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Address: Büyükdere Cad. 199/6, 34394, Şişli, İstanbul, Türkiye
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Editors in Chief:
Oğuz KILINÇ
İpek Kıvılcım OĞUZÜLGEN
Address: Turan Güneş Bulvarı, Koyunlu Sitesi No: 175/19 Oran, Ankara, Türkiye
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ABOUT

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

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Abstracting and indexing

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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.

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Thoracic Research & Practice
Official Journal of the Turkish Thoracic Society

CONTENTS

ORIGINAL ARTICLES

171 **Türkiye's 3-Year Coronavirus Disease 2019 Publication Performance in the Shadow of the Pandemic: A Bibliometric Analysis**
Yağmur Ekenoğlu Merdan, Okan Aydoğan

178 **Normative Values and Calculation Formulas of Respiratory Muscle Strength of Adults in Turkish Society: A Population-based Study**
Esra Pehlivan, Halit Çınarka, Kürşad Nuri Baydili, Mehmet Burak Uyaroğlu, Pınar Baştürk, Amine Ataç

184 **Clinical Course of Coronavirus disease 2019 C-19 in Patients with Bronchiectasis**
Ebru Çakır Edis, Aykut Çilli, Deniz Kızılırmak, Ayşın Şakar Coşkun, Abdullah Sayıner, Sedat Çiçek, İnci Gülmez, Meltem Çoban Ağca, Benan Çağlayan, Neslihan Özçelik, Nurdan Köktürk, Birsen Ocaklı, Eyüp Sabri Uçan, TEBVEB researchers*

188 **Central Sleep Apnea in Children—10 Years Experience at a Tertiary Sleep Laboratory**
Cansu Yılmaz Yeğit, Mine Kalyoncu, Mürüvvet Yanaz, Aynur Guliyeva, Merve Selçuk, Şeyda Karabulut, Meltem Sabancı, Pınar Ergenekon, Yasemin Gökdemir, Fazilet Karakoç, Refika Ersu, Bülent Karadağ, Ela Erdem Eralp

LETTER TO THE EDITOR

193 **Comments on: Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients**
Kundan Nikit Mehta, Hiral Gulab Ramnani

AUTHOR'S RESPONSE

195 **RE: Comment on: Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients**
Sonam Spalgais, Parul Mrigpuri, N Ravishankar, Raj Kumar

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Original Article

Türkiye's 3-Year Coronavirus Disease 2019 Publication Performance in the Shadow of the Pandemic: A Bibliometric Analysis

Yağmur Ekenoğlu Merdan[1], Okan Aydoğan[2]

[1]Department of Medical Microbiology, Biruni University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Medical Microbiology, İstanbul Medipol Faculty of Medicine, İstanbul, Türkiye

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Abstract

OBJECTIVE: The pandemic created by coronavirus disease 2019 (COVID-19) has led researchers to study to deal with this infection. The number of studies about it being performed and published is increasing over time. Due to the dramatic growth of COVID-19 scientific publications, we conducted a bibliometric and visualized study to better understand the progress, collaborations, and trend topics of COVID-19 publications in Türkiye.

MATERIAL AND METHODS: The scientific literature on COVID-19 research in Türkiye from 2020 to 2022 was extracted from the Scopus database and analyzed using bibliometric and scientometric techniques.

RESULTS: A total of 426.662 COVID-19-related publications were published worldwide in the 3-year period and Türkiye ranked 12th according to both publication (8.394) and case numbers (17.004.677). The most cooperations of Türkiye were with the USA, the UK, and Italy. The 5 most used keywords were determined as "COVID-19," "SARS-CoV-2," "Pandemics," "Coronavirus," and "Anxiety" respectively. It was determined by the keyword analysis that the most focused topics were related to the "COVID-19 clinic."

CONCLUSION: Türkiye did not lag behind in the number of studies on her geography, and it was seen to be in the leading position compared to the Middle East countries. It is important to periodically evaluate such a large number of research articles from a broad perspective for planning and direction of future studies.

KEYWORDS: COVID-19, bibliometric analysis, Türkiye, VOSviewer
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INTRODUCTION

The onset of the coronavirus disease 2019 (COVID-19) pandemic, the diagnosis and treatment of the disease, and the lack of knowledge about the evolution and mutations of the newly identified virus have encouraged extensive research in the academic field, which has been reflected in the scientific literature with an exponentially increasing number of publications.[1,2]

Bibliometric analyses are a popular method used to research and analyze a large number of scientific data. Bibliometric studies are widely used by researchers for various reasons, such as determining emerging trends in publication and journal performance, cooperation models and research components, and exploring the intellectual structure of a particular field in the current literature.[3,4] While these studies enable the evolutionary nuances of a particular scientific topic to be revealed, they also provide light on different areas that have emerged in this regard. Mapping by visualization in the process of generating meaningful information from big data obtained through bibliometric studies has garnered a lot of interest in recent years and has started to become widespread.[5,6] Vosviewer is a useful application that is often used in the visualization of data obtained in bibliometric analysis studies, where complex relationships are revealed in data mining. With the COVID-19 pandemic, the focus of attention of researchers all over the world has been COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and related issues. Hundreds of thousands of studies have been planned in a short time and have been included in the scientific literature as publications.[2]

In keyword network maps, the size of the circles is proportional to the frequency of the associated term. The relationship of keywords is determined by the number of times they are mentioned in the same article. Keywords with a high relationship level are located close to each other, while the colors of the circles indicate the related keyword clusters.[4,7]

In events such as pandemics and disasters that affect every segment of society and the scientific world, it is of great importance to conduct fast and effective scientific studies and submit the data to the literature. Determining the size, orientations, evolution, and research dimension of COVID-19 publications in the literature from a broad framework is important

Corresponding author: Yağmur Ekenoğlu Merdan, e-mail: ymerdan@biruni.edu.tr

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for planning new studies on the subject and identifying deficiencies. By means of bibliometric analyses and visualization of network maps, it can be ensured that the literature related to the subject is examined in all its dimensions and can be a guide for researchers.

In this study, we aimed to investigate the most cited publications, research areas, the most productive institutions, and the most cooperative countries to determine the publication performance of our country related to COVID-19 in the 3-year period since the beginning of the pandemic and to examine the keywords used. As a result of the literature research we conducted, it has been seen that our study is the research covering the widest period in which COVID-19-related data of our country are presented.

MATERIAL AND METHODS

Publications registered in the Scopus database between 2020 and 2022 with the address "Türkiye" were included in the study. Recent search query image made on Scopus is "TITLE-ABS-KEY ("COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "novel coronavirus 2019") AND PUBYEAR > 2019 AND PUBYEAR <2023 AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (AFFILCOUNTRY, "Türkiye")). The keywords of the obtained data were visualized by mapping with the VOSviewer program (version 1.6.16). In the keyword analysis, the first 2000 publications that received the most citations between 2020 and 2022 were evaluated. Bibliometrically, the number of publications by year, language of publication, country, institution /organization, research area, and author were presented. In addition, the relationship between the number of COVID-19 cases and the number of submitted articles by country was investigated. In our study, SCImago Journal Rank (SJR) indicator was used to measure journal performance.[7]

RESULTS

Between December 31, 2022 and January 1, 2020, 426 662 COVID-19-related publications were published worldwide in the 3-year period. Of these publications, 293 830 were articles in the original research type. The number of COVID-19 cases worldwide and the distribution of the number of original research by country were given in Table 1. Türkiye was 12th with both 17 004 677 confirmed cases and 8394 publications.

Table 1. List of Confirmed Worldwide Number of Cases and Coronavirus Disease 2019 Publications

	Country	Number of Cases	Country	Number of Publications
1	USA	101 211 478	USA	70 287
2	China	98 726 098	China	29 612
3	India	44 683 748	UK	26 937
4	France	38 449 944	Italy	19 423
5	Germany	37 879 714	India	18 071
6	Brazil	36 887 991	Germany	13 169
7	Japan	32 846 656	Spain	13 014
8	South Korea	30 311 979	Canada	12 142
9	Italy	25 488 166	Australia	11 011
10	UK	24 293 752	Brazil	9124
11	Russia	22 035 133	France	8924
12	Türkiye	17 004 677	Türkiye	8394

English was found to be preferred in 96.6% of the publications and Turkish was preferred in 2.79% of the publications when 8394 publications addressed to Türkiye were examined. It was found that 10 different languages were preferred in publications. The top 5 languages most frequently preferred in publications with an author from Türkiye are English, Turkish, Spanish, French, and Portuguese.

The top 10 preferred journals and their SJR values are presented in Table 2. A total of 764 (9.15%) articles have been published in the top 10 journals listed in Table 2. Of the obtained articles (n = 131), 1.57% were seen to be published in the "International Journal Of Clinical Practice."

It was found that 53% of the journals in which the publications were published were registered in the Scopus database in the area of "Medicine," 10% in "Social Sciences," 7% in "Biochemistry, Genetics, and Molecular Biology," and 6% in "Immunology and Microbiology."

When the countries of international researchers who collaborated on 8 349 articles addressed to Türkiye were examined, it was found that the most cooperations were with the USA, the UK, Italy, Spain, and Germany. In our study, it was determined that our neighbor Greece is the 15th country with the most cooperation in Türkiye-addressed COVID-19 publications. The world map showing all collaborations was given in Figure 1. The network map of the cooperated countries in the first 2000 publications that received the most citations is shown in Figure 1. Figure 1 presents a network map of 84 countries that have published at least 5 publications. It was found that the largest of the total 4 clusters on the map is the green cluster, which covers mostly Asian countries. In the presented map, it was determined that the country with the most cooperation was the UK (Yellow cluster) with 240

Main Points

- Along with the coronavirus disease 2019 (COVID-19) pandemic, research interests in the scientific world have focused on COVID-19, and the number of publications about COVID-19 has increased exponentially, surpassing the number of publications related to other topics in the scientific literature.
- In the 3-year period, Türkiye ranked 12th according to both publication and case numbers. The most focused topics were "COVID-19 clinic," "use of computer systems in COVID-19 diagnosis and follow-up," and "COVID-19 mental health effects."
- The research goals and focuses have changed from the beginning to the terminal period of the pandemic.
- It was detected that Türkiye has been in the leading position on COVID-19 publications compared to the Middle East countries.

Table 2. Top 10 Journals and the SCImago Journal Rank Values

Journal	No. of Articles	%	SJR	Country
1. *International Journal Of Clinical Practice*	131	1.56	0.646	USA
2. *Journal Of Medical Virology*	101	1.20	2.656	USA
3. *Turkish Journal Of Medical Sciences*	100	1.20	0.44	Türkiye
4. *Revista Da Associacao Medica Brasileira*	74	0.89	-	Brazil
5. *European Review For Medical And Pharmacological Sciences*	70	0.84	0.658	Italy
6. *Acta Medica Mediterranea*	63	0.75	0.118	Italy
7. *Sustainability (Switzerland)*	62	0.74	0.664	Switzerland
8. *Journal Of Experimental And Clinical Medicine Turkiye*	59	0.71	0.102	Türkiye
9. *Bratislava Medical Journal*	53	0.63	0.324	Slovakia
10. *Current Psychology*	51	0.61	0.513	USA

SJR, SCImago Journal Rank.

publications, followed by the USA (n = 209) in the blue cluster and Italy (n = 167) in the red cluster, respectively. It was seen that the least cooperation is with African, Central Asian, and South American countries.

When the institutions of the authors in 8349 articles were evaluated, it was found that the most productive institution was the University of Health Sciences (n = 1206). It is seen that 27 of the 30 most productive institutions are state universities and 3 of them are foundation universities. The University of Health Sciences is followed by İstanbul University, İstanbul University-Cerrahpaşa, Hacettepe University, and Marmara University. The 3 foundation universities included in the list are Koç University, İstanbul Medipol University, and Başkent University.

