EISSN 2979-9139

Official Journal of
TURKISH
THORACIC SOCIETY

Thoracic
Research & Practice

Formerly Turkish Thoracic Journal



Volume 24 · Issue 6 · November 2023
thoracrespract.org

Thoracic Research & Practice

Official Journal of the Turkish Thoracic Society

EDITORS in CHIEF

Oğuz KILINÇ
Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Turkey

İpek Kıvılcım OĞUZÜLGEN
Department of Pulmonary Diseases, Gazi University School of Medicine, Ankara, Turkey

EDITORS

Aylin ÖZGEN ALPAYDIN
Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Turkey

Ege GÜLEÇ BALBAY
Department of Chest Disease, Düzce University School of Medicine, Düzce, Turkey

İpek ÇAYLI CANDEMİR
Ataturk Chest Diseases and Surgery Education and Research Hospital, Ankara, Turkey

Ufuk ÇAĞIRICI
Department of Chest Surgery, Ege University School of Medicine, İzmir, Turkey

Necati ÇITAK
Department of Thoracic Surgery, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospita, İstanbul, Turkey

Aslı GÖREK DİLEKTAŞLI
Department of Chest Diseases, Uludağ University School of Medicine, Bursa, Turkey

Zuhal KARAKURT
Respiratory Intensive Care Unit, Süreyyapaşa Chest Diseases and Surgery Training and Research Hospital, İstanbul, Turkey

Leyla PUR ÖZYİĞİT
Department of Allergy and Immunology, University Hospitals of Leicester, Leicester, United Kingdom

Özge YILMAZ
Department of Pediatrics, Celal Bayar University School of Medicine, Manisa, Turkey

BIOSTATISTICAL CONSULTANT

Ahmet Uğur DEMİR
Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey

Seval KUL
Department of Biostatistics and Medical Informatics, Gaziantep University School of Medicine, Gaziantep, Turkey

PUBLICATION COORDINATOR

Begüm ERGAN
Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Turkey

Founder
İbrahim KARA

General Manager
Ali ŞAHİN

Finance Coordinator
Elif YILDIZ ÇELİK

Journal Managers
Arzu ARI
Deniz KAYA
Irmak BERBEROĞLU

Publications Coordinators
Gökhan ÇIMEN
Alara ERGİN
İrem ÖZMEN
Derya AZER
Beril TEKAY
Nuri ÇALIŞIR
Nisanur ATICI

Project Coordinators
Doğan ORUÇ
Sinem Fehime KOZ

Project Assistant
Batuhan KARA

Publishing Service: AVES
Address: Büyükdere Cad. No: 105/9 34394 Mecidiyeköy, Şişli-İstanbul
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Editors in Chief:
Oğuz KILINÇ
İpek Kıvılcım OĞUZÜ.LGEN
Address: Turan Güneş Bulvarı, Koyunlu Sitesi No: 175/19 Oran, Ankara, TURKEY
Phone: +90 (312) 490 40 50
Fax: +90 (312) 490 41 42
E-mail: editorial.office@turkthoracj.org

Thoracic Research & Practice

Official Journal of the Turkish Thoracic Society

EDITORIAL BOARD

Ian M. Adcock
Cell and Molecular Biology Airways Disease Section, National Heart and Lung Institute, Imperial College London, United Kingdom

Piergiuseppe Agostoni
Department of Clinical Sciences and Community Health, Cardiovascular Section, Università di Milano, Milano, Italy

M. Selim Arcasoy
Pulmonary, Allergy, and Critical Care Division, Department of Medicine, Columbia University New York, USA

Philippe Astoul
Thoracic Oncology - Pleural Diseases - Interventional Pulmonology, Hôpital Nord - Chemin des Bourrely, Marseille, France

Ülkü Bayındır
Retired Faculty Member, Ege University School of Medicine, İzmir, Turkey

Dominique MA Bullens
Department of Immunology and Microbiology, KU Leuven Laboratory of Pediatric Immunology Division of Pediatrics, Leuven, Belgium

Richard Casaburi
Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA

Turgay Çelikel
Department of Chest Diseases, Marmara University School of Medicine, İstanbul, Turkey

Tansu Ulukavak Çiftçi
Department of Chest Diseases, Gazi University School of Medicine, Ankara, Turkey

Lütfi Çöplü
Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey

Çağlar Çuhadaroğlu
Acıbadem Maslak Hospital, İstanbul, Turkey

Antonio M. Esquinas
International Fellow AARC, Fellow NIV, Intensive Care Unit, Hospital Morales Meseguer, Murcia, Spain

Andrew J. Ghio
US Environmental Protection Agency Chapel Hill, North Carolina, USA

James E. Hansen
St. John's Cardiovascular Research Center, Los Angeles Biomedical Research Institute at Harbor- University of California at Los Angeles, Torrance, CA, USA

İlhan İnci
University Hospital Zurich, Department of Thoracic Surgery, Zurich, Switzerland

Oya İtil
Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Turkey

A. Fuat Kalyoncu
Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey

Fazilet Karakoç
Department of Child Chest Diseases, Marmara University Pendik Training and Research Hospital, İstanbul, Turkey

Ali Kocabaş
Department of Chest Diseases, Çukurova University School of Medicine, Adana, Turkey

Emel Kurt
Department of Chest Diseases, Osmangazi University School of Medicine, Eskişehir, Turkey

Atul Malhotra
Pulmonary and Critical Care, University of California San Diego, La Jolla, California, USA

Muzaffer Metintaş
Department of Chest Diseases, Osmangazi University School of Medicine, Eskişehir, Turkey

Türk Toraks Derneği
Turkish Thoracic Society

Thoracic Research & Practice

Official Journal of the Turkish Thoracic Society

Zeynep Mısırlıgil
Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey

Nesrin Moğulkoç
Department of Chests Diseases, Ege University School of Medicine, İzmir, Turkey

Dilşad Mungan
Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey

Gökhan M. Mutlu
Division of Pediatric Critical Care Medicine, Nortwestern University, Chicago, USA

Gül Öngen
Department of Chest Surgery, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey

Kent E. Pinkerton
University of California, Davis, Center for Health and the Environment, Davis, USA

Kannan Ramar
Division of Pulmonary and Critical Care Medicine, Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

Joseph Roca
Instituto de Biología Molecular de Barcelona, CSIC, Baldiri Reixac, Barcelona, Spain

Israel Rubinstein
Section of Pulmonary, Critical Care, Sleep and Allergy Medicine, Department of Medicine, College of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

Abdullah Sayıner
Department of Chest Diseases, Ege University School of Medicine, İzmir, Turkey

Z. Toros Selçuk
Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey

Nadja Triller
Department of Pulmonary Medicine, University Pulmonary Clinic Golnik, Golnik, Slovenia

Haluk Türktaş
Department of Chest Diseases, Gazi University School of Medicine, Ankara, Turkey

E. Sabri Uçan
Department of Chest Diseases, Dokuz Eylül University School of Medicine, İzmir, Turkey

Karlman Wasserman
Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute Harbor-UCLA Medical Center, Torrance, California, USA

Mark Woodhead
Honorary Clinical Professor of Respiratory Medicine, Department of Respiratory Medicine, Manchester Royal Infirmary, Manchester, England

Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

ABOUT

About the Thoracic Research and Practice

Thoracic Research and Practice is a peer reviewed, open access, online-only journal published by the Turkish Thoracic Society.

Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

Journal History

Thoracic Research and Practice started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2008. From 2008 to 2022, the journal was published under the title "Turkish Thoracic Journal". Archives of the journals were transferred to Thoracic Research and Practice.

Abstracting and indexing

Thoracic Research and Practice is covered in the following abstracting and indexing databases; PubMed Central, Web of Science - Emerging Sources Citation Index, Scopus, EMBASE, EBSCO, CINAHL, Gale/Cengage Learning, ProQuest, DOAJ, CNKI, TUBITAK ULAKBIM TR Index.

Aims, Scope, and Audience

Thoracic Research and Practice aims to publish studies of the highest scientific and clinical value, and encourages the submission of high-quality research that advances the understanding and treatment of pulmonary diseases.

Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

Thoracic Research and Practice publishes clinical and basic research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, systematic reviews and meta-analyses, letters to the editor and editorials. Conference proceedings may also be considered for publication.

The target audience of the journal includes healthcare professionals and researchers who are interested in or working in the pulmonary diseases field, and related disciplines.

Open Access Policy

Thoracic Research and Practice is an open access publication.

Starting on January 2022 issue, all content published in the journal is licensed under the Creative Commons Attribution-NonCommercial (CC BY-NC) 4.0 International License which allows third parties to use the content for non-commercial purposes as long as they give credit to the original work. This license allows for the content to be shared and adapted for non-commercial purposes, promoting the dissemination and use of the research published in the journal.

The content published before January 2022 was licensed under a traditional copyright, but the archive is still available for free access.

All published content is available online, free of charge at thoracrespract.org.

When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Copyright Policy

A Copyright Agreement and Acknowledgement of Authorship form should be submitted with all manuscripts. By signing this form, authors transfer the copyright of their work to the Turkish Thoracic Society and agree that the article,

Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

if accepted for publication by the Thoracic Research and Practice will be licensed under a Creative Commons Attribution-Non Commercial 4.0 International License (CC BY-NC 4.0) which permits third parties to share and adapt the content for non-commercial purposes by giving the appropriate credit to the original work.

When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Authors retain the copyright of their published work in the Thoracic Research and Practice.

Publication Fee Policy

Thoracic Research and Practice is funded by the the Turkish Thoracic Society. Authors are not required to pay any fees during the evaluation and publication process.

You can find the current version of the Instructions to Authors at *https://turkthoracj.org/en/instructions-to-authors-1013*.

Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

CONTENTS

ORIGINAL ARTICLES

284 **Vaccination Status and Outcome of Hospitalized Patients with Coronavirus Disease 2019 Before and After the Spread of Omicron Variant: An Observational Study from İzmir, Turkey**
Sema Alp Çavuş, Muammer Çelik, Çağlar Irmak, Gamze Helvacı, Gökçen Ömeroğlu Şimşek, Figen Coşkun

292 **Pulmonary Invasive Fungal Disease: Ultrasound and Computed Tomography Scan Findings**
Seyed Ali Alamdaran, Raha Bagheri, Seyedeh Fatemeh Darvari, Elham Bakhtiari, Ali Ghasemi

298 **Does Telerehabilitation for Coronavirus Disease 2019 Patients Discharged with Oxygen Shorten the Time of Weaning from Oxygen?**
Sami Deniz, Celalettin Yılmaz, Onur Süneçli, Elmas Kuru Akyol

304 **Comparison of Self-Efficacy and Problem-Solving Skills Between Women with Asthma and Healthy Controls: A Cross-Sectional Study**
Melissa Köprülüoğlu, İlknur Naz, Büşra Aktaş, Berna Kömürcüoğlu, Derya Özer Kaya

REVIEWS

309 **Stepwise Approach in Asthma Revisited 2023: Expert Panel Opinion of Turkish Guideline of Asthma Diagnosis and Management Group**
Gülfem Elif Çelik, Ömür Aydın, Ebru Damadoğlu, Ayşe Baççıoğlu, Seçil Kepil Özdemir, Sevim Bavbek, Dane Ediger, Ferda Öner Erkekol, Bilun Gemicioğlu, Sacide Rana Işık, Ayşe Füsun Kalpaklıoğlu, Ali Fuat Kalyoncu, Gül Karakaya, Metin Keren, Dilşad Mungan, İpek Kıvılcım Oğuzülgen, Füsun Yıldız, İnsu Yılmaz, Arzu Yorgancıoğlu

325 **Risk Medicine and Transhumanism**
Osman Elbek

LETTER TO THE EDITOR

330 **Sarcoid-Like Mediastinal Reaction in the Context of Histiocytic Sarcoma**
Sergio Chávez Valladares, Blanca de Vega Sanchez, Clarisa Simon Perez, Carlos Disdier Vicente, Henar Borrego Pintado

Thorac Res Pract. 2023; 24(6): 284-291 DOI: 10.5152/ThoracResPract.2023.22234

Original Article

Vaccination Status and Outcome of Hospitalized Patients with Coronavirus Disease 2019 Before and After the Spread of Omicron Variant: An Observational Study from İzmir, Turkey

Sema Alp Çavuş[1], Muammer Çelik[1], Çağlar Irmak[1], Gamze Helvacı[1], Gökçen Ömeroğlu Şimşek[2], Figen Coşkun[3]

[1]Department of Infectious Diseases and Clinical Microbiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[2]Department of Pulmonary Diseases, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[3]Department of Emergency Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Cite this article as: Alp Çavuş S, Çelik M, Irmak Ç, Helvacı G, Ömeroğlu Şimşek G, Coskun F. Vaccination status and outcome of hospitalized patients with coronavirus disease 2019 before and after the spread of omicron variant: An observational study from İzmir, Turkey. *Thorac Res Pract.* 2023;24(6):284-291.

Abstract

OBJECTIVE: Despite the efforts in vaccination against coronavirus disease 2019 (COVID-19), breakthrough infections occur and the need for hospitalization continues. We aimed to determine the relationship between severe acute respiratory syndrome coronavirus 2 vaccination and the severity of COVID-19 and mortality among hospitalized patients with COVID-19.

MATERIAL AND METHODS: This cross-sectional study was conducted between September 2021 and February 2022 in a university hospital in Turkey. Hospitalized patients with COVID-19 (both in clinics and in intensive care units), ≥18 years old, and who had no previous COVID-19 were included in the study. The demographic characteristics, clinical data, vaccination status, and outcome of the patients were analyzed retrospectively and the relationship between vaccination status and mortality was determined statistically.

RESULTS: Of the 674 patients, 180 (26.7%) had no vaccination, 282 (41.8%) had incomplete vaccination, and 212 (31.5%) were fully vaccinated according to the updated vaccination recommendations. While 44.0% of the patients were fully vaccinated before the occurrence of omicron variant, 15.9% of the patients were fully vaccinated during the wave of the omicron variant. The patients with no vaccination were younger and had fewer comorbidities. The overall mortality was 31.8%. Under 50 years old, all the patients with fully vaccination survived and the patients with no vaccination or incomplete vaccination had higher (10.1%) mortality. During the omicron period, mortality was lower in fully vaccinated pateints.

CONCLUSION: Immunization with and booster doses of BNT162b2 should be encouraged to protect both healthy and vulnerable populations.

KEYWORDS: COVID-19, omicron, vaccination, breakthrough infection, hospitalization
Received: *December 14, 2022* ***Accepted:*** *July 17, 2023* ***Publication Date:*** *September 11, 2023*

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been affecting the whole world since the beginning of 2020 and has been declared a pandemic by the World Health Organization (WHO).[1] The disease has a wide clinical course ranging from asymptomatic infection to pneumonia with severe respiratory failure and death, especially among the older and vulnerable population.[2,3]

Vaccine development studies have started rapidly to reduce the spread of the pandemic and to prevent morbidity and mortality. Various technologies have been used for vaccine development, but mainly inactivated, messenger RNA (mRNA) and viral vector (adenovirus) vaccines have been produced and used for mass vaccination. Currently, there are 183 vaccines in clinical and 199 vaccines in preclinical development.[4] Studies have shown that vaccines are highly effective in preventing symptomatic infection, reducing the need for hospitalization, and mortality.[5-7] Considering the increasing number of COVID-19 cases and deaths, emergency use authorization was granted for CoronaVac (Sinovac) by the Turkish Medicines and Medical Devices Agency on January 13, 2021.[8] As of January 14, 2021, health-care workers (HCWs) were vaccinated initially with 2 doses of CoronaVac 28 days apart. In April 2021, the mRNA vaccine BNT162b2 (Comirnaty, Pfizer–BioNTech) was introduced in Turkey, and the vaccination was expanded to cover the whole population over 12 years of age, starting from the groups at risk. In our country, homologous (only CoronaVac or only BNT162b2) or heterologous (2 doses of CoronaVac vaccination followed by BNT162b2) vaccination has been carried out for rappel doses.

Due to the fact that the current vaccines do not have 100% protection and newly emerged variants during the pandemic, breakthrough infections continue to be seen even in fully vaccinated people. Breakthrough infections can cause

Corresponding author: Muammer Çelik, e-mail: muammer4677@yahoo.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

severe COVID-19 pneumonia, need for hospitalization and advanced respiratory support, and even mortality in vulnerable population.[9-11] Additionally, with the emergence and rapid spread of the omicron variant (B.1.1.529), current vaccination policies have changed, and the definition of fully vaccinated has been renewed.[12] In the course of the pandemic, because of the new emerging variants and changes in the immunity status of the population, the effectivity and safety of the current vaccination strategies should be monitored continuously.

In this study, we aimed to determine the relationship between SARS-CoV-2 vaccination status and the severity of COVID-19 and mortality among hospitalized patients with COVID-19.

MATERIAL AND METHODS

Study Design and Population

This retrospective, cross-sectional study was conducted between September 1, 2021, and February 28, 2022, in the Dokuz Eylül University Hospital located in İzmir, Turkey. Our hospital is a referral tertiary care hospital with 1100-bed capacity. At our center, a COVID-19 pandemic action plan was prepared to ensure that all patients could undergo the necessary intervention as soon as possible.[13] During the waves of the pandemic, as the number of COVID-19 patients who needed for hospitalization increased, the number of clinics for COVID-19 raised up to 7 separate clinics. Two separate intensive care units (ICUs) with 41 ICU beds were used for patients with severe/critical COVID-19.

Patients with COVID-19 [diagnosed with SARS-CoV-2 polymerase chain reaction (PCR) positivity] who needed hospitalization (both in clinics and in ICUs), were over the age of 18 years, and had no previous history of COVID-19 were included in the study. The patients who needed hospitalization for reasons other than COVID-19 but followed up in pandemic clinics or ICUs for isolation because of SARS-CoV-2 PCR positivity were also included in the study.

Data Collection

Hospitalization status of the patients (ICUs, clinics, and isolation); age; gender; comorbidities such as essential hypertension (HT), diabetes mellitus (DM), cardiovascular disease (CVD), chronic pulmonary disease, chronic kidney disease, autoimmune diseases, malignancies, solid-organ transplantation (SOT), and hematopoietic stem cell transplantation (HSCT); immunosuppressive drug use; corticosteroid use (>20 mg prednisone or equivalent >14 days); pregnancy; and the data of SARS-CoV-2 PCR positivity dates were retrospectively analyzed from hospital records. The vaccine tracking system of the Turkish Ministry of Health was used to determine the vaccination history of the patients. Vaccines administered within 14 days prior to PCR positivity were not included.

Participants and Definitions

We retrospectively evaluated 766 patients. A total of 92 patients were excluded from the study, as 34 patients were negative for SARS-CoV-2 PCR, 20 patients had a history of previous COVID-19, and 38 patients were under 18 years of age. The flowchart of the patient recruitment is given in Figure 1.

A total of 674 patients were included in the study. The patients were divided into 2 periods according to their PCR positivity time. Between September 1 and December 31, 2021 (4 months), the delta variant was predominant in Turkey, and this period was named the first period.[14] Between January 1 and February 28, 2022 (2 months), the omicron variant became predominant and caused the sixth wave in Turkey.[15] This period was named the second period.

The vaccination status of the patients was defined as ''no vaccination, incomplete vaccination, and fully vaccinated'' according to their vaccination status, for both periods separately according to their PCR positivity dates.[16]

The vaccination scheme for the first period

Fully vaccinated: ≥3 doses of CoronaVac, 2 doses of CoronaVac plus ≥1 dose(s) of BNT162b2, or ≥2 doses of BNT162b2.

Incomplete vaccination: All other vaccinations that do not match with fully vaccinated.

The vaccination scheme for the second period:

Fully vaccinated: 4 doses of CoronaVac, 3 doses of BNT162b2, or 2 doses of CoronaVac plus ≥2 doses of BNT162b2.

Incomplete vaccination: All other vaccinations that do not match with fully vaccinated.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 24.0 (IBM Corp., Armonk, NY, USA). The conformity of continuous variables to normal distribution was examined visually (using histograms and probability graphs) and statistically (using Kolmo gorov–Smirnov/Shapiro–Wilk tests). Descriptive statistics (the median and interquartile range or percentages, as appropriate) were used to summarize sociodemographic and clinical variables. A Mann–Whitney *U*-test was used to compare the continuous variables. The carriage was evaluated in terms of categorical variables using a chi-square test or a 2-sided Fisher's exact test when appropriate. A multivariate logistic

MAIN POINTS

- Despite efforts, less than one-third of hospitalized coronavirus disease 2019 (COVID-19) patients were fully vaccinated and the patients with no vaccination were younger and had less comorbidities.
- While mortality did not differ among older patients with and without vaccination, all of the younger patients with fully vaccination have survived.
- During the spread of Omicron, the patients who had boosters died less.
- The study emphasizes the necessity of targeted vaccination efforts for vulnerable populations, such as older individuals and those with underlying health conditions, to mitigate severe COVID-19 outcomes.

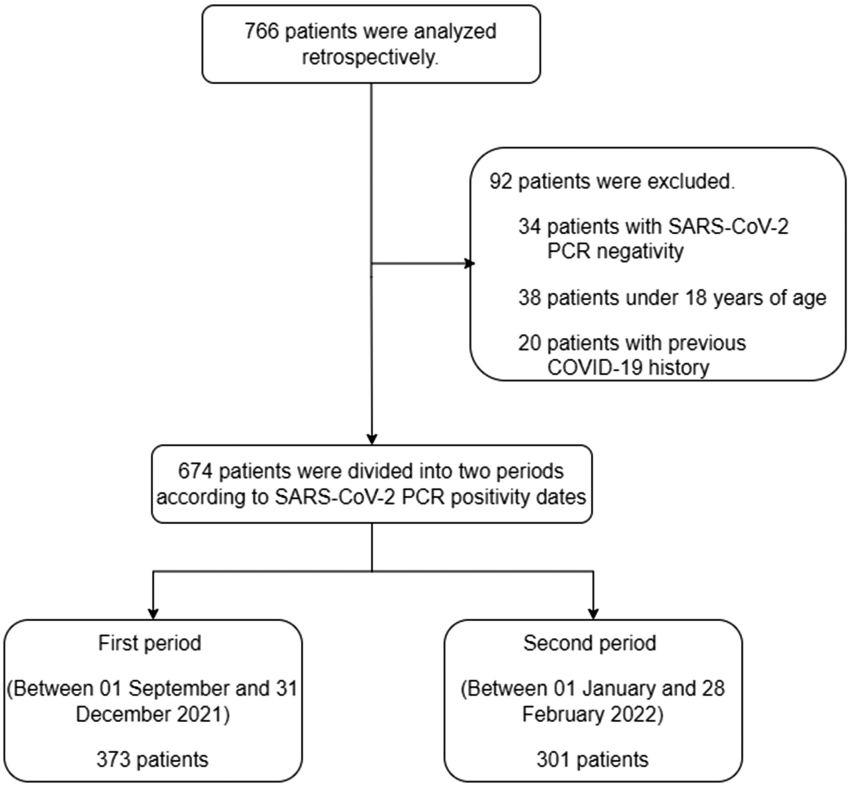


Figure 1. Flowchart of the patient recruitment.

model was applied to investigate demographic characteristics (age and sex) and clinical features (presence of comorbidities and other factors) associated with mortality. Statistical significance was set at $P < .05$.

Ethics Committee Approval

The study protocol was reviewed and approved by the Noninvasive Research Ethics Committee of Dokuz Eylül University as Decision No: 2022/10-08 on March 16, 2022. Permission was obtained from the Republic of Turkey Ministry of Health.

RESULTS

Demographic Data

The median age of the patients was 71 years (ranged between 18 and 98 years), 117 (17.4%) were younger than 50 years, 131 (19.4%) were between 50 and 64 years, and 426 (63.2%) were 65 years and over. Of the patients, 347 (51.5%) were men and 327 (48.5%) were women. Most of the patients (n = 546, 81.0%) had at least 1 comorbidity, and the median number of comorbidities was 2 (0-6). Of the patients, 166 (24.6%) had 1, 180 (26.7%) had 2, 145 (21.5%) had 3, and 55 (8.2%) had 4 or more comorbidities.

The most common comorbidities were HT (n = 343, 50.9%), CVD (n = 231, 34.3%), and DM (n = 211, 31.3%), followed by malignancy (n = 128, 19.0%), chronic pulmonary disease (n = 119, 17.7%), chronic kidney disease (n = 104, 15.4%), autoimmune disease (n = 32, 4.7%), SOT (n = 18, 2.7%), and HSCT (n = 8, 1.2%). Of the patients, 92 (13.6%) were using immunosuppressive drugs and 37 (5.5%) were using corticosteroids. The percentage of pregnancy was 3.1 among patients.

Hospitalization Status

In the first period 373 (55.3%) and the second period 301 (44.7%) patients with COVID-19 were hospitalized in pandemic clinics and ICUs. Of the patients, 398 (59.1%) patients with COVID-19, who met the criteria for hospitalization were admitted to the pandemic clinics, 134 (19.9%) patients who had severe/critical disease at presentation were admitted directly to ICU. One hundred forty-two (21.1%) patients, who were hospitalized for the indications other than COVID-19 in different clinics and had SARS-CoV-2 PCR positivity, were transferred to the pandemic clinics for isolation. In total, 284 (42.1%) patients had ICU attendance. The median hospitalization day was 8 (ranged between 1 and 116 days) and the median ICU hospitalization day was 8 (ranged between 1 and 68 days).

Vaccination Status

During the 6-month study period, 180 (26.7%) patients with COVID-19 had no vaccination, 282 (41.8%) had incomplete vaccination, and 212 (31.5%) were fully vaccinated according to the updated vaccination recommendations. In the first period, 125 (33.5%) patients had no vaccination, 84 (22.5%) had incomplete vaccination, and 164 (44.0%) were fully vaccinated. In the second period, 55 (18.3%) patients had no vaccination, 198 (65.8%) had incomplete vaccination, and 48 (15.9%) were fully vaccinated. The percentage of the patients vaccinated with only CoronaVac was 45.0% in the first and 46.8% in the second period. The percentage of the patients with BNT162b2 (homologous or heterologous) vaccination was higher in the second period (21.4% vs. 34.8%). The vaccination status of the patients according to the periods is given in Table 1.

The median age of the patients who were vaccinated was higher than the patients with no vaccination ($P < .001$).

Table 1. Vaccination Status of the Hospitalized Patients with COVID-19 According to the Periods

Vaccine Type	First Period, n (%)	Second Period, n (%)
No vaccination	125 (33.5)	55 (18.3)
1 dose of CoronaVac	3 (0.8)	0 (0)
2 doses of CoronaVac	77 (20.6)	50 (16.6)
3 doses of CoronaVac	88 (23.6)	73 (24.3)
4 doses of CoronaVac	0 (0)	18 (6.0)
2 doses of CoronaVac + 1 dose of BNT162b2	44 (11.8)	48 (15.9)
2 doses of CoronaVac + 2 doses of BNT162b2	5 (1.3)	17 (5.6)
1 dose of BNT162b2	4 (1.1)	2 (0.7)
2 doses of BNT162b2	25 (6.7)	21 (7.0)
3 doses of BNT162b2	2 (0.5)	11 (3.7)
2 doses of CoronaVac + 3 doses of BNT162b2	0 (0)	2 (0.7)
3 doses of CoronaVac + 1 dose of BNT162b2	0 (0)	4 (1.3)
Total	373 (100.0)	301 (100.0)

COVID-19, coronavirus disease 2019.

The percentage of the patients with no vaccination was higher under 50 years of age, same in the age group of 50-64 years. The number of patients with vaccination history was higher in 65 years and older. The percentage of men (P = .002) and those having comorbidities (P < .001) were higher in the vaccinated group (Table 2).

There was no difference in ICU attendance (P = .53), duration of hospitalization (P = .78), duration of ICU stay (P = .21), and mortality (P = .84) between unvaccinated, incomplete, and fully vaccinated patients (Table 2).

Outcome

In-hospital mortality was 31.8% (32.7% in the first and 30.6% in the second period, P = .552). The median age of the patients with mortality was higher (P < .001). In the deceased group, the percentage of being under 50 years of age was lower, being between 50 and 64 years of age was similar, and being 65 years and older were significantly higher than the survivors (Table 3).

The mortality was significantly higher in men (P = .034) and in the patients with comorbidities (P = .002) such as DM (P = 0.007) and malignancy (P = .05). None of the patients with pregnancy had died. The patients who died had a significantly higher need for ICU stay (P < .001) and had longer hospitalization (P < .001). There was no relationship between vaccination status and mortality (Table 3).

While overall mortality was 8.5% under 50 years of age, all the patients with full vaccination have survived and the patients with no vaccination or incomplete vaccination had higher (10.1%) mortality. Between 50 and 64 years, the overall mortality was 28.2%, 36.6% in fully vaccinated patients, and 24.4% in unvaccinated or incomplete vaccinated patients. Of the patients 65 years and older, 39.2% of patients have died.

