EISSN 2149-2530

Indexed in PubMed, Web of Science and Scopus

Turkish Thoracic Journal

Official Journal of the Turkish Thoracic Society

ISSUE 5 September 2022 VOLUME 23

Original Articles

Review

Letter to the Editor

Turkish Thoracic Journal

Official Journal of the Turkish Thoracic Society

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AIMS AND SCOPE

Turkish Thoracic Journal (Turk Thorac J) 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.

Turkish Thoracic Journal started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2007. Archives of both journals were passed on to the Turkish Thoracic Journal.

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.

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Turk Thorac J 2022; 23(5): 307-321 DOI: 10.5152/TurkThoracJ.2022.21029

Original Article

Coronavirus Disease 2019 Pneumonia Scoring System Comparison and Risk Factors

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Cite this article as: Ensarioğlu K, Kevser Erdöl A, Kurt B, et al. Coronavirus disease 2019 pneumonia scoring system comparison and risk factors. *Turk Thorac J.* 2022;23(5):307-321.

Abstract

OBJECTIVE: Coronavirus disease 2019 is a disease caused by severe acute respiratory syndrome coronavirus 2, a novel type of coronavirus, which causes pneumonia in some hosts. No specific scoring method exists for mortality evaluation in novel coronavirus pneumonia. The aim of this study was to investigate factors affecting coronavirus disease 2019 mortality and comparison of pneumonia scoring systems, pneumonia severity index, CURB-65, and MuLBSTA.

MATERIAL AND METHODS: In this single-center clinical study, 151 patients who had been diagnosed with coronavirus disease 2019 infection and pneumonia between March 11 and May 31, 2020, were evaluated retrospectively. Correlation between patients' symptoms, comorbidities, drugs in use, radiological findings, and mortality was investigated. Parameters were also evaluated regarding their contribution to additional treatment requirements and days of fever response.

RESULTS: A correlation between mortality and higher scores of pneumonia severity index, CURB-65, and MuLBSTA was found. When parameters were investigated separately, elevated glucose and urea levels, presence of diabetes, renal failure, hypertension, chronic obstructive pulmonary disease, cerebrovascular events and known malignancies, lymphocyte count, smoking history, radiological findings, and age correlated with mortality.

In addition to these parameters, elevated calcium, potassium, brain natriuretic peptide, troponin, D-dimer, C-reactive protein, HC03, and lactate dehydrogenase levels were found significant regarding mortality. These parameters were not found statistically relevant regarding additional treatment requirement, fever response day, and total treatment duration.

CONCLUSION: A modified version of present pneumonia scoring systems will be required to rigorously evaluate the severity of a patient's condition. A new scoring system that uses components of the present ones may prove useful and with further studies, a similar follow-up algorithm may be created.

KEYWORDS: Clinical Protocol, COVID-19, mortality, pneumonia, scoring methods, risk factor scores
Received: *March 31, 2021* ***Accepted:*** *March 30, 2022* ***Available Online:*** *June 14, 2022*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly identified type of coronavirus. It was deemed pandemic by World Health Organization, and the first COVID-19 case in Turkey was reported on March 10, 2020. As a novel infection, guidelines and approaches were developed on the road. The same can be said for treatment modalities, as in addition to differences between countries, hospitals within the same city often did not agree on a uniform approach. Patient isolation and follow-up protocols have also changed over time, both with the results of new studies being recently published and according to limitations of healthcare utilities.

As a novel infection, COVID-19 pneumonia has been treated in a quite similar fashion to other viral pneumonia, with key differences being in antiviral treatment and support modalities. Modifications of former treatments and follow-up protocols have been the norm so far, due to limited data available regarding the disease and its progression. The goal behind this study was to evaluate COVID-19 infection and pneumonia, starting from the first patient admitted to our hospital, to have a better understanding of the disease.

The purpose of the study was to lay the foundation of an optimal screening process for pneumonia severity by comparing 3 present scoring systems, pneumonia severity index (PSI), CURB-65, and MuLBSTA, thus eliminating unnecessary hospitalization and determining which patients may require intensive care admission. An additional goal was to evaluate which parameters, ranging from demographic to laboratory markers, have an impact on disease and its response to treatment.[1-3]

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MATERIALS AND METHODS

Study Design

In this retrospective study, patients who had been diagnosed with COVID-19 infection between March 11 and May 31, 2020, by real-time polymerase chain reaction (RT-PCR) were investigated. According to hospital policy, sampling had been done from both the nasopharynx and oropharynx with the same swab to increase accuracy. Evaluation of patients was performed only if they had been previously consulted by either Infectious Diseases or Pulmonary Medicine departments.

Patients who had been treated in outpatient care were excluded from the study. Similarly, patients who were diagnosed with COVID-19 during hospitalization for other reasons and then admitted to COVID-19 wards were also excluded from the study. These precautions were taken to ensure an unbiased evaluation regarding treatment response.

The faculty ethics board provided ethics approval (Decision No 90/12 and date June 22, 2020). Patients' data from the hospital management system and the national COVID-19 database were accessed for evaluation. Patients provided written and verbal consent for hospital admission and treatment. A spreadsheet form was utilized for initial data collection, in which demographic information, physical examination, routine blood testing results, radiological findings, and treatment regimens of the patients were present. Physical inspection notes and laboratory results were taken at the time of admission.

Definitions

Coronavirus disease 2019 RT-PCR-positive patients were defined as the study population. Patients with COVID-19 diagnosis and radiological findings, regardless of typical or atypical, were categorized under COVID-19 pneumonia diagnosis. Radiological imaging was performed on every patient, initially with direct chest radiography, and if any pathological finding is present or if the doubt of pneumonia is high, an additional computed chest tomography was requested. As such, the radiological findings section utilizes both imaging modalities in this study. Comorbidities were defined as any illness present upon admission or diagnosed during hospitalization, regardless of the presence of former treatment.

A patient was considered under treatment for a specific drug only if said drug had been used by the patient before admission to hospital. Additional treatment requirement was accepted as either a change of the present treatment regimen and/or addition of a new drug to the current regimen, which includes antiviral drugs and antibiotics.

Progression was defined as clinical worsening of a patient under treatment, which may lead to an intensive care admission. Treatment response was based on multiple parameters, including fever response of patients who had fever upon admission, reduction in inflammatory markers, and improvement in vital signs, with the most important vital sign designated as saturation above 94% in room air.

Statistical Analysis

Before statistical analysis, patients' data were unified in suitable Microsoft Excel documents. Analyses and calculations were then performed by IBM's Statistical Package for the Social Sciences software, version 22, after converting said documents. A patient's data were considered inadequate if a section of the patient's data spreadsheet was missing or was not declared, such as a lack of reported physical inspection notes or inappropriate medical background questioning. In these cases, the data of the patient were removed from the study entirely. A parameter was considered inadequate if, for any reason, it was not reported in more than 10% of the total data. In this case, the parameter itself was removed, and if it had any reliant parameters to it, they were also removed.

Mann-Whitney *U* test was used to distinguish parameters regarding mortality. Pearson's correlation analysis was used to evaluate the pneumonia scoring systems' effect on progression and mortality. Linear multiple regression analyses were performed to investigate factors affecting treatment duration, additional treatment requirement, and treatment response. If a parameter was found relevant after Pearson's analysis, linear regression analysis was utilized to investigate the degree of the parameter's effect.

Hypothesis

The hypotheses of the study can be summed in 2 parts. First, it is assumed that pneumonia scoring systems that include end-organ failure parameters (such as PSI) or are already in use for viral infections (MuLBSTA) will prove superior in terms of evaluating mortality.

Secondly, a correlation is expected between additional treatment requirements and parameters used in the study, such as inflammatory index score, initial vital signs, comorbidities, and C-reactive protein (CRP) level. This correlation is assumed to be present in both COVID-19 infection and in case of the presence of COVID-19 pneumonia.

MAIN POINTS

- Coronavirus disease 2019 (COVID-19) infection may differ from COVID-19 pneumonia in terms of factors affecting prognosis and mortality.
- Pneumonia severity index and MuLBSTA scoring systems perform better at evaluation of mortality in COVID-19 pneumonia, compared to CURB-65. This is attributed to parameters within these scoring systems.
- Additional parameters have been described, mainly increased calcium, potassium, brain natriuretic peptide, troponin, D-Dimer, C-reactive protein, HCO_3, and lactate dehydrogenase levels, that are not present in available scoring systems.
- A revision of available scoring systems or a newly designed system may prove reliable for COVID-19 pneumonia severity evaluation.

RESULTS

A total of 590 patients were evaluated during initial screening, and 181 were found positive for COVID-19 infection and

were included in the study. These patients' records were then investigated, and 30 patients were excluded from the study due to missing data criteria. The remaining 151 patients were then evaluated (Figure 1).

Average age of patients was 50 (±17) years. Patients' age varied between 18 and 91 and had a homogenous spread. Sixty-nine patients (45%) were male and 82 (55%) were female. In symptom evaluation, fever (n = 37, 41%), coughing (n = 80, 53%), and dyspnea (n = 45, 30%) were the most common symptoms. Smoking history evaluation was limited as 50% of patients either could not provide a conclusive history of smoking or were not questioned about it. Of the remaining patients who had been questioned, 59 (76%) were non-smokers. Hypertension (n = 45, 29.8%) and diabetes (n = 25, 16.7%) were the most prominent comorbidities. Treatment for these comorbidities was also the most common, however, at a lower rate (n = 28, 18.5% and n = 11, 7.3%, respectively) compared to diagnoses, indicating that for most patients, treatment of hypertension and diabetes had begun after hospital admission. Pneumonia was present in more than 86 patients (63.2%) and was often bilateral (n = 72, 84.9%). Hydroxychloroquine sulfate was the treatment of choice in 86.8% (n = 131), followed by azithromycin in 42.4% (n = 64) and favipiravir in 37.7% (n = 57).

Treatment was completed with a successful hospital discharge for most patients (78%) within 5 days. The average duration of treatment was 5.87 (±2.01) days, 124 (82.1%) of patients did not require additional treatment, while 8 (5.3%) had additional treatment and the rest 19 (12.6%) required intensive care admission in addition to treatment revision. Eight patients (5.3%) died and all were patients who had additional treatment and were in intensive care units. Oxygen saturation percentage was the only vital sign that was found significant in mortality analysis.

For all patients with COVID-19 infection, white blood cell count (WBC), glucose, urea, creatinine, calcium, potassium, N-terminal pro-hormone brain natriuretic peptide (NT-proBNP), troponin, fibrinogen, D-dimer, CRP, LDH, and serum HC03 levels were found as statistically significant laboratory markers for mortality ($P < .05$). Age, presence of comorbidities (hypertension, renal failure, cerebrovascular event history, known malignancies, diabetes, and chronic obstructive pulmonary disease (COPD)), and drug regimens (antidiabetics and acetylsalicylic acid) were found statistically significant for mortality ($P < .05$) (Tables 1 and 2).

Radiologically, as pneumonia progresses to a diffuse pattern, the need for additional treatment requirement increases. Age, hypertension, known malignancy, and elevated inflammatory markers were found to be relevant regarding increased treatment duration, response of fever, and additional treatment requirements (Table 3).

Pneumonia severity index (55 ± 21 vs. 94 ± 24) and MuLBSTA (6.4 ± 3.6 vs. 12.2 ± 3.5) scores were lower for survivors, compared to CURB-65 (0.86 ± 4.06 vs. 1.75 ± 0.89), in which a significant difference was not observed. For mortality evaluation, higher PSI, MuLBSTA, and CURB 65 scores were found to have a positive correlation with increased

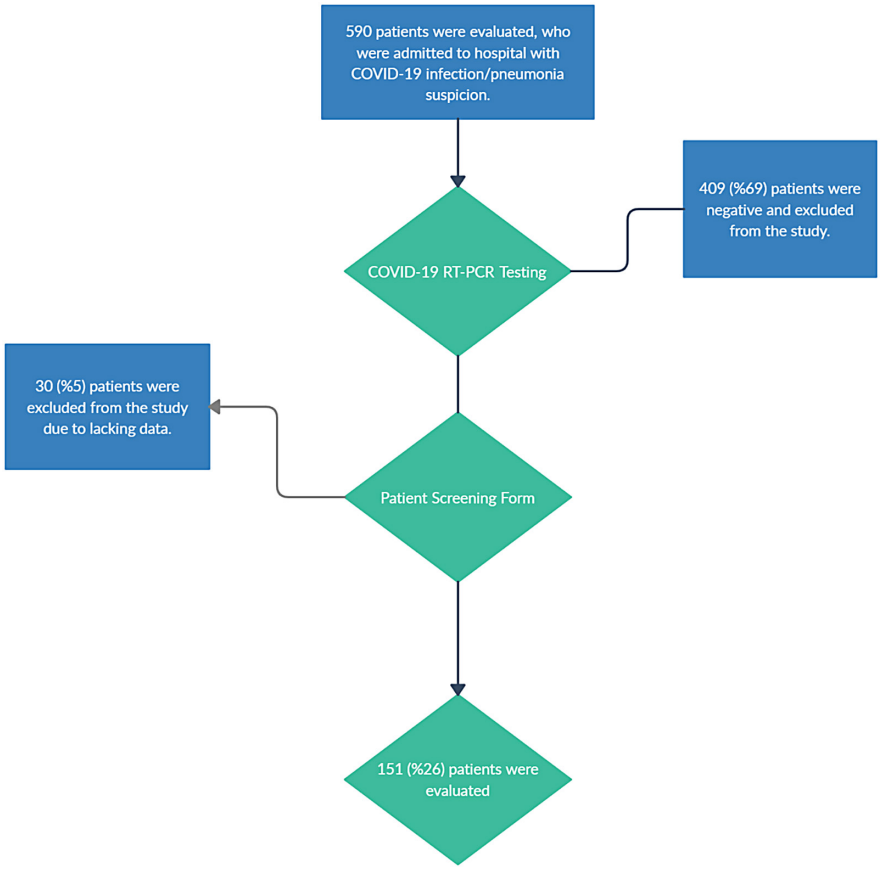

Figure 1. Patient Selection Flow Chart

Table 1. Mann–Whitney *U* Test Results, According to Survival 1

		Number	Median	25th Percentile	75th Percentile	*P*
Systolic T.	Exitus	4	130	112.50	147.50	.328
	Alive	74	120	110.00	130.00	
Diastolic	Exitus	4	76.5	63.25	80.00	.458
	Alive	74	80	70.00	87.75	
Mean	Exitus	4	2.67	81.33	102.50	.945
	Alive	74	93.33	83.33	100.00	
Pulse rate	Exitus	3	80	64.00		.209
	Alive	93	87	80.00	97.50	
Saturation	Exitus	3	87	18.00		.021
	Alive	104	95	93.00	96.00	
Fever	Exitus	4	36.55	36.13	36.90	.286
	Alive	105	36.8	36.45	37.20	
Respiratory rate	Exitus	2	23.5	20.00		.217
	Alive	59	20	17.00	22.00	
BCG	Exitus	3				.139
	Alive	85				
WBC	Exitus	8	6.23	4.09	9.30	.255
	Alive	142	4.9	3.81	6.79	
HB	Exitus	8	12.2	9.95	13.20	.026
	Alive	142	13.7	12.50	14.80	
PLT	Exitus	8	168.5	146.50	218.25	.166
	Alive	142	213	169.76	269.75	
NEU%	Exitus	8	84.15	75.50	90.10	<.001
	Alive	142	62.85	51.45	71.67	
LYM%	Exitus	8	8.8	5.43	16.70	<.001
	Alive	142	27.15	18.20	36.80	
NEU#	Exitus	8	4.4	3.55	7.56	.019
	Alive	142	3.21	2.17	4.54	
LYM#	Exitus	8	0.5	0.32	1.20	.002
	Alive	142	1.41	0.97	1.79	
MCV	Exitus	8	87.6	82.70	89.60	.294
	Alive	142	85.25	82.20	87.92	
Glucose	Exitus	8	150	120.25	238.00	.008
	Alive	137	103	91.50	121.00	
Urea	Exitus	8	48.5	38.25	74.60	<.001
	Alive	139	27	21.00	35.80	
Creatinine	Exitus	8	1.08	0.93	2.02	.001
	Alive	140	0.74	0.62	0.93	
Total bilirubin	Exitus	8	0.35	0.21	0.50	.57
	Alive	139	0.4	0.29	0.59	
Direct bilirubin	Exitus	8	0.25	0.14	0.31	.321
	Alive	139	0.19	0.14	0.26	
AST	Exitus	8	30.75	16.50	51.25	.167
	Alive	140	21.6	15.02	28.00	

(*Continued*)

Table 1. Mann–Whitney *U* Test Results, According to Survival 1 (*Continued*)

		Number	Median	25th Percentile	75th Percentile	*P*
ALT	Exitus	8	19.75	15.25	22.50	.845
	Alive	140	19.5	14.00	29.60	
Ca	Exitus	8	8.24	7.66	8.59	.024
	Alive	137	8.72	8.39	9.15	
Na	Exitus	8	136	133.50	139.25	.12
	Alive	140	139	136.00	140.00	
K	Exitus	7	4.31	4.08	4.68	.042
	Alive	140	4.08	3.79	4.35	
Cl	Exitus	7	98	93.00	102.00	.382
	Alive	138	100.5	98.00	103.00	
Procalcitonin	Exitus	8	0.56	0.16	4.77	<.001
	Alive	106	0.06	0.03	0.11	
Ferritin	Exitus	6	311.5	166.93	731.50	.135
	Alive	103	136	57.90	355.00	
BNP	Exitus	7	1766	681.50	3089.00	.004
	Alive	127	42.5	17.99	104.70	
Trop	Exitus	8	0.13	0.03	0.95	<.001
	Alive	129	0	0.00	0.00	
Fibrin.	Exitus	6	600.6	407.50	756.50	.005
	Alive	123	346	290.00	440.00	
Dimer	Exitus	8	0.92	0.35	4.10	.004
	Alive	136	0.27	0.00	0.47	
CRP	Exitus	8	207.49	131.96	273.02	<.001
	Alive	130	10.79	3.09	35.02	
LDH	Exitus	7	279	227.00	466.00	.029
	Alive	135	197	164.00	248.00	
CK	Exitus	8	119.5	40.50	607.50	.385
	Alive	138	74.5	54.00	137.00	
CK-MB	Exitus	8	26	13.20	43.50	.235
	Alive	132	16	13.00	21.00	
Sedimentation	Exitus	1	4			.17
	Alive	61	16	7.00	35.50	
Ph	Exitus	8	7.42	7.33	7.46	.86
	Alive	79	7.4	7.36	7.43	
Lactate	Exitus	8	1.5	1.15	4.55	.752
	Alive	79	1.7	1.30	2.40	
HC03	Exitus	8	21.35	13.10	24.85	.032
	Alive	79	24.7	22.80	26.60	
INR	Exitus	7	1.14	1.03	1.21	.095
	Alive	132	1.04	1.00	1.11	
Total Pro.	Exitus	3	58	50.00		.261
	Alive	79	64.4	60.40	68.60	
Albumin	Exitus	4	30.9	26.45	42.25	.152
	Alive	84	38.6	35.05	42.37	

(*Continued*)

Table 1. Mann–Whitney *U* Test Results, According to Survival 1 (*Continued*)

		Number	Median	25th Percentile	75th Percentile	*P*
GGT	Exitus	2	16.5	16.00		.298
	Alive	75	27	15.00	50.00	
ALP	Exitus	2	57	41.00	16.00	.374
	Alive	73	68	58.50	80.00	
CURB 65	Exitus	8	1	1.00	2.75	<.001
	Alive	79	0	0.00	1.00	
PSI	Exitus	8	94	68.75	118.75	<.001
	Alive	79	52	41.00	65.00	
Mulbsta	Exitus	8	13	11.00	14.50	<.001
	Alive	79	5	5.00	9.00	
Inflam. Ind.	Exitus	8	1118.5	759.25	2009.25	.002
	Alive	142	469	274.75	852.75	

BCG, Bacillus Calmette-Guerin; WBC, white blood cell; HB, hemoglobin; PLT, platelet; NEU, neutrophil; LYM., lymphocyte; MCV, mean corpuscular volume; BNP, brain natriuretic peptide; Trop, troponin; fibrin, fibrinogen; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatinine kinase; Total Pro, total protein; PSI, pneumonia severity index; Inflam. Ind, inflammatory index.

additional treatment requirements and increased mortality. (For mortality, all had $P < .001$ and correlation coefficient was −0.382, −0.383, and −0.434 respectively. For treatment requirement, all had $P < .001$ and correlation coefficient was 0.352, 0.484, and 0.463 respectively.)

The correlation to mortality was more significant with a higher score in PSI and MuLBSTA compared to CURB 65. Pneumonia severity index scoring was also observed as more significant for correlation between treatment requirement and a higher score, compared to PSI and MuLBSTA. Thus, it can be assumed that PSI is overall superior at evaluation of treatment and mortality, followed by MulBSTA which is only superior in the prediction of mortality compared with CURB-65 (Tables 4, 5, and 6).

In linear multiple regression analysis, fever, additional treatment requirement, and total treatment duration have not been found statistically correlated with patients' age, smoking history, inflammatory index, WBC, CRP, procalcitonin, and D-dimer ($P = .894$, adjusted $R^2 = -0.297$, $P = .184$, adjusted $R^2 = 0.208$ and $P = .409$, adjusted $R^2 = 0.057$, respectively).

Regarding patients with pneumonia, a positive correlation between treatment duration and antihypertensive usage was observed in linear multiple regression analysis, as patients under calcium channel blocker treatment had a longer treatment duration ($P = .043$, correlation coefficient = 0.219 and $P = .003$, correlation coefficient = 0.314).

Additional treatment requirement for patients with pneumonia was found statistically relevant with age, inflammatory index, procalcitonin, D-dimer, lymphocyte count, and CRP levels, with the highest correlation being seen with CRP elevation ($P < .001$, $P = .026$, $P = .008$, $P = .034$, $P < .001$, $P = ,001$, respectively, and correlation coefficients were 0.348, 0.241, 0.310, 0.236, −0.416, and 0.351 respectively). Individual parameters were investigated with separate linear regression models for these results.

DISCUSSION

The success of PSI and MuLBSTA's scoring regarding mortality evaluation can be attributed to their individual parameters' role in patient prognoses, as seen in validation analysis. This observation suggests that patients with higher scores should be candidates for hospitalization/intensive care admission. The same cannot be stated for additional treatment requirements, as all 3 modalities were found relevant in the evaluation of treatment. These modalities have been supported in COVID-19 pneumonia evaluation by studies.[4,5] Superiority of PSI over CURB-65 had been reported in a case series by Satici et al.[6] which supports our results.[6] Same study also tried a modified PSI with CRP for evaluation, however, no significant differences were observed compared to non-modified PSI. New scoring system trials with new scoring systems have also been performed, such as Dong Ji and colleagues' study which utilizes age, comorbidities, lymphocyte, and LDH levels.[7] Regarding elevated levels of inflammatory markers, there was no correlation between these and additional treatment requirements, unlike stated in our second hypothesis. This pattern suggests the possibility that, while inflammatory markers certainly play a role in influencing the pneumonia modalities, due to the fact they are either not a part of them, such as in CURB-65, or partly play a role, in case of PSI, their role in the overall prediction of treatment results remain insignificant.

When all parameters affecting mortality are evaluated separately, elevated glucose and urea levels, presence of diabetes, renal failure, COPD, cerebrovascular events, and known malignancies are part of the PSI scoring system, while lymphocyte count, smoking history, and presence of hypertension are exclusive for MuLBSTA. For both scoring systems, age and radiological findings are common parameters. This

Table 2. Mann Whitney *U* Test Results, According to Survival-2

		N	Average	Avg. Order	*P*
Smoking	Exitus	3	0.67	44.83	.533
	Alive	74	0.3	38.76	
Hypertension	Exitus	8	1	120.5	<.001
	Alive	133	0.26	68.02	
Diabetes	Exitus	8	0.63	101.13	<.001
	Alive	130	0.14	67.55	
COPD	Exitus	8	0.13	77.19	.039
	Alive	131	0.02	69.56	
Asthma	Exitus	8	0.13	74.69	.401
	Alive	131	0.05	69.71	
Known malignancy	Exitus	8	0.13	77.63	<.001
	Alive	130	0	69	
Heart failure	Exitus	8	0	67	.573
	Alive	130	0.04	69.65	
Coronary heart disease	Exitus	8	0.25	81.25	.068
	Alive	130	0.07	68.78	
Renal disease	Exitus	8	0.13	77.13	.007
	Alive	130	0.01	69.03	
Cerebrovascular event history	Exitus	8	0.38	92.38	<.001
	Alive	130	0.02	68.09	
Antihypertensive	Exitus	8	0.38	90.31	.158
	Alive	143	0.17	75.2	
Antidiabetic	Exitus	8	0.25	89.38	.048
	Alive	143	0.06	75.25	
Anticoagulant and antiaggregant	Exitus	8	0.25	88.38	.091
	Alive	143	0.08	75.31	
Beta blocker	Exitus	8	0	70.5	.417
	Alive	143	0.08	76.31	
Ace inhibitors	Exitus	8	0.13	80.44	.494
	Alive	143	0.06	75.75	
Calcium channel blockers	Exitus	8	0.25	88.88	.068
	Alive	143	0.07	75.28	
Aspirin	Exitus	8	0.25	89.38	.048
	Alive	143	0.06	75.25	
Spironolactone	Exitus	8	0	75	.737
	Alive	143	0.01	76.06	
Nebulizing treatment	Exitus	8	0	74.5	.68
	Alive	143	0.02	76.08	
Thyroid hormone replacement	Exitus	8	0	74	.633
	Alive	143	0.03	76.11	
Immunosuppression	Exitus	8	0	74.5	.68
	Alive	143	0.02	76.08	
Insulin	Exitus	8	0	75	.737
	Alive	143	0.01	76.06	
Oral antidiabetic	Exitus	8	0.25	90.38	.02
	Alive	143	0.05	75.2	
Anticoagulant	Exitus	8	0	74.5	.68
	Alive	143	0.02	76.08	
Total treatment duration	Exitus	8	8.25	104.5	.008
	Alive	143	5.74	74.41	
Fever response day	Exitus	8	2	91.44	.204
	Alive	143	1.08	75.14	
Additional treatment requirement	Exitus	8	1.75	132.06	<.001
	Alive	143	0.22	72.86	

COPD, chronic obstructive pulmonary disease.