Among the 8349 publications, the top 10 articles that received the most citations were given in Table 3. It is seen that there is international cooperation in 6 of the 10 most cited articles.

Totally, 2824 keywords used at least 5 times in the top 2000 most cited articles in our study were analyzed. In this context, it was determined that the 5 largest clusters were "COVID-19 clinic" (blue), "use of computer systems in COVID-19 diagnosis and follow-up" (purple), "COVID-19 mental health effects" (green), "COVID-19 treatment" (orange), and "COVID-19 and social media-related publications" (light blue), respectively (Figure 2A). The 10 most commonly used keywords were determined as "COVID-19," "SARS-CoV-2," "Pandemics," "Coronavirus," "Anxiety," "Depression," "Mortality," "Deep Learning," "Mental Health," and

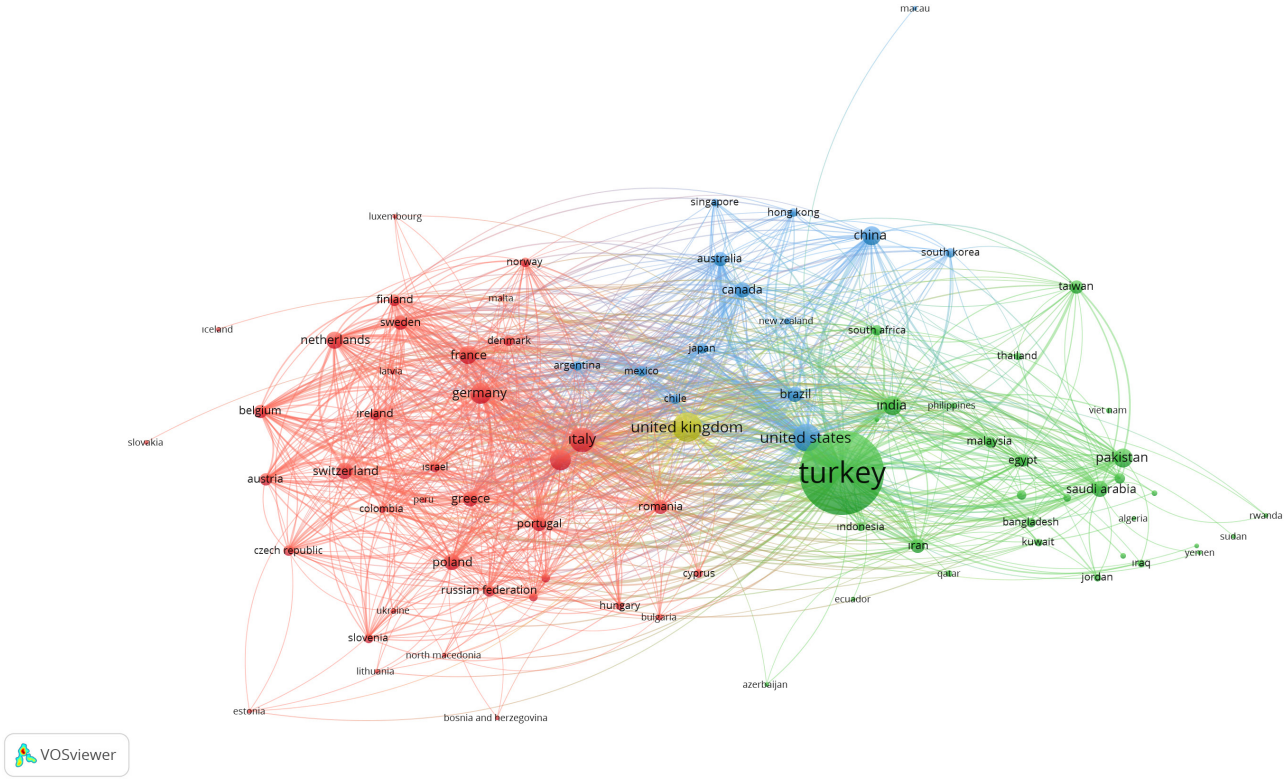


Figure 1. A network map of the countries with which Türkiye cooperates internationally.

Table 3. The 10 Most Cited Articles

	Number of Citations	Article Name	Journal Name	Year	Main Authors
1	6960	Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine	*The New England Journal of Medicine*	2020	Polack, F.P., Thomas, P.J., Kitchin, N., et al.
2	1335	Automated detection of COVID-19 cases using deep neural networks with X-ray images	*Computers in Biology and Medicine*	2020	Ozturk, T., Talo, M., Star, E.A., et al.
3	1291	Autoantibodies against type I IFNs in patients with life-threatening COVID-19	*Science*	2020	Bastard, P., Rosen, L.B., Zhang, Q., et al.
4	1146	Inborn errors of type I IFN immunity in patients with life-threatening COVID-19	*Science*	2020	Zhang, Q., Liu, Z., Moncada-Velez, M., Chen, J., et al.
5	633	Levels and predictors of anxiety, depression and Health anxiety during the COVID-19 pandemic in Turkish society: The importance of gender	*International Journal of Social Psychiatry*	2020	Ozdin, P., Flag Ozdin, S.
6	523	Safety and efficacy of the BNT162B2 mRNA COVID-19 vaccine through 6 months	*The New England Journal of Medicine*	2021	Thomas SJ, Moreira ED Jr., Kitchin N, et al.
7	472	Genomic characterization of a novel SARS-CoV-2	*Gene Reports*	2020	Khailany, R.A., Safdar, M., Ozaslan, M.
8	399	COVIDiagnosis-Net: Deep Bayes-SqueezeNet based diagnosis of the coronavirus Disease 2019 (COVID-19) from X-ray images	*Medical Hypotheses*	2020	Ucar, F., Korkmaz, D.
9	394	Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomized, placebo-controlled, phase 3 trial in Türkiye	*The Lancet*	2021	Tanriover, M.D., Doganay, H.L., Akova, M., et al.
10	385	Automatic detection of coronavirus disease (COVID-19) using X-ray images and deep convolutional neural networks	*Pattern Analysis and Applications*	2021	Narin, A., Kaya, C., Pamuk, Z.

COVID-19, coronavirus disease 2019; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2.

"Machine Learning," respectively. The time-dependent keyword network map between January 2020 and December 2022 is given in Figure 2B.

DISCUSSION

Along with the COVID-19 pandemic, research interests in the scientific world have focused on the diagnosis and treatment of COVID-19 disease, the evolution and mutations of the SARS-CoV-2, and the development of new and effective vaccines as a way of prevention. In the first 3 months of the pandemic, the number of articles published about COVID-19 has increased exponentially, surpassing the number of publications related to many topics in the scientific world.[8,9] The number of COVID-19 publications added to PubMed has increased to over 300 publications daily from period to period.[10] The pandemic that started in China has been particularly severe in the USA and European countries with the number of cases and deaths (Table 1). The similarity between the number of cases and the publishing performance of the countries is striking. This can be considered a rapid response to the devastating and deadly effects of the pandemic, as well as its rapid spread. It is normal for health professionals to turn their attention to scientific literature to control the disease and determine treatment options, so it is essential that the literature about a new disease is updated frequently after independent peer review. Studies reported that before the pandemic also show that the USA and China share the first place in the production of scientific data. While the USA and China account for about 25% of the total research and development (R&D) budget in the world, the countries following these 2 countries are listed as follows: Japan, Germany, South Korea, France, India, the UK, Russia, Brazil, Taiwan, Italy, Canada, Spain, Türkiye, and Australia.[11] There are bibliometric studies that show a positive relationship between the number of COVID-19 cases and publications, according to which it is expected that the countries most affected by COVID-19 will also be the countries that produce the most scientific documents.[12,13] Our country is 12th in both lists with the number of 17 004 677 cases and the number of 8394 publications in a harmonious way. Nine of the 12 countries where the most cases are reported are among the top 12 countries with the most publications (Table 1). However, this relationship does not apply to every country. It has been observed that 2 countries heavily affected by the pandemic, such as Italy and Iran, produce disproportionately fewer articles.[14,15] In a study covering the first 6 months of the pandemic, our country ranked 18th in terms of the number of publications, while it rose to 12th in the third year of the pandemic. In the same study, it is seen that the top 5 countries that produced the most publications in the first 6 months were the USA, China, Great Britain, Italy, and Canada. Canada, which was the fifth country that produced the most publications in the first month, has been replaced by India in the ongoing process.[16]

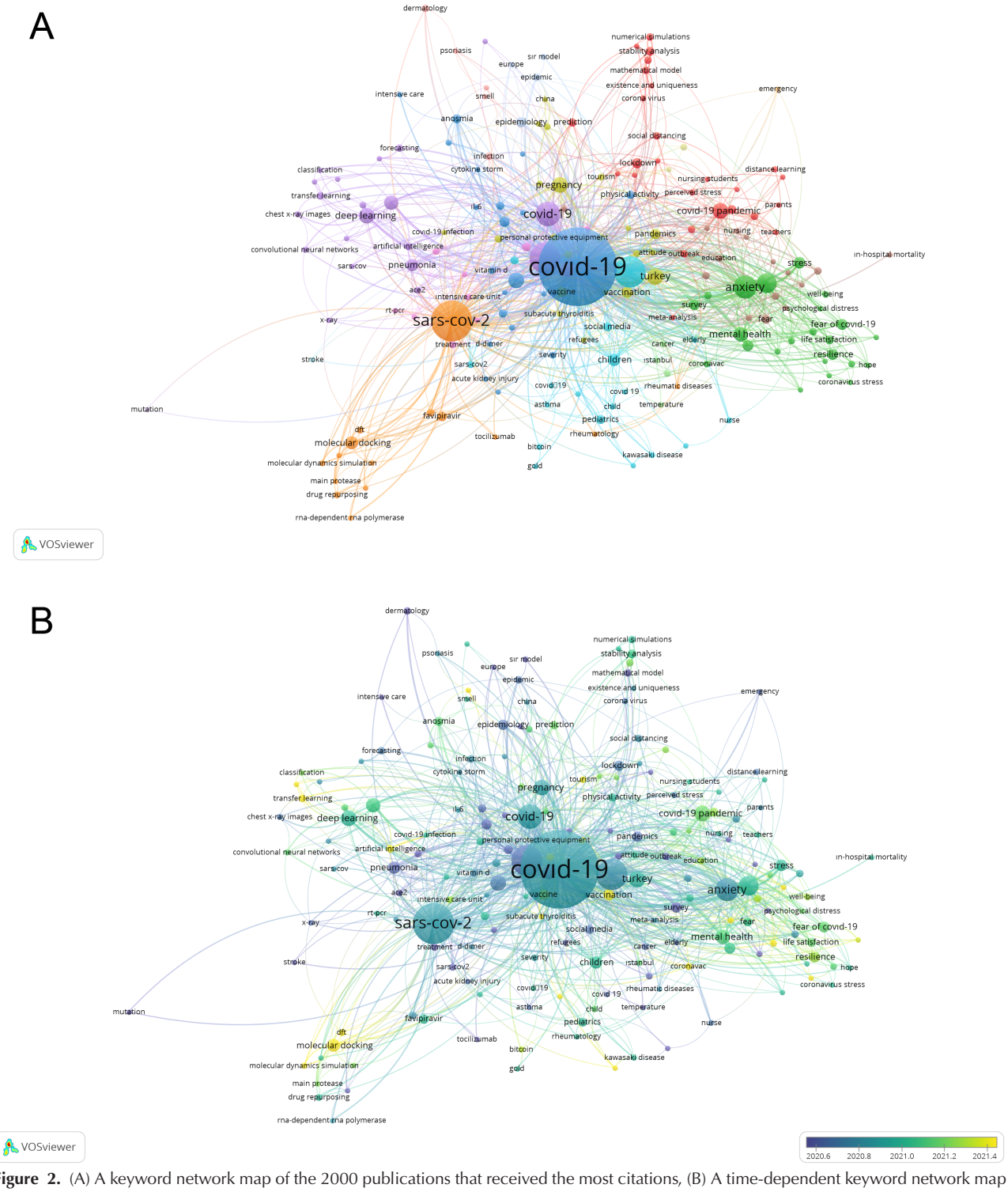


Figure 2. (A) A keyword network map of the 2000 publications that received the most citations, (B) A time-dependent keyword network map of the 2000 publications that received the most citations.