Table 2. Demographic Characteristics and Outcomes of Patients Hospitalized with Coronavirus Disease 2019 by Vaccination Status

	No Vaccination, 180 (26.7%)	Incomplete Vaccination, 282 (41.8%)	Fully Vaccinated, 212 (31.5%)	*P*
Age, years (median)	58 (18-96)	73 (19-98)	73 (18-95)	**<.001***
Age group				
<50 years	74 (41.1)	25 (8.9)	18 (8.5)	**<.001****
50-64 years	38 (21.1)	52 (18.4)	41 (19.3)	
≥65 years	68 (37.8)	205 (72.7)	153 (72.2)	
Sex (male)	76 (42.2)	143 (50.7)	128 (60.4)	**.002****
Comorbidity	105 (58.3)	250 (88.7)	191 (90.1)	**<.001****
ICU attendance	73 (40.6)	115 (40.8)	96 (45.3)	.533**
Duration of hospitalization, days (median)	9 (1-39)	8 (1-116)	8 (1-86)	.780*
Duration of ICU stay, days (median)	8 (1-30)	8 (1-68)	7 (1-57)	.207*
Mortality	54 (30.0)	91 (32.3)	69 (32.5)	.839**

*Mann-Whitney U test.**Chi-square test.ICU, intensive care unit.

Table 3. Characteristics of Patients Hospitalized with Coronavirus Disease 2019 by Mortality

	First Period (n = 373, %)			Second Period (n = 301, %)			Total (n = 674, %)		
	Survived 251 (67.3%)	**Died 122 (32.7%)**	***P***	**Survived 209 (69.4%)**	**Died 92 (30.6%)**	***P***	**Survived 460 (68.2%)**	**Died 214 (31.8%)**	***P***
Age, years (median)	66 (18-94)	75 (38-97)	**<.001***	71 (18-98)	78 (34-94)	**<.001***	67 (18-98)	77 (34-97)	**<.001***
Age group									
<50 years	70 (27.9)	8 (6.6)	**<.001****	37 (17.7)	2 (2.2)	**<.001****	107 (23.3)	10 (4.7)	**<.001****
50-64 years	50 (19.9)	24 (19.7)		44 (21.1)	13 (14.1)		94 (20.4)	37 (17.3)	
≥65 years	131 (52.2)	90 (73.8)		128 (61.2)	77 (83.7)		259 (56.3)	167 (78.0)	
Sex (male)	114 (45.4)	70 (57.4)	**.030****	110 (52.6)	53 (57.6)	.425**	224 (48.7)	123 (57.5)	**.034****
Comorbidity	187 (74.5)	103 (84.4)	**.031****	171 (81.8)	85 (92.4)	**.018****	358 (77.8)	188 (87.9)	**.002****
Essential hypertension	120 (47.8)	61 (50.0)	.691**	111 (53.1)	51 (55.4)	.709**	231 (50.2)	112 (52.3)	.608**
Diabetes mellitus	67 (26.7)	40 (32.8)	.222**	62 (29.7)	42 (45.7)	**.007****	129 (28.0)	82 (38.3)	**.007****
Cardiovascular disease	65 (25.9)	42 (34.4)	.087**	88 (42.1)	36 (39.1)	.629**	153 (33.3)	78 (36.4)	.417**
Pulmonary disease	43 (17.1)	27 (22.1)	.246**	30 (14.4)	19 (20.7)	.173**	73 (15.9)	46 (21.5)	.075**
Renal disease	38 (15.1)	22 (18.0)	.476**	27 (12.9)	17 (18.5)	.208**	65 (14.1)	39** (18.2)	.171**
Autoimmune disease	11 (4.4)	3 (2.5)	.562**	11 (5.3)	7 (7.6)	.429**	22 (4.8)	10 (4.7)	.950**
Malignancy	42 (16.7)	29 (23.8)	.104**	36 (17.2)	21 (22.8)	.253**	78 (17.0)	50 (23.4)	**.048****
Solid-organ transplantation	8 (3.2)	2 (1.6)	.509***	6 (2.9)	2 (2.2)	1.000***	14 (3.0)	4 (1.9)	.379***
Hematopoietic stem cell transplantation	4 (1.6)	1 (0.8)	1.000***	2 (1.0)	1 (1.1)	1.000***	6 (1.3)	2 (0.9)	1.000***
Immunosuppressive drug use	36 (14.3)	17 (13.9)	.916**	28 (13.4)	11 (12.0)	.713**	64 (13.9)	28 (13.1)	.770**
Corticosteroid use	13 (5.2)	6 (4.9)	.914**	10 (4.8)	8 (8.7)	.187**	23 (5.0)	14 (6.5)	.413**
Pregnancy	16 (6.4)	0 (0.0)	**.004*****	5 (2.4)	0 (0.0)	.328***	21 (4.6)	0 (0.0)	**<.001*****
ICU attendance	60 (23.9)	116 (95.1)	**<.001****	27 (12.9)	81 (88.0)	**<.001****	87 (18.9)	197 (92.1)	**<.001****
Duration of hospitalization, days (median)	8 (1-86)	10 (1-63)	**.008***	6 (1-63)	13 (1-116)	**<.001***	7 (1-86)	11 (1-116)	**<.001***
Duration of ICU stay, days (median)	7 (2-48)	8 (1-68)	.764*	7 (1-59)	8 (1-68)	.384*	7 (1-59)	8 (1-68)	.416*
Vaccination status									
No vaccination	89 (35.5)	36 (29.5)	.521**	37 (17.7)	18 (19.6)	.646**	126 (27.4)	54 (25.2)	.839**
Incomplete vaccination	55 (21.9)	29 (23.8)		136 (65.1)	62 (67.4)		191 (41.5)	91 (42.5)	
Fully vaccinated	107 (42.6)	57 (46.7)		36 (17.2)	12 (13.0)		143 (31.1)	69 (32.2)	

*Mann-Whitney U test.**Chi-square test.***Fisher's Exact test.ICU, intensive care unit.

The mortality was lower in the fully vaccinated group compared to the other group (35.3% vs. 41.4%).

Mortality was not statistically different in patients with no, incomplete or full vaccination (30.0%, 32.3%, 32.5%, $P = .839$). In the first period, mortality was 28.8% in patients with no vaccination, 34.5% with incomplete vaccination, and 34.8% with full vaccination ($P = .521$). In the second period, mortality was lower in patients with full vaccination (25.0%) than in patients with no (32.7%) or incomplete vaccination (31.3%), but the rate was not statistically significant ($P = .646$).

In multivariate analysis of all patients, age [odds ratio (OR): 1.088; 95% CI: 1.053-1.123; $P < .001$], being 65 years and older (OR: 2.794; 95% CI: 1.137-6.867; $P = .02$), having comorbidities (OR: 2.343; 95% CI: 1.056-5.196; $P = .036$), malignancy (OR: 0.334; 95% CI: 0.174-0.641; $P = .001$), and need for ICU (OR: 0.015; 95% CI: 0.008-0.029; $P < .001$) were significantly associated with mortality. In multivariate analysis stratified by periods, vaccine effectiveness against death in fully vaccinated group was 82.8% (95% CI: 34.1%-95.5%; $P = .01$) in the second period, when adjusted for age, gender, comorbidity, and need for intensive care.

DISCUSSION

In this study, we took a picture of the vaccination status of the hospitalized patients with COVID-19 before and after the emergence of the omicron variant. Less than one-third of the patients were fully vaccinated according to the updated SARS-CoV-2 vaccine recommendations. After the rapid spread of the omicron variant, the percentage of fully vaccinated patients decreased from 44.0% to 15.9%. The overall mortality was 31%. Although the mortality rate did not differ among the groups with different vaccination status, the patients with no vaccination were younger and had less comorbidities. Under 50 years of age, while all of the patients with fully vaccination survived, 10.1% patients with an incomplete or no vaccination have died. In multivariate analysis, vaccine effectiveness against death in fully vaccinated group was 82.8% in the second period.

As expected, the median age of the patients was high and most of the patients had at least 1 comorbidity in this study, in accordance with other studies evaluating the hospitalized patients with breakthrough infections.[17-19] In their study, Suleyman et al[20] evaluated 982 fully vaccinated patients with COVID-19 breakthrough infections and 16% patients required hospitalization. Age, cardiovascular disease, and immunosuppressive drug status were independent risk factors for hospitalization.

In our study, 26.7% of the hospitalized patients were not vaccinated, 41.8% had incomplete vaccination, and 31.5% were fully vaccinated. The patients with no vaccination were younger and had fewer comorbidities than the vaccinated patients. In a multicenter study from Turkey, 1401 patients were evaluated, who were hospitalized during the first 10 days of August 2021. Almost half (47.8%) of the patients had no vaccination and the patients with no vaccination were younger and had less comorbidities.[19] In a study conducted in 21 centers from 18 states of the USA, among 1197 patients with COVID-19 hospitalized between March and July 2021, 14.9% were vaccinated and 88.1% were unvaccinated. The patients with vaccination were older and had more chronic medical conditions.[9] As time passed during the pandemic, the vaccination coverage has expanded in different risk groups, and in some of the vulnerable groups, such as elderly or immunosuppressed individuals, the acquired immunity from various SARS-CoV-2 vaccines has decreased and new variants of concern (VOCs), such as the omicron variant, have emerged. Because of this, while the percentage of hospitalized patients with vaccination was low at the beginning, this percentage has increased as the pandemic continued to affect more people around the world.

CoronaVac was the first SARS-CoV-2 vaccine in Turkey and HCWs were vaccinated with CoronaVac. Studies have shown that the elicited immunity of inactivated vaccines decreases with time, especially after the fourth month of the last dose. After primary immunization, booster doses with CoronaVac or BNT162b2 have been recommended. In a study conducted at our center among HCWs with primary immunization with 2 doses of CoronaVac, the antibody level increased after BNT162b2 booster 10 times higher than that of the CoronaVac booster.[21] With the emergence of heavily mutated variant omicron, concerns of breakthrough infections among fully vaccinated patients have increased.[22] Both BNT162b2 and CoronaVac provided limited protection against the omicron variant, and a booster dose with BNT162b2 increased protection but the immunity waned over time.[23,24] In Turkey, while 93.2% of the population (18 years and older) have received a single dose of vaccine, 85.5% received a second dose, and less than half (44.8%) of the population received 3 or more doses. There are no data about the type of the vaccine and percentage of the population vaccinated with CoronaVac (homologous) or BNT162b2 (homologous or heterologous).[25] According to the results of our study, while the percentage of the patients with incomplete vaccination increased 3-fold, the percentage of the patients with complete vaccination 2.7-fold decreased in the omicron period. This significant change may be attributed to either the new definition of fully vaccinated for the omicron variant and low percentage of the fully vaccinated persons in the population of Turkey.

In this study, one-third of the patients died during their hospitalization. In multivariate analysis, advanced age, having comorbidity and malignancy, and a need for ICU attendance were associated with mortality. The percentage of mortality did not differ between groups of no vaccination, incomplete vaccination, or fully vaccinated during both study periods, but in multivariate analysis for the periods separately, mortality was 82.8% lower in the patients with full vaccination significantly. On the other hand, the group with no vaccination was younger and had fewer comorbidities. Under 50 years of age, while all fully vaccinated patients have survived, 10% patients with no vaccination or incomplete vaccination have died. In their study, Moreno-Perez et al[17] compared the mortality between the patients with fully and incomplete vaccination (a total of 145 patients). Although the main outcomes did not differ significantly between 2 groups, the patients with incomplete vaccination were younger and had fewer

comorbidities.[17] In contrast, Myers et al[26] showed that fewer fully vaccinated patients died compared to matched unvaccinated (9.0% vs. 16.3%, $P < .001$) and fully vaccinated patients were significantly older and had more comorbidities.These results show the importance of immunization and booster doses with BNT162b2 to protect both the healthy younger population and older people with multiple comorbidities.

Several limitations should be considered. The study was conducted in a single center and had a retrospective design. We evaluated only the patients with hospitalization. A population-based multicenter study evaluating both asymptomatic and symptomatic patients followed in outpatient or inpatient clinics can reflect the vaccine effectiveness accurately. We could not perform variant analysis within the scope of the study due to diagnostic limitations, but the distribution of cases was consistent with the pandemic waves caused by VOCs in Turkey. Our results are important to demonstrate the situation of countries like Turkey, where both inactivated and mRNA vaccines have been used.

CONCLUSION

Only one-third of the hospitalized patients were fully vaccinated and the patients with no vaccination were younger and had less comorbidities. While mortality did not differ among older patients with and without vaccination, all of the younger patients with fully vaccination have survived. During the spread of the omicron variant, the patients who had boosters died less. Immunization and booster doses with BNT162b2 to protect both the healthy younger population and older people with multiple comorbidities should be encouraged. Vaccination recommendations should be updated with the emergence of new variants for public health.

Ethics Committee Approval: This study was approved by Ethics Committee of Dokuz Eylül University (Approval No: 2022/10-08, Date: March 16, 2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.A.Ç., M.Ç., Ç.I.; Design – S.A.Ç., M.Ç., Ç.I., G.Ö.Ş, F.C.; Supervision – S.A.Ç., G.Ö.Ş, F.C.; Resources – S.A.Ç., M.Ç., Ç.I., G.H.; Materials – S.A.Ç., M.Ç., Ç.I., G.H.; Data Collection and/or Processing – M.Ç., Ç.I., G.H.; Analysis and/or Interpretation – S.A.Ç., M.Ç., Ç.I., G.H.; Literature Search – S.A.Ç., M.Ç., Ç.I., G.H.; Writing – S.A.Ç., M.Ç., Ç.I., G.H., G.Ö.Ş, F.C.; Critical Review – S.A.Ç., M.Ç., Ç.I., G.H., G.Ö.Ş, F.C.

Acknowledgments: The authors would like to thank all health-care workers who have worked in pandemic clinics and ICUs for their support and hard work during this unprecedented health-care crisis.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91(1):157-160. [CrossRef]
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13): 1239-1242. [CrossRef]
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. [CrossRef]
4. World Health Organization. *COVID-19 vaccine tracker and landscape*. Accessed June 7, 2023. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
5. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384(15):1412-1423. [CrossRef]
6. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalizations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet*. 2021;397(10287):1819-1829. [CrossRef]
7. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296): 213-222. [CrossRef]
8. Turkish Medicines and Medical Devices Agency. Accessed August 21, 2022. https://www.titck.gov.tr/haber/kamuoyunun-dikkatine-13012021185623.
9. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA*. 2021;326(20):2043-2054. [CrossRef]
10. Bozio CH, Grannis SJ, Naleway AL, et al. Laboratory-confirmed COVID-19 among adults hospitalized with COVID-19-like illness with infection-induced or mRNA vaccine-induced SARS-CoV-2 immunity - nine states, January-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(44):1539-1544. [CrossRef]
11. Çoban MM, Yakar MN, Küçük M, et al. COVID-19 pneumonia after SARS-CoV-2 vaccination with CoronaVac: a case series from Turkey. *Turk Thorac J*. 2022;23(2):185-191. [CrossRef]
12. Chen J, Wang R, Gilby NB, Wei GW. Omicron (B.1.1.529): infectivity, vaccine breakthrough, and antibody resistance. *Arxiv*. 2021;[CrossRef]
13. Yapar N, Uçan ES, Bayraktar F, et al. COVID-19 pandemic action plan of a University Hospital. *Turk Thorac J*. 2021;22(1):95-98. [CrossRef]
14. Akçeşme FB, Kul-Köprülü T, Erkal B, et al. Tracking the circulating SARS-CoV-2 variants in Turkey: complete genome sequencing and molecular characterization of 1000 SARS-CoV-2 samples. *BioRxiv*. 2022. [CrossRef]
15. Turkish Republic Ministry of Health. *Statement on the last 10 days of the omicron variant becoming dominant in Turkey*. Accessed August 21, 2022. https://www.saglik.gov.tr/TR,87028/turkiyede-baskin-hale-gelen-omicron-varyantinin-son-10-gunluk-seyrine-iliskin-aciklama-31122021.html
16. Turkish Society of Clinical Microbiology and Infectious Diseases. *Updated vaccine recommendations against COVID-19 from Turkish Society of Clinical Microbiology and Infectious Diseases*. Accessed August 21, 2022. https://www.klimik.org.tr/wp-content/uploads/2022/03/KLI%CC%87MI%CC%87K.Derneg%CC%86inden.COVID19a.Kars%CC%A7i.Gu%CC%88ncel.Bag%CC%86is%CC%A7iklama.O%CC%88nerileri_31.Mart_.2022-1.pdf
17. Moreno-Perez O, Ribes I, Boix V, et al. Hospitalized patients with breakthrough COVID-19: clinical features and poor outcome predictors. *Int J Infect Dis*. 2022;118:89-94. [CrossRef]

18. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*. 2021;27(11):1652-1657. [CrossRef]
19. Uzun O, Akpolat T, Varol A, et al. COVID-19: vaccination vs. hospitalization. *Infection*. 2022;50(3):747-752. [CrossRef]
20. Suleyman G, Fadel R, Brar I, et al. Risk factors associated with hospitalization and death in COVID-19 breakthrough infections. *Open Forum Infect Dis*. 2022;9(5):ofac116. [CrossRef]
21. Çağlayan D, Süner AF, Şiyve N, et al. An analysis of antibody response following the second dose of CoronaVac and humoral response after booster dose with BNT162b2 or CoronaVac among healthcare workers in Turkey. *J Med Virol*. 2022;94(5):2212-2221. [CrossRef]
22. Araf Y, Akter F, Tang YD, et al. Omicron variant of SARS-CoV-2: genomics, transmissibility, and responses to current COVID-19 vaccines. *J Med Virol*. 2022;94(5):1825-1832. [CrossRef]
23. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med*. 2022;386(16):1532-1546. [CrossRef]
24. Lu L, Mok BW, Chen LL, et al. Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *Clin Infect Dis*. 2021:ciab1041.
25. Turkish Republic Ministry of Health. *The Platform of COVID-19 Vaccine Information*. Accessed August 21, 2022. https://covid19asi.saglik.gov.tr
26. Myers LC, Kipnis P, Greene J, et al. Adults hospitalized with breakthrough COVID-19 have lower mortality than matched unvaccinated adults. *J Intern Med*. 2022;292(2):377-384. [CrossRef]

Thorac Res Pract. 2023; 24(6): 292-297 DOI: 10.5152/ThoracResPract.2023.23013

Original Article

Pulmonary Invasive Fungal Disease: Ultrasound and Computed Tomography Scan Findings

Seyed Ali Alamdaran[1], Raha Bagheri[1], Seyedeh Fatemeh Darvari[1], Elham Bakhtiari[2], Ali Ghasemi[3]

[1]Department of Radiology, Mashhad University of Medical Sciences Faculty of Medicine, Mashhad, Iran
[2]Research Center for Patient Safety, Mashhad University of Medical Sciences Faculty of Medicine, Mashhad, Iran
[3]Department of Pediatric Hematology and Oncology and Stem Cell Transplantation, Mashhad University of Medical Sciences Faculty of Medicine, Mashhad, Iran

Cite this article as: Ali Alamdaran S, Bagheri R, Fatemeh Darvari S, Bakhtiari E, Ghasemi A. Pulmonary invasive fungal disease: Ultrasound and computed tomography scan findings. *Thorac Res Pract.* 2023;24(6):292-297.

Abstract

OBJECTIVE: The importance of ultrasound in diagnosing pulmonary invasive fungal diseases (IFD) has yet to be assessed. Thus, this study aimed to evaluate the frequency of sonographic findings in patients suspected of an invasive pulmonary fungal infection.

MATERIAL AND METHODS: This prospective longitudinal study examined all patients with lung lesions in imaging modalities and suspected IFDs referred to Dr. Sheikh and Akbar pediatric hospitals from 2019 to 2022. Considered variables were the halo sign in the computed tomography (CT) scan; the target sign in the ultrasound and contrast-enhanced CT scan; the cavity; wedge-shaped consolidation; and pleuritis and extrapulmonary invasion to the chest wall or subdiaphragmatic invasion in both modalities. All patients who underwent lung CT scans and ultrasounds until the final diagnosis were followed up. The degree of agreement between ultrasound and CT scan findings and the sensitivity, specificity, and diagnostic accuracy of these signs were assessed.

RESULTS: This study involved 40 patients with an average age of 7.16 ± 4.23 years. Acute leukemia was the commonest underlying disease detected in 17 (42.5%) cases. The target sign in ultrasound (61.9%) and the halo sign in CT scan (71.4%) had the highest frequency among the variables in patients with IFD. Cohen's kappa coefficient agreement in both modalities was 0.5 for the cavity, with significant relation ($P = .02$). The Cohen's kappa was less than .17 for other findings ($P > .05$). The diagnostic criteria in the simultaneous examination of the fungus target in ultrasound and halo in CT scan showed a sensitivity of 82.4% and specificity of 76.5%, respectively.

CONCLUSION: Combining the characteristic findings of ultrasound and CT-scan provides a higher value in diagnosing pulmonary invasive fungal disease.

KEYWORDS: Diagnostic methods, pediatric lung disease, respiratory infections, invasive fungal disease
Received: *February 28, 2023* ***Accepted:*** *July 25, 2023* ***Publication Date:*** *September 11, 2023*

INTRODUCTION

Invasive fungal disease (IFD) is one of the major causes of death in immune-compromised children, such as cancer patients and those treated by hematopoietic stem cell transplants.[1,2] The people who live in areas where mycoses are persistently endemic are also at high risk of IFD.[3] However, diagnosis is supposed to be difficult in the mentioned populations, although it is critical for disease management and outcome improvement.[4,5] The early diagnosis of patients with fungal pneumonia is of utmost importance since treatment outcome highly depends on early interventions. On the other hand, delayed diagnosis is associated with high mortality, for example, >70% mortality rate for *Aspergillus* respiratory infections.[4]

Diagnosis of IFD based only on history and clinical examination is unreliable due to low sensitivity and specificity[6,7] and lack of determining the etiology of infection.[8] Although culturing the biopsy or bronchoalveolar lavage is the gold standard diagnosis of IFD, these methods are time-consuming and have complications.[9,10] Therefore, radiological imaging for quick assessment and diagnosis plays an important role. Imaging in children can help determine the spread of the infection from its primary origin and help antifungal treatment follow-up.[11]

Ultrasound has always been interesting of all radiological imaging modalities due to its greater availability, lower cost, and less ionizing side effects. Chest ultrasound (transthoracic ultrasound or TTUS) is well-known for diagnosing pleural effusion, pneumonia, and lung masses.[12,13] However, there are few case reports on the role of ultrasound in diagnosing invasive fungal infections of the lung.[14,15] In this regard, the present study was designed to determine the frequency of lung ultrasound findings in patients suspected of pulmonary IFD and compare the diagnostic accuracy of this modality with a lung computed tomography (CT) scan in the diagnosis of IFD.

MATERIAL AND METHODS

Study Design and Participants

This prospective longitudinal study examined all patients with lung opacity in imaging modalities and suspected IFD referred to 2 children's hospitals in Mashhad University of Medical Science from 2019 to 2022.

Corresponding author: Seyed Ali Alamdaran, e-mail: alamdarana@mums.ac.ir

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Before participating in this research, all required exams were described to the parents of the participants, and informed consent was obtained. First, the immune-compromised patients under 18 years of age were suspected of having a fungal infection with a history of cough and sputum production, fever, pleuritic chest pain, shortness of breath, and physical examination indicating pneumonia (body temperature >38°C or <36°C, respiratory rate above 22/min, heart rate >90/min, and auscultation rales on chest examination) were subjected to a chest x-ray (CXR). In cases where the CXR was consistent with the diagnosis of pneumonia, patients who had responded to pneumonia treatment were excluded from our study. However, additional examinations were performed by thoracic ultrasound and CT scan in cases of lack of response to treatment and suspicion of fungal infections. Then, the patients were followed up until the final diagnosis.

Diagnostic Method

An experienced pediatric radiologist performed the ultrasound examination (Figure 1). In lung ultrasound, 10 chest regions were examined, including 5 regions in each hemithorax: 2 anterior, 2 laterals, and 1 posterior region on each side. The anterior chest wall is defined from the parasternal line to the anterior axillary line. This area was divided into 2 upper and lower areas to align with the nipple landmark. The lateral area was defined from the anterior axillary line to the posterior axillary line, divided into upper and lower halves. The posterior region was defined from the posterior axillary line to the paravertebral line.

In ultrasound, a healthy lung has pleural sliding, A-line (repetitive lines parallel to the pleural line), and B-line (that is defined as long vertical hyperechoic reverberation artifacts originating from the interlobular septa that extend down the screen and that move and fade simultaneously with the pleural sliding). However, in interstitial lung abnormalities, there are multiple B lines (more than 3 lines in 1 area). The presence of focal interstitial abnormalities is considered early evidence of pneumonia. Ultrasonic diagnosis of pneumonia depends on lung consolidation with a tissue-like pattern (due to reduced alveolar ventilation and increased liquid content). On real-time ultrasound, consolidations may contain air bronchograms or multiple branching echogenic spots. A pleural effusion is an anechoic space between the parietal and visceral pleura with the respiratory movement of the lung inside the effusion.

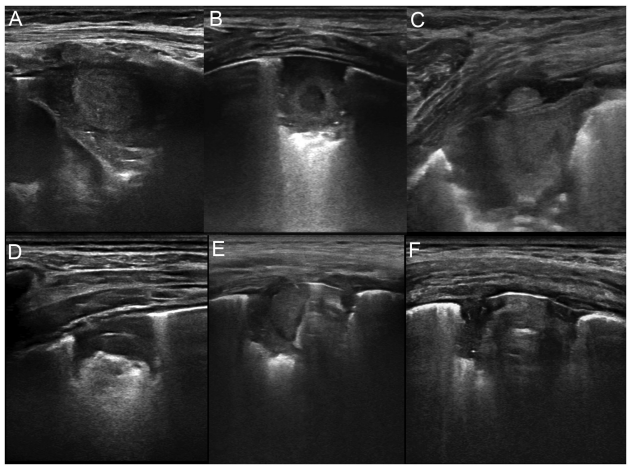


Figure 1. Ultrasound images of some patients with invasive pulmonary fungal infections. (A) The hyperechoic nodule (fungus ball) within the consolidation. (B) Target lesions as a hypoechoic center with a hyperechoic rim. (C) A wedge-shaped lesion associated with pleuritis and invasion on the chest wall. (D) Hyperechoic fungus ball with peripheral hypoechoic rim and reactive pleuritis. (E) Hyperechoic fungus ball with cavitation and air crescent sign. (F) A wedge-shaped consolidation with cavitation.

The IFD in the transthoracic ultrasound has 4 characteristic appearances: the target lesion (as a hyperechoic central nodule with a hypoechoic rim or as a hypoechoic center with a hyperechoic rim), the cavitary lesions (U-shaped consolidation), wedge-shaped consolidation, and pleuritis and extrapulmonary invasion to the chest wall or diaphragm. Computed tomography scan findings of the IFD are a nodule with halo sign, reverse halo sign, crescent sign, wedge-shaped opacity, and cavitary consolidation. The extrapulmonary invasion has been defined in ultrasound as the passage of the lesion along the pleura and in CT scan as a focal pleural thickening or periosteal reaction. The target sign in high-resolution computed tomography (HRCT) has been defined as the lesions with the hypodense center with a hyperdense rim in the mediastinal window of contrast-enhanced slices.

Diagnostic methods of IFD were paranasal sinuses debridement (5 cases), core needle biopsy (3 cases), surgery (4 cases), galactomannan test (2 cases), simultaneous target lesions in liver or spleen ultrasound (1 case), specific signs such as halo (14 cases) and crescent sign (6 cases) in lung CT scan, appropriate response to start of antifungal treatment (13 cases), and past medical history (7 cases).

Statistical Analysis

The data related to ultrasound and CT scan of the patients, their outcome, and general information were all collected and categorized. Sampling was done in a full census manner. The demographic data and general characteristics of the study population were described in tables using descriptive statistics methods, including central tendency indices, dispersion indices, and frequency distribution.

MAIN POINTS

- The characteristic ultrasound appearances of invasive fungal disease (IFD) included the target sign, the cavity, wedge-shaped consolidation, and pleuritis and extrapulmonary invasion to the chest wall or subdiaphragm.
- The characteristic computed tomography (CT) scan appearances of IFD included the halo sign and the crescent sign, the target signs in contrast-enhanced CT; wedge-shaped consolidation; and extrapulmonary invasion.
- There is a slight-to-moderate degree of agreement between the related findings in thoracic ultrasound and CT scan.
- The simultaneous use of contrast-enhanced CT scan and targeted ultrasound has a higher diagnostic value in diagnosing pulmonary fungal infections.

The Statistical Package for the Social Sciences, version 25.0, (IBM Corp.; Armonk, NY, USA) was used for statistical analysis, and tables were created in Microsoft Word 2016. The Cohen's kappa (κ) coefficient of agreement was used to evaluate the agreement of the results of different imaging modalities. A Cohen's κ value 0 was considered no agreement, .1-.2 as slight agreement, .21-.4 as fair agreement, .41-.6 as moderate agreement, .61-.8 as substantial agreement, .81-.99 as near-perfect agreement, and 1 as perfect agreement. Correlations were also analyzed between the 2 modalities, and a $P < .05$ was considered statistically significant. Also, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the imaging variables in ultrasound and CT scan were calculated.

