvaney[5]

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2. Medical University of South Carolina, Charleston, USA
3. Erasmus University Medical Centre, Rotterdam, the Netherlands
4. Open Source Imaging Consortium (OSIC), Saugatuck, Michigan, USA
5. Irish Centre for Genetic Lung Disease, Dublin, Ireland

Disclosure: Stolz is affiliated with, has financial interests in, or has received grants or research support from AstraZeneca, Boston Scientific, and Curetis; and has received honoraria or consultation fees from Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, Merck and Co., Novartis, Sanofi, Schwabe Pharma, Vifor, and Zambon. Strange is affiliated with, has financial interests in, or has received grants or research support from Adverum, AstraZeneca, CSA Medical, Grifols, Nuvaira, Takeda, and Vertex; and has received honoraria or consultation fees from Dicerna, GlaxoSmithKline, Takeda, and Vertex. Wijsenbeek has not receive any personal fees or grants; however, Wijsenbeek's institute has received grants from Boehringer Ingelheim, Hoffman la Roche, The Dutch Pulmonary Fibrosis Patients Association, The Dutch Lung Foundation, The Netherlands Organisation for Health Research and Development (ZonMw), The Thorax Foundation, and Sarcoidosis.nl; and speaker or consultation fees from Bristol Myers Squibb, Boehringer Ingelheim, CSL Behring, Galapagos, Galecto, Hoffman-La Roche, Horizon Therapeutics, Kinevant Sciences, Molecure, Nerre Therapeutics, Novartis, PureTech Health, and Respivant Sciences. All grants and fees are paid to the Erasmus MC. Estes works for Open Source Imaging Consortium. McElvaney has received research funding from Chiesi, CSL Behring, Grifols, Kamada, pH Pharma, and Vertex; and has served on advisory boards for Dicerna, Inhibrx, Intellia, and Vertex.

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Disclaimer: The views and opinions expressed are exclusively those of the speakers.

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Meeting Summary

This industry-supported symposium was held during the European Respiratory Society (ERS) International Congress and included presentations from several internationally renowned experts in rare lung diseases. The panel discussed the need to improve clinical decision making to expedite disease recognition, prognostic prediction, and early treatment in interstitial lung disease (ILD) and alpha 1 antitrypsin (AAT) deficiency-related chronic obstructive pulmonary disease (COPD).

Daiana Stolz, Clinic for Pneumology, University Hospital Freiburg, Switzerland, and Marlies S. Wijsenbeek, Erasmus University Medical Centre, Rotterdam, the Netherlands, explained that although high-resolution CT (HRCT) scans may appear similar, ILD from different causes results in significantly different patient outcomes. Therefore, image analysis and the identification of sensitive and specific biomarkers are critical to improving diagnosis and monitoring treatment response and disease progression in ILD.

Charlie Strange, Medical University of South Carolina, Charleston, USA, and Gerry McElvaney, Irish Centre for Genetic Lung Disease, Dublin, Ireland, described the variability in CT-based lung density measurements used to assess the progression of emphysema in patients with AAT deficiency. Clinical trial data indicate that accurate CT lung density measurements are superior to lung function measurements and other endpoints to detect disease progression. However, Strange presented data that showed the considerable impact of acute exacerbations of COPD on CT imaging measurements.

One organisation working to improve the accuracy and value of imaging data in lung diseases is the Open Source Imaging Consortium (OSIC), Saugatuck, Michigan, USA. Elizabeth Estes, who works for OSIC, explained that OSIC aims to build a large, global database of anonymised patient data and CT images in ILD, with plans for future expansion into other rare lung diseases. The ultimate goals of this effort are to encourage collaboration, and to develop machine learning algorithms to improve clinical decision making in rare lung diseases.

The Challenges of Diagnosis and Differentiation in Interstitial Lung Disease

Daiana Stolz and Marlies Wijsenbeek

Stolz explained that complex cases of ILD that are difficult to diagnose are often encountered in a tertiary care pulmonary clinic. Stolz highlighted that two cases of interstitial lung disease (ILD) may appear similar from HRCT, showing lung opacities and interstitial reticulation, yet they can have dramatically different disease course and survival outcomes.

Therefore, there is an unmet need to improve diagnosis and differentiation in ILD through the use of advanced imaging techniques. Stolz stressed that such techniques provide hope for improved disease recognition, prognostic prediction, and expedited treatment. The ultimate aim for such improvements is to deliver personalised medicine by being able to forecast individual therapeutic responses.

As an example, Wijsenbeek described a clinical case of a 52-year-old patient who presented with shortness of breath during mountain climbing in 2017. The following year, the patient had developed a cough and their symptoms persisted. Over the next 3 years, they had five different diagnoses at six different institutions, including dyspnoea on heights, pneumonia, sarcoidosis, idiopathic pulmonary fibrosis (IPF), and fibrotic hypersensitivity pneumonitis (HP). Following diagnosis with HP, a treatment with prednisone was started, which reduced the symptoms of cough. However, the patient's

pulmonary fibrosis was progressing despite management, and they were started on anti-fibrotic treatment. Further diagnostic work-up at the Erasmus Medical Centre, Amsterdam, the Netherlands, revealed a pathogenic variant of the *PARN* gene and a very short telomere length (below the first percentile). The multidisciplinary team made the diagnosis of HP with progressive pulmonary fibrosis in the context of a pathogenic variant of the *PARN* gene. The patient's condition continued to decline, and they were identified as eligible for lung transplantation. Following transplantation, the patient is now doing reasonably well.

Wijsenbeek highlighted that the patient's medical history illustrates the diagnostic delays often associated with ILD. On average, it takes seven months for ILD to be diagnosed, with nearly one-third of patients (29%) waiting for 2 or more years for a diagnosis.[1] More than one-half (55%) of patients with ILD are misdiagnosed, and many (38%) are misdiagnosed more than once.[1]

Improvement in timely and accurate diagnosis is an important unmet need identified by patients with pulmonary fibrosis.[2] Studies have shown that patients with IPF diagnosed in the first year after their symptoms develop live longer than those diagnosed later.[3] Short telomere lengths have also been associated with worse outcomes, particularly in patients receiving immunosuppression therapy.[4,5]

In a panel discussion during the symposium, Wijsenbeek explained that one of the advantages of large data repositories, such as that being developed by the Open Source Imaging Consortium (OSIC),[6] is the ability to aggregate data. Wijsenbeek stressed that, in addition to imaging and physiological parameters, factors such as symptoms, quality of life, and patient preferences are also important to consider, and these data can also be included in repositories.

The Open Source Imaging Consortium: A Renaissance Approach to Imaging in Rare Lung Diseases

Elizabeth Estes

OSIC is a global, not-for-profit, co-operative effort between academia, industry, and patient advocacy groups, created to enable radical advancement in early diagnosis, disease course prediction, and disease management in ILD. To achieve these goals, OSIC aims to build the largest, most diverse, global, anonymised ILD database, with the aim of identifying meaningful biomarkers, encouraging the collaboration of competitors in the field, and enabling the cooperation of specialists such as radiologists, pulmonologists, and computer scientists (Figure 1).[6,7]

The Renaissance period of European history cultivated changes in the way people thought by blending together the fields of art, architecture, and science.[8] Estes explained that OSIC used the Renaissance as the inspiration for their approach, anticipating the breakthroughs that could be made through the collaboration of specialists that otherwise work independently in ILD.

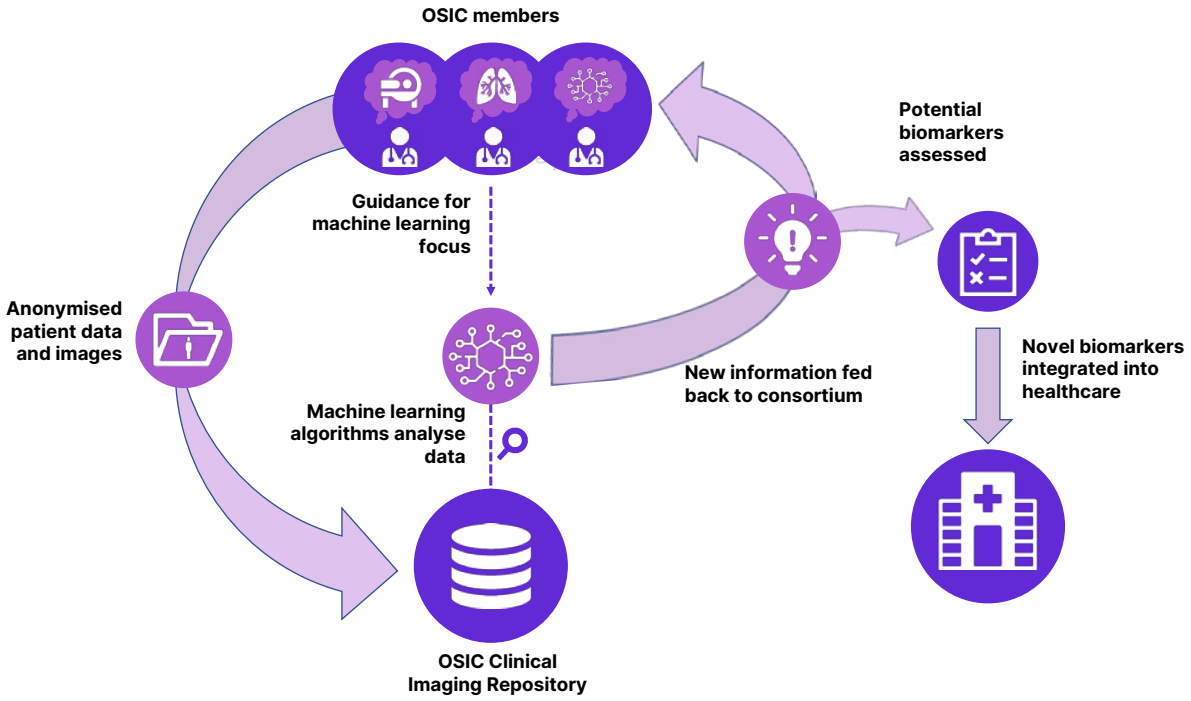
OSIC is led by Kevin Brown, Simon Walsh, and David Barner, experts in pulmonology, radiology, and computational science, respectively.[6] Consortium members include diverse experts from the pharmaceutical and medical device industries, hospitals, universities, and patient advocacy groups.[6]

One of the greatest challenges for OSIC so far is to ensure the adequate protection of patient privacy and data integrity. To meet this challenge, OSIC has been designed to be fully compliant with the European Union (EU) General Data Protection Regulation and the USA's Health Insurance Portability and Accountability Act (HIPPA).[6] All data is anonymised prior to upload, quality control testing is applied at multiple levels, and the platform is continuously monitored for potential flaws or security issues.[6]

The initial target of OSIC was to include a minimum of 15,000 CT scans in the ILD database, and Estes confirmed that this threshold has already been exceeded. Machine learning algorithms will be developed from this data to incorporate this information into commercial analysis tools for imaging, treatment, or therapeutics (Figure 1).[6,7] The ultimate goal is to enable early diagnosis, enhanced prediction of disease prognosis, and improved disease management in ILD.[6,7]

As of September 2022, the OSIC database contained more than 3,000 scans from a total

Figure 1: An overview of the process through which OSIC aims to improve diagnostics, prognostics, and prediction in rare lung diseases.[6,7]



OSIC: Open Source Imaging Consortium.

of more than 2,000 patients, including >80,000 data points such as smoking status, age, and mortality. Initially, Estes explained, OSIC working groups looked for patterns in forced vital capacity decline, which turned out to be difficult because of the noise-to-signal ratio in this endpoint. However, survival analysis for IPF using the clinical data and images from the database revealed that specific characteristics of the pulmonary vasculature were associated with increased mortality.[6] This finding suggests that prognostic markers could be developed from these characteristics, and Estes emphasised that this potential was being openly discussed and investigated among OSIC collaborators.

Survival analysis data were also made available to more than 2,500 machine learning experts worldwide in a crowd-sourced challenge to identify what could be extrapolated from the data.[6] In addition to changes in the pulmonary vasculature, the extent, patterns, and degree of pulmonary fibrosis was identified as an important prognostic factor in IPF.[6]

OSIC is currently working to bring a new patient cohort into the database that will be followed prospectively, as part of the OSIC Project OPUS.[6,7] This study is supported by the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF), the American Lung Association, and Action for Pulmonary Fibrosis (UK), and recruitment will begin in Spring 2023. The initial target recruitment is 100 patients whose medical records, X-rays, and HRCT scans reaching back for 2 years, which will be uploaded. For prospective data collection, patients will be provided with the patientMpower (Dublin, Ireland) application, which will enable home spirometry, patient-reported outcomes, geographic location, and weather data to be recorded on a daily basis.

Estes stressed that in these early stages of the OSIC repository, it is important to understand

what data is meaningful. OSIC's approach is to set up a core dataset and ask collaborators to recommend additional data they feel would be valuable. Estes reiterated that the OSIC aims to understand which analyses do and do not work to improve lung disease diagnosis and prognosis and make these findings available globally.

The initial goal for implementing OSIC learnings is to provide immediate decision support to clinicians, for example, through an algorithm integrated into the picture archiving and communication system used by radiologists. Since HRCT imaging machines and the expertise required to interpret CT scans is not available in all parts of the world, it can be difficult for clinicians to identify subtle disease characteristics from these images. Estes stressed that machine learning algorithms could make far greater use of the data contained within each image and may be able to identify patterns that a human cannot.

OSIC is working to increase the number of control CT scans in the database, to support analyses using artificial intelligence (AI), and to including X-rays and data for lung diseases beyond IPF, such as alpha 1 antitrypsin (AAT) deficiency, bronchiectasis, rheumatoid arthritis-associated ILD, and sarcoidosis.

Estes reiterated that clinicians should consider OSIC a resource for their potential needs or ideas, with the ultimate goal of making radical progress on behalf of patients, by getting solutions to clinicians at the patients' bedside.

Exacerbations in Alpha 1 Antitrypsin Deficiency: Impact on Lung Density

Gerry McElvaney and Charlie Strange

Lung densitometry uses CT scanning to assess the X-ray attenuation of pulmonary tissue, reflecting both the degree of inflation and structural lung abnormalities. Decreased attenuation is commonly seen in emphysema and cystic diseases, and increased attenuation suggests infiltration, inflammation, or fibrosis. Strange explained that lung density is best explained by a CT density histogram, in which a shift of the 15th percentile point (PD15) captures the transition from a healthy lung to an emphysematous lung (Figure 2).[9,10] The RAPID clinical trial programme assessed the effects of an alpha 1 proteinase inhibitor (A1PI)-augmentation treatment on the change in lung density in patients with severe AAT deficiency.[9]

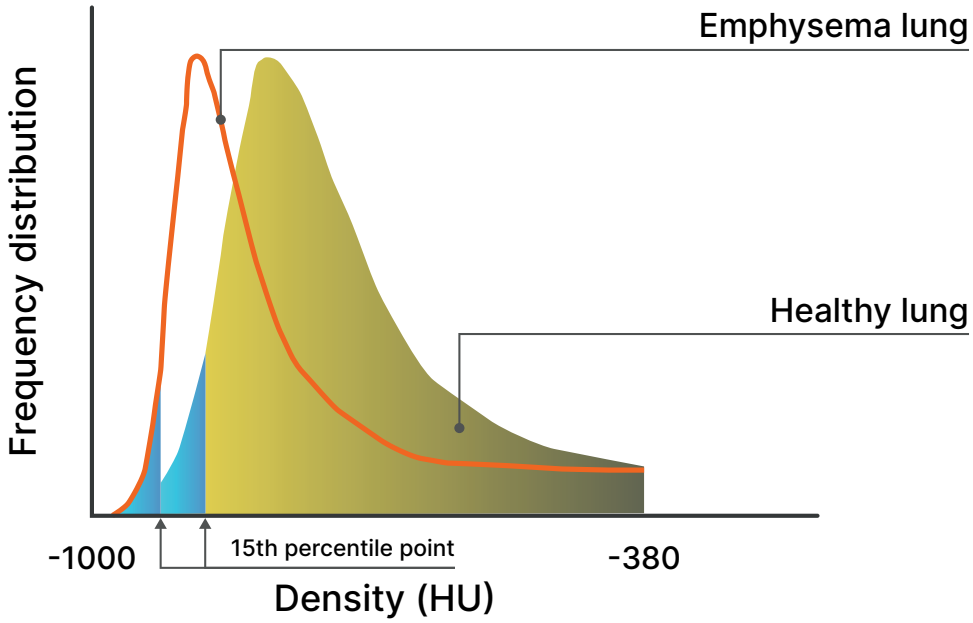
In 2017, the results were published from a 24-month randomised controlled trial on the long-term safety and efficacy of A1PI treatment for emphysema caused by AAT deficiency (RAPID-OLE).[9] The results showed a decrease in the rate of decline in PD15 (normal: 80 g/L) at total lung capacity in patients receiving an A1PI compared with those receiving placebo (-1.51 g/L per year; n=140).[9] Strange explained that this finding indicated that less lung tissue was lost over time in patients receiving AAT versus placebo. In the open-label extension of the trial, patients receiving placebo switched to A1PI, resulting in a significant reduction in the rate of decline of lung density in these patients over the following 24 months.[9] Strange emphasised that these data suggest that A1PI augmentation treatment is capable of preserving lung density.

However, Strange explained that variability is often observed in the PD15 lung density measurements of individual patients with AAT deficiency during the progression of emphysema. Strange explained that lung density decline does not always follow a straight line in these patients, suggesting that there must be variables that affect lung density at different time points. One potential variable is the occurrence of acute exacerbations of COPD.

On average, patients with AAT deficiency experience one or two acute exacerbations of COPD per year,[11] and each event can last up to 2 weeks. During exacerbations, pulmonary function changes include worsening expiratory flow, increased residual volume, and reduced inspiratory capacity.[12] A study by Parker et al.[13] showed it takes about 60 days (approximately 2 months) for pulmonary function to return to normal following an acute COPD exacerbation.

To investigate the influence of patient characteristics and acute exacerbations of COPD on PD15 lung density values, a *post hoc* analysis of the RAPID-OLE data was recently performed (Strange et al., unpublished data).[14] Strange

Figure 2: Lung density, assessed through thin slice CT acquisition, is the most direct measure of pulmonary emphysema.



Air = -1000 HU; Water = 1 HU

The 15th percentile point is the density value that covers 15% of all densities of the histogram.

Adapted from Stolk et al.[10]

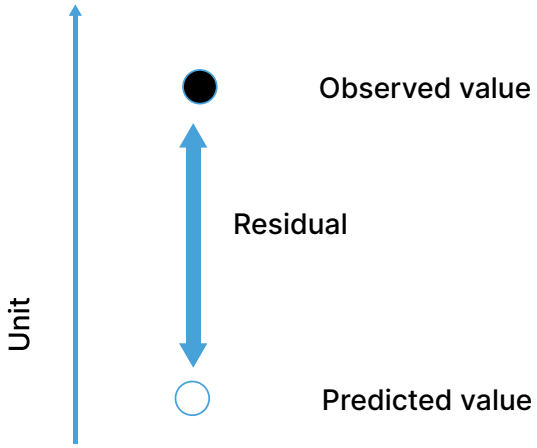
explained that in this study, regression lines were generated for each patient to provide expected PD15 values at each timepoint, and the distance from the expected versus the observed PD15 value (the 'residual') was calculated for each CT scan (Figure 3). The impact of patient baseline characteristics and the temporal proximity to a preceding acute exacerbation of COPD, on the difference between expected versus observed PD15, were investigated.[14]

Strange emphasised that while some of the deviations from the expected PD15 following an acute exacerbation event showed a lung density below the predicted value, some showed an increased density. McElvaney explained that clinicians observe different effects of emphysema in different parts of the lung. In the same lung region, some patients will have mucous impaction of airways, some will show the presence of inflammatory cells, and some will have distal hyperinflation. This clinical observation reinforces the idea that CT scans in individuals with AAT deficiency show heterogenous changes that cannot be reduced to a single pattern of emphysema on a CT image.

The presence of a recent acute exacerbation was found to be the most influential factor for large deviations from the expected PD15 value for lung density measurements.[14] Strange and McElvaney believe that AI will be helpful in decreasing variability between CT scans, and in connecting those outcomes that are particularly important to patients, with the CT-associated measurements associated with their symptoms. They stressed the importance of identifying factors introducing bidirectional deviations from the expected PD15, as this can help to minimise the number of patients needed for a clinical trial.

Overall, the RAPID-OLE trial data indicate that accurate CT lung density measurements should become the gold standard for evaluating emphysema progression in COPD.[11,14] McElvaney emphasised the need to increase the use of CT scans in patients with AAT deficiency and COPD and explained that this would require

Figure 3: Representation of the residual value, calculated from the expected and predicted 15th percentile point values.



changes to radiation protocols and other radiographic modalities.

Further studies are needed to reach the full potential of lung density measurements in these patients, and McElvaney suggested that we need to answer a series of key questions (Box 1).

McElvaney explained that there is considerable heterogeneity in disease parameters in patients with AAT deficiency-related COPD, and that more detailed analyses of CT scans could help to differentiate patients. For example, analysis tools should be refined to include measures such as regional lung density. McElvaney stated that it would be interesting to leverage the OSIC repository to analyse whether the pattern of emphysema progression in AAT deficiency, which generally starts in the lower lung and spreads upwards, differs from other types of emphysema, or between genetic subtypes of AAT deficiency.

In addition, McElvaney stressed that the current markers for acute COPD exacerbation rely on old criteria and patient-reported symptoms; there is a need to improve biomarkers for these events. McElvaney suggested that the OSIC repository might be useful to relate CT scan data during (or immediately after) an exacerbation and relate it to other disease parameters, such as pulmonary function and biomarkers. Strong evidence of this type could be used to support changes in clinical practice guidelines.

Closing Remarks

It is clear that timely and accurate diagnosis is a key unmet clinical need for patients with ILD. Visual inspection of lung CT images permits the assessment of multiple structural changes in the lung, forming an integral part of diagnosing the specific form of ILD, which is a prerequisite to tailoring a treatment regimen for the individual patient. However, sensitive and specific biomarkers are also needed to improve diagnosis, assess treatment response, and determine disease prognosis.

The imaging clinical data repository being developed by OSIC will initially focus on ILD, though this repository plans to expand into other lung diseases such as AAT deficiency in the future. Machine learning algorithms applied to such a substantial collection of data promises to identify new patterns and associations in rare lung diseases, and one that has the potential to be enhanced by AI.

In COPD that is associated with AAT deficiency, a better understanding of the impact of diverse parameters on CT assessment of lung density will help improve this technique's accuracy. When expanded to include conditions beyond ILD, machine learning algorithms applied to the OSIC repository offer the potential to reveal novel information in this arena.

Box 1: Key questions need to reach the full potential of lung density measurements.

Research questions in AAT deficiency:
- How long do changes in CT lung density last after an acute exacerbation of COPD?
- Is there residual damage?
- Do recurrent exacerbations lead to progressive lung density changes?
- Is there a recurrent phenotype for acute COPD exacerbations in AAT deficiency?
- What is the role of bronchiectasis, a condition which is known to commonly occur in patients with AAT deficiency?

AAT: alpha 1 antitrypsin; COPD: chronic obstructive pulmonary disease.

The expert discussions presented in this symposium indicated that the assessment of rare lung diseases should aim to combine data from imaging, physiology, clinical characteristics, and disease progression. AI may support the analysis of these data, increasing the precision and accuracy of diagnosis and prediction of patient prognosis. Imaging biomarkers may represent one of the next generations of biomarkers in lung disease. This is a field that needs to be developed so that it can be of value to patients, clinicians, and regulators, and so that new biomarkers can be included in the future design of clinical trials in rare lung diseases, including ILD and AAT deficiency.

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Contemporary Challenges in the Management of Asthma and Chronic Obstructive Pulmonary Disease: Expert Perspectives on Optimising Outcomes Through Guidelines Implementation, Inhaler Selection, and Patient Engagement

A summary of the presentations at two complementary symposia held on 4th and 5th September 2022 as part of the European Respiratory Society (ERS) International Congress in Barcelona, Spain

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Meeting Summary

Asthma and chronic obstructive pulmonary disease (COPD) affect millions of people throughout Europe, being one of the leading causes of death in the continent. Both conditions also impose considerable morbidity on patients, adversely affecting individuals' physical and psychological wellbeing, and their capacity to live and work normally. Asthma and COPD also impose a substantial economic burden on healthcare providers and wider society through both direct and indirect costs of care.

Inhaler-delivered therapy has been central to the successful management of both conditions for several decades. Advances in device technology and understanding of the pathophysiology of both conditions (while theoretically introducing greater flexibility and responsiveness into the repertoire of inhalation therapies) have also added complexity and sometimes confusion into the task of identifying the precise combination of medication and delivery device best suited to the needs of individual patients.

Recently published multinational consensus reports have set out best-practice frameworks for the management of both asthma and COPD. Presentations at the two symposia summarised in this report examined the implications of these guidelines for the treatment of both conditions. Special focus was on dry power inhalers (DPI) as a means of delivering effective treatment that combines ease of use and widespread acceptance among patients, with the potential to reduce medically-related emissions of greenhouses gases compared with pressurised metered-dose inhalers (pMDI).

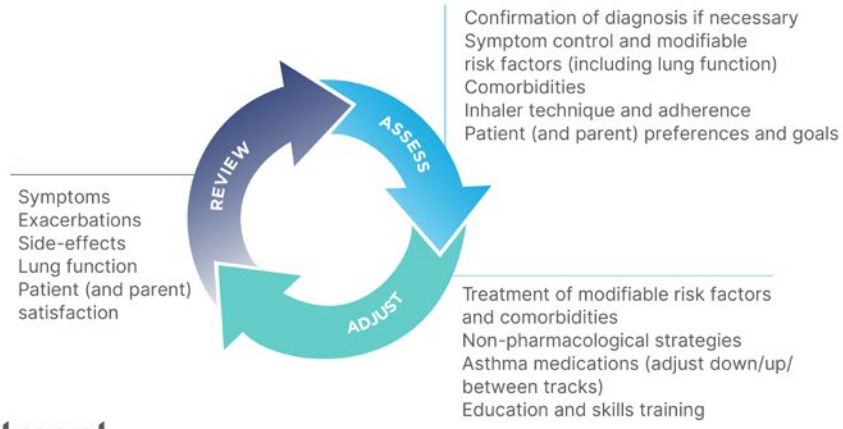
The authors emphasised the importance of patient partnership in determining the care plan, including the choice of both inhaler device and treatment; the benefits of regular monitoring of adherence to the treatment for both patients with asthma and COPD; and the benefits of simplicity, using one type of inhaler where possible to minimise critical errors in inhalation technique.

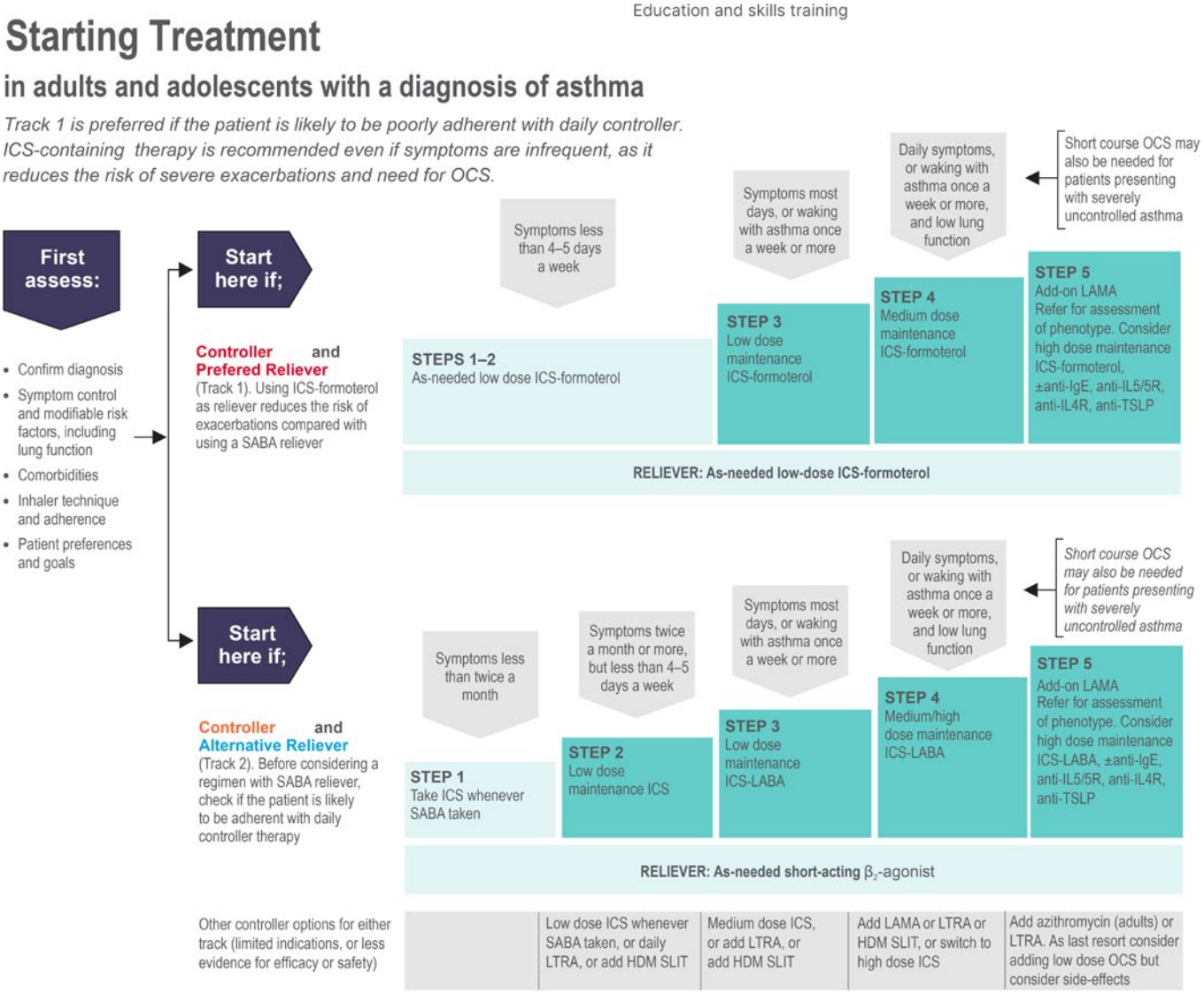
Asthma Pharmacotherapy: Are We on Track?