Table 3. Total Treatment Duration, Fever Response Day, and Additional Treatment Requirement Spearman Correlation with Other Parameters

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Age	Correlation coefficient	**0.252****	0.072	**0.357****
	Sig. (2-tailed)	.002	.377	<.001
	N	151	151	151
Smoking	Correlation coefficient	0.125	0.003	0.096
	Sig. (2-tailed)	.279	.978	.408
	N	77	77	77
Hypertension	Correlation coefficient	0.129	0.028	**0.216***
	Sig. (2-tailed)	.129	.741	.010
	N	141	141	141
Diabetes	Correlation coefficient	0.130	0.107	0.090
	Sig. (2-tailed)	.129	.210	.292
	N	138	138	138
COPD	Correlation coefficient	0.055	−0.003	0.063
	Sig. (2-tailed)	.520	.971	.463
	N	139	139	139
Asthma	Correlation coefficient	0.041	0.057	0.049
	Sig. (2-tailed)	.634	.506	.568
	N	139	139	139
Known malignancy	Correlation coefficient	0.171*	−0.054	0.189*
	Sig. (2-tailed)	.045	.526	.026
	N	138	138	138
Heart failure	Correlation coefficient	−0.068	−0.029	0.011
	Sig. (2-tailed)	.431	.736	.894
	N	138	138	138
Coronary heart disease	Correlation coefficient	0.144	0.063	**0.147**
	Sig. (2-tailed)	.093	.464	.085
	N	138	138	138
Renal disease	Correlation coefficient	−0.055	−0.077	0.105
	Sig. (2-tailed)	.522	.368	.220
	N	138	138	138
Cerebrovascular event history	Correlation coefficient	0.023	-0.040	0.089
	Sig. (2-tailed)	.790	.643	.298
	N	138	138	138
Antihypertensive	Correlation coefficient	0.237**	-0.044	0.190*
	Sig. (2-tailed)	.003	.592	.019
	N	151	151	151

(*Continued*)

Table 3. Total Treatment Duration, Fever Response Day, and Additional Treatment Requirement Spearman Correlation with Other Parameters (*Continued*)

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Antidiabetic	Correlation coefficient	0.104	0.029	0.079
	Sig. (2-tailed)	.203	.728	.335
	N	151	151	151
Anticoagulant and antiaggregant	Correlation coefficient	0.099	0.026	0.116
	Sig. (2-tailed)	.228	.753	.157
	N	151	151	151
Beta blocker	Correlation coefficient	−0.013	−0.002	−0.061
	Sig. (2-tailed)	.877	.979	.460
	N	151	151	151
Ace inhibitors	Correlation coefficient	0.081	0.063	0.168*
	Sig. (2-tailed)	.326	.439	.039
	N	151	151	151
Calcium channel blockers	Correlation coefficient	0.285**	-0.083	0.187*
	Sig. (2-tailed)	<.001	.313	.021
	N	151	151	151
Aspirin	Correlation coefficient	0.130	0.060	**0.149**
	Sig. (2-tailed)	.113	.461	.068
	N	151	151	151
SpiroNolactone	Correlation coefficient	0.093	0.068	0.105
	Sig. (2-tailed)	.255	.405	.201
	N	151	151	151
Nebulizing treatment	Correlation coefficient	−0.064	0.034	−0.066
	Sig. (2-tailed)	.434	.675	.420
	N	151	151	151
Thyroid hormone replacement	Correlation coefficient	0.011	−0.013	−0.077
	Sig. (2-tailed)	.891	.875	.349
	N	151	151	151
Immunosuppression	Correlation coefficient	−0.064	-0.091	−0.066
	Sig. (2-tailed)	.434	.267	.420
	N	151	151	151
Insulin	Correlation coefficient	−0.052	0.032	−0.054
	Sig. (2-tailed)	.525	.696	.511
	N	151	151	151
Oral antidiabetic	Correlation coefficient	0.139	0.016	0.113
	Sig. (2-tailed)	.088	.847	.168
	N	151	151	151

(*Continued*)

Table 3. Total Treatment Duration, Fever Response Day, and Additional Treatment Requirement Spearman Correlation with Other Parameters (*Continued*)

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Anticoagulant	Correlation coefficient	−0.064	−0.091	−0.066
	Sig. (2-tailed)	.434	.267	.420
	N	151	151	151
WBC	Correlation coefficient	0.066	**−0.205***	0.023
	Sig. (2-tailed)	.421	.012	.782
	N	150	150	150
LYM#	Correlation coefficient	**-0.174***	**-0.216****	-0.367**
	Sig. (2-tailed)	.033	.008	<.001
	N	150	150	150
Inflam. Ind.	Correlation coefficient	0.072	-0.011	0.200*
	Sig. (2-tailed)	.382	.897	.014
	N	150	150	150
Procalcitonin	Correlation coefficient	**0.231***	0.117	0.371**
	Sig. (2-tailed)	.014	.216	<.001
	N	114	114	114
Dimer	Correlation coefficient	0.108	−0.051	0.249**
	Sig. (2-tailed)	.197	.544	.003
	N	144	144	144
CRP	Correlation coefficient	.286**	0.068	.390**
	Sig. (2-tailed)	<.001	.428	<.001
	N	138	138	138

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
COPD, chronic obstructive pulmonary disease; WBC, white blood cell; LYM, lymphocyte; Inflam. Ind, inflammatory index; CRP, C-reactive protein.

justifies an evaluation protocol that combines both systems. On the other hand, increased calcium, potassium, BNP, troponin, D-dimer, CRP, HCO3, and LDH levels also play a role in mortality and thus point to the necessity of a different algorithm that must include them.

A machine-learning algorithm had been created by Yan Li et al.[8] which uses similar parameters for mortality prediction. A longer duration of treatment required for patients with antihypertension drug usage was an expected finding, as the presence of hypertension is an often-discussed risk factor for COVID-19 and with reports stating a more severe disease presentation seen in these patients.

Evaluation of parameters affecting additional treatment requirements was planned with the aim of targeting patients who may benefit from an aggressive approach instead of a gradually increasing treatment modality. According to our results, increased inflammatory markers in elderly patients should keep healthcare alarmed for a potential clinical deterioration. Fever appears to be an independent symptom, and thus, unless other findings support it, it should not be the sole marker for treatment response or a need for a revision of the treatment regimen. As stated in Işık's study, fever and other clinical responses may be limited in the elderly population, further supporting the need for a more detailed investigation regimen that relies on available laboratory parameters.[9]

It is our expectation that an evaluation system and/or a pneumonia scoring methodology that includes discussed comorbidities, laboratory results, and medical background history may provide adequate information regarding how and where a patient should be treated. Similar approaches in the evaluation of patients in emergency and outpatient settings had been reported with success, with 1 study relying on PSI scoring alone.[10] Our study has found similar results with the described study, as PSI was found to be reliable in the evaluation of COVID-19 pneumonia. Its superiority over CURB-65, as discussed earlier, is assumed to be caused by its multiparameter evaluation, compared to CURB-65's 5-parameter scoring system. A direct comparison between PSI and MuLBSTA, however, has not been discussed in the literature

Table 4. Spearman Correlation Analysis Results Between Total Treatment Duration, Fever Response Day, Additional Treatment Requirement, and Other Parameters in Patients with Pneumonia

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Age	Correlation coefficient	0.162	−0.089	0.348**
	Sig. (2-tailed)	.136	.416	<.001
	N	86	86	86
Smoking	Correlation coefficient	0.241	0.116	0.185
	Sig. (2-tailed)	.107	.442	.217
	N	46	46	46
Hypertension	Correlation coefficient	0.061	-0.042	0.173
	Sig. (2-tailed)	.588	.710	.123
	N	81	81	81
Diabetes	Correlation coefficient	0.056	0.097	0.002
	Sig. (2-tailed)	.627	.394	.989
	N	79	79	79
COPD	Correlation coefficient	0.061	0.002	0.075
	Sig. (2-tailed)	.591	.986	.513
	N	79	79	79
Asthma	Correlation coefficient	0.047	0.125	0.062
	Sig. (2-tailed)	.681	.269	.583
	N	80	80	80
Known malignancy	Correlation coefficient	0.161	−0.089	0.183
	Sig. (2-tailed)	.157	.433	.107
	N	79	79	79
Heart Failure	Correlation coefficient	−0.132	−0.090	-0.059
	Sig. (2-tailed)	.247	.431	.604
	N	79	79	79
Coronary Heart Disease	Correlation coefficient	0.160	0.005	0.156
	Sig. (2-tailed)	.160	.964	.171
	N	79	79	79
Renal Disease	Correlation coefficient	−0.075	−0.089	0.183
	Sig. (2-tailed)	.513	.433	.107
	N	79	79	79
Cerebrovascular event history	Correlation coefficient	0.005	−0.069	0.061
	Sig. (2-tailed)	.963	.544	.596
	N	79	79	79

(*Continued*)

Table 4. Spearman Correlation Analysis Results Between Total Treatment Duration, Fever Response Day, Additional Treatment Requirement, and Other Parameters in Patients with Pneumonia (*Continued*)

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Antihypertensive	Correlation coefficient	.219*	−0.126	0.168
	Sig. (2-tailed)	.043	.247	.121
	N	86	86	86
Antidiabetic	Correlation coefficient	0.044	0.007	0.037
	Sig. (2-tailed)	.685	.949	.738
	N	86	86	86
Anticoagulant and antiaggregant	Correlation coefficient	0.046	−0.072	0.068
	Sig. (2-tailed)	.677	.508	.534
	N	86	86	86
Beta Blocker	Correlation coefficient	−0.072	−0.080	−0.121
	Sig. (2-tailed)	.509	.467	.269
	N	86	86	86
Ace inhibitors	Correlation coefficient	0.046	-0.016	0.158
	Sig. (2-tailed)	.675	.887	.146
	N	86	86	86
Calcium channel blockers	Correlation coefficient	0.314**	-0.120	0.188
	Sig. (2-tailed)	.003	.272	.084
	N	86	86	86
Aspirin	Correlation coefficient	0.100	-0.020	0.125
	Sig. (2-tailed)	.362	.855	.253
	N	86	86	86
Spironolactone	Correlation coefficient	0.063	0.053	0.076
	Sig. (2-tailed)	.563	.629	.486
	N	86	86	86
Nebulizing treatment	Correlation coefficient	−0.071	**0.188**	−0.072
	Sig. (2-tailed)	.516	.083	.508
	N	86	86	86
Thyroid Hormone Replacement	Correlation coefficient	0.014	0.033	-0.103
	Sig. (2-tailed)	.895	.760	.346
	N	86	86	86
Immunosuppression	Correlation coefficient	−0.101	−0.120	−0.103
	Sig. (2-tailed)	.354	.272	.346
	N	86	86	86

(*Continued*)

Table 4. Spearman Correlation Analysis Results Between Total Treatment Duration, Fever Response Day, Additional Treatment Requirement, and Other Parameters in Patients with Pneumonia (*Continued*)

		Total Treatment Duration	Fever Response Day	Additional Treatment Requirement
Insulin	Correlation coefficient	−0.071	0.089	−0.072
	Sig. (2-tailed)	.516	.414	.508
	N	86	86	86
Oral Antidiabetic	Correlation coefficient	0.073	−0.026	0.065
	Sig. (2-tailed)	.504	.815	.551
	N	86	86	86
Anticoagulant	Correlation coefficient	−0.101	−0.120	−0.103
	Sig. (2-tailed)	.354	.272	.346
	N	86	86	86
WBC	Correlation coefficient	0.152	−0.156	0.105
	Sig. (2-tailed)	.166	.153	.338
	N	85	85	85
LYM#	Correlation coefficient	−0.111	−0.083	−0.416**
	Sig. (2-tailed)	.311	.452	<.001
	N	85	85	85
Inflam. Ind.	Correlation coefficient	0.046	−0.068	0.241*
	Sig. (2-tailed)	.675	.536	.026
	N	85	85	85
Procalcitonin	Correlation coefficient	0.093	-0.073	0.310**
	Sig. (2-tailed)	.441	.543	.008
	N	71	71	71
Dimer	Correlation coefficient	0.013	−0.203	0.236*
	Sig. (2-tailed)	0.911	0.070	0.034
	N	81	81	81
CRP	Correlation coefficient	0.176	−0.123	0.351**
	Sig. (2-tailed)	.109	.265	.001
	N	84	84	84

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
COPD, chronic obstructive pulmonary disease; WBC, white blood cell; LYM, lymphocyte; Inflam. Ind, inflammatory index; CRP, C-reactive protein.

for COVID-19 pneumonia as of writing this article, and unlike in the case of CURB-65, our study did not reveal a significant superiority of PSI over MuLBSTA.

This might be caused by the specific parameters of MuLBSTA, which might increase its overall power in terms of predicting viral pneumonia over PSI, despite the parameter count of PSI. Separate parameters also have been evaluated for mortality, with most studies focusing on D-dimer levels and supporting an increased mortality in the presence of elevated D-dimer.[11] Neutrophil to lymphocyte ratio, which naturally includes their absolute counts, has been proven to be correlated to mortality, as seen in Liu et al's[12] study. These studies correlate with our results, as described earlier, inflammatory parameters which include D-dimer and absolute WBC count were found to be relevant in the evaluation of patient mortality. Their role, however, remains limited in the prediction of patients' future treatment requirements. Combined, these findings suggest that while these blood testing modalities are required for initial evaluation and hospital admission,

Table 5. Spearman Correlation Analysis Results between Pneumonia Localization, Infiltration Pattern, Additional Treatment Requirement and Mortality

		Localization	Infiltration Pattern	Fever Response Day	Additional Treatment Requirement	Result (Mortality)
Localization (unilateral or bilateral)	Correlation coefficient	1.000	−0.598**	−0.058	**−0.099**	0.135
	Sig. (2-tailed)		<.001	.597	.367	.215
	N	86	86	86	86	86
Infiltration pattern	Correlation coefficient	−0.598**	1.000	0.110	**0.300****	−0.180
	Sig. (2-tailed)	<.001		.311	.005	.097
	N	86	86	86	86	86
Fever response day	Correlation coefficient	−0.058	0.110	1.000	0.189	−0.064
	Sig. (2-tailed)	.597	.311		.081	.558
	N	86	86	86	86	86
Additional treatment requirement	Correlation coefficient	**−0.099**	**0.300****	0.189	1.000	−0.437**
	Sig. (2-tailed)	.367	.005	.081		<.001
	N	86	86	86	86	86
Result (mortality)	Correlation coefficient	0.135	−0.180	−0.064	**−0.437****	1.000
	Sig. (2-tailed)	.215	.097	.558	<.001	
	N	86	86	86	86	86

**Correlation is significant at the 0.01 level (2-tailed).

Table 6. Spearman Correlation Analysis Results Between CURB 65, PSI, and MuLBSTA with Mortality and Additional Treatment Requirement

		Additional Treatment Requirement	Result (Mortality)
CURB 65	Correlation coefficient	**0.463****	**−0.434****
	Sig. (2-tailed)	<.001	<.001
	N	86	86
PSI	Correlation coefficient	0.352**	−0.382**
	Sig. (2-tailed)	<0.001	<0.001
	N	86	86
MuLBSTA	Correlation coefficient	0.484**	−0.383**
	Sig. (2-tailed)	<0.001	<0.001
	N	86	86

**Correlation is significant at the 0.01 level (2-tailed).
PSI, pneumonia severity index.

additional parameters are required for a comprehensive investigation if patients' prognoses are of interest.

To illustrate, we may assume a sample model that evaluates patients under 3 major categories. After an initial vital sign monitorization and physical examination, the medical background should be checked which involves questioning the presence of hypertension, diabetes, renal failure, COPD, cerebrovascular events, known malignancies, and smoking history. Blood sampling should, at a minimum, include routine whole blood work-up, cardiac markers, renal function testing, and inflammatory markers (consisting of CRP, D-dimer, and LDH).

The addition of radiological findings would complete the evaluation "triad," and barring other prominent pathologies a patient may have, these 3 pathways would offer a comprehensive evaluation of the patient and prognosis of COVID-19 infection. If pneumonia is seen, this system will also be adequate in suggesting where the patient should be observed or if the outpatient setting was suitable. A modified version of this investigational method may be used during patient follow-up or when clinical deterioration is seen during hospitalization.

Having a small sample size and being a single-center study are the main limitations of this study. These important limitations were mainly caused by the lack of approval given to multicenter studies when the first draft of this and other similar studies had been created. Considering similar studies have been published in Turkey recently, a new multicenter initiative with more patient participation may overcome these limitations.[13] In further studies, evaluation of patients in intensive care units and at outpatient clinics may alter pneumonia scorings impact on mortality, as this study was limited to patients admitted to wards.

Missing data, with the smoking history being the most prominent, was another major limiting factor. Most of these missing data were seen in the evaluation of patients in a mixed ward setting, where doctors from all specialties were assigned. A coordinated patient follow-up system agreed upon by all departments was later utilized by the hospital administration. Currently, most wards and intensive care units in our hospital possess a similar patient record system, which is based on a modified version of the pulmonary medicine ward patient record.

Treatment modalities were limited in this study, as its duration was from the outbreak of COVID-19 to the beginning of June. The current treatment regimen varies from the reported one, as of now, a regimen of steroids is being suggested, depending on the patient's condition, with the addition of remdesivir in select patients.

CONCLUSION

Due to the increased number of patients globally, a standardized approach for COVID-19 pneumonia and COVID-19 infection is required. Such methodological approach would not only inform healthcare providers about prognoses of patients and whenever hospital admission is required but also it will lessen the burden on healthcare systems, as follow-up testing may be limited to parameters that are proven to be cost-effective.

A new scoring system for pneumonia with the discussed parameters above and a universal follow-up algorithm that dictates where and when to perform certain tests will alleviate many problems encountered during COVID-19 pandemic.

Ethics Committee Approval: This study was approved by Ethics committee of Faculty of Health Sciences, (Approval No: 90/02, 22.06.2020).

Informed Consent: Both verbal and written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.K.; Design – B.K.; Supervision – İ.H.E., M.B.Y., S.A.D.; Data Collection: A.K.E, Analysis and Literature Review – K.E.; Writing – K.E., A.K.E.; Critical Review – B.K., İ.H.K., M.B.Y., S.A.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 322-330 DOI: 10.5152/TurkThoracJ.2022.21207

Original Article

Types of Fundus Involvement in Intraocular Tuberculosis

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Cite this article as: Kaya M, Simsek GO, Ucan ES, et al. Types of fundus involvement in intraocular tuberculosis. *Turk Thorac J.* 2022;23(5):322-330.

Abstract

OBJECTIVE: To evaluate the patients who were treated for intraocular tuberculosis retrospectively and present our findings and share our experience.

MATERIAL AND METHODS: This study was a descriptive, cross-sectional, retrospective study. Patients who were followed up with the diagnosis of intraocular tuberculosis in the Ophthalmology and Pulmonary Medicine Departments of Dokuz Eylul University Faculty of Medicine in the last 15 years and received anti-tuberculosis therapy were included.

RESULTS: A total of 16 eyes of 10 patients with a diagnosis of intraocular tuberculosis uveitis who were treated with anti-tuberculosis therapy were included in this study. The mean age was 48.1 [14.6] years (mean [standard deviation]). Four were [40%] male and 6 [60%] were female. Patients with tuberculosis uveitis had bilateral involvement (7 of 10 patients [70%]). Intraocular tuberculosis was presented in 7 eyes of 4 patients with serpiginous like choroiditis, 2 eyes of 2 patients with choroidal tuberculomas, 4 eyes of 2 patients with choroidal tubercles (miliary tuberculosis), and 3 eyes of 2 patients with intermediate uveitis. The mean duration from admission to treatment was 18.1 ± 17.4 days (range: 6-56 days). All patients in this study received a 4-drug regimen anti-tuberculosis therapy, Paradoxical reaction occurred in 30% of the patients. Eight patients had systemic steroid therapy and 4 had also topical steroid therapy. The mean length of follow-up was 14.7 months (standard deviation = 15.1, range: 6-48 months). Reactivation of intraocular tuberculosis was not observed in any patients.

CONCLUSION: High level of suspicion is a must for diagnosing intraocular tuberculosis. A complete ophthalmic examination can be performed in patients with suspected or proven tuberculosis. Early diagnosis and prompt treatment of intraocular tuberculosis can prevent serious complications and loss of vision.

KEYWORDS: Diagnosis, Intraocular Tuberculosis, Uveitis, Treatment
Received: *September 25, 2021* ***Accepted:*** *April 27, 2022* ***Available Online:*** *June 15, 2022*

INTRODUCTION

Tuberculosis (TB) still represents the leading infection globally; around 10.0 million people (range: 8.9-11 million) are infected with TB worldwide and its annual incidence is around 130 per 100 000 according to the latest report of the World Health Organization (WHO).[1] Turkey, is a member country of WHO, has a high TB incidence of 28 patients per 100 000 people.[2] However, the Tuberculosis Department of the Turkish Ministry of Health General Directorate of Public Health reported that the TB incidence in Turkey in 2018 was 14.1 per 100 000 people. Turkey is among the countries that have medium TB incidences.[3] Although pulmonary TB is the most common clinical type, TB infections can also be encountered in the extrapulmonary organs such as the pleura, lymph nodes and bones. Ocular TB is less frequently observed and its diagnosis and treatment are fraught with difficulties due to a wide variety of manifestations.[4,5] The estimated prevalence of intraocular TB ranges from 0.317% to 0.6% among the individuals with uveitis.[6,7] A few studies reported that the prevalence of intraocular TB ranges from 0.3% to 28.2% in uveitis patients who were from various countries.[8-10]

Uveitis can occur due to a broad spectrum of infectious and non-infectious causes. A comprehensive full systemic investigation and multimodal fundus imaging are often necessary to reach an accurate clinical conclusion and make the differential diagnosis in cases where the ocular findings are not specific enough. Intraocular TB is an uncommon extrapulmonary manifestation of TB and it presents with many forms of uveitis, including granulomatous anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis. Heterogeneous clinical manifestations of ocular TB and its subtle clinical features can create a challenge to form a diagnosis.[11] The collaborative ocular TB study (COTS) consensus group showed significantly higher hazard ratios of treatment failure associated with phenotypes of anterior uveitis, intermediate uveitis, and panuveitis compared to subtypes of tubercular choroiditis including serpiginous-like choroiditis, tuberculoma, and multifocal or unifocal choroiditis.

Early diagnosis and treatment of intraocular TB are very critical for achieving the optimal control of disease, and preventing or even slowing down the progression of the retinal damage and thereby lessening functional impairment. Intraocular TB should be handled and treated using a multidisciplinary approach. This case series aimed to evaluate a group of patients with intraocular TB and reflect the broad spectrum of disease presentation types.

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MATERIAL AND METHODS

A retrospective evaluation of patient data at the Department of Ophthalmology and Chest Diseases was performed. The medical files of all patients from January 2006 to January 2021 who received the diagnosis of intraocular TB and were treated with a 4-drug anti-tuberculosis therapy (ATT) were retrospectively reviewed. The study followed the tenets of the Declaration of Helsinki and received the approval of the institution's ethics committee (2021/20-04).

The diagnosis of presumed ocular TB disease was based on the proposed diagnostic criteria for ocular TB used in COTS-1.[12,13] The diagnostic criteria for TB uveitis used in COTS-1 are as follows, with patients having to satisfy both criteria 1 and 2, and at least 1 criterion from 3 or 4 (Table 1):

1. *Clinical signs that suggest TB uveitis includes the following:*
    a. Anterior uveitis (granulomatous or nongranulomatous), iris nodules, and ciliary body granuloma.
    b. Intermediate uveitis (granulomatous or nongranulomatous with exudates in the pars plana, with or without snowballs).
    c. Posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess, and serpiginous-like choroiditis.
    d. Retinitis, retinal vasculitis (RV), neuroretinitis, optic neuritis, endogenous endophthalmitis, panophthalmitis, and scleritis.
2. *Exclusion of other uveitic entities, where relevant, based on the clinical manifestations of the disease and regional epidemiologic findings.*
3. *Investigations documenting the mycobacteria or its genome:*
    a. Demonstration of acid-fast bacilli by microscopy or the culture of *Mycobacterium tuberculosis* from the ocular fluids.
    b. Positive polymerase chain reaction obtained from the ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome.
    c. Evidence of confirmed active extrapulmonary TB histopathological examination or culture of a tissue sample from the affected tissue.
4. *Collaborative investigations:*
    a. PositiveMantoux test result (must be accompanied by the information regarding the antigen and amount of tuberculin injected, along with institutional practices in interpreting the test).
    b. Interferon γ release assay, such as QuantiFERON TB Gold (must be accompanied by the information regarding the institutional practices in interpreting the test).
    c. Evidence of healed or active TB on chest radiography (must be accompanied by information regarding the practices of the radiologists on the clinical features that are considered as evidence in this context).

When the suspicion of TB arose in any patient with uveitis, full systemic screening and laboratory blood tests (such as complete blood count, electrolytes, liver and kidney function tests, angiotensin-converting enzyme, antinuclear antibodies, infectious diseases like toxoplasma, brucella, syphilis, human immunodeficiency virus (HIV)) were performed to identify any possible cause of uveitis besides intraocular TB. Patients' files were reviewed for the symptoms, medical history, tuberculin skin test (TST), QuantiFERON-TB Gold, chest x-ray or chest computed tomography scan, sputum, or bronchial sampling results. A complete ophthalmological examination, includ- ing slit-lamp biomicroscopy and dilated indirect fundoscopy, was performed on all patients. At the follow-up visits, color fundus photography, fundus fluorescein angiography, optical coherence tomography, and visual field tests were performed, where deemed appropriate (Figures 1-3). The Standardization of Uveitis Nomenclature system was used to classify and grade the type of uveitis.[14] Patients with extraocular TB, ocular inflammation due to other causes (infectious and noninfectious) and those who did not attend the follow-up visits were excluded from the study.

The files of 12 patients were retrospectively evaluated. One patient with conjunctival TB and 1 patient with scleritis were excluded. Patients who fulfilled the diagnostic criteria and received a 4-drug regimen of anti-TB treatment with directly observed treatment strategy were only enrolled for this study if they fulfilled the following inclusion criteria: (1) availability of the patient's medical history together with the detailed ophthalmic examination, (2) sufficient laboratory investigations performed to exclude other causes, and (3) a minimum follow-up 6 months after the treatment. All patients had been examined by one of the uveitis and retina specialists (AOS and MK), and clinical parameters were recorded according to the diagnostic criteria for TB uveitis used in COTS-1. A chest physician (ESU) evaluated the patients for any signs of extrapulmonary and pulmonary TB.

Anti-tuberculosis therapy was defined as a multi-drug therapy consisting of a 4-drug regimen including isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by 4 additional months of rifampicin and isoniazid, with a total therapy duration of at least 6 months, based on the clinical response. The treatment regimen in terms of the decision to

MAIN POINTS

- Diagnosis of ocular tuberculosis is more difficult due to its various presentations and requires experience.
- Tissue sampling or imaging in ocular tuberculosis (TB) is not possible in the differential diagnosis of TB.
- Tuberculosis should always be considered as a differential diagnosis in patients presenting with vague symptoms.
- To diagnose ocular TB, it is primarily to suspect the disease and evaluate the findings in line with this suspicion.
- In cases with ocular findings of chronic granulomatous inflammation, TB should be considered a differential diagnosis and investigated accordingly.
- Vision loss can be prevented by early diagnosis of ocular TB and correct treatment.
- The ocular examination should be considered in patients with suspected or proven TB.