Of the 8394 articles addressed to Türkiye, only 2.79% were published in Turkish, while 96.6% of them were published in English. In co-authored studies, the article language is of course not determined solely by the decision of 1 author, but the publication language of the journal planned to be published is determined according to the joint decision of the authors, the content of the article, and the segment it addresses. The fact that the most collaboration was made with the USA and the UK in the publications presented from our country and the publication language of the most preferred journals is mainly in English can explain the reason that the most preferred publication language is English.

It was found that 53% of the 8394 publications evaluated in our study were indexed in the Scopus database in the fields of Medicine, 10% in the Social Sciences, 7% in Biochemistry, Genetics, and Molecular Biology, and 6% in Immunology and Microbiology. Similarly, publications are showing the dominance of health sciences in the number of COVID-19-related publications and reporting that life sciences, social sciences,

and humanities publications are relatively lagging behind.[17] It seems that social science studies are mainly focused on the effects of the pandemic on mental health and psychological studies.[18]

When the countries of international researchers who collaborated on 8349 articles addressing Türkiye were evaluated, it was found that the most cooperation was with the USA, the UK, Italy, Spain, and Germany. In our study, it was determined that our neighbor Greece is the 15th country with the most cooperation in Türkiye-addressed COVID-19 publications. In a study analyzing the COVID-19-related publishing performance of Greece, the top 3 cooperating countries are reported as Italy, the USA, and the UK, while Türkiye ranked tenth.[19] When the cooperating countries of Türkiye were examined, it was seen that the least cooperation is with African, Central Asian, and South American countries. Unlike the clusters covering the top 3 countries with the most co-authorship, it is interesting that most collaborations are in the green cluster, where Asian countries are predominantly located. It suggests that geographical proximity with the Middle Eastern and North African countries, which are commonly found in the green cluster, may have motivated the cooperation.

Among the 8349 publications addressed to Türkiye, it is observed that there is international collaboration in 6 of the 10 most cited articles (Table 3). The most cited article was published in *The New England Journal of Medicine* and received 6960 citations. Two of the most cited 10 articles were published in *The New England Journal of Medicine* and 2 in *Science*. Similarly, in a study that evaluated the most cited COVID-19 publications, it was reported that *The Lancet*, *The New England Journal of Medicine*, and *JAMA* were the most cited journals.[20,21] The top 5 most cited articles were published in 2020. When the journals in which the most Türkiye-oriented publications are published are evaluated, it was seen that 2 of the top 10 journals are addressed in Türkiye (Table 2). Of the 8 non-Turkish journals, 3 are from the USA, 2 are from Italy, and 1 each is from Brazil, Switzerland, and Slovakia. It is thought that early evaluation and publication are the main criteria for selecting authors' journals during the pandemic process. Since it is essential for every data to meet the scientific world quickly in a rapidly progressing process, both the evaluation periods of published studies have decreased, and the evaluation process has become controversial during this period.[22,23]

Keyword analysis showed that COVID-19 was not only studied in our country on diagnosis, treatment, and prevention methods but also intensively studied by researchers from a psychiatric and psychological point of view. So much so that it has been reported that Türkiye ranks sixth in the world in the production of publications on the theme of "mental health and COVID-19" and ranks fifth in publications in the field of paediatrics.[24,25] Some studies report the keyword clusters that stand out in our study in a similar way.[26]

While terms such as "pneumonia," "SARS-CoV-2," and "personal protective equipment" were prominent in the time-dependent keyword analysis covering the first period of the pandemic in the first quarter of 2020, the terms "Vaccines," "Molecular Docking," and "Transfer Learning" were used extensively as of the last quarter of 2021. At the beginning of the pandemic, the research goals were aimed at preventing transmission and the effects of the disease, while at the terminal period of the pandemic, research has evolved to issues related to the development of new vaccines and diagnostic methods.

Although our study contains useful data covering large-scale COVID-19 publications, it has some limitations. In our analysis, only 1 database (Scopus) was used, although it provides more comprehensive data than other databases. It should be taken into account that journals that are not screened in Scopus, especially nationally published journals, may have been excluded from the scope of our study.

With the COVID-19 pandemic, an exponentially increasing number of scientific publications have quickly been reflected in the literature. It is important to evaluate such a large number of research articles and identify trending topics to know the evolution and progress of publications on the subject from a broad perspective. We think that the comprehensive data presented in our study will shed light on the planning and direction of future studies, as well as health and R&D policies.

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Original Article

Normative Values and Calculation Formulas of Respiratory Muscle Strength of Adults in Turkish Society: A Population-based Study

Esra Pehlivan[1], Halit Çınarka[2], Kürşad Nuri Baydili[3], Mehmet Burak Uyaroğlu[1], Pınar Baştürk[1], Amine Ataç[4]

[1]Department of Physiotherapy and Rehabilitation, University of Health Sciences Türkiye Faculty of Hamidiye Health Sciences, İstanbul, Türkiye
[2]Department of Chest Disease, University of Health Sciences, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye
[3]Health Services Vocational School Health Institutions Management Program, University of Health Sciences, İstanbul, Türkiye
[4]Department of Physiotherapy and Rehabilitation, İstanbul Gedik University Faculty of Health Sciences, İstanbul, Türkiye

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Abstract

OBJECTIVE: This study aimed to establish normative values for maximum inspiratory pressure and maximal expiratory pressure in the Turkish population while creating specific equations to calculate these values.

MATERIAL AND METHODS: The study involved 219 healthy adults, with a minimum of 50 individuals in specific age ranges: 20–29, 30–39, 40–49, and 50–60 years. Each age group comprised at least 25 males and 25 females. Participants were required to be free from health conditions influencing respiratory muscle strength and non-smokers. Measurements of maximum inspiratory pressure and maximal expiratory pressure were recorded for all participants.

RESULTS: As a result of the regression analysis performed for the maximum inspiratory pressure values, the model *P* value was < .001, and the R^2 value was found to be 0.261. The equation obtained as a result of the model was: 82.583 − 3.218 × gender − 0.093 × age + 9.534 × height + 0.343 × weight. As a result of the regression analysis performed for maximal expiratory pressure values, the model *P* value was <.001, and the R2 value was found to be 0.285. The equation obtained as a result of the model was: 157.165 − 35.522 × gender − 0.271 × age–42.036 × height + 0.787 × weight.

CONCLUSIONS: The newly developed equations offer valuable tools for evaluating respiratory muscle strength in the Turkish population. These results confirm the importance of using maximum inspiratory pressure and maximal expiratory pressure to monitor changes in each patient, while also emphasizing the necessity of reliable reference equations.

KEYWORDS: Maximal inspiratory pressure, maximal expiratory pressure, maximal respiratory pressures, respiratory muscle, predictive value of tests, race factors

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INTRODUCTION

Respiratory muscle weakness is a condition that can be detected in all chronic diseases and in healthy people. There are studies showing that respiratory muscle weakness is associated with myocardial infarction, stroke, and related mortality.[1] Determining the loss of respiratory muscle strength is beneficial when making the decision to use special rehabilitation methods for patients,[2] and when deciding when to extubate patients on mechanical ventilation.[3]

The mouth pressure measurement is the most commonly used method in the clinic to determine respiratory muscle strength. It is a non-invasive, easily applicable technique.[4] As a result of this measurement, two main parameters, maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), are determined. MIP is one of the indicators of the strength of inspiratory muscles, especially the diaphragm. Clinical decisions are made by comparing the data obtained from the patient with the normative values, although these are known to vary according to demographic characteristics and race.[5,6]

There are no respiratory muscle strength normative values specific to the Turkish population. It is common practice in this population to evaluate respiratory muscle strength by comparing it with the typical or expected values of International values[7] that do not share the same anatomical features as the Turkish population, and this can result in diagnostic errors. The aim of this study is to obtain reference MIP and MEP values for the Turkish society by measuring the respiratory muscle strength of healthy adults in different age groups, based on the city of İstanbul (Table 1).

Corresponding author: Esra Pehlivan, e-mail: fztesrakambur@yahoo.com

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Table 1. Demographic Characteristics and Respiratory Muscle Strength Values of the Groups

	Group1 (20–29 Years)	Group2 (30–39 Years)	Group3 (40–49 Years)	Group4 (50–60 Years)
Male				
Height, m	1.8 ± 0.07	1.74 ± 0.06	1.73 ± 0.06	1.73 ± 0.06
Weight, kg	79.07 ± 11.24	78.04 ± 10.12	81.17 ± 8.19	82.22 ± 8.2
BMI, kg/m^2	24.44 ± 2.93	25.86 ± 2.64	27.11 ± 2.07	27.37 ± 2.24
MIP, H_2O	103.7 ± 28.66	94.76 ± 30.72	99.07 ± 29.94	101.81 ± 26.38
MEP, H_2O	113.59 ± 40.66	111.72 ± 37.31	117.93 ± 34.04	143.85 ± 56.95
Female				
Height, m	1.64 ± 0.06	1.63 ± 0.04	1.61 ± 0.06	1.62 ± 0.07
Weight, kg	61.78 ± 10.13	63.22 ± 8.65	67.35 ± 9.15	69.48 ± 8.33
BMI, kg/m^2	22.81 ± 3.2	23.85 ± 3.23	25.85 ± 3.2	26.55 ± 2.82
MIP, cm H_2O	69.93 ± 16.47	72.63 ± 31.48	70.92 ± 20.23	67.76 ± 19.24
MEP, cm H_2O	83.14 ± 29.69	68.27 ± 18.48	90.58 ± 34.3	77.92 ± 25.33

BMI, body mass index; MIP, maximal inspiratory pressure; MEP, maximum expiratory pressure.

MATERIAL AND METHODS

Approval for this prospective, cross-sectional study was granted by the Ethics Committee of University of Health Sciences Hamidiye Non-Interventional Research Ethics Committee (Protocol Number: 19/81, date: 11/08/2019) and the study was registered in ClinicalTrial.gov (registration number: NTC0472450). All the study procedures were performed in accordance with the Helsinki Declaration. Written informed consent was obtained from all the study participants.

The study includes students who are working and studying at the Health Sciences University, along with their social and family environments, and cases were collected using stratified sampling, taking into account volunteer recruitment and exclusion criteria (Figure 1).

The study was announced to students and employees of the University of Health Sciences, and cases were collected among students, employees, and their families and social circles. In the research, stratified sampling was done according to age groups and gender. As a result of the sample analysis conducted for the research, it is known that at least 50 individuals from each age group should be included in the sample. In addition to age groups, stratification was also carried out by gender, and at least 25 women and 25 men were included in each age group. At least 50 subjects were enrolled in each of the following age groups: 20–29, 30–39, 40–49, and 50–60 years. The age ranges of the cases were determined based on similar studies.[5,6]

The inclusion criteria were defined as non-smoker status, age 20–60 years, body mass index (BMI) of 18.0–29.5kg/m^2, and no cardiac, neuromuscular, or endocrine disease that may affect respiratory muscle strength. A participant was deemed ineligible for inclusion in the study if they had any respiratory infections or diseases, exhibited sequelae from prior respiratory conditions, experienced anatomical issues, or had other systemic or chronic diseases that could potentially impede spirometric measurements. According to the results of the physician's preliminary examination, non-compliance with spirometric and mouth pressure measurement procedures also led to exclusion from the study (Figure 2).