The 2022 update of the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a choice of one of the two 'tracks' for the management of asthma symptoms and exacerbations (Figure 1).[1] There is a misconception that Track 1 is orientated toward treating symptoms at the cost of long-term asthma control, and that the second track may be superior in preventing or controlling symptoms. This is mistaken, since both tracks emphasise the need for maintenance treatment at equivalent steps, and studies that have compared symptom control, measured according to the GINA assessment tool (well-controlled or partly controlled weeks) have not shown a difference between Track 1 and 2 treatments for these endpoints.[2]

In both tracks, for steps 3 to 5, the recommended maintenance treatment is a dose of inhaled corticosteroid (ICS) plus a long-acting β2-agonist (LABA) according to the severity of disease. The difference, however, is that the reliever used in Track 1 (low-dose ICS plus formoterol instead of a short-acting β2-agonist [SABA]), significantly reduces the risk of severe asthma exacerbations.[3-5] It should be noted that the maintenance and reliever therapy (MART) approach with low-dose ICS plus formoterol may not be indicated in all regions. The efficacy of this so-called MART approach, in which a single inhaler is used as both maintenance treatment and for symptom relief, has been consistently confirmed in meta-analysis of clinical trials and in real-world studies.[3-5] The reasons that Track 1 is the preferred option for most patients are, firstly, that methods for predicting who might be at risk of an exacerbation are imprecise, and even

Figure 1: The 2022 Global Initiative for Asthma recommendation advocate a 2-track approach to asthma management.





From Global Initiative for Asthma (GINA)[1]

Anti-TSLP: anti-thymic stromal lymphopoietin; HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic agonist; LTRA: leukotriene receptor antagonists; OCS: oral corticosteroid; SABA: short acting β2-agonist; SLIT: sublingual immunotherapy.

those whose symptoms are well-controlled are at risk.[6] Secondly, as demonstrated in studies of patient adherence with maintenance treatment in asthma, particularly when assessed with electronic inhaler monitoring, only a minority are found to take their maintenance treatment as prescribed.[7] Instead, patients are over-reliant on their SABA inhaler, the overuse of which contributes to their risk of a potentially life-threatening attack.[8] As further evidence of the similar symptom relief achieved in the two tracks, several studies, including a large 12-month observational study in Europe, had a similar proportion of reliever-free days (61–66%) and a low incidence of high reliever-use days (≤15% of days for one to two as-needed inhalations; ≤2.5% of days for ≥4 as-needed inhalations).[9]

MART is thus a well-evidenced and highly practical asthma therapy; however, if Track 2 is to be used, patients must be educated and encouraged to use their maintenance inhaler consistently. However, for both tracks, regular appraisal of patients' inhaler techniques is essential, and forms an integral part of the GINA cycle of care that urges clinicians to 'assess, adjust, review', particularly before increasing or decreasing maintenance treatment.

The need for awareness and a willingness to adapt to changed circumstances are not solely the responsibility of patients. High levels of inertia have been recorded among doctors in France treating asthma, with a large proportion of patients remaining on the same ICS dose that they were started on years earlier, and only a small proportion of patients with inadequate asthma control having their controller therapy adjusted.[10] There is no reason to think that doctors elsewhere are doing notably better, although this may vary by specialty.[11-13] The role of physician inertia as an important potential limitation in asthma treatment needs to be recognised and rectified.

Takeaways from this appraisal of the GINA two-track strategies illustrate that, while each provides a position from which to work, clinical discretion, and good judgement by physicians remains, recognising that:

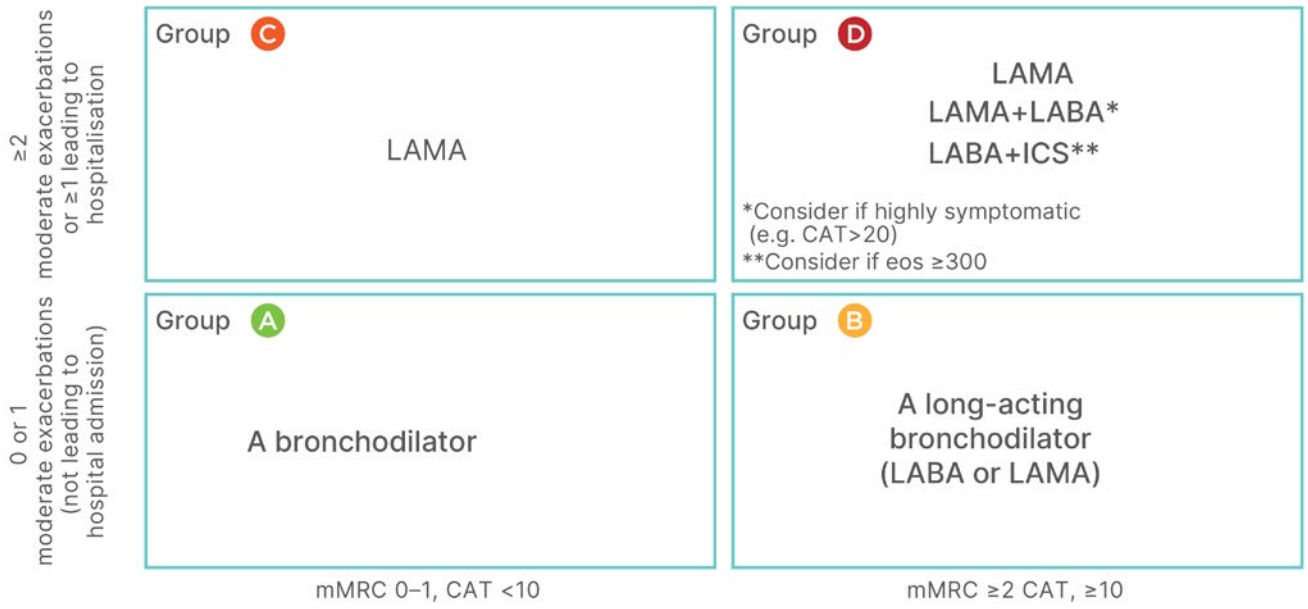
- Although both GINA tracks aim for (almost) complete symptom control, this is not achieved in a large proportion of patients.
- Predicting which patients are at heightened risk of exacerbations is a complex exercise, as is predicting adherence to controller therapy.
- The choice of a treatment track must factor in the risks associated with use of high-dose ICSs (e.g., osteoporosis, pneumonia, and cataracts), the impact of more frequent (and potentially life-threatening) exacerbations, and the convenience (and resultant possible greater efficacy) of single versus multiple inhalers.
- Patient engagement, and understanding their perspectives and choices, are key determinants of success with both GINA tracks, recognising that the demands on patients differ between tracks. This may influence their buy-in to the proposed approach. Knowing the patient (their attitudes to treatment, preferences for risk, and tolerance of symptoms) is, therefore, an important element in selecting a treatment track.

Treatment of Chronic Obstructive Pulmonary Disease: As Good as GOLD, or Easy As ABCD?

The 2022 report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) global strategy for the diagnosis, management, and prevention of COPD establishes a systematic framework for the pharmacological treatment of the condition that harnesses both disease phenotype and biomarker information to guide prescribing.

The first step in the treatment pathway is the assignment of patients to Category A, B, C, or D according to their level of symptoms (columns in Figure 2) and risk of exacerbations (rows in Figure 2). This shapes the selection of appropriate drug therapy. For patients in Category A, a short-acting bronchodilator may suffice, but for patients in other categories longer acting bronchodilators are necessary; GOLD prefers a long-acting muscarinic antagonist (LAMA) to a LABA because of the better effect on exacerbations of the former.[14]

Figure 2: The Global Initiative for Chronic Obstructive Lung Disease 2022 framework for initial pharmacological treatment of chronic obstructive pulmonary diseases stratifies patients according to patients' level of symptoms (columns) and risk of exacerbations (rows).



CAT: COPD Assessment Test; eos: eosinophils; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council.

Combination of a LABA and a LAMA as an initial treatment is still somewhat controversial, as there is limited evidence from randomised controlled trials (RCT) in newly-diagnosed patients. However, post hoc analysis of treatment-naïve patients in RCTs,[15] and the results of the EMAX[16] study (which included treatment-naïve patients or those on a single long-acting bronchodilator), support this choice in patients with a marked symptom burden (in essence, Categories B or D). The possible use of an ICS as part of a combination treatment at this stage is predicated on the eosinophil count.

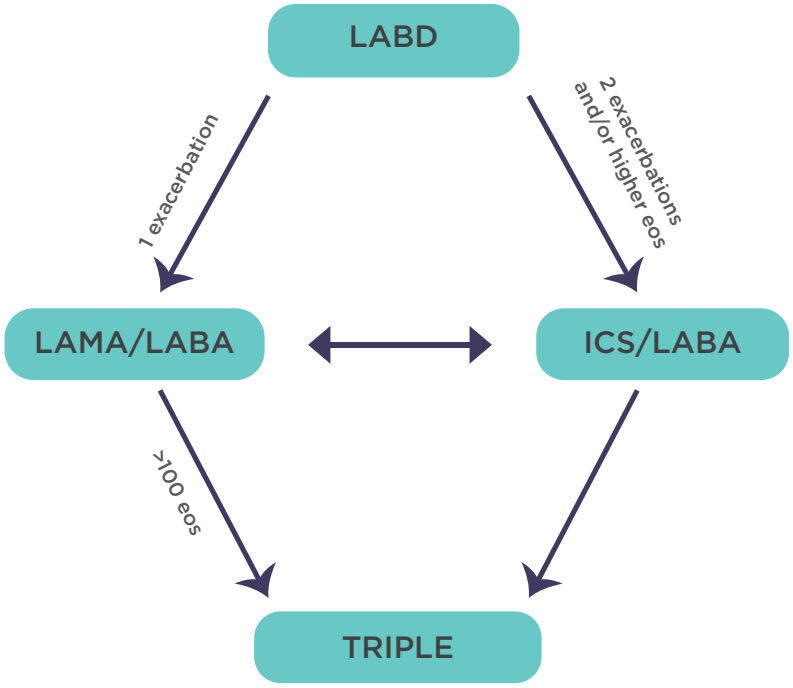
For patients with persistent exacerbations despite initial pharmacological treatment, RCT evidence supports escalation to double and triple therapies involving LAMA, LABA, and ICS. GOLD suggests a pathway for the implementation of this evidence, again using eosinophil count as a guide to the use of ICS (Figure 3).[14]

There is now ample RCT evidence indicating that the clinical responses to ICS treatment in COPD are more pronounced in patients with baseline eosinophil counts that are approximately equal to 100/µl,[17-20] with a continuous relationship above that threshold such that the exacerbation rate is approximately halved at an eosinophil count of >300/µl.[17] The benefits of ICS as an element of triple therapy is provided by the IMPACT trial, which recorded a 42% reduction in on-treatment mortality in patients with COPD at high risk of exacerbation treated with triple therapy versus LAMA plus LABA therapy.[21] A reduction in the incidence of exacerbations as seen in the IMPACT trial is likely to have contributed to the survival benefit.[22]

The pathophysiological mechanism underpinning the relationship between eosinophil status and response to ICSs is thought to involve a greater propensity to T2-mediated inflammation and shifts in the bacterial pulmonary microbiome with, in particular, a reduction in the prevalence of *Haemophilus influenzae* as eosinophil numbers increase.[22]

Despite advances in precision-medicine in COPD, the importance of inhaler device selection remains important, as multiple age-related comorbidities can complicate this issue.

Figure 3: The Global Initiative for Chronic Obstructive Lung Disease recommendations for escalation of inhaled therapy for chronic obstructive pulmonary disease are framed in terms of exacerbation risk and eosinophil levels/counts.



Adapted from Singh et al.[14]

Eos: eosinophil; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LABD: long-acting bronchodilators; LAMA: long-acting muscarinic antagonist.

Worsening hypoxaemia or hypercapnia; cognitive impairment and dementia; neurological or neuromuscular conditions such as Parkinson's disease, or the aftermath of a stroke; loss of muscle strength in the hands and fingers, or the impact of arthritis and joint pain on finger flexibility and co-ordination may all contribute to increased difficulty of inhaler use and a heightened risk for critical operator errors.[23]

To address these limitations is a multi-step approach to inhaler selection that starts with an overview of patients' ability to use any given device in the context of their cognitive function, manual dexterity, and hand strength, and then assesses; medication availability, cost, and reimbursement; and patient preferences for specific devices. Once an initial choice has been made, the healthcare provider needs to demonstrate correct technique and assess patient adoption of it before the chosen device is prescribed for a trial period. Thereafter, regular assessment includes review of adherence, continued use of correct technique, and therapeutic impact, and the imparting of information concerning changes to therapy and/or device selection.[23]

Other aspects of physical and mental health also need attention. Physical activity levels are a predictor of survival in patients with COPD. While that association does not establish cause and effect, or guarantee that increasing physical activity in patients with COPD will reduce mortality, it does create a strong *prima facie* case for rehabilitation and exercise programmes designed to foster and sustain greater physical activity.[24] The GOLD 2022 report provides a current consensus view of the feasibility and impact of various types of interventions designed to increase physical activity in patients with COPD.[25]

Exercise may also have a beneficial impact on anxiety and depression, which is noteworthy because both are frequently encountered in

COPD, and are associated with poor prognosis, lower forced expiratory volume in the first second after full inspiration, higher (i.e., worse) scores on COPD-specific questionnaires,[26,27] and a range of other comorbidities.[25] There is no reason to believe that anxiety and depression need to be treated differently in patients who also have COPD, but the finding that COPD patients are 1.9-times more likely to commit suicide than people without is a clear indication that they should not be disregarded.[28] Conversely, COPD is widely encountered, but often underdiagnosed and undertreated, in patients with other psychiatric illnesses, and this oversight also needs attention.[29]

Tailoring Therapy and Empowering the Patient

A common theme running through both symposia was the importance of matching individual patients with asthma and COPD to the type of inhaler best suited to their particular needs. Inappropriate inhaler choice and/or poor inhaler technique impact have on patient health and outcomes in both conditions.[30-32] As remarked is an earlier commentary article on this subject: 'Choosing an inhaler device for drug administration in patients with obstructive airway diseases is as critical as the choice of medication itself, and that in future, the choice of a new compound will be secondary to the need to choose the appropriate inhaler device for the patient.'[33]

Various detailed comparisons of inhalers underpin this general conclusion. For example, successful use of a pMDI requires slow inhalation and co-ordination with device actuation (unless a spacer device is also used), whereas use of a DPI avoids the need for co-ordination, but requires device preparation and fast inhalation.[34] This second requirement has raised concerns that, especially for patients with COPD, the inhalation effort required by a DPI may be infeasible. While optimal peak inspiratory flow (PIF) for good inhalation of medication varies from one DPI model to another, generally within the range of 30–60 L/min, research among patients with COPD from a large Kaiser Permanente database indicates that some 99% of patients with COPD have PIF ≥50 L/min and can, therefore, successfully use an appropriately configured DPI. Careful selection within the DPI class is nevertheless essential.[35,36] The demonstration in head-to-head comparison that the Easyhaler® (Orion Pharma, Finland) than Turbuhaler® (AstraZeneca, UK) provides better dose delivery and consistency of dosing at all PIF rates is an example of the sort of data that can guide choice.[37]

Within the DPI class, the number of preparation steps to use of the device varies from three to 11 according to the model used,[38] and the patients' ability to execute each step in the sequence may affect the success of self-medication. It is thus of some note that both patients with asthma and COPD of varying degrees of disease severity master the five preparatory steps in correct use of Easyhaler® at their first training session.[39] Similarly, there can be considerable differences in patients' reception of different inhalers due to the finger strength required for their operation, with mDPIs requiring the ability to develop markedly more force than most DPIs.[40] Patients' finger strength (and dexterity) should, therefore, be a consideration when selecting an inhaler device. Minimising the scope for error by using only one inhaler device improves clinical outcomes and reduces health care cost compared with multiple-inhaler regimens for patients with asthma or COPD.[41,42]

Both GINA and GOLD endorse regular review of patient comfort and competence with their inhalers as part of the core asthma/COPD management cycle, with adjustments as necessary. As a result, the voice of the patient is an increasingly powerful factor in discussions about what is the best inhaler device for long-term success.

Lessons relating to patient engagement and empowerment in Finland's National Asthma Programme and National COPD Programme[32,43] include:

- Respiratory disease programmes in general are cost saving, and have the potential to increase respiratory health.
- Self-management and easily accessible information for patients and the public is essential.

- Adherence to management is crucial in chronic disease; promoting adherence may have a greater effect on health than improvements in specific medical therapy.

- Building trust to optimise adherence to treatment requires patient support programmes; repeated patient education to foster high levels of self-efficacy; and healthcare professional behaviours to optimise and promote personalised care.[44-47]

- There is potential for mobile health to facilitate adherence, but evidence to date is mixed.[48-50]

Inhaled Medications and the Environment: What's Good for Patients Is Good for the Planet

Growing appreciation of the carbon footprint of respiratory care has led to a heightened emphasis on the potential for greenhouse gas emissions associated with inhaler use. Hereby, the authors reviewed some of the considerations shaping medical practice in response to climate-change concerns.

Prominent among these is the 'global warming potential' (GWP) of propellants used in pMDIs. Taking CO_2 as a referent and assigning it GWP of one, the chlorofluorocarbon propellants of early pMDIs had GWPs of between four and 10,000. Even 1,1,1,2-tetrafluoroethane, a non-ozone-depleting propellant currently favoured in many pMDIs, has a GWP of 1,300. Other candidate propellants, such as HFA152a, offer further improvement, but nevertheless HFA152a still has a GWP of 138. These data[51] identify pMDI propellants, together with industrial use of these gases which are responsible for an estimated 2% of global emissions, as being among the most potent human-generated greenhouse gases.

As a result of these properties of propellants, the carbon footprint per dose (expressed as grams of CO_2 equivalent [CO_2 e]) of conventional pMDIs is considerably higher than that of propellant-free DPIs. In its 2018 assessment, the Medical and Chemical Technical Options Committee of the Montreal Protocol estimated the carbon footprint of a typical DPI at <20 CO_2 e per dose, compared with 200–300 CO_2 e per dose for a pMDI using HFC-134a as propellant, and 600–800 CO_2 e per dose for a pMDI using HFC-227ea.[52] As an example, the Easyhaler® devices generate <5 g/CO_2/dose.[53]

Superficially, there may appear to be a tension between optimising patient care and minimising treatment-related contributions to greenhouse gas emissions. In fact, these objectives are very closely aligned because the best achievable control of asthma minimises disease-related greenhouse gas generation. For example, Kponee-Shovein et al.[54] have shown that use of a DPI to deliver SABA medication for the management of mild asthma exacerbations or moderate exacerbations not requiring a doctor's visit generates close to zero CO_2 e, compared with a carbon footprint of 0.3–2.5 kg CO_2 e depending on the severity of the exacerbation and the volume of the pMDI. (CO_2 e generation for more severe exacerbations is similar for all devices because it is dominated by other sources, such as travel- and hospital-related activities).[54]

The climate-favourable effect of good asthma control has been further illustrated by Wilkinson et al.[55] in work presented as an abstract at the 2021 International Congress of the European Respiratory Society (ERS). A cohort of >200,000 patients aged ≥12 years was identified in the UK Clinical Practice Research Datalink (2007–2017), and stratified according to whether they had well-controlled asthma (defined as use of <3 SABA canisters/year and no exacerbations at baseline) or uncontrolled asthma (≥3 SABA canisters/year or ≥1 exacerbation). Of these, 48% of patients fulfilled the definition of having uncontrolled asthma. Those patients were estimated to generate an average of the equivalent of 191.6 kg/year of CO_2 e, a result of the management of their asthma, compared with 63.6 kg/year among patients classified as having controlled asthma. Overall, about two-thirds of emissions were attributable to use of inhaled SABAs although, as in the work of Kponee-Shovein et al.,[54] the proportion attributable to inhaled medication declined as the severity of asthma exacerbations increased.

Those findings are amplified by the data from the SABINA study. This overview of SABA use in asthma in European countries identified

high levels of SABA overuse (defined as ≥3 canisters/year) in five countries, despite different healthcare frameworks and funding models. Other SABINA data have linked overuse of SABAs with increased risk of exacerbation and mortality in Sweden.[8]

These findings intimate that reducing heavy dependence on reliever medication and limiting asthma exacerbations and asthma-related hospitalisations benefits both patients and the environment. Proposals for mitigating the environmental impact of inhalation therapy, and therefore stress reduction in SABA use, including reducing need for SABAs in asthma management; replacing pMDIs with DPIs in SABA reliever treatment; and replacing pMDIs with DPIs in ICS and ICS/LABA treatment.

Overall Take-Home Messages from the Two Symposia

- Knowing your patient with asthma or COPD contributes to treatment selection; however, patient behaviour ultimately determines the outcome of the treatment selection.
- Effective treatment of COPD utilises precision medicine to help reduce mortality.
- Informed decision making must evaluate the risk of high-dose ICS treatment, more frequent exacerbations, and convenience of one versus multiple inhalers.
- There is a very large difference in carbon footprint between DPI and pMDI inhalers. Poor asthma control and overuse of salbutamol HFC-134a pMDIs are associated with a higher carbon footprint.

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Abstract Reviews

Clinical research abstracts from ERS Congress 2022.

Surgical Management of Superior Sulcus Tumours: A 20-Year Experience of an Oncological Referral Centre

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Keywords: Biostatistics, lung cancer, Pancoast syndrome, superior sulcus tumour.

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BACKGROUND AND AIMS

The authors present a study that investigated the clinical features and therapy of superior sulcus[1-3] non-small cell lung cancer during a 22-year period.

MATERIALS AND METHODS

There was a review of 100 patients who underwent curative surgery for superior sulcus non-small cell lung cancer during a 22-year period (July 1998 to December 2020). Patients with an apical tumour and Pancoast syndrome, superior sulcus tumours with invasion of the chest wall, vertebral body, and/or subclavian arteries met the inclusion criteria. The surgical strategy was determined by the location of the lesion and the architecture of the thoracic inlet. To quantify operative morbidity and mortality, all deaths occurring within 30–90 days following surgery or during hospitalisation were considered. From the date of operation to the date of death or last contact with the patient, overall survival (OS) was calculated. Using the Kaplan–Meier methodology, non-cancer-related fatalities were included in survival curves, and the log-rank test was used to compare survival rates between patient groups. Using Cox proportional hazards regression, the correlation between certain clinical and pathologic features and OS were evaluated.

RESULTS

During the study period, 54 patients were administered induction therapies: 53 patients underwent anterior thoracotomy, 30 underwent Paulson incision, and 8 underwent a combination surgical procedure. There were 84 lobectomies, three pneumonectomies, seven lobectomies with bronchoplastic reconstructions, and seven wedge resections were performed as lung resections. The median number of ribs resected was two (range: 1–5). Chest wall reconstruction was performed on 57 individuals, 23 patients underwent an accompanying vascular resection, and 85 patients underwent radical (R0) resection.

The median length of stay after surgery was 11 days (range: 5–27 days). Overall mortality at 90 days was 6.93%. The average OS lasted 24.3 months (Figure 1). After a median of 3 years of follow-up, the 5-year and 10-year OS rates were 33.9% and 26.4%, respectively. The significantly lower 5-year OS was observed in patients with the nodal disease (46.6% in pN0

Figure 1: The overall survival of patients.

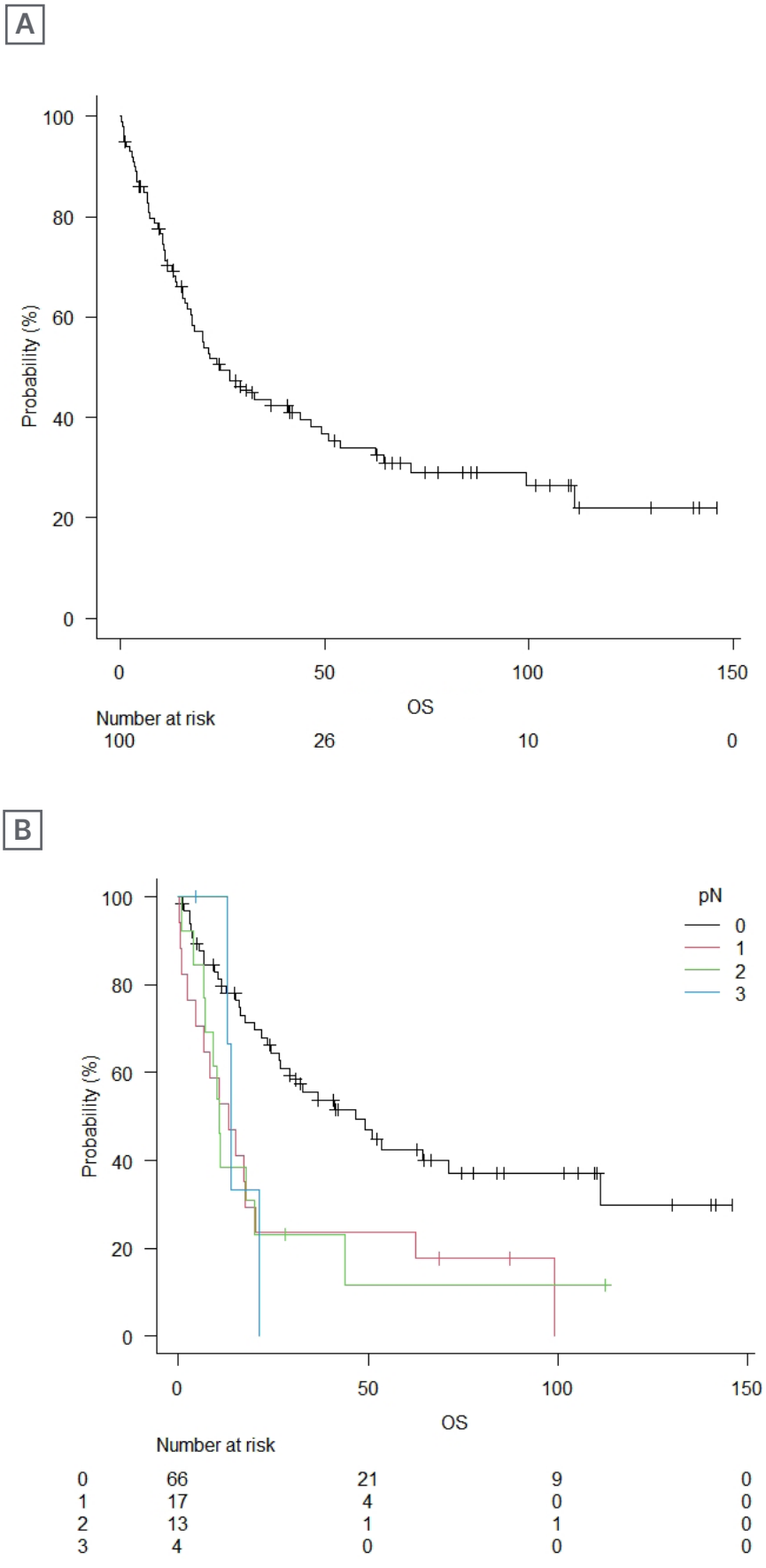

Figure 1 continued.

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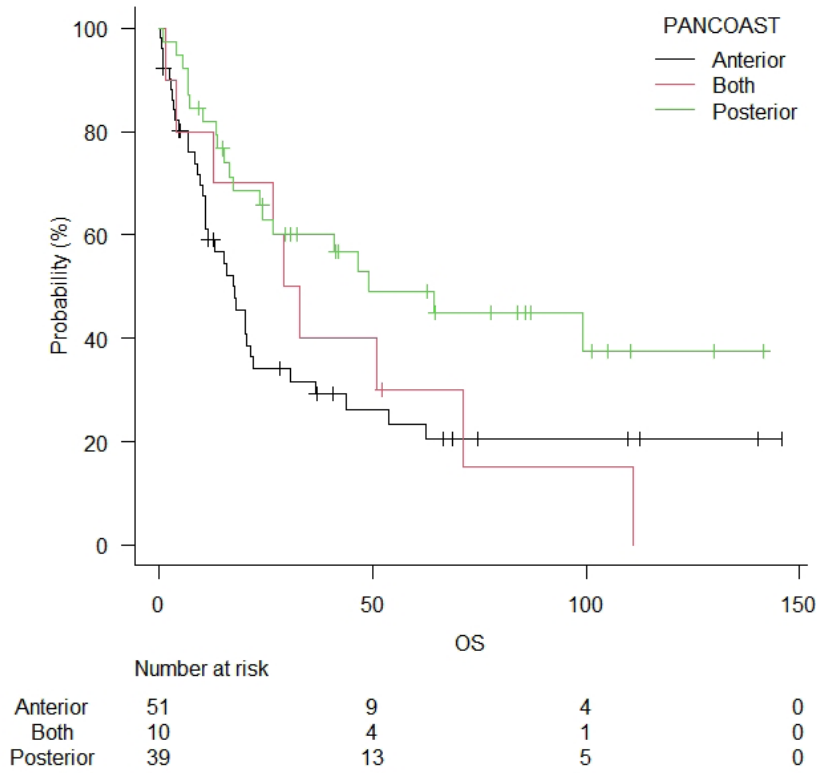

A) Overall survival. **B)** Overall survival in patients stratified for nodal disease (log-rank trend test: p=0.00065). **C)** Location of the tumour (log-rank trend test: p=0.01).

OS: overall survival.

versus 13.2% in pN+; p=0.024), without pre-operative treatments (41.0% in patients without pre-operative treatments versus 17.4%; p=0.09), and an anteriorly located tumour (17.4% versus 49.1%; p=0.032). Cox proportional hazards regression revealed superior survival in pT1 (hazard ratio: 4.6; 95% confidence interval: 1.9–11.2; p=0.00076) and R0 (hazard ratio: 4.2; 95% confidence interval: 1.4–12.5; p=0.010) stages.

CONCLUSION

Superior sulcus tumours continue to be a life-threatening illness that, despite being treatable in a substantial proportion of cases, necessitates complex operations with high surgical risks and a multimodal therapy approach. Physicians should plan the optimal surgical approach to maximise resection completeness and patient survival. Other factors influencing survival are associated with the stage of the tumour, underlining the significance of a comprehensive pre-operative evaluation and candidate selection to identify those who are anticipated to experience a survival benefit.