Ethics Committee Approval

This study was registered with the Organizational Ethics Committee of the Faculty/Region of Mashhad University of Medical Sciences on January 20, 2021, and approved with code IR.MUMS.MEDICAL.REC.1399.730 and the number 981267.

RESULTS

This study involved 40 patients, 24 male (60%) and 16 female (40%). The average age of the patients was 7.41 ± 4.23 years, and the average size of the masses was 28.48 ± 16.23 mm. The underlying diseases were leukemia (17), Wilms' tumor (1), anaplastic anemia (3), immune deficiency (4), coronavirus disease 2019 (1), and diabetes mellitus (1). There was not a known underlying disease in 13 patients. Seventy percent of lesions were multiple and 52.5% were bilateral. Opacity in CXR was seen in 47.1% of patients, and others had normal CXR. The final diagnoses of lung lesions in the examined patients were IFD (21), chronic granulomatosis disease (4), round pneumonia (4), oil aspiration (3), chloroma (2), tuberculoma (2), abscess (1), tumor (1), inflammation (1), and hydatid cyst (1). Table 1 shows the demographic and diagnostic characteristics of suspected IFD patients.

Table 1. Demographic and Diagnostic Characteristics of Patients with Suspected IFD

Variables	Number
Age (mean)	7.41 ± 4.23 (years)
Male/female	24/16
Underlying disease	
• Leukemia	17
• Unknown	13
• Known immune deficiency	4
• Anaplastic anemia	3
• Others	3
Diagnostic methods	
• Specific CT scan findings	14
• Response to treatment	13
• Past medical history	7
• Sinus debridement	5
• Surgery	3
• Core needle biopsy	3
• Galactomannan test	2
Final diagnosis	
• IFD	21
• Chronic granulomatosis disease	4
• Round pneumonia	4
• Oil aspiration	3
• Chloroma	2
• Tuberculoma	2
• Others	4

CT, computed tomography; IFD, invasive fungal disease.

The most common ultrasound finding (60%) was a nonspecific mass. The diagnosis agreement based on the ultrasound variables was the same as the final diagnosis in 33 people (82.5%), but it was different in 7 people (28.5%).

Finally, the frequency of the ultrasound and CT-scan findings of the IFD (21 cases), including fungus ball, target sign, wedge-shaped lesions, cavity, and pleuritis and extrapulmonary invasion, was investigated. The target sign was the most common ultrasound finding (61.9%) and the central hyperechoic nodule (fungus ball) was seen in 28.6% of cases (Figure 2). However, the target sign in ultrasound is occasionally seen in other diseases, such as necrotizing pneumonia.

The most common findings were the cavity and the halo sign in the CT scan, with 30% and 71.4%, respectively. Contrast-enhanced HRCT was done in a few patients; the lesions with the hyperdense center with hypodense rim (target sign) were seen in the mediastinal window (Figure 2).

Although in the CT scan, the focal pleural reaction was observed in the adjacent fungal lesions in most patients

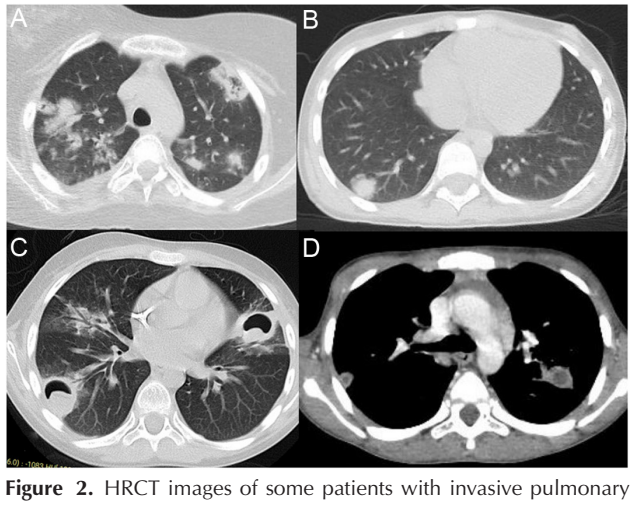


Figure 2. HRCT images of some patients with invasive pulmonary fungal infections. (A) Multiple opacity with peripheral or central ground glass (halo sign and reverse halo sign). (B) Nodular lesion with ground-glass opacity (halo sign). (C) The cavitary lesions with fungus ball and air crescent sign. (D) The hypodense center with a hyperdense rim (target sign) lesions in the mediastinal window of contrast-enhanced slices.

Table 2. Agreement Between CT Scan and Ultrasound Parameters in 21 Patients with Pulmonary IFD

		CT Scan Variable Crescent Sign		Cohen's Kappa Coefficient	*P*
Ultrasound Variable		**Negative (%)**	**Positive (%)**		
Fungus ball	Negative (%)	7 (63.6%)	4 (36.4%)	−.03	.90
	Positive (%)	4 (66.7%)	2 (33.3%)		
Target sign		Halo sign		.05	.81
	Negative (%)	1 (20%)	4 (80%)		
	Positive (%)	2 (15.4%)	11 (84.6%)		
		Target sign in contrast-enhanced CT			
		–	2		
Wedge-shaped consolidation		Wedge-shaped opacity		.08	.71
	Negative (%)	9 (69.2%)	4 (30.8%)		
	Positive (%)	3 (60%)	2 (40%)		
Cavity		Cavity		.50	.02
	Negative (%)	10 (76.9%)	3 (32.1%)		
	Positive (%)	1 (20%)	4 (80%)		
Extrapulmonary invasion		Extrapulmonary invasion		.17	.20
	Negative (%)	7 (100%)	0		
	Positive (%)	8 (80%)	2 (20%)		

CT, computed tomography; IFD, invasive fungal disease.

(9 cases), the clear invasion was seen in only 2 patients. However, ultrasound reliably showed extrapulmonary invasion in many patients (11 cases).

Cohen's κ statistical test was used to evaluate the agreement of ultrasound with CT-scan results in IFD. As presented in Table 2, the moderate agreement in both modalities and significant relation is due to the cavity (Cohen's $\kappa = .5$; $P = .02$). However, there was a slight degree of agreement (Cohen's $\kappa = -.03$; $P = .90$) between the fungus ball in ultrasound and the crescent sign in the CT scan and the target sign in the ultrasound and halo sign in the CT scan (Cohen's $\kappa = .05$; $P = .81$). Similarly, wedge-shaped lesions and extrapulmonary invasion in both modalities had a slight degree of agreement (Cohen's $\kappa = .08$ and .17; $P = .71$ and .20, respectively) that was nonsignificant.

In IFD patients, the sensitivity, specificity, and accuracy of the target sign in ultrasound were 56.25%, 81.25%, and 68.75%, that of the halo sign in CT scan were 70.58%, 88.23%, and 79.41%, and that of the simultaneous target sign in the ultrasound and halo sign in CT scan were 82.35%, 76.47%, respectively.

DISCUSSION

As a result of a recent meta-analysis, the role of lung ultrasound in diagnosing pediatric pulmonary infections is undeniable due to its high sensitivity and specificity, given the sensitivity of ultrasound to the natural determination of lung masses is higher than that of CT scan.[16,17] Due to the advantages that ultrasound has over invasive methods or other diagnostic devices with ionizing rays, there are always many efforts in clinical and even basic sciences (such as artificial intelligence and deep learning strategies) in order to enhance our knowledge and understanding of the cause and origin of artifacts in this diagnosis modality.[18,19]

Invasive pulmonary fungal infections are one of the important causes of death, especially in immunocompromised people, and early diagnosis has a key role in improving the prognosis of the disease in the mentioned people.[2,5] *Aspergillus*, *Candida*, and mucormycosis are 3 major causes of opportunistic fungal infections in immunocompromised patients with airway or angioinvasive features.[16,20]

In addition, IFD is becoming more common in premature and low-birth-weight infants, leading to decreased survival rate. In line with diagnostic problems of pulmonary infections in children and to clarify the diagnostic role of ultrasound modality, Jing Liu et al[21] investigated 7 cases of pulmonary fungal infections in newborns. They found that ultrasound features (including lung consolidations, irregular margins, shred signs, lung pulse, pleural line abnormalities, and different types of B-lines in nonconsolidated areas that show different degrees of edema) can help diagnose these patients. Similar avascular findings were reported in a case report by Grabala et al.[22]

In a prospective pilot study, Raffaella et al[23] studied 10 hematologic patients who underwent hematopoietic stem cell transplants and developed invasive fungal infections. In this study, patients were evaluated once at the beginning of the study and 10 days after the start of antifungal treatment using a CT scan and chest ultrasound. Chest ultrasound showed consolidations and hypoechoic areas with inhomogeneous

echoes and unclear margins in 40% of patients. The researchers concluded that ultrasound is highly sensitive to fungal pneumonia lesions and their follow-ups. However, these findings are nonspecific and can be seen in other conditions causing pneumonia.

Studies that show more specific findings of fungal infections are few; Rodrigues-Pinto et al[14] published a case report that endoscopic ultrasound showed an ill-defined hypoechoic paraesophageal lesion with a central annular image without vascular flow in a patient with acute myeloid leukemia. The ultrasound-guided fine-needle aspiration of the lesion revealed *Aspergillus*.[14] Alamdaran et al[15] reported some characteristic signs of invasive pulmonary fungal infections in 6 leukemia patients; they report 4 types of sonographic findings in transthoracic ultrasonography: the target sign, the cavity, wedge-shaped consolidation, and extrapulmonary invasion to the chest wall or subdiaphragmatic invasion. The target lesions have some features: a central hyperechoic nodule with a hypoechoic rim, a hypoechoic center with a hyperechoic rim, a hypoechoic nodule in the center of consolidation, and a hyperechoic nodule in the center of consolidation. The cavitary lesions are seen as an air crescent adjacent to the central hyperechoic or as a U-shaped consolidation, in which the air crescent is at the center of it. The central hyperechoic nodule is due to a fungus ball, as during cavitation, air envelopes it as a crescent sign. The extrapulmonary invasion to the pleura (focal pleuritis) and the chest wall, or to the subdiaphragmatic area, was seen in some of the subpleural lesions. Subsegmental consolidation is wedge shaped, probably due to airway or vessel invasion. We have found target signs in ultrasound frequently (61.9%) in cases where the final diagnosis was a fungal infection.

Some characteristic features of pulmonary fungal infection on x-ray or CT scan are reported; the halo sign and the "reverse-halo" sign are more specific findings of invasive pulmonary fungal infections on CT-scan images. The halo sign is a ground-glass opacity surrounding a rounded consolidation area, probably due to angioinvasion. The "reverse-halo" sign is defined by central ground-glass opacity with peripheral consolidation, probably due to necrotic or cavitary consolidation. The air crescent sign is due to central cavitation surrounding the fungus ball.[24]

In the current research, we investigated the diagnostic value of ultrasound and CT-scan findings. Our results showed that there is a different degree of agreement between variables. The target sign in ultrasound and the halo sign in CT scan and the cavity in both modalities have a significant moderate degree of agreement. These correlations suggest that we can rely on variables such as cavities and especially target signs for diagnosing invasive pulmonary fungal infection by ultrasound.

There was a slight agreement between the fungus ball in ultrasound and the crescent sign in CT scan and between wedge-shaped lesions in both modalities that were not statically significant. These 2 are probably due to the limitation of the ultrasound window after cavitation and air lung, which does not allow visualization of the fungus ball and the wedge-shaped appearance. However, this indicates the complementary role of ultrasound and CT scan in diagnosing fungal lung infections.

The low degree of agreement between the parameters of CT scan and ultrasound in pulmonary IFD emphasizes the complementary role of these 2 methods in diagnosing this disease.

Pulmonary fungal infection diagnosis based on simultaneous examination of the target sign in ultrasound and the halo sign in CT scan showed a sensitivity of 82.35%, specificity of 76.47%, and positive and negative predictive values of 77.77% and 81.25%, respectively. As a result, ultrasound and CT scan can provide more precise diagnostic accuracy in these patients.

It should be noted that although ultrasound is valuable in evaluating peripheral lung opacity, it has limitations in diagnosing central intraparenchymal parenchymal lesions. In this study, which is one of the few studies in this field, there are some limitations. The limitations of this study include the small sample size (due to the overall low prevalence of fungal lung infections), and it was impossible to match the ultrasound appearance with the pathologic appearance. We have tried to reduce this error to a minimum with careful data accumulation and using statistical methods. However, further studies need to be designed prospectively with a larger sample size and control of confounding factors to investigate this issue more precisely.

CONCLUSION

There are 4 characteristic ultrasound appearances of IFD: the target sign, the cavity, wedge-shaped consolidation, and extrapulmonary invasion to the chest wall or subdiaphragmatic invasion. Although there is a slight-to-moderate degree of agreement between the number of the related findings in thoracic ultrasound and CT scan, this research shows that the simultaneous use of both modalities has a higher value in diagnosing fungal infections.

Ethics Committee Approval: This study was approved by Ethics Committee of Mashhad University of Medical Science (Approval No: IR.MUMS.MEDICAL.REC.1399.730, Date: 12 - 10 - 2022).

Informed Consent: Written informed consent was obtained from the parents of the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.S.A.; Design – A.S.A., B.E.; Supervision – A.S.A., G.A.; Materials – G.A.; Data Collection and/or Processing – B.R., B.E.; Analysis and/or Interpretation – B.E., B.R.; Literature Search – B.R., D.S.F.; Writing – D.S.F.; Critical Review – A.S.A., G.A.

Acknowledgment: The authors thank Dr. N Zavar, Dr. Z Badiee, Dr. H Farhangi, Dr. M Mahdavi, and Mr. Jani for their cooperation in data accumulation.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This research was supported by the vice chancellor for research of Mashhad University of Medical Sciences.

REFERENCES

1. Barnes RA. Early diagnosis of fungal infection in immunocompromised patients. *J Antimicrob Chemother*. 2008;61(suppl 1):i3-i6. [CrossRef]
2. Ozsevik SN, Sensoy G, Karli A, et al. Invasive fungal infections in children with hematologic and malignant diseases. *J Pediatr Hematol Oncol*. 2015;37(2):e69-e72. [CrossRef]
3. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. [CrossRef]
4. Von Eiff M, Roos N, Schulten R, Hesse M, Zühlsdorf M, Van de Loo J. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration*. 1995;62(6):341-347. [CrossRef]
5. Caillot D, Mannone L, Cuisenier B, Couaillier JF. Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. *Clin Microbiol Infect*. 2001;7(suppl 2):54-61. [CrossRef]
6. Gereige RS, Laufer PM. Pneumonia. *Pediatr Rev*. 2013;34(10): 438-456; quiz 455. [CrossRef]
7. Pereda MA, Chavez MA, Hooper-Miele CC, et al. Lung ultrasound for the diagnosis of pneumonia in children: a meta-analysis. *Pediatrics*. 2015;135(4):714-722. [CrossRef]
8. Shah SN, Bachur RG, Simel DL, Neuman MI. Does this child have pneumonia? the rational clinical examination systematic review. *JAMA*. 2017;318(5):462-471. [CrossRef]
9. Stefanutti D, Morais L, Fournet JC, et al. Value of open lung biopsy in immunocompromised children. *J Pediatr*. 2000;137(2): 165-171. [CrossRef]
10. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med*. 2015;373(5):415-427. [CrossRef]
11. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary Zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis*. 2005;41(1):60-66. [CrossRef]
12. Alamdaran SA, Estilaee S, Farrokh D, Morovatdar N. Thoracic mass nature determination; what modality is better in pediatric age? *Int J Pediatr*. 2019;7(8):9921-9928.
13. Reissig A, Kroegel C. Sonographic diagnosis and follow-up of pneumonia: a prospective study. *Respiration*. 2007;74(5):537-547. [CrossRef]
14. Rodrigues-Pinto E, Lopes S, Principe F, Costa J, Macedo G. Pulmonary aspergillosis diagnosed by endoscopic ultrasound fine-needle aspiration. *Endosc Ultrasound*. 2016;5(1):58-60. [CrossRef]
15. Alamdaran SA, Heidarzadeh H, Zavvar SN, Badiee Z, Jaberi M, Ghasemi A. Presentation of sonographic features of pulmonary invasive fungal disease in six children with leukemia. *Int J Pediatr*. 2020;9(2):13203-13211.
16. Najgrodzka P, Buda N, Zamojska A, Marciniewicz E, Lewandowicz-Uszyńska A. Lung ultrasonography in the diagnosis of pneumonia in children—a metaanalysis and a review of pediatric lung imaging. *Ultrasound Q*. 2019;35(2):157-163. [CrossRef]
17. Lameh A, Seyedi SJ, Farrokh D, Lavasani S, Alamdaran SA. Diagnostic value of ultrasound in detecting causes of pediatric chest X-ray opacity. *Turk Thorac J*. 2019;20(3):175-181. [CrossRef]
18. Demi M, Prediletto R, Soldati G, Demi L. Physical mechanisms providing clinical information from ultrasound lung images: hypotheses and early confirmations. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2020;67(3):612-623. [CrossRef]
19. van Sloun RJG, Demi L. Localizing B-Lines in lung ultrasonography by weakly supervised deep learning, in-vivo results. *IEEE J Biomed Health Inform*. 2020;24(4):957-964. [CrossRef]
20. Panse P, Smith M, Cummings K, Jensen E, Gotway M, Jokerst C. The many faces of pulmonary aspergillosis: imaging findings with pathologic correlation. *Rad Infect Dis*. 2016;3(4): 192-200. [CrossRef]
21. Liu J, Ma HR, Fu W. Lung ultrasound to diagnose pneumonia in neonates with fungal infection. *Diagnostics (Basel)*. 2022; 12(8):1776. [CrossRef]
22. Grabala J, Grabala M, Onichimowski D, Grabala P. Possibilities of using ultrasound for diagnosis of invasive pulmonary mucormycosis–A case study. *Pol Ann Med*. 2017;24(2):224-227. [CrossRef]
23. Raffaella G, Lorenzo L, Elisabetta X, et al. Lung ultrasound to evaluate invasive fungal diseases after allogeneic hematopoietic stem cell transplantation. *Infect Chemother*. 2019;51(4):386-392. [CrossRef]
24. Choo JY, Park CM, Lee HJ, Lee CH, Goo JM, Im JG. Sequential morphological changes in follow-up CT of pulmonary mucormycosis. *Diagn Interv Radiol*. 2014;20(1):42-46. [CrossRef]

Thorac Res Pract. 2023; 24(6): 298-303 DOI: 10.5152/ThoracResPract.2023.23036

Original Article

Does Telerehabilitation for Coronavirus Disease 2019 Patients Discharged with Oxygen Shorten the Time of Weaning from Oxygen?

Sami Deniz[1], Celalettin Yılmaz[1], Onur Süneçli[2], Elmas Kuru Akyol[3]

[1]Department of Chest Diseases, Health Sciences University, Dr. Suat Seren Chest Diseases and Thoracic Surgery Research and Education Hospital, İzmir, Turkey
[2]Department of Physiotherapy, Health Sciences University, Dr. Suat Seren Chest Diseases and Thoracic Surgery Research and Education Hospital, İzmir, Turkey
[3]Department of Physical Medicine and Rehabilitation, Health Sciences University, Dr. Suat Seren Chest Diseases and Thoracic Surgery Research and Education Hospital, İzmir, Turkey

Cite this article as: Deniz S, Yılmaz C, Süneçli O, Kuru Akyol E. Does telerehabilitation for coronavirus disease 2019 patients discharged with oxygen shorten the time of weaning from oxygen? *Thorac Res Pract.* 2023;24(6):298-303.

Abstract

OBJECTIVE: Early pulmonary rehabilitation (PR) and acute and post-acute mobilization with telemonitoring and telerehabilitation (TR) have been recommended for coronavirus disease 2019 (COVID-19) patients. We aimed to compare the duration of weaning from oxygen in patients with hypoxemic COVID-19 who received PR and those who did not.

MATERIAL AND METHODS: This study was designed as a quasi-experimental study and was conducted on patients discharged with oxygen supplementation between December 2021 and May 2022. They were compared with patients who received PR and those who did not in terms of the duration of oxygen use.

RESULTS: A total of 61 patients (9 women in each group) completed the study. The mean age was 65 ± 12. Thirty patients underwent PR (group 1) and the remaining 31 patients were classified as control group (group 2). When the groups were compared in terms of duration of oxygen use, patients who performed PR were statistically significant shorter duration than those who did not (P = .012). In addition, PR improved their quality of life compared to group 2.

CONCLUSION: It was concluded that although PR has many indications, it is also effective, feasible, and safe in prolonged infections and it was thought that TR may also be effective as supervised PR.

KEYWORDS: COVID-19, pulmonary rehabilitation, telerehabilitation, oxygen supplementation, quality of life
Received: *March 31, 2023* ***Accepted:*** *August 14, 2023* ***Publication Date:*** *October 27, 2023*

INTRODUCTION

In December 2019, 27 cases of pneumonia of unknown origin were detected in Hubei.[1] With the number of infected people and severe pneumonia cases increasing, the World Health Organization (WHO) officially declared a pandemic in February 2020. Since then, different variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV) have been defined by the WHO.[2] Compared with patients infected with the alpha or delta variants, omicron patients were hospitalized significantly less often, required less intense respiratory support, and had a shorter length of stay.[3] National ensemble predicts that the number of daily coronavirus disease 2019 (COVID-19) hospital admissions will decrease.[4]

Studies have shown that oxygen support at discharge is safe and reduces mortality and hospital readmission in patients with hypoxemic COVID-19.[5,6] The use of modern technology has allowed us to facilitate discharge in patients with mild-to-moderate disease in a safe and appropriate manner in COVID-19.[7] Early pulmonary rehabilitation (PR) and mobilization in the acute and post-acute phase with telemonitoring and telerehabilitation (TR) have been recommended for COVID-19 patients.[8,9] Many recommendations regarding PR have been reported in the literature; however, these are not based on the experience of COVID-19 patients, so there is a need for an individualized approach and the use of behavior change strategies.[9]

In this study, we aimed to investigate the effect of TR on the duration of weaning from oxygen in hypoxic COVID-19 patients discharged with oxygen supplementation. The primary endpoint was to compare the duration of weaning from oxygen, and the secondary endpoint was to examine the change in quality of life.

MATERIALS AND METHODS

Study Design and Participants

This study was designed as a quasi-experimental study and was conducted in patients discharged with oxygen supplementation between December 2021 and May 2022. The study was approved by the Institutional Review Board

Corresponding author: Sami Deniz, e-mail: sami_deniz@yahoo.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

for Human Studies and Ethics Committee of University of Health Science Turkey, Dr Suat Seren Chest Diseases and Thoracic Surgery Research and Training Hospital (Approval Acceptance Number: 2020-KAEK-139) and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient.

We studied 127 patients who were hospitalized with hypoxemic COVID-19 (non-intensive care unit setting), of whom 15 patients did not give consent and 39 patients were excluded because they had concomitant respiratory diseases. These diagnoses were obtained from the hospital information management system and verified by patient self-report. In addition, 9 patients with other comorbidities were excluded (rheumatoid arthritis n = 1, pregnancy n = 1, uncontrolled hypertension n = 2, uncontrolled diabetes mellitus n = 2, cardiac arrhythmia n = 1, orthopedic disability n = 1, neurological disorders n = 1). These patients were assessed and verified by the relevant department. One patient was unable to complete the program due to unwillingness. Two patients were lost to follow-up due to relocation. Sixty-one hypoxemic patients with COVID-19 who were deemed clinically suitable to be discharged with oxygen supplementation were included. Patients were allocated 1:1 and divided into 2 groups: the intervention group (group 1) and the control group (group 2).

Inclusion Criteria

1. Patients >18 years of age with COVID polymerase chain reaction (PCR) (+) and radiologically compatible with COVID-19 pneumonia.
2. Patients discharged with oxygen supplementation.
3. Those able to communicate remotely.

Exclusion Criteria

1. Pregnancy or lactation.
2. Concomitant diseases (Chronic obstructive pulmonary disease [COPD] group B, C, D, uncontrolled or severe asthma, other respiratory diseases, cancer, immunological disorders, concomitant other infection diseases).
3. Orthopedic, neurological conditions that preclude participation in an exercise program.
4. History of unstable cardiovascular conditions such as cardiac arrhythmia, uncontrolled hypertension (HT), pulmonary hypertension, and uncontrolled diabetes mellitus (DM).
5. Thrombotic diseases.

Procedures

Demographic characteristics, comorbidities, and medical history were recorded in detail. Patients were examined for all systems. If any problem was identified during the examination, the relevant department was consulted. Blood samples were taken from each patient (liver and kidney function tests, glucose, D-dimer, ferritin, C-reactive protein, and blood cell count).

Health-related quality of life (HRQOL): This was assessed using the nationally validated version of the St George's Respiratory Questionnaire (SGRQ). The Hospital Anxiety and Depression Scale (HADs) was used to assess anxiety and depression separately. The Modified Medical Research Council (mMRC) dyspnea scale was used to assess the perception of dyspnea. All questions and assessments were carried out by a pulmonologist and all patients were assessed before and after PR.

Oxygen saturation follow-up: National Health Service guidelines suggest that unless there is a suspicion of CO_2 retention, arterial gases are not required and patients can be monitored using continuous peripheral arterial oxygen saturation (SpO_2).[10] At discharge, it was recommended that patients be monitored with daily pulse oximetry (PO) on their own. After discharge, patients were followed up by daily telephone calls to discuss their condition. If the patient was able to walk for 30 minutes without supplemental oxygen with an SpO_2 above 90%, it was recommended to wean them off oxygen during the day; if the SpO_2 was stable above 92% during the day at rest, the patients were called in for an arterial blood gas analysis (ABGa) in the hospital.

Arterial blood gas analysis: This was performed at rest on 100 µL of arterial blood taken from the radial artery (Nova Biomedical Critical Care Xpress, Waltham, Mass, USA). If SpO_2 was greater than 92% at rest on ABGa, the patient was completely weaned from oxygen. All interventions and assessments were reviewed by a pulmonologist.

Pulmonary Rehabilitation

Patients were informed about PR and trained by a physiotherapist and a specialist in physical and rehabilitation medicine at discharge; however, PR was not delivered in the hospital. Pulmonary rehabilitation consisted of treatment, education, self-management intervention, patient interview, exercise, and maintenance program. Home COVID-19 maintenance treatment and education with self-management interventions were provided. Patient education was provided with a booklet, healthy lifestyle education, family encouragement, and social activities. Patients were called by a physiotherapist at least twice a week to discuss the frequency and intensity of the exercises and to give motivational speeches about continuing the exercises. Patients were followed until they stopped using oxygen or completed the 8-week PR period. Pulmonary rehabilitation included breathing exercises (slow inhalation and exhalation through the nose and mouth, respectively, pursed-lip breathing, and diaphragmatic breathing), peripheral muscle training including lower and upper limb strength (initially warm-up, bed exercises, then low-intensity exercise, aerobic exercise, and stretching), bronchial hygiene techniques (postural drainage, and percussion), and secretion clearance. Warm-up exercises include shoulder shrugs and circles, side bends, knee lifts, ankle taps, and circles. Fitness exercises included marching on the spot, step-ups, walking, and jogging. Physical

MAIN POINTS

- We have shown that telerehabilitation (TR) can be implemented in post-infection conditions such as coronavirus disease 2019 and that TR can be as effective as pulmonary rehabilitation.
- Telerehabilitation is cost-effective and feasible.
- In particular, patients who had difficulties in transport to a hospital because of general health situations or socioeconomic problems are logical candidates for TR.

exercise was performed as aerobic exercise (low intensity, short duration, 3-5 sessions/week, 20-30 minutes per session). Strength training started with a reduced load and was repeated in the target muscle group 8-12 times, 1-3 sets/time, with 2 minutes rest between sets, at least 3 sessions/week for up to 8 weeks, depending on the patient's condition. The load was increased by 5%-10% each week. In addition, balance training (hands-free balance training, posture, flexibility, and rhythmic breathing) and activities of daily living (mobilization, dressing, undressing, toileting, and bathing) were recommended to be performed under supervision as much as possible. The program to be followed was completely individualized according to the patient's condition. Patients were encouraged to continue with the exercise program.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) Statistics (IBM Corp., Armonk, NY, USA). Group comparisons were made using a non-parametric test and, where appropriate, a *t*-test. Median (minimum, maximum) as well as mean ± SD and interquartile range (IQR) (Q1 and Q3) are presented for all variables. Repeated measures analysis of variance (ANOVA) and Mann–Whitney *U* test (comparison of post-pre values) were used to determine differences between groups for parametric and non-parametric tests, respectively. The duration of oxygen weaning in patients was assessed using the Kaplan–Meier method. For all statistical comparisons, the significance level was set at $\alpha = 0.05$ (probability of a type 1 error) and 2-sided. A *P*-value <.05 was considered statistically significant.