Procedure

Participants who satisfied the requirements for inclusion and finished the preliminary evaluation provided written informed consent. After the preliminary interviews, respiratory function tests were conducted on subjects deemed suitable for participation. The tests were performed using the Cosmed Pony Fx desktop spirometer in accordance with the guidelines. Any abnormalities in spirometric values were assessed by a chest diseases specialist, and for subjects without abnormalities, mouth pressure measurements were carried out.[8] The mouth pressure measurement was conducted using the Pony Fx Desktop Spirometer (Cosmed Inc., Italy). For MIP measurement, participants were instructed to exhale slowly until reaching the residual volume level, and then to perform a rapid inspiration. During this rapid inspiration, the shutter in the tubing was closed. Participants' inspiratory strength was measured using a pressure gauge against the closed shutter. Standard mouthpieces and nose clips were used during the test. To prevent the spread of unwanted harmful microorganisms, a bacterial filter was incorporated into the setup. Additionally, particular attention was given to ensure that there were no leaks from the lip edges. For MEP measurement, the participant was asked to reach the total lung volume level and then perform a forceful exhalation through the mouthpiece, simulating the act of inflating a balloon, for

Main Points

- This study reveals essential normative values for maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) specific to the Turkish population, bridging a significant gap in respiratory health research.
- By recognizing the variability of normative values across different races, this research underscores the potential impact on precise diagnoses and effective treatment strategies for respiratory conditions.
- Through rigorous regression analysis, the study formulates accurate equations for calculating MIP and MEP values, providing healthcare professionals with robust tools to assess respiratory muscle strength in individuals of Turkish descent.
- By implementing these normative values in clinical and research settings, this study contributes to improved healthcare outcomes and better-informed, decision-making processes concerning respiratory muscle function in the Turkish population.

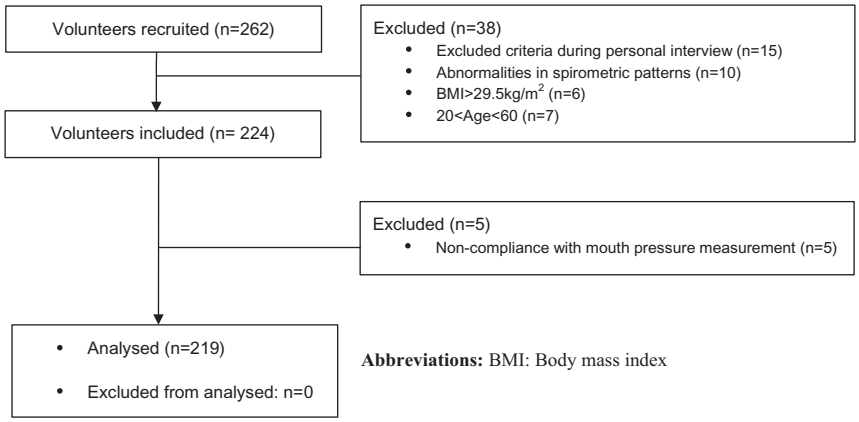


Figure 1. Study flowchart.

at least 1.5 seconds. In the meantime, the pressure created by rapid expiration was measured by sensors. The shutter opened after 1.5–2.0 seconds, and the test was terminated. In cases where multiple tests were required, a maximum 3–5 tests were performed and the participant rested for at least 1 minute between each test. Care was taken to ensure that there was no more than a 10 cm H_2O difference between the measurements. The highest rating achieved was recorded and compared with the expected value.[4] All measurements were performed by the same person.

Statistical Analysis

Data obtained in the study were analyzed statistically using the Statistical Package for the Social Sciences version 25 software (IBM Corp., Armonk, NY, USA). The measurement results were presented as arithmetic mean and standard deviation values. Estimation equations for MIP and MEP values were created using multiple linear regressions, and the mean values of the measured and estimated values according to gender and age groups were presented. The Type I error rate was taken as 0.05 in the study (Figure 3).

Sample Analysis

Sample analysis was performed using G Power statistical software. The estimated effect size was taken from a similar study on this subject. The sample size required was calculated as a minimum of 200 people, with at least 50 in each of the age ranges of 20–29, 30–40, 40–49, and 50–60 years, based on a 95% confidence level, 80% power, and 0.176 correlation coefficient.[5]

RESULTS

The study included 219 healthy adult Turkish individuals. The gender distributions were: group 1: 27 males and 29 females, group 2: 25 males and 30 females, group 3: 30 males and 26 females, and group 4: 27 males and 25 females. The BMI values of all the groups were <29.5 kg/m^2. The demographic characteristics of the age groups according to gender and the mouth pressure measurement results are given in Table 1.

As a result of the regression analysis performed for MIP values, the model *P* value was < .001, and the R2 value was found to be 0.261. The equation obtained as a result of the model was: 82.583 – 23.218 × Gender – 0.093 × Age + 9.534 × Height + 0.343 × Weight (Table 2).

As a result of the regression analysis performed for MEP values, the model *P* value was < .001, and the R2 value was found to be 0.285. The equation obtained as a result of the model was: 157.165 – 35.522 × Gender – 0.271 × Age– 42.036 × Height + 0.787 × Weight (Table 3).

DISCUSSION

Maximum inspiratory and expiratory pressures, which are indicators of respiratory muscle strength, may vary according to race. According to the models obtained in this study, the mean MIP value of the Turkish population can be estimated using the formula: 82.583 – 23.218 × Gender – 0.093 ×

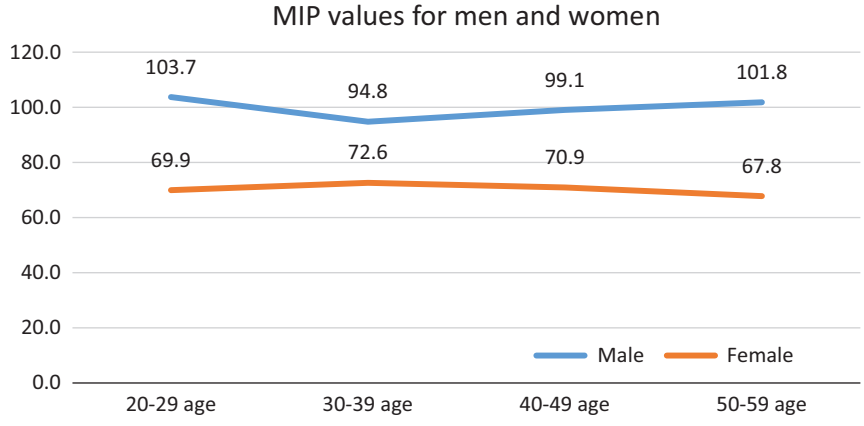


Figure 2. Distribution of MIP values for men and women by age groups.

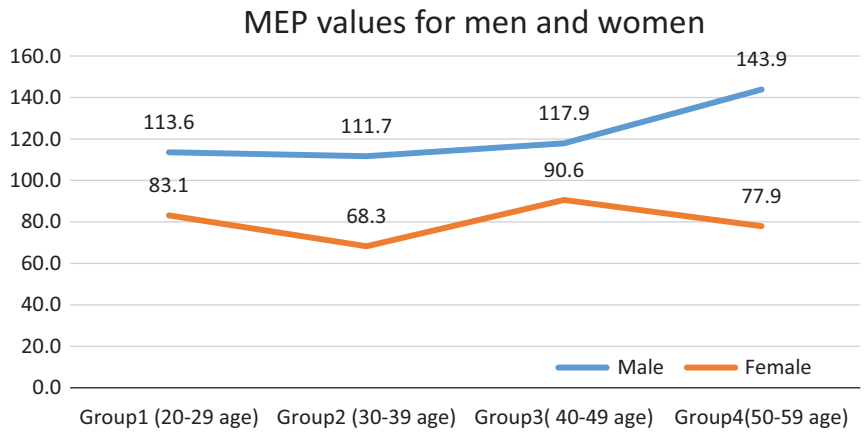


Figure 3. Distribution of MEP values for men and women by age groups.

Age + 9.534 × Height + 0.343 × Weight and the MEP value with the formula: 157.165 – 35.522 × Gender – 0.271 × Age – 42.036 × Height + 0.787 × Weight.

Respiratory muscle dysfunction is a clinical condition that can occur in neuromuscular diseases,[9] long-term mechanical ventilation applications,[10] and chronic respiratory diseases such as chronic obstructive pulmonary disease.[11]

The presence of respiratory muscle weakness is closely related to patient-reported disease symptoms. In a prospective cohort examining the respiratory muscle strength of cases diagnosed with COVID-19, it was found that respiratory muscle strength decreased in parallel with the severity of the disease, and respiratory dysfunction was associated with psychological disorders and decreased quality of life.[12] In another study examining Long COVID-19 symptoms, it was emphasized that respiratory muscle strength is a clinical parameter that should be taken into account when determining the causes of ongoing respiratory symptom.[13] In order to evaluate the respiratory muscle strength level, which is important in revealing the patient's clinical status and determining the cause of the symptoms, real reference values specific to the population and comparisons with these values are needed. The results of the current study have made it possible to determine the normative value for the Turkish population.

Many studies have attempted to determine the reference values of respiratory muscle strength according to different populations.[5,6,14] In a study conducted in Brazil on 60 healthy male and female subjects aged 20–80 years, it was reported that previously used reference values were insufficient to predict the normative MIP and MEP values of the Brazilian population.[6] Researchers have also stated that age is the most effective demographic parameter in the estimation of these values. In a cross-sectional study conducted in the Indian

Table 2. Regression Analysis (MIP)

	B	Std. Error	Beta	*t*	Sig.	95% CI	
(Constant)	82.583	59.479	–	1.388	.166	–34.656	199.822
Gender	–23.218	5.151	–0.391	–4.507	<.001*	–33.371	–13.064
Age	–0.093	0.17	–0.036	–0.545	.586	–0.428	0.243
Height	9.534	34.398	0.028	0.277	.782	–58.269	77.336
Weight	0.343	0.22	0.139	1.56	.120	–0.09	0.776

$R^2 = 0.261$.
*ANOVA $P < .001$.

Table 3. Regression Analysis (MEP)

	B	Std. Error	Beta	*t*	Sig.	95% CI	
(Constant)	157.165	83.924	–	1.873	.062	–8.26	322.589
Gender	–35.522	7.268	–0.417	–4.887	<.001*	–49.849	–21.196
Age	0.271	0.24	0.074	1.129	.260	–0.202	0.745
Height	–42.036	48.536	–0.085	–0.866	.387	–137.706	53.633
Weight	0.787	0.31	0.223	2.536	.0120	0.175	1.398

$R^2 = 0.285$.
*ANOVA $P < .001$.

Mangalore population, measurements were made in 250 cases. It was similarly reported that the respiratory muscle strength of the healthy local population was lower than that of the normative values calculated according to international standards.[5] In a recent study conducted in Spain, researchers declared the utilization of the largest patient dataset in Europe, employing a method parallel to these studies.[15] Upon examining the averages of respiratory muscle strength data across all these studies, it is observed that the reference values obtained in our study are different. This highlights the rationale and necessity for the implementation of our study.