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Home Mechanical Ventilation in Children: Experience of Paediatric Pulmonology Divisions in Istanbul

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BACKGROUND AND AIMS

Advances in technology in recent years increased the long-term survival rate of patients with chronic respiratory failure. As a result, the number of patients receiving long-term home mechanical ventilation (LTHV) support is increasing worldwide.[1] The most important step in the management of patients with home mechanical ventilation (HMV) is to ensure adequate oxygenation and ventilation. Successful care at home requires the presence of trained caregivers and accessibility to medical devices and a care team.[2] The aims of this study were, to describe the characteristics of children on LTHV in Istanbul, to compare the patients receiving non-invasive ventilation (NIV) and invasive ventilation, and to evaluate the frequency and risk factors of hospital admission in this population.

MATERIALS AND METHODS

This multicentre, cross-sectional study included LTHV patients followed by paediatric pulmonology divisions of six tertiary hospitals in Istanbul. LTHV was defined as the requirement of a mechanical support for breathing for all or part of the 24-hour day and living for at least 3 months outside the hospital or in a non-acute care setting.[3,4] Children on HMV for less than 3 months and children with tracheostomy but without ventilator support were excluded. Demographic characteristics, underlying diseases, presence of concomitant diseases and comorbidities, characteristics of ventilation including location of initiation of LTHV, ventilation parameters, equipment, duration between decision to discharge with LTHV, duration and time period, feeding method, swallowing dysfunction, and nutritional status were recorded. Data regarding emergency department visits and hospitalisations at ward or intensive care unit during the last 12 months were obtained from medical records.

RESULTS

A total of 416 patients were included. The median age was 4.3 years (interquartile range: 2.0–10.3 years). Of the patients, 54.1% were male. While 49.5% (n=206) received NIV, 50.5% (n=210) received invasive ventilation. The median age at initiation of HMV was lower in the invasive ventilation group (10 versus 41 months; p<0.001). The duration between the decision to start and the actual start of HMV was longer

in the invasive ventilation group (30 versus 8 days; p<0.001). Most of the subjects in the NIV group (81.1%) received support during sleep while most of invasive ventilation group (55.7%) received continuous life support (p<0.001). In addition to ventilation support, 41.9% of the invasive ventilation group and 28.6% of the NIV group were also on O_2 therapy (p=0.002). Neuromuscular diseases (NMD) were the most common primary diagnosis: 35.1% (n=146) of the patients had NMD. Most of children with NMD (n=102) had Type 1 spinal muscular atrophy. HMV decision was made according to polysomnography in 26.9% (n=56) of the children and based on blood, gas, and clinical status in the remaining patients. Data regarding demographic characteristics, underlying disorders, and indications for HMV in NIV and invasive group are presented in Table 1. Fifty-nine percent of the patients were hospitalised (ward or intensive care unit) within the last year. Risk factors for hospitalisation were invasive ventilation, continuous life support, O_2 need, tube feeding, and swallowing dysfunction

Table 1: Demographic characteristics, underlying disorders, and indications for home mechanical ventilation in non-invasive ventilation and invasive group.

	NIV (n=206); median (interquartile range)	Invasive ventilation (n=210); median (interquartile range)	Total (n=416); median (interquartile range)	p
Ventilation data				
- Age at initiation of HMV, months	41 (11–123)	10 (5–43)	18 (7–83)	<0.001
- Duration between HMV decision and start of HMV, days	8 (2–16)	30 (15–45)	15 (5–30)	<0.001
- Duration of HMV, months	14 (6–32)	17 (6–37)	16 (6–36)	0.210
- HMV during sleep, n (%)	167 (81.1)	71 (33.8)	238 (57.2)	<0.001
- Continuous life support, n (%)	30 (14.6)	117 (55.7)	147 (35.3)	
- Number of patients receiving O_2, n (%)	59 (28.6)	88 (41.9)	147 (35.3)	0.002
Underlying disorders				
- NMD, n (%)	71 (48.63)	75 (51.37)	146 (35.10)	N/A
- Neurological diseases, n (%)	36 (33.64)	71 (66.36)	107 (25.72)	
- Lung parenchymal diseases, n (%)	48 (80.00)	12 (20.00)	60 (14.42)	
- Airway anomalies, sleep apnoea, n (%)	10 (76.92)	3 (23.08)	13 (3.13)	
- Congenital heart diseases, n (%)	6 (46.15)	7 (53.85)	13 (3.13)	
- Genetic, syndromic, metabolic diseases, n (%)	29 (43.28)	38 (56.72)	67 (16.10)	
- Congenital central hypoventilation syndrome, n (%)	4 (57.14)	3 (42.86)	7 (1.68)	
- Thorax deformities, n (%)	2 (66.67)	1 (33.33)	3 (0.72)	
Indications				
- Hypoxia, n (%)	6 (2.91)	23 (10.95)	29 (6.97)	N/A
- Hypoxia and hypercapnia, n (%)	94 (45.63)	119 (56.67)	213 (51.20)	
- Persistant atelectasis, n (%)	9 (4.37)	7 (3.33)	16 (3.85)	
- Increased work of breathing, n (%)	41 (19.90)	61 (29.05)	102 (24.52)	
- OSAS, n (%)	46 (22.33)	0	46 (11.06)	
- Central apnoea, n (%)	7 (3.40)	0	7 (1.68)	
- Mixed apnoea, n (%)	3 (1.46)	0	3 (0.72)	

HMV: home mechanical ventilation; NIV: non-invasive ventilation; NMD: neuromuscular diseases; OSAS: obstructive sleep apnoea syndrome.

(p=0.002, 0.009, <0.001, <0.001, and <0.001, respectively). Additionally, 65.2% of the subjects (n=86) with no hospitalisation in the last year had no swallowing dysfunction, whereas 59.1% (n=143) of subjects who had hospitalisation had swallowing dysfunction (p<0.001).

CONCLUSION

Multidisciplinary follow-up of children on LTHV with complex medical problems is important in order to decrease morbidity and mortality.

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Phenotypes of Post-COVID-19 Interstitial Lung Disease: Clinical, Radiological, and Pathological Correlations

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Keywords: COVID-19, cryobiopsy, interstitial lung disease (ILD), multidisciplinary diagnosis, post-COVID-19 damage.

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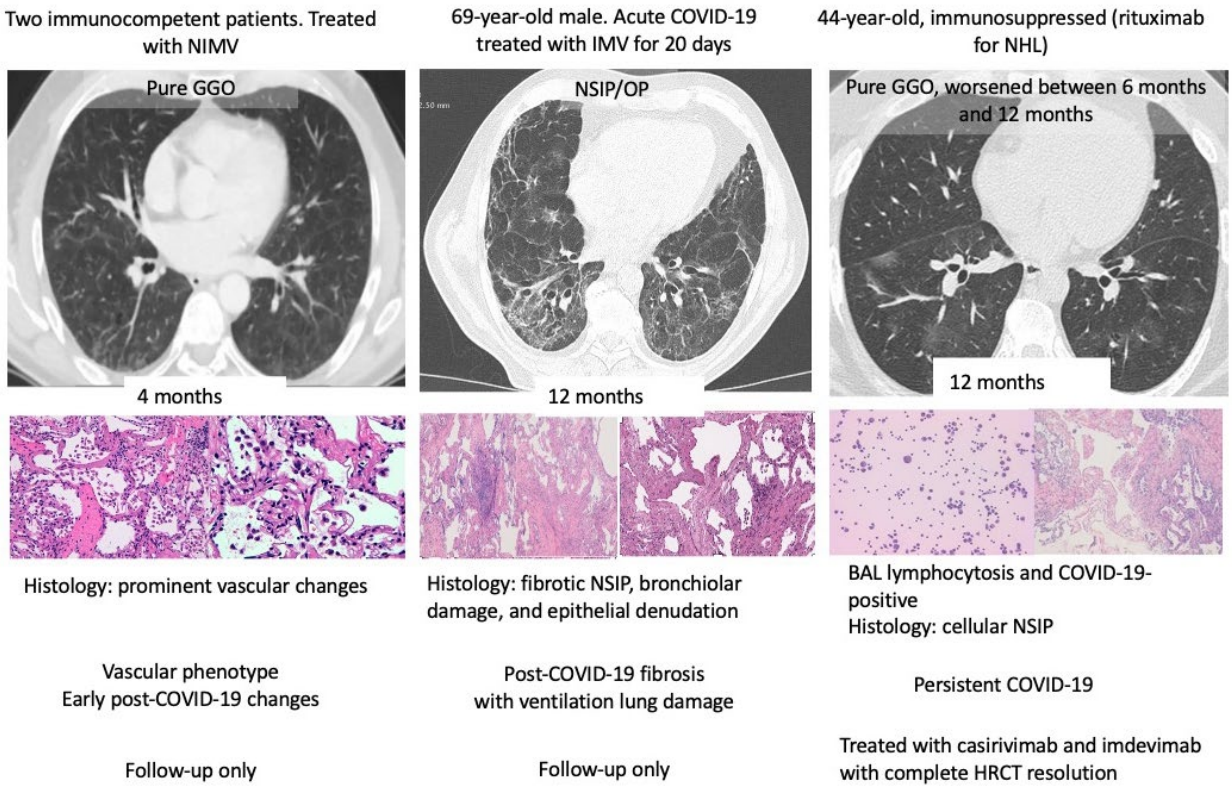
BACKGROUND AND AIMS

Pulmonary sequelae after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection range from limited abnormalities to major interstitial lung diseases (ILD). Bronchoalveolar lavage (BAL) and cryobiopsy findings, integrated with the clinical and radiological scenario, may help clinicians to correctly manage patients and aid researchers in better understanding the features and pathogenic mechanisms of post-COVID-19 fibrosis.

MATERIALS AND METHODS

The authors conducted PCOILS, a prospective, multicentre, national (Italian) study. In two centres, Florence and Forlì, subsequent patients seen at 4–18 months after the acute infection. They underwent transbronchial lung cryobiopsy and BAL if they showed a significant ILD on follow up with high-resolution CT (HRCT; progressive and/or symptomatic and/or with pulmonary function impairment). The authors enrolled 266 patients with follow-up HRTC at

Figure 1: Three post-COVID-19 phenotypes were identified by the authors.



BAL: bronchoalveolar lavage; GGO: ground-glass opacity; HRCT: high-resolution CT; IMV: intermittent mandatory ventilation; NHL: non-Hodgkin lymphoma; NIMV: non-invasive motion ventilation; NSIP/OP: nonspecific interstitial pneumonia overlap organising pneumonia.

6 months after infection. Patients underwent chest HRTC during follow-up (after 6, 12, and 18 months) and in anticipation of biopsy. Cryobiopsy was proposed to patients when the post-COVID-19 ILD was persistent and clinically significant.

RESULTS

In total, 19 patients were biopsied. Patients underwent cryobiopsy at different timings with respect to SARS-CoV-2 infection, with an interval that varied between 4 months and 18 months (median: 6 months). The median age of patients was 66 years (range: 39–76 years). Of the patients, 18 were male (95%) and one was female (5%). Eleven cases (58%) were former smokers. Eight out of 19 (42%) patients had occupational exposure that may result in ILD. The authors' radiologists evaluated the cases and found a median extent of damage of 40% (range: 10–70%).

The patterns according to Solomon-Lynch were 10 cases of mixed ground-glass opacity (GGO) and fibrosis; five cases of GGO, three predominantly fibrotic; and one case of sarcoid-like reaction. Pulmonary function tests were performed in all patients with median forced vital capacity values of 89% (53–123), and median diffusing capacity of the lungs for carbon monoxide values of 66% (37–106). Once the histological preparations were acquired, three different pathologists (University Hospital of Careggi, Hospital of Reggio Emilia, and Hospital of Forlì, Italy) evaluated the images in blind, entering the data in the platform. Then, a multidisciplinary (pulmonologists, pathologists, and radiologists) evaluation was performed reaching a consensus.

As shown in Figure 1, the authors identified three post-COVID-19 phenotypes: prominent vascular changes, post-COVID-19 fibrosis, and persistent SARS-CoV-2 infection. The first phenotype (vascular) was detected in two cases that were biopsied early after acute COVID-19 (4 months and 5 months, respectively). Their HRCT showed pure GGO and the histology showed haemangiomatosis-like features (Figure 1). The patients were followed up without treatment.

The second phenotype (post-COVID-19 fibrosis) was detected in seven patients, all with HRCT nonspecific interstitial pneumonia (NSIP) with organising pneumonia overlap features. Histology showed fibrotic or mixed NSIP, fibrotic organising pneumonia, fibrotic diffuse alveolar damage, and bronchiolar damage, possibly correlated with ventilation injury in one case (Figure 1). Patients were variably treated with steroids, depending on disease extent and symptoms. In the case with post-ventilation injury, which did not show inflammation on biopsy, corticosteroids were stopped.

The third phenotype (persistent COVID-19) was detected in a patient who was immunosuppressed (rituximab for non-Hodgkin lymphoma) and the HRCT showed GGOs that worsened between 6 months and 12 months. COVID-19 was detected by BAL (SARS-CoV-2 positivity and $CD8^+$ lymphocytosis [53% total lymph; CD4/CD8: 0.1]) and biopsy showed cellular NSIP. This patient was treated with casirivimab and imdevimab with complete resolution.

The remaining nine patients were reclassified as known ILDs and treated according to current guidelines.

CONCLUSION

The authors identified three phenotypes of post-COVID-19 damage with heterogeneous pictures and leading to different treatment choices. The multidisciplinary evaluation was crucial to reach the most accurate diagnosis for the patient. ●

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Safety and Efficacy of Transbronchial Lung Cryobiopsy Versus Forceps Biopsy in the Diagnosis of Fibrotic Lung Disease: Biopsies and Beyond

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Keywords: Fibrotic lung disease, forceps biopsy, transbronchial lung cryobiopsy (TBLC).

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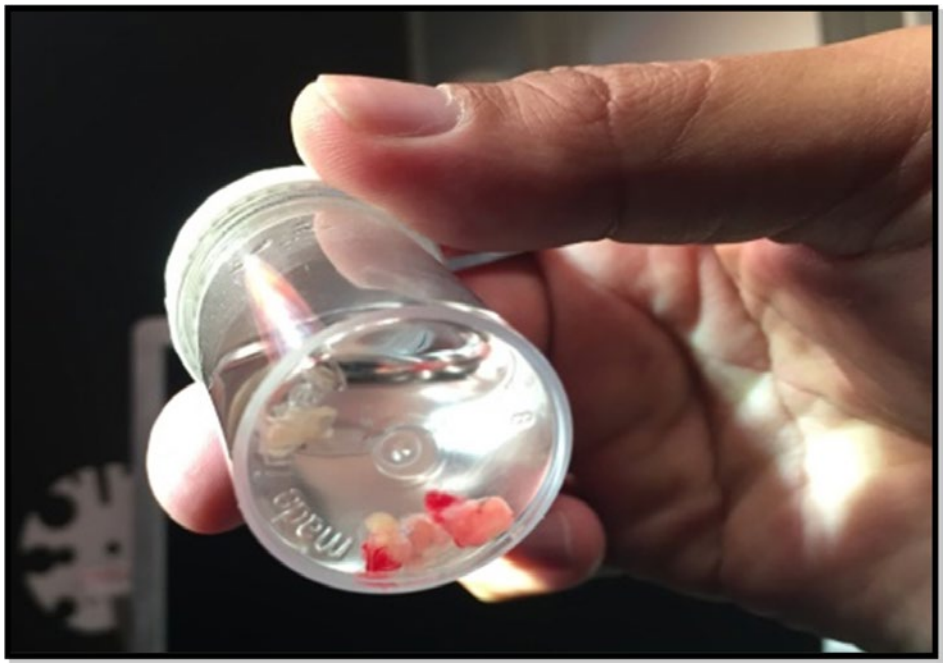
BACKGROUND AND AIMS

Histology is a key element for the multidisciplinary diagnosis of fibrotic diffuse parenchymal lung diseases (f-DPLD) when the clinical–radiological setting of f-DPLD with high-resolution CT features diagnostic of usual interstitial pneumonia (UIP) are not present.[1]

The author compared the diagnostic yield and safety of transbronchial lung cryobiopsy (TBLC)

Figure 1: Freshly obtained transbronchial lung cryobiopsy specimens floating in formalin.[6]



with cryoprobe sampling versus conventional transbronchial lung biopsy (TBLB) forceps sampling in the same patient.

MATERIALS AND METHODS

A prospective, single-centre clinical study of 135 patients with f-DPLD indicated for lung biopsy with histopathology. TBLB subsequently was followed by TBLC. Airway management with rigid bronchoscope was done according to protocol, and the procedure was performed using fluoroscopy and Fogarty occlusion balloon (Edwards Lifesciences, Irvine, California, USA).[2]

RESULTS

According to multidisciplinary committee results, the diagnostic yield for TBLC was 79.6% and 51.4% for TBLB ($p<0.0001$). The diagnostic yield was higher for TBLC compared with forceps TBLB for two groups: idiopathic interstitial pneumonias and interstitial lung disease of known cause or association (odds ratio: 2.5; 95% confidence interval [CI]: 1.4–4.2 and odds ratio: 5.8; 95% CI: 2.3–14.3, respectively). Agreement between pathologists in the detection of UIP was very good, with a κ coefficient of 0.83 (95% CI: 0.69–0.97). Grade 3 (moderate) bleeding after TBLC occurred in 5.5% of patients compared with 0.8% after conventional TBLB, which confirms the need for safe airway management and prophylactic occlusion balloon use. Incidence of pneumothorax was seen in four patients when sampling two sites or when using a larger probe, while bleeding was not influenced by the site of the biopsy or by the size of the probe.[3] No patient required intubation with invasive mechanical ventilation and there were no procedure-related deaths.

CONCLUSION

The advent of TBLC has generated enthusiasm and has provided a higher diagnostic yield than TBLB, with fewer complications than surgery. TBLC specimens are larger in biopsy size, with better parenchymal architecture preservation, contain more alveoli, and have fewer artefacts compared with TBLB (Figure 1).[4]

The author has attempted to identify which patient may benefit from the use of combined

techniques by performing both techniques in the same patients, which included idiopathic, connective tissue disease-related, and other disease process that have not been previously investigated with TBLC techniques. The diagnostic yield for TBLC was higher than TBLB, especially for idiopathic interstitial pneumonia and interstitial lung disease of known cause or association. The incidence of pneumothorax is mainly related to necessity of biopsy of the subpleural areas in patients with f-DPLDs. TBLC findings suggesting UIP, such as temporal heterogeneity, fibroblastic foci, and honeycombing, were strongly correlated with final diagnosis of f-DPLD.[1]

Patients with f-DPLD represent a diagnostic challenge and often limited by a smaller size and fewer artefacts; however, a clinician can be hesitant to pursue this surgical biopsy due to more acute exacerbations observed after procedure or due to intraparenchymal shear forces induced by mechanical unilateral ventilation, which is used when performing a surgical lung biopsy.[5] Complications such as pneumonia, persistent pleural fistula, neuropathic pain, and empyema have been often observed in surgical lung biopsy studies.

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Pollen Exposure Increases the Risk of Respiratory Symptoms in Infants: A Longitudinal Study

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Keywords: Aeroallergen, cohort study, infancy, interaction, longitudinal study.

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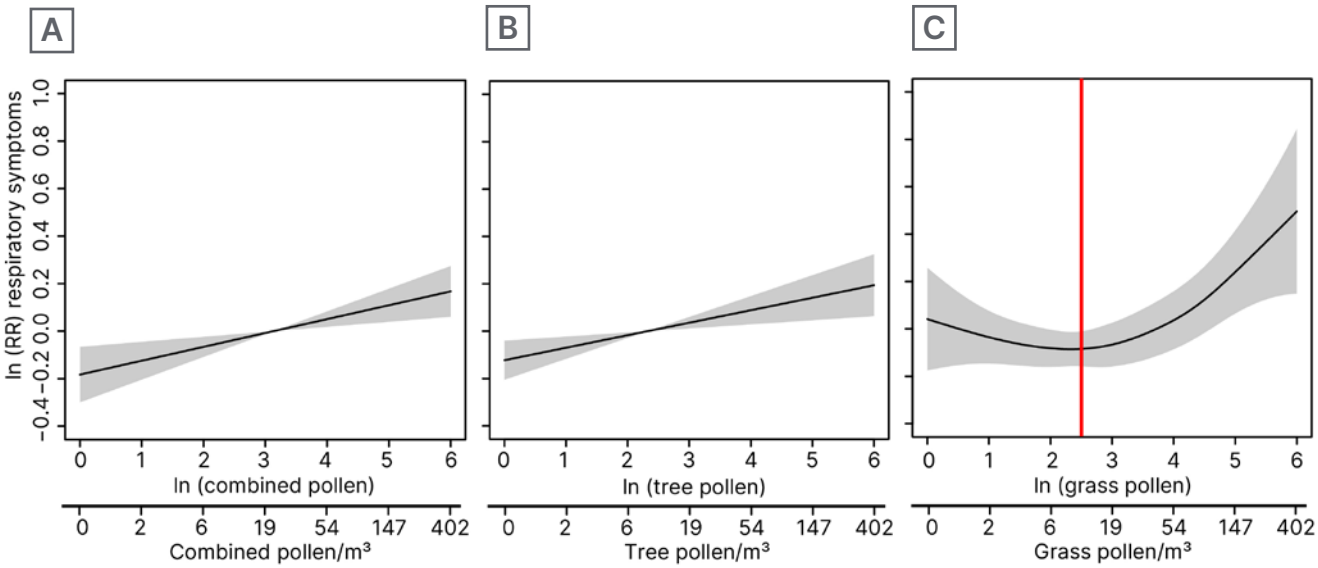
BACKGROUND AND AIMS

Exposure to pollen has been associated with an increased risk of respiratory symptoms in both allergic[1] and nonallergic individuals.[2] However, the association of pollen exposure with respiratory symptoms during infancy, a particularly vulnerable period for lung development,[3] remains unclear. The goal of this study was to examine whether pollen exposure is associated with respiratory symptoms (cough, wheezing, and dyspnoea) during the first year of life and to test if maternal atopy, infant's sex, and air pollution modify this association.

MATERIALS AND METHODS

In total, 14,874 repeated measures from 401 healthy infants of the prospective Basel Bern Infant Lung Development (BILD) cohort were analysed. Generalised additive mixed models were used to assess the association between weekly exposure to tree and grass pollen estimated for each child's address and weekly respiratory symptom scores. The scale for respiratory symptom scores ranged from 0–4, with 0 indicating no symptoms and scores ≥1 indicating symptoms with increasing severity. Effect modification by maternal atopy, infant's sex, and air pollution (nitrogen dioxide and fine particulate matter with a diameter ≤2.5 µm [$PM_{2.5}$]) was assessed with interaction terms.

Figure 1: Marginal effects of pollen exposure on the risk of daytime respiratory symptoms.



Pollen exposure is shown on transformed scale and back-transformed scale. The shaded areas represent the 95% CI. Models were adjusted for NO_2, $PM_{2.5}$, siblings, childcare, sex, breastfeeding, age, maternal smoking during pregnancy, temperature, and month. **A)** Shows an association between combined pollen and daytime respiratory symptoms, while **B)** highlights an association between tree pollen and daytime respiratory symptoms. **C)** Association between grass pollen and daytime respiratory symptoms. The red line indicates the cut-off used to assess linear relationship between grass pollen and respiratory symptoms.

CI: confidence interval; ln: natural logarithm; NO_2: nitrogen dioxide; $PM_{2.5}$: particulate matter with a diameter ≤2.5 µm; RR: risk ratio.

RESULTS

Per infant, 37±2 (mean±standard deviation) respiratory symptom scores were assessed during the analysed months of the first year of life (from January up to and including September due to operation time of pollen traps). The symptom severity was overall rather low with a mean±standard deviation respiratory symptom score across all years (2005–2016) of 0.13±0.13 for daytime respiratory symptoms and 0.12±0.14 for night-time respiratory symptoms. Significant associations were found for grass and tree pollen exposure, both combined and separately, with respiratory symptoms during the first year of life (Figure 1). An increase in pollen exposure was associated with an increased risk of respiratory symptoms during daytime (combined risk ratio [RR]: 1.006 [95% confidence interval (CI):1.002, 1.009]; tree RR: 1.005 [95% CI: 1.002, 1.008]; and grass RR: 1.009 [95% CI: 1.000, 1.23] per 10% pollen/m^3) and night-time (combined RR: 1.003 [95% CI: 0.999, 1.007]; tree RR: 1.003 [95% CI: 0.999, 1.007]; and grass RR: 1.014 [95% CI: 1.004, 1.024] per 10% pollen/m^3). Results remained significant after the exclusion of observations from the first 6 months of life, when the infant's blood could potentially be contaminated by maternal Ig. The effect of pollen on respiratory symptoms was not modified by maternal atopy and infant's sex. However, a complex crossover interaction between exposure to combined pollen and $PM_{2.5}$ was found (p=0.003). For low pollen concentrations, the risk of respiratory symptoms increased with increasing levels of $PM_{2.5}$, while the risk of respiratory symptoms decreased with increasing levels of $PM_{2.5}$ for high pollen concentrations.

CONCLUSION

This study provides first evidence that, even as early as during the first year of life, increased exposure to grass and tree pollen, both combined and separately, is associated with an increased risk of respiratory symptoms. While $PM_{2.5}$ modified the effect of pollen in a complex manner, maternal atopy and infant's sex did not affect the association of pollen with respiratory symptoms. As infancy is a particularly vulnerable period for lung development, the observed association should be further investigated. This includes an evaluation of the underlying mechanism linking pollen exposure with respiratory symptoms in infants.

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Interview

J. Brady Scott

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EMJ are delighted to introduce Professor J. Brady Scott, Director of Clinical Education, Respiratory Care at Rush University, who provided an insight into their diverse and prestigious career as a respiratory therapist, researcher, and educator.

Q1 With over 20 years of clinical experience as a respiratory therapist, what initially sparked your interest in pursuing a career in this field, and what motivated you to get involved with research?

My interest in medicine began as a child. In elementary school, I recall that most of my peers were reading fiction books, but I was reading my dad's emergency medical technician books. My dad was a coal miner by occupation, but he was also an emergency medical technician. When I enrolled in college, I initially registered as a pre-nursing student with the plan to pursue a Bachelor's degree in nursing. After a couple of years, I did not feel a passion for nursing as a career, and I began exploring other career options. Respiratory care interested me most.

Regarding research, my interest started 3–4 years into my career as a bedside respiratory therapist. There were clinical questions I thought should be answered, but I did not know how to answer them. Luckily, I had mentors willing to help me better understand research. I eventually became more interested in formal research training, so I completed my Master's degree and, ultimately, my PhD.

Q2 Do you think there are any misconceptions about your specialty of respiratory medicine?

A major misconception is that respiratory therapists are trained as technicians. Instead, respiratory therapists have strong patient assessment skills, apply evidence-based medicine, educate patients, and participate in interprofessional care planning. Respiratory therapists address quality control and testing standards to assure accuracy and precision during diagnostic testing. Although they practice predominately in acute care settings, respiratory therapists also work in long-term care facilities, pulmonary rehabilitation, outpatient clinics, air and ground transport, academic institutions, and increasingly in public health settings.

Q3 What are the most significant advances or changes that you have seen in respiratory care over the past two decades?

Professionalisation has advanced over the past two decades. In the USA, almost every state requires that a respiratory therapist be licensed in their state. Licensure requires a certified or registered respiratory therapist credential and, often, continuing education. Additionally, there have been increasing calls for the Bachelor of Science degree to be the entry-level degree for the profession. Over a decade ago, Master's degrees in respiratory therapy emerged for entry into the profession. Additionally, there has been significant growth in Bachelor's and Master's degree programmes for working therapists.

Q4 As a researcher and practitioner, how do you think that respiratory research can contribute to patient outcomes, and what direction to you see your research focus taking in future?

Respiratory research can have a tremendous impact on a variety of patient outcomes. For example, our team has been working hard to understand how awake prone positioning can impact outcomes such as the need for intubation, and survival for patients with COVID-19 not yet requiring mechanical ventilation. Other researchers have evaluated disease management programmes to reduce hospital readmission for chronic obstructive pulmonary disease exacerbations.

Q5 You recently co-authored an article entitled 'Predictors of Treatment Success in Awake Prone Positioning for Non-Intubated COVID-19 Patients with Acute Hypoxemic Respiratory Failure'. What were the key findings in this analysis, and the overall message you were hoping to deliver?

We found that oxygenation responses to awake prone positioning on Day 2, specifically improvements in peripheral capillary O_2 saturation/fraction of inspired O_2, were possible predictors of treatment success in patients with acute respiratory failure from COVID-19. Additionally, it appeared that higher pre-

prone positioning peripheral capillary O_2 saturation/fraction of inspired O_2, were possible predictors of treatmen was also a predictor. The overall message is that it may be important to evaluate oxygenation response, particularly on the second day, when awake patients are placed in the prone position while using high-flow nasal cannula oxygen therapy. That said, it is noted that this is a post hoc analysis, and our findings need to be further evaluated by well-designed clinical trials.

"Respiratory therapists have strong patient assessment skills, apply evidence-based medicine, educate patients, and participate in interprofessional care planning"

Q6 You have also been involved in work surrounding mechanical ventilation alarms and alerts. Could you tell us more about this?

Device alarm management practices generally aim to simultaneously maximise patient safety and reduce nuisance alarms. Unfortunately, due to the large number of alarms and their seeming omnipresence in our intensive care units, clinicians can become desensitised to alarms, a phenomenon called alarm fatigue. Alarm fatigue is a patient safety issue recognised by organisations such as The Joint Commission. While mechanical ventilator alarms are not the only alarms found in our intensive care units, they do contribute significantly. Work has been done to understand and improve mechanical ventilation alarm management, but much is still needed. Evidence-based standards to guide mechanical ventilator alarm management do not yet exist due to the variations in devices, device terminology, and alarm practices between facilities.

Q7 As well as research and clinical practice, you are also heavily involved in education, having lectured both locally and internationally, and now in your role as Director of Clinical Education and Associate Professor for Rush University's Respiratory Care programme, Chicago, Illinois, USA. What changes have you brought into effect whilst serving in this position, and what impact do you think this has had?

I joined the Rush University Respiratory Care program team only a couple of years after the programme began. Since then, I have frequently utilised simulation as an educational approach. We have used simulation, in its various forms, to help students better navigate complex clinical situations and refine thought processes before having actual patient contact. We have also used simulation for interprofessional training. Each year, we team up with the Speech-Language Pathology faculty to train respiratory therapists and Speech-Language Pathology students on using speaking valves with and without mechanical ventilation. We have found that students enjoy learning with and from each other, and the simulation activities improve their confidence and skills in the devices, procedures, and communication.

