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Official Journal of the Turkish Thoracic Society

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AIMS AND SCOPE

Thoracic Research and Practice (Thorac Res Pract) is the double-blind, peer-reviewed, open access publication organ of Turkish Thoracic Society. The journal is a bimonthly publication, published on January, March, May, July, September, and November and its publication language is English.

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

The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Turkish Thoracic Journal is indexed in PubMed Central, Web of Science - Emerging Sources Citation Index, Scopus, EMBASE, EBSCO, CINAHL, Gale/Cengage Learning, ProQuest, DOAJ, CNKI and TUBITAK ULAKBIM TR Index.

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Turkish Thoracic Journal annually publishes an acknowledgement letter to thank all the reviewers of the previous year. Among the reviewers, some are distinguished with their performances and categorized as "Special Distinction in Reviewing". "Editor's Recognition Awards" category includes the reviewers who consistently provide top level service to Turkish Thoracic Journal. Many thanks to all reviewers, authors, and section editors for their priceless contribution to our journal.

Editor's Recognition Award

Züleyha Bingöl

Ayşe Baha

Gülru Polat

Special Distinction in reviewing – 2022*

Name	Completed reviews (n)	Average time (day)
Züleyha Bingöl	8	30
Ayse Baha	6	17
Gülru Polat	6	17
Onur Fevzi Erer	6	20
Tülin Sevim	6	21
Tuğba Göktalay	5	9
Aylın Babalık	5	27
Füsun Öner Eyüboğlu	5	28

*In the order of number of submitted reviews within a shorter period.

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Distinction in reviewing – 2022*

Name	Completed reviews (n)	Average time (day)
Tevfik Akçam	4	19
Öner Balbay	4	18
Pelin Duru Çetinkaya	4	26
Fatma Çiftçi	4	22
Canan Gündüz Gürkan	4	3
Dilek Karadoğan	4	7
Buğra Kerget	4	9
Pervin Korkmaz Ekren	4	22
Serpil Öcal	4	1
Eylem Acartürk	3	3
Nilüfer Acet Öztürk	3	9
Hüseyin Arıkan	3	44
Morteza Bagheri	3	8
Baran Balcan	3	21
Özlem Ediboğlu	3	2
Erdem Erkoyun	3	23
Sebahat Genç	3	2
Yavuz Havlucu	3	56
Eylem Özgür	3	12
Ilias Porfyridis	3	22
Melda Sağlam	3	15
Banu Salepçi	3	4
Yasemin Saygıdeğer	3	16
Sezai Taşbakan	3	11
Yelda Varol	3	0
Pınar Yıldız Gülhan	3	19
Meltem Ağca	2	32
Faisal A. Alzahrani	2	0
Ali Nihat Annakkaya	2	0
Dilek Aslan	2	3
Müge Aydoğdu	2	0
Safa Barış	2	26
Güntuğ Batıhan	2	12
Muhammed Ali Beyoğlu	2	3
Pınar Çelik	2	3
Bülent Çiftci	2	18
Claudia Crimi	2	0
Hülya Doğan Şahin	2	9
Neşe Dursunoğlu	2	16
Neslihan Durutürk	2	2
Nagehan Emiralioğlu	2	31
Dorina Esendağlı	2	22
Hakan Evren	2	11
Pınar Gürsoy	2	14
Sinem Güngör	2	17
Roger C. Ho	2	0
Özen Kaçmaz Başoğlu	2	3
Murat Kara	2	0
Bülent Karadağ	2	39
Y. Altemur Karamustafaoğlu	2	0
Demet Karnak	2	2
Özgecan Kayalar	2	10
Adem Koyuncu	2	27
Şerif Kurtuluş	2	3
Özlem Moçin Yazıcıoğlu	2	25
Tateaki Naito	2	0
Ayşe Önal Aral	2	2
Sedar Onat	2	24
Sevgi Özalevli	2	1
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Serir Özkan	2	12
Şeref Özkara	2	30
Önder Öztürk	2	15
Nesrin Öcal	2	0
İpek Özmen	2	15
Selin Özuygur	2	29
Sevgi Pekcan	2	12
Celal Satıcı	2	5
İrem Şerifoğlu	2	35
Deniz Şenol	2	1
Cantürk Taşcı	2	6
Şeyma Toy	2	4
İsmail Toygar	2	10
Murat Türk	2	0
Gaye Ulubay	2	39
Mehmet Uysal	2	20
Dilber Yılmaz Durmaz	2	29
Ufuk Yılmaz	2	7
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Sacide Pehlivan	1	6
Melda Sağlam	1	0
Cüneyt Saltürk	1	22
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Sema Saraç	1	57
Nuran Sarı	1	25
İsmail Savaş	1	2
Sema Savcı	1	8
Abdullah Sayıner	1	0
Filiz Selen	1	0
Celal Sezen	1	4
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Distinction in reviewing – 2022* (*Continued*)

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Utku Tapan	1	30
Halil Taşkaynatan	1	0
Mahmood Tavallaie	1	1
Ahmet Tekneci	1	18
Kemal Can Tertemiz	1	36
Nursel Türkoğlu Selçuk	1	19
Haluk Türktaş	1	6
Hakkı Ulutaş	1	7
Atilla Uysal	1	27
Oğuz Uzun	1	13
Tullio Valente	1	31
Naciye Vardar Dağlı	1	3
Khalid Waheed	1	37
Murat Yalçınsoy	1	0
Elif Yılmazel Ucar	1	5

*In the order of reviews within a shorter period.

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Editorial

It's Time to Move Forward: Thoracic Research and Practice!

This editorial introduces major changes that will take place in the journal as of 2023. Firstly, the journal's name has been changed to *Thoracic Research and Practice*.

Thoracic Research and Practice began publication in 2008 with the merger of two journals previously published under the titles "Turkish Respiratory Journal" and "Toraks Journal." For the period 2008-2022, the journal was published under the title "Turkish Thoracic Journal".

The decision to change the title was not an easy one from a personal standpoint. There is a nostalgic element to looking at a journal. While it is important to acknowledge the journal's past, it is also crucial that it continues to be supported by the scientific community in order to maintain, as well as develop further for the journal. The academic focus of Thoracic Research and Practice and its editors remain the same, and continuity is assured. Hopefully, this new title will assist in making the journal more identifiable to international scientists.

The cover of the journal also has been updated with the new title. The goal is to update the journal's design along with its title and to give it a fresh and modern appearance.

Lastly, please be aware that the journal will no longer accept submissions of case reports as of 2023. Instead, we ask our authors to refer to the types of articles available on the journal's website.

These changes are just the beginning of the future of the journal and we would like to thank all the editors, reviewers, authors and editorial board members involved who have shaped the future course!

On behalf of the editorial board,

Editors in Chief

Oğuz Kılınç

İpek Kıvılcım Oğuzülgen

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Original Article

Are Lymphocytes and Eosinophils Associated with the COVID-19 Severity: A Large, Retrospective Study

Dildar Duman[1], Zuhal Karakurt[2], Nagihan Durmuş Koçak[1], Nalan Adıgüzel[2], Tekin Yıldız[1], Gökay Güngör[2], Huriye Berk Takır[1], Fatma Merve Tepetam[3], Hakan Günen[1], On Behalf of the COVID-19 Interest Group

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Abstract

OBJECTIVE: Coronavirus disease 2019 is an ongoing disease with high morbidity and mortality. We aimed to investigate the relationship between demographics, lymphocytes, eosinophils, and the coronavirus disease 2019 severity at hospital admission.

MATERIAL AND METHODS: A retrospective, observational cross-sectional study was carried out with 5828 coronavirus disease 2019 patients between March 11, 2020, and November 30, 2020. Patients were divided into 3 groups according to where they were followed up as an indicator of disease severity, namely outpatients, inpatients, and critically ill patients. The patients' demographics and hemogram values on admission were recorded. The predictive accuracies of lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage for predicting severity were determined using receiver operating characteristic curves. Logistic regression analysis was used to predict intensive care unit demand according to lymphocyte and eosinophil values.

RESULTS: Of the 5828 coronavirus disease 2019 patients, 4050 were followed up as outpatients, 1581 were hospitalized in a ward, and 197 were hospitalized in the intensive care unit. Lymphocyte count and lymphocyte percentage were significantly different between the groups, but the difference for eosinophil count and eosinophil percentage was not significant as it was for lymphocytes. Cutoff values for lymphocyte count (1.0×10^9/L), lymphocyte percentage (22%), eosinophil count (0.052×10^9/L), and eosinophil percentage (0.08%) were found to indicate a high risk for intensive care unit admission. Coronavirus disease 2019 patients >55 years of age, with a lymphocyte count $<1.0 \times 10^9$/L, a lymphocyte percentage <22%, and an eosinophil percentage <0.08% had a 2-fold higher risk of requiring intensive care unit management.

CONCLUSION: Lymphocyte counts and percentages are quick and reliable biomarkers for predicting coronavirus disease 2019 severity and may guide physicians for proper management earlier.

KEYWORDS: COVID-19, lymphocyte, eosinophil, intensive care unit, hospitalization
Received: *October 10, 2021* ***Accepted:*** *August 19, 2022* ***Publication Date:*** *February 10, 2023*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared to be a pandemic by the World Health Organization on March 11, 2020, and is an ongoing disease with high morbidity and mortality.[1,2] Using laboratory predictors of severity before any clinical deterioration occurs may be helpful for the selection and early intervention of these patients.

Lymphopenia, defined as a low count of lymphocytes, has been predicted to be associated with COVID-19 severity.[3-7] Allergic reaction characterized by eosinophils was inversely related to Angiotensin-converting enzyme 2 (ACE2) expression, and eosinophilia could be protective for COVID-19. Coronavirus disease 2019 causes eosinopenia , and the correlation of eosinopenia with severity has not been properly elucidated.[8] It is also unclear what the cutoff values for lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage are for predicting disease severity. The lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage are routinely, easily, and cheaply measured in complete blood counts.[3] Studies looking at the utility of these biomarkers as predictors of COVID-19 severity have thus far been limited and conducted with small population groups.

A better understanding of the relationship between lymphocytes, eosinophils, and disease severity on admission and identifying severe cases earlier may help direct appropriate clinical management of COVID-19 and decrease fatality rates.[3,4]

We aimed to investigate the relationship between demographics, lymphocytes, eosinophils, and the COVID-19 severity at hospital admission.

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MATERIAL AND METHODS

This retrospective, observational cross-sectional study was conducted at the University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital between March 11, 2020, and November 30, 2020. The study protocol was approved by the ethics committee of University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (date of approval/no.: 07.01.2021/116.2017.R-209) and was conducted in full accordance with the ethical principles stated in the Declaration of Helsinki. All data were collected retrospectively from the hospital database.

Using the hospital electronic system, patients coded U07.3 using the International Classification of Diseases, namely COVID-19, were enrolled in the study. A COVID-19 diagnosis was made according to the Republic of Turkey Ministry of Health COVID-19 (SARS-CoV-2 Infection) Guide, 2020. Cases diagnosed as COVID-19 with polymerase chain reaction (PCR) positivity in nasopharyngeal and/or nasal swab samples, or cases with a negative PCR but who were diagnosed with COVID-19 according to the National COVID-19 Guide with characteristic clinical, laboratory, and radiological findings, and who received COVID-19 therapy, were included in the study. All patients were over 18 years of age. Patients without hemogram values on the first day of hospital admission were excluded from the study. Patients were categorized into 3 groups according to where they were followed up as an indicator of disease severity, namely outpatients, inpatients, and critically ill patients. In the study center, COVID patient hospitalization and outpatient follow-up were determined using the Republic of Turkey Ministry of Health COVID-19 (SARS-CoV-2 Infection) Guide 2020.

Uncomplicated patients were followed up as outpatients. Criteria for these patients were:

a. Symptoms of fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate <24, SpO_2 >93% at room air).
b. No underlying comorbid disease (mainly cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic pulmonary disease, and other immunosuppressive conditions) and patients under 50 years old.
c. A normal chest x-ray and/or thorax computed tomography.

MAIN POINTS

- Coronavirus disease 2019 (COVID-19) is an ongoing pandemic with high morbidity and mortality.
- Our results revealed that if the lymphocyte count on admission is below 1.0×10^9/L, and/or lymphocyte percentage is below 22%, eosinophil percentage is below 0.08%, and the patient age is over 55 years, there is a greater than 2-fold risk of intensive care unit demand.
- Lymphopenia showed a strong association with the severity of COVID-19, and lymphocyte values can facilitate earlier decision-making for the physicians on admission.

Criteria for ward hospitalization of COVID-19 patients were:

a. Symptoms such as fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate ≥30, SpO_2 <90% at room air).
b. Evidence of extensive bilateral pneumonia on chest x ray or thorax computed tomography.

Patients with COVID pneumonia were admitted to the intensive care unit (ICU) using the following criteria:

a. Dyspnea and respiratory distress (respiratory rate ≥30, PaO_2/FiO_2 <300, increasing oxygen need, SpO_2 <90%, or PaO_2 <70 mmHg despite 5 L/min nasal oxygen therapy).
b. Systolic blood pressure (SBP) <90 mmHg and 40 mmHg from usual SBP, mean arterial pressure <65 mmHg, and tachycardia >100/min.
c. Development of acute organ dysfunction such as acute renal injury, acute liver dysfunction, and immunosuppression.
d. High levels of troponin and arrhythmia.
e. Lactate >2 mmol/L.
f. Capillary refilling disorders and the presence of mottling.

Patient enrollment is summarized in a flowchart in Figure 1.

Data were obtained from the hospital electronic database. Patient characteristics and hemogram values on admission were recorded. A Coulter LH 780 Hematology Analyzer (Beckman Coulter Inc., Brea, Calif, USA) was used for complete blood counts (leukocyte, neutrophil, eosinophil, lymphocyte, and platelet) analysis.

Statistical Analysis

Patient demographics and all clinical data were summarized by descriptive analysis. The patient groups were designated according to place of admission, that is, outpatients, inpatients, or critically ill patients. The 3 study groups were compared using the analysis of variance–post hocTukey test for normally distributed continuous variables, i.e., age and hemogram values, and the values were defined as the mean and SD. If continuous variables were distributed non-normally, the Kruskal–Wallis test was used for analysis, and the values were defined as the median and interquartile range (25%-75%).

The chi-square test was employed for dichotomous variables, that is, gender and the cutoff values group. Count and percentage were used when applicable. The receiver operating characteristic (ROC) curve was used to define the cutoff values for lymphocyte count and percentage and eosinophil count and percentage, and the area under curve (AUC) was obtained to determine optimal cutoff values. Logistic regression analysis was done for predicted ICU demand for lymphocyte and eosinophil values. The model included age, gender, and studied cutoff values for lymphocytes and eosinophils. P <.05 was accepted as statistically significant.

RESULTS

A total of 5828 patients with COVID-19 were assessed within the study period. Patients were categorized according to where they were followed up in the hospital. Four thousand

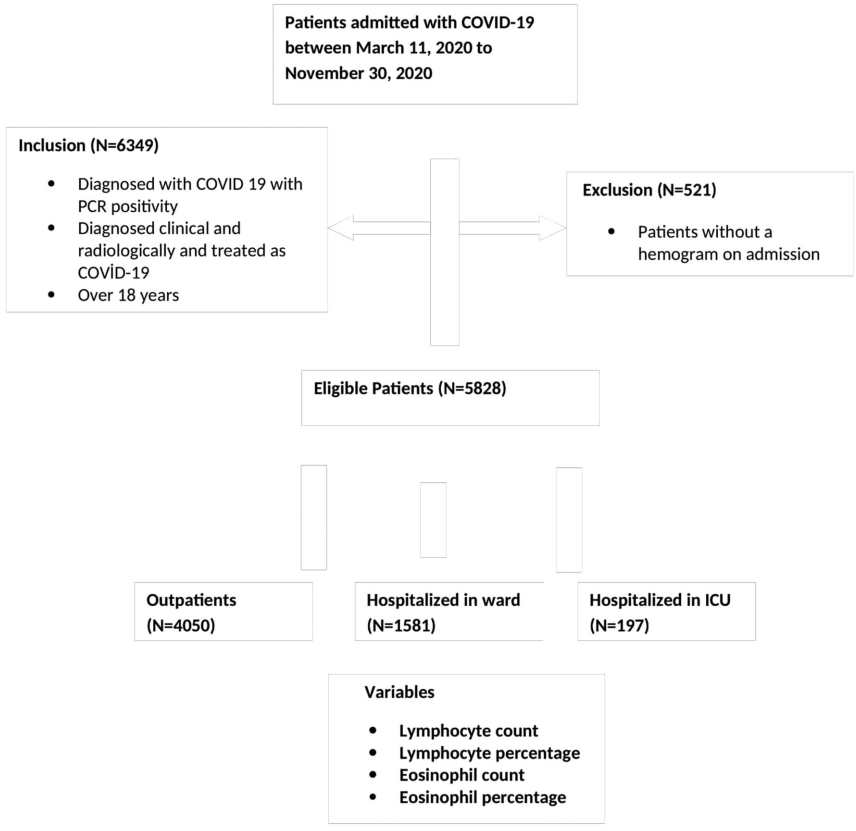


Figure 1. A flowchart of patients included in the study.

fifty patients were followed up as outpatients, 1581 patients were hospitalized in a ward, and 197 patients were hospitalized in the ICU (Figure 1).

Table 1 shows a comparison of demographics and hemogram values on the admission of the 3 groups. The older age and male ratio were significantly higher in ICU patients compared to outpatients and patients hospitalized in the ward. The median age was 46 (IQR, 35-60) years for outpatients, 56 (IQR, 44-68) years for inpatients, and 66 (IQR 55-77) years for critically ill patients. Lymphocyte count and percentage were significantly different between the groups. The median lymphocyte count was significantly lower in the ICU group [0.88 (0.54-1.63) × 10^9/L] compared with the outpatient [1.74 (1.26-2.34) × 10^9/L] and ward groups [1.43 (1.05-1.91) × 10^9/L], $P < .001$. Lymphocyte percentage was also significantly lower in the ICU group (10%) compared with the outpatient group (26%) and ward group (23%), $P < .001$. Our analysis revealed that eosinophil count and percentage in the ICU group (0.17 × 10^9/L and 0.14%, respectively) were lower than that in the outpatient (0.78 × 10^9/L and 1.06%, respectively) and ward groups, but the difference was not significant, as it was for lymphocytes. We found that the cutoff points for eosinophil cell count and percentage were 0.052 × 10^9/L and 0.08%, respectively, for predicting ICU follow-up.

The cutoff values for lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage were analyzed by the ROC and AUC and are summarized in Figure 2 and Table 2, respectively. Being over 55 years was found to be a predictor of ICU admission. The greater AUC was obtained with lymphocyte count and lymphocyte percentage for ICU demand. The results of the ROC analysis revealed the cutoff values predictive for admission to ICU were 1.0 × 10^9/L for lymphocyte count, 22% for lymphocyte percentage, 0.052 × 10^9/L for eosinophil count, and 0.08% for eosinophil percentage (Table 2).

Table 3 summarizes the logistic regression analysis results showing that being over 55 years of age, lymphocyte count <1.0 × 10^9/L, lymphocyte percentage <22%, eosinophil count <0.052 × 10^9/L, and eosinophil percentage <0.08% were all predictors for ICU demand, although eosinophil count and male gender were not statistically significant (Table 3).

Table 4 shows the forward stepwise logistic regression analysis (likelihood ratio), where only 4 parameters were found to be predictive for ICU demand. The odds ratio (95% CI lower and upper values) for these parameters were as follows: lymphocyte count 1.0 × 10^9/L: 2.14 (1.55-3.00), lymphocyte percentage 22%: 2.53 (1.70-3.77); eosinophil percentage 0.08%: 2.57 (1.86-3.55), and age 55: 2.87 (2.03-4.04) (for each $P < .001$). Our results revealed that lymphopenia on admission had a strong association with COVID severity, but eosinopenia did not.

DISCUSSION

We reviewed and analyzed the association between demographics, the counts and percentages of lymphocytes, and eosinophils on admission of COVID-19 patients with disease severity. The findings revealed that COVID-19 patients over 55 years, with a lymphocyte count below 1.0 × 10^9/L, a lymphocyte percentage below 22%, and an eosinophil

Table 1. Comparisons of Demographics and Hemogram Values in COVID-19 Patients on Admission to the Outpatient Clinics, the Ward, or ICU

	Outpatients (A)		Inpatients (B)		Critically Ill Patients (C)		*P*		
	n	Values	n	Values	n	Values	A vs. B	B vs. C	A vs. C
Number of patients (n, %)	4050	69, 5%	1581	27, 1%	197	3, 4%			
Male (n, %)	2103	51, 9%	905	57, 2%	129	65, 5%	<.001	<.001	<.001
Age, years (Median 25%-75%)	4050	46 (35-60)	1581	56 (44-68)	197	66 (55-77)	<.001	<.001	<.001
Hemogram values									
Leucocyte count, 10^9/L	4050	7.3 (5.7-9.2)	1581	6.7 (5.0-8.7)	197	9.0 (6.8-12.8)	<.001	<.001	<.001
Neutrophil count, 10^9/L	4050	4.53 (3.37-6.13)	1581	4.23 (2.99-6.17)	197	7.26 (4.74-11.09)	.268	<.001	<.001
Neutrophil %	4050	63.40 (55.97-72.31)	1581	65.13 (57.73-74.16)	197	82.65 (70.33-91.26)	<.001	<.001	<.001
Erythrocyte count, 10^{12}/L	4050	4.73 (4.39-5.09)	1581	4.42 (4.04-4.81)	197	4.14 (3.55-4.63)	<.001	<.001	<.001
Hemoglobin, g/dL	4050	13.5 (12.3-14.7)	1581	12.5 (11.4-13.6)	197	11.5 (9.6-13.0)	<.001	<.001	<.001
Hematocrit, %	4050	41.1 (37.7-44.4)	1581	38.2 (34.8-41.6)	197	36.6 (30.3-40.1)	<.001	<.001	<.001
MPV	4050	7.9 (7.4-8.6)	1581	8.0 (7.4-8.7)	197	8.8 (7.9-9.5)	.046	<.001	<.001
Platelet count,10^9/L	4050	260 (210-314)	1581	292 (220-381)	197	259 (182-378)	<.001	.001	.192
Lymphocyte count, 10^9/L	4050	1.74 (1.26-2.34)	1581	1.43 (1.05-1.91)	197	0.88 (0.54-1.63)	<.001	<.001	<.001
Lymphocyte, %	4050	25.90 (17.78-32.49)	1581	23.10 (15.65-30.26)	197	10.23 (4.59-18.34)	<.001	<.001	<.001
Eosinophil count, 10^9/L	4050	0.078 (0.022-0.16)	1581	0.072 (0.021-0.159)	197	0.017 (0.003-0.084)	.269	.117	.020
Eosinophil, %	4050	1.06 (0.34-2.16)	1581	1.12 (0.29-2.45)	197	0.14 (0.02-1,.8)	.037	<.001	.010

COVID-19, coronavirus disease 2019; ICU, intensive care unit; MPV, mean platelet volume.
Results are presented as median (25%-75%).

percentage below 0.08%, had a greater than 2-fold risk of ICU demand.