In a study conducted on a young healthy Arab population, the relationship between respiratory muscle strength and maximal voluntary ventilation values with anthropometric characteristics and physical activity level was investigated. Gender and height were found to be associated with respiratory muscle strength, while physical activity level was not a determining factor.[16] In another study, reference values were calculated according to age and gender.[14] In contrast, there is also a study in the literature which included demographic characteristics such as height and weight, as well as BMI.[5] Gender is a significant determinant for spirometric measurement results[17] and respiratory muscle strength.[18] The chest cage, lung volumes, and cross-sectional areas of respiratory muscles influence these measurement outcomes. It is an interesting result that especially in our study, the MEP value was measured lower in women than in other studies. We think this may be due to demographic variables such as height. In the current study, gender, height, and weight parameters were taken into account in the calculation of reference formulas, similar to the literature. In our study, unlike past reference formulas developed for different populations,[5,19] separate reference formulas for men and women have not been established. This is because regression analyses conducted separately for both gender groups in the study did not yield statistically significant regression models. Therefore, including gender as a variable in the model was deemed unnecessary, and separate calculations for each gender were not pursued.

Different techniques and different devices are used to determine respiratory muscle strength. MIP, sniff nasal pressure, mouth pressure, transdiaphragmatic pressure, and electrical and magnetic phrenic nerve stimulation can be considered the main methods.[20] Of these techniques, mouth pressure measurement is frequently used in clinics as it is not an invasive method and is easy to apply. The technique can be applied with different model devices, and the method of application is standardized according to the European Respiratory Society statement.[21] The measurements in the current study were performed in accordance with these standards. Mouth pressure measurement has been preferred in all of the other studies conducted to determine the reference values of respiratory muscle strength in different societies.[5,6,14]

The study has some limitations. In the current study, there were problems in finding healthy subjects over 60 years of age, so the age range of the study was limited to 60 years, which could be considered a limitation. Our age range had to be limited to 60 years due to the inability to reach a sufficient number of cases over the age of 60 with comorbidities. There is a need for future studies that will include individuals over the age of 60 years. This cross-sectional study was conducted in the city of Istanbul. There is a need for more comprehensive studies on case groups formed from samples from every province of the country. However, the cosmopolitan structure of Istanbul and the immigration from all parts of the country alleviate the effects of this limitation. Another limitation is that passive smoking or cigarette smoke exposure was not questioned. Furthermore, the lack of specified information regarding the subjects' levels of physical activity in the study constitutes a limitation. Given the attempt to include participants from all segments of the community, the situation can be considered as reflecting real-life data that represents the general composition of the community.

With the formulas obtained from the modeling in this study, reference respiratory muscle strength values can be determined according to the demographic characteristics of the Turkish population. However, it is important to note that further studies, including a larger sample from various regions of Turkey, are still needed to prepare new tables or equations based on population-based data, as this study was conducted using an Istanbul-based sample.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Hamidiye Non-Interventional Research Ethics Committee (approval number: 19/81; date: 11/08/2019).

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 – E.P.; Design – E.P.; Supervision – H.Ç.; Resources – E.P., H.Ç.; Data Collection and/or Processing – H.Ç., A.A., E.P., P.B., M.B.U.; Analysis and/or Interpretation – K.N.B.; Writing Manuscript – E.P., H.Ç., A.A., P.B., M.B.U., K.N.B.; Critical Review – E.P., H.Ç., A.A., P.B., M.B.U., K.N.B.

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

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Original Article

Clinical Course of Coronavirus disease 2019 C-19 in Patients with Bronchiectasis

Ebru Çakır Edis[1], Aykut Çilli[2], Deniz Kızılırmak[3], Ayşın Şakar Coşkun[3], Abdullah Sayıner[4], Sedat Çiçek[2], İnci Gülmez[5], Meltem Çoban Ağca[6], Benan Çağlayan[7], Neslihan Özçelik[8], Nurdan Köktürk[9], Birsen Ocaklı[6], Eyüp Sabri Uçan[10], TEBVEB researchers*

[1]Department of Pulmoner Medicine, Trakya University Faculty of Medicine, Edirne, Türkiye
[2]Department of Pulmoner Medicine, Akdeniz University Faculty of Medicine, Antalya, Türkiye
[3]Department of Pulmoner Medicine, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye
[4]Department of Pulmoner Medicine, Ege University, Faculty of Medicine İzmir, Türkiye
[5]Department of Pulmoner Medicine, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[6]Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Türkiye
[7]Department of Pulmoner Medicine, Koç University Faculty of Medicine, İstanbul, Türkiye
[8]Department of Pulmoner Medicine, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Türkiye
[9]Department of Pulmoner Medicine, Gazi University Faculty of Medicine, Ankara, Türkiye
[10]Department of Pulmoner Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
*TEBVEB researchers: Gülşah Günlüoğlu, Yelda Niksarlıoğlu, Adil Zamani, Serdar Berk, Serap Argun Barış, İlknur Başyiğit, Pınar Yıldız Gülhan, Mehmet Kabak, Mustafa Çolak, Oya Baydar Toprak, Huriye Berk, Kıvılcım Oğuzülgen, Ezgi Demirdöğen, Füsun Öner Eyüboğlu, Yavuz Havlucu, Cenk Babayiğit.

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Abstract

OBJECTIVE: Coronavirus disease 2019 (COVID-19) has affected the whole world and caused the death of more than 6 million people. The disease has been observed to have a more severe course in patients with chronic lung diseases. There are limited data regarding COVID-19 in patients with bronchiectasis. The aim of this article is to investigate the course of COVID-19 and factors affecting the clinical outcome in patients with bronchiectasis.

MATERIAL AND METHODS: This study was conducted using the Turkish Adult Bronchiectasis Database (TEBVEB) to which 25 centers in Türkiye contributed between March 2019 and January 2022. The database consisted of 1035 patients, and COVID-19-related data were recorded for 606 patients.

RESULTS: One hundred nineteen (19.6%) of the bronchiectasis patients (64 female, mean age 57.3 ± 13.9) had COVID-19. Patients with bronchiectasis who developed COVID-19 more frequently had other comorbidities (P = .034). They also more frequently had cystic bronchiectasis (P = .009) and their Bronchiectasis Severity Index was significantly higher (P = .019). Eighty-two (68.9%) of the patients who had COVID-19 were followed up in the outpatient clinic, 27 (22.7%) in the inpatient ward and 10 (8.4%) patients in the intensive care unit. There tended to be a higher percentage of males among patients admitted to the hospital (P = .073); similarly, the mean age of the patients admitted to the hospital was also higher (60.8 vs 55.8 years for the outpatients), but these differences did not reach statistical significance (P = .071).

CONCLUSION: In conclusion, this study showed that severe bronchiectasis, presence of cystic bronchiectasis and worse Bronchiectasis Severity Index are associated with the development of COVID-19, but not with the severity of infection.

KEYWORDS: COVID-19, bronchiectasis, disease severity

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the most important pandemic of the century, affecting the whole world and causing the death of more than 6 million people.[1] COVID-19 may be more lethal in patients with comorbidities.[2] The disease has also been observed to have a more severe course in patients with chronic lung diseases such as COPD.[3-5] There are very limited data on the course and clinical outcomes of COVID-19 in patients with bronchiectasis.[6,7] In the literature, bronchiectatic changes, which have been observed mostly during the COVID-19 pandemic, have been described. Publications related to the patient population known to have bronchiectasis before the pandemic focus on the effect of the pandemic on bronchiectasis exacerbation or anxiety in patients with bronchiectasis.[6,8]

The aim of this study is to investigate the course of COVID-19 and the effects of demographic characteristics and disease severity in patients with bronchiectasis.

MATERIAL AND METHODS

Turkish Adult Bronchiectasis Database (TEBVEB) is an internet-based database where the demographic data of patients, the etiology of bronchiectasis, accompanying comorbidities, pulmonary function tests, microbiological and radiological

Corresponding author: Deniz Kızılırmak, e-mail: dr_dkizilirmak@yahoo.com

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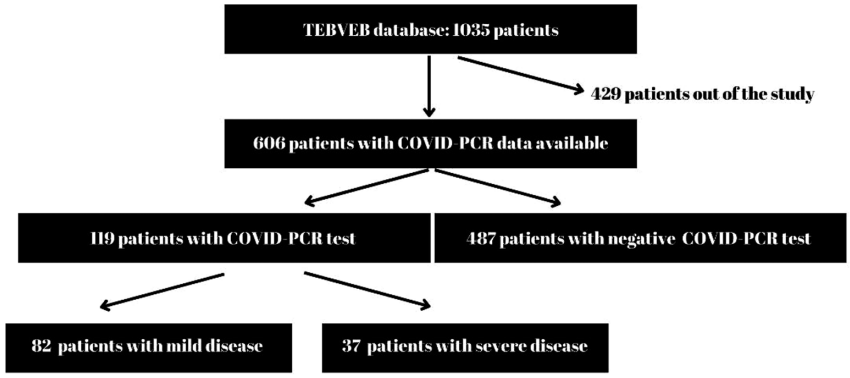


Figure 1. Consort diagram.

data, and treatment are recorded. This study was conducted using the TEBVEB, to which 25 centers in Türkiye contributed between March 2019 and January 2022. The COVID-19 pandemic occurred during the time period when the study was conducted. The COVID-19-related data of our patients were recorded, and this study was completed in line with these data. All patients over 18 years of age, with symptoms such as cough, sputum production, and shortness of breath, in whom bronchiectasis was diagnosed with high-resolution computed tomography (HRCT), and who consented to participate in the study were enrolled in the database. Patients with cystic fibrosis were excluded from the study. Ethics committee approval was obtained from the Trakya University Medicine Faculty Scientific Research Ethics Committee (approval number: TUTF-BAEK-2018/77, date: February 19, 2018).

This was an internet-based database, to which each participating center could register the patients' data. The quality of the data was regularly checked by one of the investigators, and corrections and/or additional data were requested when needed and/or when available. The database included parameters related to history, demographics, clinical, radiological (chest radiogram and HRCT), and laboratory findings, bronchiectasis severity index (BSI)[9] treatment and clinical outcomes.

Of the 1035 patients recorded in the database, 606 patients whose COVID-PCR data were available were included in the study. Patients who were found to be COVID-PCR positive were considered to have had the disease. Patients who required hospitalization were considered to have a serious disease (Figure 1).

Statistical Analysis

Regarding statistical analysis, the conformity of the data to the normal distribution was evaluated with the Shapiro–Wilk test. Mann–Whitney *U*-test was used to compare the non-normally distributed variables in two groups. Relationships between categorical variables were evaluated with the chi-square comparison test. Logistic regression test was applied for risk factors that may affect the severity of COVID-19. The Statistical Package for the Social Sciences for Windows version 24.0 program (IBM Corp., Armonk, NY, USA) was used in the analysis and a $P < .05$ was considered statistically significant.

Main Points

- Comorbidities were more common among bronchiectasis patients who contracted coronavirus disease 2019 (COVID-19).
- Severe bronchiectasis was more common in patients with COVID-19 than in patients without COVID-19.
- The presence of bronchiectasis is not a sign of severe COVID-19 infection.

RESULTS

Overall, 1035 patients were registered to the bronchiectasis database. COVID-19-related data were recorded for 606 patients. Of these patients, 119 (19.6%) [64 female, mean age 57.3 ± 13.98 (23-83)] had COVID-19 disease. Patients with bronchiectasis who developed COVID-19 more frequently had other comorbidities (cardiovascular diseases, obstructive lung diseases, etc.) ($P = .026$). They also more frequently had cystic bronchiectasis and their Bronchiectasis Severity Index (BSI) was significantly higher (Table 1).

There was no significant difference between patients who had and those who did not have COVID-19 in terms of age, gender, smoking status, presence of *Pseudomonas aeruginosa* colonization, steroid use, history of frequent exacerbations, and presence of eosinophilia.