Table 1. Demographic Data of the Patients

	PR (+)		PR (−)		
Variables	**Mean ± SD**	**Median (minimum, maximum)**	**Mean ± SD**	**Median (minimum, maximum)**	***P***
Age*	63 ± 12	64 (35, 89)	67 ± 12	70 (39, 89)	.165
Gender (female)	62 ± 11	64 (37, 88)	68 ± 14	70 (35, 81)	.112
Smoking*	34 ± 21	40 (39, 89)	40 ± 18	40 (5, 80)	.401
PR duration	24 ± 13	21 (10, 60)			NA
Use of O_2 (days)	28.7 ± 21.9	21 (10, 90)	41.1 ± 26.6	30 (15, 90)	NA
mMRC	3 ± 1	4 (2, 4)	4 ± 0	4 (3, 4)	.054
HADa*	7.9 ± 5.1	7.5 (1, 19)	9.6 ± 5.8	9 (1, 21)	.239
HADd	7.7 ± 4.6	6 (2, 16)	10 ± 6.3	8 (2, 21)	.210
Symptom	20.3 ± 19.4	19.7 (0, 56.3)	23.3 ± 23.2	21.3 (0, 88)	.678
Activity	79.7 ± 16.9	82.5 (47.3, 100)	82.4 ± 12.6	86.3 (55.1, 100)	.813
Impact	43.6 ± 15.6	39.8 (20.8, 78.6)	45.8 ± 14.2	46.4 (18.2, 80.5)	.248
Total*	50.5 ± 14.2	48.1 (28, 79)	53.2 ± 12.8	54.3 (29, 79)	.454
AST*	27 ± 12	26 (7, 53)	22 ± 13	18 (9, 71)	.188
ALT	64 ± 47	43 (8, 178)	32 ± 28.5	23 (9, 143)	**.001**
Urea	47 ± 17	43 (18, 88)	56 ± 32	51 (16, 158)	.327
Creatinine*	0.82 ± 0.25	0.8 (0.4, 1.3)	0.9 ± 0.28	0.8 (0.4, 1.6)	.226
Ferritin	518 ± 387	411 (16, 1799)	480 ± 458	318 (70, 2299)	.363
D-dimer	952 ± 786	720 (259, 4369)	1421 ± 959	1100 (404, 4500)	**.013**
CRP	4.4 ± 4.0	3.4 (0.2, 14.3)	3.7 ± 4.3	2.1 (0.1, 17.2)	.427
WBC ($\times 10^3$)	10.7 ± 4.0	9.4 (5.0, 19.5)	10.6 ± 3.7	11 (4.8, 21.5)	.971
Hemoglobin*	12.3 ± 1.4	12.7 (8.3, 14.9)	12.2 ± 2.3	12 (8.8, 18.5)	.863
Hematocrit*	36.4 ± 4.1	37 (28, 44)	36.7 ± 6.9	36 (22, 54)	.876
Neutrophil ($\times 10^3$)*	8.8 ± 3.9	8.0 (1.8, 17.0)	8.4 ± 3.4	8.1 (4.2, 19.4)	.754
Lymphocyte ($\times 10^3$)	1.2 ± 0.8	1.2 (0.3, 3.8)	1.2 ± 0.5	1.2 (0.3, 2.3)	.670
pO_2	51 ± 4	52 (40, 58)	49 ± 6	51 (33, 59)	.453
pCO_2	36 ± 5	35 (29, 48)	40 ± 9	37 (26, 72)	.145
SpO_2	87 ± 3	87 (76, 92)	84 ± 6	86 (61, 93)	.182
HCO_3*	26 ± 3	26 (20, 33)	28 ± 5	27 (20, 43)	.360

*Normal distribution, if variables were fitted normal distribution, the means of variables were compared, if not, the medians of variables were compared. Statistically significant results are given in bold.HADa and d, hospital anxiety and depression; mMRC, Modified Medical Research Council Dyspnea Scale.

RESULTS

A total of 61 patients (9 women in each group) completed the study (1 patient who was unable to complete the program and 2 patients who were lost to follow-up were 67, 71, and 63 years old, respectively). The mean age was 65 ± 12. Thirty patients were performed PR (group 1) and the remaining 31 patients were classified as group 2. Significance was not found in terms of smoking history between groups [smokers, non-smokers, and ex-smokers (P = .963). The patients' comorbidities were similar in each group (P = .489). There was no significance in terms of basic demographic data of the patients and is presented in Table 1.

Patients who received PR improved their HRQOL. While significant changes were observed in the impact, activity, and total SGRQ domains, no significance was detected in the mMRC and HAD assessments (Table 2, Figure 1).

When the groups were compared in terms of duration of oxygen use, patients who performed PR were statistically significantly shorter than those who did not (Figure 2).

DISCUSSION

The results of the study provide the benefits of exercise interventions delivered by TR for recently discharged from hospital with oxygen supplementation in hypoxemic patients with COVID-19. Patients who received TR improved their quality of life and were weaned oxygen off in a statistically significantly shorter time compared to patients who did not receive TR.

A randomized controlled trial (RCT) of 120 patients showed the superiority of TR over no rehabilitation for 6 minute walking test (6MWD), lower limb muscle strength, and HRQOL.[11] In our study, TR resulted in an improvement in patients' quality of life. Cardiorespiratory exercise is dependent on adequate oxygen transport by the respiratory and circulatory systems and efficient use of oxygen. Skeletal muscle, like all tissues, requires a constant supply of oxygen at a rate that keeps pace with changing metabolic demands. These needs increase proportionally with increasing exercise intensity.[12] Although we did not measure muscle strength and exercise capacity, the fact that oxygen saturation improved in the PR-treated

Table 2. Comparison of Variables Before and After Pulmonary Rehabilitation

	PR (+)		PR (–)		
Variables	**Mean**	**Median (Q1, Q3)**	**Mean**	**Median (Q1, Q3)**	***P***
mMRC	−1.6	−2 (−2, −1)	−1.19	−1 (−2, −1)	.109
HADa	−3.83	−3 (−5, −1)	−3.9	−3 (−7, 0)	.794
HADd	−3.77	−3 (−5, −2)	−4.1	−3 (−7, −1)	.664
Symptom	−5.5	−1.9 (−10, 0)	0.1	0 (−6, 0.6)	.086
Activity*	−28.9	−25.4 (−44, −18)	−17.7	−17 (−26, −4)	**.039**
Impact*	−24.8	−22 (−31, −15)	−12.5	−13 (−20, −6)	**.002**
Total*	−23.3	−23 (−31, −15)	−12.2	−13.7 (−21, −2)	**.001**
AST	−8.9	−4 (−17, 0)	−4.5	−2 (−7, 1)	.083
ALT	−37.8	−28 (−49, −9)	−16	−7 (−20, −2)	**.005**
Urea	−18.7	−19 (−30, −8)	−16.8	−9 (−27, −2)	.296
Creatinine	−0.01	0 (−0.1, 0.1)	−0.02	0 (−0.1, 0.1)	.100
Ferritin	−314	196 (−461, −107)	−134	−95 (−271, −11)	.051
D-dimer	22	33 (−237, 378)	−174	−118 (−896, 268)	.180
CRP	−2.7	−1.6 (−5.4, −0.1)	−1	−0.4 (−1.6, −0.3)	.061
WBC ($\times 10^3$)*	−2.3	−1.8 (−4.8, −0.4)	−1.7	−1.5 (−4.7, −0.1)	.571
Hemoglobin*	0.14	0.5 (−0.5, 1)	−0.07	−0.1 (−0.7, 1)	.578
Hematocrit	1.23	2 (−1, 3)	0.59	0 (−2, 4)	.400
Neutrophil ($\times 10^3$)*	−3.4	−3.6 (−5.6, −0.8)	−1.99	−1.8 (−4.6, 0.2)	.143
Lymphocyte ($\times 10^3$)	0.8	0.7 (0.4, 1.1)	0.34	0.3 (−0.2, 0.7)	**.031**
pO_2*	22.48	23.5 (14.1, 29.6)	14.7	14.5 (5.4, 19.6)	**.016**
pCO_2	−0.08	−0.65 (−3.2, 3)	−1.24	0 (−5, 5)	.902
SpO_2*	7.67	7.9 (5.3, 10.1)	7.54	6.1 (3, 11.7)	.933
HCO_3*	−1.77	−2.4 (−4.8, 1)	−2.77	−1.5 (−5, 0.5)	.709

*Normal distribution, if variables were fitted normal distribution, the means of variables were compared, if not, the medians of variables were compared.Statistically significant results are given in bold. HADa and d, hospital anxiety and depression; mMRC. Modified Medical Research Council Dyspnea Scale.

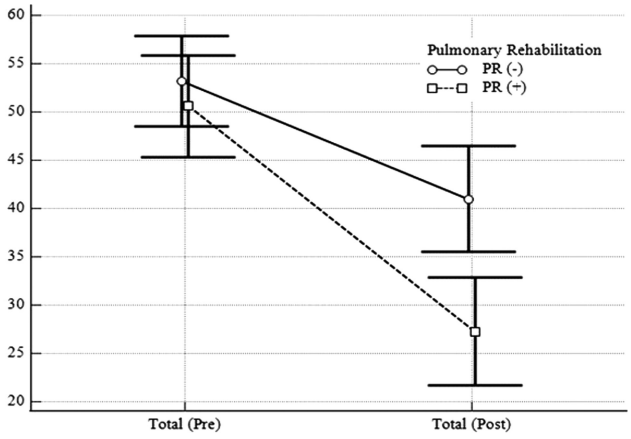


Figure 1. Comparison of St George's Respiratory Questionnaire total values between groups.

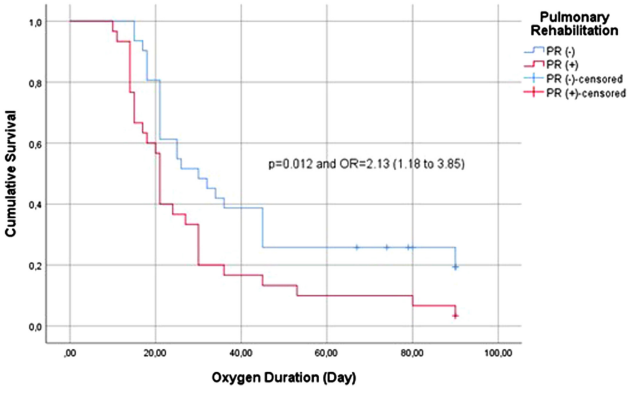


Figure 2. Comparison of duration of weaning off oxygen between groups.

patients in a shorter period of time may indirectly translate into improved exercise capacity and muscle strength.

With pandemic situations, technology has become an integral part of our lives. Telerehabilitation, which is a part of technology, is promising and cost-effective, and it facilitates patient participation in PR. In addition, TR may be safe and feasible, and it leads to a reduction in the need for conventional PR; furthermore, TR should be considered during the COVID-19 pandemic in COPD.[13] Meanwhile, TR has also been performed in patients with COVID-19. A review showed that TR influences physical activity and positive clinical outcomes and is similar to conventional PR in patients with COVID-19.[14]

An RCT, consisting of a small sample size, was carried out on 36 patients with COVID-19 in the acute stage, with only 1 week of TR. The 6-minute walk test, multidimensional dyspnea-12, 30-second sit-to-stand test, and Borg scale were evaluated. It was found that all 3 variables changed significantly in favor of the intervention group.[15] Compared to our study, we delivered TR varying between 1 and 8 weeks. Similarly, only 1 week of TR was effective, safe, and feasible as in the study and it paved the way for weaning from oxygen in our study. Patients in our study also improved their quality of life. In addition, patients who were weaned off oxygen for a shorter time showed a greater improvement in HRQOL, as expected. Telerehabilitation can improve exercise capacity, dyspnea, and HRQOL and does not significantly increase adverse events.[16] We did not observe any adverse events in our patients until the end of the study in each group.

A study conducted in patients with COPD, 12 weeks, 2 sessions per week, outpatient PR, showed that oxygen uptake, oxygen pulse (mL/beat), and work rate increased significantly in favor of the interventional group, but the oxygen saturation of the patients did not change compared to before and after PR (pre- and post-SpO_2 93.9%-94%).[17] Another study performed in a similar population showed that participants significantly improved oxygen saturation and exercise capacity (6MWT).[18] Although participants had different diagnoses, PR improved oxygen saturation and HRQOL in patients with COVID-19 in our study.

A case report showed that a patient with post-acute COVID-19, 80 years old, reported improvement in gait speed, exercise capacity, and oxygen saturation after PR. The patient's oxygen saturation was 88% on the first day and reached 98% after 10 days of PR.[19] Similarly, the earliest weaning time from oxygen was 10 days in group 1 and 15 days in group 2.

Patients with COVID-19 can suffer from various dysfunctions such as impaired lung function, physical deconditioning, muscle weakness, delirium, and other cognitive impairments.[20] Previously defined in patients with COPD, PR improves dyspnea, health status, and exercise tolerance.[21] Telerehabilitation is recommended for patients with COVID-19 to reduce viral spread, but there is little information on how best to do this in these patients.[22] Our study showed that TR improved the quality of life and oxygenation in patients with COVID-19 as in patients with COPD.

CONCLUSION

It was concluded that although PR has many indications, it is also effective, feasible, and safe in prolonged infections and it was thought that TR may be also effective as supervised PR.

Ethics Committee Approval: The study was approved by the Institutional Review Board for Human Studies and Ethics Committee of University of Health Science Turkey, Dr Suat Seren Chest Diseases and Thoracic Surgery Research and Training Hospital (Approval Acceptance Number: 2020-KAEK-139) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.D.; Design – S.D.; Data Collection and/or Processing – S.D., C.Y., E.K.A., O.S.; Analysis and/or Interpretation – S.D.; Literature Search – C.Y., E.K.A., O.S.; Writing Manuscript – S.D.; Critical Review – S.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. *Pneumonia of Unknown Cause ¿ China: Disease Outbreak News*. Geneva: World Health Organization. Available at: https ://www.who.int/csr/don/05-january-2020-pneumonia-of-unk own - cause-china/en/
2. World Health Organization. *Coronavirus (COVID-19) Dashboard*. Available at: https://covid19.who.int. Accessed March 13, 2022.
3. Christensen PA, Olsen RJ, Long SW, et al. Signals of significantly increased vaccine breakthrough, decreased hospitalization rates, and less severe disease in patients with coronavirus disease 2019 caused by the omicron variant of severe acute respiratory syndrome coronavirus 2 in Houston, Texas. *Am J Pathol*. 2022;192(4):642-652. [CrossRef]
4. *COVID-19 Forecasts: Hospitalizations*. Centers for Disease Control and Prevention (CDC); 2023. Available at: https://ww w.cdc.gov/coronavirus/2019-ncov/science/forecasting/hospital izations-forecasts.html
5. Banerjee J, Canamar CP, Voyageur C, et al. Mortality and readmission rates among patients with COVID-19 after discharge from acute care setting with supplemental oxygen. *JAMA Netw Open*. 2021;4(4):e213990. [CrossRef]
6. Dinh A, Mercier JC, Jaulmes L, et al. Safe discharge home with telemedicine of patients requiring nasal oxygen therapy after COVID-19. *Front Med (Lausanne)*. 2021;8(8):703017. [CrossRef]
7. O'Carroll O, MacCann R, O'Reilly A, et al. Remote monitoring of oxygen saturation in individuals with COVID-19 pneumonia. *Eur Respir J*. 2020;56(2):2001492. [CrossRef]
8. de Sire A, Andrenelli E, Negrini F, Negrini S, Ceravolo MG. Systematic rapid living review on rehabilitation needs due to COVID-19: update as of April 30th, 2020. *Eur J Phys Rehabil Med*. 2020;56(3):354-360. [CrossRef]
9. Goodwin VA, Allan L, Bethel A, et al. Rehabilitation to enable recovery from COVID-19: a rapid systematic review. *Physiotherapy*. 2021;111:4-22. [CrossRef]
10. Radiometer. ABL90 flex blood gas analyzer 2020. https://ww w.radiometer.com/en/products/blood-gas-testing/abl90-flex-bl ood-gas-analyzer Accessed 10 Jun 2020; 2020.
11. Li J, Xia W, Zhan C, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax*. 2022;77(7):697-706. [CrossRef]
12. Burtscher M. Exercise limitations by the oxygen delivery and utilization systems in aging and disease: coordinated adaptation and deadaptation of the lung-heart muscle axis – A mini-review. *Gerontology*. 2013;59(4):289-296. [CrossRef]
13. Taito S, Yamauchi K, Kataoka Y. Telerehabilitation in subjects with respiratory disease: a scoping review. *Respir Care*. 2021;66(4):686-698. [CrossRef]
14. Suso-Martí L, La Touche R, Herranz-Gómez A, Angulo-Díaz-Parreño S, Paris-Alemany A, Cuenca-Martínez F. Effectiveness of telerehabilitation in physical therapist practice: an umbrella and mapping review with meta-meta-analysis. *Phys Ther*. 2021;101(5):pzab075. [CrossRef]
15. Rodriguez-Blanco C, Gonzalez-Gerez JJ, Bernal-Utrera C, Anarte-Lazo E, Perez-Ale M, Saavedra-Hernandez M. Short-term effects of a conditioning telerehabilitation program in confined patients affected by COVID-19 in the acute phase. A pilot randomized controlled trial. *Medicina (Kaunas)*. 2021;57(7):684. [CrossRef]
16. Vieira AGDS, Pinto ACPN, Garcia BMSP, Eid RAC, Mól CG, Nawa RK. Telerehabilitation improves physical function and reduces dyspnoea in people with COVID-19 and post-COVID-19 conditions: a systematic review. *J Physiother*. 2022;68(2):90-98. [CrossRef]
17. Lan CC, Chu WH, Yang MC, Lee CH, Wu YK, Wu CP. Benefits of pulmonary rehabilitation in patients with COPD and normal exercise capacity. *Respir Care*. 2013;58(9):1482-1488. [CrossRef]
18. Santos LM, Pedro PI, Dias A, Forte CB, Raposo P, Rodrigues MF. Relationship between dyspnea/oxygen saturation and leg discomfort/6-minute walking distance in patients with COPD participating in pulmonary rehabilitation. *Pulmonology*. 2019;25(6):357-360. [CrossRef]
19. Shan MX, Tran YM, Vu KT, Eapen BC. Postacute inpatient rehabilitation for COVID-19. *BMJ Case Rep*. 2020;13(8):e237406. [CrossRef]
20. Pan American Health Organization (PAHO). Rehabilitation considerations during the COVID-19 outbreak; 2020. Available at: https://iris.paho.org/handle/10665
21. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease*; 2022. Available at: www.goldcopd.org
22. Holland AE, Cox NS, Wolloff LH, et al. Defining modern pulmonaryrehabilitation. Official american thoracic society workshop report. Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc*. 2021;18(5):e12-e29.

Thorac Res Pract. 2023; 24(6): 304-308 DOI: 10.5152/ThoracResPract.2023.23032

Original Article

Comparison of Self-Efficacy and Problem-Solving Skills Between Women with Asthma and Healthy Controls: A Cross-Sectional Study

Melissa Köprülüoğlu[1], İlknur Naz[1], Büşra Aktaş[1], Berna Kömürcüoğlu[2], Derya Özer Kaya[1]

[1]Department of Physiotherapy and Rehabilitation, İzmir Katip Celebi University Faculty of Health Sciences, İzmir, Turkey
[2]Chest Diseases Clinic, Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, University of Health Sciences, İzmir, Turkey

Cite this article as: Köprülüoğlu M, Naz İ, Aktaş B, Kömürcüoğlu B, Özer Kaya D. Comparison of self-efficacy and problem-solving skills between women with asthma and healthy controls: A cross-sectional study. *Thorac Res Pract.* 2023;24(6):304-308.

Abstract

OBJECTIVE: Problem-solving skills and self-efficacy are among the topics that are frequently investigated in people with various chronic conditions. However, there are limited studies on asthma patients. Our study aims to compare self-efficacy and problem-solving skills in asthma patients and healthy controls.

MATERIAL AND METHODS: We included 23 women with asthma [age: 39 (34-56) years] and 23 healthy controls [age: 42 (30-55) years] in the study. Participants' sociodemographic and disease-related characteristics, Asthma Control Test, and the Modified Medical Research Council Dyspnea Scale scores were recorded. We examined problem-solving skills with the Problem-Solving Inventory and self-efficacy with General Self-Efficacy Scale. We compared groups with the chi-square test, Mann–Whitney *U*-test, and Independent Sample *t*-test.

RESULTS: Age, body mass index, educational status, marital status, and occupational status were similar among the groups ($P > .05$). However, smoking was significantly higher in healthy controls ($P < .05$). It was found that women with asthma had worse self-efficacy and problem-solving skills compared to healthy controls ($P < .05$).

CONCLUSION: These results showed that there may be problems in socio-cognitive skills associated with the disease. Our study focused on the possibility that female asthma patients may have low levels of self-efficacy and problem-solving skills. Therefore, health professionals designing the rehabilitation program should take these skills into account while conducting the assessment as they may be useful in developing an efficient rehabilitation program.

KEYWORDS: Asthma, women, self-efficacy, problem-solving
Received: *April 6, 2023* ***Accepted:*** *August 15, 2023* ***Publication Date:*** *October 27, 2023*

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways in which many cells and cellular elements play a role. It progresses with exacerbations and presents with many respiratory symptoms such as shortness of breath, chest tightness, and cough.[1] The primary goal of healthcare professionals in treatment is to control symptoms during the disease process.[2] The integration of self-management strategies in disease treatment is one of the key aspects stressed in the asthma guidelines. Self-management in asthma refers to the actions taken by patients to monitor the disease situation, control the disease symptoms, and avoid exacerbations.[2] A Cochrane review showed that patients with asthma who were trained in asthma management, periodically under medical supervision, and who had an action plan for disease management had fewer emergency applications, fewer hospital admissions, improved lung function, and peak expiratory flow, had less symptoms, and used less frequent rescue medication during the disease process.[3] Experts in the National Asthma Education and Prevention Program expert panel underlined that a self-management program should include approaches for cognitive components in asthma patients.[2] Experts mentioned that the improvement of self-efficacy and problem-solving skills may also be used as a strategy to manage disease in addition to disease knowledge and action.[2] The generic set of abilities identified by Lorig and Holman[4] for effective self-management includes problem-solving, decision-making, resource utilization, creating a partnership between patients and healthcare providers, and taking action. The development of these abilities boosts self-efficacy.

Self-efficacy is a concept that has become a main topic of discussion following Bandura's Social Cognitive Theory. According to this theory, self-efficacy is an important psychosocial parameter emphasizing that a person's belief or confidence is a powerful indicator of the initiation and maintenance of future behavior.[5] Self-efficacy theory identifies that the power of the belief in one's capacity, motivation, and behavior can affect outcomes. Furthermore, the theory includes explanations that enhanced self-efficacy will pave the way for improved behaviors, motivation, thought patterns, and emotional well-being.[6] The improvement of self-efficacy often comes to the fore as strengthening the patient's physiological and psychosocial aspects and being a part of the patient's self-management criteria.[7]

Corresponding author: Melissa Köprülüoğlu, e-mail: kopruluoglumelissa@gmail.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Along with self-efficacy, the problem-solving ability is a crucial component of a healthy life process and is crucial for the management of stressful situations. Problem-solving skill contains the personal context and barriers of patients' lives and is a crucial step for successful disease management.[8] Advanced problem-solving skills are among the key elements in disease management and can provide positive outcomes.[9]

Self-efficacy and problem-solving skills are among the topics frequently in the adolescent group; however, there are only limited studies evaluating these concepts in adult asthma patients.[10-12] The aforementioned studies have different characteristics of the aforementioned problem-solving skill which is a metacognitive skill in terms of evaluating the problem-solving skills based on mathematics in the adolescent group. Additionally, self-efficacy examined in the studies has been reflected in asthma-specific self-efficacy. Uncertainty exists regarding general self-efficacy and problem-solving skills in adult asthma. In addition, one potential factor affecting these cognitive variables is gender.[13] Women are more likely to develop asthma after puberty, and it worsens more quickly. Additionally, Pignataro et al[14] indicated that women with asthma have more symptoms, and more rescue medication usage results in reduced quality of life than in men. This gender difference may affect psychocognitive skills. However, to the best of our knowledge, there is no study that investigated self-efficacy and problem-solving skills among women with asthma. Most of the studies examined self-efficacy and problem-solving skills in adolescent asthma participants and investigated disease-related self-efficacy but not focused on women. Therefore, our purpose is to examine the self-efficacy and problem-solving skills in women with asthma and determine if there are any differences in self-efficacy and problem-solving skills between women with asthma and healthy controls. We hypothesized that women with asthma have poor self-efficacy and problem-solving skills.

MATERIAL AND METHODS

We carried out our cross-sectional study between April and June 2022 at the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital in İzmir, Turkey. All of the participants in our study provided informed written consent. The Ethics Committee of İzmir Katip Çelebi University approved the study protocol (Approval Number: 114). We performed our study following the principles of the Helsinki Declaration.

MAIN POINTS

- Self-efficacy and problem-solving skills play a crucial role in the self-management of chronic diseases such as asthma.
- Most of the studies that examined the self-efficacy and problem-solving skills in asthma had adolescent participants and investigated disease-related self-efficacy but did not focus on women.
- Our aim is to examine the self-efficacy and problem-solving skills in women with asthma and determine if there are any differences in self-efficacy and problem-solving skills between women with asthma and healthy controls.
- We found that the self-efficacy and problem-solving skills of women with asthma deteriorated compared to healthy controls.

Participants

We selected the study participants according to the inclusion and exclusion criteria among patients who applied to the outpatient clinic in Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital between April and June 2022. We included the women diagnosed with bronchial asthma according to GINA criteria[1] by a physician who is a specialist in chest diseases, on regular medical treatment, and aged 18-65 years who volunteered to participate in our study. We included the study participants for control groups as follows: volunteering to participate, being a woman aged between 18 and 65 years, and having no pulmonary disease. The healthy control group consisted of hospital staff and patient relatives. After explaining the purpose and content of the study to the volunteers, those who wanted to participate were included in the control group. We excluded all participants who were unable to understand the Turkish commands, had psychiatric, musculoskeletal, and neurological disorders, symptomatic heart disease, or any kind of malignancy that could affect variables.

Outcome Measures

Before the assessment, we recorded participants' information such as sociodemographic, physical, and clinical variables, respiratory symptoms (cough, dyspnea, sputum), asthma control status, and dyspnea severity. We used the Asthma Control Test for asthma control status and the Modified Medical Research Council (mMRC) Dyspnea Scale for dyspnea severity. Following, we assessed self-efficacy levels by the General Self-Efficacy Scale and problem-solving skills by the Problem-Solving Inventory.

General Self-Efficacy Scale

The original 23-item form of the scale was developed by Sherer et al.[15] The Turkish adaptation, validity, and reliability study of the scale was performed by Yildirim and İlhan.[16] The scale includes the main question "How well does it describe you?" and all of the items are scored on a 5-point Likert-type scale. The total score varies between 17 and 85. A higher score indicates better self-efficacy.

Problem-Solving Inventory

Problem-Solving Inventory developed by Heppner and Petersen[17] is a self-report scale that measures an individual's self-perception about problem-solving skills. The inventory consists of 32 items, and a Likert-type scale is scored between 1 and 6 (1 = I always act like this and 6 = I never act like this). The total score varies from 32 to 192. A high total score on the scale indicates inadequate problem-solving skills.[18]

Asthma Control Test

The Asthma Control Test is a self-reported questionnaire consisting of 5 items and scores from 0 to 5. It is used to identify patients with insufficient control. As an assessment tool, the patient uses day and night symptom frequency, activity limitation, use of medication, and self-perception of asthma control. The control status of the patient is determined by summing the scores. The maximum score is 25, and the

minimum score is 5. A score of 19 and below indicates that the disease is not under good control.[19] Its Turkish adaptation was made by Uysal et al.[20]

Modified Medical Research Council Dyspnea Scale

It measures perceived dyspnea. It is a categorical scale scored 0-4 points, and patients choose the statement that best describes their dyspnea level out of 5 statements about dyspnea.[21]

Statistical Analysis

Before the study started, the pilot study was performed with 10 patients with asthma and 9 healthy controls. The sample size was calculated at a minimum of 23 per group for a power of 0.80 with a 5% type 1 error and 0.748 effect size in a 2-sided test at the 0.05 level (G*Power, ver. 3.1., Universität Düsseldorf, Düsseldorf, Germany). The main results did not include data from the pilot study.

All analyses were performed using Statistical Package for the Social Sciences 20.0 (IBM Inc., Armonk, NY, USA) Windows statistics software. The normality was checked by Shapiro–Wilk tests. Continuous variables were presented as mean ± standard deviations or median (interquartile range), and categorical variables were presented as percentages (%). Mann–Whitney *U*-test and Independent Sample *t*-test were used to compare the groups. The chi-square test was performed for comparison of the categorical variables. A *P* value of <.05 was considered statistically significant.