Table 1. The Proposed Classification of Intraocular Tuberculosis (IOTB) (10)

Clinical Diagnostic Group	Case Definition Criteria
Confirmed IOTB (both 1 and 2)	1. At least 1 clinical sign suggestive of IOTB. 2. Microbiological confirmation of *Mycobacterium tuberculosis* from ocular fluids/tissues.
Probable IOTB (1, 2, and 3 together)	1. At least 1 clinical sign suggestive of IOTB (and other etiologies excluded). 2. Evidence of chest x-ray consistent with tuberculosis (TB) infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites. 3. At least one of the following: a. Documented exposure to TB. b. Immunological evidence TB infection.
Possible IOTB (1, 2, and 3 together, or 1 and 4)	1. At least 1 clinical sign suggestive of IOTB (and other etiologies excluded). 2. Chest x-ray not consistent with TB infection and no clinical evidence of extraocular TB. 3. At least one of the following: a. Documented exposure to TB. b. Immunological evidence TB infection. 4. Evidence of chest x-ray consistent with TB infection or clinical evidence of extraocular TB but none of the characteristics given in 3.

initiate ATT or immunosuppression treatment, and the duration of the treatments were directed by the attending physicians in collaboration with the same Pulmonary Medicine specialist in accordance with the individual institutional protocols. The route of drug delivery for corticosteroids and use of corticosteroid-sparing immunosuppressive agents was determined by the ophthalmologist (uveitis specialist) on a case-by-case basis, with the consideration of clinical phenotypes, the severity of intraocular TB, patients' comorbidities, and treatment response. Patients continued their treatment with corticosteroids and other immunosuppressive therapies for uveitis during ATT. Ocular topical medications were also administered if deemed necessary, according to the anatomic location of the inflammation. Additional ocular therapies, including intraocular pressure-lowering medications, pars plana vitrectomy, argon laser photocoagulation over ischemic retina in association with neovascularization, and photodynamic therapy for the vascularized granuloma were performed when needed.

Demographic features and clinical findings including posterior segment manifestations, follow-up time, anatomic region of uveitis, treatment, response to treatment, duration of the treatment, several recurrences of inflammation, ocular complications, and complete ophthalmological examination, including best-corrected visual acuity (BCVA) at baseline and final visit, slit-lamp biomicroscopy and indirect ophthalmoscopy were taken into account. Recurrence of inflammation was described as any intraocular inflammation occurring in the same eye 6 or more months after the uveitis was treated.

Statistical Analysis

All statistical analyses were performed by using Statistical Package for the Social Sciences version 24.0 (IBM, Armonk, NY, USA). Values were recorded as n (%) and mean ± standard deviation (SD). Best-corrected visual acuity was recorded using Snellen charts and converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis, using conventional conversion tables. A P value <.05 was considered statistically significant.

RESULTS

A total of 16 eyes belonging to 10 patients with the diagnosis of intraocular TB uveitis who were treated with ATT were included in this study. The mean age was 48.1 [14.6] years (mean [SD]. Four patients were [40%] male and 6 of them were [60%] female. No contact of previous TB was present in the study group. Two patients were diagnosed with miliary TB, and 4 patients had radiological pulmonary findings compatible with the sequela of pulmonary TB. Furthermore,

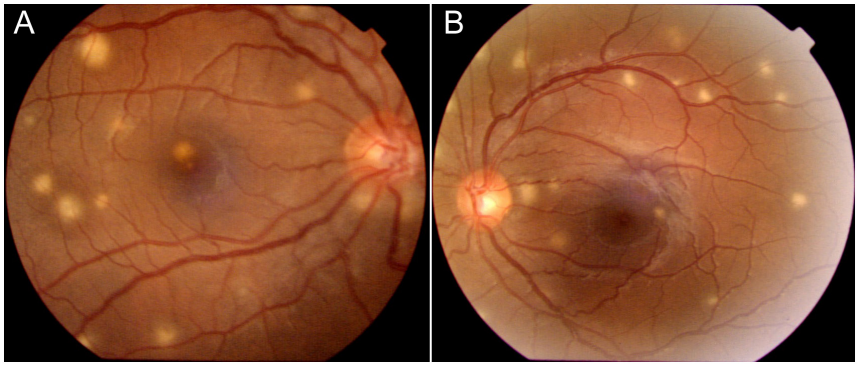

Figure 1. Fundus photograph of the right (A) and left (B) eyes of a 23-year-old male patient shows in the posterior fundus multiple tubercles (miliary choroidal lesions) (14).

Table 2. Pulmonary Features and Clinical Diagnostic Groups of Patients

Patient No.	Age	Ocular Findings	Pulmonary Findings	Exposure to TB	PPD	Quantiferon	Clinical Diagnostic Group (COTS-1)
1.	49	Miliary tuberculosis	Common micronodular densities	None	None	Positive	Probable IOTB
2.	23	Miliary tuberculosıs	Common micronodular densities	None	None	Positive	Probable IOTB
3.	29	Choroidal granuloma	No pulmonary radiological findings	None	21 mm	None	Possible IOTB
4.	43	Choroidal granuloma	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
5.	57	Serpiginous-like choroiditis	No pulmonary radiological findings	None	None	Positive	Possible IOTB
6.	37	Serpiginous-like choroiditis	No pulmonary radiological findings	None	20 mm	None	Possible IOTB
7.	66	Serpiginous-like choroiditis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
8.	55	Serpiginous choroiditis	No pulmonary radiological findings	None	None	Positive	Possible IOTB
9.	60	Intermediate uveitis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB
10.	62	Intermediate uveitis	Sequelae pulmonary TB findings	None	None	Positive	Probable IOTB

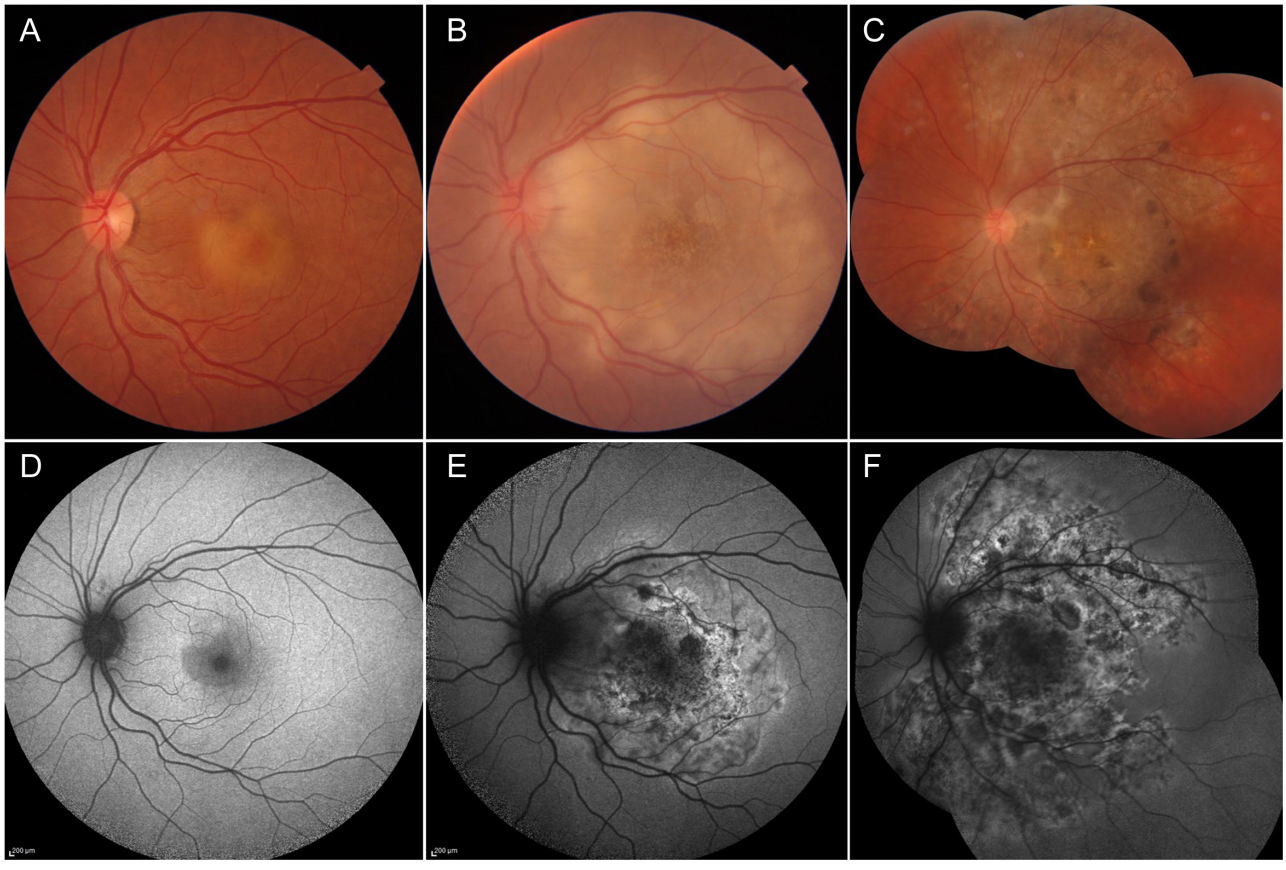

Figure 2. Fundus photograph (A-C; top line) and fundus autofluorescence (FAF; D-F; bottom line) of the left eye showing tubercular granuloma at the macular area. One month later, treatment delay due to the pandemic of COVID-19, tubercular granuloma exhibited an enlargement. (Please pay attention to the change seen in A-D to B-E). B and E images before the anti-tuberculosis therapy (ATT) (baseline), and tubercular granuloma FAF image (E) shows hyperautofluorescent lesion with surrounding blurred hypoautofluorescence ring in the patient (active choroidal granuloma). C and F images show inactive choroidal granuloma after 4-drug regimen of ATT.

Table 3. Demographics and Clinical Features of Patients with TB Uveitis

Patient No.	Age, years	Gender	Presentations of Uveitis	Visual Acuity		Time for Diagnosis (days)	Paradoxical Reaction	Systemic Steroid	Anterior Uveitis		Intermediate Uveitis	Panuveitis	Retinal vasculitis/ Serpiginous like choroiditis	Choroidal Granuloma	Retinal or vitreous hemorrhages	Neuroretinitis/ optic retinitis	Choroidal tubercules
				Baseline Right/Left (logMAR)	Final Right/Left (logMAR)				Granulomatous	Nongranulomatous							
1.	49	Male	Miliary tuberculosis	0.22/0.10	0.00/0.10	12	-	-	-	-	-	-	-	-	-	-	+
2.	23	Male	Miliary tuberculosis	0.00/0.00	0.00/0.00	14	-	-	-	-	-	-	-	-	-	-	+
3.	29	Female	Choroidal granuloma	1.30/-	1.00/-	23	-	+	-	-	-	-	-	+	+	-	-
4.	43	Female	Choroidal granuloma	0.40 /-	3.10 /-	22	+	+	-	+	-	+	+	+	-	-	-
5.	57	Female	Serpiginous-like choroiditis	-/ 0.05	-/ 0.40	32	-	+	-	-	-	-	+	-	-	-	-
6.	37	Female	Serpiginous-like choroiditis	0.00/0.00	0.00/0.00	29	+	+	-	-	-	-	+	-	-	-	-
7.	66	Female	Serpiginous-like choroiditis	0.10/0.90	0.00/0.22	24	+	+	-	+	-	+	+	-	-	-	-
8.	55	Male	Serpiginous-like choroiditis	0.10/0.10	0.15/0.15	26	-	+	-	-	-	-	+	-	-	-	-
9.	60	Male	Intermediate uveitis	0.22/0.40	0.10/0.10	25	-	+	-	+	+	-	-	-	-	-	-
10.	62	Female	Intermediate uveitis	0.40/-	0.05/-	31	-		-	+	+	-	-	-	-	-	-

the radiological findings of active TB were observed in only 20% of the patients. The QuantiFERON-TB Gold test of 8 patients was positive, and a positive TST (**>15 mm**) was seen in 2 patients where QuantiFERON-TB Gold test could not be obtained. Pulmonary features and clinical diagnostic groups of patients are summarized in Table 2**.**

Seven patients (70%) had bilateral involvement. The mean follow-up period was 14.7 months (SD = 15.1, range: 6-48 months). According to posterior segment manifestations, bilateral serpiginous-like choroiditis (4 out of 10 [40%]) was the most common type of fundus involvement. Two patients were presented with choroidal tuberculomas, 2 presented with multiple choroidal tubercles (miliary TB), and 2 presented with intermediate uveitis. Demographics and clinical features of the patients are described in Table 3.

No microbiologically-confirmed intraocular TB was noted in the present study. Thereby, 60% were classified as probable OTB, and 40% were as possible cases. The mean duration from admission to ATT was 23.8 ± 6.6 days (range: 12-32 days). The time between the onset of symptoms and the duration of diagnosis is shown in Table 3.

All patients received the 4-drug regimen ATT in this study. In most patients, no significant side effects were observed, except for minor side effects such as loss of appetite, nausea and vomiting. Hepatotoxicity due to pyrazinamide only developed in 1 patient, so the treatment was continued with moxifloxacin instead of pyrazinamide. Except for 1 patient, all patients completed the 6-month treatment without any problems. The patient with hepatotoxicity was treated for 9 months in a pyrazinamide-free regimen. Paradoxical reaction occurred in 30% of the patients. Corticosteroids were used to treat 8 patients (80%); a total of 4 eyes of 2 patients (25%) with topical and 8 patients (80%) with systemic corticosteroids. All patients taking corticosteroids experienced the resolution of intraocular inflammation. Reactivation of intraocular TB was not observed in any patients. Ocular complications that occurred following the diagnosis of uveitis were posterior subcapsular cataract in 2 eyes (12%), vascularized retinal granuloma in 1 eye (6%) and elevated intraocular pressure in 1 eye (6%).

Table 3 also shows the baseline and final BCVA. At the uveitis diagnosis, the mean BCVA was 0.27 ± 0.36 (1.3-0.0) logMAR units. During the follow-up, the mean visual acuity was 0.34 ± 0.78 (3.1-0.0) logMAR. During the follow-up, the BCVA was stabilized in 5 eyes (decrease and increase of less than 1 line), improved in 7 eyes (1 line), and decreased in 4 eyes (decrease of 1 line). Decreased visual acuity occurred due to the progression of serpiginous-like choroiditis towards the macula in 3 eyes and direct choroidal tuberculoma involving the macular area in 1 eye at presentation.

DISCUSSION

In the present study, serpiginous-like choroiditis was the most common presentation of fundus involvement in intraocular TB. Seven (70%) patients had bilateral involvement. The mean duration from admission to treatment was about 24 days. Three (30%) patients had a paradoxical response

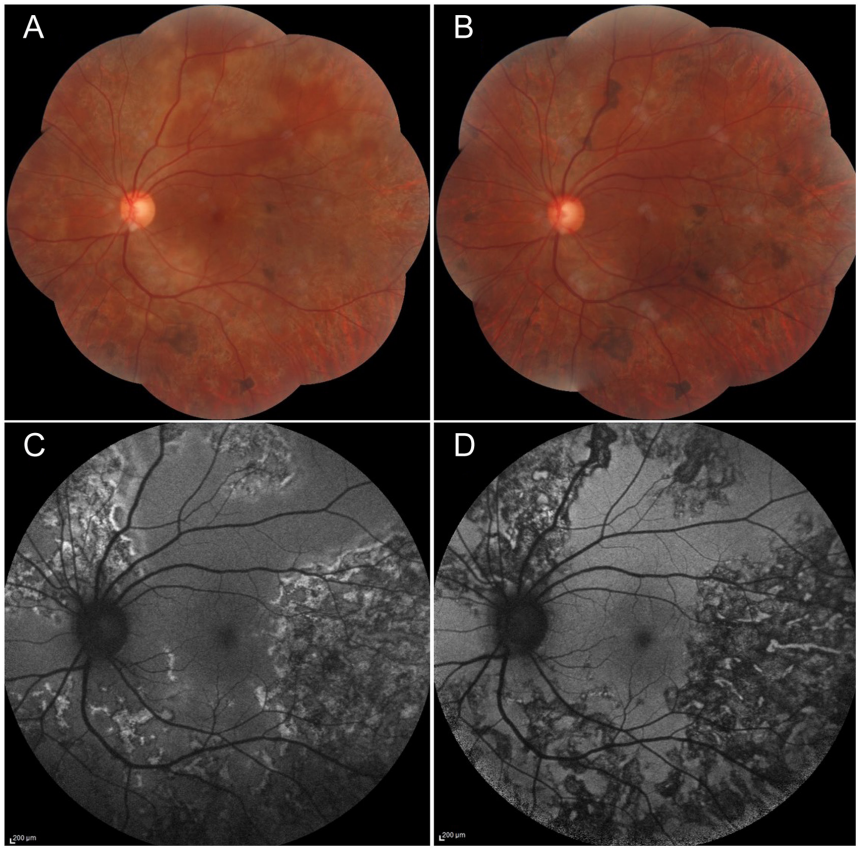

Figure 3. Color fundus photography (top line) and fundus autofluorescence (bottom line) in a 37-year-old woman with intraocular tuberculosis depicting the active serpiginous-like choroiditis prior to anti-tubercular therapy (A and C) and inactive serpiginous-like choroiditis after 4-drug anti-tubercular therapy plus systemic corticosteroids in the left eye (B and D).

to antituberculous therapy, and systemic corticosteroids were employed in these cases. All patients achieved remission, and no relapses had occurred until the follow-up.

A high degree of suspicion is warranted for diagnosing intraocular TB, which is often difficult to diagnose and treat. The diagnostic challenges include a variety of clinical presentations occur due to intraocular involvement, absence of related systemic findings in many patients and limitations of the currently available diagnostic tests and tools.[14] In many studies, the diagnosis of intraocular TB was evaluated on the basis of clinical features and systemic evaluation with the exclusion of other possible etiologies. Local tests such as the tissue culture test and polymerase chain analysis of the anterior or posterior fluids to support the diagnosis of intraocular TB were performed only in 6 of the 28 (21%) studies.[15] Moreover, the absence of pulmonary TB does not rule out the diagnosis of ocular TB. Gupta et al.[16] in a series with 386 patients, observed a relatively high positive predictive value for establishing the diagnosis of ocular TB and aimed to point out the ocular findings that might increase the accuracy of the diagnosis, especially in endemic areas for TB, even if bacilli could not be detected. They recommended to start ATT when one or more of the findings such as broad-based posterior synechia, serpiginous-like choroiditis, and RV with or without choroiditis who have positive TST results or QuantiFERON-TB Gold test results were present after ruling out the other possible causes for the uveitis. Delay in treatment may lead to permanent structural damage that can affect the long-term functional visual abilities. Hence, immediate diagnosis and treatment of intraocular TB are critical to achieve a better visual outcome. In this case series, 80% of the patients experienced a delay in the diagnosis, as a duration of over 21 days from the onset of symptoms was considered as a delay in diagnosis according to the WHO criteria in 1997, which might cause limited visual improvement. We concluded that the compliance of the patients, macular and/or optic disc involvement, and paradoxical reaction (therapy-induced Jarisch–Herxheimer reaction) could be factors affecting the treatment success and visual outcomes.

Clinical phenotypes of the disease are well-known and can be categorized as pulmonary and extrapulmonary manifestations. There has been an increase in the prevalence of extrapulmonary TB, most likely due to better reporting and improvements in diagnostic tools. Tuberculosis most commonly affects the lungs, but it may have various other extrapulmonary manifestations as well, including intraocular involvement. Ocular TB is an extrapulmonary mycobacterial infection with variable manifestations. Tuberculosis can have a variety of ocular manifestations, and consequently, may mimic several ocular inflammatory diseases. Making a diagnosis and establishing the specific therapeutic protocols generates a significant challenge. Ocular involvement occurs in approximately 1% to 2% of TB patients.[16] Most commonly, TB presents as posterior uveitis.[17,18] Intraocular TB usually occurs in apparently healthy individuals, it is rarely observed in patients with active pulmonary diseases. In this case series,

Table 4. All Case Reports on Intaraocular TB as of June 2021 in Turkey

S/N	Author(s) (Published year)	Study Design	Period of Study	Sample Size	Age Mean ± SD (range)	Gender Male (%)	No. of Patients Who Received ATT	No. of Drop outs /loss of Follow-ups	Phenotypes						Relevant History (Patients)		
									AU	IU	PU	Panuveitis	Retinitis/ Retinal vasculitis	Neuroretinitis/ Optic Neuropathy	Previous TB	Systemic TB	Contact History
1	Tunç et al (2003)	Case Report	2003	1	36	Female	1	-	-	-	MFC	-	-	-	-	+	+
2	Uysal et al (2007)	Case Report	2007	1	21	100	1	-	-	-	1	-	-	-	-	+	-
3	Kahraman et al (2009)	Retrospective Case Series	1997-2007	71	40.39 ± 16.45 (10-74)	60	1	-	-	-	-	-	1	-	-	+	-
4	Sızmaz et al (2010)	Retrospective	1996-2006	275	43.9 ± 17.3 (5-83)	42.5	17	-	8	-	2	7	-	-	-	4	-
5	Şen et al (2011)	Case Series	2011	2	25-45	50	2	-	-	-	2	-	-	-	-	2	-
6	Esgin et al (2013)	Case Report	2012	1	21	Female	1	-	-	-	1	-	-	-	-	+	-
7	Sungur et al (2015)	Case Report	2014	1	30	100	1	-	-	-	1	-	-	-	-	+	-
8	Özdal et al (2016)	Case Series	2010-2015	10	31.6 (6-46)	70	10	-	10	1	8	1	4	4	-	3	7
9	Metin et al (2015)	Case Report	2014	1	57	100	1	-	1	-	-	-	-	-	-	-	+
10	Esen et al (2016)	Case Report	2016	1	40	Female	1	-	-	-	1	-	-	-	-	+	-
11	Türker et al (2018)	Case Report	2017	1	20	Female	1	-	-	-	1	-	-	-	-	+	-
12	Oray et al (2017)	Retrospective	1995-2013	28	40.9 ± 12.6 (28-64)	64	17	-	-	-	17	-	-	-	-	-	17
13	Başarır et al (2017)	Case Report	2017	1	23	100	1	-	-	-	+	-	+	-	-	-	+
14	Özyurt et al (2019)	Case Report	2019	1	25	100	1	-	-	-	+	-	-	+	-	+	-

AU, anterior uveitis; IU, intermediate uveitis; PU, posterior uveitis; ATT, anti-tubercular therapy; MFC, multifocal choroiditis; SD, standard deviation; TB, tuberculosis; S/N, study number.

all patients were healthy except for visual symptoms. TB and HIV are often called as an intersecting epidemic. However, extra-pulmonary TB, which is more common among HIV-positive people than HIV-negative people, is difficult to detect through either sputum smear microscopy or chest x-rays. In the present study, HIV was not detected in any of the patients with intraocular TB.

Anterior and posterior uveitis, choroiditis, RV, optic disc nodules, solitary, or multiple choroidal nodules are common clinical findings of intraocular TB.[19-21] Anterior uveitis secondary to TB could be presented with unilateral or bilateral symptoms of conjunctival hyperemia, photophobia, and floaters. In patients with bilateral diseases, the disease is usually asymmetric. Anterior uveitis is characterized by large mutton-fat keratic precipitates, several or diffuse over the corneal endothelium.[22] Intermediate uveitis associated with TB particularly shows nonspecific clinical features. Patients generally present with a low-grade, smoldering chronic uveitis, vitreous snowball opacities, peripheral vascular sheathing, and peripheral retinochoroidal granuloma. The choroid is the most commonly affected site.[19] In this study, 18.75% of the eyes had intermediate uveitis, 18.75% had posterior uveitis, and 62.50% had panuveitis. As of June 2021, all published intraocular TB cases from Turkey are summarized in Table 4. The majority of the patients were published as case reports featuring a variety of the intraocular involvement.

To our best knowledge, this is the first manuscript reporting various clinical types of intraocular TB in Turkey. However, several drawbacks are present, such as its retrospective nature, and unstandardized clinical documentation and follow-up period. Additionally, the sample size was small, especially in the less common clinical phenotypes, and no TB-related anterior uveitis cases were evaluated.

CONCLUSION

The current study presents various ocular findings and discusses the difficulties faced in the diagnosis and treatment of intraocular TB. Outcomes of ATT was favorable in most of the patients with choroidal involvement, even in those with a delay in the initiation of therapy. It can be concluded that the compliance of the patients, macular and/or optic disc involvements and paradoxical reactions are factors affecting the treatment success and visual outcome. Intraocular TB still remains as a diagnostic and management problem for both ophthalmologists and pulmonologists. Ocular examinations can be considered in patients with suspected or proven TB. Early diagnosis and prompt treatment of ocular TB can prevent the severe complications and subsequent potential visual impairments. Tuberculosis should be considered in the differential diagnosis of cases especially with chronic intraocular granulomatous inflammation and those patients should be investigated accordingly.

Ethics Committee Approval: This study was approved by Ethics committee of Dokuz Eylül University, (Approval No: 2021/20-04).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., G.Ö.Ş., E.S.U., A.O.S., F.A., D.G., B.T.; Design – M.K., G.Ö.Ş., E.S.U., A.O.S.; Supervision – E.S.U., A.O.S.; Data Collection and/or Processing – M.K., G.Ö.Ş., F.A., D.G., B.T.; Analysis and/or Interpretation – M.K., G.Ö.Ş., F.A.; Literature Review – M.K., G.Ö.Ş.; Writing – M.K., G.Ö.Ş.; Critical Review – M.K., G.Ö.Ş., E.S.U., A.O.S.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 331-335 DOI: 10.5152/TurkThoracJ.2022.21304

Original Article

Changes in the Number of Newly Diagnosed Lung Cancer Patients Before and During the COVID-19 Pandemic: A Single-Center Experience

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Cite this article as: Gül Ş, Atilla Uysal M, Çifter A, Yelda Özgün Niksarlıoğlu E, Bilici D. Changes in the number of newly diagnosed lung cancer patients before and during the COVID-19 pandemic: A single-center experience. *Turk Thorac J.* 2022;23(5):331-335.

Abstract

OBJECTIVE: The coronavirus disease-2019 pandemic has affected the entire health system and patients other than coronavirus-infected patients. Hospital admissions of cancer patients decreased during the closure periods due to the pandemic. This study was conducted to determine whether there was an effect on the hospital admissions of newly diagnosed lung cancer patients in Turkey during the coronavirus disease-2019 pandemic.

MATERIAL AND METHODS: In this retrospective study, newly diagnosed lung cancer patients were recorded from the Hospital Information Management System between January 1, 2017, and December 31, 2020, at our tertiary hospital. The number of newly diagnosed lung cancer patients diagnosed in 2020 was compared with each year from 2017 to 2019.

RESULTS: Between 2017 and 2020, 15 150 newly diagnosed lung cancer cases were analyzed. According to Global Cancer Observatory data, in 2018, 34 703 newly diagnosed lung cancer cases, and in 2020, 41 264 newly diagnosed lung cancer cases were observed in Turkey. Although a decrease was not observed in the number of patients according to Global Cancer Observatory data, both the total number of patients admitted to our hospital and the number of newly diagnosed lung cancer patients decreased in 2020. The number of newly diagnosed lung cancer patients by year was 4030 patients in 2017, 4004 patients in 2018, 4391 patients in 2019, and 2725 in 2020, respectively. In 2020, newly diagnosed lung cancer patients decreased by 38%, 32%, and 32% compared to 2019, 2018, and 2017, respectively. Also, a significant decrease was seen in the number of newly diagnosed lung cancer patients in the months with closure due to the pandemic compared to the months without closure.