Table 1. Demographic Data of Bronchiectasis Patients with COVID-19

Clinical data	Patients with COVID-19 (*n* = 119)	Patients Without COVID-19 (*n* = 487)	*P*
Age (mean ± S.D.)	57.3 ± 13.9	55.32 ± 15.8	.198
Gender (Female)	64 (53.8%)	253 (52%)	.759
Presence of comorbidity	93 (78.2%)	329 (67.6%)	**.026**
Presence of cystic bronchiectasis	83 (69.7%)	276 (56.7%)	**.009**
BSI	7.15 ± 4.7	5.99 ± 4.4	**.019**
Presence COVID-19 vaccine	99 (83.2%)	366 (75.2%)	.070
Mortality	13 (11%)	48 (9.86%)	.605

Eighty-two (68.9%) of the patients who had COVID-19 were followed up in the outpatient clinic, 27 (22.7%) in the inpatient ward, and 10 (8.4%) patients in the intensive care unit. Patients who were admitted to the ward or to the intensive care unit were considered to have severe disease. When patients with severe and mild COVID-19 were compared, no significant difference was found in terms of comorbidity, smoking status, modified medical research council (mMRC) dyspnea score, body mass index (BMI), BSI, history of *Pseudomonas aeruginosa* colonization, and presence of cystic bronchiectasis. There was a higher percentage of males (60% vs 40%) among patients admitted to the hospital, and their mean age tended to be higher (60.8 ± 11.3 vs 55.81 ± 14.82 years for the outpatients), but these differences did not reach statistical significance (P = .073 and .057 respectively) (Table 2). Parameters that may be associated with severe COVID-19 (age, gender, vaccination status, presence of comorbidities, BMI, BSI) were also evaluated with logistic regression analysis. No significant risk factor was identified.

Out of the 606 patients, 465 (76.7%) had received the COVID-19 vaccine. Of the 119 patients who developed COVID-19, 99 (84%) had been vaccinated. Similarly, 30 out of the 37 hospitalized patients (81%) had been vaccinated. Vaccination status was not found to be associated with the severity of COVID-19 (P = .73). None of the patients admitted to the intensive care unit had received the mRNA vaccine, 5 had received the inactivated vaccine, and 5 had not been vaccinated.

During the follow-up, 61 out of 606 patients (10%) died. Of the 119 patients who had COVID-19, 13 (11%) died; 2 of these (1.7%) were found to be attributable to COVID-19 infection. One of these 2 patients was not vaccinated, and the other was vaccinated with the inactivated vaccine. The causes of death in the remaining 11 patients were determined as respiratory failure due to bronchiectasis and associated COPD (n = 9) and congestive heart failure (n = 2).

Table 2. Characteristics of Patients with Mild and Severe COVID-19

	Patients with Mild COVID-19 (n = 82)	Patients with Severe COVID-19 (n = 37)	P
Age (mean ± SD)	55.8 ± 14.82	60.81 ± 11.34	.057
Gender (Female)	49 (59.8%)	15 (40.5%)	.073
Vaccinated for COVID-19	69 (84.1%)	30 (81.1%)	.792
Vaccinated with Biontech	44 (53.7%)	14 (37.8%)	.126
Smoking status	56 (69.1%)	19 (51.4%)	.091
Comorbidities	65 (79.3%)	28 (75.7%)	.0641
Cystic bronchiectasis	58 (70.7%)	25 (67.6%)	.830
BMI	26.05 ± 5.88	26.44 ± 5.99	.951
BSI	7.15 ± 5.07	7.16 ± 4.02	.065
Mortality	5 (6.8%)	8 (24.2%)	**.022**

BMI, body mass index.

DISCUSSION

There is limited information about COVID-19 in patients with bronchiectasis. This study showed that patients with more severe bronchiectasis, as assessed by the presence of cystic bronchiectasis and by the Bronchiectasis Severity Index, more frequently developed COVID-19. Besides, male gender and older age appeared to be associated with more severe disease, as has already been shown in other studies,[10] but no other variable, including the presence of other comorbidities or vaccination status, was found to be related to the severity of COVID-19.

In bronchiectasis, dilatation of the airways, dysregulated immune response, and damaged mucociliary clearance lead to an increase in the risk of infection.[11] Viral infections may play a role in exacerbations of bronchiectasis.[12] In a study involving 119 patients in China, viruses were detected more frequently by polymerase chain reaction (PCR) during the exacerbation period than in the stable condition.[13] The most common viral agents were identified as coronaviruses, rhinovirus, and influenza. According to the report published by the European Multicenter Bronchiectasis Audit and Research Collaboration (EMBARC), exacerbations in patients with bronchiectasis decreased during the pandemic period. This was explained by social distance compliance and preventive measures during the pandemic.[14] In another multicenter study evaluating exacerbations in patients with bronchiectasis, decreases in exacerbation rates were also found during the pandemic.[6]

In a cohort study investigating the frequency and course of bronchiectasis in patients with COVID-19 in Korea, bronchiectasis was found in 1.6% of the patients, and it was reported to be 1.22 times more common when compared with the general cohort.[7] Bronchiectasis was present in 12 (0.8%) patients in a multicenter study involving 1500 patients with COVID-19 conducted by the Turkish Thoracic Society. It was reported that 1 of these 12 patients died (8.3%), in comparison to 66 (4.4%) of the patients without bronchiectasis. While mortality rates due to COVID-19 were found to be increased in patients with COPD and interstitial lung disease, the mortality rate in patients with bronchiectasis has not been found to be statistically different than the general population.[15] The lack of a significant difference may be related to the lower numbers of patients with bronchiectasis compared with the more prevalent comorbidities.

While 69% of our bronchiectasis patients with COVID-19 had mild disease, 8% were followed up in the intensive care unit. The patients followed in the intensive care unit were either unvaccinated or vaccinated with an inactivated vaccine, as observed in another study.[16] Although the majority of patients with severe COVID-19 had comorbidities, there was no significant difference in frequency compared to patients with mild disease. In a study conducted in Korea, bronchiectasis patients who had COVID-19 more frequently had comorbidities.[7]

This study has several limitations. First, the data on the history of COVID-19 were only available for 606 of the 1035 bronchiectasis patients recorded in the database. Second,

the database included a limited number of parameters, and a more thorough analysis of all potential risk factors for severe COVID-19 could not be made. Third, as the database did not include any COVID-19 patients without bronchiectasis, we were unable to compare the clinical outcomes of COVID-19 between bronchiectasis patients and the general population. The strengths of the study are that it was conducted in a multicenter manner, COVID-19 diagnoses were microbiologically confirmed, and bronchiectasis severity was evaluated with objective parameters.

While severe bronchiectasis, the presence of cystic bronchiectasis, and a worse BSI could be identified as risk factors in the development of COVID-19, a definite finding about the clinical course of COVID-19 in this patient group has not been found. Prospective, comparative studies are needed to determine whether COVID-19 manifests more severely in patients with bronchiectasis.

Data Availability Statement: All materials described in the articlemanuscript, including all relevant raw data, will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participantparticipants' confidentiality.

Ethics Committee Approval: Approval was obtained from Trakya University Medicine Faculty, Scientific Research Ethics Committee (approval number: TUTF-BAEK-2018/77; date: February 19, 2018).

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

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Author Contributions: Concept – E.Ç.E., A.Ç., A.Ş.C., A.S.; Design – E.Ç.E., A.Ş.C., D.K., E.S.U.; Supervision – A.S., E.S.U., N.K.; Resources – E.Ç.E., B.O., E.S.U.; Materials – A.Ş.C., N.K., İ.G. B.Ç.; Data Collection and/or Processing – E.Ç.E., A.Ç., D.K., A.Ş.C., S.Ç., İ.G., M.Ç.A., B.Ç., N.Ö., B.O.; Analysis and/or Interpretation – E.Ç.E., A.Ç., D.K., N.Ö., B.O.; Literature Search – E.Ç.E., A.Ç., A.Ş.C., N.Ö.; Writing – E.Ç.E., D.K., A.Ç.; Critical Review – A.S., S.Ç., B.Ç., E.S.U.

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

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Original Article

Central Sleep Apnea in Children—10 Years Experience at a Tertiary Sleep Laboratory

Cansu Yılmaz Yeğit[1], Mine Kalyoncu[1], Mürüvvet Yanaz[1], Aynur Guliyeva[1], Merve Selçuk[1], Şeyda Karabulut[1], Meltem Sabancı[2], Pınar Ergenekon[1], Yasemin Gökdemir[1], Fazilet Karakoç[1], Refika Ersu[3], Bülent Karadağ[1], Ela Erdem Eralp[1]

[1]Division of Pediatric Pulmonology, Marmara University School of Medicine, İstanbul, Türkiye
[2]Sleep Center, Marmara University School of Medicine, İstanbul, Türkiye
[3]Division of Respirology, University of Ottawa, Children's Hospital of Eastern Ontario, Ottawa, Canada

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Abstract

OBJECTIVE: Central sleep apnea (CSA) is a rare condition in children; however, it can cause significant morbidity if not diagnosed early. We aimed to increase the knowledge about CSA in children by describing the clinical characteristics of children diagnosed with CSA at our sleep center.

MATERIAL AND METHODS: We retrospectively reviewed 1263 polysomnographies (PSG) performed between 2012 and 2023 at our tertiary sleep center and evaluated the clinical characteristics of the patients with CSA. Underlying diseases, clinical symptoms, sleep parameters, and short-term management of the patients were recorded.

RESULTS: Of the 1263 patients aged between 1 month and 18 years, 122 (9.65%) had CSA, with 54.9 % (n = 67) of them being female. Only 56.6% (n = 69) of the patients' parents had reported a symptom indicating sleep-disordered breathing. The most common underlying disease was genetic, including Down and Prader-Willi syndromes, followed by neurological diseases. Obstructive sleep apnea was detected in addition to CSA in 103 of the patients (84.4%). Bi-level positive airway pressure with a backup rate was the most common treatment modality.

CONCLUSION: While CSA is a rare clinical condition in children, it occurs more commonly in those with an underlying disease. Awareness of the disease and timely referral of the patients for sleep studies are critical to prevent long-term sequelae.

KEYWORDS: Sleep apnea, central apnea, children

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INTRODUCTION

Central sleep apnea (CSA) is a rare condition in the pediatric age group that occurs more commonly in children with an underlying disease. Even though central apneas can be physiological in newborns and infants, they can be an indicator of a serious condition in children, which may be related to desaturation, hypercarbia, and life-threatening arousals.[1]

A full night in-laboratory polysomnography (PSG) is the gold standard method to diagnose the disease. The central apnea index (CAI) is defined as the number of central apneas per hour of sleep and is considered pathological if higher than ≥ 5/h.[2]

Central sleep apnea is classified into 2 main groups, including primary CSA and CSA due to other conditions.[3] Primary CSA is the hallmark of congenital central hypoventilation syndrome, which is a rare genetic condition characterized by defective ventilatory control resulting in alveolar hypoventilation.[2] However, CSA is more commonly seen in children secondary to an underlying disease. Central sleep apnea can accompany a variety of diseases, including neuroanatomical diseases; genetic diseases like Prader–Willi syndrome (PWS) and Down syndrome; neuromuscular diseases; obesity; hypothyroidism; heart failure; and upper airway abnormalities including laryngomalacia and craniofacial abnormalities. Central sleep apnea may also be idiopathic or accompanied by other sleep-disordered breathing (SDB) conditions, including obstructive sleep apnea.[2-4]

Central sleep apnea is a poorly defined condition in children, with a prevalence of lower than 5% in healthy children.[1,2,5] Ghiardo et al[5] reported that the frequency of patients with CSA was 3% in their retrospective study, which included 2981 children older than 1 month over 6 years in their sleep laboratory. They also reported that Chiari malformation was the most common underlying etiology of patients with CSA, with a frequency of 13%.[5] Similarly, Felix et al[1] also reported the frequency of CSA as 4.1%, with the most common underlying etiology being neurosurgical diseases in their retrospective study, which included 441 children older than 1 year.