Table 1. Sociodemographic Characteristics of Participants

	Asthma Patients (n = 23)	Asymptomatic Controls (n = 23)	*P*
Age, years	39 (34-56)	42 (30-55)	.178
Weight, kg	63 (53-80)	71 (56-75)	.635
Height, cm	165 (160-169)	165 (161-166)	.733
Body mass index, kg/m^2	23.05 (20.47-27.82)	26.07 (20.75-27.95)	.635
Educational status, n (%)			
Primary school	4 (17.39)	3 (13)	.541
High school	5 (21.74)	6 (26.09)	
University	3 (12.04)	6 (26.09)	
Postgraduate	11 (48.83)	8 (34.82)	
Marital status, n (%)			
Single	6 (26.09)	8 (34.78)	.380
Married	14 (61.87)	13 (56.52)	
Divorced	3 (12.04)	2 (8.70)	
Occupational status, n (%)			
Employed	18 (78.26)	21 (91.30)	.812
Unemployed	5 (21.74)	2 (8.70)	
Retired	0	0	
Smoking status, n (%)			
Smoker	3 (12.04)	10 (43.48)	
Ex-smoker	10 (43.48)	8 (34.78)	.041*
None	10 (43.48)	5 (21.74)	
Smoking consumption (pack-years)	7 (4-10)	20 (13-32)	.037*

Values are expressed as median (1 and 3 quartiles) or n (%).
Mann–Whitney *U*-test and chi square test were used.
*$P < .05$.

RESULTS

We included 23 women with asthma (median age: 39 years) and 23 healthy controls (median age: 42 years) in the study. Participants had similar sociodemographic characteristics such as age, weight, height, body mass index, educational status, marital status, and employment status except for smoking variables ($P < .05$). Participants in the control group were more active smokers and had higher pack years ($P > .05$) (Table 1).

The clinical and disease-related characteristics of asthma patients are summarized in Table 2. Most patients with an average of 4.66 ± 3.05 years of diagnosis had partially controlled asthma (66.7%) and dyspnea (85.7%) (Table 2). Moreover, the mMRC scores of the patients were between 0 and 2 and there were no patients with scores 3 and 4 (Table 2).

In terms of problem-solving skills and self-efficacy, asthma patients scored better on problem-solving skills and lower on self-efficacy when compared to healthy controls ($P < .05$) (Table 3).

DISCUSSION

In our study, we compared the self-efficacy and problem-solving skills of women with asthma with those of the control

Table 2. Clinical and Disease-Related Characteristics of Asthma Patients

	Asthma Patients (n = 23)
Time of diagnosis, years	4.66 ± 3.05
Symptoms, n (%)	
Breathlessness	18 (78.26)
Cough	8 (34.78)
Phlegm	0 (0)
Chest pain	7 (30.43)
Number of asthma attacks in last year, n	1 (0/2)
mMRC dyspnea scores, 0-4	
0	3 (12.04)
1	13 (57.53)
2	7 (30.43)
Asthma control group, n (%)	
Well-controlled asthma	8 (34.78)
Partially controlled asthma	14 (61.87)
Uncontrolled asthma	1 (4.35)

Values are expressed as mean ± standard deviation or n (%).
mMRC, Modified Medical Research Council.

Table 3. Problem-Solving and Self-Efficacy Scores of Participants

	Asthma Patients (n = 23)	Asymptomatic Controls (n = 23)	*P*
Problem-solving scores, 35-210	98 (74/112)	72 (65/84)	.047*[a]
Self-efficacy scores, 0-85	48.5 ± 6.85	58.8 ± 7.62	.036*[b]

Data presented as median (1 and 3 quartiles) and mean ± standard deviation.
[a]Mann–Whitney *U*-test.
[b]Independent Sample *t*-test.

group. We found that the self-efficacy and problem-solving skills of women with asthma deteriorated compared to the healthy controls.

Patients with asthma, especially those who have poor asthma control and exacerbations, may encounter intermittent, temporal, and prolonged hypoxemia periods.[22] This clinical characteristic of asthma may result in hypoxia-related hippocampal neurotoxicity and end in poor cognition.[23] Although it has been argued in recent studies that cognitive impairment may be associated with asthma, the mechanism of cognitive impairment in asthma has not been understood. Rhyou and Nam[24] found that cognitive impairment in adult asthma patients was frequently observed (44.1%) and older adults experienced more prevalent. Additionally, it implies that low cognition may be linked to depression and anxiety.[25] It may indicate how these fundamental cognitive impairment mechanisms and the processes associated with them may impact socio-cognitive abilities including self-efficacy and problem-solving abilities.

Self-efficacy reflects individuals' belief in their ability to achieve goals and accomplish tasks, and it has a subjective feature. In other words, it expresses how the person perceives their capacity to deal with the challenges they will face.[26] Considering these definitions, it is undeniable that self-efficacy is one of the key parts of chronic disease management. It was said that self-efficacy might change by the experienced emotions and individual behaviors when managing exacerbations in asthma patients.[27] Melgarejo González-Conde et al[28] reported that 40% of the participants had low self-efficacy in their study evaluating self-efficacy in adolescents with asthma. There are no clear results in the literature that self-efficacy was affected in adult asthma patients compared to the healthy control group. In comparison to healthy controls, we discovered that women with asthma had lower levels of self-efficacy. To the best of our knowledge, our study was the first to compare asthma patients with the control group for self-efficacy. Therefore, this outcome might serve as a new and important foundation for future studies.

One of the criteria defined by Lorig and Holman[4] among a group of abilities that have been successfully used to manage chronic diseases and enhance the disease management process is problem-solving skills.[29] People with chronic lung diseases are reported to have cognitive problems, such as impairments in problem-solving skills, which have an impact on disease management.[30] When we searched the literature, no study examined the problem-solving skills of asthma patients. In our study, we observed that the perceived problem-solving skills of asthmatic women were lower compared to the healthy controls. More research, however, is required to corroborate these findings because problem-solving skills are involved in various contexts.

Our participants consisted of young adults of the same age, physical characteristics, and educational, marital, and occupational status except for smoking status between asthma and control groups. In our study, women with asthma were relatively recently diagnosed, had few attacks in the previous year, had partially low mMRC scores, and had good asthma control. However, most of the patients experienced dyspnea symptoms. Despite the comparatively good disease-related characteristics, the asthma group's self-efficacy and problem-solving skills were lower than those of the healthy controls. In the last 5 years, research has underlined the importance of enhancing and promoting self-efficacy and problem-solving in the practice of basic healthcare.[29] Therefore, if possible, after diagnosis, both self-efficacy and problem-solving skills should be taken into account and evaluated.

Our study had some limitations. In this study, we investigated only sociodemographic variables such as age, educational status, and occupational status. Assessment of participants' functional status and getting information about daily living activities, physical activity status, and challenges in daily life might help to interpret these differences in detail. Additionally, our study did not look into psychocognitive characteristics such as anxiety level, decision-making ability, and asthma-self efficacy did not investigate in our study. These variables might be important to clarify the mechanism of deterioration of self-efficacy and problem-solving skills in women with asthma. The other limitation was that we only included adult women with asthma in this study. However, we did not ask the participants about their menopausal status. Menopausal status may be a parameter that influences self-efficacy and problem-solving skills. Also, the sample size of our study could have been larger. In future studies, these limitations might be considered. Besides, we did not analyze the factors related to self-efficacy and problem-solving skills in women with asthma because of the small sample size for correlation analysis. First of all, the sample size of our study could have been larger. It should investigate these factors in future studies.

CONCLUSION

Self-efficacy and problem-solving skills play a crucial role in the self-management of chronic diseases such as asthma. In chronic disease management, the assessment and improvement of self-efficacy and problem-solving skills constitute the biggest steps to be taken in the self-management process within the scope of providing the patient with healthy life behaviors such as exercise and nutrition. Our study showed that self-efficacy and problem-solving skills were worse in women with asthma compared to the healthy control group. Our study, which we conducted on women asthma

patients considering that these parameters will vary specifically for gender, underlines the need to consider self-efficacy and problem-solving skills when planning rehabilitation programs.

Ethics Committee Approval: This study was approved by Ethics committee of İzmir Katip Çelebi University (Approval Number: 114, Date: 24.03.2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., İ.N.G., D.Ö.K.; Design – M.K., İ.N.G., D.Ö.K.; Supervision – D.Ö.K., B.E.K.; Data Collection and/or Processing – M.K., B.T.; Analysis and/or Interpretation – M.K., İ.N.G., B.E.K.; Literature Search – M.K., B.T.; Writing – M.K., İ.N.G.; Critical Review – M.K., İ.N.G., B.T., B.E.K., D.Ö.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Horak F, Doberer D, Eber E, et al. Diagnosis and management of asthma - Statement on the 2015 GINA Guidelines. *Wien Klin Wochenschr*. 2016;128(15-16):541-554. [CrossRef]
2. *National Heart, Lung and BI. Guidelines for the Diagnosis and Management of Asthma*. U.S. Department of Health and Human Services; 2007.
3. Gibson PG, Powell H, Wilson A, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003;1:CD001117. [CrossRef]
4. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med*. 2003;26(1):1-7. [CrossRef]
5. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84(2):191-215. [CrossRef]
6. Bandura A, Freeman WH, Lightsey R. Self-efficacy: the exercise of control. *J Cogn Psychother*. 1999;13(2):158-166. [CrossRef]
7. Ritter PL, Lorig K. The English and Spanish self-efficacy to Manage Chronic Disease Scale measures were validated using multiple studies. *J Clin Epidemiol*. 2014;67(11):1265-1273. [CrossRef]
8. Lin MY, Weng WS, Apriliyasari RW, VAN Truong P, Tsai PS. Effects of patient activation intervention on chronic diseases: a meta-analysis. *J Nurs Res*. 2020;28(5):e116. [CrossRef]
9. Tousman S, Zeitz H, Taylor LD, Bristol C. Development, implementation and evaluation of a new adult asthma self-management program. *J Community Health Nurs*. 2007;24(4):237-251. [CrossRef]
10. Lavoie KL, Bouchard A, Joseph M, Campbell TS, Favreau H, Bacon SL. Association of asthma self-efficacy to asthma control and quality of life. *Ann Behav Med*. 2008;36(1):100-106. [CrossRef]
11. Mancuso CA, Sayles W, Allegrante JP. Knowledge, attitude, and self-efficacy in asthma self-management and quality of life. *J Asthma*. 2010;47(8):883-888. [CrossRef]
12. McCormick SP, Nezu CM, Nezu AM, Sherman M, Davey A, Collins BN. Coping and social problem solving correlates of asthma control and quality of life. *Chron Respir Dis*. 2014;11(1):15-21. [CrossRef]
13. Williams B, Beovich B, Ross L, Wright C, Ilic D. Self-efficacy perceptions of interprofessional education and practice in undergraduate healthcare students. *J Interprof Care*. 2017;31(3):335-341. [CrossRef]
14. Pignataro FS, Bonini M, Forgione A, Melandri S, Usmani OS. Asthma and gender: the female lung. *Pharmacol Res*. 2017;119:384-390. [CrossRef]
15. Sherer M, Maddux JE, Mercandante B, Prentice-Dunn S, Jacobs B, Rogers RW. The self-efficacy scale: construction and validation. *Psychol Rep*. 1982;51(2):663-671. [CrossRef]
16. Yildirim F, İlhan İÖ. Genel öz yeterlilik ölçeği Türkçe formunun geçerlilik ve güvenilirlik çalışması. *Türk Psikiyatr Derg*. 2010;21(4):301-308
17. Heppner PP, Petersen CH. The development and implications of a personal problem-solving inventory. *J Couns Psychol*. 1982;29(1):66-75. [CrossRef]
18. Şahin N, Şahin NH, Heppner PP. The psychometric properties of the problem solving inventory. *Cognit Ther Res*. 1993;17:379-396. [CrossRef]
19. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65. [CrossRef]
20. Uysal MA, Mungan D, Yorgancioglu A, et al. The validation of the Turkish version of asthma control test. *Qual Life Res*. 2013;22(7):1773-1779. [CrossRef]
21. Stenton C. The MRC breathlessness scale. *Occup Med (Lond)*. 2008;58(3):226-227. [CrossRef]
22. Moss M, Franks M, Briggs P, Kennedy D, Scholey A. Compromised arterial oxygen saturation in elderly asthma sufferers results in selective cognitive impairment. *J Clin Exp Neuropsychol*. 2005;27(2):139-150. [CrossRef]
23. Leblond J, Krnjevic K. Hypoxic changes in hippocampal neurons. *J Neurophysiol*. 1989;62(1):1-14. [CrossRef]
24. Rhyou HI, Nam YH. Association between cognitive function and asthma in adults. *Ann Allergy Asthma Immunol*. 2021;126(1):69-74. [CrossRef]
25. Caldera-Alvarado G, Khan DA, Defina LF, Pieper A, Brown ES. Relationship between asthma and cognition: the Cooper Center Longitudinal study. *Allergy*. 2013;68(4):545-548. [CrossRef]
26. Zulkosky K. Self-efficacy: a concept analysis. *Nurs Forum*. 2009;44(2):93-102. [CrossRef]
27. Gau BS, Hung CC. The self-efficacy scale for preschool teachers regarding asthma care: instrument development and validation. *J Sch Health*. 2014;84(2):91-98. [CrossRef]
28. Melgarejo González-Conde V, Pérez-Fernández V, Ruiz-Esteban C, Valverde-Molina J. Impact of self-efficacy on the quality of life of children with asthma and their caregivers. [Impacto de la autoeficacia en la calidad de vida de niños con asma y sus cuidadores]. *Arch Bronconeumol (Engl Ed)*. 2019;55(4):189-194. [CrossRef]
29. Dineen-Griffin S, Garcia-Cardenas V, Williams K, Benrimoj SI. Helping patients help themselves: a systematic review of self-management support strategies in primary health care practice. *PLoS One*. 2019;14(8):e0220116. [CrossRef]
30. Emery CF, Green MR, Suh S. Neuropsychiatric function in chronic lung disease: the role of pulmonary rehabilitation. *Respir Care*. 2008;53(9):1208-1216.

Thorac Res Pract. 2023; 24(6): 309-324 DOI: 10.5152/ThoracResPract.2023.23035

Review

Stepwise Approach in Asthma Revisited 2023: Expert Panel Opinion of Turkish Guideline of Asthma Diagnosis and Management Group

Gülfem Elif Çelik[1], Ömür Aydın[1], Ebru Damadoğlu[2], Ayşe Baççıoğlu[3], Seçil Kepil Özdemir[4], Sevim Bavbek[1], Dane Ediger[5], Ferda Öner Erkekol[6], Bilun Gemicioğlu[7], Sacide Rana Işık[8], Ayşe Füsun Kalpaklıoğlu[3], Ali Fuat Kalyoncu[2], Gül Karakaya[2], Metin Keren[9], Dilşad Mungan[1], İpek Kıvılcım Oğuzülgen[10], Füsun Yıldız[11], İnsu Yılmaz[12], Arzu Yorgancıoğlu[13]

[1]Division of Allergy and Immunology, Department of Chest Diseases, Ankara University Faculty of Medicine, Ankara, Turkey
[2]Division of Allergy and Immunology, Department of Chest Diseases, Hacettepe University Faculty of Medicine, Ankara, Turkey
[3]Division of Allergy and Immunology, Department of Chest Diseases, Kırıkkale University Faculty of Medicine, Kırıkkale, Turkey
[4]Division of Allergy and Immunology, Department of Chest Diseases, University of Health Sciences, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey
[5]Division of Allergy and Immunology, Department of Chest Diseases, Uludağ University Faculty of Medicine, Bursa, Turkey
[6]Division of Allergy and Immunology, Ankara Medicana International Hospital, Ankara, Turkey
[7]Department of Chest Diseases, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[8]Koç Healthcare, American Hospital, İstanbul, Turkey
[9]Immunology and Allergy Clinic, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
[10]Department of Chest Diseases, Gazi University Faculty of Medicine, Ankara, Turkey
[11]Department of Pulmonary Diseases, Cyprus International University Faculty of Medicine, Nicosia, Turkish Republic of Northern Cyprus
[12]Division of Immunology and Allergic Diseases, Department of Chest Diseases, Erciyes University, Kayseri, Turkey
[13]Department of Pulmonology, Celal Bayar University Faculty of Medicine, Manisa, Turkey

Cite this article as: Çelik GE, Aydın Ö, Damadoğlu E, et al. Stepwise approach in asthma revisited 2023: Expert panel opinion of Turkish guideline of asthma diagnosis and management group. *Thorac Res Pract.* 2023;24(6):309-324.

Abstract

Introduction of inhaled corticosteroids (ICS) has been the cornerstone of the long-term management of asthma. ICSs either alone or in combination with long-acting beta-2 agonists have been shown to be associated with favorable asthma outcomes. However, asthma control is still reported to be below expectations all around the world. Research in the last decades focusing on the use of ICS/formoterol both as maintenance and as needed (maintenance and reliever therapy approach) showed improved asthma outcomes. As a result of recent developments, Turkish Asthma Guidelines group aimed to revise asthma treatment recommendations. In general, we recommend physicians to consider the risk factors for poor asthma outcomes, patients' compliance and expectations and then to determine "a personalized treatment plan." Importantly, the use of short-acting beta-2 agonists alone as a symptom reliever in asthma patients not using regular ICS is no longer recommended. In stepwise treatment approach, we primarily recommend to use ICS-based controllers and initiate ICS as soon as possible. We define 2 different treatment tracks in stepwise approaches as maintenance and reliever therapy or fixed-dose therapy and equally recommend each track depending on the patient's risks as well as decision of physicians in a personalized manner. For both tracks, a strong recommendation was made in favor of using add-on treatments before initiating phenotype-specific treatment in step 5. A strong recommendation was also made in favor of using biologic agents and/or aspirin treatment after desensitization in severe asthma when indicated.

KEYWORDS: Asthma, long-term management, reliever, controller, severe asthma
Received: *March 26, 2023* ***Accepted:*** *July 25, 2023* ***Publication Date:*** *October 27, 2023*

INTRODUCTION

Since its first publication in 1996, Turkish Asthma Guidelines: Diagnosis and Treatment has been updated regularly. The last update was published in December 2020 and was carried out under the auspices of the Turkish Thoracic Society and Turkish National Society of Allergy and Clinical Immunology. However, owing to dramatical changes in the management of asthma recently, particularly in stepwise approach in terms of treatment arms, a revision is needed in our recent recommendations. In this context, online meetings were held with an author group of the guidelines team. All of the authors were experts on asthma. For the updating process, a careful review of MEDLINE, PubMed, and Cochrane databases, after the last update in 2020, was carried out. The panel discussions were held via online meetings during which treatment goals and strategies as well as treatment steps were discussed in line with current literature data.

While making the recommendations, the relevant existing evidence, the current situation and evidence and health legislation in our country, and the clinical experiences of the experts were taken into consideration. The decision on recommendations were made based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method.[1] The quality of evidence was decided based on Global Initiative for Asthma (GINA) A, B, C, and D criteria.[2] In brief, when the benefit of the patient is high, a strong recommendation was issued. If the risk–benefit ratio

Corresponding author: Seçil Kepil Özdemir, e-mail: secilkepil@gmail.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

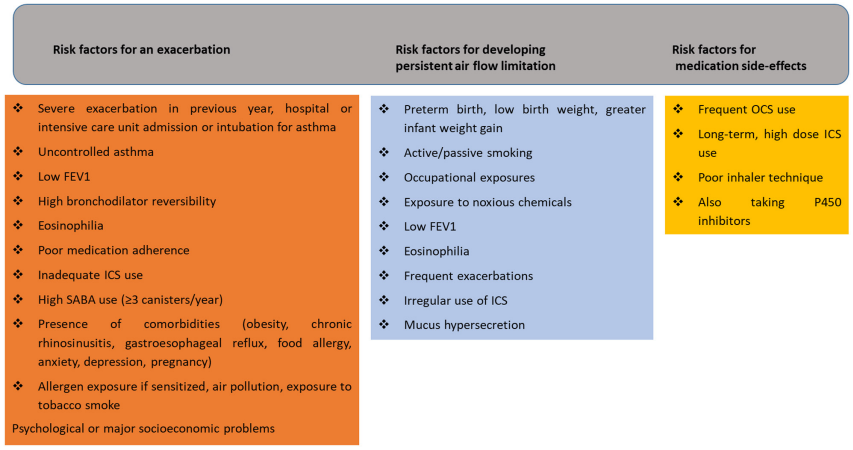


Figure 1. Risk factors for poor prognosis of asthma. FEV1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid; OCS, oral corticosteroid; P450, cytochrome P450; SABA, short-acting beta-2 agonist.

was not clear enough, a weak recommendation was made. The word "recommended" was used for strong recommendation in a positive sense, while "not recommended" indicated a strong recommendation in a negative sense. Weak recommendation was made as "suggestion" or as "could benefit."

After several meetings, recommendations were finalized. Recommendations were sent to all members of the expert panel via Google Forms and voting was performed confidentially. Recommendations were interpreted as "strong consensus" if there was more than ≥90% agreement, as "consensus" when there was 70%-89% agreement, and as "majority agreement" if the agreement was between 51% and 69%.[2] Each recommendation was numbered in order to be easily followed up by the readers. The final version of the manuscript including the voting results was shared with the expert panel, and the last version was established. The update includes 7 sections, 116 recommendations for treatment, and 9 recommendations created by the expert panel to improve asthma management in the country. The details of each section are provided here.

MAIN POINTS

- Using short-acting beta-2 agonists alone as a symptom reliever in asthma patients not using regular inhaled corticosteroids (ICS) is no longer recommended.
- We recommend using ICS-based controllers and initiating ICS therapy as soon as possible in stepwise treatment approach.
- Two different treatment tracks are defined in stepwise approaches as maintenance and anti-inflammatory reliever therapy or fixed-dose therapy and each track is equally recommended. Decision should be made according to the patient's risks as well as choice of physicians in a personalized manner.
- We recommend using add-on treatments before initiating phenotype-specific treatments in step 5.
- We recommend using biologic agents and/or aspirin treatment after desensitization in severe asthma when indicated.

CLINICAL AND RESEARCH CONSEQUENCES

Section 1: Goals of Asthma

Achieving asthma control is the target in the long term-management of asthma. Within the scope of this, we recommend daily symptom control and prevention for future risk factors that will adversely affect the course of the disease [Evidence A/strong recommendation] [Recommendation 1, strong consensus].[2,3] In order to minimize future risks, we recommend to reduce/prevent exacerbations to prevent persistent airflow limitation and to keep the drugs used within safe limits in terms of side effects (Figure 1) [Evidence A/strong recommendation] [Recommendation 2, strong consensus].[2,3] Therefore, we recommend that patients with asthma should be reviewed in terms of these risk factors in their initial evaluation and during the annual follow-up [Evidence A/strong recommendation] [Recommendation 3, strong consensus].

Section 2: General Principles of Asthma Treatment

Considering the treatment goals in asthma, we urge physicians to consider the need for "biopsychosocial strategic approaches" that will provide success in patient care in the long term.[2,3] We recommend that physicians take care of patients from a biopsychosocial point of view and exhibit the necessary attitudes in terms of both medical treatment and psychosocial support. [Evidence A/strong recommendation] [Recommendation 4, strong consensus].[2,3] A multimodality approach that consists of medications, nonmedical therapies, treatment of risk factors, and ensuring patient compliance is recommended (Figure 2) [Evidence A/strong recommendation] [Recommendation 5, strong consensus].[2,3] It is essential to ensure patients' compliance with the treatment.[2,3] We recommend to determine the conditions/factors that will lead to poor compliance of the patients with the treatment and to take an approach toward this [Evidence A/strong recommendation] [Recommendation 6, strong consensus]. We recommend that these evaluations be made at the first visit as the initial evaluation and be reviewed annually [Evidence A/strong recommendation] [Recommendation 7, strong consensus].[2,3]

One of the main factors that will affect the compliance of patients with the treatment is the effective communication

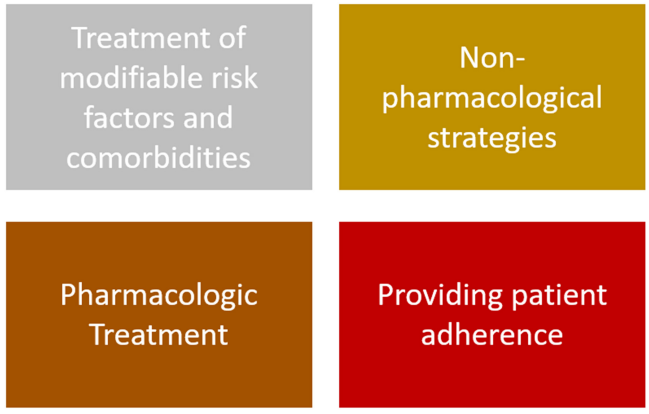


Figure 2. General treatment strategies for adjusting chronic follow-up of asthma.

of physicians with patients and family members. We recommend physicians to use effective communication skills, as it will increase the patient's compliance with the treatment and cause positive effects in the treatment outcomes [Evidence A/strong recommendation] [Recommendation 8, consensus].[2,3] We recommend patient-centered approaches as it has been shown that the participation of patients and, if necessary, their family members in the treatment processes increases the success of the treatment [Evidence A/strong recommendation] [Recommendation 9, strong consensus].[2,3]

The chronic nature of the disease requires patients to have knowledge and skills related to disease management. In this context, we recommend patients to be informed about asthma and to be guided in terms of the health resources they can access, to improve their inhaler device use skills, to increase their health literacy level, and to learn to use a written asthma action plan [Evidence A/strong recommendation] [Recommendation 10, strong consensus].[2,3]

Section 3: General Principles of Pharmacological Treatment

ASTHMA MEDICATIONS

We recommend controller medications, reliever medications, and add-on therapies for the long-term management of asthma [Evidence A/strong recommendation] [Recommendation 11, strong consensus].[2-5] **Controller medications** are medications that are used on a regular basis or as needed in the form of inhaled corticosteroid (ICS)/formoterol (FOR) in step 1 and 2 treatments. Inhaled corticosteroid-based medications are the main controllers that suppress airway inflammation and consequently symptom control is achieved, exacerbations are prevented, and respiratory function loss is reduced.[2,3]

Reliever medications are used in order to relieve the symptoms only when the patient has a symptom or assumed to have symptoms (i.e., before exercise). Frequent need for reliever medications is an indication of insufficiency or lack of proper usage of controller medications.[2,3] **Add-on medications** are added to the current treatment for patients in whom good symptom control cannot be achieved despite ICS/long-acting beta-2 agonists (LABA) combination or for patients with exacerbations despite steps 3-5 treatment, and they are not used alone.[2,3,6] These include phenotype-specific and not phenotype-specific treatments.

Using "controller" medications in order to control symptoms and prevent future risks and using "symptom reliever" medications when the patient has symptoms forms the basis of pharmacological treatment of asthma.

TREATMENT STRATEGY [STEPWISE APPROACH]

We recommend long-term introduction of the pharmacological treatment in the context of "Stepwise approach" (Figure 3) [Evidence A/strong recommendation] [Recommendation 12, strong consensus].[2,3] Stepwise treatment is an approach to adjust pharmacological therapy according to asthma control level, in which steps are dynamic (up and down) and are changed based on asthma control level.

CHOICE OF CONTROLLER MEDICATIONS

We primarily recommend to use ICS-based controllers and initiate their use as soon as possible in the stepwise treatment approach [Evidence A/strong recommendation] [Recommendation 13, strong consensus]. It has been reported that initiating ICS use early in asthma provided good outcomes in terms of preventing disease progression.[4] Delayed initiation of controller medications resulted in reduced response rates and may cause to use higher doses of medications for similar treatment response.[4] More frequent exacerbations and increased pulmonary function loss over the years may be seen in patients who are not on ICS treatment.[5] For this reason, ICS-based treatments are recommended to be initiated starting from step 1.[2-5]

Leukotriene receptor antagonists (LTRAs) are not recommended as the first option at step 2 [Evidence A/strong recommendation] [Recommendation 14, strong consensus].[6] Compared with ICS-based treatments at step 2 and ICS/LABA combination treatments at steps 3-4, LTRAs have been shown to have a limited effect in preventing exacerbations.[6] Moreover, caution should be exercised in terms of neuropsychiatric adverse effects while using this treatment.[2,3] However, they are recommended when ICS-containing medication cannot be given at this step [Evidence A/strong recommendation] [Recommendation 15, Consensus].[2,3,6]

CHOICE OF SYMPTOM RELIEVERS

We do not recommend to use short-acting beta-2 agonist (SABA) alone as a symptom reliever in adult patients not using regular ICS-based controller therapy [Evidence A/strong recommendation] [Recommendation 16, strong consensus].[2,3,7-9] For this reason, we recommend taking ICS whenever SABA is taken for mild asthmatic patients who are not using regular controller therapy [steps 1-2] [Evidence B/strong recommendation] [Recommendation 17, strong consensus] (Box 1).[2,3,10]

Box 1. Rationale for not using SABA alone.

Severe exacerbations may occur in mild asthmatic patients and for this reason this group of patients need ICS-based therapies. However, it has been showed that ICS usage is irregular,[2-3] and SABA usage is inappropriately high in patients with mild asthma.[2-3,8]

SABA usage-related deaths have been reported in patients not using ICS treatment regularly.[9] Because of this, patients who are not using regular controller medications should use ICS-containing medication whenever SABA is taken, as ICS/SABA combination therapy if it is possible or as taking SABA and ICS-containing medication consecutively.[10] This recommendation is primarily for primary care physicians.