Q8 One of your research interests includes simulation-based education. Could you tell us a bit more about your research in this area and if, in your expert opinion, you think this is the future for respiratory education?

Beyond using simulation-based education for our students, we have also tried to understand how it impacts the learners. One study evaluated a method for placing patients requiring mechanical ventilation in the prone position. We used healthy volunteers attached, by tape only, to intravenous lines, a urinary catheter, and an endotracheal tube to enhance the realism of turning a patient from the supine position to the prone position in the study. Our

findings suggested the method helped to improve knowledge and confidence in the prone positioning procedure. The study was published in 2018, and turned out to be timely for our institution. As we developed our treatment guidelines and approach to initiate prone position during the COVID-19 pandemic, we utilised this method to drive our training.

Q9 During the course of your career, you have received a multitude of honours and awards. For you personally, what has been your proudest achievement?

This is a difficult question to answer, as I am very proud and appreciative of all of those honours and awards. That said, my institution and the American Respiratory Care Foundation (ARCF) recognised me for various clinical, research, and media contributions during the COVID-19 pandemic. This recognition was meaningful to me as it demonstrated an appreciation for what and how respiratory therapists contributed to patient care at an unprecedented time. Beyond that, I would be remiss not to mention the times our program graduates selected me to place their Master's hood during their commencement ceremony. It's a real honour and privilege to participate in that memorable moment in their lives.

"Our team has been working hard to understand how awake prone positioning can impact outcomes such as the need for intubation, and survival for patients with COVID-19 not yet requiring mechanical ventilation."

Current Perspectives and Future Directions of Repeat Pulmonary Rehabilitation Programmes in People with Chronic Obstructive Pulmonary Disease: A Narrative Review of the Literature

Editor's Pick

My Editor's Pick explores pulmonary rehabilitation (PR) programmes in patients with chronic obstructive pulmonary disease. Examining trial and study data, the authors consider evidence for different approaches to repeat PR programmes, and discuss factors such as frequency, duration, ethical factors, and patient-related factors (e.g., financial burden). Furthermore, the article provides evidence for the value of exploring alternative approaches to repeat PR programmes in light of emerging evidence for home-based PR and telerehabilitation programmes.

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Abstract

The benefits of pulmonary rehabilitation (PR) diminish over 12–24 months following programme completion. A repeat PR programme may potentially prevent or reverse this decline in gains and may provide additional benefits. The aim of this narrative review was to discuss the current available evidence regarding repeat PR programmes and provide perspectives on unresolved questions, future areas of inquiry, and suggestions for clinical practice. Randomised controlled trials showed PR repeated at 6, 12, or 24 months after the initial PR programme resulted in similar short-term improvements in exercise capacity and quality of life; however, they did not result in long-term benefits beyond 12–24 months. In uncontrolled studies, the improvements in exercise capacity achieved following repeat PR were of a smaller magnitude than after the initial PR programme, but the improvements were still clinically significant. There is limited evidence to guide the optimal timing and characteristics of a repeat PR programme, such as frequency, duration and content, as well as which patients may benefit. There are ethical factors to consider in offering repeat PR programmes, including availability and access, the impact on resources and capacity of PR programmes, and patient-related factors such as financial burden and difficulties with transport. Alternate means of delivering a

repeat PR programme should be explored, especially with emerging evidence for home-based PR and telerehabilitation programmes. A modular approach to a repeat PR programme by offering only certain elements rather than a comprehensive programme may also address the aspects of access, resources, capacity, and patient burden.

Key Points

1. Pulmonary rehabilitation (PR) is used as a treatment for patients with chronic obstructive pulmonary disease to optimise functional exercise capacity and to improve quality of life.

2. In this literature review, the authors looked into previous studies, some of which indicated that repeat PR had less success in some patients, however, the improvements were still clinically significant.

3. Unless patients engage in regular exercise, the improvements made during the initial PR will decline; but, there is no consensus on when PR should be repeated.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) may progress over time, resulting in a gradual worsening of symptoms and decline in functional capacity and quality of life.[1] Pulmonary rehabilitation (PR) aims to reduce symptoms and optimise functional capacity in people with COPD via a comprehensive intervention of exercise training, education, and behaviour change.[2] However, the benefits of PR appear to diminish over time[3] and seem to be time-limited to 12–24 months.[4]

A repeat PR programme at a future point after completion of the initial PR programme may prevent or reverse the decline of the initial training effects and may provide additional benefits. Whilst repeating a PR programme appears worthwhile considering the positive benefits of PR reduce over time, there are no strong recommendations for repeating a PR programme in current clinical practice guidelines. Therefore, the aim of this narrative review was to discuss the current evidence regarding repeat PR programmes and to provide perspectives on unresolved questions and future areas of inquiry.

METHODS

A literature search was performed in February 2022 using PubMed, Medline, PEDro, and Google Scholar. Initial keywords searched included "repeat" and "pulmonary rehabilitation." An additional search using the keyword "refresher" found no further studies. Another search using the keyword "booster" found three extra studies. The reference lists of all reviewed literature were handsearched for additional references. There was no limitation applied to study design for a study to be reviewed. Only studies written in English and full-text were considered.

EVIDENCE OF REPEAT PULMONARY REHABILITATION PROGRAMMES

A modest number of studies examining the benefits of repeat PR programmes have been published since 2001. Two small randomised controlled trials with a combined total of 96 participants demonstrated that PR repeated at 6, 12, or 24 months after the initial PR programme resulted in similar short-term improvements in exercise capacity and quality of life; however, did not result in long-term benefits beyond 12–24 months.[5,6] In uncontrolled studies, the overall results demonstrated that the improvements in exercise capacity achieved following a repeat PR programme were of a lower magnitude than after the initial PR programme, but the improvements were still clinically significant.[7-11] There also appeared to be a reduction in the number of exacerbations per year[6,11] and a reduction in days spent in hospital[5] in people with COPD who received a repeat PR programme. However, the small number of exacerbations and hospitalisations limited the generalisability of these findings. Evidence suggests that

people with more severe disease and those on long-term oxygen therapy may be less likely to respond to a repeat PR programme,[7] although this requires further investigation.

EVIDENCE GAPS

The British Thoracic Society (BTS) guideline on PR recommends that repeat PR programmes should be considered in patients who have completed a course of PR more than 1 year prior and that repeat PR programmes should be considered sooner in individuals with accelerated physiological decline.[12] The American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on PR examined the evidence regarding repeat PR programmes to prevent decline in PR outcomes and/or following a decline in function, and identified the optimal duration and frequency of repeat PR programmes over time to be a key area for future research.[2] Despite this, little progress has been made in this research area, and no randomised controlled trials have been published since 2009. Of note, evidence emerging in more recent years includes uncontrolled studies reporting real-world PR programme data, where clinicians have identified a clinical need for repeat PR programmes in their patients and have been offering these programmes for many years.[7-10]

Although there is a paucity of high-quality trials regarding repeat PR programmes, expert consensus appears to mirror that of PR clinicians, with repeat PR programmes likely suitable for patients at risk of decline.[12-16] The authors hypothesise that other research priorities in clinical practice have overshadowed the need to further investigate repeat PR programmes. These research priorities include the effect of PR in diseases other than COPD,[17-19] particularly the severe acute respiratory syndrome coronavirus 2 infection[20,21] and the identification of post-COVID-19 condition,[22,23] and different models of PR delivery, including home-based PR[24] and telerehabilitation.[25]

In clinical practice, the authors further hypothesise that there are growing numbers of actual and perceived barriers to offering repeat PR programmes, including increased demands on PR programmes to deliver PR to a larger population of people living with chronic respiratory disease beyond COPD; increased referral to PR programmes due to an increase in awareness and diagnosis of COPD, along with a greater understanding of the evidence and benefits of PR; a lack of availability of PR programmes or limited/no change to historical funding models for PR, which has led to difficulty offering repeat PR programmes in some countries; perceived reduced value of repeat PR programmes in some people attending PR with advancing age, disease progression, and an increasing number of comorbidities; cost–benefit considerations with an impetus to use limited healthcare resources on new patients referred to PR rather than returning patients, as it may be difficult to financially justify additional healthcare resource utilisation on people who have already accessed a service; and finally, an ethical consideration of offering a place in a PR programme to patients who never attended over those who previously attended in the context of waiting lists and accessibility to an evidence-based programme.

DEFINING REPEAT PULMONARY REHABILITATION PROGRAMMES: COMPONENTS AND DURATION

In clinical practice, it is unclear if repeat PR programmes should be the same or different to the initial PR programme. To date in literature, repeat PR programmes have been reported to consist of the same components as the initial PR programme (i.e., exercise training, education, and support).[6,7,9,11,26] The reported duration of the repeat PR programmes ranges from outpatient programmes of 8–12 weeks,[6,7,9-11] to inpatient programmes of 4 weeks.[27]

With this limited evidence, one key question arises: should repeat PR programmes be the same as the initial PR programme (i.e., consist of the same components and duration)? Repeat PR programmes have the opportunity to provide a different approach to the initial PR programme, including consideration of shorter programmes with or without the education component, as people with COPD may not require all aspects of the repeat PR programme. Heng et al.[10] demonstrated that a repeat PR programme achieved greater gains in disease mastery than the initial PR programme, suggesting that more time and support was required to help

patients achieve these gains. A personalised and individualised repeat PR programme seems intuitive, yet the repeat PR programme duration and required components remain unclear.

OPTIMAL TIME TO REPEAT A PULOMARY REHABILITATION PROGRAMME

How often should PR programmes be repeated? In clinical practice, the time between completion of an initial PR programme and a repeat PR programme varies, and is frequently dependent on available resources, waiting lists, and patient needs. Patients may be re-referred by the general practitioner or respiratory specialist but may also self-refer to the PR programme if they need assistance. However, not all PR programmes have the ability to offer a repeat PR programme due to programme demands and waiting lists.

Following the completion of the initial PR programme, repeat PR programmes have been offered at 6 months,[26] 12 months,[10] 10–24 months,[7] 24 months,[27] and five times over 7 years,[11] indicating that there is no clear consensus about the ideal duration between the initial PR programme and repeat PR programme, or the frequency of repeating a PR programme. Therefore, determining the time point and frequency of repeat PR programmes is important in future research.

REPEAT PULMONARY REHABILITATION PROGRAMMES AS A MAINTENANCE PROGRAMME

Following the completion of an initial PR programme, benefits in exercise capacity, dyspnoea, and health-related quality of life begin to decline unless the person continues to engage in regular exercise.[28] Supervised maintenance exercise programmes may be offered, but the ideal frequency of maintenance exercise is unclear,[17] and many PR programmes are unable to provide supervised maintenance exercise classes because of programme demands and staffing constraints. Instead, patients are encouraged to engage in regular supervised community exercise classes or exercise independently. However, if patients do not engage in regular exercise, or if a maintenance exercise programme lacks the appropriate intensity, and patients experience a decline in the initial PR programme benefits, a repeat PR programme may be indicated to address this. Encouraging people to continue to regularly exercise following the completion of the initial PR programme is best practice[2,12] and may negate the need for a repeat PR programme. However, repeat PR programmes may be an option for people who have not engaged in ongoing exercise or if maintenance exercise programmes have been unable to maintain gains from the initial PR programme.

WHO SHOULD BE OFFERED A REPEAT PULMONARY REHABILITATION PROGRAMME?

It is important to try to distinguish those who would benefit from repeat PR programmes. Whilst repeat PR programmes may benefit people who are showing signs of physical decline since the completion of the initial PR programme[9] or following an exacerbation,[26] it is unclear from previous studies whether the repeat PR programmes were planned at certain time points or offered on an as-needed basis. Based on the studies to date, there is no clear guidance about what characteristics a patient may exhibit to indicate a need to repeat a PR programme. Further, there is no defined level of deconditioning or decline that would currently indicate a need for a repeat PR programme, for example, a percent decline in 6-minute walk distance since completion of the initial PR programme; a patient no longer achieving the minimal clinically important difference for improvements in exercise capacity, dyspnoea, or health-related quality of life; or an increase in the number of exacerbations or hospitalisations over a defined period of time (e.g., 12 months). Defining the repeat PR programme patient is an area for future investigation.

Repeating the PR programme implies that the patient attending the repeat PR programme has completed the initial PR programme. Therefore, it may be assumed that they are more likely to also complete the repeat PR programme. However, should every completer be offered a repeat PR programme at a specific time interval, e.g., 12 months following completion of the initial PR programme, or should they be

empowered during an initial PR programme to continue to exercise and remain active? If a patient has not experienced a decline following the initial PR programme, then a repeat PR programme is unlikely to be required. This also raises an important issue that repeating a PR programme may only target a relatively small number of people who have completed the initial PR programme.

It is important to note that patients who complete the initial PR programme may or may not be responders (i.e., have achieved the minimal clinically important difference for one or more of the outcomes measured). In a recent study of 190 people with COPD who completed two PR programmes 10–14 months apart, 54% of non-responders following the initial PR programme become responders following the repeat PR programme. Of the 149 responders, 44 (30%) became non-responders.[7] Perhaps unsurprisingly, the more severe patients (those on long-term oxygen therapy and with severe dyspnoea) often remained non-responders.[7] This study raises important issues for clinicians as one cannot predict how a patient will respond to a repeat PR programme and whether they will or will not experience important and meaningful gains. It is suggested that patients should not be offered places in repeat PR programmes based on past performance but on current needs such as functional capacity or recent decline.[7]

Repeat PR programmes on a predetermined periodical basis may not be indicated for some people with COPD at that particular point in time. Rather, offering repeat PR programmes to people with COPD on an as-needed basis appears to be beneficial even after a prolonged period of time between the interventions.[9] Clinically, it appears the reasons for a repeat PR programme are varied and locally tailored to individual programmes, ranging from yearly reviews where a worsening state indicates a need to repeat a PR programme[27] to being re-referred by respiratory physicians "based on clinical necessity."[8] The element of patient desire and choice, which in the authors' experience is a significant factor, has not been reported as a reason for repeating a PR programme. In summary, it is unclear which people are ideally suited to repeat the PR programme. Suggestions include patients (both responders and non-responders) who have shown decline,[8,9,27] patients who have not achieved improvements or mastery in some aspects of the initial PR programme,[10] and patients following an exacerbation.[26]

REPEATING A PULMONARY REHABILITATION PROGRAMME AFTER A HOSPITAL ADMISSION OR AN ACUTE EXACERBATION OF COPD

Patients who show a decline in function following an acute exacerbation of COPD (AECOPD) or hospital admission may need a short repeat PR programme, such as a booster PR programme of 3–4 weeks duration. An AECOPD within 6 months of an initial PR programme has been shown to significantly decrease health-related quality of life and exercise capacity.[26] A 3-week repeat PR programme following an AECOPD compared with control (no exercise training) demonstrated that there was a greater reduction in dyspnoea and improved 6-minute walk distance compared with the control group.[26] The results from this study support the concept of providing a booster PR soon after an AECOPD.

A Cochrane review recommended that access to PR within 28 days of hospital discharge could prevent readmission in people with COPD.[29] This recommendation supports early attendance at PR to avoid readmission and the concept of a booster PR programme may provide an option to prevent readmission. Whilst in the authors' experience, booster PR programmes following hospital admissions or AECOPD are frequently offered in the clinical setting, currently there is no evidence to support repeat PR programmes as booster programmes.

PATIENT PERSPECTIVE

There is a paucity of studies examining patient perceptions around repeating a PR programme. Storey et al.[30] identified external drivers, such as hospitalisation, changes in health, and physical fitness or breathing, rather than personal motivation, to be key factors in a patient repeating a PR programme. Participants identified supervision within PR to be a key external motivator to maintaining regular exercise, with a repeat PR programme improving confidence and motivation. However, patient experiences varied with repeat PR

programmes. Compared with the initial PR programme, some participants found the repeat PR programme similar or easier, whilst some participants were confronted by their decline in health status when repeating the PR programme. Further, re-referral to PR was predominantly led by health professionals (despite acknowledging numerous barriers to repeating a PR programme) rather than through self-referral, with no consensus reached on the optimal time to repeat PR. For those patients that self-referred, it remains unclear if they can be defined by particular demographics or characteristics. Whether patients that re-refer to a repeat PR programme have common characteristics, such as age, disease severity, personality traits, previous improvement or lack thereof in PR outcomes, psychosocial aspects and needs, or presence of comorbidities, poses an interesting future research question. Importantly though, through the understanding of patient drivers to re-engage in PR, it may assist in supporting and facilitating the offering of alternative modes of PR that align with patient requirements,[31] including to those people repeating a PR programme.

AVAILABILITY AND ACCESS TO PULMONARY REHABILITATION PROGRAMMES

Availability of PR services has been reported to be as low as 1.2% of the estimated number of people with COPD, regardless of country.[32] Ongoing accessibility issues with centre-based PR continue to prevail,[33] raising three key issues to offering a repeat PR programme to those who have already attended the programme: will offering a repeat PR programme further impact on the capacity of PR services to deliver their programs by increasing demand and reducing availability, will offering a repeat PR programme exacerbate ongoing patient access issues such as cost of travel and difficulty with transport,[34] and can alternative models of repeat PR programmes mitigate the increased demand on service delivery.

FUTURE MODELS OF REPEAT PULMONARY REHABILITATION PROGRAMMES

Over the last decade, especially since the emergence of COVID-19, alternative modes of delivering PR have increased availability and popularity. Home-based PR[35] or home-based telerehabilitation delivered via different technologies, such as videoconferencing, mobile applications,[25] or social media,[36] have shown similar clinical outcomes compared to traditional centre-based PR programmes. Further, many people with COPD attending PR have reported a willingness to use telerehabilitation.[37] With the emergence of innovative PR delivery models, it is conceivable that a repeat PR programme could be offered through similar alternate models to centre-based PR, thus minimising the impact on traditional centre-based PR programmes, and potentially appealing to a wider range of patients. Further research is needed to determine whether participants repeating a PR programme would consider or participate in repeat PR via alternate delivery modes.

If a PR programme cannot facilitate a repeat PR programme through alternate modes of PR or a patient does not want to engage in alternate models, modular repeat PR programmes,[33,38] which are individualised to a patient's needs and impairments where there is an indication of a decline in function or limitation, may be another possible alternative. Offering only the elements of PR that the patient requires, such as exercise training only, an aspect of self-management education (for example, inhaler devices, smoking cessation, or healthy eating), or a combination of a few elements,[33] may reduce the burden on PR programme resourcing while simultaneously facilitating patient-centred repeat PR programmes. Modular repeat PR programmes are a further avenue of future research. Despite the lack of evidence supporting an optimal model of a repeat PR programme, the authors have some key suggestions that healthcare professionals working in PR can take away from this narrative review of the literature (Table 1) and contemplate when thinking about a repeat PR programme for their patients.

Table 1: Suggestions for repeat pulmonary rehabilitation programmes in clinical practice.

Suggestion	Description
Maintenance exercise first	Always prescribe an ongoing exercise programme on completion of an initial PR programme. Consider ongoing supervised exercise sessions
Do not presume	Non-responders from an initial PR programme may become responders with a repeat PR programme
Booster PR	Consider a short 3–4 week booster repeat PR programme following hospital admission or exacerbation
Think alternatives	Alternative modes for repeat PR programme delivery may be available and accessible, including a home-based PR or a telerehabilitation programme
Establish the level of decline	Consider a repeat PR programme if there is a decline below the achieved MCID for an outcome, or if a decline towards an initial PR programme baseline result is identified
Break it up	Offer modular PR programmes that are tailored to an individual patient's needs by delivering specific components of exercise or education that are clinically indicated. An entire comprehensive PR programme may not always be necessary

PR: pulmonary rehabilitation; MCID: minimal clinically important difference.

CONCLUSION

Following an initial PR programme, there is limited evidence to guide the optimal timing and characteristics of a repeat PR programme, such as frequency, duration, and content, as well as which patients may benefit. Further, patient perspectives have not been widely considered. There are ethical factors to consider in offering repeat PR programmes, including equity of access, the impact on resources and capacity of PR programmes, and patient-related factors such as financial burden and difficulties with transport and access.

Alternate means of delivering a repeat PR programme should be considered, especially in light of emerging evidence for home-based PR programmes and telerehabilitation programmes. A modular approach to a repeat PR programme by offering only identified elements rather than a comprehensive programme may also address the ethical aspects of access, capacity, resources, and burden to patients. It is exciting to consider the large number of research questions this review has posed and the potential for important findings identifying optimal models for repeat PR programmes.

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Modulating the Expression of Multiple Surface Receptors on Epithelial Cells and Promoting Lung Macrophage Anti-viral Functions by OM-85 Inhibits Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Summary

The emergence of a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019 triggered a global pandemic, forcing much of the world to adopt lockdown strategies and leading to extraordinary threats to the global healthcare system. The clinical manifestations of the disease, referred to as COVID-19, range from mild, self-limiting flu-like respiratory illness to life-threatening multi-organ failure and death. The rapid progress in our understanding of COVID-19 pathogenesis has led the development of effective vaccines, monoclonal antibodies, and anti-viral agents. However, a major cause of concern is the continuous and rapid emergence of new mutations that can progressively decrease sensitivity to the existing anti-COVID-19 tools. Safe, affordable, and widely available treatments are therefore urgently needed to reduce the frequency and/or severity of SARS-CoV-2 infection. OM-85 is a standardised lysate of bacterial strains widely used for the prophylaxis of airway recurrent infections in adults and children with an excellent safety profile. In experimental animal models and in clinical trials this compound was shown to possess anti-viral activities through immunomodulatory responses, but also by inhibiting infection.

The positive results reported in models of common respiratory virus infection has recently encouraged researchers from three independent groups to evaluate whether OM-85 could also affect SARS-CoV-2 infection. The results of these studies are summarised in this review.

INTRODUCTION

SARS-CoV-2, a member of the coronavirus family, was first detected in December 2019 in Wuhan, China, and identified as the causal agent of a viral pneumonia named COVID-19.[1] COVID-19 rapidly became pandemic, and has led to an extraordinary threat to the global healthcare system and economic stability. SARS-CoV-2 infection is characterised by a wide clinical spectrum, ranging from asymptomatic infection to a multi-organ dysfunction disorder leading to respiratory failure and death.[2,3] The severity of the disease is related to a variety of factors that, in addition to SARS-CoV-2 virulence, involve a deficient innate and adaptive immune response associated with an exaggerated inflammatory reaction.[3] The rapid development and global distribution of effective vaccines, monoclonal antibodies and anti-viral agents have greatly improved control of the infection and its related health complications.[4] However, the continuous, fast emergence of new mutations can significantly reduce the protection elicited by the existing anti-COVID-19 prevention and treatment tools.[5,6] Novel, relatively inexpensive, safe, and widely available preventative and therapeutic treatment strategies which inhibit viral infection and replication and stimulate the host immune response are therefore urgently needed. OM-85, an oral standardised bacterial lysate isolated from human respiratory strains, possesses strong immunomodulatory properties, and is widely used to prevent recurrent infections and/or exacerbations in at risk populations. Specifically, it has been shown to exhibit anti-viral activities in cell culture experiments, experimental animal models, and in clinical trials.[7-12] These observations prompted researchers from three independent groups to evaluate whether OM-85 could also affect SARS-CoV-2 infection.[13-15] The results of these studies are summarised and discussed in this review.

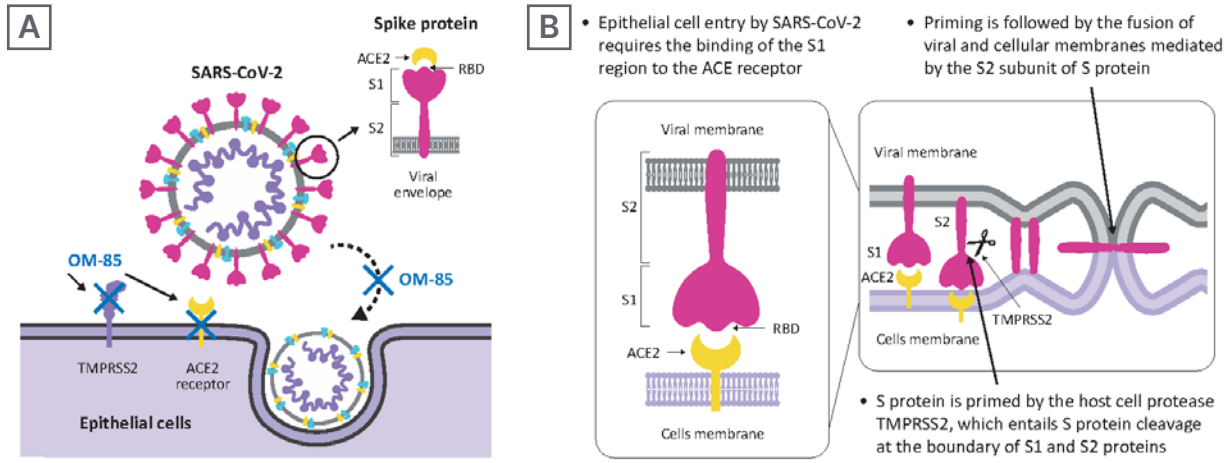
OM-85 DOWNREGULATED SARS-COV-2 ACE2 RECEPTOR AND TMPRSS2 TRANSCRIPTION AND EXPRESSION

SARS-CoV-2 infection targets airway epithelial cells through the structural spike (S) protein, which contains a receptor-binding domain specifically recognising the angiotensin-converting enzyme 2 (ACE2) protein as its receptor on host cells (Figure 1A).[2] After initial binding of the ACE2 receptor, proteolytic cleavage between the S1 and S2 subunits by the transmembrane serine protease 2 (TMPRSS2) is required to facilitate fusion of the viral and the host cellular membranes and for viral entry (Figure 1B).[2] Experimental studies using murine models, cells derived from SARS-CoV-2 target organs, and human bronchial cells, have demonstrated that exposure to OM-85 can effectively inhibit the transcription of ACE2 and TMPRSS2 proteins.[13]

Inhibition of Angiotensin-Converting Enzyme 2 and Transmembrane Serine Protease 2 Transcription and Expression in Murine Lungs and Human Epithelial Cell Cultures

To further determine whether OM-85 treatment could protect non-human primate and human epithelial cells against SARS-CoV-2 infection, Pivniouk et al.[13] measured ACE2 and TMPRSS2 transcription lungs of mice treated with intranasal OM-85. They observed an inhibition of ACE2 and TMPRSS2 transcription at Day 2 and Day 7 after the last OM-85 treatment.[13] Given the ability of OM-85 to modulate dendritic cell functions, which are engaged in anti-viral responses and depend on myeloid differentiation primary response 88 (Myd88)/TIR-domain-containing adapter-inducing interferon-β (Trif) innate immune signalling,[16] the involvement of this pathway in ACE2 and TMPRSS2 transcription was consequently assessed in wild type and in *Myd88*$^{-/-}$*Trif*$^{-/-}$ mice. As few as four intranasal OM-85 instillations were sufficient to reduce ACE2 and TMPRSS2 transcription in lung cells

Figure 1: SARS-CoV-2 infection of epithelial cells.



A) SARS-CoV-2 targets airway epithelial cells through the structural S protein, which contains a receptor-binding domain specifically recognising the ACE2 protein as its receptor on host cells. B) Binding of the S1 subunit to ACE2 receptor and virus attachment to the host cell is followed by TMPRSS2-induced cleavage of the S2 subunit from S1 subunit necessary for virus-host cell membrane fusion.

Adapted from Zhang et al.[17]

ACE2: angiotensin-converting enzyme; S: spike; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RBD: receptor binding domain; TMPRSS2: transmembrane serine protease 2.

isolated from wild-type mice by more than 55%, whilst negligible changes were observed in *Myd88*$^{-/-}$*Trif*$^{-/-}$ mice (Figure 2A).[13]

The inhibitory activity of OM-85 was then tested on cell lines derived from three SARS-CoV-2 target organs: Vero E6 cells, non-human primate derived kidney epithelial cells; Calu-3 cells, human lung cancer cells; and Caco-2 cells, human colorectal adenocarcinoma cells (Figure 2B).[13] OM-85 had a significant and strong inhibitory effect on ACE2 and TMPRSS2 transcription in Vero E6 cells after 24- and 48-hour stimulation, whereas, in Calu-3 cells, significant inhibition of ACE2 transcription was only detected after 72 and 96 hours and of TMPRSS2 transcription, at 24, 72, and 96 hours. Moreover, 48-hour stimulation with OM-85 significantly reduced ACE2 and TMPRSS2 transcription in intestinal Caco-2 cells.[13] Taken together, the overall OM-85-induced downregulation of ACE2 and TMPRSS2 transcription occurred more rapidly in Vero E6 cells compared with the other two cell lines.

In line with these findings, Fang et al.[14] observed a significant reduction in ACE2 and TMPRSS2 transcription at 24 and 48 hours after OM-85 (1:50 dilution) stimulation in human bronchial epithelial cell lines (BEAS-2B and Nuli) and primary human bronchial epithelial cells (isolated from subjects without chronic inflammatory lung disease).[14] In addition, kinetic studies on protein expression were performed in bronchial epithelial cell cultures undergoing daily OM-85 treatment over 4 days. OM-85 significantly reduced ACE2 protein expression at all time points, whereas downregulation of TMPRSS2 protein expression became significant only at 4 days.[14]

MODULATION OF THE TRANSCRIPTION AND EXPRESSION OF DIPEPTIDYL PEPTIDASE-4, A DISINTEGRIN, METALLOPROTEASE 17, HEPARANASE, AND HYALURONIC ACID BY OM-85

To evaluate the ability of OM-85 to modulate transcription and expression of multiple proteins involved in SARS-CoV-2 infection (dipeptidyl peptidase-4 [DPP4], a disintegrin and metalloprotease 17 [ADAM17], heparanase [HPSE], and hyaluronic acid [HA]), Fang et

Figure 2: OM-85 can interfere with various step of the infection cycle, decreasing virus adhesion to the cell membrane and virus entry by inhibiting cell surface proteins recognised by the binding site of the S protein, promoting the release of the soluble form of some of these receptors and the synthesis of hyaluronic acid which can inhibit virus cycle at different stages.