Corresponding author: Cansu Yılmaz Yeğit, e-mail: cansuuuuyilmaz@gmail.com

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The management of CSA depends on the underlying etiology, clinical findings, and complications. Surgery may be successful for neuroanatomical diseases such as Arnold–Chiari malformation and brainstem compression, craniofacial deformities, or upper airway obstructions. Some patients may benefit from nocturnal oxygen therapy, while others may require noninvasive/invasive ventilation support.[5] If CSA and OSA are not diagnosed and managed early, they can cause sympathetic nervous system activation, oxidative stress, and systemic inflammation, resulting in irreversible damage, including cardiovascular and neurocognitive complications due to chronic hypoxia and hypoventilation. Since CSA is a relatively rare condition and may be asymptomatic in some children, underdiagnosing is a major challenge.[2] Pediatricians must be aware of CSA, and sleep studies for children at increased risk of CSA should be performed timely and routinely. There are few studies investigating CSA in children. Our aim is to describe the clinical characteristics of children with CSA and demonstrate the results of sleep studies and management of the patients at a pediatric sleep laboratory.

MATERIAL AND METHODS

The study is designed as a single-center retrospective study. Children who had in-laboratory PSG between January 2012 and June 2023 and had a CAI ≥ 5/h were included. Patients had been referred for PSG because of SDB symptoms and/or an underlying disease associated with an increased risk of sleep apnea. Patients who had symptoms and/or findings of an acute infection were excluded. Demographic and clinical characteristics of the patients, including underlying diseases, comorbidities, and SDB-related symptoms, were recorded from medical records. Short-term interventions after the sleep study were also recorded.

All of the PSGs were performed in the Pediatric Sleep Laboratory with the same polysomnogram (Embla N700 PSG System®). None of the patients received any drugs or sedation during the study. Recorded parameters included airflow by a nasal flow cannula and/or thermistor, pulse oximetry by a pulse oximeter, chest and abdominal movements by inductance plethysmography, electroencephalogram, electrooculograms, submental and anterior tibialis electromyogram, and electrocardiography. The scoring and reporting were performed by experienced sleep technicians and sleep physicians. Scoring of the sleep stages and the respiratory parameters was performed according to the scoring rules of the American Academy of Sleep Medicine.[6,7]

Main Points

- Even though central sleep apnea is a rare condition in children, it can cause significant morbidity if not diagnosed and treated early.
- Children with underlying diseases, including genetic diseases and neurological conditions, have an increased risk for central sleep apnea.
- Timely referral of patients for polysomnography is critical in order to prevent long-term sequelae.

Sleep parameters including total sleep time, sleep stages, CAI, obstructive apnea–hypopnea index (oAHI), oxygen desaturation index, and minimum oxygen saturation were recorded. Central apnea was defined as a reduction in airflow of at least 90% without any respiratory effort for at least 20 seconds or more than 2 baseline respiratory cycles, associated with arousal, awakening, or oxygen desaturation of at least 3%. In addition, for infants under 1 year old, if the apnea persists for more than 2 breaths and was associated with a decrease in heart rate to less than 50/minute for at least 5 seconds or less than 60/minute for 15 seconds, it was also scored as central apnea. Obstructive apnea was defined as the absence of nasal airflow with the presence of a chest wall and abdominal movements for at least 2 breaths. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in pulse oximetry (SpO2) of at least 3% and/or arousal. The CAI was calculated as the sum of central apneas per hour of total sleep time and considered normal if <5. The oAHI was calculated as the sum of obstructive apneas and hypopneas and was considered normal if <1.[7,8]

The modified Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) and Pediatric Sleep Questionnaire (PSQ) were completed by the participants or their parents. Epworth Sleepiness Scale for Children and Adolescent is a validated, simple scale assessing daytime sleepiness, including 8 questions with 4-point Likert scale answers.[9] Pediatric Sleep Questionnaire is also a validated questionnaire used to evaluate SDB-associated symptoms.[10] Epworth Sleepiness Scale for Children and Adolescents and Pediatric Sleep Questionnaire are valid and reliable tools for use in Turkish children and adolescents.[11,12]

Written informed consent was obtained from the parents of the children. The study was approved by the Ethical Committee of Marmara University School of Medicine Approval number: 09.2024.300, date: 09.02.2024).

Statistical Analysis

Statistical analysis was carried out with the Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using graphs and normality tests. Continuous variables that were normally distributed were presented as means and standard deviations, whereas the data with asymmetrical distribution were presented as medians and percentiles. Categorical variables were presented as proportions. Spearman's rho was used for correlation analysis. Results were evaluated with 95% CIs, and statistical significance level was set at a *P* value of <.05.

RESULTS

About 1263 PSGs were reviewed retrospectively, and 122 (9.65%) of them with a CAI ≥ 5 were included. Of these, 54.9% (n = 67) were female. Patients' ages ranged from 1 month to 18 years old, with a median age of 23 months. Only 56.6% (n = 69) of the patient's parents reported a symptom indicating SDB. Witnessed apnea was the most common symptom, with a frequency of 34.4% (n = 42). Table 1 shows the baseline demographic and clinical characteristics of the patients.

Table 1. Demographic and Clinical Characteristics of the Patients (n = 122)

Age, months Median (25-75th percentile)	23 (8-96)
Sex, n (%) Female	67 (54.9)
Underlying disease* Yes, n (%) No, n (%)	 103 (84.3) 19 (15.7)
SDB-related symptoms, n (%) Witnessed apnea Mouth breathing Snoring Nighttime sweating Daytime sleepiness Dry mouth Abnormal sleep positions Difficulty in wake-ups Headache Hyperactivity	 42 (34.4) 33 (27) 30 (24.6) 16 (13.1) 15 (12.3) 9 (7.4) 8 (6.6) 6 (4.9) 5 (4.1) 5 (4.1)
Positive family history for SDB, n (%)	25 (20.5)
Prematurity, n (%)	24 (19.7)
Venous carbon dioxide level (mean ± SD)	42.48 ± 7.78

Polysomnography had been performed because of an underlying disease with a high risk of SDB in 24.6% (n = 30) of the patients. The most common underlying etiology was genetic diseases (14.8%, n = 18), including Down syndrome and PWS. Nineteen patients (15.6%) did not have a diagnosed underlying disease at the time of sleep study. Table 2 shows the underlying diseases of the patients known before PSG. Central apnea index was not correlated with age ($P > .05$), while it was positively (weakly) correlated with BMI (Spearman's $P = .398$, $P < .01$).

Table 2. Underlying Diseases of the Patients (n = 103)

Underlying disease	n (%)
Genetic syndromes *Prader–Willi, Down syndrome*	 18 (14.8)
Neurological disorders *Cerebral palsy, epilepsy*	 15 (12.3)
Neuroanatomical disorders *Arnold–Chiari, tumors, hydrocephaly*	 14 (11.5)
Metabolic diseases, n (%) *Mucopolysaccharidosis, Pompe, Krabbe, urea cycle defect*	 11 (9)
Neuromuscular diseases, n (%) *DMD, myasthenia gravis, myopathies*	 7 (5.7)
Craniofacial malformations *Nager syndrome, Pierre Robin, pycnodysostosis, Crouzon syndrome*	 7 (5.7)
Bronchopulmonary dysplasia	
Other Obstructive sleep apnea Chronic lung diseases Pulmonary hypertension Central hypoventilation Chest wall restriction (scoliosis, pectus excavatum	7 (5.7) 7 (5.7) 6 (4.9) 5 (4.1) 4 (3.3) 2 (1.6)

Table 3. Polysomnography Results of the Patients

	Median (25-75th Percentile)
TST (minutes)	203 (97.5-371)
AHI (events/h)	19.2 (9.5-35.2)
oAHI (events/h)	6.7 (2.6-17.2)
CAI (events/h)	8.4 (5.9-21.9)
Min SpO2	83 (80-87)
ODI (events/h)	23.5 (9.8-38.2)
REM sleep (%)	6.2 (0-13.2)
N1 sleep (%)	4.6 (1.9-10.4)
N2 sleep (%)	47.3 (36.4-59.8)
N3 sleep (%)	34.1 (24.1-46.2)

AHI, apnea–hypopnea index; CAI, central apnea index; oAHI, obstructive apnea hypopnea index; ODI, oxygen desaturation index; TST, total sleep time.

According to ESS-CHAD, 4 (3.3%) patients had daytime sleepiness, while 49 (40.2%) patients had SDB according to PSQ. In 103 patients (84.4%), there was accompanying obstructive sleep apnea in addition to central apnea. Table 3 shows the PSG results of the patients. There was no significant correlation between CAI and PSQ. Similarly, CAI and ESS-CHAD were not significantly correlated ($P > .05$ for both).

After PSG, bi-level positive airway pressure (BPAP) with a backup rate was initiated in 46 (37.7%) patients, while 5 (4%) patients required continuous positive airway pressure (CPAP) support. Sixteen (13.1%) patients were treated with BPAP and oxygen together, while 1 patient was treated with CPAP and oxygen together. Thirteen (10.6%) patients were treated with nocturnal oxygen support only. Two patients needed invasive ventilation support. Sixty of the patients (49.2%) needed a follow-up PSG.

DISCUSSION

The present study is one of the largest-scale studies demonstrating the demographics, clinical characteristics, and polysomnographic features of CSA in children. We evaluated the results of all PSGs performed between 2012 and 2023 (n = 1263) and found that the prevalence of CSA was 9.65%. The most common underlying etiology was genetic diseases, including Down syndrome and PWS, in the present study. While witnessed apnea was the most common symptom, more than one-third of the patients' parents had not reported a symptom indicating SDB, which shows the importance of a full-night PSG for the diagnosis of CSA.

Central sleep apnea is a poorly defined clinical condition in children. As central apneas may be accepted as a physiologic phenomenon in healthy infants and children in particular situations, it is important to distinguish between pathological and physiological central apneas.[13] Short-duration central apneas in the context of a sigh, movement, arousal, or REM (rapid eye movement) sleep are considered physiological, and with the maturation of the central nervous system, central apneas are expected to decrease.[2] Studies have reported various results regarding central apnea in healthy children. Verhulst et al[14] conducted a study including 60 healthy children (6-16 years)

without SDB-related symptoms and reported that the mean CAI was 0.85 ± 1.06, with a range between 0.0 and 5.5. Similarly, Traeger et al[15] also reported that a mean CAI was 0.08 with a range between 0 and 6/h, in their study involving 66 healthy children aged between 2 and 9 years. Although our study did not evaluate CAI values in healthy children, these results are important to demonstrate that CAI values up to 5/h can be seen in healthy children. Based on previous literature, we accepted CAI ≥ 5/h as pathological.

Different definitions of central apnea may explain the difference in frequency and severity reported across different studies. In our study, we defined central apnea as a reduction in airflow of at least 90% without any respiratory effort for at least 20 seconds or more than 2 baseline respiratory cycles, associated with arousal, awakening, or oxygen desaturation of at least 3%, according to AASM guidelines. Traeger et al accepted central apnea criteria as 20 seconds,[15] while Verhults et al. accepted 10 seconds as a threshold. This discrepancy may explain the higher median CAI results reported by Verhults study (0.85 vs. 0.08/h).[14] Felix et al[1] retrospectively evaluated 441 PSG records of children older than 12 months and reported that the frequency of patients with CAI > 5 was 4.1 % in their study. The study by Felix et al[1] has also accepted the same definition and cut-off value with our study. Kritzinger et al[13] reported the prevalence of CSA as 5.4% in their retrospective study, including patients between 3 and 156 months. The higher prevalence of CSA in our study may be related to the inclusion of patients older than 1 month. In addition, our sleep center is one of the few pediatric sleep centers in our country. We may speculate that the selected referral of patients with severe disease can be the reason for the higher prevalence of CSA in our center.