CONCLUSION: There was a significant decrease in hospital admissions of newly diagnosed lung cancer cases in the coronavirus disease-2019 pandemic in our referral hospital. Precautions should be considered to diagnose and treat lung cancer patients in specialized centers during a pandemic due to epidemic diseases such as coronavirus disease-2019.

KEYWORDS: COVID-19, hospital admission, lung cancer
Received: *January 10, 2022* ***Accepted:*** *May 25, 2022* ***Available Online:*** *June 14, 2022*

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has become a significant health crisis affecting the world after its first appearance in Wuhan, China. According to the data of the World Health Organization (WHO), on April 26, 2021, 146 881 882 cases were detected worldwide, causing 3 104 743 deaths.[1] Since March 11, 2020, when the first case was seen in Turkey, 4 667 281 cases and 38 711 deaths were reached, according to the data of the Ministry of Health on April 26, 2021.[2] After the date of the first case, restrictions have been implemented, and stay-at-home orders took place on March 20 and continued until May 11, 2020. With the end of lockdown and releasing restrictions, an increase in COVID-19 cases was observed. Stay-at-home recommendations were begun on November 17, 2020. With the lockdown and restrictions again, the number of COVID-19 cases has tended to decrease. During all these stay-at-home recommendations and lockdown periods, the health system was also affected, and there were problems in patients' access to the health system.

According to the Global Cancer Observatory (GCO) 2020 data, lung cancer is the second most common cancer type globally and the most common cause of death.[3] In Turkey, 41 264 (17.6%) lung cancer cases were seen in 2020, and lung cancer was the most common type of cancer. It ranked first in cancer-related deaths with a rate of 29.3%.[4] Several studies show that the survival and cure rates increase with a lung cancer diagnosis at an early stage.[5] During the COVID-19 pandemic, the number of hospital admissions, screening, and diagnostic tests and access to treatment of lung cancer patients are affected.[6,7]

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Table 1. Demographic Characteristics of Newly Diagnosed Lung Cancer Cases by Year and the Ratio to the Total Number of Cases Admitted to the Hospital

	2017	2018	2019	2020	*P*
Age (mean ± SD)	62.69 ± 10.62	62.25 ± 10.75	62.42 ± 11.04	61.67 ± 11.43	.08
Gender, n (%)					
Male	3242 (80.44)	3178 (79.37)	3421 (77.90)	2189 (80.31)	.09
Female	788 (19.56)	826 (20.63)	970 (22.10)	536 (19.69)	
Newly diagnosed lung cancer cases in our hospital (n)	4030	4004	4391	2725	
Total number of hospital admissions (n)	185 647	221 589	234 289	208 003	-
Ratio (%)	2.17	1.81	1.87	1.31	
Newly diagnosed lung cancer cases in Turkey (n)	No data available	34 703	No data available	41 264	-

SD, standard deviation.

This study aimed to evaluate the changes in the number of newly diagnosed lung cancer (NDLC) patients during the COVID-19 pandemic in a big hospital for chest diseases and thoracic surgery.

MATERIALS AND METHODS

The patients who applied to our hospital between January 1, 2015, and December 31, 2020, were evaluated. Ethical approval for this study was obtained from the University of Health Sciences Hamidiye Scientific Ethics Committee (June 18, 2021-21/4). The recorded patients were recruited from Hospital Information Management System according to their first admission dates. Written informed consent of patients was not obtained because of the retrospective nature of the study. Patients diagnosed with definite lung cancer among these patients were extracted according to the International Classification of Disease (ICD)-10 codes (C34, C34.0, C34.1, C34.2, C34.3, C34.8, and C34.9). Lung cancer patients between 2015 and 2016 were excluded from the analysis to avoid recurrent cancer diagnosis, yet, the NDLC patients between 2017 and 2020 were included in the study. In the statistical data of the Public Health Cancer Department, the latest lung cancer data in our country belonged to 2016. Cancer data of our country are also available in the GCO system of the WHO in 2018 and 2020. Glocal Cancer Observatory uses the data of Ankara, Antalya, Bursa, Edirne, Erzurum, Eskişehir, İzmir, Samsun, and Trabzon Cancer Registries for incidence estimates for Turkey. Cancer data of our country are given by the ratio of the population of the regions represented by the centers and Turkey's population data. With the GCO 2018 and 2020 lung cancer data, the rate of NDLC patients in our hospital according to country data was determined as point prevalence. The number of NDLC patients in 2020 was compared with the number of NDLC patients in 2017, 2018, and 2019. Between 2017 and 2020, NDLC cases were converted into monthly time series according to their admission dates.

Statistical Analysis

For continuous data, percentages, mean, and standard deviation (SD) values were used. There is seasonal variation in hospital admission in NDLC cases, and seasonal adjustment was applied using the X-13ARIMA-SEATS method via WinRATS (2021) software. A structural break in seasonally adjusted monthly lung cancer admissions was investigated by Bai and Perron structural break test.[7,8] This test can detect the time and statistical significance of structural breaks in time series data.[9] Analysis of variance and chi-square test were performed to compare the qualitative and quantitative variables.

RESULTS

The number of NDLC cases admitted to our hospital between January 1, 2017, and December 31, 2020, was 4030 in 2017, 4004 in 2018, 4391 in 2019, and 2725 in 2020, respectively. A total of 26 895 cases were extracted from the database to evaluate the lung cancer patients. In 2018, 34 703 NDLC cases were observed in Turkey, according to GCO data. In the same year, 4004 patients were diagnosed in our hospital. Thus, in 2018, 11.54% of the cases in Turkey were diagnosed in our hospital. In 2020, according to GCO data, 41 264 NDLC cases were detected in our country. In our hospital, 2725 lung cancer patients were diagnosed. Therefore, by 2020, 6.6% of all cases in Turkey were diagnosed in our hospital (Table 1).

The demographic data of the patients admitted between 2017 and 2020 and the ratio of all cases admitted to the hospital were given in Table 1. There were no significant changes in the age and gender of the patients by years ($P > .05$). The ratio of male patients compared to females was higher for all years. Although there was no decrease in the total number of hospital admission in 2020, compared to previous years, the number of NDLC patients decreased by 38%, 32%, and 32% compared to 2019, 2018, and 2017 years ($P = .000$, $P = .001$,

MAIN POINTS

- Hospital admissions of cancer patients were affected due to coronavirus disease-2019 pandemic.
- This study showed a significant decrease in hospital admissions of lung cancer cases in a tertiary chest diseases hospital.
- A decrease was seen especially during the lockdown periods of the pandemic.

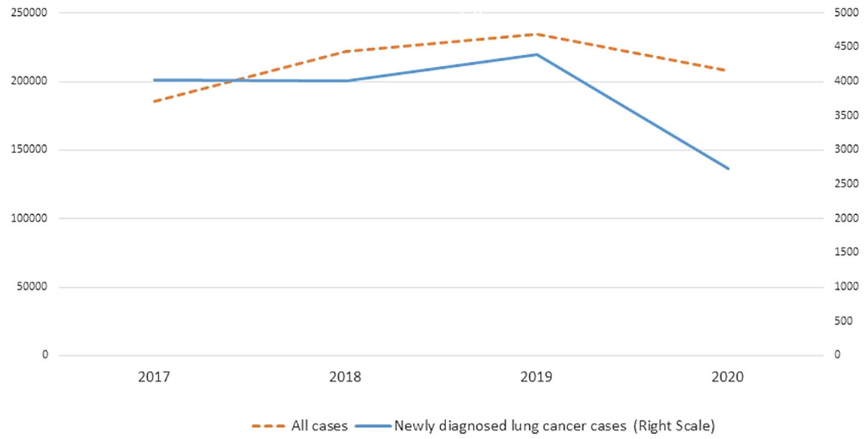

Figure 1. The structural break period with a graph.

and $P = .002$, respectively) (Table 1 and Figure 1). The number of admissions by months of NDLC cases was shown in Figure 2. There was a significant decrease in the number of NDLC cases in March 2020, when there were stay-at-home restrictions. The number of lung cancer cases increased in the subsequent months by releasing restrictions. However, the number of NDLC patients decreased again from October to November 2020, when the restrictions were applied due to the increase in COVID-19 cases.

lung cancer cases should be seasonally adjusted due to variations between the raw and adjusted observations. Secondly, we use Bai and Perron test to figure out if there is a statistically significant structural break in 2020 and found that there was

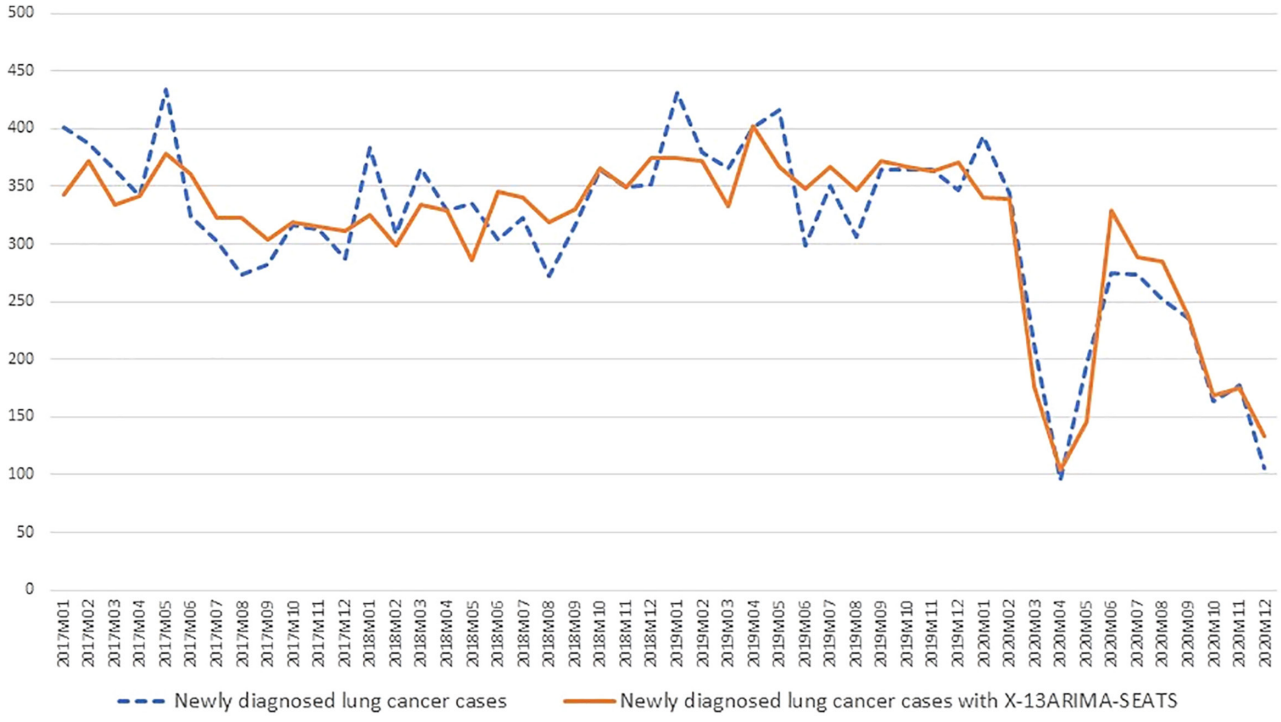

Figure 2. Number of newly diagnosed lung cancer cases and seasonally adjusted data.

The mean number of NDLC cases per month was 335.8 ± 50.9 (min-max: 273-434) in 2017, 333.6 ± 31.3 (min-max: 272-383) in 2018, 365.9 ± 39.2 (min-max: 299-432) in 2019, and 227 ± 88.5 (min-max: 96-394) in 2020. The number of NDLC cases was seasonally dependent, and we firstly adjusted the cases using the X-13ARIMA-SEATS method. Figure 2 shows the raw and seasonally adjusted number of newly diagnosed lung cancer data. This figure indicates that

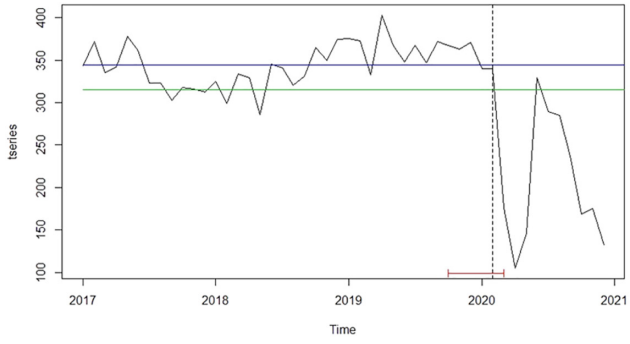

Figure 3. Number of all cases and newly diagnosed lung cancer cases between 2017 and 2020.

a structural break date in March 2020 with a 5% significance level (Figure 3). Turkey announced its first COVID-19 patient on March 11, 2020, and this structural break date shows fear of coronavirus and its impact on hospital admission for lung cancer.

DISCUSSION

Our study showed a significant decrease in NDLC cases in 2020 compared to the previous 3 years, especially during the COVID-19 pandemic onset and stay-at-home restriction period.

Early diagnosis of lung cancer and an early stage are factors that increase survival by increasing the chance of surgery. While the 5-year survival rate is 50% in stage 1A lung cancer, this rate drops to 2% in stage 4.[10] Only less than 20% of patients present at the operable stages.[5] There are patient or system-related reasons for patients' late admission to the hospital. Patient-related causes include age, gender, socioeconomic status, employment status, and awareness of smoking. Patients with chronic illnesses might apply late due to their chronic symptoms or health condition. The reasons originating from the physicians or the health system might be summarized as follows: examination by a physician from other than chest diseases, misinterpretation of radiology, focusing on different diagnoses, not getting an appointment due to systemic problems, or late diagnostic procedures.[10]

Pandemic such as COVID-19 affect the entire health system, affecting patients' hospital admission and receiving adequate health care. Several studies show a decrease in the number of cranial imaging performed to detect stroke or hospitalization due to acute myocardial infarction during the COVID-19 pandemic.[11,12] Cancer patients may also be affected by this situation, and diagnosis may be delayed due to late hospital admission. It has been shown that there is a 25% reduction in cancer cases in the March to May 2020 pandemic period in the Netherlands.[13] In Spain, between March and June 2020, the number of new cancer cases decreased by 20.8% compared to 2019, the number of biopsies performed for diagnosis was lower, and the number of visits for patients receiving cancer treatment decreased.[14] In a study from the USA, the number of cases of 6 cancer types, including lung cancer, decreased significantly in March and April compared to the first 2 months of 2020.[15] In our study, there was a significant decrease in hospital admissions in NDLC cases, especially during the lockdown periods of the pandemic. According to GCO 2020, the total number of lung cancer cases detected in Turkey was not lower than in 2018. However, the number of NDLC cases diagnosed in our hospital in 2020 was lower than in previous years. This difference might be due to the GCO registry system using other 9 cities' hospital data in the country except for our tertiary chest diseases hospital. The other factors contributing to the low number of NDLC cases may be as follows: caring for active COVID-19 patients in our hospital, not performing interventional procedures in the first period of the pandemic, and then performing less in number than in previous years during the entire pandemic period.

A published meta-analysis observed that a 12-week delay in surgery in lung cancer patients significantly reduced survival.[16] In Park et al[6]'s study, during the COVID-19 pandemic in Korea, NSCLC patients applied at a more advanced stage than in previous years. Although the stages of the patients and the treatments they received could not be documented in our study, the decrease in the admissions of NDLC patients, especially during the restriction periods of the pandemic, may cause to apply in the advanced stages and reduce the survival. A modeling study from England showed that there might be a 4.8%-5.3% higher mortality within 5 years in lung cancer patients due to delayed diagnosis in the COVID-19 period.[17]

It should also be kept in mind that lung cancer patients have a higher risk of contracting COVID-19, and mortality may be higher due to infection. In a study from UK, the rate of hospitalization due to COVID-19 in patients with thoracic malignancies was 76% and a mortality rate was 33%.[18] Since there is no significant difference between the survival of lung cancer patients infected with COVID-19 and the survival of advanced lung cancer due to late presentation, even in lung cancer patients who are candidates for surgery, if the perioperative risk of COVID-19 is greater than 13%, the operation may be delayed. Still, immediate surgery increases survival if there is a low risk of COVID-19.[19] For this reason, it is crucial to arrange centers where the diagnosis and treatment of lung cancer patients can be carried out, even during the most intense periods of restrictions during the pandemic period. Considering that epidemic diseases such as COVID-19 can exist in any period, necessary precautions should be taken beforehand.

There are some limitations of our study. Firstly, it is a study that includes only 1 center from Turkey. Secondly, the pathological diagnoses, stages, and treatments of the patients could not be documented. For this reason, although it was shown that there was a decrease in the number of admissions, patients' cancer stages and whether the cancer treatment was affected could not be demonstrated. Thirdly, we do not know whether the patients were infected with COVID-19 and caused late admission.

CONCLUSION

In our center, lung cancer patient admissions statistically decreased during the COVID-19 pandemic period. Early diagnosis and treatment are essential in lung cancer, one of the leading causes of death. During the pandemic period, failure of patients to be diagnosed on time may cause patients to apply at an advanced stage and decrease survival. It is crucial to allocate suitable and separate hospitals where patients can use and maintain diagnosis and treatment for lung cancer and other malignancies during the pandemic period.

Ethics Committee Approval: This study was approved by Hamidiye Scientific Ethics committee of the Health Sciences University (Approval No: 18.6. 2021-21/4).

Informed Consent: Written informed consent was not obtained because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 336-342 DOI: 10.5152/TurkThoracJ.2022.21268

Original Article

The Use of High-Flow Nasal Oxygen Therapy in the Management of Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Feasibility Study

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Cite this article as: Hancı P, Öcal S, Kıvanç Kaya E, Topeli A. The use of high-flow nasal oxygen therapy in the management of severe acute exacerbation of chronic obstructive pulmonary disease: A feasibility study. *Turk Thorac J.* 2022;23(5):336-342.

Abstract

OBJECTIVE: This study investigated the efficacy of high-flow nasal oxygen therapy in patients with severe acute exacerbation of chronic obstructive pulmonary disease admitted to the intensive care unit.

MATERIAL AND METHODS: Totally, 23 patients were enrolled in the study. High-flow nasal oxygen therapy was administered with a predefined protocol. Vital signs, Visual Analog Scale for dyspnea, and arterial blood gas parameters were recorded at the beginning under low-flow oxygen support therapy and the 1st, 6th, 12th, and 24th hours of high-flow nasal oxygen therapy. High-flow nasal oxygen therapy duration, intensive care unit length of stay, and intensive care unit, in-hospital, and 60-day mortality were recorded as outcomes and compared according to the presence of pneumonia upon admission.

RESULTS: In 12 patients (52.2%), pneumonia was present. High-flow nasal oxygen therapy was applied for a median of 57 hours [49.2-104.5]. Overall decreases were detected in heart rate ($P = .001$), respiratory rate ($P < .001$), and Visual Analog Scale for dyspnea ($P = .001$) during the first 24 hours of the therapy. Although there was an increase in $PaCO_2$ ($P = .001$), pH increased ($P < .001$) over time too. No change in partial arterial oxygen pressure ($P = .63$) and partial arterial oxygen pressure/fraction of inspired oxygen ratio ($P = .22$) was noted. Nineteen patients (77%) were successfully weaned from high-flow nasal oxygen therapy. While the high-flow nasal oxygen therapy failure rate was 23%, the in-hospital and 60-day mortality rates were 8.6%. Outcomes were not different between patients with and without pneumonia.

CONCLUSION: High-flow nasal oxygen therapy was efficient in relieving respiratory distress and well-tolerated with no adverse outcome in severe acute exacerbation of chronic obstructive pulmonary disease patients admitted to the intensive care unit.

KEYWORDS: Oxygen inhalation therapy, chronic obstructive pulmonary disease, pneumonia, critical care, intensive care, critically ill
Received: *November 24, 2021* ***Accepted:*** *June 6, 2022* ***Available Online:*** *June 15, 2022*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a life-threatening progressive lung disease with airflow limitation that predisposes to exacerbations. According to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) 2017 Report, symptoms including sudden respiratory distress during rest, respiratory rate > 30/min, use of assisted respiratory muscles, paradoxical abdominal respiration, decrease in oxygen saturation, a tendency to sleep or confusion, and the absence of response to initial medical treatment are considered as severe acute exacerbation of COPD (AE-COPD).[1] Non-invasive ventilation (NIV) has been proven to reduce intubation rate and mortality and is being widely used to support ventilation in these patients.[2] Non-invasive ventilation increases tidal volume and minute ventilation by adding inspiratory pressure support so that dynamic hyperinflation resolves and respiratory workload and respiratory rate decrease.[3] However, NIV failure may occur in COPD patients, with common causes being intolerance to mask, agitation, excessive secretions, and presence of pneumonia.[4] Some studies reported an association between pneumonia and NIV failure and the need for intubation in approximately two-thirds of patients with pneumonia treated initially with NIV.[5] The optimal non-invasive respiratory support for patients with COPD and pneumonia remains unclear.[6]

Although high-flow nasal oxygen (HFNO) has been used widely in hypoxemic respiratory failure,[7] its role in hypercapnic respiratory failure has been investigated. Chronic obstructive pulmonary disease being the most common cause of hypercapnic respiratory failure,[8] some studies have evaluated the effectiveness of HFNO among COPD patients in clinically different situations, such as acute exacerbation[9-15] and weaning from mechanical ventilation.[16] Although the system is an open circuit and does not provide inspiratory support as in NIV, it has some theoretical advantages for COPD patients providing positive end-expiratory pressure effect,[17] more stable fraction of inspired oxygen (FiO_2), and comfort[18] by delivering

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heated and humidified air-oxygen mixture at flow rates up to 60 L/min.

We investigated the efficacy of HFNO therapy in addition to standard medical treatment in patients admitted to the intensive care unit (ICU) because of severe AE-COPD. Our primary endpoints were changes in respiratory rate, heart rate, dyspnea, arterial blood gas (ABG) results, and the ratio of partial arterial oxygen pressure (PaO_2) to FiO_2 (PaO_2/FiO_2) within 24 hours, whereas our secondary endpoints were HFNO failure rate; in ICU, in hospital, and 60-day mortality after ICU admission and the effect of coexisting pneumonia on outcomes.

MATERIAL AND METHODS

Consecutive patients admitted to the medical ICU for severe AE-COPD between October 2017 and January 2019 were included. The study was conducted as a prospective feasibility study which was approved by the Hacettepe University Clinical Research Ethics Committee (2018/14-18), and written informed consent was taken from patients or their relatives.

Patients who had been diagnosed with COPD and admitted to our emergency department with symptoms including sudden respiratory distress during rest, respiratory rate > 30/min, use of auxiliary respiratory muscles, paradoxical abdominal breathing, oxygen saturation <90%, and lack of response to initial medical treatment were transferred to the ICU and included in the study. Exclusion criteria were pH < 7.30, hemodynamic instability, age under 18 years old, presence of active upper gastrointestinal system bleeding, and a recent history of upper airway surgery.

MAIN POINTS

- High-flow nasal oxygen therapy relives respiratory distress without worsening arterial corbon dioxide pressure in patients with chronic obstructive pulmonary disease exacerbation and is believed to be safe in the co-existence of pneumonia.
- Chronic obstructive pulmonary disease is a life-threatening progressive lung disease with airflow limitation that predisposes to exacerbations.
- Noninvasive ventilation has been proven to reduce intubation rate and mortality. However, NIV failure may occur in COPD patients especially in the presence of pneumonia.
- High Flow Nasal Oxygen Therapy has some physiological advantages for AE-COPD patients (PEEP effect, decrease in dead space-tidal volume ratio, stable fraction of inspired oxygen and facilitation of excessive secretions).
- This study investigated the efficacy of high flow nasal oxygen therapy (HFNO) in patients with severe acute exacerbation of chronic obstructive pulmonary disease (AECOPD) admitted to the intensive care unit and patients were compared according to the presence of pneumonia.
- High flow nasal oxygen therapy relives respiratory distress without worsening arterial carbon monoxide pressure in patients with COPD exacerbation and safe in co-existence of pneumonia.

Pneumonia was defined as a new radiographic pulmonary infiltrate upon admission with signs or symptoms of lower respiratory tract infection.

Patients' demographic data, body mass index, smoking history, comorbidities, Charlson Comorbidity Index,[19] Acute Physiology and Chronic Health Assessment score (APACHE II),[20] Sequential Organ Failure Assessment score,[21] pulmonary function test results within the last 6 months, modified Medical Research Council (mMRC) dyspnea scale,[22] number of exacerbation and hospitalization in the past year, GOLD COPD stages[1], and treatments including long-term oxygen therapy (LTOT) or home-NIV therapy, were recorded.

The visual analog scale (VAS) for dyspnea was used to assess temporal changes in patient's respiratory distress.[23] Subjects were asked to rate the severity of dyspnea ranging from 0 to 10 with 10 being the maximum.

High-flow nasal oxygen therapy was administered in the ICU with Optiflow™ (Fisher and Paykel Healthcare Limited, New Zeland), which is set to deliver flow rate of 40 L/min with FiO_2 of 30%, at a temperature of 37°C as the initial set-up. Then, the flow rate was increased by 10 L/min with an interval of 20 minutes up to 60 L/min that the patient could tolerate, and FiO_2 was set to keep the patient's SpO_2 above 90%.

Vital signs, VAS for dyspnea, signs of respiratory distress, and ABG parameters were recorded at the beginning under low-flow oxygen support therapy via nasal cannula or face mask and at the 1st, 6th, 12th, and 24th hours of HFNO therapy.

If deterioration in patients' level of consciousness, worsening dyspnea (signs of respiratory muscle fatigue), pH < 7.30, malign arrhythmia, or hemodynamic instability without response to fluids were detected, it was recorded as treatment failure, commencing NIV or IMV as rescue therapy in accordance with indication, at the discretion of the primary treating physician. After 24 hours of follow-up, the flow was reduced by 50% if the patient's respiratory rate decreased without paradoxical respiration or accessory muscle use and PaO_2 > 60 mmHg with <35% FiO_2 was noted. High-flow nasal oxygen therapy was discontinued if the patient was stable during the follow-up. Patients received proper medical treatments (nebulized short-acting beta-2 adrenergic agonist and muscarinic antagonists, systemic corticosteroids, empiric intravenous antibiotics) for COPD exacerbation and pneumonia.

Intensive care unit length of stay (LOS), hospital LOS, and ICU and in-hospital mortality were recorded. Patients were called to obtain 60-day mortality status. The Turkish Ministry of Health online death notification system was checked for patients who could not be reached by phone.