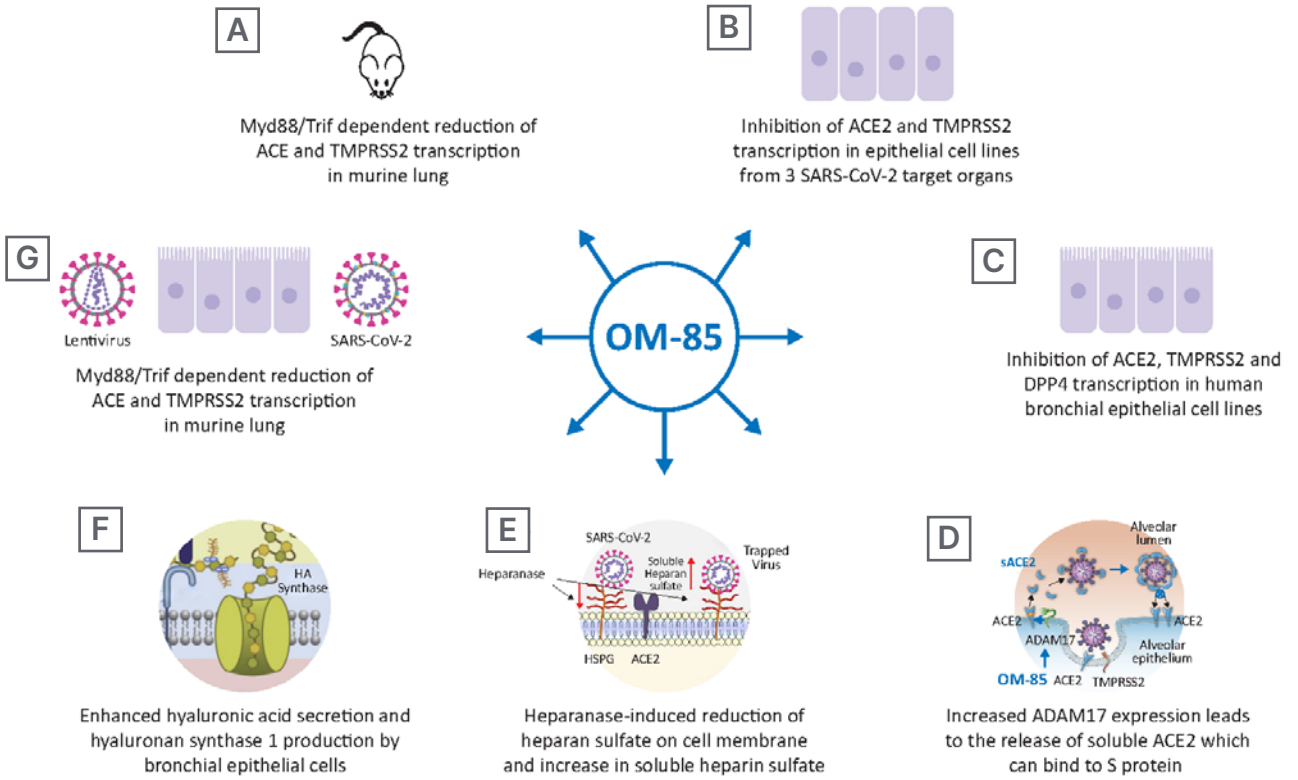


Figure 2D was adapted from 1 image by Zipeto et al.[18] (2020). Figure 2E was adapted from 1 image by Kinaneh et al.[19] (2021) under the terms of the Creative Commons Attribution License (CC BY). Figure 2F was reproduced with permission from Garantziotis and Savani (2019), who retain its copyright.

ACE2: angiotensin-converting enzyme; ADAM17: a disintegrin and metalloprotease 17; DPP4: dipeptidyl peptidase-4; HA: hyaluronic acid; HPSE: heparanase; Myd88: myeloid differentiation primary response 88; S: spike; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TMPRSS2: transmembrane serine protease 2; Trif: TIR-domain-containing adapter-inducing interferon-β.

al.[14] utilised two immortalised human bronchial epithelial cell lines (BEAS-2B and Nuli), and primary human bronchial epithelial cells.[14]

Modulation of Dipeptidyl Peptidase-4, A Disintegrin and Metalloprotease 17 Transcription and Expression

DPP4 is a serine exopeptidase expressed in several tissues, including the lung, kidney, liver, gut, and immune cells, which can be used as functional receptor by SARS-CoV-2.[20,21] Daily treatment of human bronchial epithelial cells with OM-85 (1:50 dilution) significantly reduced the DPP4 messenger RNA (mRNA) levels at 48 hours post-exposure. Moreover, in kinetic studies it was observed that DPP4 protein levels significantly declined after 24 and 96 hours, whereas they reached control levels in between (48 and 72 hours).[14] Interestingly, daily treatment of these cells with OM-85 significantly increased ADAM17 mRNA levels at 48 hours, and ADAM17 protein over a 4-day timespan.[14] ADAM17 is engaged in the cleavage and release of a variety of membrane-anchored cytokines, cell adhesion molecules, receptors, ligands, and enzymes, including ACE2.[22] As expected, OM-85 induced increased expression of ADAM17 protein was associated with ACE2 cleavage and a significantly increased extracellular release of ACE2 in its soluble form (sACE2), on Day 4 and 5 (Figure 2D).[14] The levels of sACE2 protein in

OM-85-treated cells were dose-dependent and became significant on Day 4 and 5 (1:20 and 1:50 dilution). Moreover, a positive linear correlation was detected between sACE2 and ADAM17 concentrations. Circulating sACE2 can bind to the virus effectively, acting as soluble decoy and blocking attachment to the membrane-bound receptor and virus entry;[23] therefore, an OM-85 induced increase in sACE2 may be beneficial in prevention and amelioration of SARS-CoV-2 infection.

Overexpression of Heparanase and Stimulation of Hyaluronic Acid Production

In human bronchial epithelial cell OM-85 treatment (1:50, and 1:100 dilution) induced an increase in HPSE secretion at 3 and 4 days after exposure.[14] HPSE is an enzyme that acts both at the cell-surface and within the extracellular matrix to degrade polymeric heparan sulfate. This linear polysaccharide, which occurs as proteoglycan, is produced by epithelial cells.[24] Expressed on the cell surface, heparan sulfate serves as a receptor for several viruses and, in the case of SARS-CoV-2 infection, facilitates the interaction between the S protein and its homing receptor ACE2.[25,26] The observed increase in HPSE secretion following OM-85 exposure was associated with an increase of soluble heparan sulfate and a decrease of heparan sulfate expression on the cell membrane 3 and 4 days following treatment (Figure 2E).[14] Moreover, a significant correlation was detected between soluble heparan sulfate molecules and HPSE concentration.[14] HA is a non-sulfated glycosaminoglycan distributed throughout connective, epithelial, and neural tissues.[27] Being one of the chief components of the extracellular matrix, HA participates in a variety of processes, including the response to bacterial, fungal, and viral infections.[28] Stimulation of human primary epithelial cells with OM-85 led to enhanced synthesis and secretion of HA (Figure 2F). This observed elevation of HA following OM-85 exposure correlated with increased expression of hyaluronan synthase 1 (Has-1), but not of Has-2 and Has-3, after 24 hours of OM-85 stimulation. Has-1, Has-2 and Has-3 show differences regarding substrates, localisation within the cellular compartment, and cleavage products. In addition, their role in airway viral infections is largely unknown. However, the upregulation of Has-1 detected by Fang et al.[14] suggests that OM-85 supports the *de novo* synthesis of long-chain hyaluronic acid, which has been shown to reduce viral infections.[29,30]

Taken together, it was observed that OM-85 exposure led to modulation of DPP4, ADAM17, HPSE, and HA. However, it is important to note that these effects are most likely indirect given that cellular signalling mechanisms to explain the effect of OM-85 on SARS-CoV-2 binding host proteins and glycosaminoglycans remain undetermined.

INHIBITION OF VIRUS ATTACHMENT AND EPITHELIAL CELL INFECTION

To investigate whether modulation of the expression of molecules involved in SARS-CoV-2 infection could also reduce SARS-CoV-2 S protein attachment to host cells, a recombinant histidine-tagged S1 subunit, comprising the SARS-CoV-2 receptor binding domain was used.[13,31] Validation of the ability of this assay to specifically detect ACE2-mediated S1 protein cellular binding was assessed in non-transfected or stably transfected HEK293T cells with human ACE2 (ACE2/HEK293T), in addition to Vero E6 and Calu-3 cells.[13] S1 binding was detected in only 5% of non-transfected HEK293T cells, whereas more than 99% of PBS-treated ACE2/HEK293T cells and a substantial proportion of Vero E6 (22±0.5%) and Calu-3 (24±1%) epithelial cells bound SARS-CoV-2 S1 protein. Moreover, a dose-dependently reduction in S1 binding was detected (Figure 2G).

Furthermore, to evaluate whether OM-85-induced inhibition of SARS-CoV-2 S1 protein attachment to epithelial cells also reduces S protein-mediated SARS-CoV-2 cell entry, replication-deficient lentiviral particles, pseudotyped with the SARS-CoV-2 S protein or with the G glycoprotein of the vesicular stomatitis viruses (VSV) were used.[13,31] OM-85 pre-treatment strongly inhibited Vero E6 cell transduction by SARS-CoV-2–pseudotyped particles but not by VSV-G–pseudotyped particles, because VSV-G does not recognise ACE2 as receptors. Interestingly, HEK293T cells expressing the ACE2 protein (ACE2/HEK293T) were readily transduced by SARS-CoV-2 pseudotyped particles, but OM-85 failed to inhibit viral entry into these cells since

these cells do not downregulate ACE2 on OM-85 stimulation. Therefore, the most important event characterising the OM-85–induced suppression of SARS-CoV-2 infection is the reduction of ACE2 expression. Similar results were obtained using pseudotyped lentivirus expressing the SARS-CoV-2 S-protein and human primary epithelial cell lines BEAS-2B and Nuli.[14] Finally, to assess whether OM-85 treatment suppressed epithelial cell infection with live SARS-CoV-2, Vero cells were pre-treated with PBS or OM-85 and consequently incubated for 2 hours with SARS-CoV-2 (isolate USA-WA1/ 2020).[13] SARS-CoV-2 infection was strongly and significantly inhibited in cultures pre-treated with OM-85, but not in PBS-pre-treated cultures, and this inhibition was evident even at the lowest OM-85 concentration. SARS-CoV-2 infection of Calu-3 cells was also significantly inhibited by pre-treatment with OM-85.

These results demonstrate that OM-85 inhibits SARS-CoV-2 infection of epithelial cells sourced from distinct tissues in an *in vitro* setting.

DECREASED MURINE CORONAVIRUS BURDEN RELATED TO PROMOTION OF LUNG MACROPHAGE ANTI-VIRAL FUNCTIONS

To identify cellular and molecular processes characterising the inhibitory effects of OM-85 on β-CoV infection, a murine coronavirus (MCoV) model was utilised by Salzmann et al.[15] They evaluated the effects of oral OM-85 treatment on viral load, lung cell apoptosis, and lung macrophage anti-viral function promotion. In this study, the prototypical laboratory variant of MCoV (also called murine hepatitis virus [MHV]) A59 was used. Intranasal infection with MHV-A59 induces an acute, self-resolving respiratory infection, recapitulating the acute pneumonia observed in the majority of individuals infected with SARS-CoV-2.[32,33] In addition, multi-organ involvement can be recapitulated using different infection routes. However, there are major differences between SARS-CoV-2 and MHV.[34] The viral receptor for SARS-CoV-2 is ACE2 (with co-receptors), whereas carcinoembryonic antigen-related cell adhesion molecule 1a (without co-receptors) is the receptor for MHV.[35] In addition, viral transmission of MHV occurs mainly via oral exposure and direct contact, whereas transmission of SARS-CoV-2 happens via inhalation or via the eyes, and can happen via both direct contact and contact with contaminated surfaces.[35] Moreover, SARS-CoV-2 can infect different species, where MHV is limited to mice.

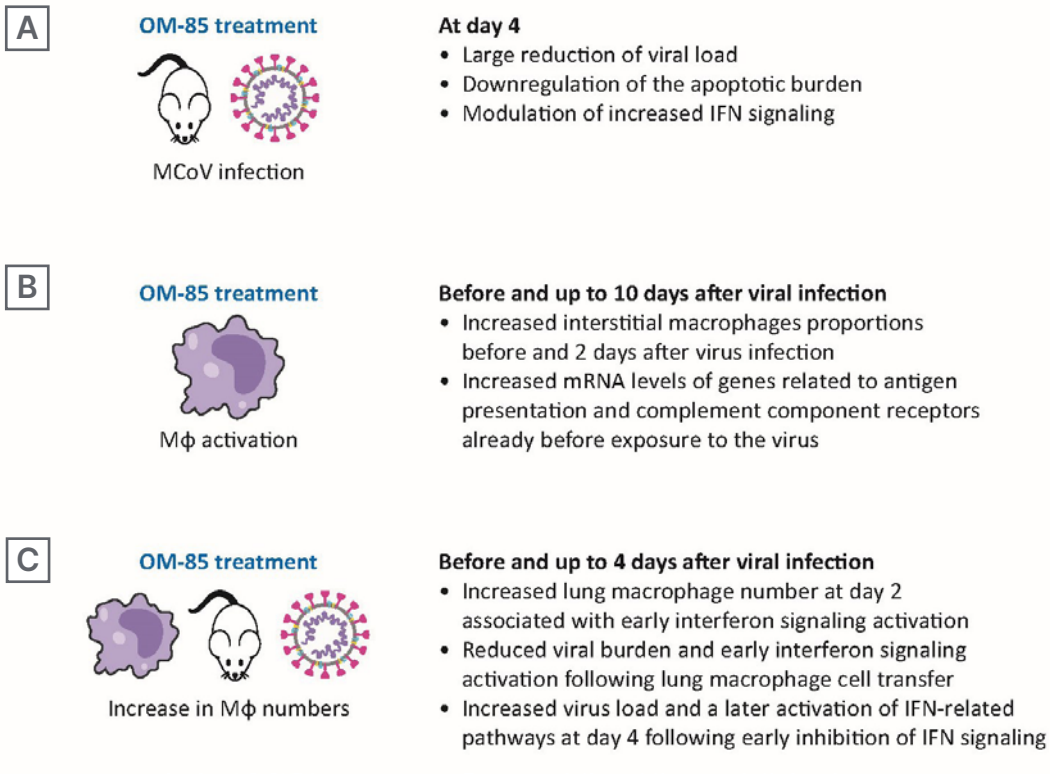
Reduction of Viral and Apoptotic Burden and Modulation of Interferon Signalling Activation

To determine whether OM-85-mediated immunomodulation was beneficial during MCoV infection, mice were pre-treated with OM-85, on 10 consecutive days, before viral infection and then analysed 2, 4, and 10 days after intranasal MCoV infection. A large reduction in viral load was observed at Day 4 post-infection and retained at Day 10.[15] This observation was associated with enhanced viral clearance and downregulation of the apoptotic burden in lung tissue at 4- and 10-days post-infection (Figure 3A). The lack of adverse effects on lung pathology in the OM-85-treated animals indicated that pre-activation of the immune system did not magnify MCoV infection-induced injury. Gene ontology analysis of differentially expressed genes in infected control versus OM-85-treated animals revealed a strong activation of the immune response towards viral infection, and of pathways linked to innate immune cells and inflammation. Consistent with the knowledge that interferon (IFN) signalling is crucial in the early phases of viral infections, it was observed that the reduction in viral load observed at Day 4, i.e., early control of the infection, was associated with a significant downregulation of IFN-α, IFN-β, IFN-γ, and IFN-induced protein with tetratricopeptide repeats 1 (IFIT1) mRNA levels in lung tissue.

Lung Macrophage Expansion and Activation

RNA sequencing data indicated differences in antigen processing and presentation and macrophage activation between treated and untreated mice. Therefore, differences in lung macrophage number and state of activation were determined (Figure 3B). There are two distinct macrophage populations in the lung: alveolar macrophages, with embryonic origin; interstitial alveolar macrophages, derived from circulating monocytes;[36,37] and both populations

Figure 3: OM-85 treatment decreased murine coronavirus burden promoting lung macrophage anti-viral functions.



A) At Day 4, viral load and apoptotic burden reduction and modulation IFN signalling. **B)** Before and at Day 2, Mφs proportions and mRNA levels of genes related to anti-viral activities. **C)** Before and up to Day 4 after viral infection, lung Mφ number, early IFN signalling activation, effects of lung Mφ cell transfer, and of early inhibition of IFN signalling.

IFN: interferon; MCoV: murine coronavirus; mRNA: messenger RNA; Mφ: macrophage.

express ACE2 and TMPRSS2, required for SARS-CoV-2 attachment and are activated by SARS-CoV-2 infection.[38,39] Interstitial macrophages increased after OM-85 treatment, even before virus infection, and the increase was retained 2 days post-infection. Macrophage recruitment to the lung in OM-85 treated mice was associated with phenotypical changes characterised by increased mRNA levels of genes related to antigen presentation (cluster of differentiation [CD] 86 and MHC-II) and to complement component receptors, already detectable at baseline, i.e., before exposure to MCoV infection.

To test whether the reduced MCoV load and enhanced viral clearance could be related to an early innate immune training, lung macrophage numbers and IFN pathway activation values were determined at baseline and at Day 1 and 2 after infection (Figure 3C). Increased lung macrophages numbers and INF regulatory factor 1 protein levels were detected in isolated lung cells from OM-85 treated animals. OM-85 treatment did not increase baseline IFN-α levels, but induced a strong and significant upregulation of IFN-α and of IFN-β after infection. Moreover, a strong upregulation of IFIT1 was observed with OM-85 pre-treatment from baseline (until Day 2 after virus infection). Finally, a significant OM-85-induced increase in expression was detected in the retinoic acid-inducible gene 1, an intracellular receptor involved in the identification of RNA viruses.

To assess whether early increase in lung macrophages could be sufficient to reduce MCoV infection, monocytes and macrophages isolated from naïve lung tissue were adoptively transferred to recipient mice, then infected with MCoV. Similar to the observations following OM-85 treatment, mice receiving an adoptive

macrophage transfer showed a 53.91% reduction in lung viral burden compared to control mice, and reduced IFN-α, IFN-β, and IFIT1 mRNA levels, indicating a faster IFN signalling and, thereby, a faster viral resolution.

Early Blocking of Interferon Signalling Activation and Inhibition of OM-85 Anti-viral Activity

To test if the accelerated induction of IFN and its downstream targets was the main mode of action in OM-85 treated lung tissue viral defence, blocking antibodies to IFN-α/β receptor 1 (anti-IFNAR1) were used to inhibit early IFN signalling. As expected, viral load was significantly increased in animals receiving anti-IFNAR1 treatment, which also displayed a lower activation of IFN-related pathways, compared to animals receiving OM-85 treatment prior to virus infection.[15] Viral burden and IFN pathway activation was comparable in OM-85 anti-IFNAR1-treated animals and in untreated control infected animals.

DISCUSSION

SARS-CoV-2 infection is a multistep process that involves binding to ACE2 via the surface S protein, employment of the cellular serine protease TMPRSS2 for S protein priming, and fusion between the cellular and viral membranes for cell entry.[38-40] Viral genomic RNA is consequently released and translated into viral polymerase proteins, viral RNA, and the proteins are replicated, transcribed, translated, and assembled to form mature virions that are finally released from the host cell.[38-40] The severity of the clinical manifestation of SARS-CoV-2 infection depends on a variety of factors which, in addition to the viral virulence and load, include the efficiency of the innate and adaptive immune response.[2,41,42] The results of the reported studies suggest that OM-85 is effective in inhibiting SARS-CoV-2 infection in several experimental models by interfering with various step of the infection cycle. Pivniouk et al.[13] showed that, downregulation of ACE2 and TMPRSS2 transcription on epithelial cells by OM-85 decreased virus attachment to the host cell membrane and SARS-CoV-2 S1 protein–mediated cell entry. Moreover, they demonstrated that the OM-85 induced reduction of ACE2 and TMPRSS2 transcription in lung cells was Myd88/Trif dependent. Interestingly, it was previously shown that the involvement of the Toll-like receptor adaptors MyD88 and Trif are required to promote the production of interferon-β by OM-85 activated bone marrow-derived dendritic cells.[16]

Type I IFN T are critical cytokines for protection against viruses during the acute phases of the infection, directly suppressing viral replication, thereby activating the immune responses.[43] Interestingly, in the experiment evaluating epithelial cell infection, they further demonstrated the key event characterising the OM-85–induced suppression of SARS-CoV-2 infection is the reduction of ACE2 expression. The OM-85-induced suppression of epithelial cells infection obtained using SARS-CoV-2 pseudotyped particles were confirmed by experiments performed with live SARS-CoV-2 obtained from the World Reference Center for Emerging Viruses and Arboviruses (WRCEVA). The 'anti-SARS-CoV-2' activities of OM-85 were evaluated on human bronchial epithelial cells by Fang et al.,[14] who reported the inhibition of the transcription and of the expression of ACE2, TMPRSS2, but also of DPP4 proteins. The DPP4 serine exopeptidase, also known as CD26, is involved in multiple physiological processes, including the cleavage a broad range of substrates, such as growth factors, chemokines, neuropeptides, and vasoactive peptides.[18] Recent evidence suggests that human DPP4/CD26 may interact with the S1 domain of the SARS-CoV-2 S glycoprotein and that DPP4 modulation or inhibition may prevent infection and/or progression of COVID-19.[44] There is also evidence suggesting that DPP4 inhibitors could prevent an excessive inflammatory response, thereby reducing the production of pro-inflammatory cytokines, and exert anti-fibrotic activity.[44] These properties may be of potential use for halting progression to a hyper-inflammatory state associated with severe COVID-19.

Fang et al.[14] also showed that OM-85 treatment was effective in upregulating ADAM17, HPSE and HA production in human bronchial epithelial cultures. Upregulating ADAM17 expression, OM-85 promoted the cleavage of the ACE2 from the epithelial cell membrane with release in the extracellular milieu of a high amount of that protein in the soluble form. sACE2 may

compete with membrane-anchored ACE2 receptors for binding sites of the SARS-CoV-2 virus S proteins, and act as a soluble decoy that can broadly block extracellular virus particles with limited potential for viral escape.[45] Also, the soluble form of heparan sulfate, whose release is promoted by OM-85, can act as a target decoy, and contribute to the inhibition of epithelial cell infection.[46,47]

Finally, OM-85 also induced synthesis of hyaluronic acid which can inhibit virus cycle replication at different stages, including internalisation and transcription phases, and even by directly killing the virus.[48] The ability of OM-85 to counteract CoV infection through induction of an effective immune response was evaluated in a mouse model by Salzmann et al.[15] They demonstrated that oral OM-85 treatment reduced a MCoV lung infection via the promotion of lung macrophage anti-viral functions through an early IFN signalling activation. In OM-85 treated mice, massive reduction of viral load was associated with reduced apoptotic burden in lung tissue, and with an early recruitment of lung macrophages. The recruitment was associated with a phenotypical change characterised by increased mRNA levels of genes related to antigen presentation already detectable before exposure to MCoV infection and a faster activation of the IFN system genes in the first 2 days following infection in OM-85-treated animals. This rapid 'innate immunity training', leading to lung macrophage pre-activation, was able to enhance viral clearance and to reduce the virus-induced lung damage, confirming the immunomodulatory properties of OM-85. Finally, transplantation of naïve macrophages, and monocytes to recipient mice which were consequently infected with MCoV resulted in enhanced IFN signalling and, thereby, a faster viral resolution, suggesting that the overall number is even more essential than an additional pre-activation for a fast recovery. Due to the similarities between the MCoV used in this model and human COVID-19, it is possible to speculate that similar mechanisms, i.e., oral training of the immune system using OM-85, could be beneficial also in SARS-CoV-2 infection.

CONCLUSION

In experimental model of respiratory infections, OM-85 has the capacity to modulate both the innate and the adaptive immune response, conferring efficacious broad Ig-related and cell-mediated immunity to the respiratory system. The outcomes of the experimental studies reported in this review support the hypothesis that OM-85 may aid in preventing SARS-CoV-2 infection and/or reduce COVID-19 severity by inhibiting multiple steps of SARS-CoV-2 cell infection and by its immunomodulatory properties. The proven safety profile of OM-85 demonstrated by decades of clinical use as an immunomodulator,[49] warrants future testing of this standardised bacterial extract in clinical trials to assess its potential as a complementary prophylactic and therapeutic approach in the current COVID-19 pandemic.

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Eosinophilic Pneumonia Due to Toxocariasis: A Rare Case Report in a Paediatric Patient and Literature Review

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Abstract

Human toxocariasis is a zoonosis caused by the larvae of *Toxocara* genus parasites. It is usually asymptomatic and self-limiting. However, due to either the direct action of parasites or by immunological mechanisms, it can affect several organs resulting in many clinical manifestations. Among paediatric patients, lung involvement occurs in 20–85% of cases of visceral toxocariasis, as Löffler's syndrome, chronic pneumonia, eosinophilic pneumonia, or baby wheezing syndrome. Because of its rarity, eosinophilic pneumonia due to *Toxocara* larvae is not well-documented amongst medical records.

This article presents a clinical case of a 2-year-old with a history of daily sand and soil ingestion, followed by sudden pulmonary symptoms, 9-day fever, abnormal chest X-ray, and intense peripheral eosinophilia. Due to the suspicion of toxocariasis pneumonia after a series of laboratory tests, the diagnosis of eosinophilic pneumonia caused by the parasite was confirmed. After treatment with albendazole for 5 days, the patient displayed progressive improvement in respiratory symptoms and a reduction in peripheral eosinophilia.

Key Points

1. Human toxocariasis is a zoonotic infection that occurs secondary to ingestion of infective larvae following contact with contaminated soil. It is usually an asymptomatic and self–limiting illness.

2. In children, lung involvement occurs in 20–85% of visceral toxocariasis cases. Eosinophilic pneumonia secondary to toxocariasis, most commonly caused by *Toxocara canis* or *Toxocara cati*, is a rare complication.

3. Diagnosis is made through a combination of clinical history, physical examination, serology, radiology, and bronchoalveolar lavage results. Treatment with anthelmintic medication leads to symptom improvement and reduction in eosinophilia.

INTRODUCTION

Human toxocariasis is a zoonosis caused by parasite larvae of *Toxocara* spp. The most prevalent pathological species are *Toxocara canis* and *Toxocara cati*, intestinal parasites from dogs and cats, respectively.[1]

Reported prevalence of this zoonosis varies geographically. It has a relatively high prevalence in tropical areas worldwide, mostly in regions with low socioeconomic levels, low urbanisation, and with poor access to sanitary conditions.[1,2] Human beings, especially children, infect themselves after contact with contaminated soil found mainly in parks and gardens, and they subsequently ingest infective eggs by habitually putting their hands in their mouths.[3]

Toxocariasis is usually an asymptomatic and self-limiting disease; however, it can cause various manifestations according to the organs affected.[1] Amongst children, lung involvement can occur in up to 20–85% of visceral toxocariasis cases, with presentations such as Löffler's syndrome, chronic pneumonia, eosinophilic pneumonia, and wheezing.[4,5]

Eosinophilic pneumonia is a heterogeneous group of lung diseases characterised by infiltration of lung parenchyma by eosinophils, resulting in alveolar eosinophilia (>25%) and pulmonary infiltrates, with or without evidence of peripheral blood eosinophilia (>1×10^9 eosinophils/L). Its precise incidence is unknown, estimated at <0.1 cases/100,000 inhabitants per year.[6]

Parasitic infestation is the main cause of eosinophilic pneumonia worldwide. Clinical manifestations are nonspecific and can range from asymptomatic pulmonary infiltrates to respiratory failure, requiring application of appropriate methods to establish the diagnosis.[4]

The present study reports a clinical case of a paediatric patient with eosinophilic pneumonia secondary to toxocariasis and provides a literature review on this subject.

CASE DESCRIPTION

A 2-year-old male, with a previous diagnosis of epilepsy, developed a 9-day fever with associated cough and dyspnoea. Following emergency services evaluation, the patient was noted to have an increased work of breathing, diffuse wheezing, and crackles, and was subsequently hospitalised.

During hospital stay, the patient's chest X-ray revealed diffuse interstitial infiltrate and laboratory findings showed significant peripheral eosinophilia (Table 1). Following these results, the hypothesis of *T. canis* infection was raised, especially after the mother's narrative that the patient had a daily habit of eating sand from their back garden.

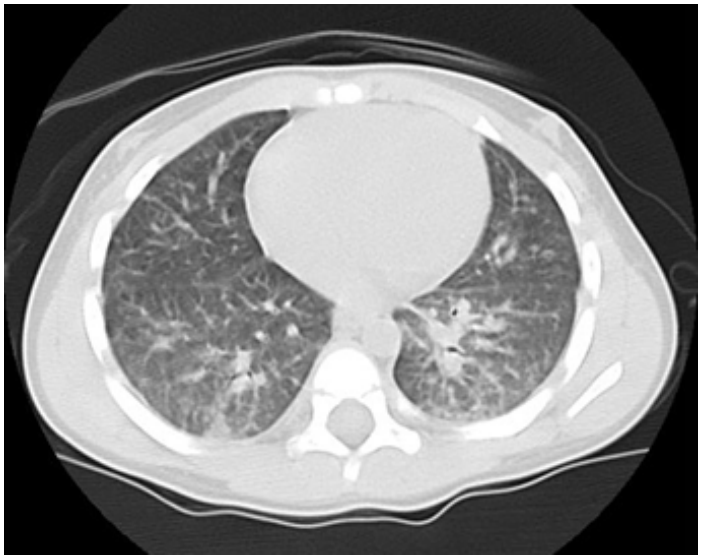
The diagnosis was confirmed with positive serology (IgG) for toxocariasis (Table 1). The possibility of systemic involvement of this condition was investigated, and an echocardiogram and abdominal ultrasound were performed, without significant abnormalities. A chest CT scan (Figure 1) showed diffuse involvement of centrilobular nodules combined with areas of ground glass opacity. As a result of this pulmonary involvement, bronchoalveolar lavage (BAL) was performed (Table 1), which showed peripheral eosinophilia compatible with eosinophilic pneumonia secondary to toxocariasis. The patient was treated with albendazole for 5 days, resulting in a reduction in peripheral eosinophilia and progressive clinical improvement. The patient remains under outpatient follow-up with paediatric pulmonology, with ongoing reduction in eosinophilia, and no respiratory symptoms or sequelae of any kind.

Table 1: Laboratory findings of the patient before and after treatment.