In our study, 103 of 122 (84.4%) patients had a diagnosis of an underlying disease while the sleep study was performed. Felix et al[1] reported that all patients with CSA had an underlying disease, while Ghirardo et al[5] reported that only 1 patient did not have an underlying disorder in their retrospective study, including 102 patients with a CAI > 5. As our study included a 10-year period, some of our patients may have been diagnosed during long-term follow-up. To our knowledge, our study is a retrospective study covering the longest period in this field. The most common underlying etiology was genetic diseases, including Down syndrome and PWS, in our study. Ghirardo et al[5] reported the most common underlying etiology as Chiari malformation, while upper airway malformations/dysfunctions followed. Similarly, Felix et al also reported Chiari malformation as the most common underlying etiology, in addition to ganglionoroma.[1] Kritzinger et al[13] reported that the most common risk factor was a neurological disorder. Similar to previous literature, the second most frequent underlying disease was neurological disorders, while neuroanatomical disorders, including Chiari malformation, followed in our study. The most common underlying etiology was PWS in the present study (n = 10). The relationship between PWS and central apnea is a well-known entity with a frequency as high as 43% in infants, according to previous reports. Additionally, before the initiation of growth hormone, which is a Food and Drug Administration-approved treatment for individuals with PWS, performing a sleep study is recommended due to the increased risk of obstructive apneas after the treatment.[16] The possible explanation for the relatively high frequency of PWS in our study is the need for a sleep study before growth hormone administration. In addition, we may also suggest that the awareness of clinicians regarding the relationship between central apnea and other diseases, including neuroanatomical diseases, may be less than necessary.

More than a third of the patients did not have symptoms regarding SDB in our study. Similar to our study, previous studies have also emphasized the same pattern, as opposed to patients with OSA.[1,13] Many children with a polysomnographic diagnosis of CSA were asymptomatic, including Arnold Chiari malformations, Down syndrome, and achondroplasia.[2] Thereby, it is highly important to know high-risk patient groups for CSA, mainly including neuroanatomical and neuromuscular diseases, craniofacial malformations, genetic conditions, and cardiac diseases. In addition, BMI was found to be positively correlated with CAI (weakly), similar to previous studies.[17] Clinical suspicion and referring for PSG play a key role in the diagnosis of CSA in these groups.

Interestingly, the majority of patients (85%) had concurrent OSA with CSA in our study. Several studies have demonstrated an association between OSA and CSA.[5,13] Elevated loop gain and the presence of pharyngeal narrowing have been suggested to be responsible for this association. In addition, treatment of OSA can reveal CSA, which is also called treatment emergent apnea.[18] Even though only 7 patients had a diagnosis of OSA before PSG in our study, a possible relationship between OSA and CSA should not be underestimated.[18]

Continuous positive airway pressure, oxygen support, and BPAP are the cornerstones of the treatment of central apnea. In our study, we initiated CPAP, oxygen support, and BPAP in 4%, 10.6%, and 13.1% of the patients, respectively. A combination of BPAP/CPAP together with oxygen was required in some patients. The most commonly selected treatment was BPAP in our study. BPAP with a backup rate increases ventilation independent of the patients' ventilatory drive.[18] Even though finding an appropriate interface and patient noncompliance can be a problem in pediatric patients, noninvasive ventilation support is still the most preferred treatment method for CSA. As the optimal mode for ventilation support is not clear in the pediatric age group and the studies have mostly been performed in adult patients, further studies are urgently needed in this area.[19] Additionally, the heterogeneity of the disease and the wide spectrum of underlying diseases make the management of CSA more complex, and an individualized approach is required to find optimal treatment.

The present study has some limitations. First, our study was designed as a retrospective single-center study. We could not evaluate the progress of the patients as we did not include the following PSG results of the patients. Additionally, there may be some patients who may receive a new diagnosis in the long-term follow-up. We could not measure carbon dioxide levels of the patients during sleep due to technical issues, which is necessary to diagnose hypoventilation. It is possible that the number of patients with hypoventilation may be underestimated. Lastly, as our center is one of the

few reference centers regarding SDB in children, a higher prevalence of CSA may be overestimated by the priority of high-risk patients.

CSA is not a well-defined clinical condition in children. Patients may be asymptomatic, and thereby late diagnosis is a major clinical problem. Awareness of CSA, close monitoring of high-risk patients with an underlying disease, and timely referral of patients for PSG are highly critical to prevent long-term sequelae. The heterogeneity of the underlying etiology, the complex course of the disease, and the lack of a standard pediatric treatment protocol make the management of the disease difficult. There is an urgent need for a universal clinical protocol for the optimal management of the disease.

Ethics Committee Approval: This study was approved by the Ethics Committee of Marmara University (approval number: 09.2024.300; date: 09.02.2024).

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

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Letter to the Editor

Comments on: Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients

Kundan Nikit Mehta, Hiral Gulab Ramnani
Department of Respiratory Medicine, Institute of Dr DY Patil Vidyapeeth, Pune, Maharashtra, India

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Dear Editor,

We found Spalgais et al's[1] article titled "Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients" engaging and insightful. It is surprising that this study[1] stands as the only examination of pulmonary function tests (PFT) in Hypersensitivity Pneumonitis (HP), and the extensive 6-year dataset is commendable. However, we have some observations:

1. It is a well-established fact that the diagnosis of HP is done on the basis of exposure to the inciting antigen, high resolution computed tomography (HRCT) chest, bronchoalveolar lavage, and lung biopsy.[2] So, using PFT as a tool for diagnosis cannot be established. Pulmonary function tests and diffusing capacity of the lungs for carbon monoxide (DLCO) can be used only for monitoring the progression of the disease and the effectiveness of treatment on follow up.[3]
2. Aim of the study is unclear as we are not sure whether the study wants to clarify the already known relation of PFT and DLCO in HP or wants to establish PFT as criteria to diagnose HP, which is not practical.
3 American Thoracic Society/European Respiratory Society (ATS/ERS) has never used PFT as a diagnostic parameter for HP.[4]
4. The duration of 3-6 months for inciting antigen exposure is crucial in diagnosing acute HP, yet lacking a specific reference in your text is concerning. Waiting for a minimum of 3 months for diagnosis risks delaying treatment unnecessarily, given the condition's potential severity.
5. In total, 118 patients had an abnormal spirometry where all PFT parameters were reduced except Forced expiratory volume in first second/ Forced vital capacity (FEV1/FVC) and Residual volume/Total lung capacity (RV/TLC), i.e., they were either increased or normal, so if the FEV1/FVC ratio was normal, we don't look up for FEV1 to classify it as obstruction, so how could you get mixed and obstructive pattern is unclear.[5]
6. FEF25-75% is not used as a parameter to measure small airway obstruction these days; there is no relevance to calculate it.
7. Highlighting instances where reduced DLCO is observed in isolation despite normal spirometry and lung volumes in 50% of cases raises questions about the likelihood of such findings, particularly without comparative data between early and late stages of HP. Including comparative data could shed light on the evolution of pulmonary function abnormalities over time in HP patients. This approach would enhance the understanding of how DLCO reductions manifest relative to disease progression, providing valuable insights into the diagnostic and prognostic implications of isolated DLCO impairment in HP. Isolated reductions in DLCO have been observed in some cases of COPD, as supported by studies, reducing the specificity of this finding as a diagnostic marker for HP.[6]
8. Oxygen desaturation was noted highest in restrictive pattern but mean walk distance was lowest in mixed pattern, if the patient desaturated significantly, then how was it that the 6MWD was not affected. This needs clarification and referencing.
9. Respectfully acknowledging the comprehensive nature of your study and its extensive dataset, it is important to note that while PFT and DLCO measurements are useful for monitoring prognosis, they are generally not employed as diagnostic criteria for HP.

Corresponding author: Hiral Gulab Ramnani, e-mail: hiralramnani23@gmail.com

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Author's Response

RE: Comment on: Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients

Sonam Spalgais[1], Parul Mrigpuri[1], N Ravishankar[2], Raj Kumar[1]

[1]Department of Pulmonary Medicine, University of Delhi Vallabhbhai Patel Chest Institute, Delhi, India
[2]Department of Biostatistics, University of Delhi Vallabhbhai Patel Chest Institute, Delhi, India

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We thank Remnani and Kundan[1] for their Letter to the Editor titled "Comment On: Pulmonary Function and Diffusing Capacity of Carbon Monoxide In Hypersensitivity Pneumonitis: An Observational Study of 152 Patients." Here are our responses to their well-taken queries:

1. The diagnosis of HP is done by multidisciplinary discussion with the identification of the inciting antigen, HRCT chest, bronchoalveolar lavage, and lung biopsy. PFT and DLCO can be used only for monitoring of the disease. The identification of the inciting antigen was not possible in 30%-50% cases.[2,3] Studies have found a highly variable diagnostic yield of lung biopsy in HP (9%-75%). A meta-analysis of TBLB revealed a diagnostic yield of 64.3% and is not 100% specific. The BAL lymphocytosis is also not specific and yields variable results.[3-5] We propose that PFT and/or DLCO can be considered among patient where the inciting agent cannot be identified, and patients are contraindicated or not willing to undergo a lung biopsy.
2. There are limited data on PFT in HP. So the role of PFT in diagnosing HP is questionable or unclear. Recent ATS documents on HP diagnosis and Delphi HP diagnostic criteria for chronic HP did not mention PFT in HP.[6,7] The earlier diagnostic criterion did mention spirometry and DLCO as minor diagnostic criteria.[8-11] We conducted the study with the aim to determine the type of defect, lung volume, and DLCO in HP and to assess their importance in diagnosing and monitoring HP.
3. We have already mentioned in the article that major recent documents did not include it, which is why we conducted the study to find any value and correlation for HP diagnosis and monitoring.
4. Confirmed exposure history with matching clinical profiles should be considered for acute HP, even with shorter durations. The duration of 3 months should also be considered for further investigation of HP, even if there is no direct or confirmed exposure, such as the presence of pigeons on roof and window. The newer classifications of HP mentions that a duration of <6 months are considered acute/inflammatory and possibly reversible.[2]
5. The PFT classification and severity were done as per ERS and Indian guidelines, with references mentioned in the manuscript. The details of all parameters according to abnormality classification are mentioned in Table 2.
6. The overall FEF 25%-75% was reduced in most of the patients. We presented the details of FEF 25%-75% with the type of PFT abnormality in Table 2. A small paragraph in the text describes it. We did not discuss it in detail, but this can be considered for further discussion.
7. The isolated decreased DLCO was seen in only 10% of cases, not in 50% cases. Yes, this may be due to the stage of the disease and early presentation. Similar to this study, previous 2 studies also mentioned isolated reduced DLCO in 7%-10% of cases. We presented a comparative table of all studies (Table 3) and also mentioned it in the discussion with references.
8. The patient distribution is not uniform, with the majority (87) of patients showing restriction and a small population showing mixed results (18). This finding may be explained by the unequal number of cases. Further studies are needed to clarify this with the same number of cases.
9. Thanks you for your kind comments about our data and study. The aim of the study was to consider the importance of PFT in HP for diagnosis, prognosis, and patient follow-up.

Corresponding author: Raj Kumar, e-mail: rajkumarvpci@gmail.com

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