Previous studies have shown that the severity of COVID-19 increases with increased age.[5] A meta-regression analysis showed that lymphopenia was affected by age, but not by gender, in patients with poor outcome.[5] Our findings revealed that age and male ratio differed significantly between patients in outpatients, the ward, and ICU, but male ratio was not found to be an independent variable for ICU demand. We also found that being over 55 years of age was a predictor for ICU demand.

Lymphopenia is a common finding in patients with COVID-19 and is believed to indicate a defective immune response to the virus.[9] The cutoff values for lymphopenia range from 0.5 to 1.5 × 10^9/L in different studies[7] and is defined as an absolute lymphocyte count below 1.0 × 10^9/L in some studies.[10-12] Lymphopenia has been reported in 35%-75% of COVID-19 patients and found to be a frequent feature of severe disease.[13] The study reported it to be the most common hematological abnormality, present in up to 83% of hospitalized patients with COVID-19.[12] The meta-analysis noted that lymphopenia, defined as a lymphocyte count of less than 1.5 × 10^9/L, is associated with a 3-fold increased risk of severe COVID-19 infection.[3] In another meta-analysis, it was indicated that lymphopenia, defined as a lymphocyte count <1.1 × 10^9/L, was associated with severe COVID-19.[11] Zhang et al[13] found a median lymphocyte count of 1.3 × 10^9/L in discharged patients but a value of 0.56 × 10^9/L in those COVID-19 patients whose condition had deteriorated following hospital admission. Our results showed the cutoff value for lymphocyte count was 1.49 × 10^9/L for outpatients versus 1.26 × 10^9/L for COVID-19 patients hospitalized in the ward. A lymphocyte count of more than 1.49 × 10^9/L may be helpful for physicians in cases with possible non-severe COVID-19 that may be followed as outpatients, whereas patients with a lymphocyte count of lower than 1.26 × 10^9/L can be hospitalized in a ward for possible worsening of the disease.

Fan et al[14] reported that lymphopenia, with a median lymphocyte count of 0.4 × 10^9/L, featured prominently in the

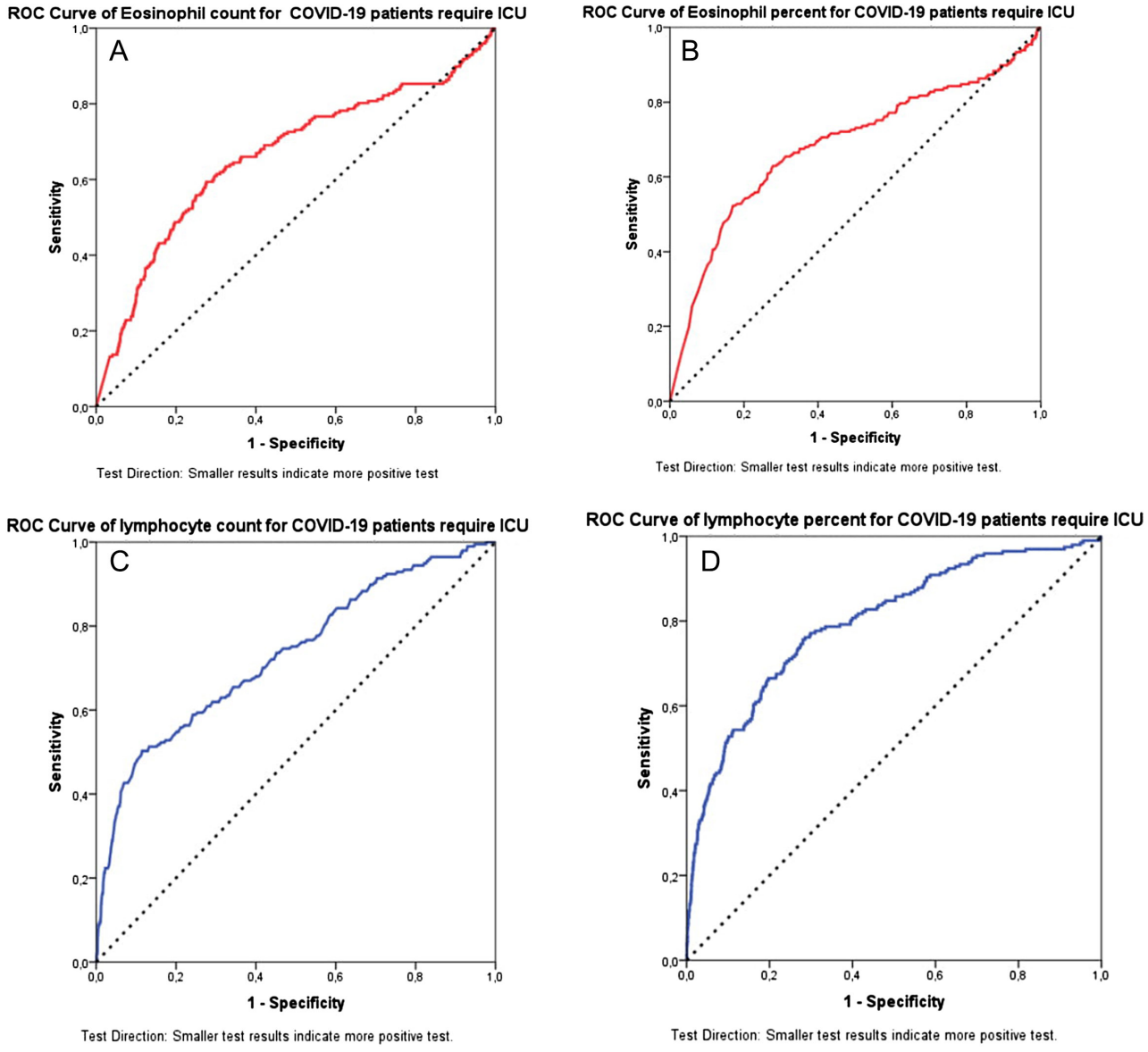


Figure 2. Receiver operating characteristic (ROC) curve analysis of (A) eosinophil count for predicting intensive care unit (ICU) demand, (B) eosinophil percent for predicting ICU demand, (C) lymphocyte count for predicting ICU demand, and (D) lymphocyte percent for predicting ICU demand.

COVID-19 ICU group, compared to 1.2 × 10^9/L in the non-ICU group. They proposed that a lymphocyte count of <0.6 × 10^9/L may be predictive for early admission to ICU. Tanriverdi et al[15] noted that lymphocyte count was significantly lower in the deceased group (1.5 × 10^9/L) compared to survivors (0.83 × 10^9/L).

We identified a lymphocyte count of 1.0 × 10^9/L as predictive of a 2.10-fold admission to the ICU. Monitoring the lymphocyte count on admission may help with early identification of patients who may need ICU care before clinical deterioration. Physicians should take care of patients with a lymphocyte count below 1.0 × 10^9/L and be aware of the potential

Table 2. Cutoff Values of Lymphocyte Count, Lymphocyte Percentage, Eosinophil Count, and Eosinophil Percentage for ICU Follow-up, as Determined with ROC Analysis

		95% CI					
Variables	**AUC**	**Lower Limit**	**Upper Limit**	***P***	**Cutoff**	**Sensitivity, %**	**Specificity, %**
Eosinophil count, 10^9/L	0.66	0.61	0.72	<.001	0.052	66	60
Eosinophil percentage	0.68	0.64	0.73	<.001	0.078	70	60
Lymphocyte count, 10^9/L	0.73	0.69	0.77	<.001	1.0	52	84
Lymphocyte percentage	0.80	0.76	0.83	<.001	0.22	80	60

AUC, area under curve; ICU, intensive care unit; ROC, receiver operating characteristic.

Table 3. Logistic Regression Analysis of the Parameters Included in the Model for Intensive Care Unit Demand

		95% CI		
	Odds Ratio	Lower	Upper	*P*
Age >55 years	2.868	2.033	4.047	<.001
Lymphocyte percentage <22%	2.383	1.593	3.564	<.001
Eosinophil percentage <0.08%	2.366	1.627	3.440	<.001
Lymphocyte count <1.0 × 10^9/L	2.100	1.489	2.961	<.001
Male gender	1.363	0.999	1.859	.051
Eosinophil count <0.052 × 10^9/L	1.177	0.799	1.733	.409

Table 4. Forward Stepwise Logistic Regression Analysis (Likelihood Ratio) Result for Prediction of ICU Demand

		95% CI		
	Odds Ratio	Lower	Upper	*P*
Lymphocyte count <1.0 × 10^9/L	2.14	1.53	3.00	<.001
Lymphocyte percentage <22%	2.53	1.70	3.77	<.001
Eosinophil percentage <0.08%	2.57	1.86	3.55	<.001
Age >55 years	2.87	2.03	4.04	<.001

ICU, intensive care unit.

severity and the need for ICU. Potential fatalities may be prevented with the timely management of these patients.

Lymphocyte percentage has been reported to decrease as the severity of disease increases.[16] While lymphocyte percentage was found to be 31% in non-severe patients, it was found to be 19% in severe patients.[16] Zhang et al[17] reported lymphocyte percentages as 20% in all COVID-19 patients, 25% in the non-severe group, 14% in the severe survival group, and 8% in the non-survival group.

According to our analysis, a lymphocyte percentage below 22% was predictive for ICU demand. Lymphocyte percentage, together with lymphocyte count, appears to present a useful, easy biomarker for predicting disease severity.

Eosinopenia has been observed in nearly 80% of COVID-19 patients on admission, with a median eosinophil count of 0.015 × 10^9/L.[18] The pathophysiology for eosinopenia in COVID-19 is not clear, but it is considered multifactorial, like reduced production and release of eosinophils from bone marrow and increased apoptosis induced by type 1 interferons during COVID-19 infection.[18]

Peripheral blood eosinophils are reduced at the early stage of COVID-19, regardless of the severity of the disease.[19] The usefulness of eosinopenia as a diagnostic and prognostic indicator has been investigated, but there is conflict regarding the association between eosinopenia and unfavorable disease progression.[18] Eosinopenia has been suggested to have a prognostic value in COVID-19 and an association with disease severity.[19,20] An early prediction of severity using eosinophil count on admission before clinical deterioration may be important to improve the prognosis of patients with COVID-19.[20] Xie et al[19] reported a low eosinophil count as an absolute number below 0.02 × 10^9/L.

In a study by Zhang et al.[17] the median eosinophil count was 0.01 × 10^9/L in 289 COVID-19 patients and did not significantly differ between the non-survival, severe but survival, and non-severe groups. However, the eosinophil percentage was found to differ between the non-survival (0.00%) and non-severe groups (0.30%). In another study, eosinophil counts and percentages were found to be lower in severe COVID-19 patients compared with non-severe ones.[16] Sun et al[16] reported that while the eosinophil count was 0.16 × 10^9/L, and eosinophil percentage was 2.35% in non-severe patients with COVID-19, the eosinophil count and percentage was lower in the severe cases (0.03 × 10^9/L and 0.44%, respectively). Sun et al[21] also reported that eosinophil count was significantly lower in critically ill patients compared to those with mild disease (0.09 × 10^9/L and 0.14 × 10^9/L, respectively).

The utility of eosinophils to predict COVID-19 severity is not clear. Our analysis revealed that eosinophil count and percentage in the ICU group (0.17 × 10^9/L and 0.14%, respectively) was lower than in the outpatient (0.78 × 10^9/L and 1.06%, respectively) and inpatient group, but the difference was not significant, as it was for lymphocytes. We found the cutoff points for eosinophil cell count and percentage were 0.052 × 10^9/L and 0.08%, respectively, for predicting ICU follow-up. However, eosinophil count was not found to be an independent predictor of ICU need.

A systematic review suggested that eosinopenia may not be associated with unfavorable progression of COVID-19.[22] A meta-analysis including 17 articles with 3396 (ranging from 12 to 1099) patients who were 720 in severe and 2676 in non-severe groups reported that decreased eosinophils in severe cases need more investigations through future studies.[23] Our results indicate that, unlike lymphopenia, eosinopenia does not have a strong association with COVID severity.

There are some limitations in this study. Firstly, it was of a retrospective nature. Nonetheless, the COVID-19 pandemic presents an urgent situation that cannot wait for prospective studies, and a retrospective study with a large sample size can provide valuable clinical information. Secondly, other patient data, such as previous history, comorbidities, and smoking history, were not recorded in the hospital database, although these values are not the primary information required for our study. Thirdly, this study is a single-centered study. Nonetheless, it was conducted in the largest chest disease teaching and research hospital in our country and reflects the whole population. All patients were evaluated by a pulmonary specialist.

The strength of this study lies in the large study population; the number of patients is indeed greater than many meta-analyses. In addition, data values were obtained using an electronic system to prevent human data entry errors. The study results are reliable and could be used to compare with other study results.

CONCLUSION

The present study findings revealed that lymphopenia showed a strong association with the severity of COVID-19 regardless of gender. Lymphocyte values can be obtained easily, cheaply, quickly, and routinely and facilitate earlier decision-making for the physicians on admission. Our results indicate that if the lymphocyte count on admission is below 1.0 × 10^9/L, and/or lymphocyte percentage is below 22%, eosinophil percentage is below 0.08%, and the patient age is over 55 years, there is a greater than 2-fold risk of ICU demand. These values may thus guide physicians to make early decisions for appropriate management in place regarding disease severity on admission.

COVID-19 Interest Group

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 07.01.2021, Number: 116.2017.R-209).

Informed Consent: Owing to the retrospective nature of the study, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.D., Z.K., N.D.K.; Design – D.D., Z.K., N.D.K.; Supervision – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G.; Resources – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Materials – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Data Collection and/or Processing – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Analysis and/or Interpretation – D.D., Z.K., N.D.K., N.A., T.Y.; Literature Search – D.D., Z.K., N.D.K.; Writing – D.D., Z.K., N.D.K., N.A., T.Y.; Critical Review – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group.

Declaration of Interests: The authors declare that they have no competing interest.

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Original Article

A Retrospective Assessment of the Continuous Health Care Provided to COVID-19 Patients Consulted Via Videoconference

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Abstract

OBJECTIVE: Telemedicine has been defined as a valuable tool in delivering care for COVID-19 patients. However, clinicians and policymakers should be convinced that traditional and new technological methods of clinical management may be equally effective. The purpose of this study was to generate some initial recommendations based on the clinical utility of videoconference consultation in forward triage and follow-up for COVID-19 patients.

MATERIAL AND METHODS: This retrospective cross-sectional study evaluated the medical records of 100 COVID-19 patients consulted using a videoconference program (Skype), from September 1, 2020, to February 3, 2021. The data were analyzed on demographic characteristics, disease history, the need for physical examination after videoconference consultation, pre-diagnostics and diagnostics, treatment decisions, number of videoconference consultation sessions in follow-up, duration of sessions, and final outcome.

RESULTS: The male COVID-19 patients constituted 54% of the total sample. The median age was 51 (42-61) years. The median duration of the initial videoconference consultation session was 16 (12-21) minutes. Following the initial videoconference consultation session, 14 patients required follow-up with all face-to-face visits; the remaining patients were primarily followed with videoconference consultation sessions. For 25 patients, it was sufficient to provide only videoconference consultation sessions; they were not required to be in the hospital for physical examination or any subsequent investigation at all. A total of 14 patients were hospitalized. There was no statistically significant difference between the high-risk group and the other patients according to the components of the disease management process via videoconference consultation.

CONCLUSION: Videoconference consultation enables a holistic assessment regardless of the patient's characteristics and allows for more time to be spent on each patient, particularly during the pandemic period without risk of contagion. It can be used as a forward triage and follow-up tool to identify patients in need of emergency hospitalization and continuous health care.

KEY WORDS: COVID-19, telemedicine, teleconsultation, outpatient clinic, triage, follow-up
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INTRODUCTION

The World Health Organization (WHO) officially announced the coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020.[1] This day coincided with the day when Turkey declared its first case of COVID-19. Since then, until the next 3 months, the pulmonology and infectious disease clinics in both public and private hospitals were transformed into isolated COVID clinics. In June 2020, the majority of outpatient clinics resumed face-to-face consultations, but access to healthcare facilities remained restricted due to the risk of COVID-19 contagion. Furthermore, delivering required care and follow-up was not always possible for COVID patients, with the exception of hospitalized patients. However, mild or moderate cases were not hospitalized. In this context, telemedicine's use for providing health care and self-quarantine guidance to COVID-19 patients, before they arrive at hospitals via a central strategy called forward triage, can protect clinicians, other patients, and the community from exposure.

A comprehensive review depicts the utility of telemedicine for different purposes in various epidemics, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome, and it outlines the enhanced preferences for telemedicine due to many advantages.[2] Several reports suggest that remote monitoring, sensors, and warning systems can be applied in COVID-19 intensive care services.[3] Telemedicine has been assessed as a *virtually perfect solution* to ensure that COVID-19 patients receive the required care and has been defined as a valuable tool in delivering care for COVID-19 patients.[4-6]

However, clinicians and policymakers should be convinced that traditional and new technological methods of clinical management may be equally effective, at least with evidence that telemedicine worked well for COVID-19 patients during the pandemic.

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Due to strict requirements for contagion prevention, this group of patients may be an excellent candidate for implementing telemedicine in medical practice. However, numerous studies have been conducted to determine the necessary interventions for COVID-19 patients.[2,5,7] Similarly, there is a need for studies revealing the clinical utility of remote approaches and the effectiveness of using telemedicine. Precisely at that point, the urgency for studies demonstrating the clinical utility and effectiveness of using telemedicine for initial clinical evaluation, follow-up, and emergency guidance for COVID-19 patients becomes apparent. The purpose of this study was to generate some initial recommendations based on the clinical utility of videoconference consultation in forward triage and follow-up for COVID-19 patients.

MATERIAL AND METHODS

Although all outpatient clinics in the university hospital, in Aegean Region, were opened for traditional face-to-face visits after the first 3 months of the pandemic, 1 physician (a pulmonologist) initiated a voluntary videoconference consultation (VCC) service. In this internet-based teleconsultation, the telemedicine implementation process utilized a personal account for a videoconference program (SkypeTM, version 6.4, Microsoft, Redmond, Wash, USA), as recommended by the University's Information Technologies Department as being free, user-friendly, easy to join without downloading the program, and most importantly, suitable for real-time videoconferencing. On the hospital's website, an announcement for an "online physician meeting" and an appointment system were posted. Although telemedicine was advocated by the Ministry of Health at the onset of the pandemic, there was no official videoconferencing infrastructure in place at that time. As suggested by the hospital's IT department, Skype was utilized within the limited known parameters of the data security level for personal communications, with no video recording. The patient has registered, and the conversation link has been sent through a short message to that registered smartphone number. The patient and his or her attendant, if one is present, accept the invitation to join the VCC. For consent to be verbal, the physician begins to explain the rationales and procedure to the patient, and after agreement, the VCC process begins. During the initial VCC session, all traditional patient evaluation practices, including also general views of inspection, are part of good clinical practice while excluding physical examination practices and this serves as a "forward triage." All sessions were conducted with the patients personally, as well as their family if they accompanied them with the patient's permission. After the initial VCC session, the physician tells the patient about the findings and plans for further VCC follow-ups, or a hospital visit for further examination at a scheduled time to help avoid lengthy waits. Reciprocal communication continues according to the same videoconference program (Figure 1). Videoconference consultation is completely free of charge, the virtue of the physician's initiative, since working for government prohibits and the regulations for reimbursement are still lacking.

MAIN POINTS

- Alternative methods should be developed to care for the patient burden during the COVID-19 pandemic.
- Telemedicine can be an alternative to providing patient care during the pandemic period.
- Clinical results regarding the care of COVID-19 patients with the videoconferencing consultation are presented.

In the given context, this retrospective cross-sectional study evaluated the medical records of 100 COVID-19 patients from September 1, 2020, to February 3, 2021. The reasons COVID-19 patients applied for VCC varied according to their current health situation, ranging from their suspicion of persistent symptoms after treatment completion to their attempt to get a second opinion. The data were extracted from the detailed medical records of officially registered patients and anonymized before being stored on the researchers' personal computer. The study analyzed data on demographic characteristics (age, gender, location, occupation, and working status) and disease history (comorbidities and new or previously diagnosed COVID-19). It also analyzed information about how the physician attended to the COVID-19 patients, the need for physical examination after the videoconference consultation, on-hold investigations, pre-diagnostics and diagnostics, treatment decisions, number of VCC sessions in follow-up, duration of sessions, and final outcome. The data also noted the need for in-hospital or intensive care unit treatment at any time before the first VCC session and whether a treatment has been initiated. Patients evaluated by the initial VCC session within the first 14 days after the diagnosis of COVID-19 were classified as "active COVID-19" cases. Patients who completed their quarantine period (14 days) prior to receiving their initial VCC were classified as "after active COVID-19" patients, regardless of the duration passed since their quarantine.