Laboratory	Before treatment	After treatment
Blood count	Haemoglobin 12.6 g/dL; leukocytes 44,680 /µL (63% eosinophils; 13% neutrophils; 1% band neutrophils; 22% lymphocytes) Platelets 459,000 /µL	Haemoglobin 11.1 g/dL; Leukocytes 10,080 /µL (28% eosinophils; 22% neutrophils; 42% lymphocytes) Platelets 360,000/µL
Viral panel (influenza A and B and respiratory syncytial virus)	Not detected	N/A
IgG anti-SARS-CoV-2	Not detected	N/A
Total IgE	> 5,000 kU/L	N/A
Toxocara canis IgG	4.98 (Positive: higher than 1.1)	N/A
Parasitological stool examination	No eggs or larvae of helminths, cysts, and protozoan trophozoites were found. Presence of Charcot-Leyden crystals	N/A
Bronchoalveolar lavage	41 leukocytes with 39% eosinophils; 26% neutrophils; 30% macrophages; and 5% lymphocytes	N/A

N/A: not applicable; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 1: CT scan of the patient revealing ground glass opacity, nodules and micronodules, and bilateral peribronchovascular interstitial thickening.



DISCUSSION

Pathophysiology

The most prevalent species of *Toxocara* responsible for visceral symptomatic infections among humans are *T. canis* and *T. cati*. The definitive hosts are usually the domestic dog or cat and, when infected, they eliminate adult worms spontaneously. Female worms produce thousands of eggs that are resistant to hostile factors in the external environment. When favourable conditions of humidity and temperature occur, those eggs are embryonated and become infectious. Domestic pets become infected by ingestion of embryonated eggs, ingestion of the larvae, transplacental migration, and transmission by colostrum during lactation amongst other causes. Infections in children usually develops after the ingestion of eggs secondary to contact with infected pups or contact with objects containing eggs or larvae.[2]

After ingestion of *Toxocara* eggs, the larvae hatch and migrate to different tissues, resulting in a systemic inflammatory reaction.[7,8] Symptoms vary according to the host's immune response and the number and location of these larvae. In individuals infected by a large volume of *Toxocara* eggs, there is significant eosinophilia and retention of large amounts of the parasite in liver and lung tissue, causing classic manifestations of *Toxocara* pneumonia.[9] Pulmonary involvement of *Toxocara* is uncommon and responsible for causing a local allergic reaction after parasite infiltration. Lung injuries are more frequent in children under 1 year of age.[7]

One of the pulmonary affections related to infection by *T. canis* is eosinophilic pneumonia, which occurs due to several factors, including Type I hypersensitivity reaction, activated by alveolar macrophages following an external trigger; direct action of the infectious agent; or resulting from an inflammation cascade triggered by inflammatory cytokines, which cause eosinophilic recruitment.[9,10] Some parasites bind to alveolar or parenchymal epithelial cells, causing the release of IL-33 and thymic stromal lymphopoietin, which are potent triggers of the Th2 immune response, responsible for the recruitment of eosinophils and T-helper cells.[10]

The mechanisms of lung injury caused by eosinophils are not fully understood. Eosinophilic inflammation is responsible for the release of granules between alveolar spaces and lung parenchyma, causing direct damage to the tissue. Other cells such as neutrophils, macrophages, and lymphocytes can also activate similar inflammatory responses; however, their role is not well understood.[10]

Clinical Manifestations

The majority of *Toxocara* infections are asymptomatic and systemic toxocariasis occurs in approximately 15% of diagnosed cases.[2] The current classification of toxocariasis divides it into asymptomatic, systemic, compartmentalised (ocular and neurological), and covert. Ocular and neurological manifestations are probably the final stages of larvae migration, a consequence of non-treated toxocariasis complications.[2] The visceral larva migrans syndrome is the most severe systemic form of toxocariasis, with fever, hepatosplenomegaly, leukocytosis, and high eosinophilia. The possible complications of prolonged extreme eosinophilia are eosinophilic myocardial or pulmonary fibrosis.[2]

Pulmonary toxocariasis is usually asymptomatic or causes only mild, non-specific symptoms. The classic, or symptomatic, form of the disease manifests itself in children with a previous history of geophagia. It starts with fever, hyporexia, and cough, mainly at night. On physical examination, there are commonly changes in respiratory auscultation, especially in the middle and lower lung lobes, with wheezing and/or crackles, similar to the physical examination of the patient in this case report. The condition may be accompanied by cervical adenomegaly, moderate hepatomegaly, and/or mild splenomegaly. In rare cases, it may progress to acute respiratory distress syndrome.[6,11]

In a study of 119 children positive for *Toxocara* serology, 23 children had chest X-ray abnormalities. Among them, only 15 children presented with clinical respiratory complaints such as chronic cough, wheezing, asthma, or haemoptysis. Cough (67%) was the most common symptom among patients. Other symptoms included chronic wheezing (47%), dyspnoea (13%), haemoptysis (7%), and general weakness (7%).[7]

The severe pulmonary manifestations seen in this case can be considered exceptional.[8] There may be complications from prolonged eosinophilia, more common in cases of the classic (or symptomatic) form, such as pulmonary fibrosis.[2]

Diagnosis

The diagnosis of *Toxocara* eosinophilic pneumonia is based on the characteristic findings in the BAL associated with a positive anti-*Toxocara* ELISA serological test, in addition to the clinical and radiological findings suggestive of the disease.[12] Definitive diagnosis is made through microscopy evaluation of infected tissues with direct visualisation of *Toxocara* larvae. It is the gold standard diagnostic test, but also an invasive method. Moreover, sometimes the larvae may not be found in the eosinophilic granuloma tissue wedge.[13,14] Currently, the most used method for the diagnosis of human toxocariasis is the serological test anti-*Toxocara* ELISA, which detects antigens excreted and secreted by Stage 3 larvae of *T. canis* (*Toxocara* excretory-secretory antigen-based ELISA). Studies have shown that this test has 78% sensitivity and 92% specificity.[13,14]

There are other laboratory findings that can help in diagnosis, such as hypergammaglobulinemia (increased isohemagglutinin A and B), anaemia, and leukocytosis with marked eosinophilia.[14] However, there are cases in which eosinophilia may be minor or absent. This situation may occur in milder and chronic cases.[15] Peripheral eosinophilia is established when the eosinophil count is above 500 cells/mm^3 and intense eosinophilia when above 1000 cells/mm.^{3} In cases with pulmonary involvement, there may be eosinophilia in the BAL.[8,16]

Eosinophilic pneumonia encompasses a heterogeneous group of diseases that are characterised by the presence of one or two criteria: pulmonary infiltrate with blood eosinophilia or eosinophilia on lung biopsy or BAL.[16] Pulmonary eosinophilia most often occurs due to migration of the larval stage to the lungs, and is defined by an eosinophil count of greater than 5% in BAL, with intense eosinophilia when the eosinophil count is greater than 25%.[16] The diagnosis of eosinophilic pneumonia is made when the level of eosinophils in BAL exceeds 25%, as in the reported clinical case.[17] Among other causes of eosinophilic pneumonia, it is important to investigate other types of infections, such as fungal or parasitic, ingestion of drugs or toxins, smoking or other inhalational substance exposure, and multisystemic diseases such as eosinophilic granulomatosis with polyangiitis. It is fundamental to differentiate eosinophilic pneumonia from other distinct types of pneumonia, because early treatment of the underlying condition has an impact on patient outcome.[10]

Lung biopsy may be necessary in more complex cases with differential diagnoses for instance, to rule out neoplasms or other infections.[16] Studies suggest that performing the serological ELISA test for *Toxocara* in patients with pulmonary infiltrate associated with eosinophilia may demonstrate a higher-than-expected number of cases of *Toxocara* pneumonia.[12]

Treatment

Even though the majority of patients with toxocariasis have a favourable prognosis, the larvae can remain in the human body for approximately 2 years. All hosts can suffer from new infective reactivation and larvae migration into brain or ocular tissues. Treatment is recommended for all symptomatic patients and helps to prevent the aforementioned complications.[2]

Studies on the topic of pharmacology treatment consist of the administration of anthelmintic drugs, such as albendazole at a dose of 400 mg twice per day for 5 days.[18] Mebendazole 100–200 mg twice per day for 5 days is an alternative, but abendazole is preferred as it crosses the blood–brain barrier.[19] Ivermectin does not appear to be effective for toxocariasis.[20] Diethylcarbamazine at a dose of 3–5 mg/kg per day for 21 days was effective in a small number of cases, but it has potential adverse effects, and therefore is not widely used. Prospective studies are needed to evaluate the best drug therapy and its duration.[20]

The efficacy of treatment is difficult to evaluate because of toxocariasis subtle symptomatology. It remains unclear if reduction in hepatomegaly and/or eosinophilia can indicate reduction of larvae infectivity. Some serology markers can be helpful to demonstrate successful treatment,

combined with eosinophil count and serum IgE antibodies.[2] After a series of experimental studies and drug trials among paediatric and adult populations, high rates of successful therapy for symptomatic toxocariasis are well established, mainly with anthelmintic drugs. In contaminated environments, it is more common to see multiple reinfections rather than untreatable infections.[21]

Prevention is the most important strategy and includes good hygiene practices, appropriate disposal of pet faeces, and regular deworming of pets. Hand washing should be encouraged after contact with pets or areas at high risk of soil contamination such as litter boxes.[15,21]

CONCLUSION

The presentation of this article aimed to report a paediatric case of eosinophilic pneumonia secondary to toxocariasis, an uncommon condition with few well-documented medical records. The report brings to light the importance that for a good clinical outcome in this condition, it is necessary to correlate clinical history, physical examination, laboratory tests (blood count, serology for *Toxocara*, BAL), and imaging (chest radiography and CT). With a well-established diagnosis and adequate treatment, the patient's clinical improvement is remarkable, making it possible for the child to return to their usual daily activities with no pulmonary symptoms or impairment.

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Incidentally Detected PET-CT Imaging Findings Of Covid-19 Pneumonia: A Retrospective Study During Local Pandemic Era

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Abstract

Background: COVID-19 has been declared a global health emergency by the World Health Organisation (WHO). Commonly, a CT chest scan is performed to detect any early findings of COVID-19 pneumonia before the onset of clinical symptoms. In this article, the authors reported COVID-19 pneumonia in patients undergoing positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with CT (18F-FDG PET/CT) examinations for early isolation and necessary management.

Methods: One hundred and twelve patients who underwent 18F-FDG PET/CT imaging for routine oncological examination were considered for the study, and these subject scans were taken during a period of December 2020–August 2021. Following which, reverse transcription-PCR testing was requested for confirmation.

Results: Amongst the 112 patients, 45 (40%) patients showed features of COVID-19 pneumonia on PET/CT imaging. Reverse transcription-PCR testing carried out for these patients confirmed the infection in 38 individuals (84%).

Conclusion: 18F-FDG PET/CT is sensitive for early detection of COVID-19 pneumonia, so as to minimise further spread of infection and apply adequate measures for prevention.

Key Points

1. At the time of publication, no specific imaging modality had been adopted as first-line investigation for diagnosis of COVID-19 pneumonia.

2. Typical findings on chest X-rays and CT scans of patients with COVID-19 are ground-glass opacities or pulmonary consolidations in multiple lobular and segmental areas.

3. The authors' study concluded that COVID-19 pneumonia showed standardised uptake value (SUV) on FDG PET/CT imaging, therefore can be detected as an incidental finding in asymptomatic patients.

INTRODUCTION

The novel COVID-19 pneumonia is a continuing global pandemic that has caused deaths of 5 million people worldwide as of November 2021. This aggressive acute respiratory disease occurred in Wuhan, China, in the month of December 2019. After it spread globally, the World Health Organization (WHO) declared COVID-19 a pandemic.[1]

The majority of individuals present with non-specific symptoms, including a fever, cough, and breathlessness, while others remain asymptomatic. These asymptomatic patients are thought to disperse the infection within the population, and can potentially i nfect family members.[2] Reverse transcription-PCR (RT-PCR) testing remains the gold standard for the diagnosis of COVID-19, even though its sensitivity has been reported as 60–70%.[3] No imaging modality has been accepted as the first line of investigation to diagnose COVID-19 pneumonia.[4]

Ground-glass opacities (GGO) or pulmonary consolidations in multiple lobular and segmental areas are typical findings on chest X-rays and CT scans that are suggestive of COVID-19 pneumonia.[5-7] Radiological manifestations of COVID-19 can persist for a while, irrespective of the clinical course.[8] As pulmonary parenchymal opacities evolve, progressive atypical respiratory system distress develops, leading to eventual multiorgan failure in few patients.[9] It is known that positron emission tomography with 2-deoxy-2-(fluorine-18)fluoro-D-glucose integrated with CT (^{18}F-FDG PET/CT) imaging demonstrates increased uptake in pathologies such as neoplastic aetiologies, inflammatory, and infective processes. Even though ^{18}F-FDG PET/CT imaging is not considered for the primary diagnosis of COVID-19 pneumonia, it is essential to detect infective changes in the chest for further management of patients.[10] The incidental use of this type of imaging can detect changes in patients that are asymptomatically infected with COVID-19, and RT-PCR testing can then be used to confirm this diagnosis. It is helpful in terms of patient management on deciding the course of the planned treatment of the underlying disease. It is also important for healthcare workers to undergo necessary safety measures, use personal protective equipment, and sanitise the imaging room at the end of each procedure. Strict containment measures can be undertaken to limit the spread of infection. The rate of asymptomatic infection amongst healthcare workers shows general community transmission; therefore, careful planning is a must to protect staff and patients during an imaging examination.[11]

The first confirmed case of COVID-19 infection in India was on 27th January 2020. Since then, cases have attained a steady, rising course.[12] To suppress this infection, even though there was a nationwide lockdown, hospitals continued to provide comprehensive cancer care with modified protocols and strategies.

The main aim of this study is to highlight occasional radiological findings of COVID-19 pneumonia in patients undergoing ^{18}F-FDG PET/CT examinations and to depict certain considerations to enable a safe scanning process.

MATERIALS AND METHODS

The study was conducted in the authors' hospital, A. J. Institute of Medical Sciences, Mangalore, Karnataka, India, during a period of eight months from December 2020–August 2021. One hundred and twelve patients who underwent ^{18}F-FDG PET/CT imaging for routine oncological examination on appointment basis were included in the study. Patients considered in this study were asymptomatic at the time of examination and were allowed to undergo the PET/CT study without the need for a negative rapid antigen test or RT-PCR test. However, due to the high prevalence of COVID-19 infection in hospitals, all patients underwent adequate precautions before general access to hospital. According to the hospital's COVID-19 protocol, patients underwent temperature screening and careful history-taking prior to the initial access to the hospital; based

on initial assessment, they were deemed to be asymptomatic for COVID-19 infection. The ^{18}F-FDG PET/CT examination was performed after obtaining informed written consent from patients. The study protocol was approved by the Institutional Research Ethics Committee.

PET-CT Imaging

All the PET/CT images were acquired via the standard protocol using Biograph mCT 20 Time of Flight PET-CT scanner (Siemens Healthineers, Erlangen, Germany), a hybrid 3D PET/CT system. Patients were asked to fast 6–8 hours before the study, and blood glucose levels were kept <200 mg/dL during the time of tracer injection. The scan was performed about 1 hour after an intravenous injection of 0.1 mCi of ^{18}F-FDG/kg, according to the patient's weight. The acquisition started with non-contrast CT in a cephalocaudal direction. The scan was performed with the patients' arms placed above the head and normal breathing. The PET data were acquired using a whole body protocol, from vertex to mid-thighs. All emission scans were performed in 3D mode, and the acquisition time per bed position was 2 minutes. Immediately after PET scanning, a contrast-enhanced CT scan was performed using the following parameters: 350 mA, 120 kV, and 5 mm slice thickness. Iodinated non-ionic contrast agent Omnipaque™ 350 (GE Healthcare, Boston, Massachusetts, USA) was administered intravenously (100 ml) with a flow rate of 5 mL/sec. The lung CT images were reconstructed by filtered back projection into 512×512 pixel images and iterative reconstruction, lung filter with window setting of 1,600 Hounsfield units window width, and 480 Hounsfield units window level. A dedicated workstation was used to view and interpret the CT, PET-CT, and PET images. The images were interpreted by an experienced nuclear medicine specialist and radiologist. The cases that showed indeterminate findings of COVID-19 pneumonia were reported and, for confirmation, RT-PCR testing was requested. The data was then collected, tabulated, and analysed.

RESULTS

Among 112 patients, 64 (57.1%) patients were male and 48 (42.8%) were female. The age group of these patients ranged from 33–78 years, with a mean age of 48.5±3.8 years. Fifty-two patients came for diagnosis and initial PET/CT evaluation; the remaining 60 patients came for follow-up and surveillance scans. Forty patients (35.7%) had lymphoma; 26 patients (23.2%) had lung cancer; 18 patients (16%) had breast cancer; 12 (10.7%) patients had colon cancer; 12 (10.7%) patients had renal cell carcinoma; and four (3%) patients had head or neck malignancies.

Amongst 112 patients, 45 patients (40%) showed high suspicion of COVID-19 pneumonia. These patients were asymptomatic for COVID-19 infection, and lung changes were detected incidentally (Figure 1, 2). Bilateral lung findings were found in 30 patients (66.7%), whereas unilateral lung findings were found in the remaining 15 patients (33.3%). The CT findings included multifocal GGOs and pulmonary consolidations. Pure GGOs were seen in 26 patients (57.7%). Mixed GGOs and pulmonary consolidations were seen in 17 patients (37.7%). One patient had patchy areas of pulmonary consolidation with fibrosis. One more patient had GGO with interlobar septal thickening in bilateral lung fields.

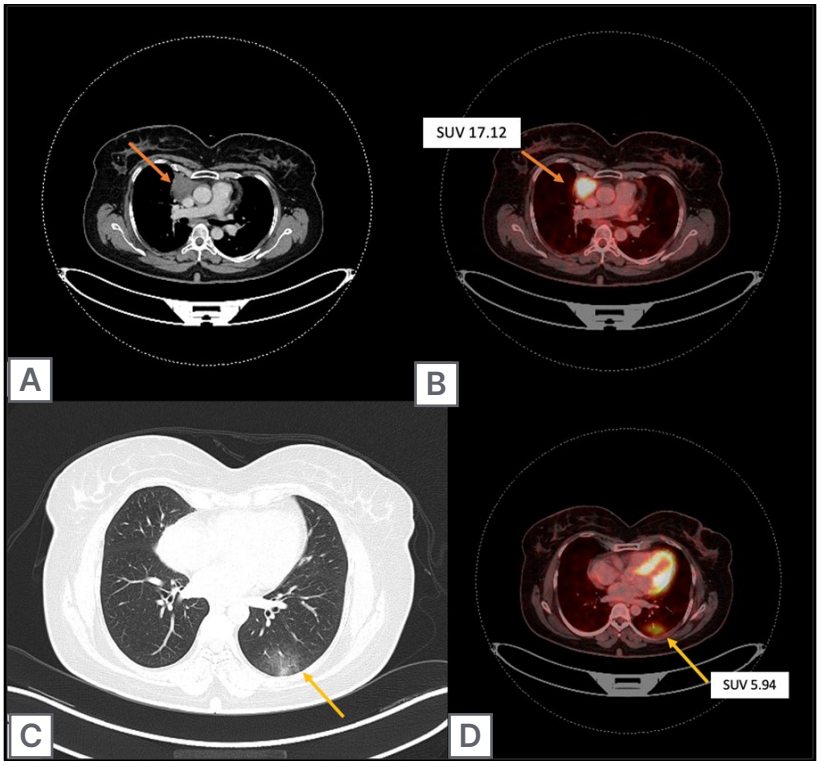
The findings of pneumonia on PET images showed variable FDG avidity. The maximum standardised uptake value (SUVmax) ranged between 1.54–3.0 in 32 patients (71.1%), and between 3.0–7.46 in 13 patients (28.9%). Table 1 shows lung imaging findings and SUVs of the cases considered for the study.

RT-PCR testing was done for these patients within 24–48 hours of imaging, for confirmation of COVID-19 infection. The test was found to be positive in 38 patients (84%). Patients with moderate to severe disease were carefully monitored with the help of medical management and oxygen supplementation, while others were advised for home or institutional quarantine.

DISCUSSION

RT-PCR testing for the diagnosis of COVID-19 has been shown to have lower sensitivity and few studies have shown that positive CT findings with negative RT-PCR result has to be treated as COVID-19 pneumonia.[13,14] At present, high-resolution CT imaging of the chest has

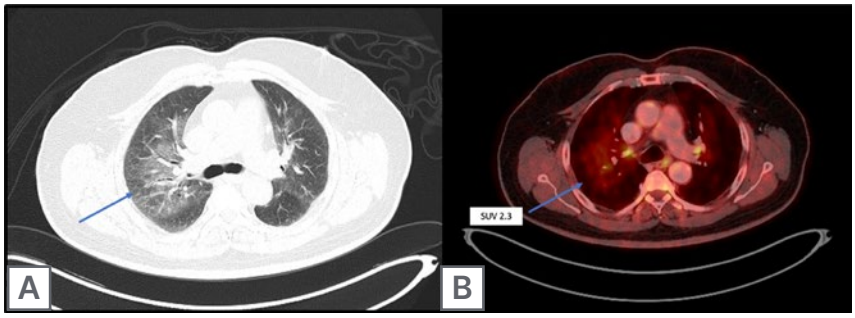
Figure 1: A 47-year-old female patient, with Hodgkin's lymphoma, was referred for PET/CT evaluation.



Axial contrast enhanced CT image (a) and corresponding fused axial PET/CT image (b) shows a FDG avid anterior mediastinal mass on right side (SUV 17.12). Axial lung window CT image (c) shows unilateral ground-glass opacity in subpleural location of left lower lobe, that shows FDG uptake in corresponding fused PET/CT image (d) with a SUVmax value of 5.94, which was suspicious for COVID-19 pneumonia.

FDG: 2-deoxy-2-(fluorine-18)-fluoro-D-glucose; SUV: standardised uptake value; SUVmax: maximum standardised uptake value.

Figure 2: A 70-year-old male patient, another case of Hodgkin's lymphoma.



Axial lung window CT image (a) shows bilateral ground-glass opacities (right > left) predominantly in perihilar regions, which could suggest infective aetiology. This shows mild FDG uptake in corresponding fused PET/CT image (b) with a SUVmax value of 2.3 (arrows).

FDG: 2-deoxy-2-(fluorine-18)-fluoro-D-glucose; SUV: standardised uptake value; SUVmax: maximum standardised uptake value.

Table 1: Imaging features and demographics of the study population.

Characteristics	Frequency	Percentage
Lung involvement on imaging		
Bilateral	30	
Unilateral	15	
COVID-19 pneumonia findings on imaging		
Pure GGOs	26	57.7
GGOs + pulmonary consolidations	17	37.7
Patchy areas of pulmonary consolidation with fibrosis	1	2.3
GGOs with interlobar septal thickening	1	2.3
SUV value on imaging		
1.54–3.0	32	71.1
3.0–7.46	13	28.9

GGO: ground glass opacities; SUV: standardised uptake value.

been chosen as the preferred tool for diagnosis, screening, severity assessment, and monitoring of patients with COVID-19.[15,16] CT findings range from pure patchy to multifocal GGOs, to pulmonary consolidations with air bronchograms, which can eventually lead to parenchymal fibrosis. Other ancillary findings include crazy-paving sign, interlobar septal thickening, pleural effusion, reverse halo sign, and reactive lymphadenopathy.[17]

Since this global pandemic has begun, there have been several case reports, research studies, and investigations in assessing the importance of chest CT in diagnosis, and determining the severity of the disease. Few indices that are used in the clinical practice include the COVID-19 Reporting and Data System (CO-RADS) and CT severity score. However, these indices have been primarily tested in symptomatic patients, and there have not been many studies performed regarding the role of chest CT or other imaging techniques in diagnosis of COVID-19 pneumonia in asymptomatic individuals. A nuclear medicine study, ^{18}F-FDG PET/CT is performed mainly in diagnosis, detection, and staging of malignant lesions.[18,19] Apart from malignant tumours, FDG uptake is also seen in active inflammation and infection.[20] Since a chest CT component is included in a routine PET/CT study, it would be helpful in diagnosing an asymptomatic cancer patient with COVID-19 pneumonia. Few case reports and studies have been performed in the past showing the presence of COVID-19 pneumonia in patients undergoing FDG PET/CT imaging. It would also be helpful in evaluating the metabolic characteristics of the pulmonary parenchymal opacities, and its FDG uptake.

Few studies and case reports in the past have reported findings of COVID-19 pneumonia in patients who have undergone nuclear medicine imaging studies, including ^{18}F-FDG PET/CT.[21,22] In this study of 112 patients, 45 patients (40%) showed COVID-19-associated pneumonic changes in the chest, that were FDG avid on the corresponding PET images (ranged between 1.54–7.46 SUVmax). These results were correlated with the studies performed by Setti et al.,[23] Albano et al.,[24] and Pallardy et al.,[25] who had also incidentally detected COVID-19 pneumonia in patients with cancer who were

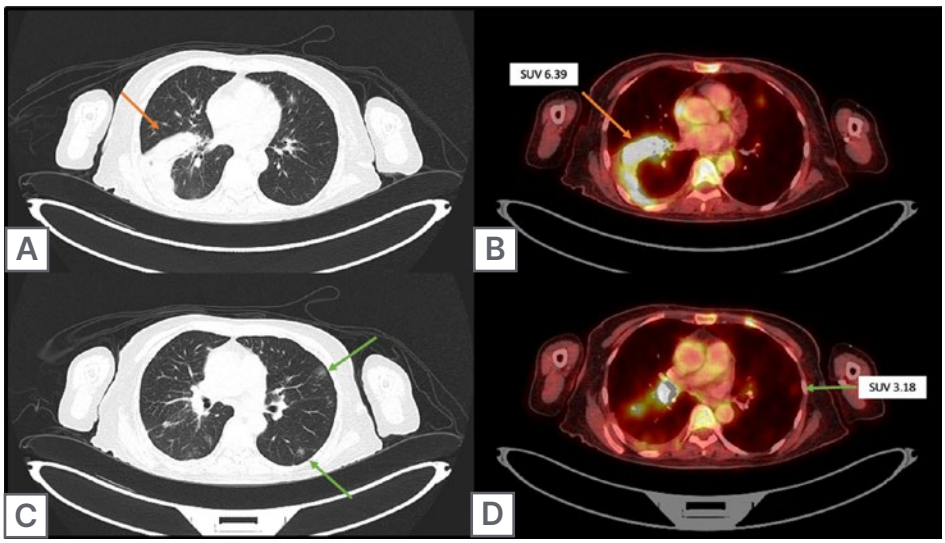
asymptomatic on ^{18}F-FDG PET/CT examinations. Setti et al.[23] detected chest changes in five out of 13 patients whose SUVmax ranged between 4.3–11.3. The study conducted by Albano et al.[24] showed typical findings of COVID-19 pneumonia in six out of 65 patients, of which four patients tested positive on RT-PCR testing. Pallardy et al.[25] detected abnormalities in 3.8% of patients with cancer who were asymptomatic, with an SUVmax range between 1.58–13.64. One of the authors' patients had parenchymal consolidation with peripheral GGOs, which is an indeterminate finding of COVID-19 pneumonia (Figure 3). A study conducted by McDermott et al.[26] showed that benign GGOs show a significantly higher ^{18}F-FDG uptake in PET/CT than malignant GGOs or nodules, which correlated in this study. These are a few of the studies showing that the risk of spread of infection is increased when patients are referred for routine imaging examinations. Patients who showed incidental lung findings were either undergoing active cancer treatment, or had recently completed treatment. Figure 4 gives a brief summary of the results of this study.

The repercussion of cancer disease, as well as cancer treatment, adversely affects the immune system, making patients more susceptible to infection and its complications. Making use of PET/CT in detection of asymptomatic COVID-19 infections in these patients provides an added benefit beyond its oncological aim.[27] Few studies also showed the importance of the application of hygienic measures, contact minimisation, and usage of personal protective equipment for the safety and protection of the health personnel as well as patients.[28] Another important aspect to be noted is that, once the findings are detected, appropriate action and treatment can be undertaken with clinical monitoring. The main limitation of this study was that the sample size was small; larger studies needs to performed to give accurate results.

CONCLUSION

The authors concluded that COVID-19 pneumonia showed SUV uptake on FDG PET/CT

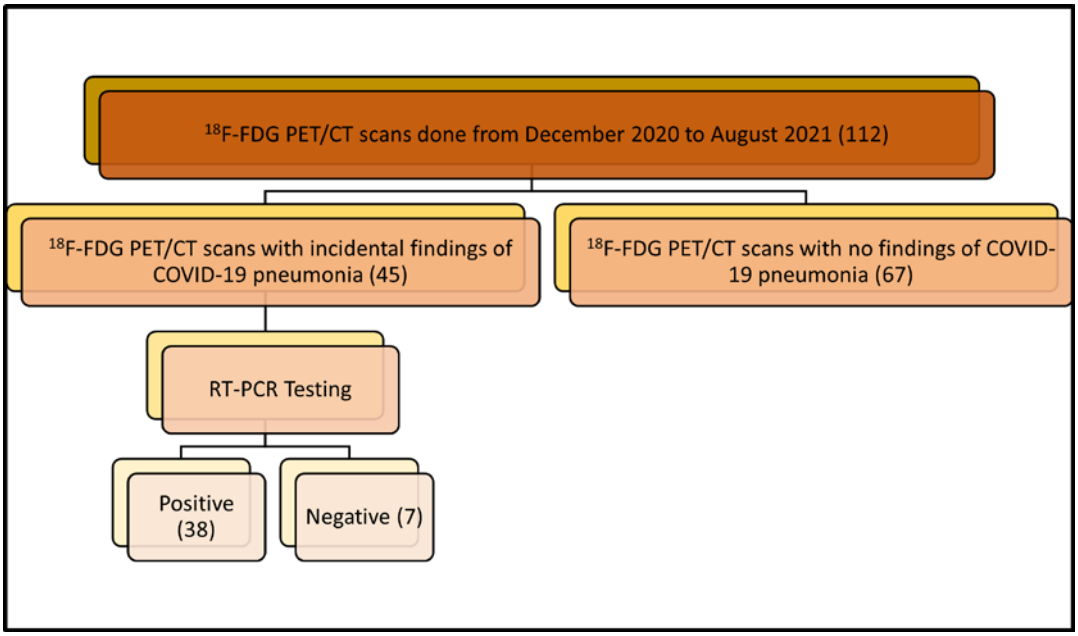
Figure 3: A 58-year-old female patient with of carcinoma of right lateral aspect of tongue.