Statistical analyses were performed using the International Business Machines (IBM) Statistical Package for the Social Sciences software version 22. Descriptive analyses are presented using medians [25-75 percentiles] for ordinal variables and n (%) for categorical variables. Friedman tests were conducted to test whether a significant change in the vital signs, VAS, and ABG variables was noted. An overall 5%

Table 1. Patients' Characteristics at Admission and Outcomes According to the Presence of Pneumonia at Admission to ICU

	All, n = 23	With Pneumonia, n = 12	Without, Pneumonia n = 11	*P*
Age, year*	68 [64-75]	72 [62-75]	65 [59-68]	.14
Male sex, n (%)	17 (74)	11.0 (91.7)	6.0 (54.5)	**.046**
BMI, kg/m^2*	23.4 [21.5-28.0]	23.1 [21.9-25.9]	27.5 [20.7-32.4]	.23
Smoking history, pack/year*	40 [25-60]	55 [30-100]	30 [11-45]	**.030**
Comorbidities, n (%)**				
Cardiovascular	14 (60.9)	9 (75)	5(45.5)	.15
Hypertension	9 (40)	5 (41.7)	4 (36.4)	.56
Diabetes mellitus	6 (27)	3 (25)	3 (27.3)	.45
Cancer	4 (18)	2 (16.7)	2 (18.2)	.67
Neurological disease	1 (4.5)	0 (0)	1 (0.4)	.40
Charlson Comorbidity Index	5 [4-6]	5 [4-7]	5 [3-6]	.38
APACHE II score*	15 [12-17]	17.0 [14.2-18.7]	13.0 [10.0-15.0]	**.048**
SOFA score*	2 [2-4]	3 [2-4]	2 [2-4]	.32
Visual Analog Scale for dyspnea	6 [4-8]	5 [4-9]	7 [5-8]	.56
Pulmonary function test	n = 16	n = 8	n = 8	
FEV1 (L)	0.99 [0.79-1.36]	0.68 [0.53-1.45]	1.05 [0.87-1.29]	.91
FEV1, %	37.5 [25.5-46.7]	21.2 [18.0-43.0]	34 [27.5-49.5]	.95
FVC (L)	2.0 [1.5-2.4]	2.0 [1.2-2.5]	1.9 [1.5-2.3]	.67
FVC,%	37.5 [36.7-69.2]	50.5 [36.0-75.0]	44.0 [37.0-56.7]	.75
FEV1/FVC	55.5 [48.5-64.7]	57.0 [50.0-65.0]	53.0 [44.2-63.8]	.37
mMRC Dyspnea Scale, n (%)				.40
1	2 (8.7)	0 (0)	2 (18.2)	
2	5 (21.7)	2 (16.7)	3 (27.3)	
3	8 (34.8)	6 (50.0)	2 (18.2)	
4	8 (34.8)	4 (33.3)	4 (36.4)	
AE-COPD* (per year)	2 [1-3]	2.5 [2-3]	2 [1-3]	.52
Hospitalization (per year)*	2 [1-2]	2 [1-2]	2 [1-3]	.82
GOLD COPD stage, n (%)				.90
A	0 (0)	0	0	
B	2 (8.7)	1 (8.3)	1 (9.1)	
C	4 (17.4)	2 (16.7)	2 (18.2)	
D	17 (73.9)	9 (75.0)	8 (73.0)	
Baseline ABG parameters				
pH	7.37 [7.32–7.40]	7.37 [7.32–7.43]	7.38 [7.32–7.40]	.97
$PaCO_2$ (mmHg)	56.3 [48.3–63.3]	52.8 [43.0–61.7]	59.8 [54.3–64.5]	.17
PaO_2 (mmHg)	65.1 [56.7–81.7]	62.3 [52.9–66.2]	71.0 [54.7–91.0]	.11
PaO_2/FiO_2 (mmHg)	179 [150–222]	167 [142-208]	193 [159-303]	.17
HFNO failure rate, n (%)	5 (21.7)	3 (25)	2 (18)	.67
ICU length of stay, day*	9 [6-9]	9.0 [8.0-9.0]	8.0 [5.0-10.2]	.24
Hospital length of stay, day*	10 [8-11]	11.0 [9.0-29.0]	10.0 [6.7-12.5]	.23
ICU mortality, n (%)	1 (4.3)	1 (8.3)	0	.70
Hospital mortality, n (%)	2 (8.7)	1 (8.3)	1 (9.1)	.95
60-day mortality, n (%)	2 (8.7)	1 (8.3)	1 (9.1)	.99

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment; FEV1, forced expiratory volume; FVC, forced vital capacity; mMRC, Modified Medical Research Council; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ABG, arterial blood gas; $PaCO_2$, partial arterial carbon dioxide pressure; PaO_2, partial arterial oxygen pressure; FiO_2, fractional oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit.
*Median [25-75 percentile];**22 patients had one or more coexisting conditions. $P < 0.05$ values are bolded.

type 1 error level was used to infer statistical significance. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons; $P < .005$ was considered statistically significant. The Mann–Whitney *U* test was used to compare the patient's characteristics and outcomes according to the presence of pneumonia.

RESULTS

Out of 43 screened patients, 23 patients who met the inclusion criteria had been enrolled in the study between October 2017 and January 2019. Twenty patients were excluded from the study because of pH < 7.30, hemodynamic instability, and refusal to written informed consent. Table 1 summarizes patients' characteristics, COPD state, patient outcomes, and comparison according to the presence of pneumonia. In 12 patients (52.2%), pneumonia was present. Male gender ($P = .046$), smoking history ($P = .03$), and APACHE II score ($P = .048$) were higher in patients with pneumonia compared to those without pneumonia. Sixteen patients had a pulmonary function test in the last 6 months, 12 (75%) of whom had severe or very severe airflow limitation. The mMRC dyspnea index of 21 patients was 2 and above. All patients had 1 or more exacerbations and hospitalization history in the last year. Patients were mostly in stage D (n=17) according to the GOLD COPD staging. Eighteen patients had been using LTOT, and 6 of them had home therapy with NIV. At enrolment, the median pH was 7.37 [7.32-7.40], $PaCO_2$ was 56.3 [48.3-63.3] mmHg, PaO_2 was 65.1 [56.7-81.7] mmHg, and PaO_2/FiO_2 was 179.2 [150.8-222.0].

High-flow nasal oxygen was applied for a median of 57 hours [49.2-104.5]. Sixteen patients (70.0%) tolerated 60 L/min flow rate in the first hour of the therapy, and the median flow rate was 60 L/min [40-60] at the 24th hour. High-flow nasal oxygen duration was not different in patients with pneumonia (54.0 [43.5-84.0]) than those without pneumonia (75.0 [49.5-111.2]) ($P = .55$). While 19 patients were successfully weaned from HFNO, 5 (23.0 %) were not; 2 of them were intubated and the other 2 underwent NIV. A patient who was transferred to the ward was lost due to cardiac arrest within the first 72 hours, and it was recorded as a failure. The median ICU length of stay was 9 days [6-9], while the hospital length of stay was 10 days [8-11]. The ICU mortality rate was 4.3%, while the in-hospital and 60-day after ICU admission mortality rates were 8.6%. The HFNO failure rate, ICU LOS, and 60-day mortality were not different between the groups.

Figure 1 shows the temporal changes of heart rate, respiratory rate, and VAS for dyspnea. There was an overall decrease in heart rate ($P = .001$). Pairwise analyses revealed differences between baseline (89.5 [79.7-105.2]) and 6th

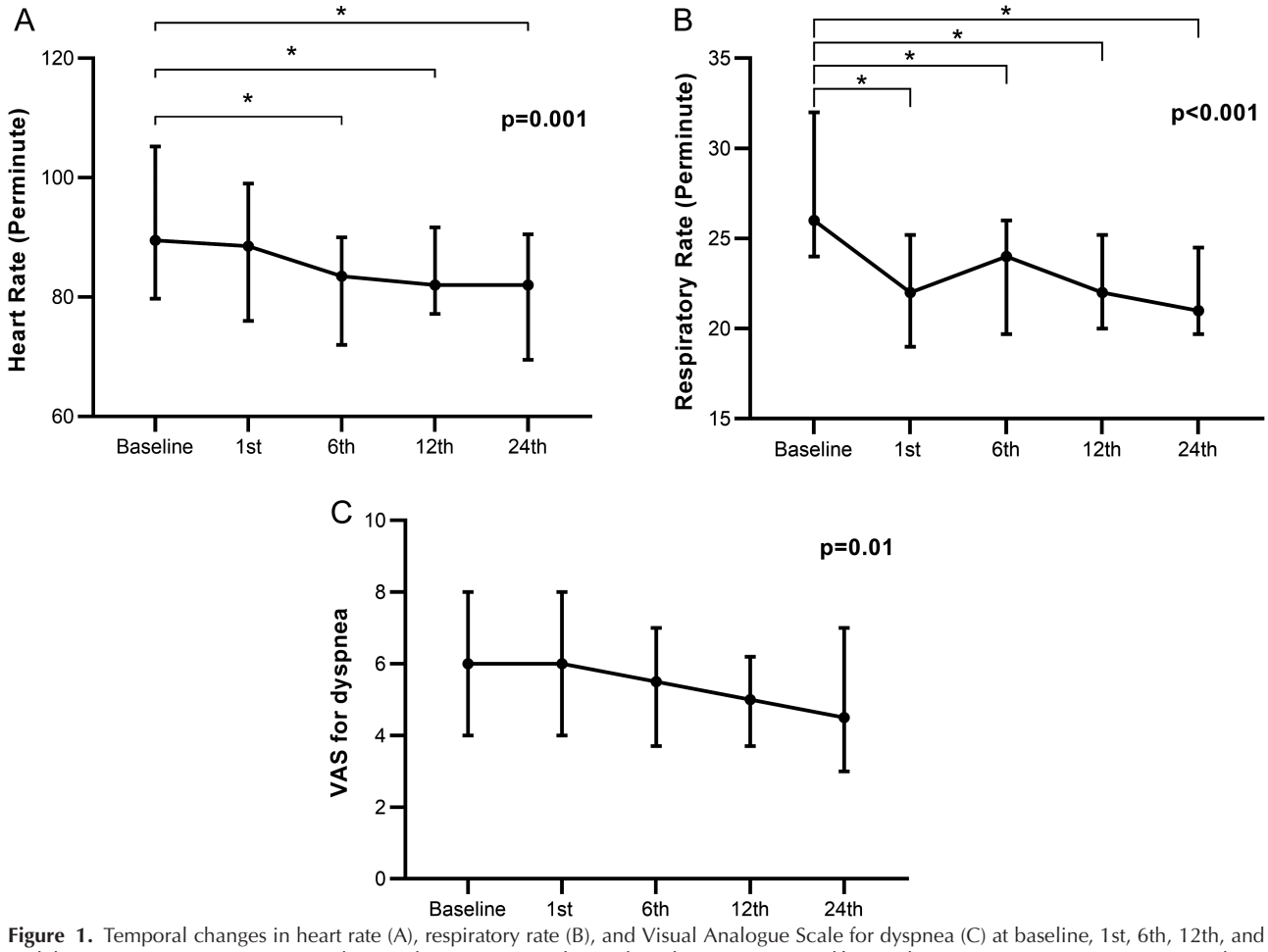

Figure 1. Temporal changes in heart rate (A), respiratory rate (B), and Visual Analogue Scale for dyspnea (C) at baseline, 1st, 6th, 12th, and 24th hours. Data points represent medians with 25-75 percentiles, and *P* values were assessed by Friedman test. *$P < .005$ in pairwise analyses with Wilcoxon test.

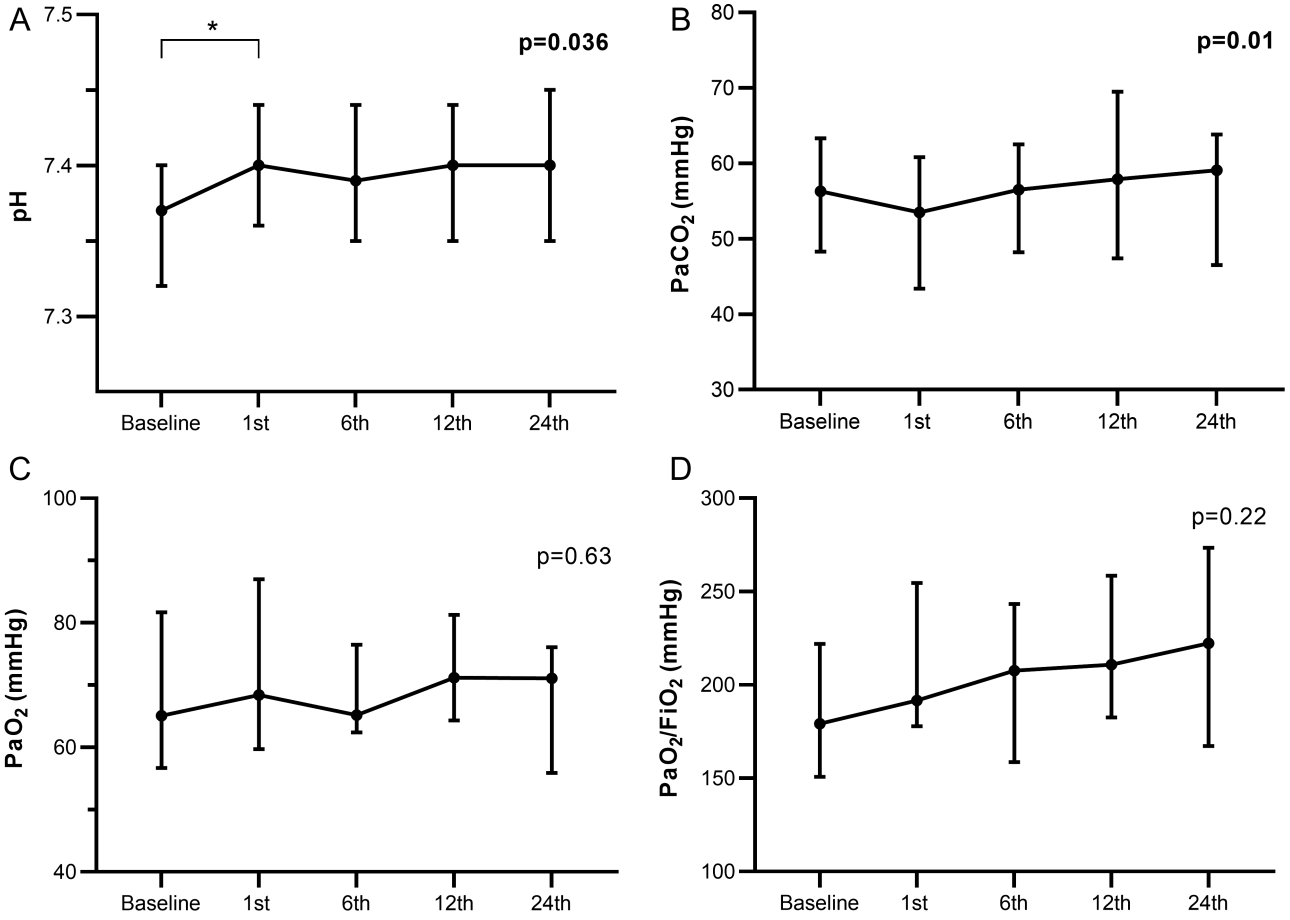

Figure 2. Temporal changes in pH (A), $PaCO_2$ (B), PaO_2 (C) and PaO_2/FiO_2 ratio (D) at baseline, 1st, 6th, 12th, and 24th hours. Data points represent medians with 25-75 percentiles, and *P* values were assessed by Friedman test. **P* < .005 in pairwise analyses with Wilcoxon test.

hour (83.5 [72.0-90.0]) (*P* = .001), baseline and 12th hour (82.0 [77.2-91.7]) (*P* = .002), and baseline and 24th hour heart rate (82.0 [69.5-90.5]) (*P* = .001). Respiratory rate also decreased over time (*P* < .001) from baseline (26.0 [24.0-32.0]) to the 1st hour (22.0 [19.0-25.2]) and remained stable during the 6th (24.0 [19.7-26.0]), 12th (22.0 [20.0-25.2]), and 24th (21.0 [19.7-24.5]) hours. There was an overall decrease in VAS for dyspnea during follow-up (*P* = .001); however, no significant differences were found in pairwise comparisons.

Figure 2 shows the ABG results. The difference in pH between baseline (7.37 [7.32-7.40]) and first hour (7.40 [7.36-7.44]) (*P* < .001) contributed to the overall significant variation (*P* = .036). Although there was an overall increase in $PaCO_2$ (*P* = .001), there were not any differences in pairwise analyses. No change in PaO_2 (*P* = .63) and PaO_2/FiO_2 ratio (*P* = .22) was noted.

DISCUSSION

The results of this study revealed that HFNO therapy decreased respiratory rate and heart rate without deterioration of respiratory acidosis in patients with severe AE-COPD hospitalized in the ICU. Outcomes were not affected by the presence of pneumonia.

In AE-COPD, expiratory flow limitation and increased respiratory rate and respiratory muscle fatigue lead to dynamic hyperinflation and an increase in dead space–tidal volume ratio. By inspiratory pressure support, NIV diminishes respiratory workload and resolves dynamic hyperinflation.[7] High-flow nasal oxygen system does not provide positive inspiratory pressure as in NIV; however, in stable COPD patients using LTOT, HFNO has been found to decrease respiratory rate and inspiration–expiration ratio which can reduce dynamic hyperinflation.[24] Rezai et al[25] compared the therapeutic effects of HFNO and NIV in severe AE-COPD patients. They found that NIV and HFNO with a flow rate of 20-30 L/min were similarly efficient in improving the respiratory rate and heart rate after 30 minutes. In a multicenter randomized trial comparing HFNO and NIV in mild to moderate hypercapnic respiratory failure in AE-COPD patients, respiratory rate decreased at the second and sixth hours (baseline mean, 27/min; at 2 hours, 22/min; and at 6 hours, 20/min) under HFNO support with a flow rate up to 60 L/min but not in a standardized therapy protocol. High-flow nasal oxygen was found to be non-inferior to NIV in improving patient's condition regarding respiratory rate.[15] Our study included patients with severe AE-COPD. Respiratory rate started to decrease in the first hour of the therapy and remained stable during the 24-hour duration. We also observed an apparent decrease in heart rate beginning at the sixth hour of the treatment, which might indicate a decreased respiratory workload and respiratory distress.

High-flow nasal oxygen was associated with improved VAS score for dyspnea and respiratory rate in patients with

"do not intubate" order at 30 minutes outside the ICU setting.[16] Lenglet et al[26] investigated the efficacy of HFNO with VAS score in patients admitted to the emergency department for acute respiratory failure. They found that VAS score decreased within as early as 15 minutes. In this study, the main cause of respiratory failure was pneumonia, and none of the patients had COPD. In the study by Rezai et al.[25] the level of dyspnea was evaluated using BORG scale and a decrease was found in 30 minutes of HFNO therapy. Similar to these studies, we found a temporal reduction in VAS for dyspnea during the first 24 hours.

Reduction of hypoxic vasoconstriction and increase in venti lation-perfusion mismatch by oxygen therapy in patients with acute exacerbation of COPD may aggravate hypercapnia. Therefore, both to prevent hypoxemia and to reduce the risk of hypercapnia, oxygen therapy should be titrated to achieve saturation of 88%-92%.[27] Compared to low-flow oxygen delivery systems, high-flow systems can control the inhaled gas mixture without affecting the respiratory rate and therefore provide stable FiO_2.[28] Also, HFNO therapy has been considered to be safe in hypercapnic patients due to the reduction of carbon dioxide rebreathing by the wash-out effect of high flow through the dead space and enhance adequate alveolar ventilation with the decrease in dead space–tidal volüme ratio.[18,29,30] Bräunlich et al[31] investigated ABG results of stable hypercapnic COPD patients with HFNO therapy under 4 leakages and flow conditions up to 40 L/min. They found that by increasing the leakage and flow, hypercapnia decreased. In another study by the same group, in moderate and severe hypercapnic patients of AE-COPD who could not tolerate NIV, HFNO therapy was applied up to the flow that the patient can tolerate, and the most remarkable improvement in pH and $PaCO_2$ was observed in patients with respiratory acidosis (baseline pH < 7.35).[9] In a randomized–controlle d multicenter trial, HFNO was found non-inferior to NIV in decreasing $PaCO_2$ in life-threatening AE-COPD patients with moderate hypercapnia with a pH of 7.25-7.35.[15] In this study, the device was set to a maximum flow of 60 L/min initially, and it was well tolerated by 15 (65%) patients during the first 24 hours. Since exclusion criterias of our study was based on ABG results; median pH and $PaCO_2$ of the patients were lower than other studies. Although the $PaCO_2$ improvement was expected to be higher with an increase in the gas flow, we observed a slight increase in $PaCO_2$. Despite this, arterial pH was improved. It may be due to the initiation of renal compensation and the increase in $PaCO_2$ was not excessive. Although the FiO_2 was titrated to maintain a SaO_2 > 90%, patients were also protected from hyperoxemia. Our patients were transferred from the emergency room to the ICU under low-flow oxygen support, and baseline blood gases were not in room air. Compared to the low flow systems, we did not observe any increase in PaO_2 or PaO_2/FiO_2 ratio.

In our study, severe AE-COPD patients with HFNO therapy showed an acceptably lower rate of HFNO failure and mortality. Although more than half of our patients had pneumonia, HFNO failure rate and mortality were not different in subgroup analysis based on the presence of pneumonia.

Acute exacerbation of chronic obstructive pulmonary disease leads to substantial morbidity and mortality. In-hospital mortality due to respiratory causes was found as 25% in patients with severe AE-COPD[32,] and the presence of pneumonia was associated with increased mortality.[33] How to manage respiratory failure in the presence of COPD and pneumonia together is a matter of debate. Non-invasive ventilation failure rate increases in patients with excessive secretions. Previously published studies have shown HFNO therapy failure rate of 17%-32%[10,15] which was similar to NIV failure[3] in AE-COPD patients and also similar to the HFNO failure observed in this study. Carillo et al.[6] assessed the outcomes of patients with community-acquired pneumonia and acute respiratory failure treated with NIV. They found that NIV failure was more frequent (46% vs. 26%), and the mortality was higher (67% vs. 49%) in patients with previous respiratory disease compared to de novo Acute respiratory failure (ARF).[6] Lee et al[11] compared the outcome of HFNO and NIV in moderate hypercapnic respiratory failure with AE-COPD patients of whom 40% had concomitant pneumonia. Thirty-day mortality was not different between 2 groups (15.9% vs. 18.2 %, *P* = .85). They found pneumonia as the common cause of death (46%).[11] In a similar study conducted in China, there was no difference between HFNO and NIV groups based on treatment failure and mortality, but the presence of pneumonia in patients with treatment failure was found to be 65% in the NIV group and 55% in the HFNO group (*P* = .268).[10] Since that HFNO avoids mucosal dryness and facilitates the removal of secretions by delivering heated and humidified air, it might be better tolerated than NIV by these patients.

This study has some limitations. First, it is a single-center study with a small number of patients, with no comparative group. Respiratory workload was tested clinically. Lastly, clinical improvement of the patients could be due to adjunctive medical treatments (bronchodilators, corticosteroids, and antibiotics). Since the follow-up duration was 24 hours, it could be insufficient to detect medical treatment efficiency. However, it was shown that HFNO therapy could be beneficial even in severe AE-COPD, which needs to be tested in controlled studies with significant number of patients.

In conclusion, HNFO therapy was found to be useful to reduce tachypnea, dyspnea, and respiratory distress and was well tolerated with no adverse outcomes in severe AE-COPD patients admitted to ICU.

Ethics Committee Approval: This study was approved by Ethics committee of Hacettepe University, (Approval No: 2018/14-18).

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 – P.H., S.Ö.; Design – P.H., S.Ö., A.T.; SupervisiÖn – A.T.; Materials – P.H., E.K.K.; Data Collection and/or Processing – P.H., E.K.K.; analysis and/or Interpretation – P.H, S.Ö. A.T.; Literature Review – P.H., S.Ö.; Writing – P.H., S.Ö., A.T.; Critical Review – A.T.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 343-347 DOI: 10.5152/TurkThoracJ.2022.22061

Original Article

Should Pneumothorax Developing During the Recovery Period After COVID-19 in Patients with Previously Healthy Lungs be Considered a Primary Spontaneous Pneumothorax or a Secondary Spontaneous Pneumothorax?

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Cite this article as: Köse S. Should pneumothorax developing during the recovery period after COVID-19 in patients with previously healthy lungs be considered a primary spontaneous pneumothorax or a secondary spontaneous pneumothorax? *Turk Thorac J.* 2022;23(5):343-347.

Abstract

OBJECTIVE: It is still unknown how to call the pneumothorax that develops during the recovery period after coronavirus disease 2019. Patients who developed pneumothorax during the recovery period after coronavirus disease 2019 were compared with those who had a primary or secondary spontaneous pneumothorax without a coronavirus disease 2019 history.

MATERIAL AND METHODS: Between 2020 and 2021, 160 patients with pneumothorax were retrospectively analyzed. Twenty-three patients had a history of coronavirus disease 2019 (coronavirus disease recovery) confirmed by real-time reverse transcriptase-polyme rase chain reaction, whereas the remaining 137 patients did not have a history of coronavirus disease 2019 (18 of the patients with secondary spontaneous pneumothorax group and 119 patients with primary spontaneous pneumothorax group).

RESULTS: The median time between discharge and readmission to the hospital because of pneumothorax was 9 days in the coronavirus disease recovery group. There were statistically significant differences in regards to age ($P < .001$), gender ($P = .02$), the presence of bullae ($P = .02$), and dystrophic severity lung score ($P = .04$) between the coronavirus disease recovery and primary spontaneous pneumothorax groups, whereas no difference was found between the coronavirus disease recovery and the secondary spontaneous pneumothorax groups ($P > .05$). The prolonged air leak was observed in 17.6% (n = 25). Patients who had prolonged air leak were statistically higher in the coronavirus disease recovery group than the primary spontaneous pneumothorax group (56.5% vs. 10.1%), although it was almost similar between the coronavirus disease recovery and secondary spontaneous pneumothorax groups ($P = .951$). On logistic regression analysis, the coronavirus disease recovery group was the independent factor for prolonged air leak (odds ratio = 9.900, 95% CI = 1.557-62.500, $P = .01$).

CONCLUSION: Pneumothorax may be developed during the recovery period after coronavirus disease 2019 in patients with previously healthy lungs, and it should be called as secondary spontaneous pneumothorax.

KEYWORDS: Thoracic surgery, SARS-CoV-2, recovery, pneumothorax, primary, secondary
Received: *March 23, 2022* ***Accepted:*** *June 10, 2022* ***Available Online:*** *August 8, 2022*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19), is associated with pneumothorax (PNMX).[1] The incidence of PNMX (either spontaneous or ventilation-related) was reported between 0.6% and 19% in the COVID-19 pandemic, and it was related to high mortality and morbidity.[2-5] Since the patients examined in the published studies show different changes such as follow-up in the intensive care unit (ICU) or not, is connected to mechanical ventilation (MV), and the degree of parenchymal involvement, the incidence of PNMX is varied so much. Although there are many studies about PNMX as a consequence of COVID-19, the delayed occurrence of PNMX in the follow-up after recovery from the infection is less commonly reported.[6-10] Pneumothorax may develop during the recovery period after COVID-19 since it was observed that the lungs of patients with COVID-19 showed distinctive vascular features, consisting of severe endothelial injury associated with the disrupted cell membranes in an autopsy study.[11] Patients who had PNMX in the follow-up after recovery from COVID-19 can be previously healthy without any risk factors as well as those who have received positive pressure ventilation caused by COVID-19 pneumonia.[9,10]

To the best of our knowledge, the present study has the largest number of patients with PNMX developing during recovery from COVID-19, and there was no study that investigated whether PNMX developing during recovery from COVID-19 is primary or secondary spontaneous PNMX yet.