This treatment may be administered as ICS/SABA combination therapy in fixed-dose preparation or using the 2 drugs consecutively at the same time. However, the use of a fixed combination of ICS/SABA as a symptom reliever could be safer and more effective in the management of asthma when available. As-needed ICS/FOR is preferentially recommended as a reliever medication by the expert panel [Evidence A/strong recommendation] [Recommendation 18, strong consensus] (Box 2).[10-17]

Box 2. Rationale for recommending ICS/FOR as a reliever.

It is strongly recommended because this treatment method ensures patients receive ICS. In step 2, it has been shown that this treatment is similarly effective in preventing exacerbations and symptom control and more effective in preventing severe exacerbations compared to regular low-dose ICS and as-needed SABA.[11-13]

In other steps (steps 3-4), it has been shown that it prevents exacerbations and provides similar symptom control compared to treatments including as-needed SABA as a reliever.[14-17]

ADD-ON THERAPIES

Add-on therapies are additional therapies that can be applied in both tracks at steps 3-5 and are given in addition to current ICS-based medications.[2,3] [Evidence B/strong recommendation] [Recommendation 19, strong consensus]. These therapies are not recommended to be used alone. Add-on therapies include phenotype-specific and not phenotype-specific treatments (Boxes 3 and 4).[2,3]

Box 3. Phenotype specific add-on therapies.

- Anti-IgE (step 5)
- Anti IL-5, IL-5R (step 5)
- Anti-IL-4/IL-13 (step 5)
- Aspirin treatment after desensitization (step 5)

Box 4. Add-on therapies that are not phenotype specific.

- Add-on LAMA (steps 4-5)
- Add-on LTRA (steps 3-5)
- Low-dose OCS (steps 4-5)
- Azithromycin (step 5)

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Subcutaneous allergen immunotherapy with house dust mite [SCIT] could be beneficial in patients with mild-to-moderate allergic asthma accompanied by allergic rhinitis who are sensitized to house dust mites and whose asthma is under control. Subcutaneous allergen immunotherapy with house dust mite is added to regular treatment to reduce symptoms and medication use, provided that forced expiratory volume in the first second of expiration (FEV1) is ≥70% [Evidence B/weak recommendation] [Recommendation 20, majority agreement].[18]

Sublingual allergen immunotherapy with house dust mite [SLIT] could be beneficial in patients with allergic asthma accompanied by allergic rhinitis, who are sensitized to house dust mites and whose asthma is under control or partially controlled with low–medium-dose ICS and FEV1 ≥70% predicted, when added to the regular treatment to reduce exacerbations and improve symptom control [Evidence B/weak recommendation] [Recommendation 21, consensus].[18] House dust mite sublingual tablets are not currently available in our country and are not covered by reimbursement.

Allergen-specific immunotherapy is recommended to be performed primarily by immunology and allergy specialists in allergy clinics when indicated [Evidence D/strong recommendation] [Recommendation 22, strong consensus].

TRACKS IN STEPWISE APPROACH

The stepwise approach includes 2 different arms. The main discrepancy in the both arms is the preferred reliever medication. In the first track, the reliever consists of a fixed combination of ICS/formoterol, whereas SABA is the recommended reliever in the second track. The main idea in the first track is to prevent SABA use alone due to high risks for morbidity and mortality and guarantee to administer ICS in combination with formoterol.[10]

In the first track, ICS/FOR combination in a single inhaler is used only as needed in steps 1 and 2 in the context of "Anti-inflammatory reliever" and both in maintenance and as-needed treatment, which is called the ''maintenance and reliever (MART) approach'' at steps 3-5.[11-17] This includes using low-dose ICS/FOR containing medications as maintenance treatment and as needed.[11-17] Contrary to fixed-dose approach, the dose of ICS is flexible in the MART approach. The patient can take a certain number of extra doses daily according to his/her needs in addition to the regularly used

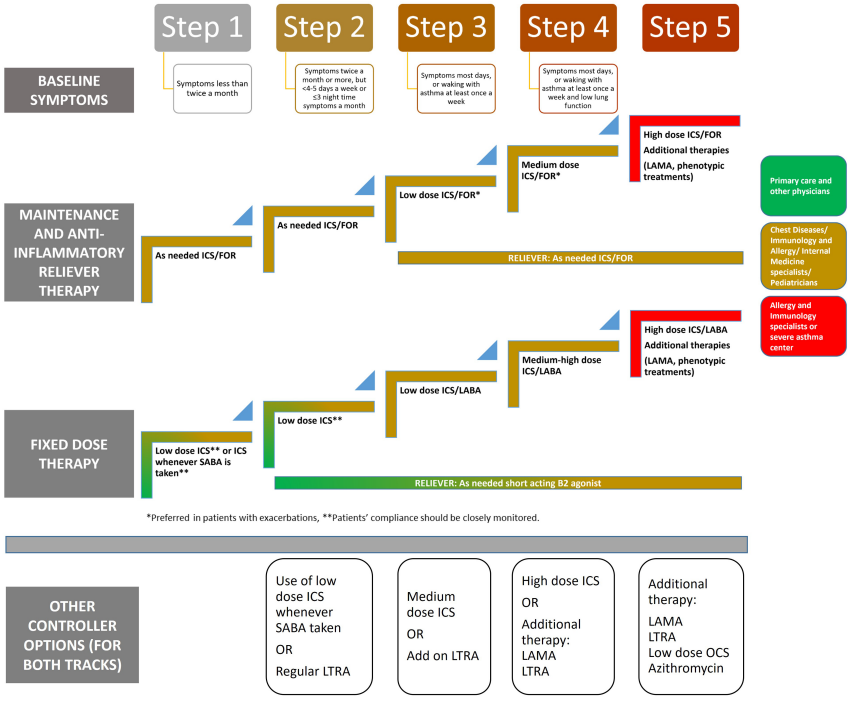


Figure 3. Stepwise approach for chronic treatment of asthma based on treatment tracks. ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting beta-2 agonist.

maintenance dose; by this way, daily ICS dose taken may change.[15-17]

In the other track, SABA is used as a reliever.[19-22] The applied ICS dose in this track is fixed, and ICS is given alone (steps 1-2) or in combination with LABA (steps 3-5) depending on the treatment step.[19-22] This approach is called the "fixed-dose approach" as the dose of ICS is fixed and determined by physicians.[2,3,19-22]

In the stepwise treatment approach, we equally recommend to apply ICS-based therapies in 2 different treatment tracks as MART or fixed-dose therapy (Figure 3) [Evidence A/strong recommendation] [Recommendation 23, strong consensus].[2,3] The choice of either treatment track is affected by not only available current evidence but also other risk factors, factors related to patients' compliance and expectations, and opinion of the treating physician; therefore, a "personalized treatment" is determined accordingly [Tables 1-4] [Evidence

Table 1. Initiation of Step 1 Therapy [Recommendations 26-29]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Patients with asthma symptoms less than twice a month [Recommendation 26, strong consensus]	As-needed low-dose ICS/FOR[11,12] [Recommendation 27, strong consensus]	B	Strong	This treatment method ensures patients to receive ICS while using reliever medication. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Regular low-dose ICS and as-needed SABA [Recommendation 28, majority agreement]	D	Strong	It is recommended to prevent SABA-related adverse events, as the rate of taking SABA alone in patients with mild asthma is high in our country. It is recommended for patients at risk for poor prognosis of asthma. Close monitoring of patient adherence to treatment is recommended. Recommended for primary care physicians.
	Concomitant low-dose ICS whenever SABA is needed[20-22] [Recommendation 29, strong consensus]	B	Strong	Recommended for primary care physicians. Close monitoring of patient adherence to treatment is recommended.

FOR, formoterol; ICS, inhaled corticosteroid; SABA, short-acting beta-2 agonist.

Table 2. Initiation of Step 2 Therapy [Recommendations 30-33]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Two or more daytime symptoms per month but less than 4-5 days per week OR Reliever use 2 or more per month but less than 4-5 days per week OR Patients with complaints of ≤3 nights per month [Recommendation 30, strong consensus]	As-needed low-dose ICS/FOR[12] [Recommendation 31, strong consensus]	A	Strong	It is recommended because it is a treatment type that allows the patient to receive ICS in the use of rescue medication. It is recommended for respiratory diseases, allergy and immunology, internal medicine, and pediatrics physicians.
	Regular low-dose ICS* and as-needed SABA[21] [Recommendation 32, consensus]	A	Strong	It is recommended in patients with risk for poor prognosis of asthma. Close follow-up of the patient's adherence to treatment is recommended. It is a priority recommendation for physicians working in primary health care.
	Additional low-dose ICS with each SABA use[20-22] [Recommendation 33, consensus]	B	Weak	Regular low-dose ICS can be considered in patients with treatment adherence problems.
	Regular LTRA use[6] [Recommendation 15, strong consensus]	A	Strong	It is not the primary treatment in the treatment of asthma.
			Strong	Recommended in patients who cannot use ICS-based therapy. Recommended for respiratory diseases, allergy and immunology, internal medicine, and pediatrics physicians.

FOR, formoterol; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SABA, short-acting beta-2 agonist.
*Low-dose ICS is lower than budesonide 400 µg/day or equivalent.

Table 3. Initiation of Step 3 Therapy [Recommendations 34-37]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Symptoms on most days OR Patients with at least 1 nighttime awakening in a week [Recommendation 34, strong consensus]	MART approach: Maintenance and reliever use of low-dose ICS/FOR[14-17] [Recommendation 35, strong consensus]	A	Strong	It is a priority recommendation for patients with an asthma exacerbation in the previous year. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Fixed-dose approach: Regular low-dose ICS/LABA, as-needed SABA[2,3,19] [Recommendation 36, strong consensus]	A	Strong	Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Regular medium-dose ICS*/as-needed SABA[2,3] [Recommendation 37, strong consensus]	A	Strong	It is a priority recommendation for physicians working in primary health care. Recommendation for primary care physicians; to patients who are candidates for step 3 therapy. Initiation of this therapy and referral to a specialist is recommended.

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; OCS, oral corticosteroid; MART, maintenance and reliever therapy; SABA, short-acting beta-2 agonist.
*Low-dose ICS is lower than budesonide 400 µg/day or equivalent.

A/strong recommendation] [Recommendation 24, strong consensus].

Section 4: Initiation of Pharmacological Therapy

The treatment is commenced with determination of the appropriate treatment step in previously untreated patients. In this context, the frequency of the patient's daytime and nighttime symptoms in the last 4 weeks and the presence of risk factors for poor prognosis of asthma are recommended to be considered [Evidence B/strong recommendation] [Recommendation 25, strong consensus], (Figure 3, Tables 1-4) [Recommendations 15, 26-41].[2,3]

Table 4. Initiation of Step 4 Therapy [Recommendations 38-41]

Symptom Characteristic	Recommendation	Evidence	Strength of Recommendation	Comment
Asthma symptoms most days OR Nocturnal asthma symptom at least once a week OR Low PFT values [Recommendation 38; strong consensus]	MART approach: Maintenance: medium-dose ICS/FOR As-needed low-dose ICS/FOR[14-17] [Recommendation 39, strong consensus]	A	Strong	It is a priority recommendation for patients with an asthma exacerbation in the previous year. Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
	Fixed-dose approach: Regular medium-dose ICS/LABA, as-needed SABA[2,19] [Recommendation 40, strong consensus]	A	Strong	Recommended for pulmonologists, allergy and immunology, internal medicine, and pediatrics specialists.
Patients with quite uncontrolled asthma symptoms or patients with an exacerbation	Short-term use of OCS [Recommendation 41, strong consensus]	A	Strong	

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; MART, maintenance and reliever therapy; OCS, oral corticosteroid; PFT, pulmonary function test; SABA, short-acting beta-2 agonist.

Maintenance and reliever therapy is recommended to be applied with low-dose ICS/FOR [160/4.5 µg for BUD/FOR or 100/6 µg for BDP/FOR [Evidence A/strong recommendation] [Recommendation 42, strong consensus].[2,3] Care should be taken not to exceed the maximum daily dose of formoterol in MART approach [Evidence A/strong recommendation] [Recommendation 43, strong consensus]. In patients with asthma 12 years of age and older, the maximum recommended daily dose is a total of 54 µg formoterol (delivered dose) including doses used for maintenance for BUD/FOR [Total maximum number of dose/days: 12].[2] The maximum recommended daily dose is a total of 36 µg formoterol (delivered dose) including doses used for maintenance for BDP/FOR [Total maximum number of dose/days: 8].[2]

Section 5: Monitorization of Treatment

We recommend to achieve good asthma control and to prevent and/or control future risks in the follow-up of the asthmatic patient [Evidence A/strong recommendation] [Recommendation 44, strong consensus].[2,3] In this regard, treatment is monitored, the response is assessed, and the treatment is reviewed in line with the data obtained.[2]

FOLLOW-UP SCHEDULE

Regular follow-up at certain intervals is recommended for asthmatic patients [Evidence A/strong recommendation] [Recommendation 45, strong consensus].[2,3] After initiation of asthma treatment for the first time, a control visit is recommended to schedule within 4 weeks after the initial evaluation [Evidence A/strong recommendation] [Recommendation 46, strong consensus]. During this visit, accuracy of the diagnosis, exposure to environmental triggers and their control, response to treatment, patient's acceptance/perception of the disease, and factors related to adherence are recommended to be assessed (Box 5) [Evidence A/strong recommendation] [Recommendation 47, strong consensus].[2,3]

Box 5. Maintenance and reliever treatment (MART) approach

This includes using low dose ICS/FOR containing medications as maintenance treatment and as-needed.[14-17] It is a flexible treatment approach. The ICS dose used by the patient is not fixed. The patient can take a certain number of extra doses daily according to his/her needs in addition to the regularly used maintenance dose, by this way daily ICS dose taken may change.

Afterward, it is recommended to evaluate the patient's asthma every 4 weeks until the control is achieved, and then every 3-12 months according to the clinical features as well as underlying severity of the disease [Evidence A/strong recommendation] [Recommendation 48, strong consensus].[2,3] A follow-up visit is recommended 2-4 weeks after an exacerbation [Evidence D/strong recommendation] [Recommendation 49, strong consensus].[2,3]

ASSESSMENTS PERFORMED AT FOLLOW-UP

Initial characteristics of asthma should be recorded while commencing initial treatment [Evidence A/strong recommendation] [Recommendation 50, strong consensus]. Assessing symptom control during the last 4 weeks, risk factors, FEV_1, treatment adherence, exacerbation history, and factors like patient's satisfaction is recommended at each control visit (Figure 4) [Evidence A/strong recommendation] [Recommendation 51, strong consensus].[2,3] Monitoring the course of the disease with recording annual follow-up of certain parameters of patients regularly is recommended in order to determine individual asthma progress of patients (Figure 4) [Evidence A/strong recommendation] [Recommendation 52, strong consensus].

Reviewing Treatment

Pharmacological treatment is routinely reviewed during follow-up visits. In this regard, pharmacological therapy can be

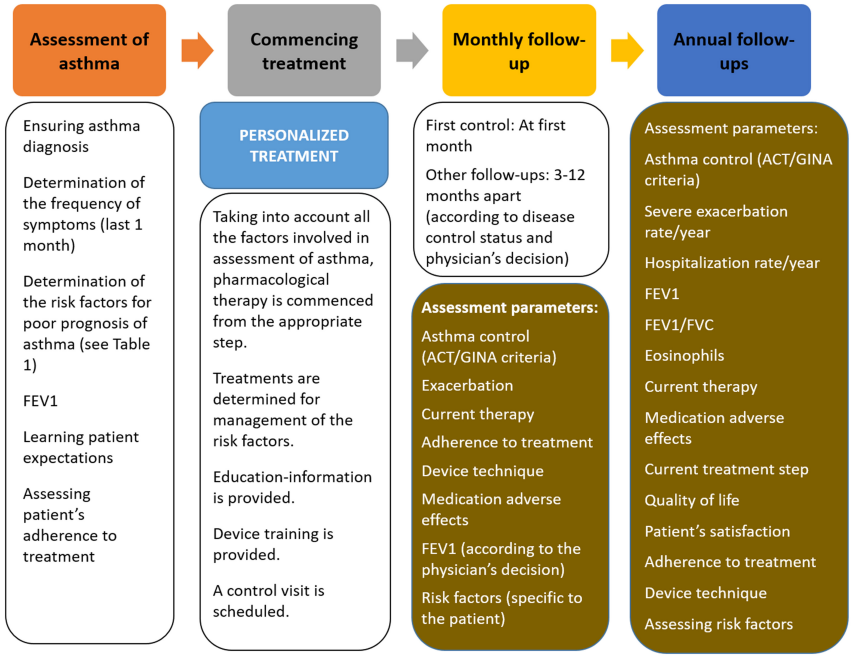


Figure 4. Monitoring parameters of asthma at initial diagnosis and follow-up. ACT, asthma control test; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; GINA, Global Initiative for Asthma.

continued as it is, and medications used can be changed or their doses can be increased or decreased.

If Asthma Is Not Controlled with Current Therapy

First of all the reasons for uncontrolled asthma should be clarified (Figure 5). In this context, confirmation of the diagnosis may be needed; treatment adherence should be checked, comorbidities are treated, and environmental control measures are taken [Evidence A/strong recommendation] [Recommendation 53, strong consensus].[2,3] In case of treatment nonadherence or an adverse event requiring discontinuation of the medication, change of therapy is recommended [Evidence A/strong recommendation] [Recommendation 54, strong consensus].

If asthma control is still not achieved after assessing and controlling each of these conditions and providing an appropriate/effective approach, then asthma is considered uncontrolled. In this case, a step-up may be considered or if in steps 4-5 initiating add-on therapies may be considered before stepping up (Figure 5) [Evidence A/strong recommendation] [Recommendation 55, strong consensus].[2,3,23-26]

Adjustment of Treatment in Case of Poor Medication Adherence and/or Increased Risk of Medication Side Effects

Patients should be trained and checked for inhaler device technique at each visit [Evidence D, strong recommendation] [Recommendation 56, strong consensus].[2,3] If there is a difficulty in inhaler device technique that cannot be corrected, switching to another device by considering the patient's opinion as well is recommended [Evidence D/strong recommendation] [Recommendation 57, strong consensus].

We recommend to make changes in the treatment if side effects are observed with current medications that necessitate changing [Evidence D, strong recommendation] [Recommendation 58, strong consensus]. In this context, other controllers can be used [Evidence A, strong recommendation] [Recommendation 59, consensus].[23-26]

If ICS-based therapies cannot be used in step 2 treatment [poor adherence or side effect], LTRA use can be considered [Evidence A/strong recommendation] [Recommendation 15, strong consensus].[25,26]

It is recommended to initiate another LABA-containing combination therapy in patients if side effects of LABA are observed using ICS/LABA in fixed-dose approach tracks of step 3-5 treatments [Evidence D/strong recommendation] [Recommendation 60, majority agreement].[2,3,19] We recommend to initiate LTRA in addition to low-dose ICS treatment in patients with side effects of LABA on low-dose ICS/LABA in fixed-dose approach in step 3 treatment [Evidence A/strong recommendation] [Recommendation 61, majority agreement].[25,26] In patients who have side effects of LABA on low-dose ICS/LABA use in step 3 treatment, it may be beneficial to discontinue LABA and start theophylline in addition to low-dose ICS treatment [Level of evidence B/weak recommendation] [Recommendation 62, strong decision].[2,3]

If there is a poor medication adherence in either fixed-dose or MART therapy and cannot be corrected, introduction of other track is recommended to be considered [Evidence D/strong recommendation] [Recommendation 63, strong consensus].[2,3]

Stepping Up in Uncontrolled Asthma

Stepping up is recommended in patients whose symptom control cannot be achieved and who are at risk of an asthma exacerbation despite current treatment and appropriate measures to control environmental factors, comorbid conditions, adherence to treatment, with a definiteasthma diagnosis

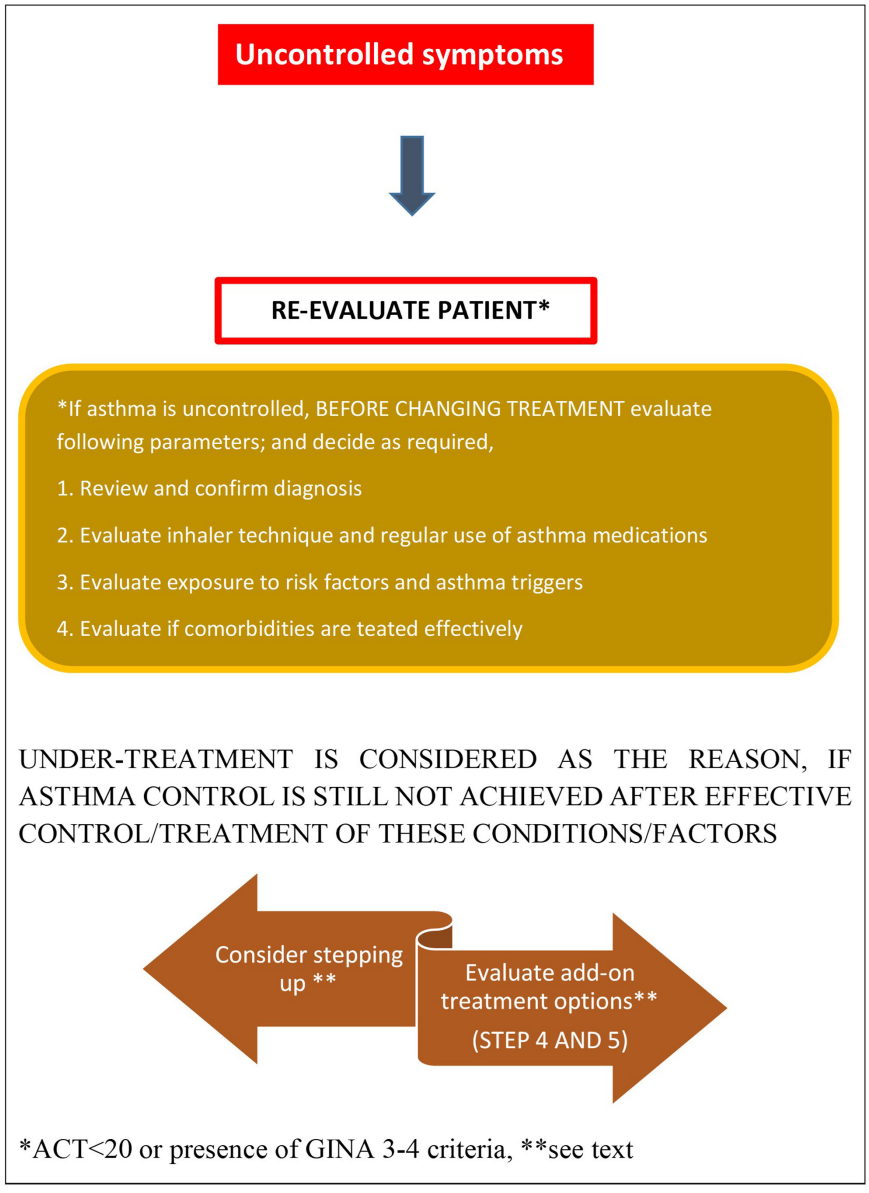


Figure 5. Approach to patient whose asthma is not well controlled under treatment. ACT, asthma control test; GINA, Global Initiative for Asthma. *ACT < 20 or presence of GINA 3-4 criteria. **See text.

[Evidence C/strong recommendation] [Recommendation 64, strong consensus].[2,3] We recommend to step up the treatment at the track in which the patient is currently on [Evidence A/strong recommendation] [Recommendation 65, strong consensus].

Stepping up the treatment is recommended in 2 different ways:[2]

- *Sustained step up under chronic treatment:* In patients whose asthma is uncontrolled for at least 1 month on treatment, a step-up in treatment is done (Figure 3) [Recommendation 66, strong consensus].[14,15]
- *Short-term step up [for 1-2 weeks]:* The ICS dose is increased in patients with loss of asthma control during viral respiratory tract infections or allergen exposure. This application is recommended for 1-2 weeks [Evidence C/strong recommendation] [Recommendation 67, strong consensus].[16,17]

Initiation of "Add-On Treatments" in Uncontrolled Asthma

In uncontrolled asthma at step 4, initiation of add-on treatments may be considered before stepping up (Figures 3 and 5) [Evidence D/weak recommendation] [Recommendation 68, consensus].[2,3] However, at step 5, we strongly recommend to initiate add-on non-phenotype-specific treatments before phenotype-specific treatment (Figures 3 and 5) [Evidence D/strong recommendation] [Recommendation 69, consensus].[2,3,23-26] These therapies can be used in both tracks [Evidence A/strong recommendation] [Recommendation 70, strong consensus].

Addition of LAMA therapy may be beneficial in patients who are not under control with medium-dose ICS/LABA in step 4 [Evidence B/weak recommendation] [Recommendation 71, consensus].[23,24]

Adding LTRA to medium-dose ICS/LABA therapy in step 4 may provide benefit [Evidence A/weak recommendation]

[Recommendation 72, consensus].[2] We recommend to add LTRA to ICS/LABA therapy in both tracks in patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease in steps 3-5 [Evidence B/strong recommendation] [Recommendation 73, strong consensus].[25,26]

Stepping Down in Controlled Asthma Under Current Treatment

The aim of stepping down is to find the minimum effective dose that maintains good control of symptoms and prevents exacerbations, the risk of persistent airflow limitation, and progression of the disease while minimizing drug side effects and the costs of treatment.[2,3] There is not enough evidence about optimal timing of step-down, which drugs and how much dose should be reduced first.[27-31] For this reason, we recommend to make a decision individually by taking into account personal and environmental risks of the patients. Therefore, if asthma is under control with the treatment initiated, stepping down the treatment should be considered, by taking into account individual risks (Figure 6) [Evidence D/strong recommendation] [Recommendation 74, strong consensus].[27]

Stepping down is not recommended based on symptom control alone [Evidence D/strong recommendation] [Recommendation 75, strong consensus]. The mainstay of stepping down is well asthma control that is composed of control of symptoms, risks for asthma exacerbations or persistent airflow limitation, and development of side effects.[27-31]

We recommend going 1 step down in patients who have remained under control for at least 3 months after asthma symptom control has been achieved, and if there is no risk for an asthma exacerbation or persistent airflow limitation [Evidence B/strong recommendation] [Recommendation 76, strong consensus].[2] This period can be extended up to 6 months. If there is a risk factor for the development of asthma exacerbation or persistent airflow limitation, the current treatment is recommended to continue for at least 1 year with observation of no exacerbation.[27] If there is no asthma exacerbation in the last year, in this case, in line with the decision of the physician, 1 step-down can be considered with close follow-up of the patient [Evidence D/strong suggestion] [Recommendation 77, strong consensus].[27-31] However, if the side effects pose a risk for the use of the drug, the treatment is adjusted according to the profit–loss ratio.