The analysis of follow-up period was analyzed in 3 groups—only face-to-face follow-ups, only VCC follow-ups, and hybrid follow-ups (alternating between VCC and face-to-face follow-ups according to the need). The groups were spontaneously formed during the process, based on the physician's preference and need. The time and duration of each VCC session were retrieved from the historical part of the videoconferencing program. The statistical analyses were performed using the statistical package for the social sciences (SPSS 26.0) software (IBM SPSS Statistics Data Editor, IBM Corp., Armonk, NY, USA). The descriptive analysis was performed for all the demographic features. The continuous variables were reported as medians (25th to 75th percentile) with the interquartile range, which implies that the variables were not distributed normally. Categorical variables were reported as numbers and percentages. A chi-square test was performed to analyze differences in categorical groups. For the variables assuming an abnormal distribution, the Mann–Whitney *U* test and Kruskal–Wallis test were used for 2-group and more than 2-group comparisons, respectively. A *P*-value of .05 was used for statistical significance. This study was carried out following the Helsinki Declaration; it was approved by the Institutional Review Board of Pamukkale University (decision no: 03; date: February 02, 2021) and additional permission from the Ministry of Health.

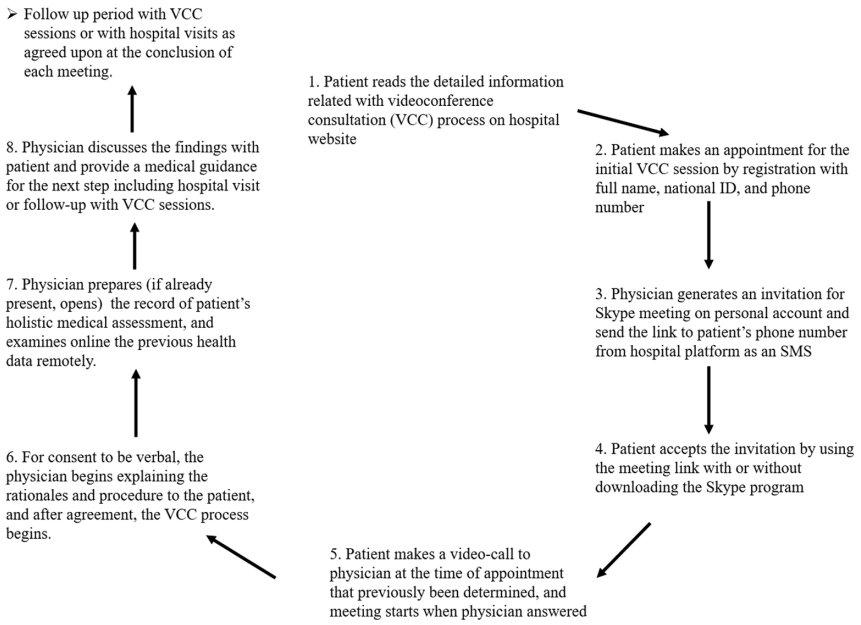


Figure 1. Diagram for videoconference consultation (VCC) process.

RESULTS

Patient Population

The male COVID-19 patients accounted for 54% of the total sample. The median age was 51 (42-61) years and 20% of the patients were in the 65-year-old age group. According to the occupations, 40% of the patients had a job that required at least an undergraduate or 2-year degree study program. The healthcare workers accounted for 11% of the total sample. The sample comprised 19% of patients from cities other than the location of the university hospital. The analysis revealed accompanying diseases in 56 of the patients, and pulmonary diseases in half of them. Table 1 summarizes the demographic characteristics of the patients.

Data from Initial Videoconference Consultation Sessions

At the time of the initial VCC session, 95 of 100 sampled patients were already diagnosed in a different (62 patients) or the same hospital (33 patients) where the interviewer physician was working. The median duration since the diagnosis was 27 (14-42) days. Of these 95 patients, 35 were previously hospitalized for COVID-19, while 13 were hospitalized in the intensive care unit. The remaining 5 patients in the sample were diagnosed within the initial VCC session by the physician. Table 2 presents the related data.

While 90 patients directly approached the physician for the initial VCC session, 5 patients were referred by another physician. In the remaining 5 instances, the patient's relative contacted the physician before doing the initial VCC personally with the patient.

The median duration of the initial VCC session was 16 (12-21) minutes. The shortest duration of the initial VCC session was observed for patients who produced medical records from pre-pandemic face-to-face visits with the same physician.

Patients who had previously been diagnosed by physicians other than those at the university hospital did not have a medical record at the university, but 50 of them were known to have been tested in other hospitals prior to their application, and the physician obtained data on medical test results, particularly radiological images, for 27 of these 50 patients from eNabiz (a national health record system). Table 3 presents the details of the applications and VCC process.

For 25 patients, it was sufficient to provide only VCC sessions; they were not required to be in the hospital for physical examination or any subsequent investigation. 74 Seventy-five patients underwent a physical examination in the hospital; 31 on the same day as the initial VCC.

At the time of booking the initial VCC session slot, 63 of the 95 patients who had previously been diagnosed with COVID-19 were taking treatment either for active COVID-19 or for ongoing COVID symptoms. For almost half of all attended patients (47%), the physician performing the teleconsultation suggested a novel treatment or some additional drugs. Table 4 presents the characteristics of the patient population according to their diagnosis and treatment information within the initial VCC session.

About 11 patients were hospitalized on the same day, as well as provided the initial VCC; of these, while 3 patients were diagnosed as "active COVID-19" cases (2 of them were newly diagnosed by the physician), 8 were diagnosed as "after active COVID-19."

Follow-Up Videoconference Consultation Sessions

The median duration of the follow-up VCC sessions was 5 (3-6) minutes. The median interval between follow-up VCC sessions was 13 days (9-24).

No follow-up was required in 17 patients. After the initial VCC session of 83 patients, 14 patients required follow-up with only face-to-face visits; the remaining 69 patients were primarily followed with VCC sessions. Around 39 of those 69 patients followed up with VCC sessions without the need to be in the hospital at all; 30 patients were given appointments for face-to-face visits as needed (Figure 2).

Table 1. Demographic Characteristics of the Patient Population

Parameter	N = 100
Gender	
Men	54
Women	46
Age (years) median (P25-P75)	51 (42-61)
Age groups	
≤45	30
46-64	50
≥65	20
Settlement	
In the city where the university hospital is located	81
In cities from the same geographical region	16
In cities from other regions	3
Occupation	
Requirement for undergraduate education	40
Housewife	12
Healthcare workers	11
Others (mostly farmers)	37
Working status	
Active working	62
Unemployed/disabled	21
Retired	17
Comorbidities	
Asthma	28
Interstitial lung diseases	4
Other lung diseases	6
Hypertension	14
Diabetes mellitus	10
Rheumatic disease	11
Cardiovascular disease	5
Thyroid disease	5
Chronic kidney disease	4
Other	7
Total	56

Three patients were hospitalized during the follow-up period, and 1 of them was pursuing follow-up as an "active COVID-19" case. Two other patients with ongoing COVID-19 symptoms were hospitalized, owing to bacterial superinfection in 1 patient and acute cholecystitis in the other.

Follow-Up Outcomes

A total of 83 patients needed to be followed up on. Five patients did not attend their most recent VCC appointment, and thus, the final outcome of the disease process for these patients could not be determined. Among the 78 remaining patients who received follow-up, 71 were cured, and 5 patients were still being followed due to persistent respiratory symptoms following COVID. Two patients died. The first patient died shortly after being admitted to the hospital following the initial VCC session due to severe respiratory failure. The second patient was cured of respiratory problems but died of sudden cardiac death after a 68-day follow-up.

Follow-Up in the Risk Group

The disease process was classified as high-risk in 12 previously diagnosed COVID-19 patients (9 female and 3 male), all of whom had chronic diseases or were over the age of 65. Among those patients, 7 patients had been hospitalized prior to submitting the initial VCC application. One patient among 12 was classified as having "active COVID-19," diagnosed by another physician prior to the first VCC session, and the remaining patients were from "after active COVID-19" group. While 3 patients received face-to-face follow-ups, 9 participated in hybrid follow-ups (followed up with VCC sessions and additionally face-to-face visits when needed). None of these patients required hospitalization. There was no statistically significant difference between this high-risk group and the other patients according to the components of the disease management process via VCC (Table 5).

DISCUSSION

The key findings of this study demonstrate the utility of VCC in terms of forward triage, clinical follow-ups, and emergency guidance for COVID-19 patients both during and after the quarantine period of COVID-19. Additionally, these VCCs provide physicians with an option for safety meetings with patients who may be contagious and thus pose a high risk during traditional face-to-face consultations. This option may result in a decrease in the number of people who visit the hospital for COVID-19 follow-ups, except when diagnostic intervention is required. If a diagnostic intervention was

Table 2. Characteristics of the Patient Population by Diagnosis and Prognosis of COVID-19 in the Period of the Initial Videoconference Consultation (VCC) Session

	Diagnosis Before First VCC Session	Hospitalization Before First VCC Session	ICU Need Before First VCC Session
In the university hospital	33	15	6
In another hospital in the same city	47	15	5
In a hospital in another city	15	5	2
Total	95	35	13

ICU, intensive care unit; VCC, videoconference consultation.

Table 3. Characteristics of the Patient Population by Attendance and Procedure in the Period of the Initial Videoconference Consultation (VCC) Session

Attendance	
First and self-attendance	49
Previously followed up by the university hospital	26
Previously followed up by the physician who made VCC sessions	12
Attended by the family members on behalf of the patient	5
Referred by another physician	5
A member of known healthcare workers	3
Investigation reports	
None	12
Exist	88
Having the university hospital records	38
Having national health system records	27
Having the reports held themselves	23
Procedure	
The initial VCC session + follow-up with only VCC sessions (never needed to be in the hospital)	25
The initial VCC session + physical examination and/or investigation in the hospital	75
Physical examination on the same day with the initial VCC session	31
Physical examination on another day after the initial VCC session (in their investigation appointment day)	44

ICU, intensive care unit; VCC, videoconference consultation.

required within the initial or follow-up VCC sessions, a time slot for the planned investigation was scheduled following the sessions. As a result, their hospital stay was reduced, and the results of the investigations were evaluated via additional VCC sessions, most of which occurred on the same day. In other words, this option enables online follow-ups that do not require lengthy hospital visits.

The home isolation of patients and those residing with them has become one of the main methods of preventing the spread of the virus; this practice stipulates a quarantine period of 14 days.[8] It must be noted that, besides the symptoms, increased levels of anxiety, depression, and stress were also observed in patients quarantined as a result of the diagnosis or for prevention of the contagion.[9] The COVID-19 symptoms and an increased level of anxiety increase the need for medical advice. However, the difficulty to get a hospital appointment owing to quarantine and lockdown regulations may make it difficult for active COVID-19 patients to receive continuous health care. This difficulty emphasizes the critical nature of remote medical assistance for them. Around 29% of the study population was evaluated during the home quarantine period, 45% (13 patients) were offered new/additional treatment, and the remaining patients were not offered additional treatment. While medical guidance was the primary intervention for those with mild to moderate disease, face-to-face follow-ups were only received for those with severe symptoms and follow-up investigations indicated were conducted in the hospital.

Studies show that about 85% of COVID-19 patients have mild to moderate symptoms.[10] However, unnecessary hospital admissions of patients linked to an intense fear called "*Coronaphobia*" have increased the burden on the healthcare system.[11] The unnecessary hospital appointments can be avoided by placing the patients under the supervision of a physician. However, patients determined as non-responsive to treatment and/or those with worsening conditions can be referred to the hospital immediately. Along with the forward triage, there must be a focus on the use of telemedicine for daily clinical practice. This option can be used for informing laboratory results to patients and for shortening the waiting time to see a specialist physician in healthcare

Table 4. Characteristics of the Patient Population by New Diagnosis, Therapy After the Initial Videoconference Consultation (VCC) Session, and Hospitalization Outcome

	Active COVID-19	After Active COVID-19	Total
New diagnosis by the physician	5	35	40
The duration between the diagnosis of COVID-19 to the initial VCC session			100
≤14 days	29	-	
15-29 days	-	30	
30-90 days	-	33	
>90 days	-	8	
Having treatment while pursuing the initial VCC session	11	52	63
New/added therapy after the initial VCC session	13	34	47
Hospitalization	3	8	11
Newly diagnosed	2	5	
Previously diagnosed	1	3	

VCC, videoconference consultation.

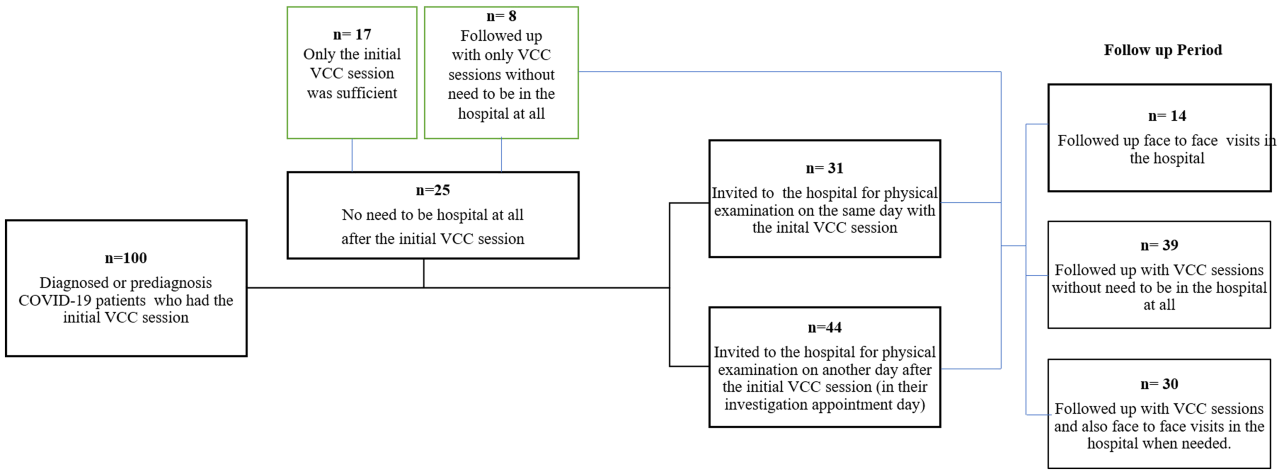


Figure 2. Flowchart of videoconference consultation (VCC) sessions.

units. This intervention can be more fruitful for patients having sophisticated device support and monitoring devices in their homes.[6,12] The clinical history and monitoring data with patient interviews may provide important information for determining health status; telemedicine also establishes a solid foundation for the relationship between a physician and the patient.[13]

The restrictions and individual follow-up avoidance may more adversely affect patients in the aforementioned high-risk group—elderly patients and those with accompanying chronic diseases.[14] This is attributed to the fact that such patients might need to visit hospitals frequently. In this study, 20% and 56% of the total sample, respectively, were 65 years and older and had an accompanying chronic disease. Twelve patients with these risk factors were found to be comparable to those without risk factors; according to the components of the disease management process via VCC, there was no statistically significant difference between this high-risk group and the other patients. Thus, it can be stated that VCC is also suitable for the evaluation of the patients with risk factors. Particularly, concerning COVID-19 patients who had a higher possibility to be symptomatic and a high-risk disease process, telemedicine can be an appropriate alternative for close follow-up. This could facilitate effective guidance in case of immediate remote triage.

While spending a considerable amount of time in patient evaluation is considered good medical practice, the pandemic has unfortunately forced a change in this medical practice, as in many other areas. Our knowledge of the spread of COVID-19 by aerosols and larger droplets and the factors affecting this situation is increasing every day.[15] Hence, it has become important to reduce the time spent in gatherings in a close environment and to create a safe atmosphere because of contagion risk. This can also be attributed to uncomfortable work conditions owing to the use of personal protection equipment for long periods. Vidal-Alaball et al[3] focused on the implementation of telemedicine, as a new channel, for facilitating more fluent, easy, and efficient patient and physician communication, during and maybe even after the pandemic. The collection of medical history has been addressed as the longest part of the medical evaluation, with a mean duration of 5-36.6 minutes.[16] The median duration of the initial VCC in the recent study was 16 (12–21) minutes. As the diagnostic spectrum in general pulmonology practice is quite broad, the needed time may be longer than that of a recent study. This duration may vary for examining COVID-19 patients who have already been diagnosed, have no comorbid conditions, and require only follow-up, as indicated by our data for this specific ailment. The test results of the previous examinations of patients in other hospitals could also be examined in detail with remote access by obtaining their consent during

Table 5. Univariate Analysis of the Disease Process in 12 Previously Diagnosed COVID-19 Patients (9 Female and 3 Male) with Chronic Diseases and Those Aged Over 65 Years, Relative to Others

	Patients in Risk Group N = 12	Others N = 88	*P**
Duration of the initial videoconference consultation (VCC) session in minutes**	16 (10.75)	16 (9.75)	.8
Number of total follow-ups**	3 (5)	2 (4.75)	.4
Number of VCC sessions in follow up**	3 (3.50)	3 (3)	.3
Number of face-to-face visits in follow up**	1 (0)	1 (1)	.1
Duration of VCC sessions in follow up**	5 (1)	4 (3)	.1
Average time in days between VCC sessions in follow-up**	14 (20)	13 (15)	.3
Duration of total follow-up period in days**	50 (31)	35 (61)	.4

*Mann–Whitney *U* test was used;**Median (inter-quartile range).
VCC, videoconference consultation.

the VCCs. When necessary, the current radiological images were compared with the previous ones. The proportion of patients who were investigated before in other state hospitals in the same province or another, except for the university hospital, was 62% among the study population but the physician could view prior investigations during the teleconsultation by retrieving data from eNabiz with patient's consent. This database reduced unnecessary examination, cost, and time. Given this, it must be noted that the need for the patients to come to the hospital can be reduced by combining anamnesis and prior investigations. These provisions comprise the priority expectations for the fruitful implementation of telemedicine during pandemic conditions.

According to a recent comprehensive review of studies from 18 countries (mostly United States and China), the most common purpose for different sorts of telemedicine applications in various disciplines was follow-up (53%), followed by prevention, screening, triage, diagnosis, and treatment aspects of COVID-19. In the review, the primary impediments to widespread use of telemedicine approaches were identified as data and resource availability, as well as patient and provider access to them, standards and legal considerations, insurance policies and reimbursement, and data privacy and security.[17] It is worth noting that the majority of the studies analyzed in that review were experimental in nature, with only a few publishing real-world results, possibly due to the pandemic's critical conditions. The uniqueness of our study appears to be in its representation of real-world data, and the areas in which the benefits of VCC implementation for COVID-19 patients appear to be promising. Our study is also significant in terms of acquiring experience and institutionalizing telemedicine as a non-inferior alternative to traditional healthcare delivery, particularly in exceptional circumstances such as the ongoing pandemic but is limited to this one instance of telemedicine implementation for diagnosing and monitoring COVID-19 patients in Turkey, countrywide recommendations and comparisons were not possible.

One limitation of the study may be the digital inequality, due to the lack of technical infrastructure and the ability to use technology that hindered many other patients to access VCC. However, the increased use of videoconference programs for work and educational activities, as well as for social support provision through family communication by cell phones, may enhance convenience in this regard. The pandemic situation teaches us a valuable lesson about overcoming similar technological equipment deficiencies in the future (creating different internet access areas outside the hospital, etc.).[18]

As a conclusion, while this study focused on the experience of a single physician in a single center, the findings indicate that VCC enables holistic assessment regardless of the patient's characteristics and allows for more time to be spent on each patient, particularly during the pandemic period without risk of contagion. It can be used as a forward triage and follow-up tool to identify patients in need of emergency hospitalization and continuous health care. Since telemedicine has been demonstrated to be a safe and beneficial practice over the world, particularly in special situations such as the pandemic, Turkey has yet to regulate its legal and ethical principles on telemedicine.

Ethics Committee Approval: This study was approved by Ethics committee of Pamukkale University, (Approval No: 03, Date: 02.02.2021).

Informed Consent: Written informed consent was obtained from the patient for publication of this research and accompanying image.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.A.; Design – N.C, G.A.; Data Collection – P.B., N.C.; Analysis and/or Interpretation – P.B., N.C.; Methodology: P.B., N.C., G.A.; Supervision: P.B., G.A.E.; . Writing – P.B., N.C.,G.A., Critical Review – P.B., N.C.,G.A.

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Original Article

Initial COVID-19 Severity and Long-COVID Manifestations: An Observational Analysis

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Abstract

OBJECTIVE: New-onset or persistent symptoms beyond after 4 weeks from COVID-19 are termed "long-COVID." Whether the initial severity of COVID-19 has a bearing on the clinicoradiological manifestations of long COVID is an area of interest.

MATERIAL AND METHODS: We did an observational analysis of the long-COVID patients after categorizing them based on their course of COVID-19 illness into mild, moderate, and severe groups. The clinical and radiological profile was compared across these groups.

RESULTS: Out of 150 long-COVID patients recruited in the study, about 79% (118), 14% (22), and 7% (10) had a history of mild, moderate, and severe COVID-19, respectively. Fatigue ($P = .001$), breathlessness ($P = .001$), tachycardia ($P = .002$), tachypnea ($P < .001$), raised blood pressure ($P < .001$), crepitations ($P = .04$), hypoxia at rest ($P < .001$), significant desaturation in 6-minute walk test ($P = .27$), type 1 respiratory failure ($P = .001$), and type 2 respiratory failure ($P = .001$) were found to be significantly higher in the long-COVID patients with a history of severe COVID-19. These patients also had the highest prevalence of abnormal chest X-ray (60%) and honeycombing in computed tomography scan thorax (25%, $P = .027$).

CONCLUSION: The course of long COVID bears a relationship with initial COVID-19 severity. Patients with severe COVID-19 are prone to develop more serious long-COVID manifestations.

KEYWORDS: Walk test, breathlessness, respiratory failure, COVID-19
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INTRODUCTION

The ongoing COVID-19 pandemic has posed a significant challenge to healthcare workers. Not only this, but even after acute COVID-19, patients continue to suffer from persistent symptoms. New-onset or persistent symptoms, unexplained by alternate etiology, after 12 weeks of COVID-19 have been termed as "post-COVID" and after 4 weeks as "long-COVID."[1,2] The various clinical findings of long COVID include fatigue, breathlessness, cough, and chest pain.[3] Its radiological sequelae include ground-glass opacities and parenchymal bands.[4]

From the very beginning of the COVID-19 pandemic, periods of crest and trough in the positivity rate and number of active cases of the disease have been documented, but from then only, the healthcare system has been burdened with the ever-rising long-COVID cases. It has now become equally important to recognize long-COVID symptoms at the earliest and to manage them appropriately.