Axial lung window CT image (a) shows unilateral consolidation in right lower lobe, that shows SUVmax of 6.39 in corresponding fused PET/CT image (b). Axial lung window CT image (c) shows few ill-defined patchy ground-glass opacities in subpleural location of bilateral lung fields (arrows), which shows mild FDG uptake in corresponding fused PET/CT image (d) with a SUVmax value of 3.18. These findings were more in favour of infective aetiology than metastatic disease. Therefore, reverse transcription-PCR test was advised, which was positive.

FDG: 2-deoxy-2-(fluorine-18)-fluoro-D-glucose; SUV: standardised uptake value; SUVmax: maximum standardised uptake value.

Figure 4: Flowchart depicting the study results and interpretation.



18F-FDG PET/CT: 2-deoxy-2-(fluorine-18)-fluoro-D-glucose integrated with CT; RT-PCR: reverse transcription-PCR.

imaging and can be detected as an incidental finding in asymptomatic patients. Although FDG PET/CT imaging is not the first-line imaging modality in detecting COVID-19 pneumonia, it can be effectively used during this pandemic. It is advised to undergo adequate safety measures before undergoing any imaging procedure, as well as ensuring the safety of healthcare workers, and the appropriate preparation of imaging services. These measures could not only help in patient management but could also reduce the community spread of infection.

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An Observational Study on Unique High Resolution Computed Tomography Pattern of Post-COVID Pulmonary Fibrosis

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Abstract

Background: As the severe acute respiratory syndrome coronavirus 2 era commenced, a new entity was added to the already hefty bulk of parenchymal lung diseases in post-COVID-19 pulmonary fibrosis. A wide range of findings from mild ground glass opacities to exuberant fibrosis are seen on high resolution CT of the thorax. However, the authors came across a pattern that was frequently repeated, and therefore conducted an observational study on the radiological findings.

Method: The study was conducted for a period of 6 months in the departments of Respiratory Medicine and Radiodiagnosis at King George's Medical University, Lucknow, India. The radiological findings on high resolution CT thorax of consecutive patients who reported to the Department of Respiratory Medicine after recovering from COVID-19, and were previously reverse transcriptase-PCR-positive or serologically confirmed, were studied.

Result: There were a total of 56 subjects (32 males; mean age: 56 years). The most common finding was ground glass opacities (89%). Reticulations were seen in 86% of patients, with a unique dome-shaped fibrosis parallel to pleural surface in 54%, patchy consolidation in 49%, and scattered cysts in 43%. The distribution was mostly bilateral with slight predominance of lower lobes (57%).

Conclusion: Ground glass opacities, reticulations, and consolidation are fairly common in patients with pulmonary sequelae of COVID-19. It has a peculiar predilection for involvement of subpleural space with cupola or band-shaped fibrosis.

Key Points

1. Parenchyma of the lungs can undergo fibrosis due to a number of known aetiology and is associated with a poor outcome.

2. This observational study of 56 subjects highlights the most common complaints in post-COVID-19 pulmonary fibrosis, which includes fatigue, coughing, and dyspnoea.

3. The authors used high resolution CT to study the different radiological findings in post-COVID-19 pulmonary fibrosis and indicate that it should be considered in the aetiology of fibrotic lung diseases.

INTRODUCTION

The parenchyma of the lungs can undergo fibrosis due to known aetiology such as radiation or drug induced fibrosis; occupational or connective tissue related interstitial lung disease; or it may have genetic basis or remain idiopathic, as in idiopathic pulmonary fibrosis. Over 200 interstitial lung diseases are known, and repeated attempts are made to reclassifying them as understanding improves.[1] The latest classification proposed by Cottin et al.[1] was based on their progression to fibrosis. Those with tendency to have a fibrotic course are associated with a poor outcome. A new undesirable addition to this is post-COVID-19 pulmonary fibrosis and the rapidity of development of lung scarring.[2]

When the world was jostled by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, little was known that the aftermath would be so long-lasting. Both virus-mediated cytopathic effects and host immune response causing cytokine storm are blamed for the pulmonary sequelae. The inflammatory milieu of the lungs with high levels of TNF-α; IL 6, 8, and 12; and interferon-γ cause tissue damage, with subsequent healing and evolvement into widespread fibrosis.[2,3] Other likely mechanisms include angiotensin-induced pulmonary vasoconstriction and activation of pro-fibrotic molecules such as tumour growth factor β1, ventilator-induced lung injury, and oxygen toxicity.[2,4] Changes were more pronounced in males, the elderly, those with comorbidities, chronic alcoholics, smokers, those with severe disease, and those requiring mechanical ventilation.[5-9] The disease not only wreaked a new havoc of its own, but also affected the course and epidemiology of other disorders by producing an intense inflammatory state, as well as afflicting healthcare services.[10-12]

Certain characteristic radiological findings were identified in patients with COVID-19, and CT scans of the thorax played a crucial role not only in diagnosis but also in assessing severity. The second week of illness was more commonly associated with the development of radiological abnormalities.[13-16] Multiple scoring systems such as Coronavirus Disease 2019 Reporting and Data System (CO-RADS) and CT severity score (CSS) were developed.[17,18] In this study, out of the typical findings described in CO-RADS 5, such as crazy paving, consolidations, and the subpleural bands, fibrotic bands were seen to persist long in nearly half of subjects long after they became normoxic. The most frequent remnants were ground glass opacities and interlobular septal thickening with predominant peripheral distribution.

MATERIAL AND METHODS

This observational study was conducted in the department of Respiratory Medicine, in collaboration with the department of Radiodiagnosis, at King George's Medical University, a tertiary care center in Northern India, from August 2020–January 2021 (total duration: 6 months), after obtaining clearance from the Institutional Ethics Committee.

Inclusion criteria was all consecutive patients aged ≥13 years who had moderate to severe COVID-19 infection that was serologically confirmed; had a CT thorax obtained at the time of diagnosis; had passed a duration of at least 3 months since the time of diagnosis; and

provided written informed consent. The severity of COVID-19 was defined on the basis of Indian Council of Medical Research (ICMR) guidelines, according to which a respiratory rate ≥24 breaths/min or percentage saturation of oxygen ≤93% on room air constituted moderate disease, while a respiratory rate of >30 breaths/min or percentage saturation of oxygen <90% was needed to categorise the disease as severe.[19] Those individuals who had their baseline CT thorax carried out at other centres but had their investigation records were allowed. The range of duration included since the time of diagnosis was between 94±4 days. Individuals who failed to provide consent, or had pre-existing respiratory comorbidity, were excluded.

Statistical Analysis

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM, Armonk, New York, USA). The data was expressed as mean, median, standard deviation, or percentage, as was appropriate. All the categorical data were compared using a chi-squared test. Continuous variables in two groups were compared by t-test. Pearson's correlation was used for correlation. Binary multivariate logistic regression analysis was performed in each patient to determine the independent risk factors for severity of COVID-19. The p-value <0.05 was considered as significant.

Participants and CT Scoring

Eighty-nine patients who presented to the outpatient department with persistent symptoms 3 months after suffering from COVID-19 were screened for the study. A detailed clinical history, including the history of treatment received and past history, were taken. After applying the inclusion and exclusion criteria, 56 subjects were included in the study. All were subjected to high resolution CT (HRCT) thorax in supine position (standard-of-care) using 120 kVp/80 mAs with scan time of 1 sec with slice thickness of 1 mm, using the same machine and settings. The lungs were evaluated at window width of 1,000–1,500 HU and window level of -550 to -650 by the same radiologist and findings noted.

CSS was calculated by assigning each of the five lung lobes a score from 0–5 based on percentage involved.[18] Score 0 implied no involvement; 1 was allotted if there was <5% involvement; 2 if 5–25% was involved; 3 for 25–50%; 4 in cases of 50–75% involvement; and the maximal lobar score of 5 for >75% involvement. The individual lobar scores were added to arrive at the final score ranging from 0–25.

RESULTS

A total of 56 subjects were recruited, out of which 32 (57.1%) were males. The mean age of the study population was 40.1 years. Other baseline characteristics are compiled in Table 1. Out of 56 subjects, 15 had suffered from moderate COVID-19, while 41 had had severe disease. Smoking history was comparable among the subjects. Diabetes was the most frequent comorbidity and pneumothorax the most common associated complication. The mean age was 45.67±14.50 and 38.05±11.56 years, respectively, for patients with and without comorbidities (difference: -7.61; [-14.82; -0.41]; p=0.043).

The mean duration of hospital stay for moderate cases was 9.20 days, while that for severe cases was 16.56 days. None of the subjects had undergone invasive ventilation. Median CSS at the time of admission among moderate and severe cases were 16 and 17, which reduced to five and six, respectively, by the end of 3 months. At the time of diagnosis most patients had total leukocyte count within the normal range with lymphopenia (Table 1 and Figure 1). Only 52 subjects out of 56 were able to perform acceptable pulmonary function test. The mean values fell within the range of mild restriction with mild diffusion defect. The history of corticosteroid intake was significantly higher among the severe group. A significant positive correlation (Karl Pearson's correlation coefficient 0.302; p=0.024) was seen between the CSS and duration of steroid intake.

The most common complaint was persistent fatigue in over 90% subjects of both groups, followed by cough (32.1%) and dyspnoea (28.6%). Diarrhoea persisted in only two subjects of severe COVID-19 (Table 2).

The radiological findings persisted more in severe COVID-19 subjects. Bilateral involvement was seen in 89.3% (n=50) with peripheral

Table 1: Baseline data of the study population.

Characteristic	Total (N=56)	Moderate (n=15)		Severe (n=41)		p
		n	%	n	%	
Sex						
Male	32	10	66.7	22	53.7	0.571
Female	24	5	33.3	19	46.3	
Age (years [mean±SD])	56	43.5±15.7	N/A	39.4±12.2	N/A	0.302
BMI (mean±SD)	56	23.4±3.6	N/A	23.7±3.9	N/A	0.784
Residence						
Rural	31	6	40.0	25	60.9	0.274
Urban	25	9	60.0	16	39.0	
Smoking status						
Current	4	2	13.3	2	4.9	0.098
Ex-smoker	5	3	20.0	2	4.9	
Non-smoker	47	10	66.7	37	90.2	
Comorbidities						
Diabetes	10	6	40.0	4	9.8	0.026
HTN	5	2	13.3	3	7.3	0.865
CAD	2	0	0.0	2	4.9	0.954
Hypothyroidism	1	0	0.0	1	2.4	0.542
Oxygen delivery						
Oxygen mask	18	8	53.3	10	24.4	0.084
Nasal cannula	19	10	66.7	9	21.9	0.005
NR mask	36	9	60.0	27	65.8	0.928
HFNO	13	1	6.7	12	29.3	0.157

Table 1: continued.

NIV	23	7	46.7	16	39.0	0.835
Invasive ventilation	0	0	0.00	0	0.0	N/A
Complications						
Pneumothorax	5	1	6.7	4	9.8	0.720
Pleural effusion	2	1	6.7	1	2.4	0.450
Duration of admission (days)	56	9.2±4.9	N/A	16.6±7.8	N/A	N/A
mMRC grade	56	2 (1.3±0.6)	N/A	1 (1.0±0.9)	N/A	0.248
Desaturation on 6MWT	56	2.1±1.7	N/A	1.2±1.6	N/A	0.069
Duration of steroid intake (days)	56	9.27±3.81	N/A	16.60±10.6	N/A	0.012
Laboratory parameters						
Haemoglobin (mean±SD)	56	12.7±2.2	N/A	13.1±1.5	N/A	N/A
TLC						
<11,000 /uL	49	14	93.3	35	85.37	0.727
>11,000 /uL	7	1	6.7	6	14.6	N/A
Lymphocytes						
<1,000	43	12	80	31	75.6	0.942
>1,000	13	3	20	10	24.4	N/A
LDH (mean±SD)	56	484.0±103.8	N/A	786.0±115.6	N/A	N/A
CRP (mean±SD)	56	9.4±2.9	N/A	10.4±3.9	N/A	N/A
Ferritin (mean±SD)	56	400.8±86.4	N/A	739.7±107.9	N/A	N/A
D-dimer (mean±SD)	56	0.5±0.2	N/A	0.61±0.4	N/A	N/A

Table 1: continued.

CSS						
Prior CSS						
<15	19	9	60	10	24.4	0.049
≥15	37	6	40	31	75.6	N/A
CSS at 3 months						
<5	11	4.0	26.7	7.0	17.1	0.726
≥5	45	11.0	73.3	34.0	82.9	N/A
PFT at 3 months						
Mean FVC	52	2.1±0.7	N/A	1.9±0.8	N/A	N/A
Mean FVC % predicted	52	71.7±16.1	N/A	68.2±14.3	N/A	N/A
Mean DLCO	52	69±14.5	N/A	64±13.7	N/A	N/A

CAD: coronary artery disease; CRP: C-reactive protein ; CSS: CT severity score; DLCO: diffusion capacity of the lungs for carbon monoxide; FVC: forced vital capacity; HFNO: high flow nasal oxygen; HTN: hypertension; LDH: lactate dehydrogenase; mMRC: modified Medical Research Council; N/A: not applicable; NIV: non-invasive ventilation; NR: non-rebreathing; PFT: pulmonary function test; SD: standard deviation; TLC: total leukocyte count; 6MWT: 6-minute walk test.

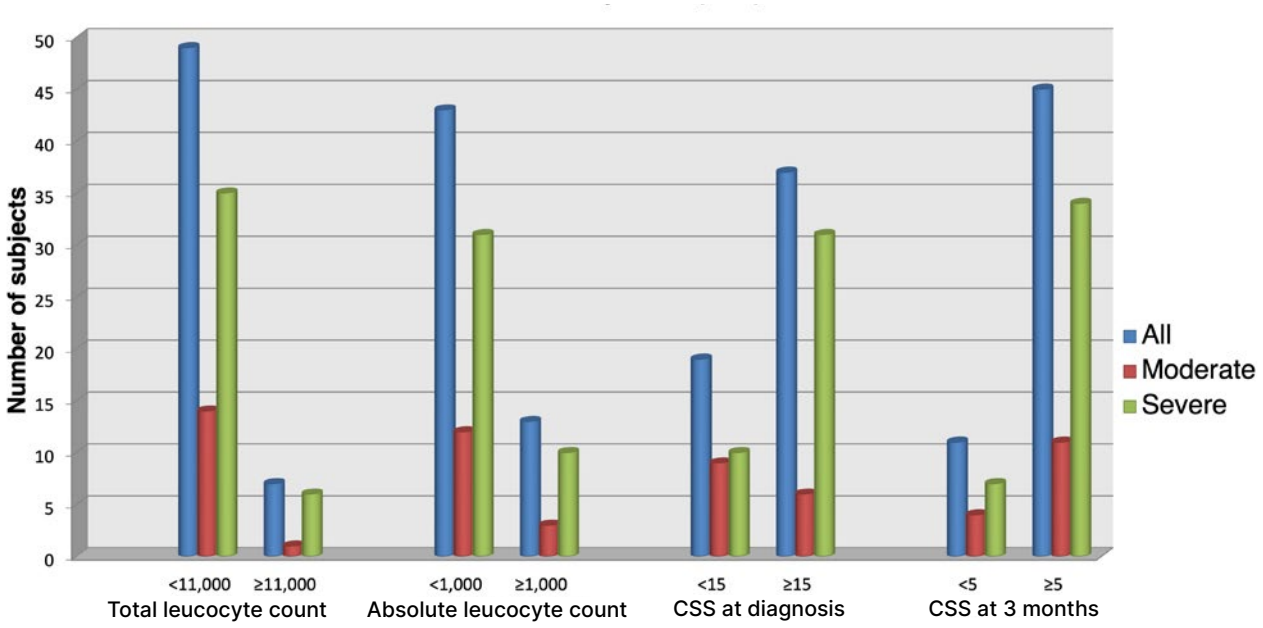
distribution in 69.6%. Lower lobes were most frequently involved in the severe group. The most common residual radiological abnormality was patchy ground glass opacity that was seen in 89% patients; the next most common finding was reticulation (86%) with a specific pattern of distribution in the subpleural region (Figure 2). Crazy paving, pneumothorax, and pleural effusion were the least common findings. Other features are tabulated in Table 3. Few interesting cases are depicted in Figure 3.

On bivariate analysis, the mean age was 45.67 years; this was significantly higher (p=0.043) in subjects with coexistent comorbidity than those without it (mean age: 38.05 years). The mean age was 41.87±13.83 and 38.92±11.95 years, respectively, for patients with and without subpleural bands (difference: 2.94 [-4.04; 9.92]; p=0.41). The authors could not find any significant association between dyspnoea and CSS (Karl Pearson's correlation coefficient 0.171; p=0.166). In multivariate analysis, no correlation could be found between age, BMI, duration of hospital stay, comorbidities, and persistent subpleural band at the end of 3 months.

DISCUSSION

In this cross-sectional study, the authors aimed to study the different radiological findings in post-COVID pulmonary fibrosis. Fifty-six subjects were recruited, excluding the paediatric population. The most common presenting complaints were fatigue, dry cough,

Figure 1: Graph depicting most of the subjects having normal leukocyte count, low lymphocytes, a CT-severity score of >5 at 3 months and >15 at the time of diagnosis.

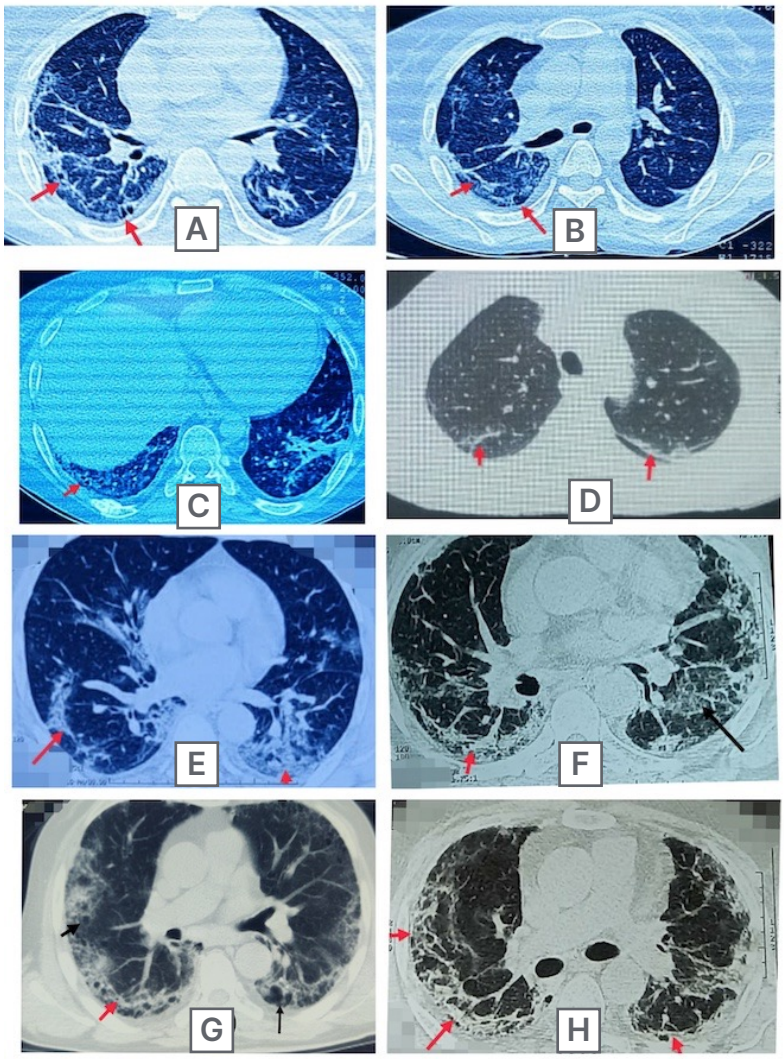


CSS: CT-severity score.

Table 2: Comparisons of persistent complains after 3 months in between patients with moderate and severe COVID-19.

Complaint	Total	Moderate		Severe		p
		n	%	n	%	
Cough	18	8	53.3	10	24.4	0.084
Dyspnoea	16	5	33.3	11	26.8	0.886
Fatigue	51	14	93.3	37	90.2	0.720
Myalgia	11	4	26.7	7	17.1	0.674
Headache	3	0	0.0	3	7.3	0.684
Diarrhoea	2	0	0.0	2	4.9	0.954

Figure 2: Three month follow up high resolution CT thorax images of multiple post-COVID-19 subjects demonstrating the curvilinear subpleural fibrotic band (red arrows) with development of cystic changes (black arrows).



and shortness of breath on exertion. The HRCT findings were mostly bilateral with no sex predilection. Ground glassing continued to persist in most cases, followed by reticular markings. The curvilinear fibrosis parallel to pleural surface with radiating thin fibrotic bands to the pleura, as have been defined in CO-RADS 5 staging, was a classic finding.[17]

While most studies included patients in either diseased or early recovery phase, the authors recruited patients after a period of at least 3 months to assess which abnormalities continue to persevere. The authors' results correspond to the aftermath of the first wave of COVID-19 in India. Shi H et al.[2] have reported similar prevalence of ground glassing and fibrotic changes. Nabahati et al.[7] reported septal thickening in 83.3% and parenchymal bands in 64.4% of their subjects at the end of 3 months, similarly to this study. Ali and Ghonimy[8] reported residual fibrosis in nearly one-third of their subjects; this was lower than in the authors' study. Ali and Ghonimy[8] had excluded subjects with chronic comorbidities, which might be responsible for a lower percentage of residual abnormalities, along with geographical variation in management facilities and protocols.

Initially, the management of COVID-19 revolved around antiviral and immune-modulatory drugs only, along with supportive care.[20-23] The

Table 3: Comparisons of persistent radiological findings after 3 months in between patients with moderate and severe COVID-19.

Characterstic	Total	Moderate		Severe		p
		n	%	n	%	
Lobe involved						
Upper	3	1	6.7	2	4.9	0.882
Lower	23	5	33.3	18	43.9	
Middle	0	0	0.0	0	0.0	
Lower+middle	8	2	13.3	6	14.6	
All	22	7	46.7	15	36.6	
Distribution						
Unilateral	6	0	0.0	0	0.0	0.972
Bilateral	50	0	0.0	0	0.0	
Peripheral	39	11	73.3	28	68.3	
Diffuse	17	4	26.7	13	31.7	
Findings						
Reticulations	48	12	80.0	36	87.8	0.758
Subpleural bands	30	10	66.7	20	48.8	0.376
GGO	50	13	86.7	37	90.2	0.702
Consolidation	27	6	40.0	21	51.2	0.658
Crazy paving	5	2	13.3	3	7.3	0.865
Cystic changes	24	7	46.7	17	41.5	0.965
Pneumothorax	5	1	6.7	4	9.8	0.720
Pleural effusion	2	1	6.7	1	2.4	0.450

GGO: ground glass opacity.

turnaround point was the RECOVERY trial[24] that reported mortality benefit with the use of corticosteroids; since then, these have been part of treatment protocols all across the world in moderate to severe disease.[25] The authors' subjects too had received glucocorticoids for an average duration of 14 days, and the duration of usage was significantly higher in the severe group. Despite that, a fairly high percentage had abnormal parenchyma on CT thorax. Even for the treatment of post-COVID-19 pulmonary fibrosis, corticosteroids have been utilised and have been associated with improved clinical and radiological outcome.[26]

Linear parenchymal bands have been long associated with asbestosis, representing septal fibrosis along with distortion of the architecture.[27,28] Less classically, linear fibrotic subpleural opacities have been seen in sarcoidosis, ankylosing spondylitis, systemic lupus erythematosus, etc.[29-31]

These disease conditions are all associated with chronic ongoing inflammation. Among acute conditions, in some survivors of acute respiratory distress syndrome, Middle East respiratory syndrome, and SARS, fibrotic sequelae have been reported in the lungs.[32-34] Presence of these bands early in the course of COVID-19 were also described as predictor of pulmonary fibrosis by Yu et al.[35] The pathophysiology responsible for such rapid development of fibrosis in the lungs is believed to be over-triggered host immune response, along with the accompanied cytokine storm of molecules such as tumour growth factor β.[36]

It is worth remarking that the authors included only those subjects who presented with persistent symptoms, while several others followed up their cohort of consecutive COVID-19 patients, irrespective of symptom status, and yet the persistence of HRCT findings is similar. This suggests even asymptomatic subjects may be having parenchymal abnormalities, as 'happy hypoxia' was a common phenomenon during the first wave of COVID-19.[37,38] However, this sample size is too small for a conclusive comment.

Remnant parenchymal changes were also seen in SARS and Middle East respiratory syndrome, and were seen to regress with time.[39] Nabahati et al.[7] reported diminution of fibrosis in nearly one-third of their subjects in the 6-month follow-up. More long-term follow-up studies with larger sample sizes will further help to assess the course of such fibrotic changes.

This study has the limitations of recruiting only moderate to severe cases, and not following the entire cohort. The authors could not include mild cases, as most patients attending their department with residual symptoms had suffered from moderate and severe disease. The small size of only 56 subjects is certainly a drawback in drawing significant conclusions.

CONCLUSION

Whenever the differential of fibrotic lung diseases will be considered, post-COVID-19 pulmonary fibrosis also needs to be discussed as a potential aetiology. The prominent patterns include ground glassing, septal thickening, and patchy consolidaton. Subpleural arcade of fibrosis was a peculiar feature.

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A Cross-Sectional Survey On the Psychological Effects of COVID-19 on Doctors and Non-doctors in Pakistan

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Abstract

Objective: The COVID-19 pandemic is still showing fluctuating trends and rapidly increasing case numbers, naturally creating a significant air of panic and hopelessness. This study aimed to investigate the mental health status of doctors in comparison to non-doctors, and its suggestive determinants amidst the COVID-19 pandemic.

Methods: An online cross-sectional survey was conducted during January–March 2021, using a convenience sampling technique. A sample size of 377 was calculated through RaoSoft (RaoSoft Inc., Seattle, Washington, USA) software. Inventories used are Zung Self-Assessment Anxiety Score (SAS) and Self-Assessment Depression Score (SDS), for the purpose of comparing different groups. The survey was distributed as an online Google form via social media. Results were evaluated by IBM Statistical Package for Social Sciences version 26.0 (Endicott, New York, USA).

Results: A total of 395 participants responded, out of which 10% showed extreme levels of anxiety. Among doctors, 14% had moderate levels of anxiety while 10% of unmarried respondents had extreme self-reported anxiety. Out of non-doctors, 15% showed signs of depression, among which a moderate level of depression was seen in 13% males, and severe depression was seen in 4% of married respondents. Higher depression scores were recorded in non-doctors, while there was no significant difference in anxiety levels of both groups.

Conclusion: A significant impact on mental health has been noted in various groups of respondents, with severe depression as well as severe anxiety. This should be alarming enough to instigate authorities to conduct mental health programs to counter this negative impact of COVID-19. Quick interventions and strategies can save countries from a grim future.

Key Points

1. The authors compared the mental health status of doctors, who have faced stigma as COVID-19 carriers, with non-doctors to determine who has been the most psychologically affected.

2. The COVID-19 pandemic is associated with major mention health issues, including psychological distress and depression, with 35% of people claiming to be affected.

3. Mental health issues are a global public health challenge, with the pandemic predominantly affecting the mental health of younger individuals, females, and those who are single.

INTRODUCTION

The first case of the novel COVID-19 in Pakistan was reported on 26th February 2020 in its trade-hub city, Karachi. Pakistan entered its first lockdown in March 2020. Educational institutes, markets, trade centres, and entertainment centres were closed. Though the lockdown lasted for just a few weeks, it was enough to trigger mass panic, fear, and depression. Since then, more than 900,000 people have been affected and 20,465 deaths have been reported to date by the Ministry of National Health Services Pakistan.[1] According to National Health Services, Regulations, and Coordination (NHSRC), doctors are the most affected segment of healthcare providers as 3,275 (61%) have so far contracted the viral infection, followed by 1,453 paramedics. A total of 27% healthcare providers have been infected with the virus.[2]

Globally, healthcare workers have been frequent victims of COVID-19 and face the stigma of being carriers. A study reported a high percentage of individuals who believed that social interactions with healthcare workers during pandemics should be avoided.[3] In earlier reports, the incidence of COVID-19 was recorded to be about 29% in healthcare individuals.[4] Their moral obligation towards duty and social isolation leaves them in a dilemma, which is yet again a challenge for mental health.

It is very well known that the initial phase of virus spread was associated with high levels of unfamiliarity and uncontrollability, which made it difficult for healthcare workers to adopt a safe and effective action plan.[5] In addition, fake news and myths regarding this virus were widespread on social media, making it even more difficult for doctors and authorities to function properly. There are sour memories of past pandemics, where high mortality rates and infection in healthcare providers were recorded. A study in Canada recorded that around 37% of total cases of severe acute respiratory syndrome were in healthcare providers.[6] Keeping in view all of these circumstances, anxiety and depression among doctors is not unexpected. Studies are predicting a high impact on mental health as a result of this pandemic.[4] The unpredictable nature of the course of the disease, unexpected post-infection consequences, new emerging mutated forms of the virus, and rumours of fourth and fifth hybrid waves in Pakistan could nevertheless increase psychological strain on healthcare workers.

Moreover, there is a lack of availability of essential resources such as medications, isolation wards, personal protective equipment,[7] oxygen cylinders, and artificial ventilation systems across Pakistan, which has compromised the standard of healthcare provided to the public.[8] Acknowledging the need and still not being able to provide optimum services due to limitations has challenged communities, and added to the psychological strain on frontline workers, including doctors, nurses, and paramedics. This has left many healthcare workers in a dilemma, questioning their moral stance.[8]

Despite providing mass vaccination, the healthcare burden has undoubtedly been one of the major concerns of every country. The COVID-19 crisis has targeted the economical sustainability of many countries, especially developing countries like Pakistan and Bangladesh. The Asian Development Bank

predicted the Pakistani economy would decrease by 3.3% in 2019 to 2.6% by 2020, and inflation was likely to persist around 11.5% for 2020.[9] With the addition of a health emergency in the country, it is not difficult to imagine the economic blow that Pakistan is facing. Economic recession, unemployment, and fear of food unavailability has inevitably flared up the rising trends of stress, anxiety,[10] and suicide rates in society.[11,12]

Recent studies have reported 20–44% of adults with clinical levels of anxiety and depression.[13] It is well established that depression is a leading cause of 90% of global suicide cases.[14] The first suicide case due to the COVID-19 pandemic was reported from Bangladesh.[15] In Japan, around a 70% rise in female suicide cases was observed after COVID-19.[16] Sixteen suicide cases have been reported in Pakistan during COVID-19. The reason behind most of the suicide cases was the fear of being infected by the virus.[17] The rapidly increasing counts of COVID-19 victims that individuals see every day on social networks have naturally created a significant air of panic and hopelessness. Studies conducted during the H1N1 and severe acute respiratory syndrome pandemics show that pandemics and lockdowns have always put a strain on mental health issues. Social isolation has been marked as one of the major causes of depression in such scenarios.[4]

The good mental health of an individual is valuable and allows them to provide optimum services to society. As this pandemic is projected to last for a long time, more research is needed to evaluate mental health status in Pakistan. This study aimed to investigate the mental health status of doctors in comparison to non-doctors, its suggestive determinants amidst the COVID-19 pandemic, and to determine which category among the public is most psychologically affected by this outbreak. These results can regulate appropriate intervention and modifications, and aid medical workers and the public alike.