Step-down approach may differ from patient to patient, depending on their actual treatment, the presence of risk factors, and the patient's preferences. Pulmonary function test values, symptom scores, and exacerbation risks are recorded before stepping down.[27-31] The patient is provided clear instructions. The patient's active participation is ensured, and the patient is closely followed up. Patients should be closely monitored for symptom control and exacerbation risk, following step-down.[22,23] [Recommendation 78, strong consensus]. Stepping down too quickly in a short time can lead to an increased risk of symptoms and asthma exacerbations.[27,28] Complete cessation of ICS therapy in adult and

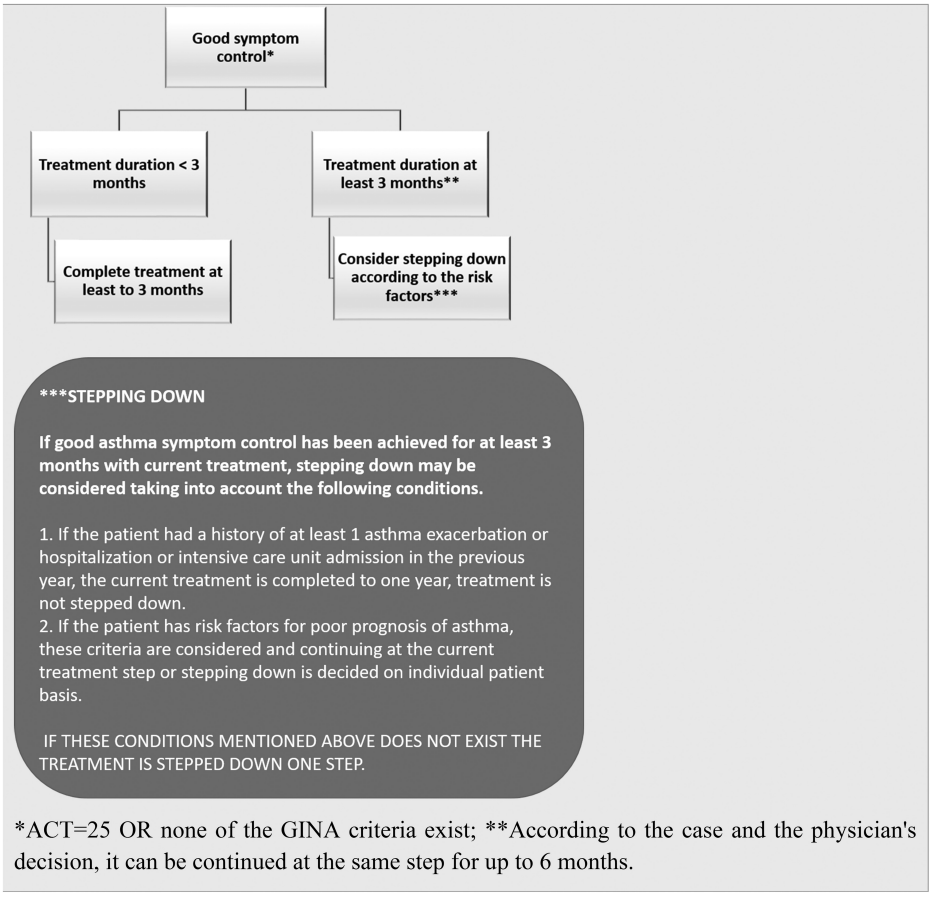


Figure 6. Approach to stepping down treatment. ACT, asthma control test; GINA, Global Initiative for Asthma. *ACT = 25 OR none of the GINA criteria exist. **According to the case and the physician's decision, it can be continued at the same step for up to 6 months.

adolescent patients is not recommended because it is associated with a significantly increased risk of asthma exacerbations [Evidence B/strong recommendation] [Recommendation 79, consensus].[29-31]

SPECIFIC COMMENTS FOR STEPPING DOWN OPTIONS IN TRACKS

Maintenance and Reliever Therapy Approach

In maintenance treatment of MART approach, first the dose of ICS and then its frequency are reduced (Figure 7) [Recommendation 80, consensus].[2,10-17] When stepping down, as-needed use of low-dose ICS/FOR is recommended in the lowest steps (steps 1 and 2)[Recommendation 81, strong consensus].[2,27]

Fixed-Dose Approach

We recommend first a 25%-50% reduction in ICS doses at 3-month intervals for the fixed-dose approach (Table 5) [Evidence B/strong recommendation] [Recommendation 82, strong consensus].[2,10,11,27,30,31]

Step Movements in Tracks

We recommend to perform stepping up or down through the same track from any of the conventional fixed-dose or MART approaches (Figure 7) [Evidence D/strong recommendation] [Recommendation 96, strong consensus].[2] If there is no response and/or poor adherence to treatment at any step, switching from one track to another is considered (Figure 7) [Evidence D/strong recommendation] [Recommendation 97, strong consensus].[2]

Section 6: Special Conditions

Asthma Treatment and Management for Primary Care Physicians

Asthma cases requiring primary and secondary care can be treated in primary health care settings (Figure 3, Tables 1 and 2) [Evidence D/strong recommendation] [Recommendation 98, consensus].[2,3] Because of the risks of SABA-only treatment, these patients should be closely monitored for adherence to ICS therapy as recommended [Evidence D/strong recommendation] [Recommendation 99, strong consensus].[7-9]

Primary care physicians are expected to refer adult patients for expert assessment in the presence of certain conditions [pulmonologists, allergy and immunology, and internal medicine specialists] [Evidence D/strong recommendation] [Recommendation 100, strong consensus].[2,3] These conditions are patients with diagnostic difficulties; patients in whom asthma and COPD cannot be differentiated or suspicion of overlap (ACO); need for use of ICS/LABA combination, LABA, LTRA, or LAMA that specialist prescription is required in Turkey; patients whose asthma is difficult to

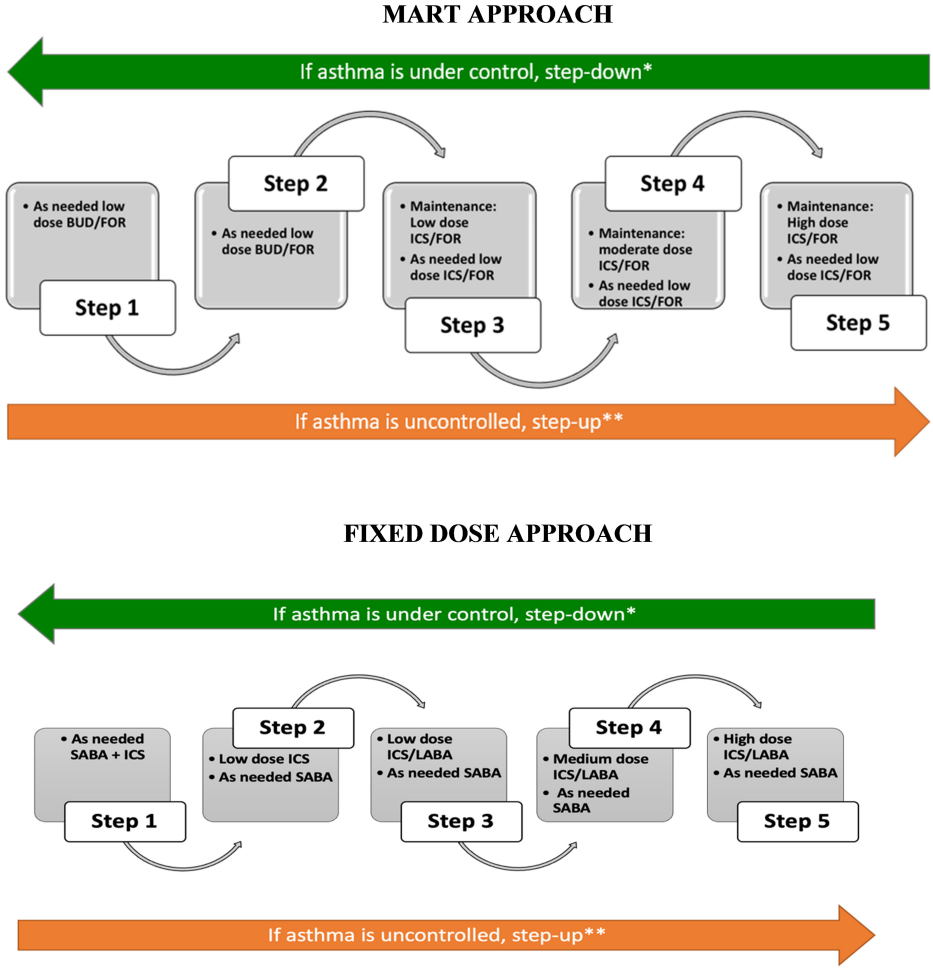


Figure 7. Step-up and step-down based on tracks. BUD, budesonide; FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; SABA, short-acting beta-2 agonist. *See Table 5. **See Figure 3.

control; suspicion of occupational asthma; patients with allergen-induced asthma who require allergy testing (referral to an allergy and immunology specialist); and patients who require specialist care, follow-up, and treatment in terms of comorbidities.[2,3] Before referral of patients to a secondary or tertiary care center from primary care centers, we recommend to initiate an appropriate treatment [Evidence D/strong recommendation] [Recommendation 101, strong consensus].[2,3,20-22] Before referral, we recommend initiation of an appropriate dose of ICS according to the patient's treatment step (Figure 3, Tables 1 and 2) [Evidence A/strong recommendation] [Recommendation 102, strong consensus].[20-22]

When considering referral of patients whose asthma remains uncontrolled despite step 2 treatment, we recommend increasing the ICS daily dose to moderate dose and then referral of the patient to specialist care [Evidence D, strong recommendation] [Recommendation 103, strong consensus].[2,3] Avoidance measures are recommended against asthma triggers that patients are exposed to [Evidence D/strong recommendation] [Recommendation 104, strong consensus].

REFERRAL OF SEVERE ASTHMA

Before the diagnosis of severe asthma, we recommend to ensure the accuracy of the diagnosis of asthma, evaluate adherence to treatment, and improve any existing problems, treat comorbidities, and control triggers appropriately [Evidence A/strong recommendation] [Recommendation 105, strong consensus].[2,32] Despite having these conditions under control, the patients whose asthma remains uncontrolled with high-dose ICS/LABA therapy or is becoming uncontrolled when this treatment is reduced is defined as severe asthma.[2,32]

We recommend referral of patients receiving step 4-5 treatment and followed by specialists who have difficulty in diagnosis and treatment, to the centers experienced in severe asthma, especially for phenotypic evaluation [Evidence D/strong recommendation] [Recommendation 106, strong

Table 5. Recommendations for Stepping Down Treatment for Fixed-Dose Approach [Recommendations 83-90]

Treatment Step	Current Medications	Options for Stepping Down	Evidence
Step 5	High-dose ICS/LABA and OCS	High-dose ICS/LABA is continued, OCS dose is reduced [Recommendation 83, strong consensus]	D
		Following up with sputum eosinophils to reduce OCS dose [No consensus was reached on the form of the recommendation.]	B
		Alternate day OCS [Recommendation 84, consensus]	D
		Using higher-dose ICS instead of OCS [Recommendation 85, strong consensus]	D
		Get expert opinion [Recommendation 86, strong consensus]	D
Step 4	Medium–high-dose ICS/LABA maintenance	ICS dose of the ICS/LABA combination is reduced by 50% [Recommendation 87, strong consensus]	B
		Discontinuation of LABA is not recommended [Recommendation 88, strong consensus]	A
	High-dose ICS and another controller	ICS dose is reduced by 50% while continuing the other controller [Recommendation 89, strong consensus]	B
Step 3	Low-dose ICS/LABA maintenance	ICS/LABA dose is reduced to once a day [Recommendation 90, consensus]	D
		Discontinuation of LABA is not recommended [Recommendation 91, strong consensus]	A
	Medium–high-dose ICS	ICS dose is reduced by 50% [Recommendation 82, strong consensus]	B
Step 2	Low-dose ICS	Switch to once-daily dose [budesonide, ciclesonide, mometasone] [Recommendation 92, consensus]	A
		Switch to as-needed low-dose ICS/FOR treatment [Recommendation 93, Consensus]	A
		Adding LTRA (weak recommendation) [Recommendation 94, consensus]	B
	Low-dose ICS	Switch to as-needed low-dose ICS/FOR treatment [Recommendation 93, consensus]	A
		Discontinuation of ICS totally is not recommended [Recommendation 95, majority agreement]	A

FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

Table 6. Non-Phenotype-Specific and Phenotype-Specific Treatments in Step 5 [Recommendations 109-115]

Non-Phenotype-Specific Treatments			
Recommendation	**Evidence**	**Strength of Recommendation**	**Comment**
High-dose ICS/LABA[2,19]	A	Strong [Recommendation 109, strong consensus]	• In most patients increasing ICS dose provides minimal benefit; however, it is recommended before phenotype-specific therapy. • Be careful for systemic side effects of high-dose ICS.
Add-on LAMA[34,35]	A-B	Strong [Recommendation 110, strong consensus]	• Recommended for uncontrolled patients on high-dose ICS/LABA. • LAMA can be prescribed in a separate inhaler [tiotropium] or as a combination in triple therapy [beclomethasone–formoterol–glycopyrronium, fluticasone furoate–vilanterol–umeclidinium, mometasone–indacaterol–glycopyrronium]. • Add-on LAMA moderately affects pulmonary functions and delays exacerbations. • Combination therapy should include at least medium-dose ICS. • Recommended in ACO. • Recommended before initiation of phenotype-specific therapy.
Add-on azithromycin[36]	B	No consensus	• 500 mg/day 3 times a week for at least 6 months was shown to be beneficial in patients taking high-dose ICS/LABA with persistent asthma symptoms. • Prolongation of QT interval and development of antimicrobial resistance are concerns. • Used in eosinophilic and noneosinophilic asthma. • Consultation with an infectious diseases specialist regarding development of antimicrobial resistance is required.
Low-dose oral corticosteroids[2,37,38] [<7.5 mg prednisolone equivalent]	D	Weak [Recommendation 111, majority agreement]	• Can be beneficial in some severe asthma patients. • Can be tried with close monitoring for severe side effects in patients taking step 4-5 treatment with inadequate response to other treatment options
Phenotype-Specific Treatments			
Recommendation	**Evidence**	**Strength of Recommendation**	**Comment**
Anti-IgE[39]	A	Strong [Recommendation 112, strong consensus]	• It is recommended in patients with uncontrolled asthma despite step 5 treatment and has perennial allergy [compatible clinical symptoms with diagnostic tests] and has a total IgE level between 30 and 1500 IU/mL.
Anti-IL-5 and IL-5R[40-43]	A	Strong [Recommendation 113, strong consensus]	• It is recommended in patients with uncontrolled eosinophilic asthma despite step 5 treatment.
Anti-IL-4/-13[44]	A	Strong [Recommendation 114, strong consensus]	• It is recommended in patients with uncontrolled eosinophilic asthma despite step 5 treatment.
Aspirin treatment after desensitization[45]	B	Strong [Recommendation 115, Strong consensus]	• It is recommended in patients with a diagnosis of NERD and uncontrolled disease despite Step 5 treatment. It has been shown to prevent recurrence of nasal polyps. • Close monitoring is required for adverse effects. • It is recommended to be performed by allergy and immunology specialists in cooperation with ENT physicians. • Doses of 100 mg-1300 mg are used in aspirin desensitization. The experiences in our country show that 300 mg dose is usually sufficient. The effects are mostly related to reduction of inflammation in rhinitis/rhinosinusitis and nasal polyps. It has been shown to prevent exacerbations and reduce OCS usage in asthma.
Bronchial thermoplasty[46]	B	No consensus	• Long-term consequences are not known. It can be performed on a clinical trial basis. • It may be beneficial in experienced centers in selected patient groups.

ACO, asthma-COPD (chronic obstructive pulmonary disease) overlap; ENT, ear–nose–throat; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; NERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroid.

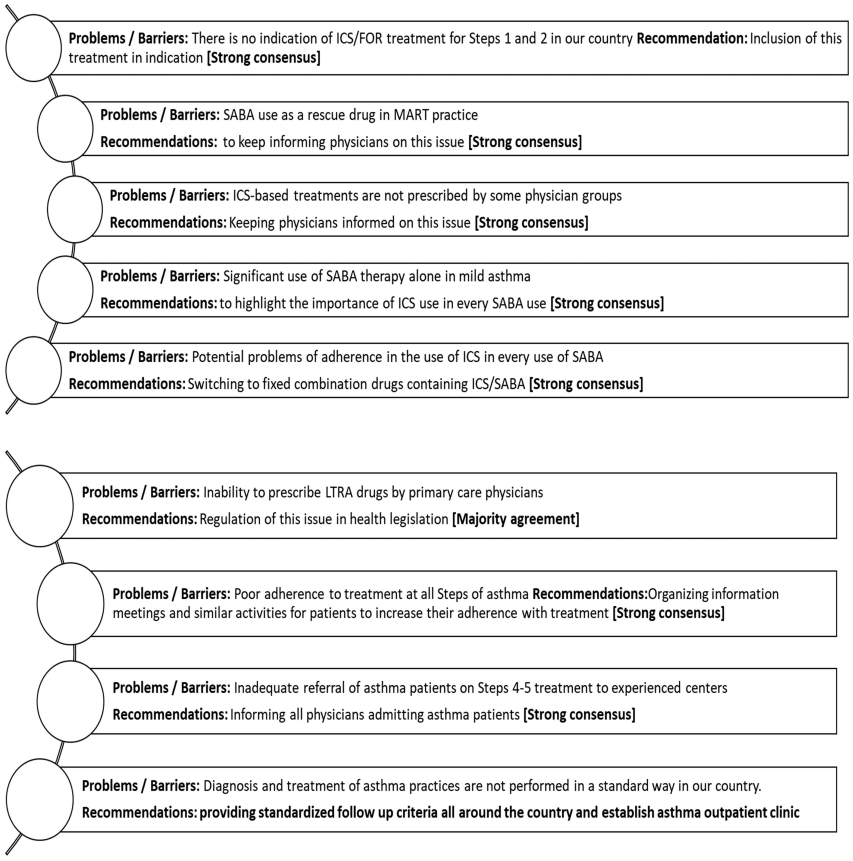


Figure 8. Problems and barriers in Turkey and recommendations provided by expert panel [recommendations 1-9]. ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; OCS, oral corticosteroid; SABA, short-acting beta-2 agonist.

consensus].[32,33] Referral criteria are as follows: cases where diagnostic difficulties are experienced and/or interventional procedures and tests are required for differential diagnoses which cannot be performed, history of a life-threatening exacerbation or intensive care unit admission and mechanical ventilation because of an asthma exacerbation, any suspicion of severe asthma and/or presence of referral criteria for severe asthma, patients who are candidates for a biologic agent, presence of marked eosinophilia, suspicion of occupational asthma, presence of a history of anaphylaxis, venom [bee], food and drug allergies, allergic bronchopulmonary aspergillosis, and exacerbation with nonsteroidal anti-inflammatory drugs.[32,33]

In patients with severe asthma, we strongly recommend to use non-phenotype-specific add-on treatments in steps 4-5 before initiation of phenotype-specific treatments (Table 6) [Evidence A/strong recommendation] [Recommendation 107, consensus] [Recommendations 109-111].[23-26,32,34-38] In these cases, phenotyping studies are performed and evaluated in terms of eligibility for treatment options available in our country (Table 6) [Evidence D/strong recommendation] [Recommendation 108, strong consensus] [Recommendations 112-115].[33,39-46]

COUGH VARIANT ASTHMA

The type of asthma with the only or principal symptom as cough is defined as "cough variant asthma."[47] Although these cases have been shown to benefit from medium-dose ICS/LABA, adding LTRA, and short-term OCS treatment in case of no response was recommended [Recommendation 116, majority agreement].[47] Patients have been reported to benefit from codeine 20-30 mg capsules [red prescription] when added to their treatment, up to 6 times daily.[47]

Conclusion and Recommendations

Asthma management in our country is an up-to-date treatment process because of its high prevalence, an important reason of health service admission, and a high cost especially in patients with severe asthma. It is anticipated that some of the recommendations in our updated treatment approach may cause difficulties in the field. In this context, there is a need for some arrangements and initiatives to be done by individual, social, and country managers in order to reduce and control the burden of asthma in our country. Our suggestions for problems in this regard are given below (Figure 8).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Design – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Supervision – A.F.K., A.F.K., A.Y., B.G., D.E.,F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B.; Resources – G.E.Ç., Ö.A.; Materials – G.E.Ç., Ö.A.; Data Collection and/or Processing – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.; Analysis and/or Interpretation – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K.,

Ö.A., S.B., S.K.Ö., S.R.I.; Literature Search – A.B., E.D., F.Ö.E., G.E.Ç., Ö.A., S.K.Ö., S.R.I.; Writing – A.B., E.D., G.E.Ç., Ö.A., S.K.Ö.; Critical Review – A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., E.D., F.Ö.E., F.Y., G.E.Ç., G.K., İ.K.O., İ.Y., M.K., Ö.A., S.B., S.K.Ö., S.R.I.

Declaration of Interests: A.B., A.F.K., A.F.K., A.Y., B.G., D.E., D.M., F.Ö.E., F.Y., G.K., İ.Y., M.K., Ö.A., S.B. have no conflict of interest to declare. B.G. reports the following interests: grants or contracts from AstraZeneca, Sanofi, GSK, Chiesi, Abdi İbrahim, Deva, Sandoz; honoraria for lectures from GSK, Chiesi, Abdi İbrahim, Deva, Sandoz; participation on a Data Safety Monitoring Board or Advisory Board for GSK, Chiesi; participation to clinical studies for Sanofi, AstraZeneca. E.D. reports the following interests: honoraria for lectures from Novartis, GSK. G.E.Ç. reports the following interests: honoraria for lectures from GSK, Novartis; leadership or fiduciary role in other board, society, committee or advocacy group for EAACI Executive Committee (representative for working groups). İ.K.O. reports the following interests: honoraria for lectures from GSK, AstraZeneca, Novartis, Chiesi, Deva, Abdi İbrahim Pharmaceuticals; participation on a Data Safety Monitoring Board or Advisory Board for GlaxoSmithKline, Deva, Abdi İbrahim Pharmaceuticals; leadership or fiduciary role in other board, society, committee or advocacy group for GINA, Turkish Thoracic Society. S.K.Ö. reports the following interests: honoraria for lectures from Novartis, GSK. S.R.I. reports the following interests: leadership or fiduciary role in other board, society, committee or advocacy group for Turkish Thoracic Society.

Funding: This study received no funding.

REFERENCES

1. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ*. 2008;336(7652):1049-1051. [CrossRef]
2. *Global strategy for asthma management and prevention*; 2022. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf
3. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al.2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217-1270. [CrossRef]
4. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial. *Lancet*. 2003;361(9363):1071-1076. [CrossRef]
5. Busse WW, Pedersen S, Pauwels RA, et al. The inhaled steroid treatment as regular therapy in early asthma [START]. *J Allergy Clin Immunol*. 2008;121(5):1167-1174. [CrossRef]
6. Miligkos M, Bannuru RR, Alkofide H, Kher SR, Schmid CH, Balk EM. Leukotriene-receptor antagonists versus placebo in the treatment of asthma in adults and adolescents: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(10):756-767. [CrossRef]
7. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J*. 2019;53(6):53[6]:1901046. [CrossRef]
8. Bateman ED, Price DB, Wang HC, et al. Short-acting β2 -agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional sabina III study. *Eur Respir J*. 2022;59(5):2101402. [CrossRef]
9. Abramson MJ, Bailey MJ, Couper FJ, et al. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med*. 2001;163(1):12-18. [CrossRef]
10. Beasley R, Bird G, Harper J, Weatherall M. The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity. *Eur Respir J*. 2018;52(5):1800694. [CrossRef]
11. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380(21):2020-2030. [CrossRef]
12. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877-1887. [CrossRef]
13. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet*. 2019;394(10202):919-928. [CrossRef]
14. Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2013;2013(12):CD009019. [CrossRef]
15. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometha sone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomized controlled trial. *Lancet Respir Med*. 2013;1(1):23-31. [CrossRef]
16. Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomized controlled trial. *Lancet Respir Med*. 2013;1(1):32-42. [CrossRef]
17. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β-Agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma a systematic review and meta-analysis. *JAMA*. 2018;319(14):1485-1496. [CrossRef]
18. Agache I, Lau S, Akdis CA, et al. EAACI Guidelines on allergen immunotherapy: house dust mite-driven asthma. *Allergy*. 2019;74(5):855-873. [CrossRef]
19. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2010;5(5):CD005535. [CrossRef]
20. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med*. 2007;356(20):2040-2052. [CrossRef]
21. Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: A post-hoc efficacy analysis of the START study. *Lancet*. 2017;389(10065):157-166. [CrossRef]
22. Camargos P, Affonso A, Calazans G, et al. On-demand intermittent beclomethasone is effective for mild asthma in Brazil. *Clin Transl Allergy*. 2018;8:7. [CrossRef]
23. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev*. 2016;2016(1):CD011721. [CrossRef]
24. Rodrigo GJ, Castro-Rodríguez JA. What is the role of tiotropium in asthma? A systematic review with meta-analysis. *Chest*. 2015;147(2):388-396. [CrossRef]

25. Trinh HKT, Lee SH, Cao TBT, Park HS. Asthma pharmacotherapy: an update on leukotriene treatments. *Expert Rev Respir Med*. 2019;13(12):1169-1178. [CrossRef]
26. Makary CA, Holmes T, Unsal A, et al. Long-term role of zileuton in the treatment of chronic rhinosinusitis in aspirin exacerbated respiratory disease. *Am J Otolaryngol*. 2022;43(1): 103227. [CrossRef]
27. Koskela HO, Purokivi MK, Kokkarinen J. Stepping down from combination asthma therapy: the predictors of outcome. *Respir Med*. 2016;117:109-115. [CrossRef]
28. Ahmad S, Kew KM, Normansell R. Stopping long-acting beta2-agonists (LABA) for adults with asthma well controlled by LABA and inhaled corticosteroids. *Cochrane Database Syst Rev*. 2015;(6):CD011306. [CrossRef]
29. DiMango E, Rogers L, Reibman J, et al. Risk factors for asthma exacerbation and treatment failure in adults and adolescents with well controlled asthma during continuation and step-down therapy. *Ann Am Thorac Soc*. 2018;15(8):955-961. [CrossRef]
30. Rank MA, Hagan JB, Park MA, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2013;131(3):724-729. [CrossRef]
31. Hagan JB, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after reducing inhaled corticosteroids: a systemic review and meta-analysis of randomized controlled trials. *Allergy*. 2014;69(4):510-516. [CrossRef]
32. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373. [CrossRef]
33. Hardtstock F, Krieger J, Wilke T, et al. Use of biologic therapies in the treatment of asthma - A comparative real world data analysis on healthcare resource utilization and costs before and after therapy Initiation. *J Asthma Allergy*. 2022;15:407-418. [CrossRef]
34. Kerstjens HA, Disse B, Schröder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol*. 2011;128(2):308-314. [CrossRef]
35. Brittain D, D'Andrea P, Gruen E, et al. A review of the unique drug development strategy of indacaterol acetate/glycopyronium bromide/ mometasone furoate: a first-in-class, once-daily, single-inhaler, fixed-dose combination treatment for asthma. *Adv Ther*. 2022;39(6):2365-2378. [CrossRef]
36. Undela K, Goldsmith L, Kew KM, Ferrara G. Macrolides versus placebo for chronic asthma. *Cochrane Database Syst Rev*. 2021;11(11):CD002997. [CrossRef]
37. Bakakos P, Kostikas K, Loukides S, et al. Reducing tolerance for SABA and OCS towards the extreme ends of asthma severity. *J Pers Med*. 2022;12(3):504. [CrossRef]
38. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018;52(4):1800703. [CrossRef]
39. MacDonald KM, Kavati A, Ortiz B, Alhossan A, Lee CS, Abraham I. Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008-2018. *Expert Rev Clin Immunol*. 2019; 15(5):553-569. [CrossRef]
40. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLOS ONE*. 2013;8(3):e59872. [CrossRef]
41. Charles D, Shanley J, Temple SN, Rattu A, Khaleva E, Roberts G. Real-world efficacy of treatment with Benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: a systematic review and meta-analysis. *Clin Exp Allergy*. 2022; 52(5):616-627. [CrossRef]
42. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma [CALIMA]: a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141. [CrossRef]
43. Li J, Wang F, Lin C, et al. The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis. *J Asthma*. 2017;54(3):300-307. [CrossRef]
44. Domingo C, Maspero JF, Castro M, et al. Dupilumab Efficacy in Steroid-Dependent Severe Asthma by Baseline Oral Corticosteroid Dose. *J Allergy Clin Immunol Pract*. 2022;10(7):1835-1843. [CrossRef]
45. Stevens WW, Jerschow E, Baptist AP, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: a work group report from the rhinitis, rhinosinusitis and ocular allergy committee of the american academy of allergy, asthma & immunology. *J Allergy Clin Immunol*. 2021;147(3):827-844. [CrossRef]
46. Chupp G, Kline JN, Khatri SB, et al. Bronchial thermoplasty in patients with severe asthma at 5 years: the post-FDA approval clinical trial evaluating bronchial thermoplasty in severe persistent asthma study. *Chest*. 2022;161(3):614-628. [CrossRef]
47. Desai D, Brightling C. Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. *Otolaryngol Clin North Am*. 2010;43(1):123-130. [CrossRef]

Thorac Res Pract. 2023; 24(6): 325-329 DOI: 10.5152/ThoracResPract.2023.23047

Review

Risk Medicine and Transhumanism

Osman Elbek
Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Turkey

Cite this article as: Elbek O. Risk medicine and transhumanism. *Thorac Res Pract.* 2023;24(6):325-329.

Abstract

New developments in bioinformatics, artificial intelligence, and nano-biotechnologies will radically change the practice of medicine to be exhibited in the coming years. One approach that has the potential to carry this changing medical practice into a superhuman age and that has been dominating medical literature in recent years is the risk approach. This article aims to address the issue beyond the dichotomy of good or evil without wrapping the practice of medicine exhibited throughout the human body and history in the sacrament of holiness and falling into the traps of bioconservatism and solutionism.

KEYWORDS: Bioinformatics, future of medicine, omics technology, P4 medicine
Received: *April 17, 2023* ***Accepted:*** *August 28, 2023* ***Publication Date:*** *October 27, 2023*

INTRODUCTION

The new medical approach expressed itself in the persona of a—most likely fictional—physician named "Hippocrates" in the 400s BC, taking the concept of disease from the purview of the gods residing on Mount Olympus and bringing it down to earth. While Prometheus stole fire from the gods, Hippocratic medicine placed health care at the disposal of man as a mortal human being and was shaped on 2 often opposing principles, such as "first, do no harm" and "be useful." The first principle considered the healing effect of nature and advised physicians not to touch or act, while the second positioned itself alongside human action, praxis, and culture and said that in order "to be useful," one needed to take action and not leave the healing to nature.