Studies have documented that even patients with mild or no symptoms at the time of COVID-19 positivity also suffer from long-COVID manifestations.[5,6] Most common manifestations include fatigue, cough, or exertional dyspnea.[3,7,8] The long-term implications of COVID-19 infection are still not well documented and this is an area of active research. Therefore, it is universally recommended to closely follow COVID-19-infected patients in the post-COVID period, for persistent or new symptoms.[9,10] In the present study, we analyzed the clinical, laboratory, and radiological parameters of 150 long-COVID patients who presented to us with persistent or newly developed respiratory symptoms. Simultaneously, we studied the clinicoradiological findings in long-COVID patients in relation to the severity of their acute COVID-19 illness.

MATERIAL AND METHODS

The present study is an observational analysis of the long-COVID patients presenting to the outpatient department of our hospital during the period May 2020 to December 2020. Patients with a diagnosis of "long COVID," that is, presenting with persistent symptoms (without alternate etiology) even after 4 weeks from the diagnosis of COVID-19 with alternate diagnosis having been excluded, were enrolled into the study.[1] Only patients with age >18 years were included in the

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study. The demographic profile, symptomatology, physical examination findings, and blood and radiological investigation of these patients were analyzed. Patients with (1) resting hypoxia (oxygen saturation SpO_2 <90%), (2) significant exertional desaturation (>4% fall in oxygen saturation) on 6-minute walk test (6MWT), or (3) evidence of any abnormality on chest radiograph were advised to undergo computed tomography scan (CT scan) of the chest and 82 patients qualified for the same.

All the CT scans were evaluated by 2 pulmonologists (with >28 years and >16 years of experience) and 1 radiologist (with >25 years of experience). For quantitative estimation of lung abnormalities on CT scan, a scoring system was used which relied on the basis of the area involved.[11,12] In this scoring system, each of the 5 lung lobes was visually scored on a scale of 0 to 5 as follows: (a) score 0 if no involvement, (b) score 1 if less than 5% involvement, (c) score 2 if 5%-25% involvement, (d) score 3 if 26%-49% involvement, (e) score 4 if 50%-75% involvement, and (f) score 5 if more than 75% involvement. The total CT severity score (CTSS) was derived by summation of individual scores of all 5 lobes, and hence, it ranged from 0 (no involvement) to 25 (maximum involvement).

We categorized the patients based on their course of COVID-19 illness into mild, moderate, and severe groups.[13] Patients with (a) a history of home isolation or hospital admission (without oxygen support) for monitoring only during COVID-19 were categorized as "mild," (b) a history of hospital admission requiring oxygen support as "moderate," and (c) a history of hospital admission for non-invasive (NIV) or invasive ventilation as "severe."

The patients presenting to us within 4 weeks period from COVID-19 were excluded from the study.

The study was approved by Institutional Human Ethics Committee of the Vallabhbhai Patel Chest Institute, University of Delhi (approval number: VPCI/DIR/IHEC/2020/1847) and informed consent was obtained from all the participants.

Statistical Analysis

The collected data were entered into a Microsoft excel spreadsheet. The data were imported and analyzed in Statistical Package for Social Sciences version 22 statistical software (IBM Corp.; Armonk, NY, USA). The variables pertaining to this study were summarized using frequency and percentages in the case of categorical variables, mean and standard deviation for quantitative normally distributed variables, and quantitative variables which are skewed were summarized using median and interquartile range. Statistical tests namely one-way analysis of variance, Kruskal–Wallis test, and chi-square test for trend were employed to analyze the data. *P* value less than .05 was considered statistically significant.

MAIN POINTS

- Parallel to the recovery from COVID-19, there has been a rise in patients with persistent or new-onset symptoms termed "long COVID," worldwide.
- We compared long-COVID manifestations among patients with different severity of COVID-19.
- Severe COVID-19 patients were found to have significantly higher as well as more severe clinical and radiological manifestations compared to patients with mild to moderate COVID-19.
- Hence, COVID-19 patients require a planned and meticulous approach for the management of long-COVID manifestations.

RESULTS

During the study period, 150 long-COVID patients presented to the hospital. A maximum number of patients belonged to mild group (n = 118; 78.68%) followed by moderate (n = 22; 14.67%) and severe (n = 10; 6.68%). The clinical characteristics and laboratory and radiological findings of the 3 groups are depicted in Tables 1-5. Approximately 85% of patients (n = 128) had 1 or more comorbidities. Hypertension and diabetes mellitus were the commonest comorbidities (n = 34; 22.67% each). Bronchial asthma with allergic rhinitis was the most common respiratory comorbidity (Table 1). It was found that most patients with respiratory comorbidities had only mild COVID-19 (nearly 70% each, $P = .001$). No significant difference in the prevalence of respiratory comorbidities and severity of COVID-19 illness was found. Among patients with non-respiratory comorbidities, maximum had moderate COVID-19 (about 72%, $P = .027$) with diabetes mellitus being the commonest comorbidity (nearly 63%, $P < .001$). Fatigue and breathlessness (n = 108; 72% and n = 106; 70.67%, respectively) were the most frequent symptoms reported followed by cough (n = 100; 65.67%) (Table 2). Fatigue and breathlessness were found to be significantly higher in the severe category ($P = .001$), while cough was the most commonly reported symptom in the moderate category (100%, $P = .003$). Severe category patients had a significantly higher incidence of tachycardia (40%, $P = .002$), tachypnea (40%, $P < .001$), raised blood pressure record (60%, $P < .001$), and crepitations on auscultation (40%, $P = .04$). Hypoxia at rest (40%, $P < .001$), significant desaturation in 6MWT (40%, $P = .27$), type 1 respiratory failure (20%, $P = .001$), and type 2 respiratory failure (20%, $P = .001$) all were significantly more common in the severe category. Six patients presented with respiratory failure and required hospitalization on presentation (Table 3). More than 40% of patients were anemic and 6 patients (4%) had raised blood sugars for the first time during the assessment. Severe category patients had statistically higher evidence of blood abnormalities in form of either neutropenia (40%, $P < .001$) or neutrophilia (20%, $P = .037$) and lymphopenia (40%, $P = .002$). As depicted in Table 4, chest radiograph was abnormal in about 53% of patients (n = 80) and bilateral diffuse reticulations was the most common abnormality detected (n = 38; 25.34%). On presentation, patients with a history of severe COVID-19 had the highest incidence of abnormal chest x-ray (60%) and diffuse reticulations were the commonest abnormality (60%, $P = .017$). As per the criteria stated above, 82 patients underwent a CT scan of the chest (Table 5). All these patients had abnormal CT scans (Figures 1 and 2). Most common findings were diffuse ground-glass opacities (n = 36; 43.9%) and diffuse reticulations (n = 32; 39.02%). Patients with severe

Table 1. Characteristics of Long-COVID Patients (n = 150)

	Overall (n = 150)	Mild (n = 118)	Moderate (n = 22)	Severe (n = 10)	*P**
Gender (male: female)	100:50	74:44	18:4	8:2	-
Age (mean ± SD) (in years)	46.56 ± 16.03	45.38 ± 16.54	54.18 ± 10.59	43.6 ± 15.47	.05
Duration to presentation (in days)** [Median (IQR)]	26 (10-71)	30 (12-83)	19 (8-53)	25 (15-37)	.296
Co-morbidities	n (%)	n (%)	n (%)	n (%)	
i. No comorbidities	22 (14.67)	36 (30.5)	10 (45.5)	8 (80)	.001
ii. Respiratory comorbidities	96 (64)	82 (69.49)	12 (54.54)	2 (20)	.001
a. Allergic rhinitis	14 (9.34)	12 (10.16)	2 (9.09)	0 (0)	.478
b. Bronchial asthma	8 (11.42)	8 (6.78)	0 (0)	0 (0)	.229
c. Bronchial asthma with allergic rhinitis	34 (22.67)	30 (25.42)	4 (18.18)	0 (0)	.06
d. Chronic obstructive pulmonary disease (COPD)	18 (12)	16 (13.56)	2 (9.09)	0 (0)	.209
e. Interstitial lung disease (ILD)	4 (2.67)	4 (3.39)	0 (0)	1 (0)	.5
f. Asthma—COPD overlap	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
g. Obstructive sleep apnea (OSA)	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
h. Active pulmonary tuberculosis infection	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
i. Past history of tuberculosis	14 (9.34)	10 (8.47)	4 (18.18)	1 (0)	.9
j. Bronchiolitis	2 (1.34)	0 (0)	0 (0)	2 (20)	.004
iii. Non-respiratory comorbidities	72 (48)	50 (42.37)	16 (72.72)	6 (60)	.027
a. Hypertension	34 (22.67)	24 (20.34)	6 (27.27)	4 (40)	.178
b. Diabetes mellitus	34 (22.67)	16 (13.56)	14 (63.63)	4 (40)	<.001
c. Coronary artery disease and dyslipidemia	10 (6.67)	6 (5.08)	4 (18.18)	0 (0)	.572
d. Hypothyroidism	8 (5.34)	6 (5.08)	0 (0)	2 (20)	.345

**P* value represents the statistical significance between mild, moderate, and severe groups; **Duration to presentation implies duration between: completion of 4 weeks from COVID-19 and the first presentation to our tertiary pulmonary center for consultation.
IQR, interquartile range; SD, standard deviation.

COVID-19 had the highest prevalence of honeycombing in CT scans (25%, *P* = .027). There was no statistically significant difference in the prevalence of other abnormalities on CT scans in the 3 groups, while most of the patients had a CT severity score of less than 8, nearly 25% (n = 20) had a score of more than 15.

DISCUSSION

Terms like "post-COVID," "long-haulers," and "long-COVID" have been used in the literature for patients who continue to have persistent or develop new symptoms even after "severe acute respiratory syndrome coronavirus 2" negativity (after alternate etiology for the same have been ruled out).[2] "National Institute for Health and Care Excellence" guidelines have defined "long-COVID" as signs or symptoms that continue or develop after 4 weeks from acute COVID-19 illness.[1]

We found that many patients (n = 86; 57.34%), despite having a history of mild COVID-19 illness only, presented with persistent symptoms along with clinical, laboratory, and radiological abnormalities (Tables 1-5). These findings were consistent with another study which found that "non-critical COVID-19 patients" had at least 1 persistent symptom of 68% on day 30 and of 66% on day 60 from acute COVID-19 illness.[14] Further, since our center is a tertiary care referral institute, we observed a high prevalence (85%) of comorbidities in the present cohort of long-COVID patients.

Similar to other studies,[3,5,15] we found fatigue, exertional dyspnea, and cough to be the most common long-COVID symptoms (Table 2). Long-COVID manifestations in the form of fatigue and dyspnea (*P* = .001), tachycardia (*P* = .002), tachypnea (*P* < .001), raised blood pressure (*P* < .001), and crepitations on auscultation (*P* = .04) were significantly higher in the patients who suffered severe COVID-19 illness when compared to the other groups. These findings have consolidated the similar evidence generated in other studies[16-18] where the researchers have found that hospitalized COVID-19 patients had higher prevalence of fatigue and exertional dyspnea when compared with non-hospitalized ones. In the patients with long-COVID, we found that the occurrence of hypoxia at rest (40%, *P* < .001), significant exertional desaturation on 6MWT (40%, *P* = .027), type 1 (20%, *P* = .001), and type 2 (20%, *P* = .001) respiratory failure was significantly more prevalent in patients with a history of severe COVID-19 compared to mild and moderate (Table 3). Similarly, a

Table 2. Clinical Presentation of Long-COVID Patients (n = 150)

	Overall (n = 150)	Mild (n = 118)	Moderate (n = 22)	Severe (n = 10)	
	n (%)	n (%)	n (%)	n (%)	*P**
i. Fatigue	108 (72)	77 (65.25)	21 (95.45)	10 (100)	.001
ii. Cough	100 (65.67)	70 (59.32)	22 (100)	8 (80)	.003
iii. Sputum	50 (33.34)	38 (32.20)	6 (27.27)	6 (60)	.233
iv. Breathlessness	106 (70.67)	76 (64.40)	20 (90.9)	10 (100)	.001
v. Wheezing	38 (25.34)	30 (25.42)	4 (18.18)	4 (40)	.660
vi. Chest pain	30 (20)	20 (16.95)	8 (36.36)	2 (20)	.219
vii. Fever	6 (4)	6 (5.08)	0 (0)	0 (0)	.338
viii. Hemoptysis	2 (1.34)	0 (0)	0 (0)	2 (20)	.004
ix. Loss of appetite	10 (6.67)	8 (6.78)	0 (0)	2 (20)	.572
x. Loss of weight	6 (4)	6 (5.08)	0 (0)	0 (0)	.338
xi. Tachycardia	26 (17.34)	14 (11.86)	8 (36.36)	4 (40)	.002
xii. Raised blood pressure (BP)	36 (24)	20 (16.95)	10 (45.45)	6 (60)	<.001
xiii. Tachypnea	6 (1.5)	0 (0)	2 (9.09)	4 (40)	<.001
xiv. Rhonchi on auscultation	26 (17.34)	20 (16.95)	2 (9.09)	4 (40)	.353
xv. Crepitations on auscultation	34 (22.67)	22 (18.64)	8 (36.36)	4 (40)	.04

**P* value represents the statistical significance between mild, moderate, and severe groups.

Table 3. Investigations of Long-COVID Patients (n = 150)

	Overall (n = 150)	Mild (n = 118)	Moderate (n = 22)	Severe (n = 10)	
	n (%)	n (%)	n (%)	n (%)	*P*
i. Ventricular ectopic in ECG	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
ii. Hypoxia at rest	6 (4)	0 (0)	2 (9.09)	4 (40)	<.001
iii. Desaturation in 6-minute walk test	22 (14.67)	14 (11.86)	4 (18.18)	4 (40)	.027
iv. Type 1 respiratory failure on ABG	4 (2.67)	0 (0)	2 (9.09)	2 (20)	.001
v. Type 2 respiratory failure on ABG	2 (1.34)	0 (0)	0 (0)	2 (20)	.004
vi. Anemia (Hb < 13.5 g/dL in males; Hb < 12.5 g/dL in females)	62 (41.34)	50 (42.37)	10 (45.45)	2 (20)	.337
vii. Leucocytopenia (TLC < 4000 cells/mm^3)	6 (4)	6 (5.08)	0 (0)	0 (0)	.338
viii. Leucocytosis (TLC > 10 000 cells/mm^3)	28 (18.67)	20 (16.95)	4 (18.18)	4 (40)	.147
ix. Neutropenia (n < 40%)	4 (2.67)	0 (0)	0 (0)	4 (40)	<.001
x. Neutrophillia (n > 80%)	4 (2.67)	2 (1.69)	0 (0)	2 (20)	.037
xi. Lymphopenia (L < 20%)	16 (10.67)	8 (6.78)	4 (18.18)	4 (40)	.002
xii. Lymphocytosis (L > 40%)	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
xiii. Thrombocytopenia (platelets <150 × 10^3/μL)	20 (13.34)	14 (11.86)	6 (27.27)	0 (0)	.9
xiv. Thrombocytosis (platelets >400 × 10^3/μL)	20 (13.34)	14 (11.86)	4 (18.18)	2 (20)	.409
xv. Deranged LFTs	54 (36)	42 (35.59)	8 (36.36)	4 (40)	.797
xvi. Increased blood sugars (RBS > 200 mg/dL or HbA1c > 5.7%)	20 (13.34)	12 (10.17)	6 (27.27)	2 (20)	.092

**P* value represents the statistical significance between mild, moderate, and severe groups.
ABG, arterial blood gases; ECG, electrocardiography; Hb, hemoglobin; LFT, liver function test; RBS, random blood sugar; TLC, total leucocyte count.

Table 4. Chest X-Ray Findings of Long-COVID Patients (n = 150)

	Overall (n = 150)	Mild (n = 118)	Moderate (n = 22)	Severe (n = 10)	
	n (%)	n (%)	n (%)	n (%)	*P*
i. Normal study	70 (46.67)	60 (50.84)	6 (27.27)	4 (40)	.114
ii. Diffuse reticulations	38 (25.34)	26 (22.03)	6 (27.27)	6 (60)	.017
iii. Lower zone reticulations	24 (16)	14 (11.86)	10 (45.45)	0 (0)	.248
iv. Diffuse nodular shadows	6 (4)	6 (5.08)	0 (0)	0 (0)	.338
v. Cystic changes	6 (4)	4 (3.39)	2 (9.09)	0 (0)	.9
vi. Mediastinal lymphadenopathy	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768
vii. Hyperinflated lung fields	8 (5.34)	8 (6.78)	0 (0)	0 (0)	.229
viii. Consolidation	2 (1.34)	2 (1.69)	0 (0)	0 (0)	.768

**P* value represents the statistical significance between mild, moderate, and severe groups.

Table 5. CT Scan Findings of Long-COVID Patients (n = 82)

	Overall (n = 82)	Mild (n = 60)	Moderate (n = 14)	Severe (n = 8)	
	n (%)	n (%)	n (%)	n (%)	*P*
i. Normal study	0 (0)	0 (0)	0 (0)	1 (0)	-
ii. Diffuse nodular shadows	26 (31.70)	22 (36.67)	2 (14.28)	2 (25)	.217
iii. Diffuse reticulations	32 (39.02)	22 (36.67)	8 (57.14)	1 (25)	.9
iv. Lower lobe reticulations	4 (4.87)	2 (3.34)	0 (0)	2 (25)	.07
v. Diffuse GGOs	36 (43.90)	24 (40)	10 (71.42)	2 (25)	.867
vi. Lower lobe GGOs	12 (14.63)	8 (13.34)	2 (14.28)	2 (25)	.478
vii. Honeycomb change	6 (7.31)	2 (3.34)	2 (14.28)	2 (25)	.027
viii. Bronchiectasis	12 (14.63)	8 (13.34)	2 (14.28)	2 (25)	.478
ix. Fibrocavitary changes	6 (7.31)	4 (6.67)	0 (0)	2 (25)	.339
x. Emphysematous changes	8 (9.75)	8 (13.34)	0 (0)	0 (0)	.154
xi. Mediastinal lymphadenopathy	2 (2.43)	2 (3.34)	0 (0)	0 (0)	.747
CT severity score					
i. Mild (<8)	50 (60.97)	44 (73.34)	2 (14.28)	4 (50)	.005
ii. Moderate (9-15)	12 (14.63)	8 (13.34)	4 (28.57)	1 (0)	.9
iii. Severe (>15)	20 (24.39)	8 (13.34)	8 (57.14)	4 (50)	.001

**P* value represents the statistical significance between mild, moderate, and severe groups.
CT scan, computed tomography scan; GGOs, ground-glass opacities.

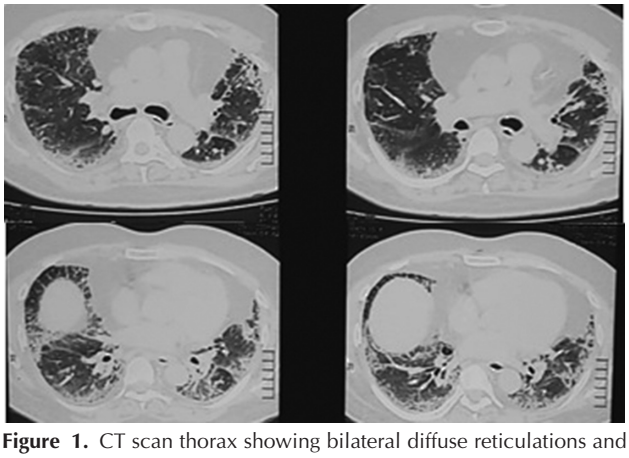


Figure 1. CT scan thorax showing bilateral diffuse reticulations and early honeycomb change in a patient with long-COVID. CT, computed tomography.

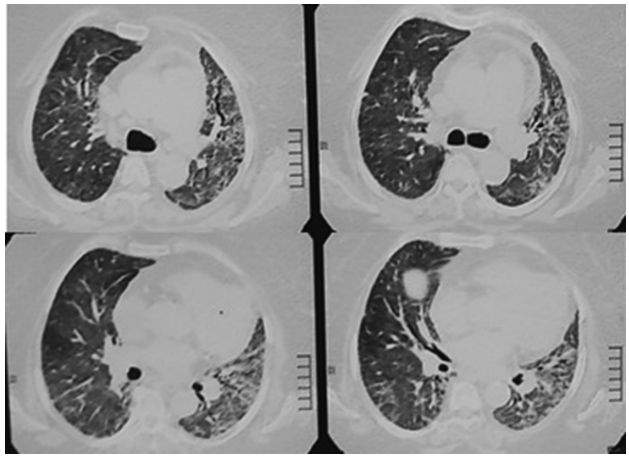


Figure 2. CT scan thorax from a patient with long-COVID showing persistent abnormalities in the form of reticulations and ground glass opacities. CT, computed tomography.

previous study[18] has also concluded that patients with severe COVID-19 have significant exertional desaturation in 6MWT and hypoxemia at follow-up when compared to patients with mild COVID-19 disease. Likewise, Townsend et al[19] found that the 6MWT distance reduced with the increased length of hospital stay during COVID-19. However, contrary to our findings, they concluded that persistent respiratory symptoms at the time of post-COVID assessment were not related to the initial severity of COVID-19.