METHODOLOGY

An online cross-sectional survey was conducted from January–March 2021 among doctors and non-doctors of four major cities in Pakistan: Karachi, Lahore, Rawalpindi/Islamabad, and Peshawar. The participants were recruited online using the convenience sampling technique. In the study, doctors are defined as all those who have a Bachelor's degree in medicine and surgery or medical doctors, while non-doctors are individuals from all other professions with a minimum qualification of 10 years of schooling. Several steps were taken to ensure data quality. Firstly, participants were asked personal details in demographics regarding profession and level of education. Those who provided nonsensical responses were removed from the analysis. All who were below 20 years of age or lacked minimum qualifications were not included in the study. Based on the target population, the margin of error was 5.0%, and confidence interval 95%. The sample size calculated through RaoSoft software (RaoSoft Inc., Seattle, Washington, USA) was 377. A total of 406 participants began the questionnaire. Out of these, three were rejected because they were less than 20 years of age and five were excluded because of incomplete responses. Three questionnaires with nonsensical responses were also excluded from the analysis. After rejecting 11 questionnaires, 395 questionnaires were used for result analysis.

Participants were invited to fill in an online questionnaire designed using Google (Mountain View, California, USA) forms via WhatsApp (Meta Platforms, Cambridge, Massachusetts, USA), Facebook (Meta Platforms), and email. The nature and purpose of the survey were explained in the message preceding the link to the survey. All participants were encouraged to forward the link to acquaintances, thereby approaching a larger number of respondents.

For psychological distress evaluation, the internationally recognized Zung Self-Rating Anxiety Scale (SAS)[18] and Zung Self-Rating Depression Scale (SDS)[19] were used. Ethical permission was not required. A set of 30 questions was asked in total, where each question carried a different score depending on the response.[20]

In the anxiety assessment, 10 questions were asked and the participant had to choose one response from: 'Never', 'Sometimes', 'Half the time', 'Frequently', and 'Always'. Each response had a score from 0 to 4, which was totalled at the end of the survey. The total score was then calculated out of 40 points. The participants whose total score lay between 0–8 points had

minimal anxiety; 8–16 points had mild anxiety; 17–24 points had moderate anxiety; and 25 points and above showed high and extreme anxiety.

For the depression assessment, a total of 20 questions were asked, and the participant had to choose from: 'Never', 'Sometimes', 'Good part of the time', and 'Mostly'. These responses were scored from 1 to 4 and the total score was calculated out of 80 points. Participants with less than 50 points had no depression and were marked 'normal'. Those with 50–59 points had mild depression, while those with 60–69 points had moderate depression. Severe depression was diagnosed for all those with 70 points or more. Responses were downloaded from the online survey and processed as a spreadsheet.

Frequency tables and proportions were computed to summarise the data. Data were stratified into different groups based on demographic characteristics and the anxiety and depression levels of the participants to give an in-depth insight into the descriptive statistics of the study. Since the data did not conform to a normal distribution, the Mann–Whitney U test for Independent Samples was used to compare SAS and SDS scores between the two different groups. One-way Analysis of Variance test with *post hoc* Bonferroni correction was applied when the variable consisted of more than two groups. All analysis was performed using IBM Statistical Package for Social Sciences version 26.0 (Endicott, New York, USA). A $p<0.05$ was taken as significant.

RESULTS

Participants' demographic profile has been summarised in Table 1. In total, 395 participants completed the survey. Among them, 260 (65.8%) were female and 214 (54.1%) were married. There were 212 (53.6%) participants belonging to the age group of 20–30 years. Most of the respondents held a Master's degree or above (179; 45.3%). Respondents belonged to different provinces of Pakistan, with 204 (51.6%) residing in the twin cities, Islamabad and Rawalpindi. Over half of participants (51.6%; 306) reported that they had not suffered from COVID-19, while 6 (1.5%) were suffering at the time of filling the survey form and 83 (21.0%) of participants had recovered from infection.

Among the participants, 148 (37%) did not suffer from anxiety while 38 (10%) reported having high or extreme levels of anxiety scores. Twenty-three (14%) doctors suffered from a moderate level of anxiety, which was a lower percentage compared to non-doctors (52: 22%). The proportion of moderate and extreme anxiety in females was 22% and 13%, respectively. Thirty-nine (22%) unmarried respondents had moderate anxiety, while 19 (10%) had extreme self-reported anxiety. Out of all the participants, 115 (38%) stayed at minimal anxiety levels after suffering from COVID-19 (Table 2).

A score indicating severe depression was observed in one respondent. Ninety per cent (n=145) of doctors and 85% (n=197) of non-doctors were found to have normal scores on SDS. A moderate level of depression was seen in 17 (13%) males. Five per cent (n=10) of married respondents had moderate depression, while 4% (n=8) had severe depression. Amongst the participants who had been affected by COVID-19, three were found to be moderately depressed compared with 15 (5%) moderately depressed individuals from the group who had not been affected (Table 2).

Table 3 reports the median SAS and SDS scores in different groups. The median SAS score was 11 for both doctors and non-doctors (range: 0–34). However, the median SDS score in doctors was significantly lower than in non-doctors ($p=0.01$). A statistically significant difference in SAS and SDS scores was observed in respondents from different age groups ($p<0.001$). It was found that the median SAS score of the 20–30 year age group (13) was significantly higher than the SAS score of respondents 50 years and above (median: 7.5). A similar trend was seen in the SDS scores of the two age groups ($p=0.005$). Females had significantly higher levels of anxiety and depression than males ($p<0.001$). Both scores differed in participants of different marital statuses ($p<0.001$). Unmarried participants had a median SAS score of 13 and a median SDS score of 37, while the scores for married people were 9 and 31, respectively. No significant difference was observed in the anxiety and depression scores of respondents from different cities, or with different educational backgrounds. Being infected with COVID-19 did not cause a significant difference in the SAS or SDS scores of this group compared to the group not affected by the virus.

Table 1: Demographic profile of survey participants.

Parameters	n	%
Total number of subjects = N	395	
Age groups		
20–30 years	212	53.67%
31–40 years	90	22.70%
41–50 years	41	10.30%
51 and above	52	13.10%
Gender		
Male	135	34.10%
Female	260	65.80%
Education		
Intermediate/A level	57	14.40%
Bachelor's	159	40.20%
Master's and above	179	45.30%
Profession		
Doctors	161	40.70%
Non-doctors	234	59.20%
Marital status		
Single	181	45.80%
Married	214	54.18%
City		
Rawalpindi/Islamabad	204	51.65%
Peshawar	102	25.82%
Lahore	32	8.10%
Karachi	57	14.43%
COVID-19 exposure		
Not affected	306	77.47%
Suffering	6	1.52%
Recovered	83	21.01%

Table 2: Anxiety and depression levels in different groups.

	Anxiety level				Depression level			
	Minimal	Mild	Moderate	High/extreme	Normal	Mild	Moderate	Severe
Profession								
Doctors	59 (37%)	61 (38%)	23 (14%)	18 (11%)	145 (90%)	4 (2%)	12 (7%)	0
Non-doctors	91 (39%)	72 (31%)	52 (22%)	19 (8%)	197 (84%)	30 (13%)	6 (3%)	1 (0.4%)
Age group								
20–30 years	70 (33%)	73 (34%)	45 (21%)	24 (11%)	178 (84%)	23 (11%)	10 (5%)	1 (0.4%)
31–40 years	33 (37%)	30 (33%)	19 (21%)	8 (9%)	76 (84%)	8 (9%)	6 (0.7%)	0
41–50 years	17 (41%)	15 (36%)	7 (17%)	2 (5%)	39 (95%)	2 (5%)	0	0
51 years and above	30 (58%)	15 (29%)	4 (8%)	4 (8%)	49 (94%)	1 (2%)	2 (4%)	0
Gender								
Male	69 (51%)	44 (33%)	18 (13%)	4 (3%)	122 (90%)	12 (9%)	17 (13%)	0
Female	81 (31%)	89 (34%)	57 (22%)	33 (13%)	220 (85%)	22 (8%)	17 (7%)	1 (0.3%)
Marital Status								
Single	57 (31%)	66 (36%)	39 (22%)	19 (10%)	146 (81%)	26 (14%)	8 (4%)	1 (0.5%)
Married	93 (43%)	67 (31%)	36 (17%)	18 (8%)	196 (92%)	8 (4%)	10 (5%)	0
Education								
A level	18 (32%)	20 (35%)	13 (23%)	6 (11%)	43 (75%)	7 (12%)	6 (11%)	1 (2%)
Graduation	56 (35%)	67 (42%)	24 (15%)	12 (8%)	141 (89%)	15 (9%)	3 (2%)	0
Post-graduation	76 42%)	46 (26%)	38 (21.2%)	19 (11%)	158 (88%)	12 (7%)	3 (2%)	0
COVID-19 exposure								
Not affected	115 (38%)	101 (33%)	62 (20%)	30 (10%)	261 (85%)	29 (9%)	15 (5%)	1 (0.3%)
Suffering	0	4 (67%)	1 (17%)	1 (17%)	5 (83%)	0	1 (17%)	0
Recovered	35 (42%)	28 (34%)	11 (13%)	7 (8%)	76 (92%)	5 (6%)	2 (2%)	0

Table 3: Zung Self-Assessment Anxiety Score and Self-Assessment Depression Score.

Parameters	SAS median (range)	p*	SDS median (range)	p
Age groups		<0.001		<0.001
20–30 years (n=212)	13.0 (0–34)		36.0 (20–74)	
31–40 years (n=90)	11.5 (0–31)		35.5 (20–68)	
41–50 years (n=41)	11.0 (0–31)		31.0 (20–54)	
51 and above (n=52)	7.5 (0–34)		28.0 (20–66)	
Gender		<0.001		<0.001
Male (n=135)	8.0 (0–31)		29.0 (20–60)	
Female (n=260)	13.0 (0–34)		36.5 (20–74)	
Education				
Intermediate/A level (n=57)	13 (0–34)		37 (20–74)	
Bachelor's (n=159)	11 (0–33)		36 (20–65)	
Master's and above (n=179)	10 (0–34)		32 (20–68)	
Profession				0.010
Doctors (n=161)	11 (0–34)		31 (20–68)	
Non-doctors (n=234)	11 (0–34)		35 (20–74)	
Marital status		<0.001		<0.001
Single (n=181)	13 (0–34)		37 (20–74)	
Married (n=214)	9 (0–34)		31 (20–68)	
City				
Rawalpindi/Islamabad (n=204)	11 (0–34)		34 (20–74)	
Peshawar (n=102)	11 (0–32)		31 (20–68)	
Lahore (n=32)	12.5 (0–33)		37.5 (21–65)	
Karachi (n=57)	12 (1–34)		34 (20–66)	
COVID-19 exposure				
Not affected (n=306)	11 (0–34)		34 (20–74)	
Suffering (n=6)	13.5 (9–34)		38 (34–66)	
Recovered (n=83)	11 (2–31)		32 (20–65)	

*Only significant values mentioned in the table. Confidence interval: 95%.

SAS: Zung Self-Assessment Anxiety Score; SDS: Self-Assessment Depression Score.

DISCUSSION

After inflicting critical physical impairment globally, the COVID-19 pandemic is now being associated with causing major emotional and mental health issues, leading to an increase in the prevalence of psychological distress, frustration, anxiety, depression,[21-23] sleep disturbances, and even suicide in certain cases.[24] Society's mental health is being adversely affected by these factors. Approximately 35% of people were reported to be psychologically

affected during the pandemic in a comprehensive study from China.[25] An extensive study from Turkey reported relatively high levels of anxiety and depression (45.1% and 23.6%, respectively) in the general population during the pandemic.[26]

The aforementioned emotional and mental health issues have become overwhelming public health challenges all over the world. Medical healthcare workers, including paramedic staff, nurses, and doctors, who are directly exposed to patients with COVID-19 are more susceptible to acquiring infection and developing psychological distress compared with the rest of the general population.[27,28]

The authors' findings showed that among all participants, 10–18% reported having moderate to extreme levels of anxiety. Similarly, 5–8% of respondents reported having mild to moderate depression scores. They observed that there was no significant difference between anxiety levels of doctors in comparison to non-doctors. On the contrary, depression levels were significantly higher in non-doctors compared with doctors. The results were in accordance with multiple studies that have identified signs of mental distress, anxiety, and depression among the general population in wake of the COVID-19 pandemic.[29] Some studies suggest that the fear of contracting the infection and uncertainties regarding the severity and outcome of the disease have produced extreme consequences related to the psychological wellbeing of the general population.[30] Pakistan appears to be a victim of such fears and uncertainties, and the results of this study support this idea. Misinformation, false data, and failure to understand and follow preventative guidelines have contributed to increasing levels of stress and anxiety among the general population.[31]

The authors' findings revealed that there was a significant difference in anxiety and depression levels between different age groups ($p<0.001$). The anxiety scores of the 20–30-year-old group were significantly higher than that of the 50-year-old and above group. Similarly, depression levels were also found to be higher in younger age groups when compared with older age groups ($p=0.005$).

The authors' findings are consistent with the findings of Ahmed et al.[32] and Gao et al.,[33] who reported that respondents belonging to the younger age group (<40 years) exhibited more anxiety and depressive symptoms compared with older age groups. The main contributory factor is exposure to social media as it is the main source of information for younger people.[33] Moreover, university and college students were also found to be more at risk of developing depression and anxiety when compared with other occupations, due to encountering situations like postponement of examinations, and unfamiliarity with online teaching methods.[34] Disturbance in academic sessions has not only affected student performance and grades but has also caused struggles in trying to adapt to new teaching strategies. This rapid change in the learning environment is also adding to anxiety and depression.[34] A cross-sectional study from Ireland reported anxiety levels of around 28% among the general population; the most vulnerable group liable to develop anxiety and depression was the younger age group.[35]

This study also found that females displayed significantly higher levels of anxiety and depression than males ($p<0.001$). These findings were consistent with that of Lei et al.[36] and Mazza et al.,[37] who reported a similar trend concerning the difference in anxiety and depression levels between males and females. The main reason is females' susceptibility to experiencing more psychological distress and post-traumatic signs and symptoms.[36,37] In contrast, a comprehensive study from the UK reported that males were associated with less probability of anxiety and depression despite experiencing a high mortality rate during the pandemic.[38]

These results displayed a significant difference in depression and anxiety scores between marital statuses ($p<0.001$). Unmarried participants exhibited significantly higher levels of anxiety and depression compared with married respondents. Emerging evidence has suggested that being single, divorced, or widowed can be one of the predictive factors for the development of anxiety and depressive symptoms, owing to a greater incidence of experiencing loneliness and lack of psychological support.[36] On the contrary, one study has reported high anxiety levels in married participants in compared with single respondents.[33]

The authors recognise a few limitations of the study. The study was carried out when the pandemic was at its peak. Lockdown made it impossible to conduct a face-to-face survey. Thus, further research is recommended post-lockdown to remove any biases concerning subjectivity and reliability. Secondly, no comparison was made to the incidence of anxiety and depression in the participants before COVID-19 in this study. The influence of pre-existing anxiety and depression on the outcome of the study should also be examined in post-COVID-19 analysis.

CONCLUSION

The current study concluded that doctors and non-doctors displayed signs of anxiety correspondingly. Consequently, signs of depression were prevalent among non-doctors compared with doctors during the pandemic. The groups most affected by anxiety and depression among the public included females, single participants, and adults from younger age groups.

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Epstein–Barr Virus-Induced Acute Hepatitis, Pancreatitis, and Pneumonitis in a Young Immunocompetent Adult: A Case Report

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Abstract

Epstein–Barr virus (EBV) is a common herpes virus (human herpesvirus type 4) that usually manifests as infectious mononucleosis or persists asymptomatically for life. EBV can also be associated with different types of malignancy such as T cell lymphoma, B cell lymphoma, Hodgkin lymphoma, and oropharyngeal squamous cell and nasopharyngeal carcinoma. Pneumonia is a very rare complication of EBV infection, but it has been reported to occur even in the absence of mononucleosis.

This article highlights the case of 35-year-old female who developed acute pancreatitis and acute respiratory failure related to EBV infection. The patient progressively recovered on antiviral therapy and steroids.

Key Points

1. Epstein–Barr virus is associated with several malignancies including T-cell lymphoma, B-cell lymphoma, Hodgkin lymphoma, oropharyngeal squamous and nasopharyngeal carcinoma, and pneumonia.

2. Infectious mononucleosis is a clinical syndrome caused by Epstein–Barr virus consisting of fever, tonsillar pharyngitis, and lymphadenopathy.

3. Immunocompetent patients with Epstein-Barr virus exhibiting cholestatic hepatitis, pancreatitis, and pneumonia can be successfully treated with IV acyclovir and steroids.

INTRODUCTION

Infectious mononucleosis (IM), caused by Epstein–Barr Virus (EBV), has been recognised as a clinical syndrome consisting of a triad of fever, tonsillar pharyngitis, and lymphadenopathy.[1] Patients with IM can also present different skin manifestations or atypical exanthems, most commonly the pruritic maculopapular rash in patients receiving β-lactam antibiotics.[2] Symptomatic infection with EBV is more likely to occur in adolescent and adult years, while primary EBV infections in children are often asymptomatic.[3] Some data suggest that older patients are more susceptible to develop a more severe clinical condition.[4] In addition, elderly patients may also develop EBV-positive diffuse large B cell non-Hodgkin lymphoma,[5] which has a poor prognosis and necessitates early diagnosis and treatment.[6] EBV is also found to be associated not only with nasopharyngeal carcinoma, but also with oral and oropharyngeal squamous cell carcinomas.[7] EBV can affect virtually any organ system and has been associated with different disease manifestations such as hepatitis or cholestasis, jaundice, hepatomegaly, pneumonia, pleural effusions, and pancreatitis.[8-10] Herein, the authors present a case of an immunocompetent adult who developed respiratory failure due to EBV pneumonitis along with cholestatic hepatitis and pancreatitis, without the suggestive clinical manifestations of IM.

CASE REPORT

A 35-year-old female with no significant past medical history presented to the emergency department with a complaint of epigastric pain which was non-radiating, had increased in intensity over time, and was associated with a fever of three days duration. The patient denied prior abdominal surgeries or trauma. They also denied any travel history, alcohol intake, or recreational drug use. The patient noted no inherited medical conditions in their family.

On physical examination, the patient was tachycardic (105 beats per min) and febrile (temperature of 38.5 °C), and their pulse oximeter saturation was measured at 98%. Diffuse jaundice was noted. There was no palpable cervical or supraclavicular lymphadenopathy, and no tonsillar exudates. On abdominal palpation, they had severe right upper quadrant and epigastric tenderness, but no hepatomegaly or splenomegaly.

Laboratory investigations revealed the following results: white blood cell count: 10,440 /L; neutrophils: 70%; haemoglobin: 13.8 g/dL; haematocrit: 40%; mean corpuscular volume: 94 fL; platelet count: 300,000 /mm^3; creatinine: 0.7 mg/dL; aspartate transmaninase: 448 IU/L; alanine aminotransferase: 110 IU/L; alkaline phosphatase: 150 IU/L; γ-glutamyltransferase: 1,670 IU/L; lipase: 408 IU/L; amylase: 129 U/L; C-reactive protein: 221 mg/L; triglycerides: 150 mg/dL; international normalised ratio: 1.1; albumin: 3.5 g/dL; and total bilirubin of 15.9 mg/dL, with direct bilirubin of 12 mg/dL.

Abdominal ultrasonography showed no evidence of acute cholecystitis, normal calibre of the common bile duct, and no gallstones. A CT scan of the abdomen and pelvis showed diffuse increase in the volume of the pancreas with no sign of necrosis, along with peripancreatic

inflammatory changes. No definite abscess or collection was seen on the CT scan. An abdominal MRI with gadolinium and magnetic resonance cholangiopancreatography revealed non-complicated pancreatitis, with absence of intra- or extra-biliary ductal dilatation or common bile duct stones.

Results of serologic tests for hepatitis A, B, and C were as follows: hepatitis B surface antigen (Ag) test: 0.16 (negative); hepatitis B core antibody (Ab) IgM: non-reactive; hepatitis B Ab total: non-reactive; hepatitis C virus Ab: 0.13 (negative); and hepatitis A virus IgM Ab: 0.12 (negative). HIV (1+2) Ag/Ab was negative. Abs for cytomegalovirus (IgM: 0.7); mycoplasma pneumonia Abs (IgM <7.7); antinuclear Abs (<1:100); anti-mitochondrial Abs (<1:100); and anti-phospholipids Abs (anti-cardiolipin Abs <2, anti-β-2 glycoprotein Abs: 9.4) were all negative. Work-up for haemochromatosis and Wilson's disease were also negative. EBV viral load in serum was 625 copies /mL; EBV nuclear Ag IgG was negative; IgM for EBV viral capsid Ag (10.24) and IgG for EBV viral capsid Ag (44.08) were positive, confirming acute primary EBV infection.

The patient was diagnosed with acute pancreatitis associated with acute cholestatic hepatitis, induced by a primary EBV infection. Bowel rest and intravenous (IV) hydration were instituted. Over the next two days, high-grade fever persisted, and the patient developed acute respiratory failure with need for mechanical ventilation (fraction of inspired oxygen: 100%; positive end-expiratory pressures: 14). Chest X-ray and CT scans (Figures 1–3) showed bilateral pleural effusion with diffuse ground glass appearance and left consolidation. The echocardiography was unremarkable.

As a bacterial co-infection could not be ruled out based on the chest CT scan findings, linezolid and meropenem were administered, in addition to antiviral drugs (oseltamivir and acyclovir), and methylprednisolone (at a dose of 40 mg IV every 12 hours at 1 mg/kg). PCR of EBV in deep tracheal aspirates was positive with a high viral load of 24,860,000 copies/mL, confirming the diagnosis of EBV pneumonitis with type one respiratory failure, in addition to acute pancreatitis and cholestatic hepatitis. The patient received acyclovir for 2 weeks and IV steroids for 1 week, which was stopped following the improvement of her condition. Jaundice spontaneously resolved over the next few days. Liver function tests and liver enzymes progressively returned to a normal level, and serum lipase levels steadily decreased. The patient was extubated on Day 10 and discharged on Day 14. EBV serum viral load and EBV serology were ordered, but unfortunately could not be carried out due to financial reasons. The patient has remained well, with follow-up visits occurring over a period of 7 months.

DISCUSSION

This article presents the case of a young female whose main complaints were abdominal pain, jaundice, and fever, with no clear symptoms of infectious mononucleosis such as pharyngitis and lymphadenopathy. Based on the laboratory and imaging findings, the first diagnosis was acute primary EBV infection with acute pancreatitis and cholestatic hepatitis. The clinical deterioration of the patient into respiratory failure warranted further investigations, including EBV PCR from endotracheal aspirate. The extensive work-up led to an additional diagnosis of EBV pneumonitis, although the first chest X-ray on admission was unremarkable. After confirmation of the diagnosis, the treatment of EBV pneumonia consisted mainly of IV acyclovir and steroids. The patient had remarkable clinical improvement, along with radiological resolution of pneumonitis, alongside recovery from pancreatitis and hepatitis with conservative measures.

The majority of individuals remain asymptomatic during EBV infection, or may develop IM, which is relatively common and self-limited. Although it is infrequent, EBV infection can lead to severe and serious complications.[11] To the best of the authors' knowledge, five cases of EBV infection associated with acute pancreatitis and hepatitis have been reported in the literature.[12,13] Unexplained abdominal pain in patients with EBV infection should raise suspicion of acute pancreatitis.[14] This patient had fulfilled the three diagnostic criteria of acute pancreatitis based on the American College of Gastroenterology (ACG) guidelines: abdominal pain, elevated serum lipase and/or amylase level (greater than three times the upper normal limit), and radiological evidence of acute pancreatitis.[15] In addition, the presence of fever and disturbed liver function tests, in the

Figure 1: Chest X-ray showing bilateral infiltrates.

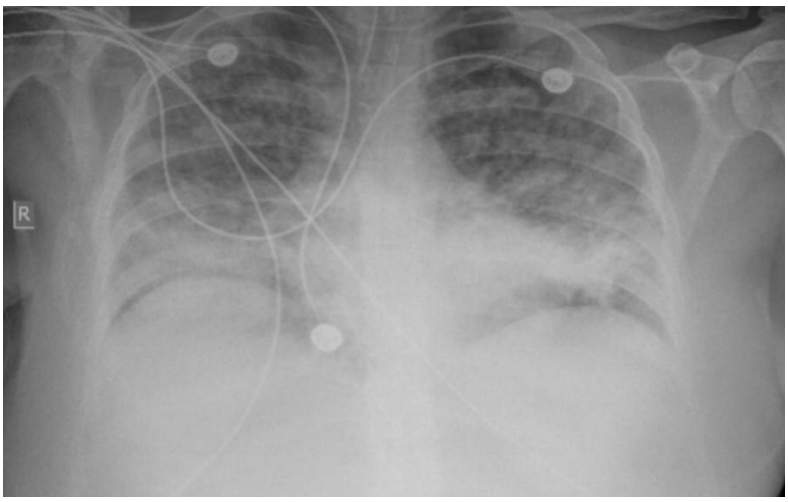


Figure 2: CT chest showing bilateral ground glass appearance.

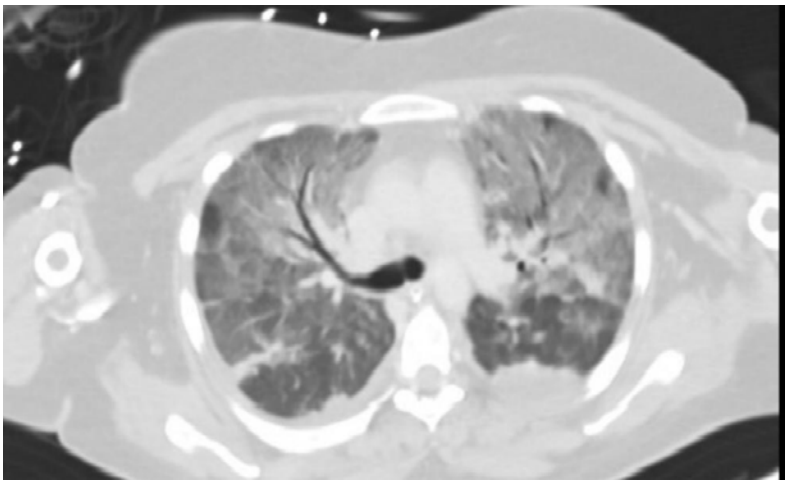
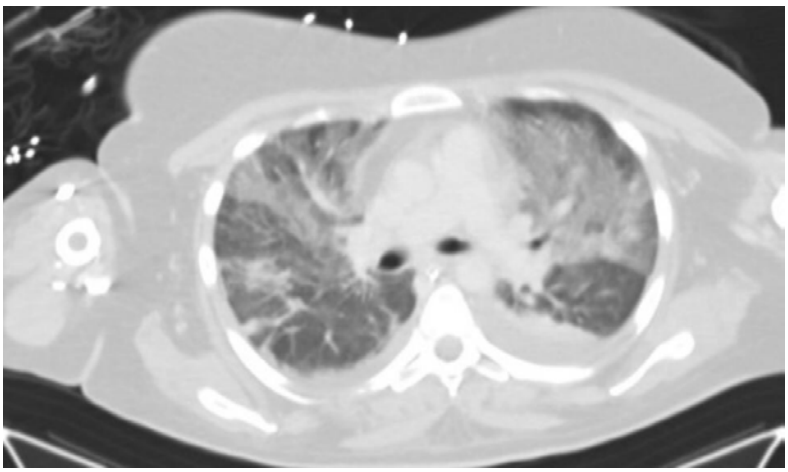


Figure 3: CT chest showing left consolidation.



absence of cholelithiasis on imaging, can occur in the setting of EBV-induced cholestatic hepatitis.[10] Hepatitis and pancreatitis associated with EBV infection have been managed, as mentioned in the literature, mainly with symptomatic and supportive treatment, which was associated with good results overall.[16]

Apart from gastrointestinal involvement, lung involvement is infrequently associated with EBV infection; it is more commonly encountered in immunosuppressed patients, but can be reported in healthy subjects as well.[17,18] Pulmonary manifestations in EBV can involve lymphadenopathy (mainly hilar and mediastinal lymph nodes), pleural effusions, and interstitial pneumonitis.[19] The mechanism of pulmonary involvement in EBV infection remains controversial; it is unclear whether it results from direct viral invasion and replication in lung tissue, immunological reaction to the infection, or a combination of both.[20] Although no specific antiviral drug has precedence over others, favourable outcomes were reported with the use of IV acyclovir in patients with EBV pneumonitis.[21,22] Timely diagnosis is pivotal in treating severe EBV infections. In fact, early clinical and radiological recoveries were achieved in patients with severe EBV pulmonary infection by initiating antiviral therapy early in the course of the disease.[23] As for the cases of delayed diagnosis, corticosteroids, Ig, and IV antivirals were used together and yielded successful results.[23] Recovery from EBV pneumonitis by receiving steroid medication alone without antiviral agents was also reported.[19]

CONCLUSION

Lung involvement, hepatitis, and cholestasis following EBV infection are considered rare manifestations of the infection, with a high risk of mortality. This article presented an uncommon case of EBV-induced acute cholestatic hepatitis, pancreatitis, and pneumonitis in an immunocompetent patient. The clinical presentation was severe, and the patient needed intubation. They were successfully treated with IV acyclovir and steroids, which resulted in a satisfactory outcome.

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