In the present study, we aimed to compare patients who developed PNMX during the recovery period after COVID-19 with those who had primary or secondary spontaneous PNMX without a COVID-19 history.

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MATERIALS AND METHODS

The present study was approved by the ethics committee of the Bakırköy Dr. Sadi Konuk Research and Education Hospital (2022–53).

Patients

Between January 01, 2021, and January 01, 2022, a retrospective analysis was performed on 220 patients with a PNMX in our center. Patients who develop PNMX when being treated in the ward and/or ICU for COVID-19 pneumonia (n = 52) were excluded because it is not known whether the disease itself or a treatment such as MV caused PNMX. Patients with a history of an underlying pulmonary pathology that alters normal lung structure who developed a PNMX during the recovery period after COVID-19 (n = 5) were excluded. Because it was not known whether changes in the lung parenchyma were caused by COVID-19 pneumonia or an underlying pulmonary pathology cause PNMX. Pneumothorax patients with COVID-19 who were discharged from hospital more than 4 weeks ago (n = 3) were also excluded, since the recovery period from COVID-19 is considered to be a maximum of 4 weeks in the published studies.[6,7]

There were 23 PNMX patients who had a history of confirmed COVID-19 by the real-time reverse transcriptase-polymerase chain reaction and were discharged with healing from the hospital less than 4 weeks ago (COVID-recovery group), and they had no major risk factors for spontaneous PNMX in their medical history. A total of 137 PNMX patients did not have a history of COVID-19 (non-COVID group). The non-COVID group was divided into 2 subgroups: primary spontaneous PNMX (PSP group, n = 119) and secondary spontaneous PNMX (SSP group, n = 18). Secondary spontaneous pneumothorax was considered as PNMX developing in patients with an underlying pulmonary pathology that alters normal lung structure.

Pneumothorax Volume Estimation, Sub-analysis for Dystrophic Lesions, and Total Lung Severity Score

For all patients, the first chest radiograph confirming the diagnosis of PNMX was carefully reviewed and was used to quantify the volume of the PNMX. It was calculated using the formulas in the same manner as described elsewhere: volume = 4.2 + [4.7 × (A + B + C).[12] In this method, A + B + C is defined as the sum of interpleural distances in the case of PNMX. The pulmonary bullae were considered as a lesion with no discernible wall which measures more than 1-2 cm in diameter, whereas the pulmonary bleb was considered as a lesion less than 1 cm. The ipsilateral dystrophic severity score (DSS) was calculated with a chest computed tomography (CT) based on the type, distribution, and the number of dystrophic lung lesions.[13]

For each of the 23 patients in the COVID-recovery group, visual CT was evaluated on the admission to the hospital, and the percentage of involvement in each lobe, as well as the overall lung "total severity score (TSS)," was recorded. According to the TSS, patients were classified as none (0%), minimal (1%-25%), mild (26%-50%), moderate (51%-75%), or severe (76%-100%).

Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (IBM SPSS 14 Statistics for Windows, Version 23.0, Armonk, NY, USA). Descriptive statistics were used to summarize pertinent study information. It was decided whether the distributions were normal or not by Kolmogorov–Smirnov analysis. Quantitative variables are presented as mean, maximum (max), and minimum (min) values and qualitative variables are presented as percentage values. The Student's *t*-test was used for comparisons between the groups. The Pearson's chi-squared test was used for the analysis of qualitative variables; however, the Fisher's exact test was used if the sample size was small. Anormal distributions were reported as median and interquartile range (IQR) values. Non-parametric continuous variables, presented as median values, were compared using the Mann–Whitney *U* test. To determine the independent risk factors affecting the prolonged air leak, logistic regression analysis (multivariate analysis) was performed using the variables. Statistical significance was set at $P < .05$.

MAIN POINTS

- Pneumothorax can be observed in the follow-up after recovery from the coronavirus disease 2019 (COVID-19) due to pulmonary sequelae of the disease.
- Pneumothorax should be kept in mind in patients recovering from COVID-19 in case of sudden-onset progressive dyspnea, and it is not related to the initial severity of COVID-19.
- Pneumothorax developed during the recovery period after COVID-19 in patients with previously healthy lungs should be considered as a secondary spontaneous pneumothorax.

RESULTS

In the COVID-recovery group, 15 patients were treated in the ward, whereas 8 patients were admitted to ICU (5 of them were invasively ventilated and the remaining 3 patients were supported by non-invasive mechanical ventilation). According to the TSS, patients in the COVID-recovery group were classified as none (n = 1), minimal (n = 9), mild (n = 6), moderate (n = 6), or severe (n = 1) at the first hospitalization. When the CT scans of the patients at the time of diagnosis of COVID-19 were examined, no bullae were observed in the chest x-ray of any patient. The median time between discharge and readmission to the hospital because of PNMX was 9 days (min = 2, max = 27 days, IQR = 18) in the COVID-recovery group.

The demographic, clinical, and radiological data of the patients are shown in Table 1.

There were no significant differences in regards to smoking ($P = .142$), the type of treatment for PNMX ($P = .771$), and the side of PNMX ($P = .685$) between the COVID-recovery group and the PSP group.

Table 1. Demographic/Radiological Data of Patients

Variables	COVID-Recovery Group (n = 23)	SSP Group (n = 18)	PSP Group (n = 119)	P^1	P^2
Age, median year (IQR)	55.0 (13.0)	54.5 (12.2)	22.0 (10.0)	.979	**<.001**
Gender, n/%					**.02**
Female	5/21.7	2/11.1	7/5.9	.438	
Male	18/78.3	16/88.9	112/94.1		
Smoking, n/%	12/52.2	12/66.7	81/68.1	.350	.142
Cigarette, median pack/years	12.0 (3.0)	15.5 (10.0)	6.0 (7.0)	.08	.09
Type of treatment, n/%					.711
Conservative	3/13.0	2/11.1	12/10.1%	1.000	
Chest tube	20/87.0	16/88.9	107/89.9		
Side, n/%					.685
Left	9/39.1	7/38.9	52/43.7	.987	
Right	14/60.9	11/61.1	67/56.3		
Collins volume, median % (IQR)	34.0 (17.0)	33.2 (17.6)	40.4 (57.0)	.906	.06
Presence of bleb (smaller than 1cm), n/%	2/11.1	4/17.4	42/35.3	.679	.143
Presence of bullae (larger than 1cm), n/%	10/43.5	9/50.0	25/21.0	.678	**.02**
DSS grade, median (IQR)	4.0 (5.0)	5.0 (1.2)	3.0 (4.0)	.128	**.04**

[1]COVID-recovery group versus SSP; [2] COVID-recovery group versus PSP.
DSS, dystrophic severity score; n, number; IQR, interquartile range; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax. (Boldface indicates statistical significance).

Patients in the COVID-recovery group were older than patients in the PSP group ($P < .001$). There were more female patients in the COVID-recovery group than the PSP group, and this difference was statistically significant ($P = .02$). There was no statistical difference in terms of the presence of bleb between the COVID-recovery group and the PSP group ($P = .143$), although the number of patients with bullae was higher in the COVID-recovery group than in the PSP group ($P = .02$). Dystrophic severity score in patients in the COVID-recovery group was statistically higher than those in the PSP group ($P = .04$).

There was a trend toward statistical significance in Collins volume ($P = .06$) and use of cigarette packs/years ($P = .09$) between the COVID recovery and the PSP groups. Compared to the PSP group, the volume of PNMX was less in the COVID-recovery group (median PNMX volume was 34.0% in the COVID-recovery group and 40.4% in the PSP group). Patients in the COVID-recovery group had more use of cigarette packs/year than those in the PSP group.

There were no significant differences in terms of all variables between the COVID-recovery group and the SSP group.

Prolonged air leak was observed in 17.6% (n = 25) of the patients. Patients who had prolonged air leak were statistically higher in the COVID-recovery group than the PSP group (56.5% vs. 10.1%, $P < .001$, odds ratio = 11.627, 95% CI = 4.184-32.258), although it was almost similar between the COVID-recovery and SSP groups (56.5% vs. 55.6%, $P = .951$, odds ratio = 1.040, 95% CI = 0.300-3.603). On logistic regression analysis, COVID recovery and SSP groups were the independent factors affecting prolonged air leak (Table 2).

The median length of stay in the hospital was 7 days (min = 1, max = 36 days, IQR = 7.0) in the COVID-recovery group, whereas it was 6 days (min = 1, max = 17 days, IQR = 6.0) in the PSP group and 8 days in the SSP group (min = 2, max = 29, IQR = 9.5) (PSP vs. COVID recovery, $P = .06$, and SSP vs. COVID-recovery, $P = .722$).

Table 2. Factors Affecting Prolonged Air Leak with Logistic Regression Analysis

Variables	OR	95%CI	P
Age (per year)	1.000	0.951-1.051	.998
Gender (male vs. female)	1.294	0.246-6.789	.761
Side (right vs. left)	0.905	0.330-2.483	.846
Collins PNMX volume (per volume)	1.003	0.990-1.017	.639
Bullae/blep (no vs. yes)	0.532	0.039-07.217	.532
DSS (per score)	1.394	0.821-2.366	.219
Group			
PSP (reference)	1		
SSP	5.347	1.223-34.482	**.04**
COVID recovery	9.900	1.557-62.500	**.01**

DSS, dystrophic severity score; OR, odds ratio; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax. (Boldface indicates statistical significance).

DISCUSSION

The COVID-19 pandemic is responsible for several hospitalizations worldwide and is characterized by wide heterogeneity in clinical presentation.[14] There is still a lack of knowledge about the short- and long-term consequences of COVID-19.[15] Although PNMX is a rare complication seen in patients with SARS-CoV-2 infection, there was an increase in the incidence of PNMX in patients with confirmed COVID-19.[2-5] Data on the incidence and outcomes of PNMX during the COVID-19 pandemic were published in large-scale studies although a review of them shows that PNMX is scarcely reported after the recovery from the illness. However, PNMX can occur during different phases of illness even in patients without a history of lung disease.[6,8] Patients who have no major risk factors for spontaneous PNMX in their medical history, or who were not intubated or even hospitalized at the time of COVID-19 infection, may develop PNMX during recovery from COVID-19.[6-10] It means that PNMX complication is still possible even after the infection has been overcome.

Since there are only case report studies on patients who develop PNMX during recovery from COVID-19, there is still no consensus regarding the acceptance of these patients as PSP or SSP. While some cases who develop PNMX during recovery from COVID-19 were followed up as PSP, some of them were accepted as SSP in the literature.[7,8,10,16] To the best of our knowledge, the present study is the first study that compared PSP and SSP patients with those who develop PNMX during recovery from COVID-19. It was found that patients who develop PNMX during recovery from COVID-19 should be considered as SSP in the current study. According to published studies, COVID-19 pneumonia results in diffuse alveolar damage, inflammation of alveolar septa, necrosis of pneumocytes, fibrosis, giant bullae, and pneumatoceles.[8,9,17,18] Since the duration of all these conditions in the recovery period is unknown, they may contribute to PNMX in the recovery period of COVID-19. It supports the acceptance of post-COVID-19 PNMX as SSP.

In a post-mortem study, it was found that pneumocytes that are identified as the synthesizing cells of the alveolar surfactant, which has important properties in maintaining alveolar and airway stability pneumocytes, were lost from multifocal (53%) to diffuse level (19%).[18] In COVID-19 patients, it is possible that the process of parenchymal destruction that will result in PNMX continues with a longer duration of illness.[9] In the present study, the median time between discharge and readmission to the hospital because of PNMX was 9 days. Therefore, in case sudden respiratory symptoms appear after discharge in patients who have overcome the active infection, PNMX should be kept in mind. On the other hand, the minimal to severe COVID-19 pulmonary involvement at first baseline in patients in the COVID-recovery group indicates that PNMX is not related to the initial severity of COVID-19.

It was observed that the rate of emphysema-like anomalies (bullae or blebs) was different between the 3 groups. The presence of bullae that was one of the emphysema-like anomalies was higher in the COVID-recovery group than in the PSP group although there was no significant difference between the COVID-recovery and SSP groups. A bullae formation can develop where first ground-glass opacities had been observed in COVID-19 patients.[16,19] It was hypothesized that pathological findings associated with COVID-19 pneumonia such as diffuse alveolar damage, inflammation of alveolar septa, and necrosis of pneumocytes may lead to bullae formation thereby predisposing to PNMX in different stages of illness.[16,18] When the chest CT scans of the patients performed at the time of the diagnosis of COVID-19 were examined, no bullae were observed; however, there was development of bullae formation in the follow-up of these patients. This situation supports the hypothesis described above. Although the information of the lung parenchyma of COVID-19 patients about the pre-COVID-19 period was not available, the rate of bullae in the COVID-recovery group in the present study was 43.5%. The prevalence of emphysema-like anomalies was reported between 6% and 15% among a small group of healthy persons.[20,21] Although the patients in these studies were not comparable with those in the current study, it is seen that emphysema-like anomalies are high in patients in the COVID-recovery group.

Although patients in the COVID-recovery group have previous healthy lungs, prolonged air leak was more common in these patients. When looking at the published studies, it has been reported that a PNMX developing both during the COVID-19 pneumonia period and during the recovery period of disease causes prolonged air leak.[22-24] There are different hypotheses about this. First, a prolonged air leak is developed due to the persistent chronic inflammatory changes and a delayed alveolar breach as part of an ongoing chronic disease process.[23] Second, focal endothelitis may cause prolonged healing in the lung parenchyma.[24] Patients in the COVID-recovery group have higher DSS than those with PSP; this supports the hypotheses of the prolonged air leak. On the other hand, it should be noted that it may represent sequelae of COVID-19.[17]

Limitations

There were some limitations in the present study. First, it was a single-center and retrospective study. However, due to being a single-center study, it can be claimed that it has achieved a standard in treatment approaches. Second, although it was accepted that patients were previously healthy lungs, it should be kept in mind that their history of pulmonary disease may have emerged with COVID-19. However, it is impossible to calculate the probability of patients developing PNMX if they did not catch COVID-19. Third, the rate of PNMX patients in the COVID-recovery group (10.4%) seems to be high. It can be attributed to the fact that our hospital serves as a pandemic hospital.

The present study also has a few strong points. First, the present study is known to be the first study to compare the outcomes of PSP, SSP, and COVID-19-recovery PNMX groups. Second, the authors' institutions are the largest-volume centers that take care of patients with COVID-19 and PNMX in Istanbul, and it can be said that treatment and follow-up quality have been highly standardized throughout the study period.

CONCLUSION

Pneumothorax may develop in previously healthy lungs during the recovery period from COVID-19, and it is not related to the initial severity of COVID-19. It should be kept in mind in patients recovering from COVID-19 in case of sudden-onset progressive dyspnea. Although the short-term follow-up showed the pulmonary sequelae of COVID-19 and the risk of PNMX in patients with a COVID-19 history, prospective studies with long-term follow-up of COVID-19 patients are needed to provide enough knowledge about the relationship between the recovery period of COVID-19 and PNMX. The underlying mechanisms responsible for PNMX in patients in the recovery period of COVID-19 should be investigated with further research. Pneumothorax developed during the recovery period after COVID-19 in patients with previously healthy lungs should be considered as a secondary spontaneous pneumothorax.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Bakırköy Dr. Sadi Konuk Research and Education Hospital (Approval No: 2022-53).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.K.; Design – S.K.; Supervision – S.K.; Funding – S.K.; Materials – S.K.; Data Collection and/or Processing – S.K.; Analysis and/or Interpretation – S.K.; Literature Review – S.K.; Writing – S.K.; Critical Review – S.K.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 348-354 DOI: 10.5152/TurkThoracJ.2022.22023

Original Article

A Single Center Experience of Super-Responders Among Severe Asthma Patients Receiving Treatment with Mepolizumab

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Cite this article as: Atayik E, Aytekin G. Mepolizumab super-responders among severe asthma patients receiving Mepolizumab: A single center experience. *Turk Thorac J.* 2022;23(5):348-354.

Abstract

OBJECTIVE: Anecdotal reports among clinicians treating severe asthma patients with novel add-on treatments such as mepolizumab suggest that a fraction of these patients may experience a much more dramatic benefit from these agents than reported in large, randomized controlled studies. Although these patients have been referred to as super-responders in some studies, currently, there is no consensus regarding the nomenclature. Therefore, our aim was to assess the real-life data among patients receiving mepolizumab treatment due to severe eosinophilic asthma, in an effort to determine potential clinical and laboratory differences between super-responders and other group of patients.

MATERIAL AND METHODS: Data from adult patients who received at least four doses of mepolizumab due to persistent severe asthma between Janury 1, 2020, and December 31, 2021, in a Tertiary Allergy Clinic were evaluated in a retrospective manner.

RESULTS: A total of 57 patients with severe asthma receiving mepolizumab treatment were included [female: 38, male: 19]. At 4th- and 12th-month after initiation of mepolizumab treatment, significant differences in forced expiratory volume in 1 second, forced vital capacity, forced expiratory volume in 1 second/forced vital capacity, blood eosinophil count, and serum immunoglobulin E level were detected as compared to baseline ($P < .001$, $P < 0.001$, $P = .027$, $P < .001$, and $P = .035$). Also, at the 12th-month of treatment with mepolizumab, there were significant differences compared to baseline in asthma control test scores, number of asthma exacerbations, non-planned emergency room visits, hospitalizations, and daily need for oral corticosteroids ($P < .001$, for all parameters). Also, there was not a statistically significant difference between super-responders and responders groups in regard to age, gender, duration of disease, duration of mepolizumab treatment, allergen sensitivities, and comorbid conditions (chronic rhinosinusitis, nasal polyps, and aspirin sensitivity).

CONCLUSION: Our results suggest that mepolizumab may be an effective therapeutic option in patients with severe asthma. On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients (responders). Obviously, further studies are warranted to better define the super-responders among patients with severe asthma who receive mepolizumab treatment.

KEYWORDS: Mepolizumab, severe asthma, FEV1, super-responders, eosinophilic asthma, eosinophil
Received: *February 2, 2022* ***Accepted:*** *June 29, 2022* ***Available Online:*** *August 8, 2022*

INTRODUCTION

Globally, asthma is one of the most common chronic diseases with approximately more than 300 million patients, 5%-10% of whom may have severe asthma (SA). It represents a major cause of disease burden, both for patients and healthcare systems.[1] Patients with SA suffer from asthma attacks despite maximum inhaler therapy. Therefore, significant efforts are being made to determine phenotypic and endotypic characteristics of these patients.[2] Eosinophilic asthma is a SA endotype, and interleukin (IL)-5 contributes to persistent inflammation and the process of eosinophilic asthma within the airways.

Mepolizumab is a monoclonal antibody directed against IL-5, with established efficacy in reducing asthma attacks in patients with severe persistent asthma who have a blood eosinophil count of ≥150 cells/μL.[2-4] It has been approved by the Food and Drug Administration as an add-on or maintenance treatment for eosinophilic SA patients aged ≥ 12 years, and a recommendation has been made to include this drug as a biological agent in existing treatment regimens in patients who are thought to have type 2 inflammation predominantly.[5] Mepolizumab is associated with improvements in asthma control and quality of life and reduces asthma attacks and need for daily corticosteroids independent of the increase in forced expiratory volume in 1 second (FEV1).[5,6] The SterolD ReductIon with mepolizumab Study (SIRIUS) showed that mepolizumab reduces asthma attacks, with a 2.39-fold decrease in the need for corticosteroids as compared to placebo.[3] Again, in the Real-World Mepolizumab in the Prospective Severe Asthma study, mepolizumab injections have been reported to decrease asthma attacks by 69%, emergency room (ER) visits and hospitalizations by 79%, and the median daily corticosteroid dose from 10 mg/day to 5 mg/day.[1]

Anecdotal reports among clinicians treating SA patients with novel add-on treatments such as mepolizumab suggest that a fraction of these patients may experience a much more dramatic benefit from these agents than reported in large, randomized controlled studies. Although these patients have been referred to as super-responders in some studies, currently,

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there is no consensus regarding the nomenclature. From a clinical viewpoint, it is important to define and understand the characteristics of these patients and to establish predictors of response.

Therefore, our aim was to assess the real-life data among patients receiving mepolizumab treatment due to severe eosinophilic asthma, in an effort to determine potential, clinical and laboratory differences between super-responders and other group of patients.

MATERIAL AND METHODS

This retrospective study was conducted between January 1, 2020, and December 31, 2021, in the Allergy and Immunology Department of a Tertiary Care Unit among adult patients who received at least 4 doses of mepolizumab treatment due to severe persistent asthma.

Exclusion criteria were previous treatment with omalizumab due to SA, a diagnosis of asthma-chronic obstructive pulmonary disease overlap, and non-compliance to treatment.

All patients were assessed by chest disease and allergy–immunology specialists. The diagnosis of SA was based on Global Initiative for Asthma guideline criteria.[7,8] Information on the following was retrieved from patient files: age, gender, body mass index (BMI, kg/m^2), duration of asthma, duration of mepolizumab treatment, allergen sensitivity, smoking status, comorbid allergic conditions, presence/absence of nasal polyps and chronic rhinosinusitis, aspirin sensitivity, current/past medications, number of asthma attacks during the 1-year period before and after initiation of mepolizumab treatment, number of unplanned ER visits due to asthma symptoms, number and length of hospitalizations, and daily oral corticosteroid (OCS) dosage. Also, information on the spirometry results before and 4 and 12 months after initiation of mepolizumab treatment was obtained from the automated hospital data management center. Asthma control test (ACT) scores in these periods were recorded. BMI was calculated using the following formula = weight (kg)/height^2 (m).

MAIN POINTS

- Mepolizumab treatment was associated with increases in forced expiratory volume in 1 second and asthma control test scores and decreases in asthma exacerbations, asthma-related emergency room visits, hospitalizations, duration of hospitalization, and need for daily oral corticosteroid.
- In this study, our findings suggest that mepolizumab treatment may have significant effects on many clinical and laboratory parameters in patients with severe asthma.
- Also, this is one of the few studies comparing responders and super-responders among mepolizumab-treated patients with similar demographic, clinical, and laboratory characteristics.
- On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients in terms of the criteria assessed in our study.

For spirometry assessments, a ZAN 100 spirometer device (Oberthulba, Bavaria, Germany) was used. Forced expiratory volume in 1 second, forced vital capacity (FVC) and the ratio of FEV1/FVC, age, sex, race, and height were recorded for each patient. Asthma was considered well controlled with an ACT score of ≥20, partially controlled with an ACT score of 15-19, and poorly controlled with an ACT score of <15.[9]

Blood samples were drawn from all patients by venipuncture. Abbott Cell Dyn 3700 series (Sheath reagent) and Siemens BN II/ BN ProSpec system (particle-enhanced immunonephelometry) were used for the measurement of whole blood count and quantitative determination of serum immunoglobulin (Ig) E, respectively.

Allergen sensitivity was determined using a skin-prick test that included 8 different allergen categories with 24 inhalant allergens (dog, cat, dust mite, grass, tree, ragweed, mold, and cockroach), or by the detection of any allergen-specific IgE. A wheal diameter of >5 mm with flare at 20 minutes was considered a positive result, and patients were considered as non-atopic in the absence of any reaction to any allergens or in the absence of allergen-specific IgE.[10]

Mepolizumab super-responders were defined as those who had no asthma attack, ER visits, hospitalizations, or need for OCS, with at least 6 point increase in ACT scores and at least 15% increase in FEV1 between the start and end of the study period

The study protocol was approved by the Ethics Committee of Karatay University University (meeting date: July 6, 2020; document no: 2020/013).

Statistical analyses of all study data recorded in the study form were performed using International Business Machines Statistical Package for the Social Sciences 20.0 statistics software (Chicago, Ill, USA). The normal distribution of discrete and continuous numerical variables was tested with Kolmogorov–Smirnov test. Descriptive statistics for discrete and continuous numerical variables were expressed as mean ± standard deviation or median (minimum–maximum), while categorical variables were expressed as the number of cases and (%). Categorical variables were assessed with chi-square test, while continuous variables were assessed using *t*-test or Mann–Whitney *U* test. Dependent variables with normal distribution were compared using paired-samples' *t* test, while those without normal distribution were compared with Wilcoxon test. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

A total of 57 patients with SA receiving mepolizumab treatment were included [female: 38 (66.7%), male: 19 (32.3)]. The mean age of participants was 45.11 ± 14.74 years, the median duration of asthma was 10 years (2-30 years), and the mean duration of mepolizumab treatment was 8 months. Non-smokers comprised 91.2% of the study population, while 64.9% had non-allergic asthma and 35.1% had allergic asthma. Related comorbid conditions included chronic rhinosinusitis in 84.2%, nasal polyps in 61.4%, and aspirin sensitivity in 36.8%. Overall, 56.9% of the patients had poorly

controlled asthma. Table 1 summarizes the demographic and clinic characteristics of the study population.

At the 4th- and 12th-month after the initiation of mepolizumab treatment, significant differences in FEV1, FVC, FEV1/FVC, blood eosinophil count, and serum IgE level were detected as compared to baseline ($P < .001$, $P < 0.001$, $P = .027$, $P < .001$, and $P = .035$, respectively) (Figure 1). Also, at 12th-month treatment with mepolizumab, there were significant differences compared to baseline in ACT scores, number of asthma exacerbations, non-planned ER visits, hospitalizations, length of hospital stay, and daily need for OCS ($P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, and $P < .001$, respectively) (Table 2) (Figure 2). At least, 50% reduction in asthma exacerbation frequency, number of ER visits, and daily OCS need was noted after 1 year treatment with mepolizumab in 84.2% of the patients ($n = 48$). Also, at least 50% reduction in the number of hospitalizations was found in 89.5% of the patients ($n = 51$) and at least 50% reduction in the duration of hospital stay was observed in 86% of the patients ($n = 49$) after 1 year treatment with mepolizumab. The median change in ACT scores with 1 year mepolizumab treatment was 6 (range: 0-13), and the median change in FEV1 was 19% (range: 0-51).

Table 1. Demographic, Clinical, and Laboratory Characteristics of Patients

Parameters	Results
Age (years)	45.11 ± 14.74
Gender, female (n, %)	38 (66.7)
BMI (kg/m^2)	27.83 ± 4.45
Duration of disease (years)	10 (2-30)
Duration of treatment (months)	8 (4-24)
Non-smoker (n, %)	52 (91.2)
Diagnosis (n, %)	
Allergic asthma	20 (35.1)
Non-allergic asthma	37 (64.9)
Allergen sensitivity (n, %)	
Non-atopic	36 (63.2)
House dust mite	9 (15.8)
Mold	5 (8.8)
Pollen mixture	5 (8.8)
Animal dander	2 (33.5)
Accompanying allergic disease (n, %)	
None	16 (28.1)
Allergic rhino-conjunctivitis	39 (68.4)
Chronic urticaria	2 (3.5)
Chronic rhinosinusitis	48 (84.2)
Nasal polyps	35 (61.4)
Aspirin sensitivity	21 (36.8)
Asthma treatment (n, %)	
ICS+LABA+ LTRA	25 (43.9)
ICS+LABA+ LTRA + tiotropium	6 (10.5)
ICS+LABA+ LTRA + theophylline	6 (10.5)
ICS+LABA+ LTRA + tiotropium+ theophylline	20 (35.1)
Asthma control	
Well-controlled asthma	-
Partially controlled asthma	23 (40.4)
Poorly controlled asthma	34 (59.6)

BMI, body mass index; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists.