In the current study, we found that nearly 53% of patients (n = 80) had abnormal chest radiographs at the time of presentation (Table 4). Reticulations in the lower zone (n = 24; 16%) and diffuse reticulations (n = 38; 25.34%) were the most common abnormalities. Another study[5] had documented the presence of bilateral reticulations (25.71%) as the most common abnormality in post-COVID-19 patients. We also found that diffuse reticulations were significantly more persistent in severe category patients (60%, *P* = .017) when compared with the mild and moderate ones indicating delayed recovery in the severe COVID-19 patients. In a study by Alarcón-Rodríguez et al.[20] it was found that patients with mild or moderate COVID-19 pneumonia tend to achieve complete radiological resolution within 1 month of follow-up. Also, they observed that patients with a history of severe disease and prolonged "intensive care unit" stay showed slow resolution. Similarly, Arnold et al[21] found that some patients with a history of admission due to oxygen requirement at the time of acute COVID-19 infection tend to show slow fibrotic lung changes in CT scan of the chest. These findings again were similar to our study.

Chest CT scan plays a vital role in diagnosis, searching for complications and prognostication of COVID-19 disease and it is the radiological investigation of choice for assessing the extent of lung parenchyma involvement at the time of acute infection as well as during follow-up.[22] In the present study, the most common abnormalities detected on CT scan of the chest (Table 5) was diffuse ground-glass opacities (n = 36; 43.90%) followed by diffuse reticulations (n = 32; 39.02%) and diffuse nodular shadows (n = 26; 31.7%). The current study has consolidated the evidence generated by other studies[5,23] where ground-glass opacities and diffuse reticulations were the commonest CT scan findings in long-COVID patients. On analysis of the CT scan of the thorax, except for the honeycomb change, the abnormal findings were not significantly different in the 3 groups of long-COVID patients. However, the honeycomb change was significantly more prevalent in patients with a history of severe COVID-19 (25%, *P* = .027) compared to patients with mild or moderate COVID-19. This finding may be indicative of the resolution of other CT scan abnormalities in due course of time, with permanent damage to the lung parenchyma evident in the form of honeycomb change, being the remaining persisting finding. The current study added to the evidence generated by another study[24] where more than one-third of the severe patients, at follow-up, had remnant fibrotic changes, defined in the study as traction bronchiectasis, parenchymal bands, or honeycombing, while mild or moderate category patients had either complete radiographic clearing or residual ground glass opacities or interstitial thickening.

We also used CTSS for the evaluation of CT scans of long-COVID patients in conjunction with another study[24] on post-COVID patients. We found that most of the long-COVID patients with a history of mild COVID-19 illness (73.34%) had mild CTSS (Table 5) and patients with severe COVID-19 infection history had severe CTSS (50%). Although a significant interpretation of this observation could not be reached.

Our study had certain limitations. First, the study was conducted in a referral tertiary care institute, and hence, the observations suffer from selection bias. Further, the patients with severe COVID-19 were in smaller numbers, which may have confounded the observations.

CONCLUSION

Our study reiterated the occurrence of pulmonary abnormalities in long-COVID patients. We observed that long-COVID pulmonary manifestations are, both clinically and radiologically, more severe as well as prolonged in severe COVID-19 patients. Hence, we can conclude that the pulmonary course of long COVID bears a relationship to initial disease severity. Therefore, a planned approach for more meticulous follow-up and management of COVID-19 patients should be advocated.

Ethics Committee Approval: Ethical committee approval was received from the Institutional Human Ethics Committee of Vallabhbhai Patel Chest Institute, University of Delhi (approval Number: VPCI/DIR/IHEC/2020/1847).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.Goel; Design – N.Goel; Supervision – N.Goel, M.V.B., M.K., B.M., R.K.; Materials – N.Goel, N.Goyal, S.S., P.M., R.N., M.V.B., M.K., B.M., R.K.; Data Collection and/or Processing – N.Goel, N.Goyal, S.S., P.M., R.N., M.V.B., M.K., B.M., R.K.; Analysis and/or Interpretation – N.Goel, N.Goyal, R.N.; Literature Review – N.Goel, N.Goyal, S.S., P.M., R.N., M.V.B., M.K., B.M., R.K.; Writing – N.Goel, N.Goyal, R.K.; Critical Review – N.Goel, N.Goyal, S.S., P.M., R.N., M.V.B., M.K., B.M., R.K.

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Original Article

Coronavirus Disease 2019 Frequency After CoronaVac Vaccine: Ascovid Study

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Abstract

OBJECTIVE: It is accepted that the only way to end severe acute respiratory syndrome coronavirus 2 epidemic is through community vaccination. The frequency and clinical features of infection after vaccination are not known clearly. The aim of this study is to determine the frequency and clinical features of coronavirus disease 2019 seen after either the first or second dose of CoronaVac vaccination in healthcare workers and their relatives.

MATERIAL AND METHODS: This is a cross-sectional retrospective survey study. The study was carried out in 2013 volunteers, including 1903 (94.5%) healthcare workers and 110 (5.5%) relatives of healthcare workers. The frequency and clinical features of coronavirus disease 2019 before and after the first or second dose of CoronaVac vaccination were retrospectively evaluated using an online questionnaire conducted in July 2021.

RESULTS: A total of 2013 people, 1312 women and 701 men, participated in the study. Of these individuals, 245 (12.1%) were polymerase chain reaction positive for coronavirus disease 2019 before vaccination. Of this group, 185 (75.5% of polymerase chain reaction positives and 9.1% of the whole population) received home-based therapy, while 38 (15.5%) received hospital admission. Asymptomatic polymerase chain reaction positivity before vaccination was seen in 22 (9%) individuals.

There were 177 (8.8%) participants who developed polymerase chain reaction positivity at any time after vaccination. In 129 (72.8%) of these participants, polymerase chain reaction positivity occurred 21 days after the second dose of vaccine. While the number of patients hospitalized before vaccination was 38 (15.5% of the polymerase chain reaction positivity group and 1.89% of the general population), the number of patients hospitalized after the vaccination was 17 (10.1% of the polymerase chain reaction positivity group and 0.80% of the general population). The decrease in hospitalization proportion was statistically significant ($P = .002$).

CONCLUSION: The frequency of coronavirus disease 2019, severe illness, and hospitalization rates were found to be lower in post-vaccination period. The vaccine is effective in preventing coronavirus disease 2019 and severe disease.

KEYWORDS: SARS-CoV-2, COVID-19, vaccines, CoronaVac, safety, PCR positivity
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a complex disease caused by the etiological agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), at the end of 2019, in the city of Wuhan, in China. As of September 2021, according to World Health Organization (WHO) data, 220 million cases and more than 4.5 million deaths were reported due to COVID-19.[1] Severe acute respiratory syndrome coronavirus 2 is accepted as a public health problem all over the world due to its easy and rapid spread, straining health systems, and clinical management.[2] As a result, although important measures have been taken, including social distancing, quarantine, and isolation, SARS-CoV-2 has adversely affected not only the infected people but also the entire population, the global economy, and resources. The only way to control the pandemic is community vaccination. For this purpose, the development of a vaccine against COVID-19 has become an urgent agenda for the whole world for the last 2 years.[3]

Since the outbreak began, researchers have worked to develop a vaccine against COVID-19. As of March 2021, there were 5 vaccines in phase IV trials: Sinovac Research and Development Corporation (CoronaVac), Pfizer/BioNTech–Fosun Pharma (BNT162b2); Moderna–National Institute of Allergic and Infectious Diseases (mRNA-1273), AstraZeneca–University of Oxford (AZD1222); and Janssen Pharmaceutical (Ad26.COV2.S, Johnson and Johnson).[4] Developing and approving effective vaccines during this time has been possible thanks to coordinated work between the scientific and medical communities and government agencies such as the Food and Drug Administration.[5] CoronaVac is an inactivated vaccine against SARS-CoV-2 developed by Sinovac Biotech, China, which was approved by World Health Organization in June 2021. The inactivated SARS-CoV-2 vaccine, CoronaVac, acquired emergency use approval from

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the Turkish Medicines and Medical Devices Agency based on the initial efficacy results of a nationwide phase III trial in January 2021; CoronaVac was first administered to healthcare workers in Turkey and afterward, the risk groups were vaccinated as stratified.[6] While information about the safety and effectiveness of vaccines is increasing, unfortunately, we have also started to encounter patients who have had a post-vaccine COVID-19 infection in real life. However, the frequency of reinfection after vaccination and the clinical features of reinfection are not clearly known yet.

The main objective of this study is to make a contribution in determining the frequency and clinical features of COVID-19 infection seen after the first or second dose of CoronaVac in healthcare workers and their relatives.

MATERIAL AND METHODS

Study Design and Population

In order to determine the polymerase chain reaction (PCR) positivity that may occur after vaccination against COVID-19, an online questionnaire was sent via e-mail to those who agreed to volunteer for the research with an informed consent. The study is approved by the Cukurova University Ethical Committee (112/2021). Our target audience in the study is healthcare professionals and their relatives. A total of 2013 volunteers, including 1903 (94.5%) healthcare workers and 110 (4.5%) relatives of healthcare workers older than 18 years of age who received a single or double dose of the CoronaVac vaccine, participated in the cross-sectional survey study. The frequency and clinical features of COVID-19 after the first or second dose of CoronaVac vaccination were retrospectively evaluated using an online questionnaire between 1 and 31 July 2021.

Individuals with positive SARS-CoV-2 nucleic acid amplification test after receiving 1 or 2 doses of CoronaVac were defined as post-vaccine COVID-19-infected participants.

Questionnaire

We designed an online self-administered questionnaire after CoronaVac vaccination. In the survey, primarily the basic demographic characteristics (age, gender, occupation, smoking history, and health status), the history of COVID-19 infection before vaccination, the presence of antibody test in the blood after CoronaVac vaccine, the presence of anti-spike antibodies, the positivity of SARS-CoV-2 PCR, the time of PCR positivity, and the symptoms related to post-vaccine COVID-19 infection were recorded.

MAIN POINTS

- The inactivated coronavirus disease 2019 (COVID-19) Vaccine (CoronaVac) reduces the rate of COVID-19 and hospitalizations due to severe acute respiratory syndrome coronavirus 2.
- The need for hospitalization due to COVID-19 infection was 15.5% before and 10.1% after CoronaVac, respectively.
- The positivity rate anytime in unvaccinated and postvaccination periods was 12.1% and 8.8%, respectively.

Antibody Test

In the questionnaire, a question was asked whether participants had their antibody levels checked voluntarily (since there was no routine use). The participants were required to answer this question as positive if the results are above the positive cut-off value specified in the anti-spike antibody kit used in the laboratory where they checked the antibody level.

Statistical Analysis

The descriptive statistics were presented as frequency and percentages for categorical variables while mean ± standard deviation was given for continuous variables. All statistical analyses were conducted by using the IBM Statistical Package for the Social Sciences version 23 program. Figure 1 was generated using the ggplot2 package in the R programming language.[7]

RESULTS

A total of 2013 volunteers, including 1903 (94.5%) healthcare workers and 110 (4.5%) relatives of healthcare workers, were included in the study. Of the volunteers, 1312 were women and 701 were men. Of the health workers, 893 (44.4%) were specialist physicians, 332 (17.5%) were family physicians, 175 (8.7%) were general practitioners, and 127 (6.3%) were nurses. Four hundred eighty-two participants (24%) had a smoking history. Detailed sociodemographic characteristics are documented in Table 1.

Of the 2013 volunteers, 245 (12.1%) were PCR positive before vaccination. Of this group, 185 (75.5% of PCR positives and 9.1% of the general population) received home-based treatment, while 38 (15.5%) received hospital-based treatment. Asymptomatic PCR positivity before vaccination was seen in 22 (9%) participants (Table 2). There were 177 (8.8%) participants who developed PCR positivity at any time after vaccination. In the group with PCR positive after CoronaVac, in 129 (72.8%) of these participants, PCR positivity occurred 21 days after the second dose of vaccine (Figure 1).

A decrease in hospitalization was observed after vaccination. While the number of patients hospitalized before vaccination was 38 (15.5% of the PCR positivity group and 1.89% of the general population), the number of patients hospitalized after the vaccination was 17 (10.1% of the PCR positivity group and 0.80% of the general population) (Table 2). The most common symptoms during PCR positivity are muscle/joint pain (140, 19.4%), fatigue (135, 18.7%), headache (113, 15.6%), runny nose/sore throat (108, 14.9%), cough (94, 13%), fever (84, 11.6%), shortness of breath (38, 5.3%), and clouding of consciousness (11, 1.5%).

The association between PCR positivity after CoronaVac and gender, age, and smoking status was examined, and no statistically significant correlation was found between PCR positivity and gender, age, and smoking status after vaccination.

Of the 2013 people who answered the question about the antibody test, 689 (34.23%) had an antibody test. Out of 689 people who had antibody tests at least 2 weeks after vaccination, 595 (86.3%) people (29.5% of the general total) were found to be above the positive cut-off value specified in the anti-spike antibody laboratory kit.

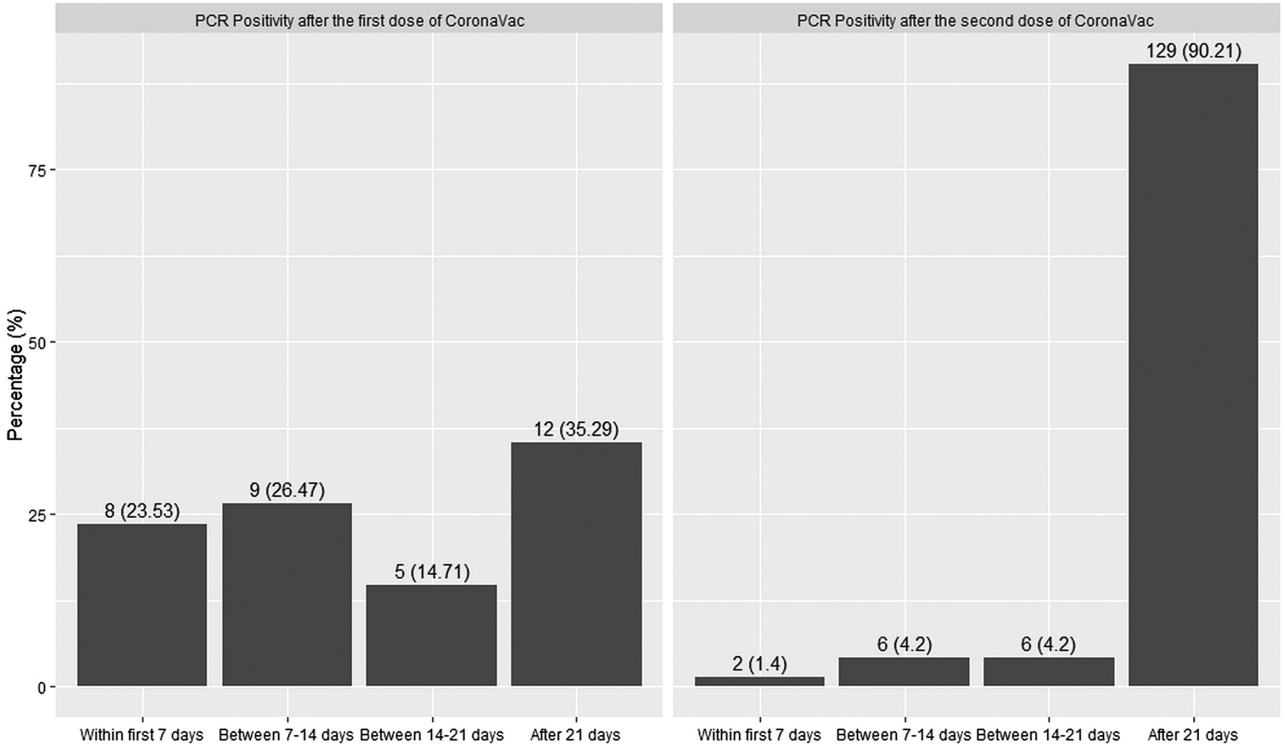


Figure 1. Polymerase chain reaction positivity days after the first and second doses of CoronaVac.

DISCUSSION

Vaccination against COVID-19 started with CoronaVac in January 2021 in healthcare workers in our country and the society stratified later on. This study was conducted in July 2021 and includes the healthcare workers and their relatives as participants. The frequency of COVID-19 was 12.1% and 8.8% before and after vaccination, respectively, based on the self-report of the participants. The need for hospitalization due to COVID-19 was 15.5% before and 10.1% after CoronaVac. An anti-spike antibody value above the laboratory-determined lower limit was found in 86.3% of participants who had tests at least 2 weeks after vaccination.

A few real-world studies concerning the effectivity of mRNA vaccines against SARS-CoV-2 have been published in the literature.[8,9] A hospital-wide cohort study determined a 71% and 97% decline in acute SARS-CoV-2 infection rates compared to the pre-vaccine period in healthcare workers after the first and second dose, respectively.[8] In another real-life study including 3950 healthcare workers with no previous laboratory documentation of SARS-CoV-2 infection, 1.38 SARS-CoV-2 infections were confirmed by reverse transcription-PCR per 1000 person-days among unvaccinated participants. In contrast, among fully immunized (≥14 days after the

Table 1. Sociodemographic Characteristics of the Participants

Variable	Descriptive Statistics
Gender, n (%)	
Female	1312 (65.18)
Male	701 (34.82)
Profession, n (%)	
Specialist physician	893 (44.36)
Primary care physician	352 (17.49)
General practitioners	175 (8.69)
Research assistants	98 (4.87)
Nurse	127 (6.31)
Dentist	74 (3.68)
Pharmacist	17 (0.84)
Other and unemployed	277 (13.76)
Age (mean ± standard deviation)	46.32 ± 11.65
Presence of smoking history, n (%)	482 (24.39)

Table 2. PCR Positivity and Clinical Characteristics of COVID-19 in Pre- and Postvaccination Periods*

PCR positivity before vaccination	245 (12.17)
Home-based treatment	185 (9.19)
Hospital-based treatment	38 (1.89)
Asymptomatic	22 (1.09)
ICU	3 (0.15)
PCR positivity after vaccination	177 (8.79)
Home-based treatment	129 (6.41)
Hospital-based treatment**	17 (0.84)
Asymptomatic	30 (1.49)
ICU	2 (0.10)

COVID-19, coronavirus disease 2019; ICU, intensive care unit; PCR, polymerase chain reaction.
*All parameters were shown as n (%).
**Hospital-based treatment includes ICU patients.

second dose) persons, 0.04 infections per 1000 person-days were reported, and among partially immunized (≥14 days after the first dose and before the second dose) persons, 0.19 infections per 1000 person-days were reported.[9] A study aimed to determine the early vaccine efficacy concluded that 1.07% of vaccinated healthcare workers had COVID-19 infection, whereas 10.29% of the unvaccinated group had acute COVID-19 infection.[10] A letter concerning healthcare workers in the United States showed that 2.61% of unvaccinated, 1.82% of partially vaccinated, and 0.05% of fully-vaccinated participants had SARS-CoV-2 infection after mRNA vaccines within the first month.[11] The positivity rate of SARS-CoV-2 was 0.05% in healthcare workers approximately in 2 months period after the inoculation of the first dose of mRNA vaccine.[12] An Israel study indicated 0.45% of the vaccinated and 7.26% of the unvaccinated groups were PCR (+) in 63 days period.[13] Severe acute respiratory syndrome coronavirus 2 PCR positivity rate was 0.85% in a comprehensive study enrolling healthcare workers within the first 3 months after inoculation of mRNA vaccine.[14]

To the best of our knowledge, this is the first report emphasizing the postvaccination PCR positivity rate and the clinical characteristics of postvaccine COVID-19 after CoronaVac vaccination. The positivity rates anytime in unvaccinated and postvaccination periods were 12.1% and 8.8%, respectively, in our study. These are relatively higher rates when compared with the studies described earlier. This may be due to the fact that the higher infectious rate in Turkey relates to disease course especially between January and July 2021.[15] Another factor contributing to the high infection rate might be that only inactivated vaccines were available during the first immunization phase. Especially starting from late March until July, the number of daily cases increased to an average of 60 000 new cases per day.[16] Parallel to the normal population, the case and death rates of healthcare workers have also changed; while the deaths of healthcare workers decreased between March 2020 and June 2020, they reached a peak value by climbing after June until December.[17]

Our questionnaire investigated a period between the beginning of the vaccination (June 2021) until end of July 2021. There was only CoronaVac available in the period of June 2021 to April 2021 in Turkey. We included the participants only after the first and second doses of CoronaVac vaccination period for follow-up information. In July, third dose of any vaccine either with BioNTech/Pfizer mRNA vaccine or CoronaVac was officially recommended to prioritize healthcare workers; however, we did not intend to collect any information about the third dose in this study.

The PCR positivity mostly occurred after 21 days of the second dose of CoronaVac. This is too early for diminished antibody response and therefore vaccine efficacy. However, we did not know the exact occurrence time of that positive result. It could have been just after 21 days after vaccination or more depending on follow-up period. Although we did not collect the exact time of SARS-CoV-2 infection, we could comment that the longest period of the second vaccine dose in the study was no longer than 6 months where we know that the efficacy of the vaccine is still acceptable.[18]

We argue that there would be 2 ways to explain the postvaccination high PCR positive rate; either the participants did not take enough precautions since several variants become predominant during the pandemic progress or the positive PCR mostly occurred when the immunity against the virus was diminished by nature after several months of vaccination. Despite all the interpretations, that data shows the vaccination reduces the SARS CoV-2 infection rates from 12.1% to 8.8% which shows statistical significance. The data need further evaluation.

Another important point of this study is that it provided the first data to the literature describing the clinical features of COVID-19 cases after CoronaVac. The need for hospitalization due to COVID-19 infection was 15.5% before and 10.1% after CoronaVac. In some of the limited number of mRNA vaccine studies, it was shown that there was no difference in clinical presentation compared to the pre-vaccine period, while in others, asymptomatic cases were more common in post-vaccine PCR (+) COVID-19 cases. A study including the healthcare workers in Madrid showed that 47% of new infections were symptomatic while the remaining 53% were detected as a part of the screening program.[8] A cohort concerning the incidence of SARS-CoV-2 infection after the first dose of mRNA vaccine determined no significant difference in clinical presentation between vaccinated and unvaccinated participants.[10] Asymptomatic acute COVID-19 infection rate was 70.4% and 30.9% in mRNA vaccinated and unvaccinated groups in a retrospective cohort, respectively.[13] In the literature review, no data were accessible showing the frequency of hospitalization with acute COVID-19 infection in the post-vaccine period. Although a head-to-head comparison could not be established, the dynamics of the epidemic and COVID-19 hospitalization criteria have changed throughout the pandemic; the increment of asymptomatic cases in the post-vaccine period in other similar studies supports the data in our study.