As we have all witnessed, life evolved mainly in favor of the second principle, with etiology and pathophysiology coming into being as the basic concepts of this action. However, for a long time—even today—patients with diseases were more interested in what the disease meant to them and the roles played by the disease in this context rather than the cause of the disease and the relationship between the factor defined as the cause and the organism. As a result, unlike the majority of physicians, they preferred to think with concepts that would create abstract mental designs of the disease in accordance with their socioeconomic levels rather than technical knowledge of the disease. They demanded information from the physicians in this vein, more often than not a futile request. This structural difference between physicians and patients also formed the basis for centuries of physician-patient miscommunication.

Furthermore, if we consider that the medical knowledge of the time in Boston in 1811 attributed people's deaths to "drinking cold water" or "teething,"[1] then taking an ever-skeptical look at the etiologies explained by medicine may well provide us all with the chance and a way to overcome this miscommunication. We do know that the medical institution and the medical profession, which heftily creates the culture of that institution, are almost always confident, often to the point of arrogance. In fact, the institution was so sure of itself that it was able to claim in 1912 that all preventable diseases would be eradicated from the world by 1993 and—with a positive beautification—eugenics would finally replace evolution![1]

HYGIENE AND VACCINATION

No doubt, there are concrete reasons for the medical institution to be sure of itself. Hygiene and vaccination are just 2 of these reasons. Indeed, hygiene and vaccination correspond to 2 important leaps in medicine's long steeplechase throughout history. The importance of hygiene was known long before Christ—in ancient Greek mythology, *Hygieia* (*Salus* in Roman mythology) was described as the daughter of the god of medicine, Asclepius. We can, however, put a date on when people understood that waste-water disposal in the context of infrastructure was more beneficial to human health than the drugs of medical science. That date is 1878 when construction began on the Paris sewers and water distribution network. For vaccination, we must accept the period 1721-1798 for smallpox vaccinations.

And when it comes to sewers and water distribution, we have to mention Edwin Chadwick. He is known as a lawyer and journalist. As such, he proves a valuable example in terms of showing that non-medical professionals can also make vital contributions to the field of health. Chadwick played a vital role in shaping the "Poor Law" and the "Factory Act" amid the negative effects on people and towns of capitalist modernization, known as the "industrial revolution," in the late 18th century.[2] Following these initiatives, he established a causal relationship between "dirt and disease" in his report on urban

Corresponding author: Osman Elbek, e-mail: osmanelbek@yahoo.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

health in 1840 and developed recommendations for sanitation conditions, waste-water drainage for houses and streets, and water supply. He believed it was possible to prevent diseases and deaths by providing adequate hygiene through sewers and preventing air pollution with good ventilation. Similarly, he underscored in his report that the lack of water resources stops people from developing cleaning habits and stated that the quality of both drinking water and utility water needed to be raised.[2] He also determined that building sewage and sewer systems in compatible with geological areas is imperative for health, particularly the health of the working class. Out of his adherence to the theory of miasma, he suggested that houses, streets, and rivers be purified from bad odors through drainage. Chadwick's perspective and efforts led to the promulgation of the Public Health Act in England in 1848. This is the first law that states that the government is responsible for the health of the people.[2]

These 2 leaps in the history of medicine in the form of hygiene and vaccinations are quite different from one another, qualitatively speaking. This is because, with vaccination, the institution of medicine succeeded in changing the protection that exists in humans *naturally* through *artificial,* man-made means. Undoubtedly, the significance of this success in terms of health was that it prevented the deaths of millions. But this achievement was also the first realization that the culture created by human civilization could change the given nature of man. To put it another way, the medical institution had been balancing nature and culture with 2 opposite principles since the 400s BC, but it was now upsetting that balance in favor of culture for the first time with vaccinations and announcing to mankind that culture could overcome nature and change its original structure. There is no doubt that this awareness and defiance of nature by the medical establishment would also give rise to the idea of creating the future in a completely different form, which could mean the road to hell is paved with good intentions.

Regardless, the competence that the medical institution gained over time led to a change in the strategies for combating diseases. For instance, plague patients were able to live in society provided that they obeyed some rules due to changing medical practices, unlike patients with leprosy, who were informed of their rights and exiled from society. In other words, as a result of the medical institution, society responded to leprosy patients with the verb "do not do" and to plague patients with the verb "do." As a result of the smallpox [and now coronavirus disease 2019 (COVID-19)] vaccinations, disease is now a problem that can be terminated (managed for COVID-19) in the community. Looking at these processes from Michel Foucault's point of view, we can identify their main themes as "sovereignty" in leprosy, "disciplinarian authority" in the plague, and "governmentality" in COVID-19 and smallpox.[3] However, it would be a mistake to think that governmentality is reflected in life through vaccination alone. Far from it, the concept of risk, which is widely used in the medical literature, is also a part of this process.

RISK

Describing any deviation of the human body from its "normal" functioning as "sickness," the medical institution has throughout history aimed to repair the body's deviant function and restore it to its original state. But is it still pursuing this goal?

It would be appropriate to consider the patenting of Viagra® in 1996 as a guiding example here. Up until that date, treatment was limited to restoring existing or accepted dysfunctions to normal functioning. But sildenafil changed the nature of the phallic manifestation of masculine power on the basis of "much more" than normal and "many more times" than normal. With Viagra®, it was now possible to go beyond the old "normal" functioning, go beyond the previously defined normal limit, and "upgrade" the function to the next level.[4]

Indeed, sildenafil has taken the concept of "maximization," denoted by the "more" of capitalism, directly into the field of medicine. Viagra® has proven that the performance of the creature known as a human being does not have to be confined to existing norms but can be "enhanced."[4] A similar masculine process had already taken place in the field of plastic and reconstructive surgery. Body parts such as the nose, breast, forehead, hips, and abdomen, which had long been accepted as "ugly" and "unacceptable" in accordance with the patriarchal beauty norms of the day, were cut and pruned to conform to the valid norms, and the bodily form was recreated, so to speak, made acceptable, and "upgraded." What is more, the fact that this "upgrade" procedure was almost always performed on women's bodies as a result of the patriarchal world showed that the reason for this aesthetic madness was the result of internalized necessities rather than personal "free choices."

Undoubtedly, this level of skill achieved by the medical institution has made it possible to beat many diseases. As such, we must consider the subject beyond the absolute concepts of "good" or "bad." Risk medicine not only eliminates disease but also upgrades the human body by eliminating the risks it carries that lead to disease and promises mankind a life where cheating old age and death is an achievable goal. Under this approach, nano- and biotechnologies that will minimize or even eliminate risks, in particular *Big Data* and artificial intelligence, are included in the medical field as elements that can maximize human performance with the objective of "human enhancement."

GENOMICS

When we consider the history of medicine, we can see that almost every new development and innovative step is based on a very legitimate and indisputable justification valid at that moment, but the step taken afterward is quickly expanded and stretched. One does not need a crystal ball to predict that we will see the same thing happen in the field of risk medicine. To illustrate, the CCR5 gene can be considered a current example in the prevention of AIDS, one of the leading health problems of our age.

The presence of the CCR5 gene in a mutant state in some people can prevent that person from getting AIDS by not allowing HIV to enter the cell. In which case, should we artificially mutate the CCR5 gene, a risk factor for AIDS, from its natural state and tamper with the human genome in this context or not?

Box: Genome Editing and CRISPR-Cas9 Technology

Genome editing is the technology that allows an organism to alter its DNA. There are multiple such technologies. The one that delivers faster, cheaper, and more accurate results than other methods is the recently developed CRISPR-Cas9 system. In this method, "Guide RNA" is created to be attached to a specifically targeted part of the DNA. The resulting RNA binds to the Cas9 enzyme, and the enzyme cuts the DNA from the desired location. It is then tampered with by adding, deleting, or replacing the cut piece.

The story of the babies named Lulu and Nana, who were brought into the world by Dr. He Jiankui using Clustered Regularly Interspaced Short Palindromic Reports/Cas9 (CRISPR-Cas9) technology to justify HIV, effectively answered this question. However, Jiankui's research and the fate of the babies he used as subjects have not been published in any academic scientific journals to date, and Jiankui has been imprisoned and fined for his unethical experiment on humans. But this should not prevent us from discussing how the CRISPR-Cas9 technique, which regulates base pairs and DNA fragments in cells and living organisms, shows its potential within the scope of risk medicine—indeed, it has not prevented this.

Dizzying developments are taking place in genomics today. To begin with, medicine and science have gained a lot of momentum in this field. For example, a complete sequence of the human genome can now be obtained in 24 hours.[5] In addition, CRISPR technology has made it possible in the last decade to form gene knockouts, create knockout mice and animals, and perform genetic screening and multiplex editing. The applications of this technology in medicine and agriculture will shape our future. Achieving an FDA-approved drug for the treatment of sickle cell anemia, producing CRISPR-based treatment options, administering CRISPR cell therapies, and changing the nature of food and animals will be commonplace developments over the next decade.[5]

Furthermore, CRISPR technology will also give us the means to eliminate the genetic risk factors behind many diseases, particularly cardiovascular diseases, the leading cause of death. But at the same time, when this technology meets Viagra®'s idea of not being confined to bodily limits but enhanced and upgraded on the basis of "more," it promises/will promise mankind a superhuman age. But we have to foresee that this superhuman age will also be an age of "positive" eugenics based on personal choice in line with the "from chance to choice" approach, and that aims to enhance rather than weed out.[4] In other words, the change in the field of medicine means neglecting and ignoring the principle of "first, do no harm," which meant letting nature take its course in 400 BC and transitioning to a process in which man completely dominates evolution and fully creates man just as the transhumanist movement intends, instead of chance-based selection.

Box: Transhumanism

It is a cultural movement that aims to leverage technology and science to increase human physical and cognitive abilities, eliminate undesirable conditions such as old age, disease, and death, and improve on the basic characteristics of human beings. This movement advocates and supports the use of advanced technologies such as nanotechnology, gene cloning, and artificial intelligence on humans to achieve its goals. One situation desired in transhumanism is to encode the human body and mind and replace them when necessary with new/artificial organs prepared using advanced technology. This is because transhumanists think that in the wake of such interventions, humanity will emerge from childhood and enter the posthuman age.

Specialized Risks

The concept of risk will play a key role in shaping a transhuman world that aims to perfect human beings in the coming decades because the use of the concept of risk, which originates from the French word *risque,* meaning "damage insured in maritime trade,"[6] has a quite different meaning in medicine from its original use.

In medicine, the concept of risk almost always corresponds to a quantitative acceptance that can be reduced or changed by a number of individual measures. In the words of François Ewald, "Nothing is a risk in itself, there is no risk in reality. But on the other hand, everything can be a risk; it all depends on how someone analyzes the danger, considers the event."[7] Yet, despite this reality, almost everything in the medical literature is placed spontaneously into the "risk concept" basket. For example, smoking, physical inactivity, poor diet, and air pollution will trigger inflammation and aging; this triggering will lead to cardiovascular diseases with chronic obstructive pulmonary disease (COPD) in various pathophysiological ways; COPD, heart failure, atrial fibrillation, diabetes, pulmonary hypertension, and ischemic heart disease will each turn into a risk factor for the other, and all these risks can be reduced with "triple (inhaler) treatment…"[8]

One of the key problems with the risk concept approach is that it increases dependence on specialties and experts. There is no need to be an expert on the health-disrupting effects of risks such as war-conflict, unemployment, poverty, and poor housing conditions. These risks are the knowledge that common sense imparts to everyone. However, common sense falls short when it comes to assessing the malignancy risk of a nodule detected in the lung. These risks require the personal opinions that only experts can provide and the percentage probability results calculated by the smart application programs developed in recent years. However, it is interesting that, contrary to the socially accepted risks that common sense shows to almost everyone, the risks requiring expertise are prioritized more in health, and health services are given depth by taking these "specialized risks" into account. Undoubtedly, the main factor underlying this strange paradox is the marketization of health services and the fact that risks exceeding common sense have created a field of commercial gain as a result of physician visits and the use of advanced technology. Clearly, the higher the risk in the shaped health market, the higher the commercial return.

Smoking and New Risks

The Framingham Heart Study began in 1948 and became a milestone in the history of medicine by proving the existence of a relationship between smoking and coronary heart disease in 1959. However, this research has been criticized in recent years in terms of the risks it predicts. The most important criticism in this context is that "smoking" is investigated as

a risk in this research, but cigarette advertisements and taxes were not investigated as a possible risk factor. Considering that advertising and taxes have a significant effect on tobacco product use, this criticism is not without reason.

However, the Framingham Heart Study addressed risks on a personal level as opposed to a societal and structural basis, such as advertising and taxation. At the time of the study, physicians were mostly working in consulting rooms, and the researchers wanted to monitor the factors that could be applied in the consulting room, were directed at the individual, and were quantitative, were easily measured, and were clinically observed to ensure the physicians did not object to the study but were involved in it.[9] Besides, the main goal of the team conducting the research was to help propagate the doctrine of "preventive medicine" applied in the consulting rooms as opposed to infrastructure improvements or free treatment for tuberculosis.[9] When the basis, structure, and ideology are all couched within this framework, it is not surprising that the research targeted individuals smoking and not advertisements or taxes. In fact, this approach not only shows that the medical institution deals with health and disease on a personal basis, but it also validates the finding that risk is shaped by how the danger is analyzed, as Ewald said.

It should be emphasized that the Framingham study has been trying to determine the genome sequence of the participants since 2017 and identify very likely new risks based on these sequences. Ulrich Beck defined the concept of "risk society." His emphasis saying "… power problem is actually a problem of definition. It is the question of who, with what legal and intellectual resources, gets to decide what counts as a 'risk,' what counts as a 'cause,' and what counts as a 'price'"[10] stands out in terms of identified risks and perceptions of medicine, shaped according to these risks.

Predictive, Preventive, Personalized, and Participatory Medicine

The medical institution today collects data from the respiratory, nasal, and systemic (blood, urine, and skin) areas using sputum, imagery, and bronchoscopy to reveal the risks of the diseases it chooses as the subject of research on the respiratory system. It attempts to describe the markers and omic deviations that predetermine the development of diseases from these data and tries to form "treatable targets" for these risk areas it detects.

In other words, the medical institution aims to identify not the disease but the risks that lead to the disease and to treat these risks on a personal basis before the disease develops, using the predictive, preventive, personalized, and participatory (P4) medical approach and by including machine learning in the process today. This is because the P4 approach mainly takes risks on an individual basis and proposes a personal treatment policy to counter the risks it detects.[11]

Box: P4 Medicine

It is a medical approach that aims to develop appropriate approaches and treatments for each person's biological, cellular, and physiological makeup. It aims to predict the disease or change by analyzing very different data with its "predictive" feature; to prevent the pre-disease period or change with the "preventive" aspect; to provide personalized health services specific to each individual with its "personalized" approach; and to take responsibility and make decisions about the individual's/patient's own health/disease with its "participatory" philosophy.

P4 medicine rightly criticizes today's medical approach as a reactive, organ-disease-centered, and symptom-oriented treatment approach and proposes a new medical practice that pays attention to the pre-disease period when symptoms have not developed by leveraging the means offered by *Big Data* and omic technologies instead, that pays attention to the pre-disease period when the symptoms have not manifested, that aims to apply proactive and preventive "treatment/upgrades" to counter the individual risks detected at this time, and that advocates a person-centered, needs-oriented, and biologically variable life-long personal health regime.[12]

Box: *Big Data*

It is the name given to the meaningful and processable form of data obtained from observation, research, search engines, blogs, forums, social media, network logs, photos, videos, log files, bank accounts, sensors, devices, and other sources. It is distinctive in that it contains much more volume compared to previous data, acquires these data much faster, and includes very broad diversity. This informatics field enables the systematic extraction of information by analyzing the collected data.

Box: Omic

Using different technologies, it aims to investigate molecules, the relationships between different molecules, and the effects of the cell to comprehensively analyze biological systems. If these studies examine genomes, they are called genomics; if they examine protein sequences, they are called proteomics; if they examine small metabolic molecules, they are called metabolomics; and if they examine mRNA transcripts, they are called transcriptomics. The study of cells, tissues, or organisms through omic technology creates system biology.

Clearly, this new medical approach, which prioritizes risk and aims to treat the detected risks before the disease develops, will deepen and diversify the health market in the context of "preventive medicine." Although the level of evidence is still very low, we can include laboratory-based tests that are rapidly entering the market, advanced technological imaging applied during screening, and some interferon examinations described as risk factors for COVID-19 in the recent epidemic, as well as glutathione or ozone-like treatments that are claimed to reduce possible risks.

Another important problem with the risk medicine approach is that it regards exposure to tobacco smoke, air pollution, etc. as the inevitable result of the human civilization we live in and does not question their existence. Risk medicine deals with the pathophysiology caused by an individual's exposure to tobacco smoke or particulate matter and the risk targets that will change the possible outcome in these pathophysiological pathways. Its radar of investigation and interest does not cover government incentives for the tobacco industry or the air pollution caused by incentivized industrialization,

unless they lead to individual consequences. Risk medicine deals with how people can protect and treat themselves physically on the individual plane and *upgrade* themselves against such "inevitable" risks of modernity. In this context, Ulrich Beck's concept of "being poisoned to the extent tolerated" adequately describes this approach by risk medicine, which ignores the social and systemic reasons behind risk.

A key problem that risk medicine has in terms of the future is the policies it proposes and will propose to control the problems it defines as risks. Undoubtedly, these individual treatments/upgrades it will recommend will primarily apply to the socioeconomically advantaged segments of society, wage-wise. Yet, the segments that neoliberalism has left unprotected are predominantly the socioeconomically disadvantaged groups that are trying to survive with real risks. Furthermore, these treatment/upgrade approaches, intended to reduce personal risks, will (or have already) easily meet up with the idea of Lula and Nana's genetically modified babies based on the performance-enhancing doctrine of Viagra® treatment soon (or covertly today). However, the intention of such a meeting this time will not be to create a protective shield against HIV; on the contrary, the meeting will take the shape of designing a perfect superhuman body to increase the performance of the yet unborn child, make it more intelligent, give it perfect vision, or reduce the risks of chronic disease and prevent omic deviations in the context of risk mitigation. Undoubtedly, such an "upgrade" intervention means that human society, which still has a socioeconomic hierarchy and is classified as sociocultural, will evolve into a hierarchical class structure and stratification based on biology with the creation of the superhuman body in the coming decades.

End of the Word

To be frank, neither a human's given body nor the practice of medicine itself is sacred. Moreover, regardless of whether this is expressed openly or secretly, the practice of medicine has been developed from the very beginning to correct and repair the body made by nature and the flaws it creates, making it an inherent act of human praxis and culture. It is a reasonable, expected, and even desired goal for this act to change in line with the knowledge, experience, and skills of the time. This is why one must not oppose omic technology, *Big Data*, and nano/biotechnology by falling into the trap of bioconservatism. Furthermore, just as in every period of history, medical practice is not free of micro- and macro-power structures. Therefore, the notion that the technology developed by being caught in the trap of solutionism will automatically bring about solutions to health problems or that it will create a better world for everyone is incorrect. On the contrary, a risk medicine approach developed on the basis of a neoliberal ideology that sacrifices everything and every value on the altar of price, success, winning, surviving, not falling, and maximizing profit–benefit and that ignores the social determinants of health could ultimately create hell regardless of its intentions.

Given this point of view, the aim of this article is not to argue that omic technology, risk reduction, and genetic interventions are wrong and that they should be abandoned. On the contrary, this article argues that these developments in the field of medicine and science should not be considered as being free from the patriarchal capitalist system and the power relations of the medical institution, including medicine, as in the dominant medical literature, and that we must describe the necessary control mechanisms on both the personal and social planes without becoming infatuated with technology and progress in a world rushing headlong into a superhuman society.

Finally, as the author of this article has tried to do, although pondering and questioning one's own praxis in the practice of medicine is valuable, it is not enough. On the contrary, knowing that the concepts of health and disease are constructs directly related to social and societal processes, we must socialize the issue and include all segments of society in common thinking and decision-making mechanisms, ultimately ensuring that future medical doctrine is grounded in a world of ethics, rules, and laws that will not be trapped within the borders of the nation-state.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author has no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Jones DS, Podolsky SH, Greene JA. The burden of disease and the changing task of medicine. *N Engl J Med*. 2012;366(25):2333-2338. [CrossRef]
2. Gürsoy Taner Ş. Edwin Chadwick. *Toplum Hekim*. 2006;21(4):262-270.
3. Keskin F. Salgın hastalık ve iktidar. Türk Tabipleri Birliği COVID-19 Pandemisi 6. Ay Değerlendirme Raporu [Accessed: 04.04.2023]. *Türk Tabipleri Birliği*. Available at: https://www.ttb.org.tr/kutuphane/covid19-rapor_6/covid19-rapor_6_Part75.pdf; September 17, 2020.
4. Ferry L. Transhümanist Devrim. Türkiye İş Bankası Kültür Yayınları; 1st edition, January 2023, İstanbul.
5. Wang JY, Doudna JA. CRISPR technology: a decade of genome editing is only the beginning. *Science*. 2023;379(6629):eadd8643. [CrossRef]
6. Available at: https://www.nisanyansozluk.com/kelime/risk (Accessed: 04.04.2023)
7. Ewald F. Insurance and risk. Available at: https://lchc.ucsd.edu/cogn_150/Readings/ewald/ewald.pdf. *The Foucault Effect: Studies in Govermentality*. The University of Chicago Press; 1991 (Accessed: 04.04.2023)
8. Solidoro P, Albera C, Ribolla F, Bellocchia M, Brussino L, Patrucco F. Triple therapy in COPD: can we welcome the reduction in cardiovascular risk and mortality? *Front Med (Lausanne)*. 2022;9:816843. [CrossRef]
9. Aronowitz R. Risk Tıbbı. *Koç Üniversitesi Yayınları*, September 2019. İstanbul.
10. Beck U. Sağa Karşı: Hayek ve Liverter Kelime Dağarcığı. *Sosyal Bilimler*. Available at: https://www.sosyalbilimler.org/wp-content/uploads/2021/10/Ulrich-Beck-Korku-ve-Risk-Toplumu.pdf (Accessed: 04.04.2023)
11. Wouters EFM, Wouters BBREF, Augustin IML, Houben-Wilke S, Vanfleteren LEGW, Franssen FME. Personalised pulmonary rehabilitation in COPD. *Eur Respir Rev*. 2018;27(147):170125. [CrossRef]
12. Sagner M, McNeil A, Puska P, et al. The P4 health specturum – a predictive, preventive, personalized and participatory continuum for promoting healthspan. *Prog Cardiovasc Dis*. 2017;59(5):506-521. [CrossRef]

Thorac Res Pract. 2023; 24(6): 330-331 DOI: 10.5152/ThoracResPract.2023.22216

Letter to the Editor

Sarcoid-Like Mediastinal Reaction in the Context of Histiocytic Sarcoma

Sergio Chávez Valladares[1], Blanca de Vega Sanchez[2], Clarisa Simon Perez[1], Carlos Disdier Vicente[3], Henar Borrego Pintado[4]

[1]Department of Orthopedic and Trauma Surgery, Hospital Clínico Universitario, Valladolid, Spain
[2]Department of Interventional Pulmonology, Hospital Clínico Universitario, Grupo Emergente de Neumología Intervencionista Sociedad Española de Neumología y Cirugía Torácica (SEPAR), Valladolid, Spain
[3]Department of Pulmonology, Hospital Clínico Universitario, Valladolid, Spain
[4]Department of Pathology, Hospital Clínico Universitario, Valladolid, Spain

Cite this article as: Chávez Valladares S, de Vega Sanchez B, Simon Perez C, Disdier Vicente C, Borrego Pintado H. Sarcoid-like mediastinal reaction in the context of histiocytic sarcoma. *Thorac Res Pract.* 2023;24(6):330-331.

Received: *November 22, 2022* ***Accepted:*** *July 25, 2023* ***Publication Date:*** *September 11, 2023*

Dear Editor,

The link between sarcoidosis and sarcoma is both infrequent and scarcely documented in the literature.[1] Histiocytic sarcoma (HS) is still a rare entity whose differential diagnosis includes histiocytic/dendritic tumors, myeloid, or lymphoproliferative neoplasm, melanoma, or carcinoma[2]

A 47-year-old male, without any remarkable personal records, consulted a fourth proximal right-hand phalanx and gummy lump. Ultrasound (US) revealed a 4-5 cm solid lump, hypervascular, and not fixed to deep layers without periosteum invasion. Magnetic resonance imaging (MRI), T2, T1, and short tau inversion recovery (STIR) showed peripheral enhancement, suggesting a mesenchymal origin. After extirpation, the pathology study was compatible with HS (atypical mesenchymal hystiocitary cell proliferation).

Therefore, an extension study was performed using computerized tomography (CT), gammagraphy, and positron emission tomography–CT. Computerized tomography showed multilevel mediastinal adenopathies in 5 (SUVmax 4.8), 4R (SUVmax 14.9), 7 (SUVmax 13.6), 11R (SUVmax 13.2), and 11L (SUVmax 13.1) territories. Endobronchial US-guided transbronchial needle aspiration (EBUS-TBNA) revealed multilevel mediastinal adenopathies suggestive of malignancy (hypoechoic round, marked margins, no hilar core) in 7 and 11R territories. Samples were taken with an ECHO-HD-22-EBU S-P-C® using 3-needle punctures. The results demonstrated both lymphoid tissue and histiocytic non-necrotizing granulomatous areas, which tested negative for mycobacteria in both the Ziehl–Neelsen stain and Löwenstein–Jensen culture.

In addition to EBUS-TBNA, further videomediastinoscopy (VM) by the Carlens technique and biopsy of 2R and 4R territories were obtained, showing non-necrotizing granulomas containing epithelioid and giant multinucleated cells. Based on these findings, a sarcoid-like reaction (SLR) was diagnosed. No relapse was observed after 1 year of follow-up with periodic CT and MRI.

Sarcoid neoplasms may be associated with other malignancies in up to 2.5%. However, the link between sarcomas and sarcoidosis remains unclear. Sarcoidosis is a well-known risk factor for skin, hematologic, digestive tract, and renal or liver malignancies.[3] Some authors have reported a lower-risk link between mediastinal non-caseating granulomas (NG) and locoregional relapse in patients with lung cancer.[4]

Unfortunately, in patients already diagnosed with both sarcoidosis and cancer, the discovery of NG may lead to a mistaken belief in sarcoidosis relapse when an SLR (NG in the absence of systemic symptoms)[5] may develop, which may lead to overestimation of tumor stratification and therefore alter correct management.[1]

The correlation between SLR and sarcomas has rarely been reported in the literature.[1] Although the pathogenesis remains obscure, there is evidence that the presence of circulating tumoral antigens and/or chemotherapy drugs may lead to a host immune response.[5] Second, there is a well established occurrence of sarcoidosis as paraneoplastic syndrome. Finally, chronic inflammation status or cancer therapy drugs may modulate the cytokine environment increasing lymphocyte rates which may lead to SLR.

Corresponding author: Sergio Chávez Valladares, e-mail: scv9925@gmail.com

Copyright@Author(s) - Available online at thoracrespract.org. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

A mandatory extension study must be performed, including histological sampling for every patient affected by sarcoma. Although EBUS-TBNA allows for a minimally invasive mediastinal approach, identification of malignancy-matched characteristics, and sample collection, VM remains the gold standard.

In the presented case, only after VM, malignancy was ruled out and it prevented from diagnosing a sarcoma metastasis when an SLR was occurring. Despite rare association with sarcomas, SLR must be included in the differential diagnosis of every patient suffering from sarcoma and presenting with lung NG.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.C.V.; Supervision – B.D.V.; Resources – C.S.P.; Materials – H.B.P.; Literature Search – C.D.V.; Writing – S.C.V.; Critical Review – B.d.V.S.

Declaration of Interests: The authors have no conflict of interest to declare.

REFERENCES

1. Espejo AP, Ramdial JL, Wilky BA, Kerr DA, Trent JC. A non-random association of sarcoidosis in patients with gastrointestinal stromal tumor and other sarcomas. *Rare Tumors*. 2018; 10:2036361318787626. [CrossRef]
2. Hung YP, Lovitch SB, Qian X. Histiocytic sarcoma: new insights into FNA cytomorphology and molecular characteristics. *Cancer Cytopathol*. 2017;125(8):604-614. [CrossRef]
3. Bonifazi M, Bravi F, Gasparini S, et al. Sarcoidosis and cancer risk: systematic review and meta-analysis of observational studies. *Chest*. 2015;147(3):778-791. [CrossRef]
4. Steinfort DP, Tsui A, Grieve J, Hibbs ML, Anderson GP, Irving LB. Sarcoidal reactions in regional lymph nodes of patients with early stage non-small cell lung cancer predict improved disease-free survival: a pilot case-control study. *Hum Pathol*. 2012;43(3):333-338. [CrossRef]
5. Ravaglia C, Gurioli C, Casoni GL, et al. Sarcoid-like lesion is a frequent benign cause of lymphadenopathy in neoplastic patients. *Eur Respir J*. 2013;41(3):754-755. [CrossRef]