Asthma control was achieved in 91.3% of the patients ($n = 52$) with 1-year mepolizumab treatment (79% well-controlled asthma, n = 45; 12.3% partially controlled asthma, n = 7) (Table 2).

Then, the study population was categorized into 2 groups as super-responders and responders. Figure 3 and 4 show the change in FEV1, FVC, ACT score, serum IgE, and blood eosinophil counts before and after mepolizumab treatment. There was not a statistically significant difference between 2 groups in regard of age, gender distribution, BMI, duration of disease, duration of mepolizumab treatment, allergen sensitivities, and comorbid conditions including chronic rhinosinusitis, nasal polyps, and aspirin sensitivity (Table 3).

DISCUSSION

Our findings suggest that mepolizumab treatment may have significant effects on many clinical and laboratory parameters in patients with SA. Also, this is one of the few studies comparing responders and super-responders among mepolizumab-treated patients with similar demographic, clinical, and laboratory characteristics.

Mepolizumab treatment was associated with increases in FEV1 and ACT scores and decreases in asthma exacerbations, asthma-related ER visits, hospitalizations, duration of hospitalization, and need for daily OCS. Gibson et al[11] also showed that mepolizumab was able to reduce asthma exacerbations and improve asthma control, quality of life, and lung functions in patients with severe eosinophilic asthma, despite the presence of comorbid conditions. Similarly, Taiile et al[12] reported 86.2% reduction in asthma exacerbations following 12 and 24 weeks of treatment with mepolizumab. In a study from Spain, a 87% of reduction in 1 year was found in patients with severe eosinophilic asthma treated with mepolizumab.[13] In our study, 84.2% of the patients experienced at least 50% reduction in asthma exacerbations after 1 year of mepolizumab therapy. In MEpolizumab as adjunctive therapy iN patients with Severe Asthma (MENSA) randomized controlled study, asthma attacks were reduced by 42% following at least 32 weeks of mepolizumab therapy,[14] while 24 weeks of treatment with mepolizumab in MUSCA randomized controlled study (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC asthma) was associated with a significant improvement in ST George's Respiratory Questionnaire.[15]

Although the clinical benefit associated with mepolizumab treatment in SA patients is independent of FEV1,[5,16] it has also been shown to increase FEV1 and ACT scores.[17] For instance, Schleih et al[18] reported a 5.31 point increase in ACT

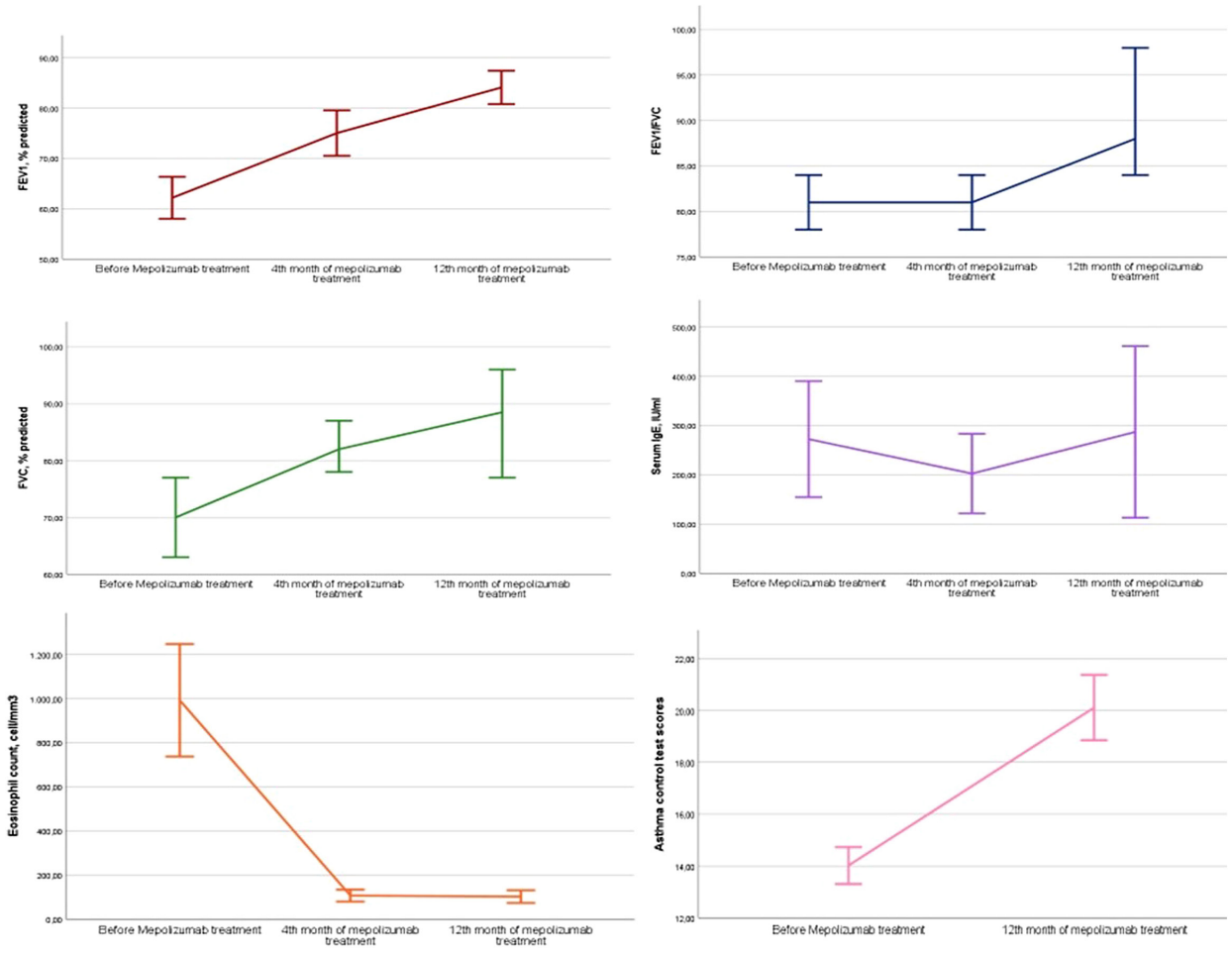

Figure 1. Change in clinical and laboratory parameters during mepolizumab treatment. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Change in Clinical and Laboratory Parameters During Mepolizumab Treatment

Parameters	Before Mepolizumab Treatment	4th-Month Mepolizumab Treatment	12th-Month Mepolizumab Treatment	*P*
FEV1, % predicted	62.18 ± 15.70	75.04 ± 17.01	84.11 ± 12.52	**<.001**
FVC, % predicted	68 (35-89)	82 (46-98)	90 (51-124)	**<.001**
FEV1/FVC	81 (58-106)	81.5 (64-108)	88 (76-110)	**.027**
ACT scores	14 (8-20)	-	22 (12-24)	**<.001**
Asthma exacerbations	4 (2-12)	-	1 (0-6)	**<.001**
Unplanned ER visits	4 (1-12)	-	0 (0-6)	**<.001**
Hospitalization	1 (0-12)	-	0 (0-2)	**<.001**
Duration of hospitalization (days)	5 (0-12)	-	0 (0-12)	**<.001**
Eosinophil count (/mm^3)	850 (120-6880)	80 (10-450)	80 (20-390)	**<.001**
Serum IgE level (IU/mL)	119 (17-2500)	122 (16-1130)	161 (22-1869)	**.035**
OCS (mg/day)	4 (0-16)	-	0 (0-4)	**<.001**
Asthma treatment				**.042**
Well-controlled asthma	-		45 (79)	
Partially controlled asthma	23 (40.4)		7 (12.3)	
Poorly controlled asthma	34 (59.6)		5 (8.8)	

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACT, asthma control test; ER, emergency room; OCS, oral corticosteroids; Ig, immunoglobulin. $P < 0.05$ was considered statistically significant.

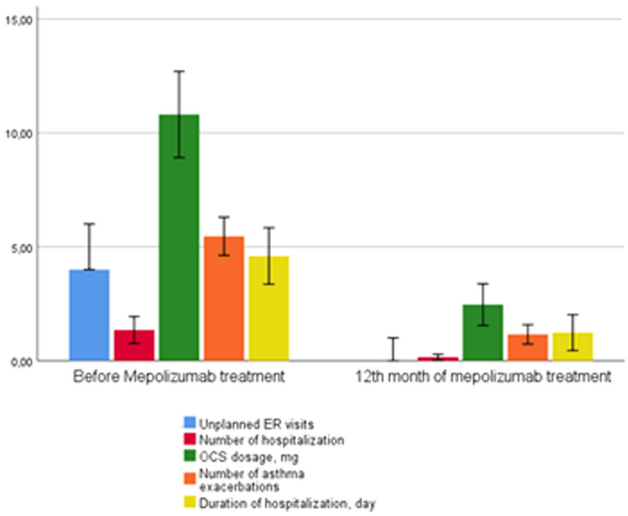

Figure 2. Change in the number of hospitalizations, asthma exacerbations, unplanned ER visits, duration of hospitalization, and daily OCS dosage during mepolizumab treatment. ER, emergency room; OCS, oral corticosteroids.

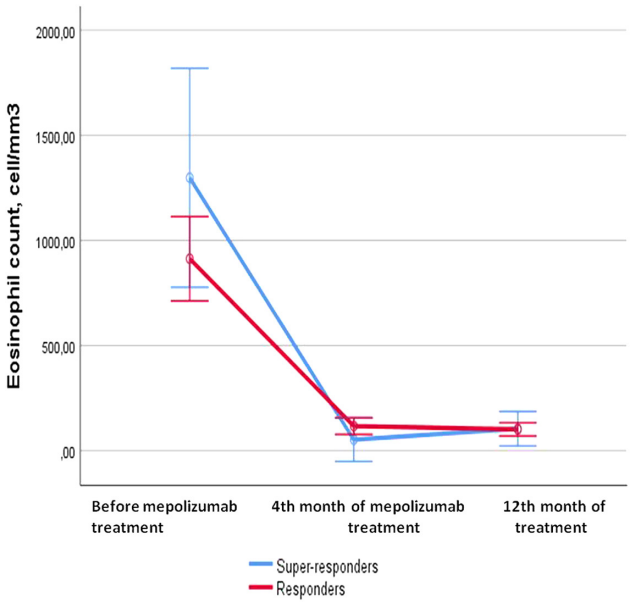

Figure 4. Blood eosinophil count in super-responders and responders during omalizumab treatment.

scores with 6 months of mepolizumab treatment. Caminati et al[19] observed a 6-point change in ACT scores and a 5% change in FEV1 with 6 month omalizumab treatment. In another study, 12 months of treatment with mepolizumab resulted in a ≥3-point increase in ACT scores in 80.65% of the patients and a ≥200 mL increase in FEV1 in 54.84.% of the patients. In the current study, 1-year treatment with mepolizumab was associated with a 6-point increase (0-13) in ACT scores and 19% change (0-51) in FEV1.

An important clinical benefit of mepolizumab is related to its ability to reduce the daily OCS dose, that is. the steroid-sparing effect. In the randomized, controlled SIRIUS study, 6 months of treatment with mepolizumab allowed 54% of the patients to reduce their daily steroid dose by at least 50% as compared to the baseline.[3] Montero-Perez et al[13] reported that 60% of their patients had reduced daily steroid requirements with mepolizumab therapy. Again, in another report, at least 50% reduction in daily corticosteroid dose was achieved in 33% and 62.5% of the patients after 6 and 12 months of treatment with mepolizumab, respectively.[12] Among our patients, 84.2% experienced at least a 50% reduction in daily OCS dose with 1-year treatment of mepolizumab, in line with the previously published figures.

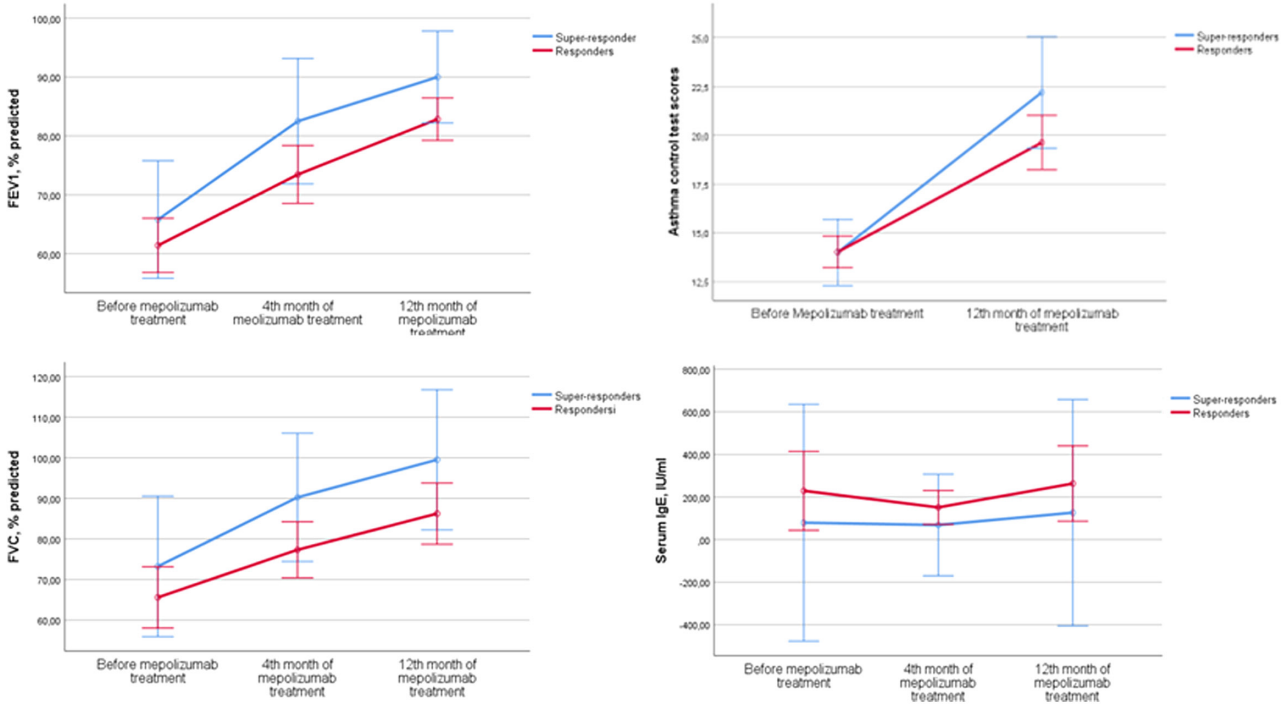

Figure 3. Change in clinical and laboratory parameters among super-responders and responders during mepolizumab treatment. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3. Comparison of Clinical and Laboratory Characteristics Among Super-Responder Patients Versus Responder Patients

	Super-responders (n = 10)	Responders (n = 47)	*P*
Age (years)	39 ± 14.02	48.02 ± 13.64	.108
Gender, female (n, %)	7 (70)	31 (66)	.805
BMI (kg/m^2)	26.09 ± 3.96	28.20 ± 4.51	.176
Duration of disease (years)	8 (3-15)	10 (2-30)	.242
Duration of treatment (months)	12 (4-19)	8 (4-24)	.298
Diagnosis (n, %)			.710
Allergic asthma	3 (30)	17 (36.2)	
Non-allergic asthma	7 (70)	30 (63.8)	
Allergen sensitivity (n, %)			.936
Non-atopic	7 (70)	29 (61.7)	
House dust mite	1 (10)	8 (17)	
Mold	1 (10)	4 (8.5)	
Pollen mixture	1 (10)	4 (8.5)	
Animal dander	0 (10)	2 (4.3)	
Accompanying allergic disease (n, %)			.558
None	4 (40)	12 (25.5)	
Allergic rhino-conjunctivitis	6 (60)	33 (70.2)	
Chronic urticaria	0	2 (4.3)	
Chronic rhino sinusitis	9 (90)	39 (47)	.580
Nasal polyps	8 (80)	27 (57.4)	.183
Aspirin sensitivity	5 (55.6)	16 (38.1)	.690
Blood Eosinophil count (cell/mm$^{3)}$	875 (360-6880)	795 (120-2390)	.500
Serum IgE (IU/mL)	99 (38-907)	136 (17-2500)	.908

BMI, body mass index; Ig, immunoglobulin.

Super-responders among patients receiving mepolizumab treatment represent a relatively new concept, with no clear-cut consensus on its definition.[20-22] Upham et al[22] attempted to define the super-responders using a modified Delphi process. Accordingly, the minor criteria included the absence of asthma exacerbations, major improvement in asthma control, and absence of the need for ACS, and the minor criteria included a 75% reduction in asthma exacerbations, well-controlled asthma, and ≥500 mL increase in FEV1. Improvement in at least 3 criteria with 2 of them being in the major criteria category was defined as super-responder. In Kavanagh et al's[21] study involving 99 patients with severe eosinophilic asthma and receiving mepolizumab therapy, a ≥50% reduction in asthma exacerbations and OCS need was used to define super-responders, although these authors failed to identify any clinical, laboratory, and demographic differences between super-responders and responders in terms of age, gender, atopy status, smoking status, and blood eosinophil parameter. In Harvey et al's[20] study involving 309 patients with eosinophilic asthma, patients with maximum Asthma Control Questionnaire (ACQ) scores (25% of the study population), and those with well-controlled asthma after 6 months of treatment with mepolizumab were defined as super-responders. As compared to responders, super-responders were more likely to be females, have lower baseline BMI and shorter duration of asthma, have higher frequency of nasal polyps, be non-smokers, and have higher IgE levels. On the other hand, the criteria used to define super-responders by Eger et al[23] included asthma control with 2 years of treatment with anti-IL-5 therapy, no use of OCS within the past 3 months, FEV1 ≥ 80% predicted, FENO < 50 ppb, and well control of comorbidities such as chronic rhinosinusitis and nasal polyps. Super-responders in that study had shorter asthma history, adult-onset asthma, higher baseline FEV1, and lower BMI and were more likely to be free of nasal polyps. In our study, super-responders and responders were comparable in terms of demographic, spirometric, or laboratory parameters. Due to a lack of consensus regarding the definition of super-responders, all patients experiencing dramatic improvements in any of the assessed parameters were considered to be super-responders in our study. Thus, our super-responder patients consisted of those with no asthma exacerbation, ER visits, hospitalizations, and OCS requirement following mepolizumab treatment and those with at least 6-point increase in ACT scores and ≥15% increase in FEV1. Due to the adoption of different criteria for super-responders, the study results may also vary. Furthermore, the pathogenesis of asthma is particularly complex in patients with severe asthma, and treatment outcomes may be determined not only by the endotypes but also by the phenotypic characteristics of the patients.[24,25] Therefore, the identification of

patients with pure eosinophilic endotype among the overall population of asthmatic patients may be a challenging task.

In conclusion, our results suggest that mepolizumab may be an effective therapeutic option for patients with SA, consistent with the published data. On the other hand, patients who were considered to be super-responders to mepolizumab treatment were not significantly different from the remaining group of patients in terms of the criteria assessed in our study. Obviously, further studies are warranted to better define the super-responders among patients with SA who receive mepolizumab treatment.

Ethics Committee Approval: This study was approved by Ethics committee of Karatay University, (Approval No: 2020/013).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A.; Design – E.A., G.A.; Supervision – G.A.; Funding – E.A.; Materials – E.A. Data Collection and/or Processing – E.A.; Analysis and/or Interpretation – E.A., G.A.; Literature Review – E.A., G.A.; Writing – E.A., G.A.; Critical Review – E.A., G.A.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 355-363 DOI: 10.5152/TurkThoracJ.2022.21302

Review

The Therapeutic Significance of Mesenchymal Stem Cells in COVID-19 Acute Pulmonary Respiratory Disease

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Cite this article as: Dilek Kançağı D, Ovalı E. The therapeutic significance of mesenchymal stem cells in COVID-19 acute pulmonary respiratory disease. *Turk Thorac J.* 2022;23(5):355-363.

Abstract

The coronavirus disease 2019 pandemic caused by severe acute respiratory syndrome-related coronavirus-2 continues its effects around the world with its new variants. Coronavirus disease 2019 infection may continue with a post-coronavirus disease period, which is characterized by high morbidity apart from the acute and subacute phases. Host immune response quality and inflammasome-induced uncontrollable inflammatory response take a role together in the pathogenesis of severe acute respiratory syndrome-related coronavirus-2 infection. Therefore, treatment of severe acute respiratory syndrome-related coronavirus-2 infection should basically include 3 measures: Viral replication, inflammation, and tissue damage control. Today, there is no effective therapy to control these points. At this point, preclinical studies have shown that mesenchymal stem cells can control inflammatory reactions and lung damage through both immune regulation and inflammasome control. Subsequently, controlled clinical studies on severe acute respiratory syndrome-related coronavirus-2 infection confirm their ability, indicating that mesenchymal stem cells may be a safe treatment option while reducing severe acute respiratory syndrome-related coronavirus-2-related morbidity and mortality. On the other hand, post-coronavirus syndrome is as important as acute coronavirus syndrome, it is a picture that can cause morbidity and mortality. Mesenchymal stem cell application can prevent the development of post-coronavirus syndrome through the mechanism of an inflammasome. However, there is no study that analyzes the effects of current treatments using mesenchymal stem cells in the post-coronavirus disease period, and that tests the use of mesenchymal stem cells when post-coronavirus syndrome develops. In this respect, studies that test the efficacy of mesenchymal stem cells in the post-coronavirus disease period are certainly needed.

KEYWORDS: SARS-CoV-2, coronavirus disease 19, mesenchymal stem cells, immunity
Received: *January 4, 2022* ***Accepted:*** *May 5, 2022* ***Available Online:*** *June 15, 2022*

INTRODUCTION

In the severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) pandemic, for which we are still far from being able to say that there is an effective treatment, another important problem is that even if patients recover after intensive care, they may face significant symptoms that can last for months.[1,2] In particular, this picture, called post-coronavirus disease (post-COVID) syndrome, actually has consequences as important as the disease.[2] After coronavirus disease 2019 (COVID-19), this syndrome is complex, the symptoms of which are muscle weakness (53%), respiratory distress (43%), anxiety, depression, cognitive disorders, confusion, neurological symptoms including sleep disorders (40%), joint pain (27%), hair loss (22%), and cardiovascular symptoms (12%), occurs at a rate of 55% and can continue to affect patients for more than 6 months.[2] Infection-induced immune reactions and mitochondrial degeneration are thought to be the main mechanisms underlying these post-COVID 19 symptoms. Therefore, post-COVID 19 treatment should not only include controlling the virus, it should also be able to control the immune reactions induced by the virus. Previous studies have shown that mesenchymal stem cells (MSCs) are effective in the treatment of many diseases.[3-6] Likewise, studies have reported that MSCs can suppress viral infection in the treatment of SARS-CoV-2 through the secretion of specific cytokines.[3,7-11] In this review, we discussed molecular, mitochondrial, and immunological events involved in the pathogenesis of novel SARS-CoV-2 as well as the clinical perspective of MSC treatment from controlled studies to improve patients' immunological response in the post-COVID period.

CORONAVIRUS DISEASE 2019 PATHOGENESIS

Severe acute respiratory syndrome-related coronavirus-2 is a virus of the corona family and initiates the infection by its entry into the cell via the angiotensin-converting enzyme II (ACE-II) receptor. Infection begins with the synthesis of transmembrane protease serine 2 (TMPRSS2) enzyme in the host cell. The spike protein of the virus first decomposes the enzyme into 2 subunits and binds to the membrane at 2 points. Afterward, the virus is taken into the cell. Prognosis of the patient is determined by the tissue damage and the severity of the cytokine storm, which depends on the effectiveness and severity of the developing immune response.[12]

The most important factor that affects the level of success of the immune response is when the patients have a chronic active inflammation for another reason. Therefore, the disease progress more severely in older individuals. The underlying

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reason for this is the exaggerated immune response caused by chronic inflammation. Therefore, one of the agents widely used in the control of the disease is steroids.[12] So why does aging go hand in hand with chronic inflammation? The most important mechanism here is thought to be mitochondrial aging or fatigue.[13] Figure 1 summarizes this finding.[14-19]

The inability of aged mitochondria to prevent the formation of the inflammasome is due to the fact that cellular stress, which increases with age, activates the nuclear factor-κB pathway. The cascade formed by the direct stimulus of the virus causes an increased presence of inflammasome (Figure 1), which is the main cause of cytokine storm in the elderly or patients with chronic inflammation.[13] For this reason, therapeutic agents that can be ideal elements of treatment in COVID-19 should not cause primary and opportunistic infections and tissue toxicities and should also prevent mitochondrial stress and post-COVID syndrome. Unfortunately, current steroid treatments do not have this feature and cease to be an ideal agent.

FUNCTIONS AND PHARMACOKINETICS OF MESENCHYMAL STEM CELLS

Mesenchymal stem cells are shown to have regenerative effects for as long as 25 years and have been used in the clinic for their different regenerative and immunomodulatory effects for 20 years. These cells are defined as cells that can be obtained from different tissue sources, adhere to plastic, can be shown to differentiate into at least 3 mesodermal cells, and express CD45, CD34, human leukocyte antigen DR negative, CD73, CD90, CD105, and CD106. In addition, since they do not carry ACE-II and TMPRSS2 receptors, which are necessary for SARS-CoV-2 infection,[20] and the use of these cells seems to have an advantage in the treatment of COVID-19 infection. It is now almost accepted that umbilical cord-derived MSCs are more effective than adipose and bone marrow-derived stem cells when tested for their efficacy according to their source.[21,22] However, another group of researchers published a report showing that especially menstrual mesenchymal stem cells can be more effective[23] in the treatment of COVID-19.[24] At this point, another important issue regarding the cell source and production method is that, MSCs tend to lead to thrombosis due to the tissue factor (TF-CD142) that they carry on their surface. The use of adipose tissue-derived MSCs is controversial, especially because of their high TF transport.[25] Therefore, researchers recommend that MSCs shall be heparinized or intramuscularly (IM) administered in order to prevent post-infusional thrombosis and the formation of pulmonary aggregates.[26] It has even been reported that the use of the IM route can increase the duration of MSC effectiveness by 4 times, and therefore IM application will be more effective and harmless.[25-28] A group of researchers also reported that extra vesicles or exosomes of MSC can be preferred over MSCs because they are independent of the risk of pulmonary aggregates and are also effective.[29]

MAIN POINTS

- Post-COVID syndrome shows high morbidity rates. Therefore, it is as important as acute and subacute COVID syndromes.
- Inflammation and inflammasome causing acute, subacute, and post-COVID syndromes play an active role in morbidity and mortality.
- Mesenchymal stem cell therapy emerges as a safe treatment option with the ability to control the cytokine storm caused by the inflammasome.