The major limitation of this study is that it is nature of descriptive online survey that questions the retrospective data. Therefore, it carries low reliability due to this design. Although there is participation from all provinces of Turkey, it still does not represent the whole country. The lack of active laboratory surveillance in the study may have resulted in an underestimation of asymptomatic or mild cases. Since the PCR test could not be performed on all patients participating in the study, post-vaccination positivity was of course made according to the person's notification, but it is already known that of Ministry of Health of the Republic of Turkey recommends SARS-CoV-2 PCR testing in the presence of at least 1 symptom during daily screening or by an identified exposure, regardless of vaccination status through the entire period of the pandemic.

CONCLUSION

Although these data need to be validated in prospective larger series, the study is remarkable as it is the first real-world study reporting on the SARS-CoV-2 infection rate and the clinical features of the disease after CoronaVac. In light of these data, CoronaVac emerges as a useful tool in reducing the rate of COVID-19 and the hospitalization due to it.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Cukurova University (Approval No: 112/2021, Date: 11.06.2021).

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 – Ş.Ö., N.K., O.B.T., B.Ö.Ş., M.T.K.; Design – B.Ö.Ş., O.B.T., Ş.Ö., N.K., M.T.K.; Supervision – N.K., Ş.Ö.; Materials – B.Ö.Ş., Ş.Ö., O.B.T., N.K., M.T.K.; Data Collection and/or Processing – O.B.T., B.Ö.Ş., Ş.Ö., N.K., M.T.K.; Analysis and/or Interpretation – N.K., Ş.Ö., B.Ö.Ş., O.B.T., M.T.K.; Literature Review – Ş.Ö., N.K., O.B.T., B.Ö.Ş., M.T.K.; Writing – O.B., N.K., Ş.Ö., B.Ö.Ş., M.T.K.; Critical Review – N.K., Ş.Ö., B.Ö.Ş., M.T.K., O.B.

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Original Article

Efficiency of Outsourcing Reporting in Thorax Computed Tomography Evaluation: Retrospective Analysis of 350 Thoracic Surgery Cases

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Abstract

OBJECTIVE: External reporting is frequently used due to the significant increase in computed tomography examinations in recent years and the insufficient number of personnel in internal reporting. We aimed to evaluate the adequacy of outsourcing reporting.

MATERIAL AND METHODS: Patients who were seen or hospitalized as a consultation by thoracic surgeons with thoracic computed tomography between January 2021 and January 2022 were included in the study retrospectively. Computed tomography results reported by radiologists working in our hospital were grouped as "internal reports," and the results reported externally by a company were grouped as "outsourcing reports." The total number of computed tomography examinations taken during the same period and the number of examinations reported by a daily average radiologist were also determined. False-negative findings in internal and outsourcing reports were evaluated and statistically compared between groups.

RESULTS: A total of 84 702 computed tomography scans were taken in 2021. In external reporting, 1 physician reported an average of 202.83 computed tomography scans per day (74 033 per year). A total of 350 thorax computed tomography reports were evaluated. A total of 304 (86.9%) thorax computed tomography examinations were reported with external reporting and 46 (13.1%) with internal reporting. False-negative findings other than those reported were found in 81 reports (23.1%). A significantly higher deficiency was observed in external reporting (77/304) compared to internal reporting (4/46). ($P = .013$).

CONCLUSION: The effectiveness of external reporting was found to be lower than internal reporting due to a possible lack of communication and audit problems. In order to minimize the errors and related liability arising from external reporting, primarily a legal standardization is required with realistic reporting numbers of external reporting.

KEYWORDS: Computed tomography, overlooked findings, outsourcing, radiology, thoracic surgery

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INTRODUCTION

With the transformation of the health system in Turkey in the early 2000s, the referral system was abolished and all patients can apply to any hospital they want. In addition, the defensive approach is adopted by physicians with malpractice regulations that are disproportionate to income. Due to these, a significant increase is observed in the number of hospital admissions and computed tomography (CT) examinations.[1]

Additionally, with technological developments, outsourcing/external reporting has been actively used in our country for the last 10 years.[1] Adding to this, the pandemic process and the evaluation of lung involvement in coronavirus disease 2019 with CT have greatly increased the burden on radiologists.[2] With the inadequacy in the number of radiologists employed, outsourcing reporting has become more widely used to solve this problem.[1]

In the radiological reporting of standard CT, an average of 3%-5% and up to 15% in 1 study, the error margin is stated in the literature.[3-4] In addition, there are studies representing that the margin of error in external reporting is higher due to fundamental reasons such as disconnection between the clinician and the radiologist and the greater number of daily CT evaluations.[5]

We aimed to evaluate the efficiency and margin of error of outsourcing reporting in thorax CT scans taken in our hospital, together with possible reasons.

MATERIAL AND METHODS

Ethics committee approval from the Niğde Ömer Halisdemir University Ethics Committee with the decision number E-958 60085-050.02.04-138333 was obtained before the study and the study was carried out in accordance with the principles

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of the Helsinki Declaration. Since it was a retrospective study and anonymous patient data were shared, patient consent was not required.

The total number of CT scans taken between January 2021 and January 2022 in our hospital was determined. Internal and external reporting and the number of evaluations per day per radiologist were calculated. When calculating the number of CT scans evaluated daily, the total number of CT scans was divided by 52 weeks in the year, since internal reporting was done 1 day per week by each radiologist. Since external reporting is used every day and especially in the emergency room, the divisor of 365 was used.

Patients who were evaluated by the thoracic surgeon after consultation in the emergency department, hospitalized after being evaluated in the outpatient clinic, or referred to the upper center for further examination were included in the study between January 2021 and January 2022 retrospectively. Patients who did not have a thorax CT and had no pathological findings found in the CT were excluded from the study.

Computed tomography results reported by radiologists working in our hospital were grouped as "internal reports," and those reported externally by a company were grouped as "outsourcing reports." Computed tomography findings were evaluated in 3 groups as "bone," "mediastinum," and "parenchyma."

Patients' age, gender, reason for admission, internal/external report status, indication for evaluation, false-negative findings outside the report, and life-threatening condition due to missed pathology were recorded retrospectively on the database. False-negative findings in internal and outsourcing reports were evaluated and statistically compared between groups. Computed tomography scans of patients with false-negative findings were re-evaluated by an employed radiologist, and false-negative findings were reconfirmed.

When determining a life-threatening situation, the effects of fractures and dislocations of the bones in the body were classified according to their degree. Fractures are classified as mild, moderate, and severe (Table 1). In case of more than 1 fracture in the body, in order to find the effect on vital functions, the squares of the degrees of each fracture are added and the square root of the total number is taken. If the number is greater than 0.5, it is graded above, if it is small, it is graded down. Two or three points for all kinds of rib fractures resulting from thoracic trauma (2 points for each 3 rib fractures, 1 point for more than 3 rib fractures). Three points are given for nondisplaced sternum fracture and 4 points for a displaced sternum fracture. In addition, pneumothorax, hemothorax, lung contusion, and major organ damage were grouped as life-threatening cases. [6]

Table 1. Rib Fracture Severity

Classification	Number of Fractured Ribs
Mild	1
Moderate	2-3
Severe	4-5-6

Statistical Analysis

All analyses of the research were evaluated with the Statistical Package for the Social Sciences version 24.0 package program (IBM Corp.; Armonk, NY, USA). Descriptive statistics were given as number of units (n), percent (%), and mean ± standard deviation (mean ± SD) for age. Pearson chi-square analysis was used to compare the distribution of categorical variables between groups. A *P* value below .05 was considered statistically significant.

RESULTS

The total number of CT scans taken in our hospital in 2021 was 84 633. Of these CT scans, 84 702 were reported in outsource reporting and 8775 in internal reporting. Two radiologists served in external reporting and 6 radiologists in internal reporting. The number of CT scans reported by each radiologist and their daily average are shown in Table 2.

A total of 350 patients included in the study. The mean age of 350 patients who participated in the study was 48.36 ± 20.64 (min: 9, max: 94), and the median age was 50.50. The demographic and clinical characteristics of the patients are shown in Table 3.

Table 2. Annual and Average Daily Number of CTs Reported per Radiologist and Internal-External Reporting Rate

Radiologist	Number of Annual Reports	Average Number of Reports per Day	Ratio (%)
OR1	74 033	202.83	89.6%
OSR2	1825	5	
IR1	2142	41.19	10.4%
IR2	1527	29.36	
IR3	808	15.53	
IR4	1346	25.88	
IR5	1444	27.76	
IR6	1508	29	

IR, internal reporter; OSR, outsourcing reporter.

MAIN POINTS

- The study reveals that there is a significant amount of overlooked data in outsourced reporting in branch-specific thoracic surgery thoracic computed tomography examinations.
- Overlooked data did not yield significant results in terms of life-threatening condition and/or hospitalization.
- The majority of tomography examinations are evaluated in external reporting.
- There is a need for standardization in evaluation and quality control in outsourcing reporting.

Table 3. Demographic and Clinical Characteristics of Patients

Characteristics	n = 350	Ratio (%)
Gender		
Female	73	20.9
Male	277	79.1
Reason for admission		
No complaint	9	2.6
Blunt trauma	195	55.4
Dyspnea	65	18.6
Chest pain	23	6.6
Penetrating trauma	21	6
Cough	17	4.9
Hemoptysis	6	1.7
Fever	5	1.4
Other	10	2.9

When our cases are evaluated in terms of thorax CT, 304 (86.9%) cases were reported with external reporting and 46 (13.1%) with internal reporting. In the evaluations between the reporting of the patients and the opinion of the surgeon, false-negative findings were found in 81 patients (23.1%). Internal and external reporting data results, along with subgroups of bone, parenchyma, and mediastinum, are shown in Table 4. When the rate of detection of false-negative findings was evaluated, a significantly higher deficiency was observed in external reporting (77/304) compared to internal reporting (4/46) (P = .013). Some overlooked CT findings at the mediastinum, bone, and parenchyma levels are shown in Figures 1-4.

Hospitalization indications of 81 patients with false-negative findings were evaluated. While 32 patients (39.5%) had an indication for hospitalization, it was observed that no hospitalization was required in 49 (60.5%) patients, and no significant correlation was found between the internal and external reporting groups (P = .543) (Table 5).

When the effect on the vital functions of the patients with false-negative findings is evaluated, 8 (9.9%) life-threatening and 73 (90.1%) non-life-threatening findings were omitted; non-life-threatening cases were also grouped as 13 (16%)

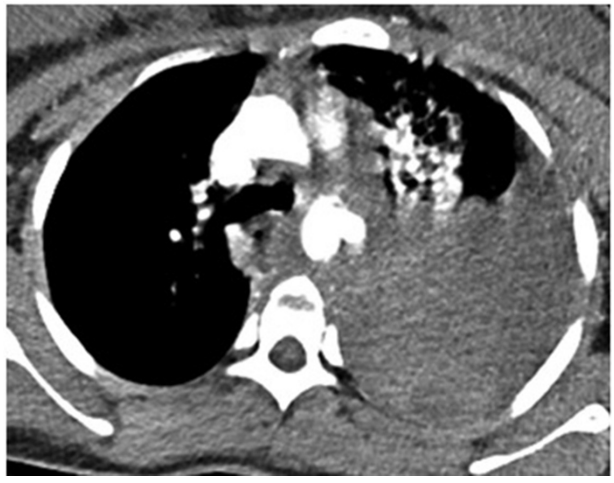


Figure 1. Extravasation from the aorta overlooked in the report.



Figure 2. Sternal fracture overlooked in the report.

Table 4. Evaluation of Insource–Outsource Reporting Effectiveness Between General and Subgroups

		Reporting				
	Total	Outsource		Insource		
False-negative finding	n = 350	n = 304	%	n = 46	%	*P*
Absent	269	227	74.7	42	91.3	**.013***
Present	81	77	25.3	4	8.7	
Mediastinum	5	4	5.2	1	25	.322
Parenchyma	10	9	11.7	1	25	
Bone	66	64	83.1	2	50	



Figure 3. Right hilar mass obliterating the bronchus overlooked in the report.

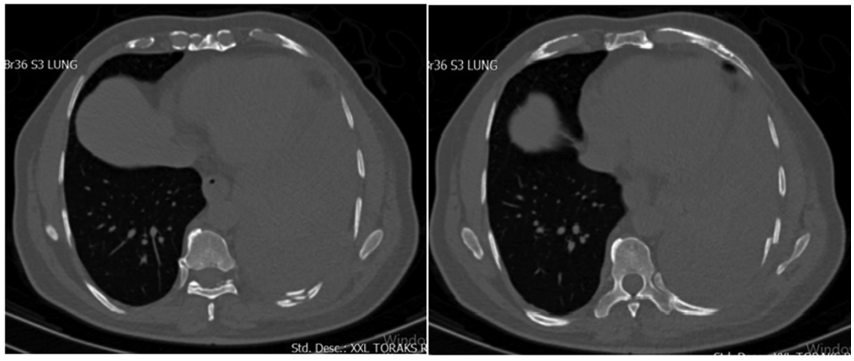


Figure 4. Rib fractures overlooked in the report.

Table 5. Evaluation of Patients with False-Negative Findings in Terms of Hospitalization Indications

Reporting	False-Negative Finding	Hospitalization Indication		*P*
		Present	Absent	
Outsource	77 (95.1%)	31 (40.3%)	46 (59.7%)	.543
Insource	4 (4.9%)	1 (25%)	3 (75%)	

mild, 42 cases (51.9%) moderate, and 18 cases (22.2%) severe in total cases.

DISCUSSION

In the outsourcing reporting, it is seen that 202.83 CT scans are reported daily by only a radiologist. While the margin of error detected in outsourcing reporting was found to be significantly higher than in internal reporting, no significant results were obtained when bone, parenchyma, and mediastinum groups were evaluated within themselves.

Outsourced reporting has become an instrument that is actively used all over the world, especially due to the need for rapid reporting and evaluation of tomography taken in emergency services, as well as the significant increase in the number of scans.[7] As a matter of fact, the reporting of 89.6% of thorax CTs taken in our hospital with outsourcing reveals a similar picture.

It is stated that the number of images read in the literature is higher in outsourced reporting than in internal reporting.[8] At the same time, the increase in the workload, combined with the lack of communication, can cause a serious increase in the margin of error.[9] Due to its low cost, especially in the USA, the use of outsourcing in all service offerings has increased considerably in the last period. In addition, outsourcing has become very common in the health system, especially in branches such as radiology, where remote imaging is evaluated. Although it is still used for pre-evaluation before health tourism for other branches, radiology has become the main field of outsourcing.[10] In this sense, it can be said that teleradiology has shaped the radiology approach of the future after the widespread use and access of the internet and covering the whole of life.[11]

When evaluating the share of diagnostic errors in outsourcing, it is stated that the margin of error in home reporting is less than 5% in the literature.[12,13] However, in a study on 2040 CT and magnetic resonance (MR) images, outsourced CT and MR reports were evaluated by 2 different radiologists and found a 21.4% disagreement (with potential clinical consequences for the patient in 2.9% of patients).[8] Apart from life-threatening factors such as pneumothorax and hemothorax, hospitalization and/or intensive care unit admission is indicated in patients over the age of 65 who have more than 2 rib fractures and develop respiratory distress.[6] In our study, 25.3% of outsourced reporting cases had discrepancies and missing findings, while 10% included pathologies that required hospitalization.

In addition, reporting through a physician who does not work in the hospital brings along the communication problem with the clinician. At the same time, the problems experienced in communicating the history and physical examination findings to the reporting unit constitute the limitations of external reporting when evaluated in light of the literature.[1] In addition, the low number of cases, especially in internal reporting, makes it difficult to obtain healthy results in further evaluations in subgroups. Of course, larger and multicenter studies

evaluating the results of whole-body CT may also enable to evaluate the efficacy of subgroup and other system CTs.

As determined by the Hospital Standards Commission of the American Society of Radiology and defined as closest to the ideal, a radiologist stated that it is appropriate to evaluate 25 patients and 30-35 examinations per day, since each patient can include more than 1 examination. Similarly, the Swedish radiologist stated that this burden is not too high, at the American College of Radiology Teachers' Conference. He stated that a total of 500 procedures per day are performed in their clinics, from simple procedures such as chest and bone to the most complex neurological-cardiovascular procedures. There were 13 radiologists who performed these procedures, 38 reports were made per person per day, and with this data, an annual average radiologist made an average of 8000 evaluations.[14]

Another study showed that lung cancer detection was impaired with reduced imaging time, and similarly, when the radiologist reported more than 20 studies per day, error rates in abdominal CT reporting increased.[15]

It may be safe to outsource a teleradiology program with an active quality assurance program. An active quality assurance program should be an integral part of any teleradiology program. Continuous feedback improves the performance of radiologists.[16] This situation, which is seen as compatible with other literature data, can only be increased by providing quality assurance.[8] In order to ensure this quality, it has been stated that standardization should be established with the items listed below[17]:

- Clinical information
- Communication with the clinician in emergency pathologies
- Standard reporting method outline
- Radiologist contact information should be included in the report
- Review by local radiologists
- Mutual audit (internal-outsourced)
- Same enrollment provisions, including specialist registration, relicensing, recertification, revalidation, reaccreditation, assessment, clinical governance, and inconsistency
- Language proficiency in the report
- Legal liability scope
- A report should be created at the end of each term regarding the reporting physicians.

However, when the idealized numbers in the literature and the number of evaluations of a single radiologist in external reporting in our study are compared, even if the number of external reporting is expected to be higher, the enormous difference explains the results of the study itself.

The value of the study is that it is one of the first studies to evaluate the effectiveness of external reporting on a branch basis. In addition, we think that total CT numbers are evaluated on a hospital basis and provide valuable data to explain the reason for the disruption in daily reporting numbers.

The limitation of the study was the inclusion of cases with findings already in the study did not make it possible to evaluate false-positive patients.

In conclusion, the effectiveness of outsourced reporting was found to be lower than internal reporting due to a possible lack of communication and audit problems. By providing standardization in outsourced reporting, legally limiting the number of reports evaluated to a certain number per radiologist will bring about an increase in quality. The multidisciplinary and multicenter conduct of this study will provide a broader illumination on the subject.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Niğde Ömer Halisdemir University (Approval No: E-95860085-050.02.04-138333).

Informed Consent: Informed consent was not obtained from the retrospective fill of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Ç.; Design – M.Ç., İ.T.; Supervision – M.Ç., K.G.; Funding – M.Ç; Materials – M.Ç.; Data Collection and/or Processing – M.Ç., K.G.; Analysis and/or Interpretation – N.S., İ.T.; Literature Review – M.Ç., N.S.; Writing – M.Ç., İ.T.; Critical Review – K.G., N.S.

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

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Original Article

Investigation of Pulmonary Artery and Ascending Aorta Morphology in the Coronavirus Disease 2019: A Radioanatomical Study

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Abstract

OBJECTIVE: This study aimed to determine the maximum diameters of the pulmonary artery and ascending aorta and their ratio to each other to enable early diagnosis and treatment of possible pulmonary hypertension and to prevent possible complications in patients infected with severe acute respiratory syndrome coronavirus 2.

MATERIAL AND METHODS: A total of 120 patients aged 40 years and older, 60 patients (30 females and 30 males) with severe acute respiratory syndrome coronavirus 2 infection and 60 individuals (30 females and 30 males), were included in this retrospective study. Maximum pulmonary artery and maximum ascending aorta diameters were measured at the level of bifurcatio trunci pulmonalis in the transverse axial plane by computed tomography, and their ratios to each other were determined.

RESULTS: Our study revealed a statistically significant increase in maximum pulmonary artery and maximum ascending aorta diameters in both genders in patients with coronavirus disease 2019 compared to the control group and a statistically significant increase was found in the maximum pulmonary artery–maximum ascending aorta ratio in women with coronavirus disease 2019 compared to the control group ($P < .05$).

CONCLUSIONS: Knowing the diameters of maximum pulmonary artery and maximum ascending aorta and the maximum pulmonary artery–maximum ascending aorta ratio in hospitalized severe acute respiratory syndrome coronavirus 2-infected patients is a valuable predictive marker of pulmonary hypertension and a guide in determining the appropriate treatment. These data, which are easy to calculate from thorax computed tomography, may be beneficial in the prognosis of the disease.

KEYWORDS: COVID-19, pulmonary artery, ascending aorta, thorax, computed tomography
Received: *June 1, 2022* ***Accepted:*** *September 15, 2022* ***Publication Date:*** *February 10, 2023*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to affect the entire world due to new variants emerging over time.[1,2] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the lungs and respiratory system. At the same time, it exerts detrimental effects on the vascular endothelium by disrupting its functional and structural integrity.[3] The virus usually presents with hypercoagulation, as it increases the load of the ventricular dexter (VD), causing deterioration of its functions. One study reported that COVID-19 pneumonia increases pulmonary artery (PA) pressure, resulting in VD dysfunction.[4] Another study showed that this relationship between PA and VD could cause mortality in hospitalized COVID-19 patients.[5] Pathophysiological changes in the lungs of COVID-19 patients are easily detectable by computed tomography (CT), and all possible clinical presentations, from viral pneumonia to acute respiratory distress syndrome (ARDS), can be distinguished from CT images.[6-12] Bilateral interstitial abnormalities initially present as subpleural ground-glass opacities (GGOs). In later stages, progressive consolidations and reticular patterns may arise, and the development of cytokine dysregulation, diffuse ARDS, and alveolar and interstitial damage may exacerbate the condition.[6,8,10] Diffuse lung consolidation and ARDS may alter pulmonary vascular features,[13] yielding pulmonary hypertension,[14,15] which in COVID-19 patients may also result from an overlap of these processes with increasingly reported pulmonary arterial thrombosis.[16-20] The ratio between the maximum diameters of the PA and the ascending aorta (Ao) on CT is a very practical and noninvasive way of diagnosing pulmonary hypertension. Patients with COVID-19 can also be given iodinated contrast material for CT pulmonary angiography, which will facilitate the diagnosis of pulmonary arterial thrombosis during the CT scan.[14,15,21,22] Several studies have shown that maximum PA diameter (MPA), maximum Ao diameter (MAo), and MPA–MAo ratio indices obtained from thoracic CT are useful parameters in predicting clinical outcomes in various lung diseases and COVID-19.[23] This study aimed to reveal the relationship between MPA, MAo, and MPA–MAo to enable early diagnosis and treatment of pulmonary hypertension in patients infected with SARS-CoV-2 and to prevent possible complications.

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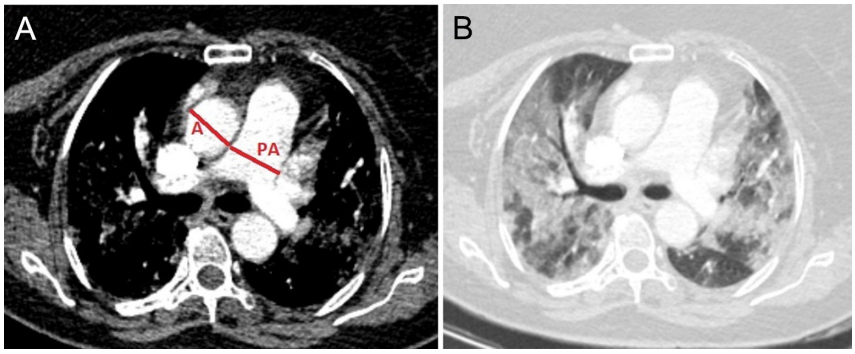


Figure 1. (A) Pulmonary artery (PA) and ascending aorta (A) measurement on contrast-enhanced thoracic computed tomography (CT) in a patient with COVID-19 pneumonia. (B) View of COVID-19 pneumonia in thoracic CT parenchymal window.

MATERIAL AND METHODS

The Malatya Clinical Researches Ethical Board (2021/25)E approved the study (2021/25). All procedures were applied in accordance with the Declaration of Helsinki.

Study Population

Individuals aged 40 and over who were diagnosed with COVID-19 in the Radiology Department between March 2019 and December 2021 and who underwent CT scans were included in the COVID-19 group, and individuals without COVID-19 with CT scans taken between January and December 2018 were included in the control group. Retrospective measurements were taken from a total of 120 people, 30 women and 30 men in the COVID-19 group and 30 women and 30 men in the control group. The study was conducted at a single center and by a specialist radiologist.

Patients aged 40 years and older who were diagnosed with COVID-19 by real-time reverse transcriptase-polymerase chain reaction test and examined with contrast-enhanced CT imaging were included in the study. Patients aged 40 years and younger, those who did not have contrast-enhanced CT imaging, pregnant women, and outpatients were excluded. Other exclusion criteria were any history of primary pulmonary arterial hypertension, chronic thromboembolism, interstitial lung disease, and severe chronic obstructive pulmonary disease (COPD). Patients with missing data were also excluded from the study.

Thoracic Computed Tomography Imaging and Analysis

Thoracic CT examinations were performed in the supine position. During inspiration, 80-100 mL of low-osmolarity non-ionic iodinated contrast material was administered with an automatic pump with an injection rate of 4-5 mL/s, followed by 40 mL of serum physiological solution injected for homogeneous distribution. A separate room was prepared for CT imaging of COVID-19 patients. Passive air ventilation was performed for at least 30 minutes after each CT scan, and machine surfaces were disinfected with ethanol and didec yldimethylammonium chloride. All CT images were evaluated in axial, sagittal, and coronal planes. Patients' CT scans were interpreted by a single radiologist to increase the reliability of the study.

Images were obtained from a dual-source spiral CT named Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany. Scanning parameters were as follows: 120 kV; 250 mAs: return time, 0.35 seconds; pitch, 1.5. Images were reconstructed at a slice thickness of 2 mm using a high-frequency reconstruction algorithm. Images were acquired during a deep inspiratory breath-hold without applying contrast.

The presence of unilateral or bilateral GGO, patchy infiltration, pleural effusion, and fibrotic changes was evaluated on CT images. Maximum pulmonary artery was measured at the level of bifurcatio trunci pulmonalis perpendicular to the vessel direction on transverse axial images, and MAo was measured at its maximal diameter using the same CT section. The data obtained were recorded in millimeters. The MPA–MAo ratio was then calculated by dividing MPA by MAo (Figure 1). The study was carried out in collaboration with an anatomist and a radiologist. Radiological examinations were performed by a specialist radiologist with 10 years of experience.

Statistical Analysis

IBM Statistical Package for the Social Sciences Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) software package was used for statistical data analysis. The conformity of the data to the normal distribution was tested with

MAIN POINTS

- Evidence from several patient populations showed that pulmonary artery (PA) enlargement, which can be calculated easily with computed tomography (CT) scanning, is a parameter that can predict negative results.
- Studies on pulmonary hypertension have reported that a maximum pulmonary artery (MPA)–maximum ascending aorta (MAo) ratio of >0.9 to 1.0 is associated with a poor prognosis and is considered a more useful marker than the peak gradient of tricuspid regurgitation measured by echocardiography.
- The diagnosis of pulmonary hypertension brings many complications. Nevertheless, these complications can be prevented by early intervention thanks to early diagnosis with CT, which allows MPA and MPA/MAo ratio to be determined even in large populations.
- The maximum diameters of PA, ascending aorta, and their ratio, which can be easily obtained from thoracic CT, can be very beneficial in the prognosis of the disease by allowing early diagnosis of symptoms that may adversely affect the patient, such as pulmonary hypertension.

Table 1. Comparison of COVID-19 and Control Group by Gender

	Female			Male		
	COVID-19 Group (n = 26)	Control Group (n = 25)	*P*	COVID-19 Group (n = 30)	Control Group (n = 25)	*P*
Age	50.33 ± 12.09	47.00 ± 9.85	.220	48.73 ± 13.99	45.56 ± 8.80	.299
MPA (mm)	30.3 ± 2.87	24.8 ± 2.60	.000	30.00 ± 2.80	24.7 ± 2.65	.000
MAo (mm)	32.01 ± 3.14	29.03 ± 3.54	.003	32.39 ± 4.18	28.00 ± 3.52	.000
MPA/MAo	0.9 ± 0.08	0.8 ± 0.06	.000	0.9 ± 0.08	0.89 ± 0.09	.870

COVID-19, coronavirus disease 2019; MAo, maximum ascending aorta; MPA, maximum pulmonary artery.

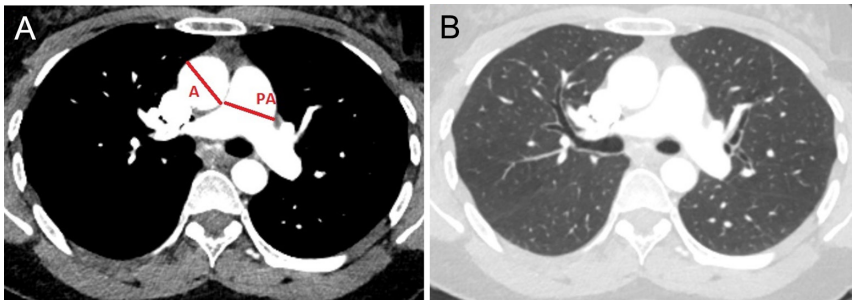


Figure 2. (A) Measurement of pulmonary artery (PA) and ascending aorta (A) in contrast-enhanced thoracic computed tomography (CT) in the control group without lung pathology. (B) Thoracic CT image of normal lung parenchyma.

the Kolmogorov–Smirnov test. Mean and standard deviation were used for numerical data, number and percentage values were used for categorical data, and independent sample *t*-test and Mann–Whitney *U*-test were used for group comparisons. A *P*-value equal to or less than .05 was considered statistically significant for all analyses.

RESULTS

The mean age of the analyzed COVID-19 patients, 50.33 ± 12.09 mm in women and 48.73 ± 13.99 mm in men, was not statistically significantly different ($P = .429$). The mean MPA diameter was 30.17 ± 2.81 mm in COVID-19 patients, 30.36 ± 2.87 mm in women, and 30.0 ± 2.8 mm in men, and the difference was not statistically significant ($P = .637$). The mean MAo diameter was also not statistically significantly different, with 32.21 ± 3.71 mm in COVID-19 patients, 32.01 ± 3.14 mm in women, and 32.39 ± 4.18 mm in men ($P = 1.710$). Finally, the mean MPA/MAo ratio was 0.94 ± 0.82 and did not differ statistically significantly by gender, with 0.94 ± 0.08 in women and 0.93 ± 0.08 in men ($P = .485$).

There was no statistically significant difference between the ages of COVID-19 and control groups in both genders ($P > .05$). The MPA and MAo mean diameters of both male and female COVID-19 patients were statistically significantly higher than that of the control groups ($P < .05$). Although the MPA/MAo ratio of men exposed to COVID-19 was higher than the control groups, the difference was not statistically significant ($P > .05$). On the other hand, this ratio was statistically significantly higher in women with COVID-19 compared to the control group ($P < .001$) (Table 1 and Figure 2).

The comparison of the COVID-19 and control groups revealed statistically significantly higher MPA, MAo, and MPA/MAo values in the COVID-19 patients than in the control group ($P < .001$) (Table 2).

Table 2. Comparison of COVID-19 and Control Group

	COVID-19 Group (n = 56)	Control Group (n = 50)	*P*
MPA (mm)	30.17 ± 2.81	24.81 ± 2.60	.000
MAo (mm)	32.21 ± 3.71	28.51 ± 3.53	.000
MPA/MAo	0.94 ± 0.82	0.87 ± 0.08	.000

COVID-19, coronavirus disease 2019; MAo, maximum ascending aorta; MPA, maximum pulmonary artery.

DISCUSSION

Besides being a primary lung disease, COVID-19 is an infectious pathology that damages the endothelial system by activating many inflammatory and prothrombotic steps. Acute lung injury and respiratory distress syndrome are the most severe forms of the disease and are related to pulmonary vascular function disorders. Therefore, pulmonary hemodynamics, vascular anatomic changes, and pulmonary hypertension development can provide prognostic clues in COVID-19 patients. Evidence from several patient populations showed that PA enlargement, which can be calculated easily with CT scanning, is a parameter that can predict negative results.[14,22] A study conducted in a healthy population reported MPA as 26.1 ± 2.4 mm in men and 22.9 ± 1.9 mm in women.[24] Another study reported the normal reference values of MPA diameter as 24.7 ± 2.7 mm in healthy individuals.[25] Similar to these studies, our study found the MPA diameter to be 24.8 ± 2.6 mm in women and 24.7 ± 2.6 mm in men in the control group. The MPA diameter was reported as 35.3 mm in patients with COPD[22] and 29 mm in patients with cystic lung disease.[26] Another study conducted on patients with COVID-19 found the MPA diameter to be 26.3 ± 4.4 mm.[27] The mortality rate of individuals with pulmonary hypertension was

reported to be high in the last 5 years in individuals with MPA diameter measurements of ≥37.7 mm,[28] while this rate was determined as ≥48 mm in another study.[29] In our study, the MPA diameter was 30.3 ± 2.87 mm in women and 30.0 ± 2.8 mm in men. The findings of our study were similar to previous studies, yet they also demonstrated an increase in MPA diameter in both genders compared to the control group. We cannot directly conclude that PA enlargement is secondary to SARS-CoV-2 infection. The contribution of right ventricular systolic dysfunction in pathogenesis should also be considered. D'Alto et al[30] reported that patients with COVID-19 showed depressed right ventricular functions with a slight increase in PA pressure. Therefore, we believe that right ventricular functions should also be evaluated in COVID-19 patients with an increase in PA diameter.

A study conducted with COPD patients found the MAo diameter to be 35.8 ± 4.9 mm.[22] Erdoğan et al[27] reported the mean MAo diameter in COVID-19 patients as 32.9 ± 5.2 mm. They also examined the patients by categorizing them according to their survival status and showed that those who died from COVID-19 had higher MAo diameters than those who survived. Another study showed that patients with cystic lung disease had a MAo diameter of 31 mm.[26] In our study, the diameter was 32.01 ± 3.14 mm in women and 32.39 ± 4.18 mm in men, with a mean value of 32.21 ± 3.71 mm. Our findings were consistent with the results of these previous studies[22,26,27]; the MAo diameter increased in the patient groups compared to the control group in both genders. Ground-glass opacity, pulmonary consolidation, air bronchogram and airway changes, pulmonary vascular enlargement, reticular pattern and linear opacification, pleural effusion, and pulmonary thromboembolism are considered the main chest CT findings of COVID-19.[15,31] The results not only show that COPD affects the MAo diameter more, but they also reveal an increase in the MAo diameter due to COVID-19 that should not be ignored by clinicians. Impairment of pulmonary hemodynamics after large-scale consolidation with inflammatory and vascular changes, referred to as vascular enlargement,[32] may also be a concern in COVID-19 patients with weak intravascular structure and high thromboembolic risk.[20,33-39]

Studies on pulmonary hypertension have reported that an MPA–MAo ratio of >0.9 to 1.0 is associated with a poor prognosis and is considered a more useful marker than the peak gradient of tricuspid regurgitation measured by echocardiography.[40,41] Other studies on patients with pulmonary hypertension reported that an MPA–MAo ratio of 1.0 or higher predicts worse outcomes.[42,43] Baldi et al[26] reported the MPA–MAo ratio as 0.95 in patients with cystic lung disease. Erdoğan et al[27] found the MPA–MAo ratio in patients with COVID-19 as 0.80 ± 1.2. Another study determined the MPA–MAo ratio as 0.80 ± 0.09.[25] Spagnolo et al[23] showed in 45 COVID-19 patients with thoracic CT scan that the MPA–MAo ratio increased after SARS-CoV-2 infection and was significantly correlated with the extent of pneumonia. In our study, the mean MPA–MAo ratio was 0.94 ± 0.82 and increased statistically significantly in women. This outcome may be associated with a poor prognosis, as in the previous studies. The diagnosis of pulmonary hypertension brings many complications.[13-15,21,22] Nevertheless, these complications can be prevented by early intervention thanks to early diagnosis with CT, which allows MPA and MPA/MAo ratio to be determined even in large populations.[14,22]

Our study lacks data from transthoracic echocardiography and right heart catheterization, which would provide more definitive conclusions about hemodynamic status and PA enlargement. Additionally, CT scan follow-ups could have yielded more beneficial results.

CONCLUSION

In conclusion, our findings reveal a significant increase in the MPA and MAo values in COVID-19 patients compared to the control group. The MPA–MAo ratio in women with COVID-19 was also significantly higher than the control group. These parameters, which are easy to obtain from thoracic CT, can be very beneficial in the prognosis of the disease by allowing early diagnosis of symptoms that may adversely affect the patient, such as pulmonary hypertension.

Ethics Committee Approval: This study was approved by the Malatya Clinical Researches Ethical Board (2021/25).

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

Peer-review: Externally peer-reviewed.

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

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Case Report

Can Coronavirus Disease 2019 Induce Sarcoidosis: A Case Report

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Abstract

Since the emergence of coronavirus disease 2019, a large spectrum of clinical manifestations following this acute viral infection has been reported especially autoimmune manifestations and inflammatory disorders. However, a causal link has not yet been established. Herein, we reported a case of pulmonary mediastinal sarcoidosis following coronavirus disease 2019 infection. A 41-year-old woman with no clinical or radiographic symptoms or signs of sarcoidosis prior to coronavirus disease 2019 infection developed dyspnea, cough, and fatigue, a few months after discharge. A chest thoracic scan performed 3 months after hospital discharge showed regression of ground-glass opacities with the appearance of pulmonary micronodules. Clinical examination and spirometry were normal. The evolution was marked by progressive worsening of dyspnea and significant weight loss. A chest thoracic scan performed 6 months after discharge showed bilateral and symmetrical hilar and mediastinal and paratracheal lymphadenopathy. Bronchoalveolar lavage with cell count showed a lymphocytosis of 19.5% and a CD4/CD8 T cell ratio of 2.2. Endobronchial lung biopsy revealed noncaseating epithelioid granulomas. Sputum culture excluded tuberculosis. The diagnosis of pulmonary-mediastinal sarcoidosis was made. She was treated with an oral corticosteroid. The patient showed significant improvement during the 3-month follow-up period. Post-coronavirus disease sarcoidosis is very rare. Complementary studies are needed to discern the link between these diseases.

KEYWORDS: COVID-19, sarcoidosis, inflammation
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INTRODUCTION

Since the worldwide coronavirus disease 2019 (COVID-19) pandemic began, a number of post-viral inflammatory disorders and autoimmune diseases have been reported.[1] While the occurrence post-COVID-19 infection of autoimmune diseases has been well elaborated, the development of sarcoidosis remains obscure and only a few cases in the literature have been reported. The link between these diseases is not clear, but several mechanisms of this virus have been proposed as a trigger for abnormal inflammatory response.

Herein, we report the third case of pulmonary mediastinal sarcoidosis following a COVID-19 infection diagnosed in a 41-year-old Tunisian patient.

CASE PRESENTATION

We present a 41-year-old patient with no history of any autoimmune diseases or sarcoidosis hospitalized in our department in November 2020 with complaints of fever and diarrhea for several days. Coronavirus disease 2019 infection was confirmed by reverse transcription-polymerase chain reaction. The oxygen saturation was 92%. Chest thoracic scan (Figures 1A and 1B) showed common manifestations of COVID-19 without lung architectural distortion. The extent of lung abnormalities was estimated at 25%-50%. The infection's severity was classified as moderate requiring low-flow oxygen therapy (2 L/min) and corticosteroid therapy. The length of the stay in the hospital was 5 days. The patient reported an initial improvement, followed few weeks later by the onset of persistent fatigue, cough, and exertional dyspnea. Clinical examination was normal, notably with no signs of bacterial infection. Chest thoracic scan at 3 months after discharge showed a significant regression of ground-glass opacities with the appearance of nodules in the lower lobes of both lungs. Bronchial fibroscopy and spirometry were normal. Six months later, the patient reported significant weight loss with progressively worsening dyspnea. Chest thoracic scan (Figures 2A and 2B) showed bilateral and symmetrical hilar, mediastinal and paratracheal lymphadenopathies, and bilateral lower lobe nodules. Bronchoalveolar lavage with cell count showed a lymphocytosis of 19.5% and a CD4/CD8 T-lymphocyte ratio of 2.2. Endobronchial lung biopsy revealed noncaseating epithelioid granulomas. Sputum smear and culture ruled out tuberculosis. The angiotensin-converting enzyme II (ACEII) level was high. The diagnosis of sarcoidosis was established on the basis of compatible clinical, radiologic, and histological findings. Spirometry was normal: forced expiratory volume in one second (FEV1: 2.320 L, 92% of predicted normal value), forced vital capacity (FVC: 2.670 L, 86%), and an FEV1/FVC ratio of 86%. Ophthalmology test, echocardiography,

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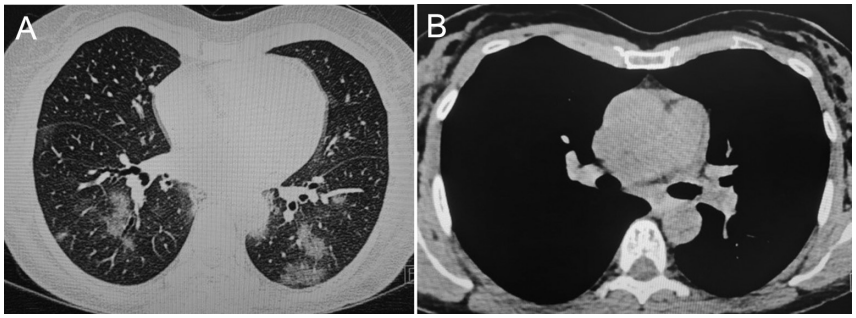


Figure 1. (A) Typical computed tomography (CT) manifestations of coronavirus disease 2019. (B) Initial CT of the mediastinum.

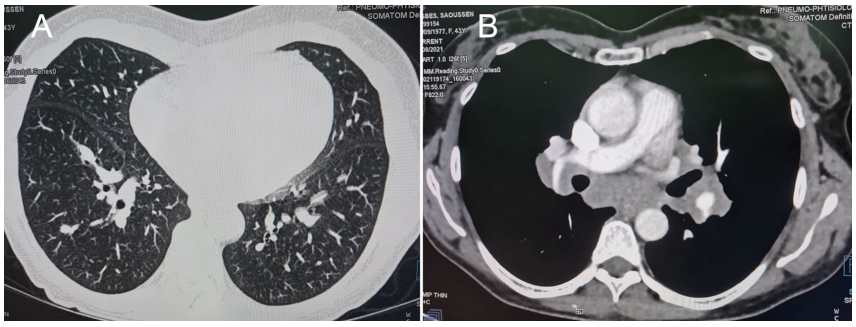


Figure 2. (A) Bilateral lung nodules. (B) Bilateral and symmetrical hilar, mediastinal lymphadenopathies.

and nervous system evaluation ruled out extrapulmonary sarcoidosis. Treatment started with prednisolone. During the 2-month follow-up period, the patient's symptoms subsided and she showed much improvement.

DISCUSSION

The occurrence post-COVID-19 infection of autoimmune diseases has been well elaborated. A systematic review of reported cases, published in October 2020, found that 33 cases of patients with COVID-19 developed an autoimmune disease after 2 to 33 days after the onset of viral illness. These autoimmune diseases included subacute thyroiditis, Kawasaki disease, coagulopathies, antiphospholipid syndrome, immune thrombocytopenic purpura, autoimmune hemolytic anemia, and Guillain–Barré syndrome.[2]

The development of sarcoidosis post-COVID-19 infection remains extremely rare. Only 6 cases were previously reported (Table 1). Recently, a case of pulmonary-mediastinal sarcoidosis following a COVID-19 infection was published on January 12, 2022. It is about a patient with a previous prostate cancer history who developed pulmonary sarcoidosis 1 year after severe COVID-19 disease. However, the patient's history of prostate cancer could be a confounding factor in attributing the development of sarcoidosis to a post-COVID-19 effect.[3] Five other case reports of sarcoidosis, including 1 case of sarcoidosis stage 1, 1 case of sarcoidosis stage 2 published on April 2021, and 3 cases of biopsy-confirmed sarcoid-like reaction, were diagnosed several weeks after COVID-19 infection.[4-6] To our knowledge, our patient was the third case of pulmonary-mediastinal sarcoidosis. He had no personal or family history of cancer or interstitial lung diseases, and he developed manifestations of sarcoidosis after 6 months of COVID-19 infection.