MESENCHYMAL STEM CELLS CAN EXERT THEIR REGENERATIVE AND IMMUNOMODULATORY EFFECTS BY THE FOLLOWING MECHANISMS

Regenerative Mechanisms of Action

While MSCs stimulate healing in damaged tissue through mitochondria transfer, mRNA, mi-RNA transfers, and cytokines such as keratinocyte growth factor, hepatocyte growth factor, vascular endothelial growth factor, and insulin-like growth factor 1, can reduce apoptosis in tissue with the activation of antiapoptotic effect (B-cell lymphoma 2).[30,31] In fact, the transformation of M1 macrophages into M2 macrophages, which starts with the phagocytosis of MSC or MSC extravesicles, is a part of the immune modulation process and is almost one of the main mechanisms of the regenerative process. Moreover, this reaction is especially responsible for the formation of the regenerative cytokine profile.[30-32] It has been reported that it can prevent fibrosis in the post-COVID-19 period.[9]

IMMUNOREGULATORY MECHANISMS OF ACTION

While MSCs decrease the functions of T and B lymphocytes, they can increase apoptosis in these cells.[30,31] In addition, they suppress tissue-specific immune responses by increasing T-regulatory (Treg), B-regulatory, and DC-regulatory levels.[30-32] While the resulting M1-M2 conversion causes Treg activation, it is also responsible for the secretion of suppressor cytokines. These cytokines interleukin-10, transforming growth factor-β, indoleamine 2, 3-dioxygenase, prostaglandin E2, and arginase secretion, and they suppress T lymphocyte functions in particular.[31] Another immunomodulatory effect of MSCs is that they can also block the alternative complement pathway because they secrete substance H.[32] In particular, the ability of MSCs to block the development of inflammasome plays an extremely important role in controlling chronic inflammatory diseases.[33] Another feature that makes MSCs unique is that these cells, which can control the immune system at every step, do not cause infection at the same time. It is even possible to talk about antibacterial, antifungal, and antiviral effects through the transfer of Hepcidin, β-defensin 2, and Lipocallin 2 small interfering RNAs.[34] Figure 2 summarizes the role MSCs can play in the pathogenesis of COVID.[35,36]

MESENCHYMAL STEM CELLS PHARMACOKINETICS

In a study conducted in the acute respiratory distress syndrome (ARDS) model, intravenous (IV) and endobronchial (EB) MSCs were administered to normal and ARDS-induced mice, and kinetic analyzes were evaluated.[34] Kinetic analyzes for intravenous and endobronchial administration of MSCs show that, in case of lung damage, 80% of MSC remains in the lung tissue after intravenous administration. However, in this study, it is reported that in the normal mice

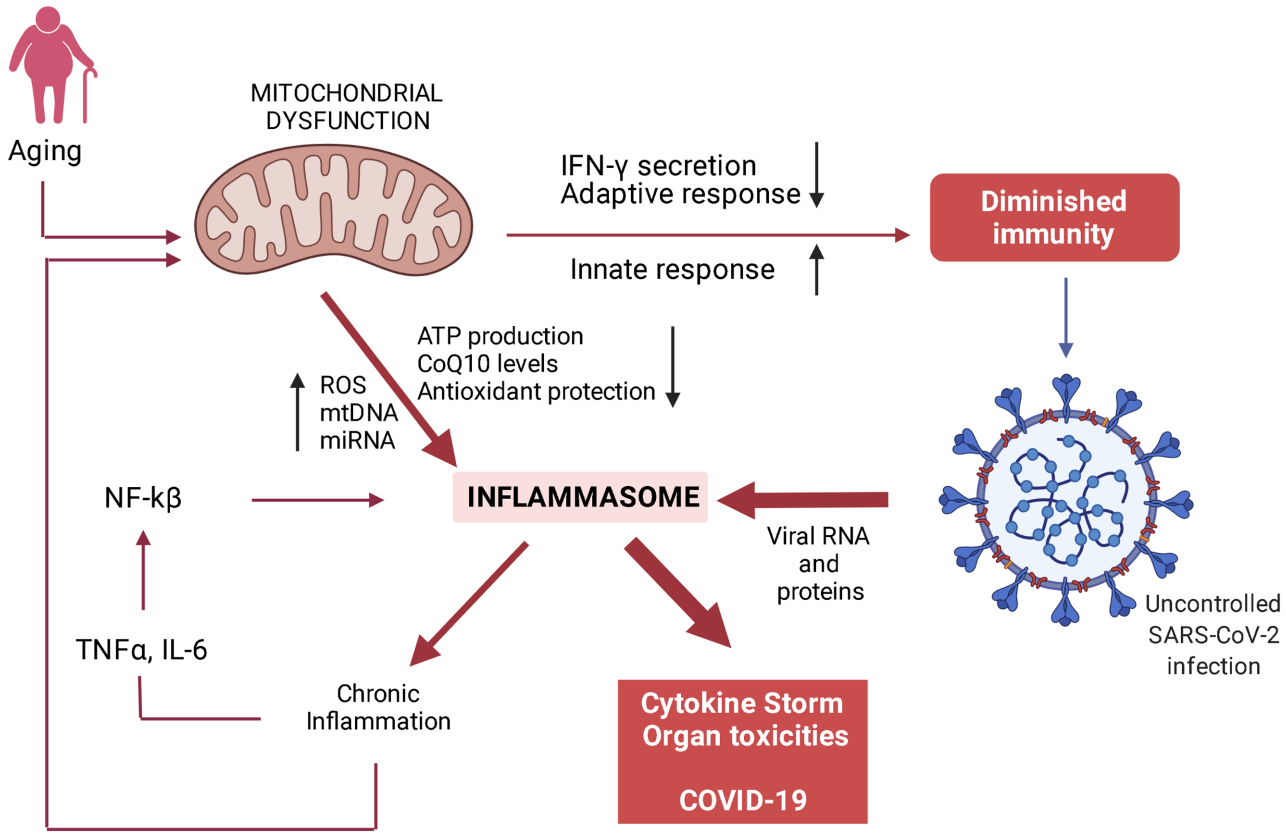

Figure 1. The mechanism of exaggerated but uncontrolled antiviral immunity observed in critically ill patients caused by mitochondrial aging/dysfunctioning (modified from Ayala DJMF, et al. 2020) ROS, reactive oxygen species; mtDNA, mitochondrial DNA; miRNA, microRNA; NF-kβ, nuclear factor kβ; TNFα, tumor ncrosis factor alpha; IL-6, interleukin 6; IFN-γ, interferon gamma.

group, a significant part of MSC administered intravenously is distributed throughout the body 5 hours after administration, and the majority of these dispersed cells are localized to the brain, liver, and kidney. Another finding in this study shows that MSCs given intravenously can be more localized in areas with aeration disorder. There was no difference between the effect of IV or EB administration on improving lung functions. In addition, studies comparing IV and IM applications reported that the effect of IM application may be longer and greater than IV application,[26,27] it has been shown that IV administration in hypercoagulant conditions can cause microemboli in the lung.[25] When all these are considered together it seems possible to say that EB and/or IM administration in COVID-19-related ARDS may be safer and even more effective.

CLINICAL DATA

When the ClinicalTrials.gov site is examined, it is seen that more than 84 studies have been conducted on ARDS and

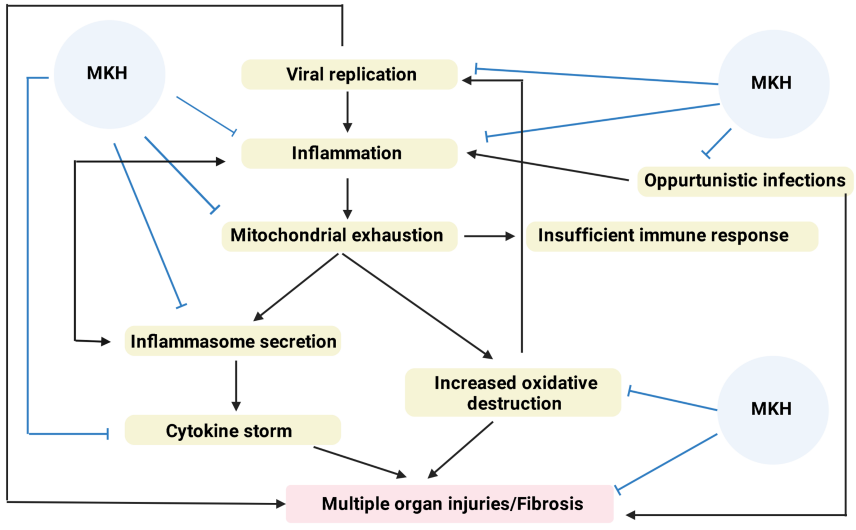

Figure 2. Mesenchymal stem cells can control the reaction at every step in coronavirus disease 2019 infection progressing with cytokine storm.

Table 1. The Available Controlled Studies (https://pubmed.ncbi.nlm.nih.gov/: last accessed: March 11, 2022)

Study	Center	Reference	Study design	Result
Lanzoni G, et al., 2021	USA	37	• A double-blind, phase 1/2a, randomized, controlled trial • UC-MSC treatment (n = 12); control group (n = 12) • UC-MSC treatment group received 2 intravenous infusions (at day 0 and 3): 100 ± 20 × 10^6 UC-MSCs; controls: 2 infusions of vehicle solution.	• No serious adverse events (SAEs) • Decreased level of inflammatory cytokines in UC-MSC-treated patients ($P < .05$). • Significantly improved patient survival (91% vs. 42%, $P = .015$), SAE-free survival ($P = .008$), and time to recovery ($P = .03$).
Shu L, et al. 2020	China	38	• A single-center open-label, individually randomized, standard treatment-controlled trial • Standard treatment group (n = 29); the standard treatment plus hUC-MSC infusion group (n = 12) • 2 × 10^6 cells/kg hUC-MSC	• The incidence of progression from severe to critical illness and the 28-day mortality rate were 0 in the hUC-MSC treatment group, • 4 patients in the control group had critical condition with invasive ventilation; 3 of them died, and the 28-day mortality rate was 10.34%. • In the hUC-MSC treatment group, the time to clinical improvement was decreased compared to the control group. • Improvement of clinical symptoms with hUC-MSC treatment: Weakness and fatigue, shortness of breath, and low oxygen saturation • IL-6 levels were decreased significantly;
Dilogo IH, et al. 2021	Indonesia	39	• A double-blind, multicentered, randomized controlled trial. • n = 40, • All patients received standard therapy • 20 patients received an intravenous infusion of 1 × 10^6/kg body weight UC-MSCs and 20 patients received 100 mL 0.9% saline solution as the control group.	• 2.5 times higher survival rate in the UC-MSCs group than that in the control group ($P = .047$; 10 patients vs 4 patients). • In patients with comorbidities, UC-MSC administration increased the survival rate by 4.5 times compared with controls. • No adverse events were reported. • Decreased CRP and interleukin 6 in the recovered patients ($P = .023$) after UC-MSC infusion.
Kouroupis D, et al. 2021	USA	40	• A double-blind Phase 1/2a randomized controlled trial • 24 patients with COVID-19 ARDS	• In control group, levels of plasma sTNFR2, TNFα, and TNFβ were not significantly different between days 0 and 6. • Significant decrease in TNFα and TNFβ levels ($P = .005$ and $P = .002$, respectively) in UC-MSC treatment group at day 6. • Significantly higher levels of sTNFR2 (26.609 ± 846 pg/ml vs. 23.111 ± 760 pg/ml, $P = .021$) and significantly lower levels of TNFα (319 ± 40 vs. 950 ± 226 pg/mL, $P = .048$) and TNFβ (810 ± 126 vs. 2.944± 735 pg/mL, $P = .032$) in UC-MSC treatment group.
Shi L, et al. 2021	China	41	• A prospective, randomized, double-blind, placebo-controlled, longitudinal, cohort study trial. • 100 patients enrolled in phase 2 trial were prospectively followed up for 1 year. • UC-MSCs (n = 65) or placebo (n = 35) in addition to standard care.	• Improved whole-lung lesion volume with a difference of −10.8% ($P = .030$) after MSC administration on day 10. • MSC therapy reduced the ratio of solid component lesion volume. • Normal CT images at month 12: 17.9% (10/56) of patients in the MSC group; none in the placebo group ($P = .013$). • No difference in adverse events

(*Continued*)

Table 1. The Available Controlled Studies (https://pubmed.ncbi.nlm.nih.gov/: last accessed: March 11, 2022) (*Continued*)

Study	Center	Reference	Study design	Result
Saleh M, et al. 2021	Iran	42	• A phase 1 clinical trial • Five patients with severe COVID-19 were treated with Wharton's jelly-derived mesenchymal stem cells (150×10^6 cells per injection). These patients were subject to 3 intravenous injections 3 days apart.	• Increased level of IL-10 and SDF-1 MSC therapy, but decreased level of VEGF, TGF-β, IFN-γ, IL-6, and TNFα. • No SAEs.
Xu X, et al. 2021	China	24	• A multicenter, open-label, nonrandomized, parallel-controlled exploratory trial. • An allogeneic, menstrual blood-derived MSC therapy and concomitant medications (3 infusions totaling 9×10^7 MSCs, 1 infusion every other day. n = 26); only concomitant medications (control group; n = 18).	• Significantly lower mortality rate in the MSC group (7.69% died in the experimental group vs 33.33% in the control group; $P = .048$). • Improved chest imaging results in the first month after MSC infusion. • Similar incidence of most AEs between the groups.
Sengupta V, et al. 2020	USA	43	• A prospective nonblinded, nonrandomized open-label cohort study • Cohort A (n = 2), Cohort B (n = 21), Cohort C (n = 4) • A single 15 mL intravenous dose of ExoFlo, a bmMSC-derived exosome agent	• No adverse events observed within 72 hours of ExoFlo administration. • A survival rate: 83%; patients recovered: 17 of 24 (71%), patients remained critically ill though stable: 3 of 24 (13%), and patients expired for reasons unrelated to the treatment: 4 of 24 (16%)
Meng F, et al. 2020	China	44	• A parallel assigned controlled, non-randomized, phase 1 clinical trial • 18 hospitalized patients with COVID-19 (n = 9 for each group) • Three cycles of intravenous infusion of UC-MSCs (3×10^7 cells per infusion) on days 0, 3, and 6.	• No SAEs related to UC-MSCs infusion. • Need of mechanical ventilation in 1 patient in the treatment group when compared with 4 patients in the control group. • Decreased serum IL-6 in the UC-MSCs-treatment group. • Decreased trend in the levels of cytokines within 14 days: interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), interferon-inducible cytokine IP-10 (IP-10), IL-22, interleukin 1 receptor type 1 (IL-1RA), IL18, IL-8, and macrophage inflammatory protein 1-alpha (MIP-1)
Ercelen N, et al. 2021	Turkey	45	• n = 210 • Every patient received UC-MSCs ($1\text{-}2 \times 10^6$ per kilogram) on average 6.4 days after positive severe acute respiratory syndrome-related coronavirus-2 diagnosis.	• Rate of good clinical progress/ discharged from intensive care unit: 52.5% (n = 52) patients (out of 99 critically severe intubated patients). • 86 (77.5%) of 111 severe unintubated patients discharged from intensive care unit. • Intubated 47 (47.5%) patients and unintubated 25 (22.5%) patients pass away. • Significantly higher survival rate was analyzed in patients infused UC-MSCs before intubation (odds ratio = 1.475, 95% CI = 1.193-1.824 $P < .001$). • No adverse events in patients received UC-MSC infusion

(*Continued*)

Table 1. The Available Controlled Studies (https://pubmed.ncbi.nlm.nih.gov/: last accessed: March 11, 2022) (*Continued*)

Study	Center	Reference	Study design	Result
Hashemian SMR, et al. 2021	Iran	46	• Case study • The patients received 3 intravenous infusions (200 × 10^6 cells) every other day; human umbilical cord MSCs (UC-MSCs; n = 6) or placental MSCs (PL-MSCs; n = 5).	• No SAEs • Significant reductions in 6 patients in serum levels of tumor necrosis factor-alpha (TNF-α; $P < .01$), IL-8 ($P < .05$). • Decreased IL-6 levels in 5 ($P = .06$) patients and interferon gamma (IFN-γ) levels in 4 ($P = .14$) patients. Four patients with the signs of multi-organ failure or sepsis died in 5-19 days (average: 10 days) after the first MSC infusion. • Remarkable signs of recovery seen in lung CT scans.
Zengin R, et al. 2020	Turkey	47	• A case report of a COVID-19 patient progressed to severe disease with intubation and intensive care need. • An investigational MSC infusion was applied in intensive care unit, via intratracheal and intravenous routes (0.7 × 10^6 cells/kg intravenous, 0.3 × 10^6 cells/kg intratracheal with 4 units of heparin). A second dose of MSC therapy (0.7 × 10^6 cells/kg intravenous, 0.3 × 10^6 cells/kg intratracheal routes with 4 unites of heparin) was given 5 days after the first dose.	• No adverse events • Improved clinical signs • An invasive ventilation for the next 5 days continued following the second dose. • On day 19 of hospitalization, lung chest x-ray showed slight regression in the ground-glass imaged infiltration in the middle right lung periphery, and significant remission in the low-density infiltrations in the lower right lung and lateral left lung.
Yalcin K, et al. 2020	Turkey	48	• Case series • 7 patients diagnosed COVID-19 • Totally 1 × 10^6 UC-MSC/kg was administered for once in each patient by combined routes, intravenous (7 × 10^5 MSC/kg) and intratracheal (3 × 10^5 UC-MSC/kg through intubation tube) subsequently. • At the time of MSC administration, all 7 patients were taking mechanical ventilation.	• Significant reduction in the level of C-reactive protein of all patients [(before MSC therapy, mean: 84.8 mg/L (2.4-272 mg/L); after MSC administration, mean: 6.5 mg/L (0.3-25.3 mg/L)]. • Decreased procalcitonin level for 6 of 7 patients, increasing lymphocyte count for 5 of 7 patients and pulmonary functions PaO_2/FiO_2. • Improved Positive End-Expiratory Pressure level for 5 of 7 patients within 7 days after MSC infusion. • After MSC infusion, 4 of 7 patients were weaned from mechanical ventilation.

COVID-19 infection, and 13 of them were performed with MSC exosomes (3 IV, 10 of them inhaled exosome application). As of today, it is seen that there are 9 studies whose results have been published in the control of COVID-19 ARDS. Of these, 5 were randomized placebo-controlled including 2 phase I/II and 1 phase II studies, 2 were non-randomized controlled, 1 was non-randomized without control and 4 were case studies. Two were uncontrolled studies including 1 phase I study and 1 non-randomized cohort study (Table 1). The common point of these studies is that the use of MSCs or exosomes is a safe practice.[24,37-48]

SUMMARY ANALYSIS OF PUBLISHED RANDOMIZED CONTROLLED STUDIES IN COVID-19

When only published controlled studies were examined, control (n = 12) and MSC (n = 12; 100 million/IV single dose) groups were compared in a phase I/II randomized controlled study conducted in the USA.[37] In this study, investigators reported that cytokine storm could be easily controlled in the MSC group. The most important result of this study is that the survival rate in the MSC group was 91%, while it was reported as 42% in the control group.

Another double-blind, multicentered, randomized controlled trial (n = 40) evaluated the UC-MSCs (1×10^6/kg body weight) vs control group (0.9% saline solution). This study reported that the survival rate in the UC-MSCs group was 2.5 times higher than that in the control group (P = .047; 10 patients versus 4 patients. In addition, UC-MSC administration increased the survival rate by 4.5 times compared with controls in patients with comorbidities.[39]

In a publication from China,[41] 66 patients who received low-dose 40 million/IV single-dose MSCs were compared with 35 control patients. In this study, nonsignificant positive differences were observed in biochemical parameters, survival, and length of stay, but the reduction in lung lesions resulted in a statistically significant difference in the MSC group.

In the study by X et al[24] with menstrual mesenchymal stem cells, 3 million/kg MSC was given to 26 patients every other day, while the placebo group was followed up with standard care. In this study, investigators reported that cytokine storm could be controlled with MSC, and this was reflected in the clinic, resulting in a significant decrease in mortality, which was 33% in the placebo arm, and 7.7% in the MSC group 10.

In another placebo-controlled study conducted by Shu L et al.[38] 12 patients who received 2 million cells/kg of single-dose MSCs originating from the human umbilical cord were compared with 29 patients who received a placebo. In this study, while C-reactive protein and interleukin-6 levels were significantly decreased in the MSC group, improvement in lymphocyte count and oxygenation levels were also detected in the MSC group. While the median recovery time was 7 days in the MSC group, it was significantly longer in the placebo group at 14 days. The 28-day mortality was 0% in the MSC group and 10.34% in the placebo group. However, these data are not statistically significant.

Contrary to these results, Meng F et al[44] compared patients in whom they infused low-dose 30 million/IV dose of cord blood-derived MSCs 3 times sequentially with 9 control patients. However, although they found improvement in cytokine levels and respiratory functions in the MSC group, this was not statistically significant.

Apart from these controlled studies, MSCs have been reported to control cytokine storm in case–control series report (Table 1). In the study conducted by our group on this subject, 80 million MSCs originating from the umbilical cord were administered intravenously, 20 million MSCs were administered via endobronchial way, with an interval of 4 days, and it was reported that stem cells could significantly control the cytokine storm in patients and positively affect respiratory parameters.[47,48]

Considering all these existing studies, the most important shortcoming of these studies is that their analysis includes the acute and subacute periods. It seems that none of these studies analyzed the post-COVID period. Especially in these patients, oxidative stress, mitochondrial aging, and the presence of inflammasome continue after the disease and may cause post-COVID syndrome. In this respect, the use of MSCs during post-COVID treatment may have a positive effect. However, clinical evidence of theoretical knowledge has not yet emerged, as studies with MSC so far have not analyzed the effects of this treatment in the post-COVID period. Therefore, the effect of MSC use on post-COVID syndrome should be studied in particular. It should even be discussed in the treatment of post-COVID syndrome.[49]

CONCLUSION

In the treatment of COVID-19 infection, MSCs, which can interfere with the pathogenesis of the disease at many points, may be effective in accordance with pre-clinical data in clinical practice data. The most important point that can be said about this subject for now is that MSCs are a reliable treatment agent in the treatment of COVID-19. However, new, large and controlled studies to be planned in terms of the effectiveness of MSCs need to confirm the available data. In addition, the effects of MSCs used for treatment on COVID and post-COVID syndrome are promising and needs to be further studied. The following 2 questions must also be answered in these studies: First, what are the effects of MSCs used in the treatment of COVID on the post-COVID that will develop over a long period of time? Second, will there be efficacy of MSCs after post-COVID develops? Studies are needed to answer these questions.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.O., D.D.K.; Design – E.O., D.D.K.; Supervision – E.O.; Data Collection and/or Processing – E.O., D.D.K.; Literature Review – E.O., D.D.K.; Writing – E.O., D.D.K.; Critical Review – E.O., D.D.K.

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

Funding: The authors declared that this study has received no financial support.

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Turk Thorac J 2022; 23(5): 364-365 DOI: 10.5152/TurkThoracJ.2022.22034

Letter to the Editor

Response to Afatinib in a Common EGFR-Mutated Lung Adenocarcinoma with a Very Rare Combination of Compound Mutations

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Cite this article as: Satoh H, Miyazaki K, Sato Y, Hizawa N. Response to afatinib in a common EGFR-mutated lung adenocarcinoma with a very rare combination of compound mutations. *Turk Thorac J.* 2022;23(5):364-365.

Received: *February 15, 2022* ***Accepted:*** *June 10, 2022* ***Available Online:*** *August 8, 2022*

To the Editor,

A 76-year-old woman was referred to our hospital due to a nodule detected by mass screening. Biopsy specimens from the lesion showed epidermal growth factor receptor (EGFR)-mutated (exon 21 858R) adenocarcinoma. She underwent surgical resection; however, a year later, intrapulmonary metastases were discovered. Therefore, afatinib therapy was initiated as first-line therapy. The best response to afatinib was evaluated as "partial response," and progression-free survival (PFS) was 24 months. Then, she received chemotherapy for 6 months, erlotinib and bevacizumab for 5 months, and nivolumab for 3 months. After these treatments, pleural dissemination and accumulation of pleural fluid developed. EGFR mutation was re-evaluated using cancer cells in the pleural fluid to confirm the presence or absence of the T790M gene mutation. Cytological diagnosis was adenocarcinoma, and T790M gene was not detected. Afatinib was given for 3 months, but the best therapeutic effect was "stable disease," and the patient died 4 months after re-administration of afatinib. Overall survival was 42 months.

We undertook a detailed analysis of compound mutations and the content ratio of tumor cells and relative allele frequency (RAF) in pathological specimens obtained by surgical resection using Non-overlapping Integrated Read Sequencing System (NOIR-SS) (DNA Chip Research Inc. Tokyo, Japan).[1,2] Briefly, DNA was extracted from the slices of formalin fixed paraffin embedded (FFPE) tissue block of the patient using a Maxwell® RSC DNA FFPE kit (Promega, Madison, Wis, USA). 50 ng of DNAs were fragmented by Covaris focused-ultrasonicator (Woburn, Mass, USA), and molecular-barcoded next-generation sequencing (NGS) library was constructed by the NOIR-SS method as described previously.[1,2] Constructed library was sequenced using the Ion Chef/Ion S5 platform with Ion 540 chip (Thermo Fisher Scientific, Waltham, Mass, USA). In this patient, in addition to exon 21 L858R of the main mutation, L861Q and C797S were also found as compound mutations. The RAF for L861Q and C797S was 12% and 15%, respectively.

With the advancement of NGS technology, information on compound mutations in patients with common EGFR mutations has become available.[1,2] In catalogue of somatic mutations in cancer (COSMIC) database v94 (COSMIC Catalog of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk> cosmic), 3169 patients had compound mutations with L858R. Only 10 of them had L861Q. Thus, among L858R-mutated patients, those with L861Q as a compound mutation were rare. In addition, to the best of our knowledge, there were no L858R-mutated patients who had L861Q and C797S as compound mutations.

In patients with the common EGFR mutant exon 21 L858R, their PFS and OS were evaluated as around 11 months and 24-32 months, respectively.[3-5] On the other hand, in a large database of 693 patients treated with afatinib for the treatment of NSCLC harboring uncommon EGFR mutations, median time to treatment failures in patients with major uncommon mutations, those with compound mutations, and those with other uncommon mutations were 10.8, 14.7, and 4.5 months, respectively.[6] The exact mechanism of the favorable outcome in our patient was unknown; however, the presence of these compound mutations seems to be unlikely and adversely affects the therapeutic effect of TKIs. Afatinib is considered to be a drug with therapeutic power that surpasses the situation with these compound mutations. It is speculated that the EGFR mutation by NGS will be clarified in more detail in the future. We considered that afatinib might be one of the drugs to be selected for the treatment of patients with complicated EGFR mutation backgrounds such as this patient.

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Ethics Committee Approval: This study was approved by the institutional ethics committee of Mito Medical Center, University of Tsukuba: NO18-46; Ryugasaki Saiseikai Hospital: No. 201904.

Informed Consent: Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Peer-review: Externally peer-reviewed.

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

Acknowledgments: The authors thank Yoshio Iwakawa for his important research advice.

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

Funding: The support for biomarker analysis was provided by Nippon Boehringer Ingelheim Co Ltd (Tokyo, Japan).

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