MAIN POINTS

- Here, we present the third case of pulmonary mediastinal sarcoidosis following a coronavirus disease 2019 (COVID-19) infection, confirmed on pathology.
- Coronavirus disease 2019 has been implicated in the development of granulomatous manifestations.
- Sarcoidosis following COVID-19 infection is very rare and the link between these diseases remains obscure.

The link between COVID-19 and sarcoidosis is not well established. It has been suggested that this virus might trigger the formation of noncaseating granulomas via the renin–angiotensin system and the innate immune system. Indeed, the S protein of this virus attaches to host cells through ACEII, allowing fusion with the cell membrane and release of viral RNA. After entry, through this host receptor (ACEII), severe acute respiratory syndrome coronavirus 2 causes an exacerbated inflammatory response and favors a "cytokine storm" that is considered central to the progression of the disease to acute respiratory distress syndrome. It activates pro-inflammatory cytokines such as interleukin (IL)-6, IL-10, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha. This cytokine dysregulation is common to the pathophysiology of both COVID-19 and sarcoidosis. Research demonstrated a high percentage of Th17.1 cells in the lung lavage of sarcoidosis patients compared with control patients and that approximately 60% of these cells, which present the dominant phenotype, produced only IFN-γ.[3,4,7]

Several studies confirm the role of ACEII expression and activity in COVID-19 pathogenesis. The physiological role of ACEII is to cleave angiotensin II to angiotensin.

Table 1. Case Reports of Sarcoidosis Following COVID-19 Infection

Authors	Publication	Case Presentation	Diagnosis
Behbahani et al[5]	July 2020	• A 72-year-old woman with a medical history of asthma, hypertension, hyperlipidemia, obstructive sleep apnea, and seizure disorder • Two weeks after COVID-19 infection: violaceous nodules on the glabella, submental chin, and anterior shin	Sarcoid-like reaction
Mertz et al[4]	April 2021	• A 32-year-old woman • Possible COVID-19 diagnosed on March 2020 • Apparition of tachycardia 2 weeks after initial improvement	Lofgren syndrome with pulmonary stage 2 sarcoidosis
		• A 51-year-old woman • SARS-CoV-2 pneumonia in April 2020 • One week later: latero-cervical lymphadenopathies	Sarcoidosis stage 1
		• A 32-year-old woman • *Possible COVID-19 infection • Next month: Isolated erythema nodosum lesions of the legs	Sarcoid-like reaction
Polat Ekinci et al[6]	August 2021	• A 55-year-old woman with a history of hypertension, hyperlipidemia, and hypothyroidism • One month after COVID-19 infection: infiltrated and tender plaques over old scar sites on both knees, subcutaneous nodules on both arms, 3 subcutaneous papules on periorbital areas, and a single papule in the glabellar region	Sarcoid-like reaction
Capaccione et al[3]	January 2022	• A 61-year-old male never-smoker with a history of prostate cancer and chronic kidney disease • One year after severe COVID-19 disease: fatigue and weight loss • Chest CT: pulmonary nodules and extensive mediastinal and hilar adenopathy	Pulmonary-mediastinal sarcoidosis

COVID-19, coronavirus disease 2019; CT, computed tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Angiotensin-converting enzyme II is highly expressed by lung epithelial cells, a major target of the disease, resulting in an inflammatory response in the lower airways of the lungs. Moreover, it is known that ACEII is regulated in macrophages located within the granulomatous tissue in sarcoidosis and plays an important role in granuloma formation and in the regulation of tumor necrosis factor-alpha production.[4,7]

Furthermore, recent finding reports that CD8+ mucosal-activated invariant T cells, which may be involved in the pathogenesis of sarcoidosis, might also play a role in self-sustaining inflammation in the lungs of patients with COVID-19.[8]

As with other autoimmune diseases, disruption of the immune system is likely a causative agent in the development of sarcoidosis after COVID-19 infection. Longer follow-up is needed to confirm the diagnosis or to differentiate it from transient symptoms due to the host's immune response to COVID-19.[9]

Because of the rarity of the disease, treatment and outcomes would be similar to those of people who are not infected with COVID-19.

CONCLUSION

This case report may be valuable for increasing awareness of the possibility of post-COVID sarcoidosis. The shared mechanism needs to be studied, but it requires more patients.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.R., S.M.; Design – S.M., A.T.; Supervision – H.R., N.C.; Materials – T.Z.; Data Collection and/or Processing – N.H., A.T., S.H.; Analysis and/or Interpretation – N.H., S.H.; Literature Review – N.C., H.R., T.Z.; Writing – T.Z., H.R.; Critical Review – N.C., H.R.

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Case Report

The First Definition of Pulmonary Component of Hypereosinophilic Syndrome: Bronchial Casts

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This case was presented as oral presentation at the Turkish Thoracic Society 24th Annual Congress with International Participation (hybrid congress) in 2021 and was deemed worthy of the "Lung Pathology Study Group Oral Presentation Award."

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Abstract

Hypereosinophilic syndrome is a heterogeneous disease characterized by eosinophilic tissue inflammation and eosinophilia. Pulmonary involvement could be seen in up to 55% among children with hypereosinophilic syndrome. A 3-year-old boy with chronic hypereosinophilia and respiratory complaints was diagnosed with idiopathic hypereosinophilic syndrome. Atelectasis was detected in the radiological evaluation, and bronchial casts with eosinophilic structures were removed by bronchoscopy. Steroid, inhaled hypertonic saline, inhaled bronchodilator, inhaled corticosteroid, and leukotriene receptor antagonist were used for 1 year in the management of hypereosinophilic syndrome, and related eosinophilic casts and repetitive bronchoscopies were administered for removal of the casts. The patient was successfully managed with an inhaled N-acetyl cysteine treatment. In children, the long-term prognosis of hypereosinophilic syndrome is uncertain. Comprehensive diagnostic tests are required for the early diagnosis and management of pediatric hypereosinophilic syndrome. In the presented case, the rare occurrence of pulmonary involvement of hypereosinophilic syndrome in a 3 year-old-boy with recurrent hypereosinophilic casts and its management were discussed.

KEYWORDS: Bronchial cast, children, hypereosinophilic syndrome
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INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare disease and characterized by an absolute eosinophil count of more than 1500/mm^3 for at least 6 months and the presence of end-organ damage.[1] In the absence of an identifiable cause of eosinophilia and the presence of end-organ damage, the diagnosis of idiopathic HES should be considered. Children with HES can have pulmonary involvement in up to 55% of cases.[2]

Plastic bronchitis (PB) or cast bronchitis is a rare condition which causes partial or complete obstruction in tracheobronchial tree with the presence of mucofibrinous plugs and may result in severe respiratory distress, dyspnea, cyanosis, and wheezing.[3,4] Pathophysiology of PB may be related to alveolar–capillary barrier damage, mucosal fragility, increased venous pressure, lymphatic congestion, or decreased lymphatic drainage. Endobronchial cast which is a rubber-like or thick gelatinous-mucoid structure may cause airway obstruction, infection, or segmental atelectasis.[5] The optimal treatment of primary disease is the priority.

Plastic bronchitis has not been previously described in the pulmonary component of HES. Herein, the first definition of pulmonary involvement of HES in a 3-year-old boy with recurrent hypereosinophilic casts removed by bronchoscopic intervention is discussed.

CASE REPORT

A 3-year-old boy was admitted to our hospital with a 6-month history of dyspnea and chronic dry cough which was unresponsive to inhaled beta-2 agonist treatment. Neither the patient nor his family had any history of atopy, recurrent bronchiolitis or wheezing, cardiac disease, recurrent skin lesions, or itching. The patient had normal growth; his oxygen saturation at room air was 98%; he had no clubbing in the physical examination. He had prolonged expirium in auscultation and other system findings were normal. In laboratory findings, the eosinophil percentage was 16.5, the absolute eosinophil count was 2200/10^3, and other total blood count parameters were in the normal range. Acute phase reactants were negative. When past medical records were examined, it was observed that the hypereosinophilia persisted for more than 6 months. In chest x-ray, a double contour sign in the lower zone of the left lung and consolidation in the right upper zone were seen on admission (Figure 1A). In thorax computed tomography (CT), on the left lung lower lobe superior segment, atelectasis sitting on the pleura at the base was observed, but common ground glass opacity was not observed.

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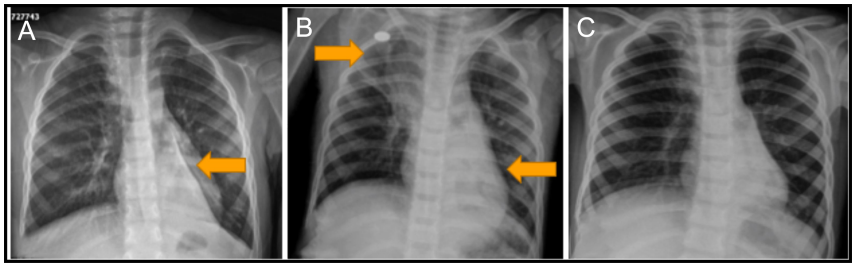


Figure 1. Left lower lobe atelectasis in the chest x-ray on admission (A). Right upper lobe and left lower lobe atelectasis on chest x-ray before the first bronchoscopy (B). Control chest x-ray a day after bronchoscopy and removal of the eosinophilic casts and a significant improvement of the atelectasis was observed (C).

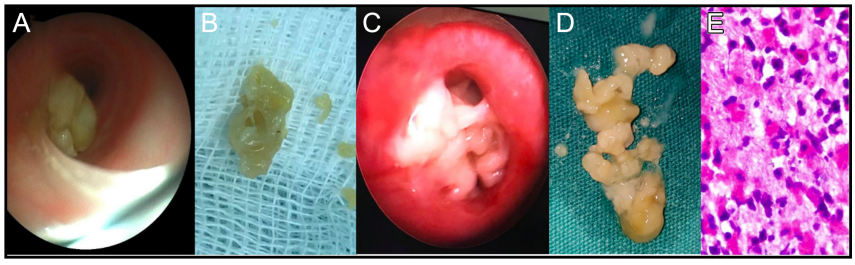


Figure 2. The appearance of the dense, mucoid structure which was in dirty yellow color at the entrance of the right lung upper lobe apical segment during fiberoptic bronchoscopy (A). The macroscopic view of eosinophilic casts removed from the right upper lobe apical segment (B). The appearance of dirty yellow tough crusty structure in the left lower lobe bronchus (C) during fiberoptic bronchoscopy and the macroscopic view after removal (D). Microscopic view of eosinophilic casts at 100× magnification with hematoxylin–eosin staining (E).

Stool parasitic investigation and serology of parasitic infections (*Toxocara canis*, *Entamoeba histolytica*, *Cryptococcus*, *Ascaris*, *Strongyloides*, *Echinococcus granulosus*) for the etiology of hypereosinophilia were negative. Abdominal ultrasound, echocardiographic examination, immunoglobulin levels (Ig G, A, M, and E), lymphocyte subgroups, serum tryptase level, and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) values were normal. The sweat chloride test was 23 mEq/L; cystic fibrosis transmembrane regulator gene mutation and skin prick test, and food and house dust mite-specific IgE levels were negative. In the bone marrow aspiration, normocellular bone marrow, hyperplasia in myeloid cells, and an increase in eosinophils (20%) were detected. FIP1LI/PDGFRA and t (9:22) mutations were both negative. No cause of chronic hypereosinophilia was detected. The patient was diagnosed with idiopathic HES after excluding parasitic, allergic, immunological, rheumatological, and hematological diseases. The consolidation in the right upper lobe was added to the left lower lobe atelectasis, which was detected during the admission process (Figure 1B).

MAIN POINTS

- Although hypereosinophilic syndrome is very rare in children, parenchymal pulmonary involvement can be seen in 55% of patients.
- In the presented case, recurrent eosinophilic casts due to underlying hypereosinophilic syndrome were first described, while pulmonary parenchymal involvement was not observed contrary to expectations in hypereosinophilic syndrome.
- Atelectasis appearing in different regions at different times on chest x-ray may be an indicator of bronchial casts.
- The basic approach for the diagnosis of a bronchial cast is bronchoscopy and cytopathological examination of the extracted cast.

The patient underwent bronchoscopy and a dense, mucoid structure which was dirty yellow in color was observed at the entrance of the right lung upper lobe apical segment (Figure 2A). Inside the left lower lobe bronchus, a dirty yellow tough crusty structure, approximately 0.5 × 1 cm in size, was detected (Figure 2C). They were removed by rigid bronchoscopy (Figure 2B and D). Eosinophilia not exceeding 15% was detected in the bronchoalveolar lavage fluid and no microorganisms were observed. After the removal of the bronchial casts, radiological appearance improved (Figure 1C). The pathological assessment of the bronchial casts showed eosinophilic mucinous structure with 80% eosinophilic infiltration (Figure 2E). Systemic steroid treatment was started as HES treatment (1 mg/kg/day). Systemic steroid, inhaled hypertonic saline, inhaled bronchodilator, inhaled corticosteroid, and leukotriene receptor antagonist were used for 1 year in the management of HES-related eosinophilic casts (Figure 3). However, 3 more fiberoptic bronchoscopy (FOB)s were required due to recurrent casts and respiratory problems in the first year of follow-up. Inhaled N-acetyl cysteine (NAC) was added to the patient's treatment and eosinophilic casts did not repeat. The patient, who was followed without treatment for the last 3 years, had no complaints during the final check-up and had an absolute eosinophil count of 800 and eosinophilia of 7.5%. Written consent was obtained from parents.

DISCUSSION

In children, small case series of HES have been described in the literature. The presentation of the disease is diverse. There could be dermatologic, pulmonary, gastrointestinal system, cardiac, and/or neurologic involvement.[6] The presentation of idiopathic HES is heterogeneous and may vary from

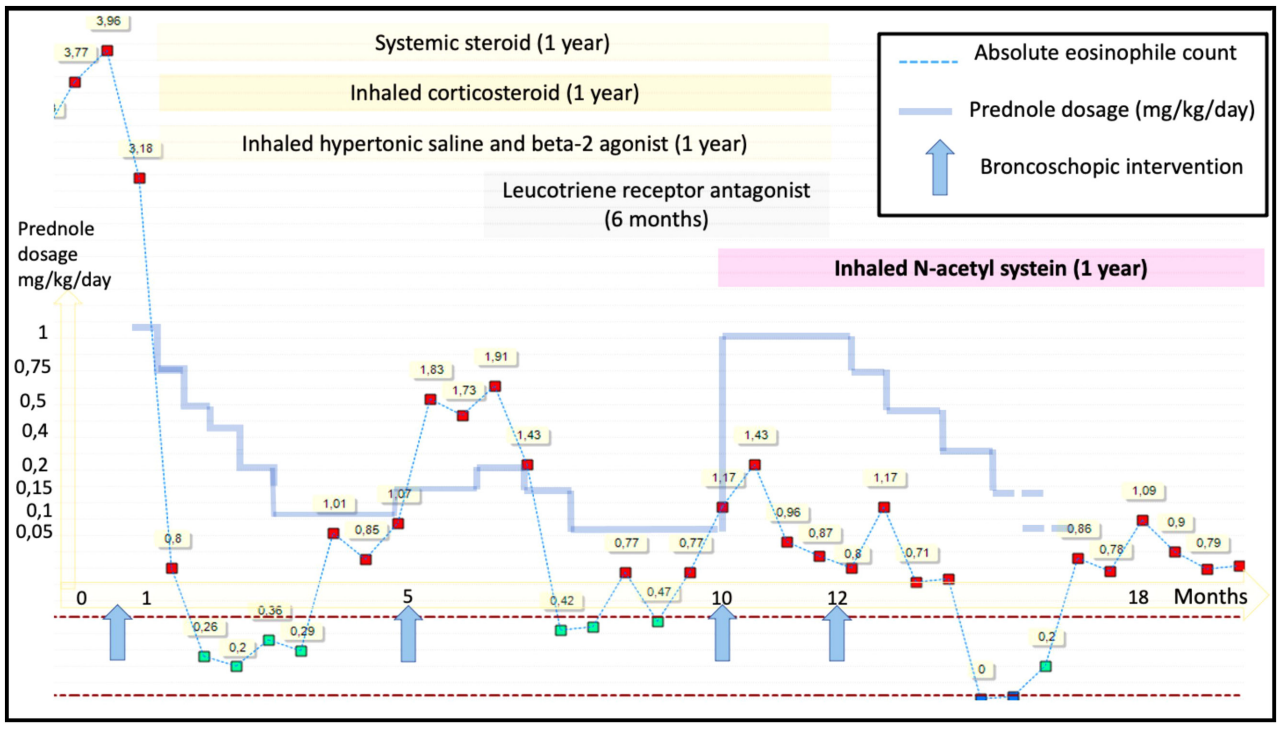


Figure 3. Figure showing the relationship between the patient's treatment scheme, peripheral blood eosinophil counts, and bronchoscopic interventions.

nonspecific complaints such as fatigue, cough, dyspnea, itching, and skin rash to life-threatening cardiac and/or neurologic findings. Cardiac, pulmonary, and skin are known to be the most common involvements in the pediatric age group.[7] The most common pulmonary findings of HES are dyspnea, cough, and wheezing. Abnormal chest x-ray and CT findings such as parenchymal infiltrates, patchy ground glass opacities, pleural effusion, intrathoracic lymphadenopathy, and pulmonary emboli could be seen.[8] In one of the largest series with 49 patients aged 12 to 88 years with HES, 45% of patients with pulmonary involvement had dyspnea, 39% had cough, and 24% had wheezing.[8] Pulmonary involvements during childhood vary from 27.5% to 55.3%.[7,9] In the study conducted by Tavil et al.[2] half of the pediatric patients had pulmonary involvement presented as cyanosis, crackles on auscultation, and thorax CT findings.[2] In the presented case, the patient had only dry cough and respiratory distress. There were no findings of parenchymal infiltration, ground glass opacity, lymphadenopathy, or pulmonary embolism on the CT scan. Atelectasis was detected only in the distal of the existing casts. In the present case diagnosed with idiopathic HES, we determined bronchial casts without parenchymal lesions. Pulmonary involvement of HES associated with recurrent casts has not been defined so far.

Plastic bronchitis, fibrinous bronchitis, bronchitis pseudomembranosa, and Hoffmann bronchitis are all terms used to describe bronchial casts. In children, it has been reported in association with a variety of cardiorespiratory disorders, such as cystic fibrosis, asthma, allergic bronchopulmonary aspergillosis, respiratory infections (H1N1, severe coronavirus disease 2019, etc.), congenital heart disease (CHD), and acute chest syndrome associated with sickle cell disease.[10,11] The presented case had no history of recurrent wheezing or atopy and did not respond to the asthma treatment. All these disorders and diseases including asthma were excluded with a detailed examination of the patient.

Bronchial casts are classified clinically and pathologically in various ways. Based on cast histology, a pathological approach was adopted by Seear et al[12], and casts were classified into type 1 or inflammatory casts and type 2 or acellular casts. Inflammatory casts were often developed due to bronchial diseases and presentation of this type was often acute. Acellular casts could be seen in idiopathic cases and cyanotic CHD. Madsen et al[13] attempted to categorize bronchial casts based on the underlying condition and form of the casts. Mucinous, inflammatory, and chylous casts may develop in patients with structural CHD. The patients without structural CHD were classified as lymphatic disease or chylous casts, acute chest syndrome associated with sickle cell disease or fibrinous casts, and atopy or eosinophilic casts.[13] In the existing literature, eosinophilic casts are commonly associated with atopy, allergy, and underlying inflammatory diseases of the lung.[13,14] We can evaluate the hypereosinophilic casts due to idiopathic HES in this group.

Management of bronchial casts can be defined as the treatment of an underlying disease.[5] In addition to the removal of the casts with rigid or flexible bronchoscopy, it has been experienced in the literature that some medical treatments may be beneficial in type 1 casts. Fibrinolytic agents and anticoagulants (tPA, unfractionated heparin, and urokinase), dornase alpha against cellular DNA and NAC as mucolytic can be administered by nebulization or intraoperatively through bronchoscope.[5,11] Systemic steroids to decrease secretions and anti-inflammatory activity and bronchodilators to assist in airway clearance and to reduce bronchospasm can be given.[5,12] Hypertonic saline with chest physiotherapy can be employed in airway clearance.[5] In addition to these

medications, oral macrolides may help reduce inflammation and secretions of the cast.[5] Type 2 casts can be removed with bronchoscopy in terms of symptomatic relief.[5] Bronchoscopy, steroids, and inhaled NAC were experienced beneficial in one of the most extensive case series with 9 children.[12] The presented case was treated with systemic steroid, inhaler hypertonic saline, inhaled bronchodilator, inhaled corticosteroid, and leukotriene receptor antagonist; however, the most effective treatment option was inhaled NAC.

The long-term prognosis of HES is unknown in children. For the early detection and management of complications in pediatric HES, comprehensive diagnostic investigations are essential. In this case, we wanted to share the rare occurrence of HES-based eosinophilic cast in the bronchial tree and how it was managed to contribute to the existing literature.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.G., Z.R.O.; Design – S.G., Z.R.O.; Supervision – S.G., Z.R.O., A.T.Y., A.C.A.; Funding – Z.R.O.; Materials – S.G., Z.R.O.; Data Collection and/or Processing – Z.R.O., Y.A., S.C.O., D.M., G.B.; Analysis and/or Interpretation – S:G., Z.R.O., Y.A., S.C.O., D.M., G.B.; Literature Review – S.G., Z.R.O., Y.A., S.C.O., D.M., G.B; Writing – S.G., Z.R.O.; Critical Review – S.G., A.T.Y., A.C.A.

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